JAMA | Review

# Management of *Staphylococcus aureus* Bacteremia
## A Review

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**IMPORTANCE** *Staphylococcus aureus*, a gram-positive bacterium, is the leading cause of death from bacteremia worldwide, with a case fatality rate of 15% to 30% and an estimated 300 000 deaths per year.

**OBSERVATIONS** *Staphylococcus aureus* bacteremia causes metastatic infection in more than one-third of cases, including endocarditis (≈12%), septic arthritis (7%), vertebral osteomyelitis (≈4%), spinal epidural abscess, psoas abscess, splenic abscess, septic pulmonary emboli, and seeding of implantable medical devices. Patients with *S aureus* bacteremia commonly present with fever or symptoms from metastatic infection, such as pain in the back, joints, abdomen or extremities, and/or change in mental status. Risk factors include intravascular devices such as implantable cardiac devices and dialysis vascular catheters, recent surgical procedures, injection drug use, diabetes, and previous *S aureus* infection. *Staphylococcus aureus* bacteremia is detected with blood cultures. Prolonged *S aureus* bacteremia (≥48 hours) is associated with a 90-day mortality risk of 39%. All patients with *S aureus* bacteremia should undergo transthoracic echocardiography; transesophageal echocardiography should be performed in patients at high risk for endocarditis, such as those with persistent bacteremia, persistent fever, metastatic infection foci, or implantable cardiac devices. Other imaging modalities, such as computed tomography or magnetic resonance imaging, should be performed based on symptoms and localizing signs of metastatic infection. *Staphylococcus aureus* is categorized as methicillin-susceptible (MSSA) or methicillin-resistant (MRSA) based on susceptibility to β-lactam antibiotics. Initial treatment for *S aureus* bacteremia typically includes antibiotics active against MRSA such as vancomycin or daptomycin. Once antibiotic susceptibility results are available, antibiotics should be adjusted. Cefazolin or antistaphylococcal penicillins should be used for MSSA and vancomycin, daptomycin, or ceftobiprole for MRSA. Phase 3 trials for *S aureus* bacteremia demonstrated noninferiority of daptomycin to standard of care (treatment success, 53/120 [44%] vs 48/115 [42%]) and noninferiority of ceftobiprole to daptomycin (treatment success, 132/189 [70%] vs 136/198 [69%]). Source control is a critical component of treating *S aureus* bacteremia and may include removal of infected intravascular or implanted devices, drainage of abscesses, and surgical debridement.

**CONCLUSIONS AND RELEVANCE** *Staphylococcus aureus* bacteremia has a case fatality rate of 15% to 30% and causes 300 000 deaths per year worldwide. Empirical antibiotic treatment should include vancomycin or daptomycin, which are active against MRSA. Once *S aureus* susceptibilities are known, MSSA should be treated with cefazolin or an antistaphylococcal penicillin. Additional clinical management consists of identifying sites of metastatic infection and pursuing source control for identified foci of infection.

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In 2019, *Staphylococcus aureus* was the leading bacterial cause of death in 135 countries.[1] Among multidrug-resistant infections in hospitalized patients in the US in 2017, an estimated 52% were caused by methicillin-resistant *S aureus* (MRSA).[2] While the rate of endocarditis in US patients with *S aureus* bacteremia has declined from more than 50%[3] in 1954 to approximately 12% in 2017, rates of infections involving implantable foreign bodies have increased.[4] Despite improvements in treatment and diagnosis, 90-day mortality among patients with *S aureus* bacteremia is 27.0% (95% CI, 21.5%-33.3%).[5]

A 2014 *JAMA* review of *S aureus* bacteremia identified only 1 high-quality trial to guide antibiotic therapy.[6] Over the past 10 years, more studies have been published about diagnostic and treatment strategies, and in 2024, the US Food and Drug Administration (FDA) issued regulatory approval of a novel antibiotic, ceftobiprole, for *S aureus* bacteremia.[7] This review will cover key aspects of the clinical management of *S aureus* bacteremia, including evidence-based treatment options.

## Methods

We conducted a search for randomized clinical trials of *S aureus* bacteremia antibiotic treatment published from January 1, 2014, through January 25, 2025, in MEDLINE (via PubMed) and the Cochrane Central Register for Controlled Trials (Wiley). Search terms included a mix of keywords and MeSH terms representing the concepts of *S aureus*, bacteremia, and antibiotics. The full, reproducible search strategies are available in the Supplement. A total of 1624 articles were identified. Of these, 22 randomized clinical trials (RCTs) were included in this review. In addition, we included 43 observational cohorts, 10 systematic reviews or meta-analyses, 11 reviews, 8 randomized clinical trial protocols, 7 guidelines, and 2 laboratory studies.

## Discussion

### Epidemiology and Risk Factors

Based on data from high-income countries, the incidence of *S aureus* bacteremia ranges from 9.3 to 65 cases per 100 000 person-years.[8] Risk factors include central venous catheters, implanted cardiac or other prosthetic devices, injection drug use, hemodialysis (particularly when vascular access is via central venous catheter),[9] recent surgical procedures, and host factors such as male sex (male to female ratio, ≈1.5), very young or older age (≤1 year and ≥70 years),[10] lower socioeconomic status,[11] diabetes,[12] corticosteroid use,[4] HIV infection, and *S aureus* nasal colonization.[13] In a 21-year prospective study of 2348 patients, 54.2% with *S aureus* bacteremia had implanted prosthetic material (most commonly a central venous catheter or cardiac device), and the proportion increased from 40% in 1995 to 54.7% in 2015.[4] In US surveillance data from 2005-2016, persons who inject drugs were significantly more likely to develop invasive MRSA infections than those who did not inject drugs (472.2 vs 29.0 per 100 000 person-years in 2011; rate ratio, 16.3 [95% CI, 15.7-16.8]).[14]

### Pathophysiology

*Staphylococcus aureus* is a gram-positive bacterium, existing as a commensal in the human nares, skin, throat, and gastrointestinal tract in about 30% of people.[15] However, *S aureus* can be a virulent pathogen if it breaches the skin or mucosal barriers and accesses normally sterile sites such as the bloodstream. After entering the bloodstream, *S aureus* can attach to the surface of host tissues (eg, native cardiac valves) or implanted devices (eg, intravascular lines, cardiac devices, prosthetic joints). Attachment is mediated by MSCRAMMs (microbial surface components recognizing adhesive matrix molecules), which are surface proteins that enable *S aureus* to bind to many human proteins, including fibronectin, fibrinogen, collagen, von Willebrand factor, and platelets.[16] After attaching to a surface, aggregates of *S aureus* cells can produce a biofilm matrix of polysaccharides, proteins, and extracellular DNA[17] that protects the bacteria from detection by the human immune system. *Staphylococcus aureus* then enters a low metabolic state, resulting in reduced susceptibility to antibiotics that are active against replicating bacteria.

*Staphylococcus aureus* bacteremia may also lead to abscess formation, facilitated by clotting factors, coagulase, and von Willebrand factor–binding protein, which promote fibrin clots and a pseudocapsule, protecting a central bacterial aggregate from phagocytic clearance.[18-20] If abscesses rupture, release of *S aureus* may potentially lead to formation of new abscesses.

Details of pathogenicity and host interactions of *S aureus* are shown in **Figure 1**.

### Clinical Presentation

*Staphylococcus aureus* bacteremia can present with fever alone, prompting diagnostic blood cultures. Conversely, patients may present with symptoms arising from a source such as a skin and soft tissue infection or a site of metastatic infection (eg, back pain from vertebral osteomyelitis). Approximately 73% of patients with *S aureus* bacteremia present with fever,[21] 42% have chills, and 18% have mental status changes.[22] Common infectious foci are osteoarticular sites (14.4%), endovascular structures (eg, infective endocarditis, septic thrombophlebitis) (17.8%), and pulmonary infection (5.9%).[4] Mucocutaneous manifestations are present in approximately 18% of patients with *S aureus* bacteremia[23] and in approximately 33% of patients with *S aureus* endocarditis.[24]

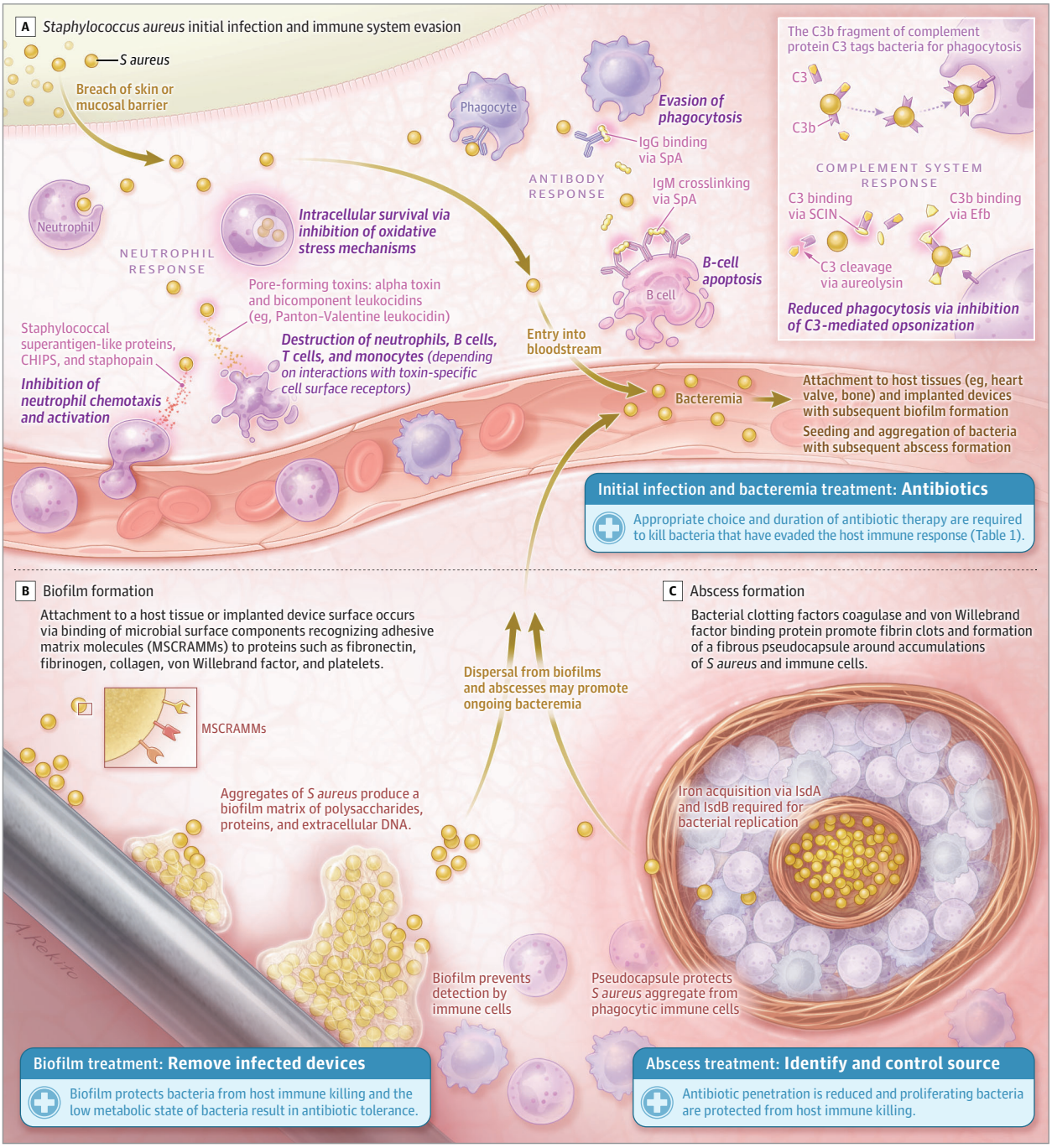
*Staphylococcus aureus* is an uncommon cause of urinary tract infection, particularly in the absence of urinary tract catheterization or recent instrumentation; thus, the finding of *S aureus* bacteriuria should prompt consideration of underlying *S aureus* bacteremia, especially in hospitalized patients and/or those with systemic symptoms.[25] In approximately 20% of patients, the source of *S aureus* bacteremia is not identified.[26]

#### History and Physical Examination

Clinicians should ask patients diagnosed with *S aureus* bacteremia about presence of indwelling cardiac devices (such as a pacemaker, implantable cardioverter-defibrillator, or cardiac resynchronization therapy device), prosthetic devices (such as joint implants), central venous catheters, recent medical procedures and injuries, history of injection drug use, use of hemodialysis, diabetes, and previous *S aureus* infections.

Because *S aureus* may infect many anatomical sites (eg, endovascular, osteoarticular, and deep tissue),[27,28] joints should be evaluated for tenderness, erythema, and effusions, and the spine should be assessed for tenderness. In a cohort of 97 patients with 166 arthroplasties in place during an episode of *S aureus* bacteremia, 38

Figure 1. Pathogenicity and Host Interactions of *Staphylococcus aureus*



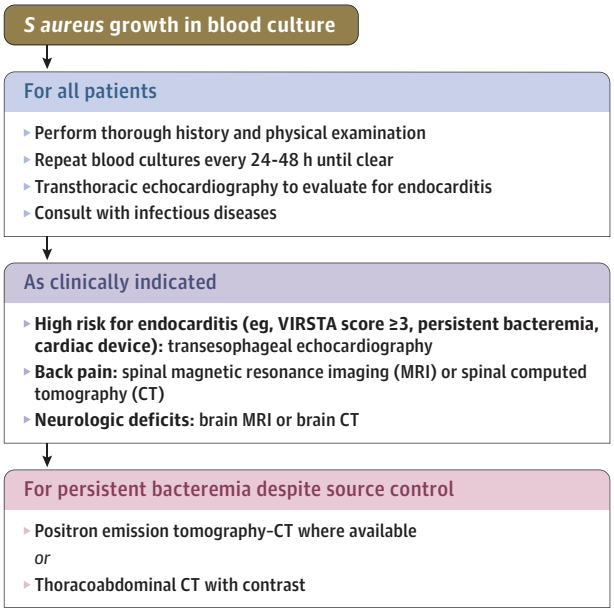

C3 indicates complement protein C3; CHIPS, chemotaxis inhibitory protein of *Staphylococcus aureus*; Efb, extracellular fibrinogen-binding protein; Isd, iron-regulated surface determinant system; SCIN, staphylococcal complement inhibitor; SpA, staphylococcal surface protein A.

of 39 (97.4%) with prosthetic joint infections presented with joint pain.[27] Pain is also the most common symptom of vertebral osteomyelitis; in a systematic review of vertebral osteomyelitis involving 14 studies (n = 1008), back pain was reported in 86% of patients.[29] Endocarditis may be suggested by cardiac murmurs, signs of heart failure such as volume overload, and embolic and vasculitic manifestations such as Roth spots (retinal hemorrhages), conjunctival petechiae, or splinter hemorrhages, Janeway lesions (nontender macules on the palms and soles), and Osler nodes (tender nodules most common on the pads of the fingers and toes). A neurologic examination may reveal evidence of focal deficits (such as weakness) caused by septic emboli.

### Diagnosis

Details of the diagnostic evaluation of patients with *S aureus* bacteremia are shown in **Figure 2**.

Figure 2. Diagnostic Evaluation of Patients With *Staphylococcus aureus* Bacteremia




See the Identifying Sites of Infection section in the text for additional discussion regarding the respective uses of transthoracic and transesophageal echocardiography and of spine imaging using CT and MRI.

*Staphylococcus aureus* bacteremia is diagnosed with growth of *S aureus* in a blood culture. Conventionally, Gram staining that shows gram-positive cocci in clusters and biochemical testing identify the organism in a blood culture, and antibiotic susceptibility testing is then performed on the isolate. Increasing availability of rapid molecular diagnostic tests performed on positive blood culture specimens may allow species identification within several hours and provide direct detection of antimicrobial resistance determinants, such as the presence of the *mecA* gene, which confers methicillin resistance in *S aureus*.[30,31] In an RCT of 89 patients with gram-positive cocci in blood cultures, use of a rapid molecular diagnostic test reduced the time to reporting of methicillin susceptibility compared with conventional microbiology (median 3.9 hours from Gram stain in the intervention group vs 25.4 hours in the control group; $P < .001$) and significantly decreased time to targeted therapy for *S aureus* (5 hours vs 25.5 hours; $P = .004$).[32] In a network meta-analysis of 88 studies (11 exclusively focused on *S aureus*) involving 25 682 patient encounters for bloodstream infections, use of a rapid diagnostic test combined with an antimicrobial stewardship program was associated with improved mortality (odds ratio [OR], 0.72 [95% CI, 0.59-0.87]) and reduced time (29 hours) to optimal antibiotic therapy compared with blood cultures alone.[33]

## Persistent Bacteremia

Despite appropriate antibiotic therapy, approximately one-third of patients with *S aureus* bacteremia have persistent bacteremia.[34] In a prospective multicenter cohort study, the 90-day mortality of patients with 2 to 4 days of *S aureus* bacteremia following initiation of antibiotics was almost twice that of patients with only 1 day of bacteremia (39% vs 22%).[34] Additionally, a new metastatic focus of infection was more likely in those with delayed clearance, occurring in 10% of patients with 2 to 4 days of bacteremia and 22% of those with 5 to 7 days of bacteremia, compared with 6% in patients who cleared their bacteremia in a single day.[34] Therefore, repeat blood cultures should be performed for patients with *S aureus* bacteremia at intervals of 24 to 48 hours until blood culture results are negative.[35]

## Uncomplicated and Complicated *S aureus* Bacteremia

The Infectious Diseases Society of America (IDSA) MRSA guidelines[35] define uncomplicated *S aureus* bacteremia as infections in which endocarditis has been excluded, there are no implanted prostheses, follow-up blood cultures 2 to 4 days after the initial blood cultures do not grow *S aureus*, defervescence has occurred within 72 hours of initiating effective therapy, and there is no evidence of metastatic sites of infection. Infections not meeting these criteria are considered complicated *S aureus* bacteremia. Across different cohorts, approximately 30% of patients with *S aureus* bacteremia are classified as uncomplicated.[23,36]

Patients with community-onset *S aureus* bacteremia, defined as an initial positive blood culture result within 48 hours of hospital admission, are at considerably increased risk of complicated disease.[4,37-39] Presumably, this is related to a longer duration of bacteremia in the community prior to commencing antibiotic treatment and thus an elevated risk of metastatic seeding. In contrast, hospitalized patients who develop a venous peripheral or central line–related infection typically have blood cultures promptly collected if they develop a fever and receive rapid administration of empirical antibiotic therapy.

## Identifying Sites of Infection

### Echocardiography

Once *S aureus* bacteremia is identified, clinicians must determine both the source and potential sites of metastatic infection, including infective endocarditis. Approximately 12% of patients with *S aureus* bacteremia develop endocarditis.[4,37] Therefore, echocardiography should be routinely obtained for all patients with *S aureus* bacteremia. Transesophageal echocardiography (TEE) is preferred but not mandatory in current IDSA guidelines.[35] In clinical practice, transthoracic echocardiography (TTE) is usually obtained first. Whether patients with *S aureus* bacteremia who do not have findings suggestive of endocarditis on TTE should undergo TEE is an area of ongoing controversy.[6] TEE is more sensitive than TTE for detection of valvular abnormalities caused by *S aureus* infective endocarditis[40,41] and for detection of perivalvular complications.[42] In a meta-analysis of 2807 patients with suspected infective endocarditis, TTE had sensitivity of only 61% (95% CI, 45%-75%) compared with TEE, which was used as the reference standard.[43] However, the increased sensitivity of TEE must be balanced with its increased costs and potential risks, including major complications such as esophageal perforation in approximately 1 in 5000 patients.[44]

Several clinical predication rules have been developed to identify the need for TEE among patients with *S aureus* bacteremia by quantifying the risk of endocarditis. The most accurate of these is the VIRSTA score (**Table 1**), which assigns points to underlying risk factors, presence of other foci of infection, severe sepsis or shock, elevated C-reactive protein level, and persistent bacteremia 48 hours after the initial positive blood culture result.[37] A lower score indicates lower risk, and a score less than 3 had a negative predictive

value of 99.3% for a diagnosis of infective endocarditis in a validation study, although it classified approximately 70% of patients as high risk, warranting TEE.[45]

Based on expert opinion, it is reasonable to forgo TEE in patients with *S aureus* bacteremia who have a VIRSTA score less than 3. In addition, TEE may not be required in patients without evidence of endocarditis based on clinical findings and TTE results, whose *S aureus* bacteremia resolves quickly, and are being treated with prolonged antibiotic therapy for complications such as osteomyelitis, discitis, or epidural abscess.

### Additional Imaging

The IDSA recommends magnetic resonance imaging with gadolinium of the spine as the imaging modality of choice for patients with *S aureus* bacteremia and back pain.[46] Computed tomography (CT) of the chest, abdomen, and pelvis may be useful to identify unrecognized foci of infection such as abscesses or septic pulmonary emboli, particularly in patients who are not clinically improving with initial antibiotics. However, currently, there are insufficient data to recommend magnetic resonance imaging or CT imaging as routine care for all patients with *S aureus* bacteremia.

Positron emission tomography (PET)-CT may be considered for the evaluation of metastatic sites of infection. A 2023 global survey of 2031 physicians (74% of whom were adult infectious disease specialists) found that there was wide variation by region in both PET-CT availability (range, 9%-78% of respondents) and use of PET-CT (range, 13%-94%) for evaluation of patients with *S aureus* bacteremia worldwide.[47]

## Treatment

Treatment of *S aureus* bacteremia requires appropriate antibiotic therapy and control of sources of infection. Clinical trials inform various aspects of *S aureus* bacteremia management (**Table 2**; eTable 5 in the Supplement).[7,49-66] See the **Box** for commonly asked questions about management of *S aureus* bacteremia.

### Choice of Antibiotic

For patients suspected to have *S aureus* bacteremia (eg, sepsis with clinically evident skin and soft tissue infection or those with a preliminary report of gram-positive cocci in blood culture), empirical antibiotic choice should be guided by local epidemiology and the individual characteristics of the patient being evaluated. Updated surveillance data on regional rates of methicillin resistance are collated by groups such as the World Health Organization–sponsored Global Antimicrobial Resistance and Use Surveillance System and the Global Burden of Disease Antimicrobial Resistance Collaborators.[67,68] Regions with very low rates (<5%) of MRSA may choose to initiate β-lactam antibiotics such as nafcillin/flucloxacillin or cefazolin. Antibiotics with activity against MRSA should be initiated in areas with MRSA rates greater than 5%, such as the US, or for patients with risk factors for MRSA such as injection drug use, recent hospitalization or surgery, presence of prosthetic implants including central lines, long-term care facility residence, hemodialysis dependence, or prior MRSA infection.

Once *S aureus* antibiotic susceptibility is determined, therapy should be tailored accordingly. For methicillin-susceptible *S aureus* (MSSA) bacteremia, guidelines[69-71] recommend using either cefazolin or an antistaphylococcal penicillin (eg, nafcillin, flucloxacillin),

**Table 1. VIRSTA Score to Determine Priority of Transesophageal Echocardiography in Patients With *Staphylococcus aureus* Bacteremia**

| Clinical condition | Weight |
|---|---|
| Cerebral or peripheral emboli | 5 |
| Meningitis | 5 |
| Permanent intracardiac device or previous infective endocarditis | 4 |
| Intravenous drug use | 4 |
| Preexisting native valve disease | 3 |
| Persistent bacteremia (defined as positive follow-up blood culture result obtained 48 h after initial positive blood culture) | 3 |
| Vertebral osteomyelitis | 2 |
| Community or nonnosocomial health care–associated acquisition | 2 |
| Severe sepsis or shock | 1 |
| C-reactive protein >190 mg/L | 1 |

Adapted from Tubiana et al, 2016.[37]

which are more rapidly bactericidal in vitro and associated with improved clinical outcomes (decreased mortality and recurrent infections) compared with vancomycin.[72-74] Recent observational data suggest that cefazolin may be associated with lower mortality and fewer adverse effects than antistaphylococcal penicillins for MSSA bacteremia.[75] In a meta-analysis of 14 observational studies comparing cefazolin and antistaphylococcal penicillins, cefazolin was associated with a lower 30-day mortality (relative risk, 0.70 [95% CI, 0.54-0.91]) and less nephrotoxicity (relative risk, 0.36 [95% CI, 0.21-0.59]).[76] Previous concerns about using cefazolin for central nervous system infections have been revisited by more recent reviews of pharmacokinetic/pharmacodynamic data.[77] Randomized clinical trials are currently directly comparing cefazolin with antistaphylococcal penicillins for *S aureus* bacteremia, and pending results should soon inform clinical practice.[78,79]

There are 3 antibiotics with an FDA-approved indication for treatment of MRSA bacteremia: vancomycin, daptomycin, and ceftobiprole. In an open-label clinical trial that included 246 participants with *S aureus* bacteremia, daptomycin was noninferior to the standard of care at the time (low-dose gentamicin plus either an antistaphylococcal penicillin or vancomycin) for MSSA (n = 157) and MRSA (n = 89) bacteremia. The primary outcome of this trial was a composite outcome of treatment success 42 days after therapy completion (53/120 [44%] vs 48/115 [42%]).[49] In a clinical trial of 390 participants, ceftobiprole, a cephalosporin with activity against both MSSA and MRSA, was noninferior to daptomycin for MSSA (n = 293) and MRSA (n = 94) bacteremia for the primary outcome of treatment success, defined as survival, bacteremia clearance, symptom improvement, no new *S aureus* bacteremia–related complications, and no receipt of other potentially effective antibiotics, at day 70 (132/189 [70%] vs 136/198 [69%]).[7] Ceftobiprole received FDA approval for *S aureus* bacteremia on April 3, 2024.

Advantages of vancomycin are its availability, clinician familiarity with use, and low cost. In addition, in well-designed clinical trials, no antibiotic has been proven superior to vancomycin for treatment of *S aureus* bacteremia. However, vancomycin has a narrow therapeutic window and requires drug monitoring to guide dosing and minimize the risk of kidney toxicity.[48]

Daptomycin is dosed once daily but is not always available in low- and middle-income countries. Additionally, treatment-emergent daptomycin resistance in *S aureus* has been reported, occurring in

Table 2. Directed Intravenous Antibiotic Treatment Options for Patients With *Staphylococcus aureus* Bacteremia[a]

| Drug | Recommended dose | Considerations | Common adverse effects (1%-10% incidence) |
|---|---|---|---|
| **For methicillin-susceptible *S aureus*[b]** | | | |
| Cefazolin | 2 g every 8 h | Use 2 g every 6 h for critically unwell patients; may be used in most cases of nonsevere penicillin allergy<br>Cefazolin associated with less toxicity and lower mortality than antistaphylococcal penicillins in observational studies | Gastrointestinal (diarrhea, nausea, vomiting) |
| Flucloxacillin | 2 g every 6 h | Use 2 g every 4 h for critically unwell patients and for infective endocarditis | Gastrointestinal (diarrhea, nausea, vomiting), local injection site thrombophlebitis, acute kidney toxicity, drug allergy |
| Cloxacillin | 2 g every 4 h | | |
| Nafcillin | 2 g every 4 h | | |
| Oxacillin | 2 g every 4 h | | |
| Benzylpenicillin | 2.4 g (4 million U) every 4 h | Only for *S aureus* isolates phenotypically confirmed as penicillin-susceptible with disk diffusion testing | Drug allergy |
| **For methicillin-resistant *S aureus*** | | | |
| Vancomycin | Loading dose of 20-35 mg/kg (maximum, 3 g), then 15-20 mg/kg (maximum, 2 g) every 12 h[c] | AUC-guided dosing is recommended, aiming for an AUC of 400-600[d]<br>When trough level-guided dosing is used, levels of 15-20 mg/L are effective but associated with increased kidney toxicity[d] | Vancomycin infusion reaction, acute kidney toxicity, ototoxicity |
| Daptomycin | 6-10 mg/kg once daily | FDA-approved dose is 6 mg/kg once daily; however, many clinicians favor higher dosing of 8 to 10 mg/kg once daily because daptomycin exhibits concentration-dependent killing<br>Do not use for methicillin-resistant *S aureus* pneumonia | Creatinine kinase elevation; eosinophilic pneumonia |
| Ceftobiprole | 500 mg every 6 h for 8 d, then 500 mg every 8 h | | Gastrointestinal (diarrhea, nausea, vomiting) |

Abbreviations: AUC, area under the receiver operating characteristic curve; FDA, US Food and Drug Administration.

[a] The recommended duration of antibiotic therapy is dependent on patient and disease factors rather than the choice of antibiotic. In general, a 2-week treatment course is recommended for uncomplicated, low-risk disease, defined as patients without community acquisition (ie, occurring <48 hours after hospitalization or without recent health care exposure), implanted prosthetic material, unremoved central venous catheters, positive follow-up blood culture results after initiation of appropriate antibiotic treatment, persistent fever, treatment delay, or clinical signs of metastatic infection. Patients who do not meet the definition for uncomplicated, low-risk disease are considered to have complicated, high-risk disease and are recommended to receive 4 to 6 weeks of antibiotic therapy.

[b] For patients with methicillin-susceptible *S aureus* and severe penicillin allergies (eg, anaphylaxis or severe cutaneous adverse reactions—Stevens Johnson or toxic epidermal necrosis), vancomycin and daptomycin can be used. Cefazolin may be used in most cases of nonsevere penicillin allergy.

[c] Use actual body weight.

[d] See American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists vancomycin consensus guidelines for vancomycin dosing and monitoring for more details.[48]

7 of 120 patients (6%) in the daptomycin registrational trial and 3 of 198 (1.5%) in the ceftobiprole vs daptomycin trial.[7,49]

## Combination Therapy for MSSA and MRSA

Eight randomized clinical trials assessing the addition of a second antibiotic to standard of care for *S aureus* bacteremia have been published since 2016 (eTable 5 in the Supplement). None demonstrated that combination antibiotic therapy improved clinical outcomes, including rifampin added to standard antibiotic therapy (1 trial [N = 758]),[55] fosfomycin added to standard therapy (3 trials [N = 397]),[59,60,80] daptomycin combined with a β-lactam for MSSA (1 trial [N = 115]),[61] and β-lactams combined with vancomycin or daptomycin for MRSA (3 trials [N = 452]).[56-58] One trial comparing the combination of daptomycin and ceftaroline vs standard of care found lower mortality in the combination group[58] but was methodologically flawed and prematurely stopped.[81] The addition of fosfomycin to cloxacillin,[60] fosfomycin to daptomycin,[59] and β-lactams to vancomycin[56,57] reduced rates of persistent bacteremia, defined variously as positive blood culture results at day 3, day 5, and day 7 following trial entry but did not improve mortality rates or treatment success, defined variously as composite end points incorporating mortality, microbiological relapse, and symptom resolution at different time points for each trial. Use of combination therapy for *S aureus* bacteremia is also associated with adverse effects, such as increased kidney injury with the addition of low-dose gentamicin.[82] Adjunctive agents such as bacteriophage-derived lysins have not been proven effective when tested in sufficiently powered clinical studies.[62,63]

### Salvage Therapy

Approximately 30% of patients have *S aureus* bacteremia for longer than 3 days despite use of appropriate antibiotics.[7,34,57] Persistent *S aureus* bacteremia is associated with increased mortality[34] and should prompt investigation for and control of sources of infection. For patients with persistent bacteremia, clinicians may consider switching antibiotics or adding antibiotics, although there are no randomized clinical trial data to provide guidance in such situations. Options include adding agents such as ertapenem to cefazolin[83] or fosfomycin to antistaphylococcal β-lactams for MSSA[60] and adding cefazolin,[57] fosfomycin,[59] ceftaroline,[58] or ceftobiprole[7] to vancomycin or daptomycin for MRSA.

### Duration of Therapy

Low-risk, uncomplicated MSSA and MRSA bacteremia is typically treated with a 2-week course of antibiotics. Patients with high-risk,

complicated MSSA and MRSA bacteremia require treatment for 4 weeks to 6 weeks or longer.[35] These recommendations, provided in the IDSA MRSA treatment guidelines, are largely based on observational data.[84]

### Transition to Oral Antibiotics

Guidelines such as the 2011 IDSA MRSA treatment guidelines have recommended prolonged durations of intravenous antibiotic therapy for *S aureus* bacteremia.[35] However, the Partial Oral Treatment of Endocarditis (POET) trial published in 2018 randomized 400 patients with infective endocarditis (87 had MSSA) who were clinically stable (afebrile for >2 days, C-reactive protein level decreased to <25% peak value, white blood cell count <15 × $10^9$/L, no sign of abscess formation on echocardiography performed within 48 hours of randomization, and received at least 10 days of parenteral antibiotics) to use of a combination of 2 oral antibiotics vs continuation of intravenous antibiotics for the remainder of the treatment course.[65] Participants received a median of 17 days of prerandomization intravenous antibiotics. Among the 87 patients with MSSA endocarditis, the primary outcome of mortality, unplanned surgery, relapse, or embolic events occurred in 3 of 47 (6.4%) allocated to oral therapy and 3 of 40 (7.5%) allocated to intravenous therapy. While the study was insufficiently powered to draw definitive conclusions about use of oral antibiotics for patients with *S aureus* endocarditis, the point estimate of treatment effect for oral vs intravenous therapy was similar for patients overall (OR, 0.72 [95% CI, 0.37-1.36]) and for those with *S aureus* infections (OR, 0.84 [95% CI, 0.15-4.78]). Limitations of the POET trial included the absence of MRSA infections, the requirement for dual oral antibiotic therapy, and more frequent outpatient follow-up than is practical in routine clinical practice.[85]

The *Staphylococcus Aureus* Bacteremia Antibiotic Treatment Options (SABATO) trial randomized 213 patients with low-risk *S aureus* bacteremia to receive oral antibiotics after 5 to 7 days of intravenous antibiotics vs continuing intravenous antibiotics, with both groups completing a total of 14 days of antimicrobial therapy.[66] Patients were not enrolled in this trial if they had complicated bacteremia (deep-seated focus of infection, septic shock, prolonged bacteremia [positive blood culture result obtained >72 hours after start of appropriate antibiotic therapy], fever in the prior 2 days), or had an intravascular catheter that was not removed, a history of *S aureus* bloodstream infection within the preceding 3 months, injection drug use, severe immunodeficiency or severe immunosuppression, or presence of a prosthetic heart valve or deep-seated vascular graft.[66] Of the 213 participants, there were 16 MRSA and 197 MSSA infections. The rates of failure, defined as a composite of relapsing *S aureus* bacteremia, deep-seated infection with *S aureus*, or death attributable to *S aureus* bacteremia, were similar in the oral antibiotic group (14/108 [13%]) and intravenous antibiotic group (13/105 [12%]). Rates of drug-related serious adverse events were low (3/107 [2.7%] in the oral antibiotic group vs 0/103 [0%] in the intravenous group).

The European Society of Cardiology 2023 Infective Endocarditis Guidelines indicate that oral antibiotic treatment should be considered in patients satisfying the POET trial eligibility criteria.[70] The WikiGuidelines for infective endocarditis support switching to oral antibiotic treatment for infective endocarditis, including that caused by *S aureus*.[71] Guidelines from the American Heart Association and IDSA have not been updated since the publication of the POET and SABATO trials. The *Staphylococcus aureus* Network Adaptive Platform trial provides details about potential oral antibiotic options and dosing recommendations within the protocol of an ongoing clinical trial for patients with *S aureus* bacteremia.[86,87]

**Box. Commonly Asked Questions About Management of *Staphylococcus aureus* Bacteremia**

**What Is the Role of Oral Antibiotics in Treatment of *S aureus* Bacteremia?**

In carefully selected circumstances, switching to oral antibiotics after an initial intravenous antibiotic phase may be considered. An important aspect of the randomized clinical trials comparing oral switch to continued intravenous therapy was the highly selected patient populations for trial inclusion among those with low-risk uncomplicated bacteremia or those with infective endocarditis. Results from these trials need to be replicated in larger studies and in patients with MRSA bacteremia before switching to oral antibiotics can be recommended more generally.

**What Are Reasonable Strategies for Echocardiography in the Management of *S aureus* Bacteremia?**

The clinical prediction VIRSTA score has been validated as able to sensitively identify patients at very low risk of infective endocarditis (VIRSTA score <3 has a negative predictive value >99%). It is reasonable to forgo transesophageal echocardiography when there are no concerns of cardiac complications based on clinical findings and transthoracic echocardiography and (1) the VIRSTA score is less than 3; or (2) for patients with complicated *S aureus* bacteremia who quickly clear their bloodstream and who already warrant an extended course of antibiotic therapy (such as osteomyelitis, discitis, or epidural abscess).

**What Is the Role of Up-Front Combination Antibiotic Therapy for *S aureus* Bacteremia?**

Eight randomized clinical trials have not demonstrated a benefit for outcomes such as mortality and treatment success for various combinations of up-front intravenous antibiotics compared with monotherapy. At this stage, up-front combination antibiotic therapy is not recommended.

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

### Source Control

Source control is a critical component of *S aureus* bacteremia treatment. Procedures may include incision and drainage of abscesses, debridement of infected tissue, and removal of implanted prosthetic material. Early source control improves outcomes; in a cohort of 884 US patients with *S aureus* bacteremia, shorter time to source control procedure (median, 1 day vs ≥3 days) was associated with earlier clearance of bacteremia and lower mortality, with each additional day of bacteremia associated with a relative risk of death of 1.16 (95% CI, 1.10-1.22; $P < .001$).[88]

Indwelling intravascular catheters should be promptly removed in patients with *S aureus* bacteremia. In a study of 324 patients with catheter-associated *S aureus* bacteremia, retention of intravascular catheters was associated with increased risk of hematogenous complications such as septic arthritis or endocarditis (relative risk, 2.28 [95% CI, 1.22-4.27]; $P = .01$).[89] In another study of 299 patients with central catheter–associated *S aureus* bacteremia, delayed intravascular catheter removal (>3 days) was associated with higher rate of *S aureus* bacteremia relapse (12.7 vs 4.7%, $P = .02$).[90]

Similarly, cardiac device removal is generally recommended for patients with *S aureus* bacteremia.[91] In a cohort of 5325 US patients with *S aureus* bacteremia and an indwelling cardiac device, in-hospital mortality was lower among patients whose device was removed (5.6% vs 16.4%; adjusted OR, 0.31 [95% CI, 0.21-0.44]).[92]

For patients who have *S aureus* bacteremia and a prosthetic joint, management should be individualized. The decision about whether to remove the prosthetic joint depends on many factors, including the timing of *S aureus* bacteremia after joint implantation; whether infection occurred through hematogenous route or during the surgical procedure; surgical expertise; and patient comorbidities.

## Prognosis

Based on a systematic review and meta-analysis of 341 studies that included 536 791 patients, the estimated mortality of patients with *S aureus* bacteremia was 10% at 7 days, 13% at 2 weeks, 18% at 1 month, 27% at 3 months, and 30% at 1 year.[5] In a 2020 cohort of 31 002 patients in the US Veterans Health Administration hospitals, the 5-year mortality rate after *S aureus* bacteremia was 61%.[93] Key predictors of mortality are increasing age, comorbidities (such as heart failure, alcohol use disorder, malignancy, immune suppression, and/or hemodialysis dependence), and disease severity at presentation.[93,94] In a pooled analysis of 3395 adult patients with *S aureus* bacteremia, crude 90-day mortality was 29.2%. However, having an unidentified infective source was associated with higher mortality of 48.7% (adjusted hazard ratio for 90-day mortality, 2.92 [95% CI, 2.33-3.67]; $P < .001$).[26] Multiple studies have reported that MRSA bacteremia is associated with increased mortality compared with MSSA bacteremia,[93,94] although this may be confounded by the older age and comorbidities of patients with MRSA bacteremia.[95]

## Practical Considerations

Infectious diseases consultation for patients with *S aureus* bacteremia has been associated with improved patient outcomes in observational studies.[93,96] In a study that included 31 002 patients with *S aureus* bacteremia, 15 360 (49.5%) received infectious diseases consultation during their hospitalization. At 5-year follow-up, infectious diseases consultation was associated with improvement in the composite outcome of all-cause mortality or recurrence of *S aureus* bacteremia (adjusted hazard ratio, 0.71 [95% CI, 0.68-0.74]; $P < .001$).[93] Importantly, the benefit of infectious diseases involvement is primarily observed with direct patient care at the bedside[97] and was not seen in a small RCT of a telehealth consultation model.[98]

## Limitations

This review has limitations. First, there is limited high-quality evidence to guide treatment recommendations for *S aureus* bacteremia. Second, the heterogeneity of *S aureus* bacteremia means that recommendations are unable to cover all circumstances. Third, relevant articles may have been missed.

## Ongoing Studies

Several completed or actively recruiting RCTs involving patients with *S aureus* bacteremia have not yet been published. Summarized in eTable 6 in the Supplement, these trials involve antibiotic choice,[78,79,99,100] duration,[101,102] and route,[86,103] as well as novel therapeutics and diagnostics.

# Conclusions

*Staphylococcus aureus* bacteremia has an incidence of 10 to 30 per 100 000 per year, a case fatality rate of 15% to 30%, and causes 300 000 deaths per year worldwide. Empirical antibiotic treatment should include vancomycin or daptomycin, which are active against MRSA. Once the *S aureus* susceptibilities are known, MSSA should be treated with cefazolin or an antistaphylococcal penicillin. Additional clinical management consists of identifying sites of metastatic infection and pursuing source control for identified foci of infection.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**Submissions:** We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.



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