

Staphylococcus aureus Bloodstream Infections: Definitions and Treatment

G. Ralph Corey

Duke University Medical Center, Durham, North Carolina

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Bacteremia caused by *Staphylococcus aureus* is a serious infection associated with high morbidity and mortality and often results in metastatic infections such as infective endocarditis, which have a negative impact on patient outcomes. We review the importance of the use of precise definitions of uncomplicated bacteremia and complicated bacteremia and present a case study to highlight the need for prolonged treatment and close monitoring of patients with risk factors for complications associated with *S. aureus* bacteremia. Traditionally, the treatment of choice for *S. aureus* bacteremia has depended to a large extent on the methicillin susceptibility of the pathogen. New antibiotics with proven efficacy against both susceptible and resistant strains are particularly attractive for empirical therapy. The antimicrobial agents that are currently available for use in the treatment of both methicillin-susceptible and methicillin-resistant *S. aureus* bacteremia and the scientific evidence that forms a basis for the use of these agents for this indication are reviewed.

Staphylococcus aureus is a versatile and virulent pathogen in humans, who serve as natural reservoirs for this pathogen [1]. The rates of infections caused by staphylococci, both community- and hospital-acquired strains, are increasing steadily [2, 3]. Concurrently, treatment of these infections is becoming more difficult because of the increasing prevalence of multidrug-resistant strains [4].

S. aureus is a leading cause of bacteremia [5, 6] and endocarditis [7, 8]. *S. aureus* bacteremia (SAB) is associated with significant morbidity. In a series of 724 consecutive patients with SAB, 246 patients (34%) developed metastatic infections, 89 patients (12%) received a diagnosis of endocarditis, and the 12-week mortality rate was 22% (157 patients died) [9]. Even among patients whose bacteremia originated from an intravenous catheter, the incidence of metastatic infections was 14% [9]. The virulent nature of *S. aureus*

demands rigorous management of both suspected and confirmed cases of SAB. This article considers the antimicrobial options that are available for treatment of SAB through a review of the outcomes evidence from clinical trials. The duration of antibiotic therapy is considered in the context of the existence and nature of complications or the likely risk of developing complications [10].

DURATION OF THERAPY FOR SAB

SAB is associated with significant mortality and with complications, such as infective endocarditis (IE) [11, 12], vertebral osteomyelitis [13], and recurrent infection. However, complications can be difficult to identify at the time of the initial positive result of blood culture [14]. Fowler et al. [9] developed a risk-scoring system based on the presence of 4 factors to estimate the likelihood of developing complications. The SAB score equals the sum of the points for individual risk factors: 1 point each for community-acquired infection, skin findings suggestive of acute systemic infection, and persistent fever at 72 h and 2 points for a positive result of follow-up blood culture at 48–96 h. The predicted rate of complications is 16% if no factors are present

Reprints or correspondence: Dr. G. Ralph Corey, P.O. Box 17969, Durham, NC 27715 (corey001@mc.duke.edu).

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and increases with the presence of each risk factor to a predicted rate of 90% if all factors are present (figure 1) [9].

The duration of therapy for SAB should depend on whether or not the infection is complicated, as defined by the following independent predictors: a positive result of follow-up blood culture at 48–96 h (OR, 5.58; $P < .001$), community-acquired infection (OR, 3.1; $P = .002$), persistent fever at 72 h (OR, 2.23; $P < .001$), and skin lesions suggestive of acute systemic infection (OR, 2.04; $P < .001$) [9]. However, skin lesions are rare, occurring in only ~7% of patients. The recommended duration of therapy for complicated SAB is 4–6 weeks [10].

Uncomplicated bacteremia has been defined by Fowler et al. [9] as cases that fulfill all of the following criteria: catheter-associated infection and removal of the catheter, negative result of follow-up blood culture, defervescence within 72 h, 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 for uncomplicated bacteremia may be adequate to achieve clinical cure [10]. However, there are data from a study on the appropriateness of 2-week therapy for catheter-related SAB that suggest that even patients with uncomplicated bacteremia are more likely to be cured when they receive >2 weeks of therapy, compared with patients who receive <2 weeks, although the number of patients who received <2 weeks of therapy was small [15]. The apparent lack of efficacy of 2-week therapy may be the result of the failure of the physicians to precisely categorize patient risks or may result from the inability of the above criteria to accurately identify appropriate patients. For example, patients with central venous catheter-associated SAB have been found to have a 71% incidence of thrombosis (definite or possible) [16]. This additional factor may help explain why therapy for >2 weeks is needed to clear these infections. Whether anticoagulation will assist in the treatment of infected venous thrombi is an issue that needs further exploration.

CASE STUDY

The following case study highlights the need for prolonged treatment of patients with risk factors for complications associated with SAB and the need for close monitoring, including ongoing efforts to identify potential complications in the form of deep-seated metastatic infections. A 44-year-old male injection drug user was admitted to the hospital with a fever and back pain and started vancomycin treatment (1 g administered intravenously every 12 h); the mean trough serum concentration was 15 $\mu\text{g}/\text{mL}$.

All 3 blood cultures were positive for methicillin-resistant *S. aureus* (MRSA), and transthoracic echocardiography and spinal MRI detected no relevant abnormalities. Fever persisted during the first week, and 1 of 3 follow-up blood cultures was positive for MRSA.

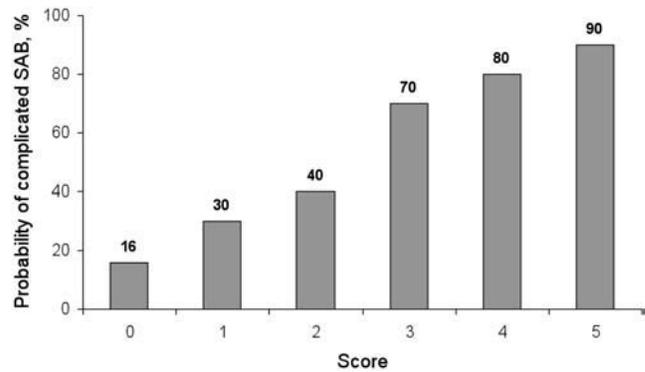


Figure 1. Association between the *Staphylococcus aureus* bacteremia (SAB) score and the probability of complicated SAB [9]. One point each is assigned for community-acquired infection, skin findings suggestive of acute systemic infection, and persistent fever at 72 h, and 2 points is assigned for a positive result of follow-up blood culture at 48–96 h.

The patient was discharged from the hospital after a complete 6-week course of vancomycin treatment but returned 2 weeks later with shortness of breath and back pain. He was febrile, with a new systolic murmur, and an additional 3 blood cultures were positive for MRSA. A transesophageal echocardiogram revealed a large mitral valve vegetation, as well as both significant mitral insufficiency and a perivalvular abscess. Spinal MRI showed lower lumbar and upper sacral osteomyelitis and a psoas abscess. The patient underwent mitral valve repair and debridement and drainage of the psoas abscess. The vancomycin MIC was determined to be 1 $\mu\text{g}/\text{mL}$; therefore, the patient restarted vancomycin treatment (1 g administered intravenously every 12 h for 6 weeks); as previously, the mean trough serum concentration was 15 $\mu\text{g}/\text{mL}$. The patient was then lost to follow-up.

ANTIMICROBIAL TREATMENT OPTIONS FOR SAB

The US Food and Drug Administration (FDA) understands and recognizes that SAB is a uniquely virulent infection, the outcome of which does not depend on the presence or absence of a definable origin. By contrast, the European Medicines Agency does not currently recognize bacteremia caused by any pathogen as a distinct “indication” for new antibiotic approval in the absence of a known or suspected underlying site of infection. Similarly, treatment guidelines for bacteremia are primarily based on specific sites of associated infections, such as IE [17, 18] and catheter-related infections [19]. The selection of antimicrobial agents for SAB is typically made on the basis of a combination of antibiotic susceptibility, local formulary restrictions, clinical experience, and often less-than-rigorous clinical trial data. Recently, the European Medicines Agency has taken a step toward the recognition of SAB as an indication with the approval of daptomycin for treatment of SAB when

associated with complicated skin and soft-tissue infections or with right-sided IE.

METHICILLIN-SUSCEPTIBLE *S. AUREUS* (MSSA) BACTEREMIA

The selection and success of an antimicrobial regimen for the treatment of SAB has depended largely on the methicillin susceptibility of the pathogen. Antibiotics that can be used for the treatment of MSSA bacteremia include the penicillinase-resistant semisynthetic penicillins, such as flucloxacillin (0.25–2 g administered intravenously every 6 h or by continuous infusion); first-generation cephalosporins, such as cefazolin (2 g administered intravenously every 8 h or by continuous infusion) [20]; and the cyclic lipopeptide daptomycin (6 mg/kg administered intravenously once every 24 h; indicated for SAB associated with complicated skin and soft-tissue infections or with known or suspected right-sided IE) [21]. The efficacy of daptomycin for the treatment of SAB and IE was investigated in, to our knowledge, the first randomized endocarditis trial conducted in >20 years. Daptomycin was shown to have efficacy similar to that of standard therapy for treatment of both MSSA and MRSA bacteremia and right-sided IE [22].

Continuous infusion of flucloxacillin was evaluated in 20 patients with MSSA bacteremia, and a clinical and microbiological cure was achieved for 82% [23]. In another small-scale study, flucloxacillin demonstrated clinical success rates of $\geq 89\%$ in the treatment of other serious infections caused by methicillin-susceptible gram-positive organisms [24]. The clinical benefit of using penicillins in combination with aminoglycosides for the treatment of staphylococcal infections has not yet been proven. Specifically, the addition of gentamicin to nafcillin for the treatment of *S. aureus* endocarditis showed no discernible effect on morbidity and mortality rates and was associated with increased nephrotoxicity [25].

Vancomycin is a glycopeptide antibiotic that is used widely in the treatment of methicillin-resistant staphylococcal and ampicillin-resistant enterococcal infections [26]. However, it is not the most effective treatment for MSSA infections [27–29], nor is it recommended for this. Stryjewski et al. [28] prospectively evaluated the clinical outcomes for 123 patients receiving hemodialysis who had MSSA bacteremia treated with vancomycin or cefazolin. Treatment failure, defined as death or recurrent infection, was determined at 12 weeks after the initial positive results of blood culture, and a multivariate analysis was used to adjust for confounders. Treatment failure occurred more frequently among patients who received vancomycin than among those who received cefazolin (31.2% vs. 13.0%; $P = .02$). Factors independently associated with treatment failure in the multivariate analysis included vancomycin use (OR, 3.53; 95% CI, 1.15–13.45) and retention of the hemodialysis access (OR, 4.99; 95% CI, 1.89–13.76). The authors concluded that,

in the absence of patient-specific circumstances (e.g., allergy to β -lactams), vancomycin should not be continued beyond empirical therapy for patients receiving hemodialysis who acquire MSSA bacteremia. Corroboration of these results was published by Chang et al. [27]. Results of a large, prospective, observational study revealed that patients with MSSA bacteremia who received vancomycin therapy had higher rates of relapse and microbiological failure than did those who received nafcillin therapy [27].

MRSA BACTEREMIA

Daptomycin, vancomycin, teicoplanin, linezolid, trimethoprim-sulfamethoxazole (TMP-SMX), and quinupristin-dalfopristin are all potential options for the treatment of MRSA bacteremia. The efficacy of daptomycin in the treatment of MRSA bacteremia has been demonstrated in a clinical trial [22]. In an open-label study reported by Fowler et al. [22], 124 patients who had SAB with or without IE were randomly assigned to receive daptomycin (6 mg/kg administered intravenously every 24 h) and 122 were randomly assigned to receive standard therapy—that is, initial low-dose gentamicin for 4 days (1 mg/kg every 8 h) plus 10–42 days of either an anti-staphylococcal penicillin (2 g every 4 h) for MSSA infection or vancomycin (1 g every 12 h, with appropriate adjustment) for MRSA infection. The primary efficacy end point was treatment success at 42 days after the end of therapy [22]. In the modified intention-to-treat analysis, treatment success was achieved for 53 (44.2%) of 120 patients who received daptomycin, compared with 48 (41.7%) of 115 patients who received standard therapy (absolute difference, 2.4%; 95% CI, –10.2% to 15.1%). These results met the prespecified criteria for demonstrating the non-inferiority of daptomycin. The similarly modest rates of clinical success in both treatment arms reflect, at least in part, the strict definition of treatment success used in the study; in many cases, treatment failed for reasons other than efficacy (e.g., lack of blood culture data). With regard to the different reasons for treatment failure, there were no statistically significant differences in incidences of these reasons between the treatment arms. However, failure attributed to persistent or relapsing *S. aureus* infection occurred more frequently among patients who received daptomycin therapy than among patients who received standard therapy (15.8% [19 of 120 patients] vs. 9.6% [11 of 115 patients]; $P = .17$); many of the patients who experienced treatment failure had deep-seated infections and did not receive the necessary surgical intervention [22]. In addition, failure associated with treatment-limiting adverse events occurred more frequently among patients who received standard therapy than among patients who received daptomycin treatment (14.8% [17 of 115 patients] vs. 6.7% [8 of 120 patients]; $P = .06$) [22]. Success rates for daptomycin treatment were greater than those for standard therapy among patients infected

with MRSA (44.4% for daptomycin vs. 31.8% for standard therapy; $P = .28$) and were similar to those for standard therapy among patients infected with MSSA (44.6% for daptomycin vs. 48.6% for standard therapy; $P = .74$)

In the absence of better alternatives, glycopeptides have been the mainstay in the treatment of MRSA bacteremia for many years. Recently, data have emerged that have fueled concerns regarding their efficacy profiles [30, 31]. For example, in a prospective study of 309 cases of SAB, treatment with vancomycin was significantly associated with relapse (OR, 4.1; 95% CI, 1.5–11.6; $P = .008$) [31]. Some of the explanations offered for the poor outcomes of vancomycin treatment included inadequate dosing [32], poor tissue penetration [33], slow bactericidal activity [34, 35], and strains with reduced susceptibility to the drug—that is, vancomycin-intermediate *S. aureus*, heteroresistant vancomycin-intermediate *S. aureus*, and vancomycin-resistant *S. aureus* [36]. The influence of vancomycin MICs on treatment outcomes has been demonstrated in several studies [32, 35, 37]. For instance, Moise-Broder et al. [37] evaluated MRSA isolates from 87 patients treated with vancomycin, and despite the fact that organisms were found to be susceptible to vancomycin, there was a significant association between increasing vancomycin MICs and vancomycin treatment failure. In addition, in a prospective cohort study involving 95 patients infected with MRSA, patients with a vancomycin MIC of 2 $\mu\text{g}/\text{mL}$ were less responsive to vancomycin treatment than were patients with MICs $\leq 1 \mu\text{g}/\text{mL}$ (percentage with response, 62% vs. 85%; $P = .02$), despite the fact that target trough levels of 15–20 $\mu\text{g}/\text{mL}$ were reached [32].

The newer glycopeptide teicoplanin has demonstrated clinical efficacy similar to that of vancomycin in the treatment of MRSA infections, including bacteremia, but showed better tolerability in small studies [38–40]. As with vancomycin, there has been a trend toward use of higher doses of teicoplanin, and several studies have indicated that higher-than-recommended doses may be required to achieve predose concentration requirements ($>20 \mu\text{g}/\text{mL}$) for effective therapy of septic arthritis, *S. aureus* IE, and other deep-seated infections [41–43]. Unfortunately, no prospective, significantly powered, randomized trials of teicoplanin have been undertaken.

The efficacy of linezolid in the treatment of MRSA bacteremia has not been established to date. Numerous reports document linezolid treatment failures among patients with MRSA bacteremia and IE [44–46]. In a systematic review of the current evidence from case reports of the efficacy of linezolid in the treatment of IE, Falagas et al. [47] demonstrated a cure rate of 63.6% (21 of 33 patients). This is somewhat higher than the success rates reported for the open-label, noncomparative, nonrandomized, compassionate-use program for linezolid, in which clinical cure rates were 38.7% (12 of 31 patients) for MRSA bacteremia and 37.5% (3 of 8 patients) for IE [48]. On

16 March 2007, an alert was issued by the FDA regarding the use of linezolid for the treatment of intravascular catheter-related bloodstream infections, including catheter-site infections, in response to the results of a phase III clinical trial in which the 84-day mortality rate for the linezolid treatment group was higher than that for the comparator group (21.5% vs. 16.0%), despite a similarly high microbiological eradication rate [49]. Treatment failures appeared to be associated with the presence of mixed gram-positive and gram-negative bacteremia. Finally, adverse events, such as thrombocytopenia, anemia, and nausea, have been found to be more common with prolonged therapy—that is, therapy for >14 days [50].

There are minimal data to support the use of quinupristin-dalfopristin for the treatment of MRSA bacteremia and IE. In a study in which patients who had experienced failure of prior antimicrobial therapy were subsequently treated with quinupristin-dalfopristin, clinical success rates among patients with IE were 54.5% (6 of 11 patients) for the all-treated group and 0% for the clinically and bacteriologically evaluable group [51]. Among patients with bacteremia, clinical success rates were 69.8% (30 of 43 patients) for the all-treated group and 55.8% (24 of 43 patients) for the clinically and bacteriologically evaluable group. In the study, 29% of patients had treatment-related adverse events, and 21.5% of patients discontinued treatment prematurely because of a treatment-related adverse event [51].

TMP-SMX was previously shown to be inferior to vancomycin for the treatment of staphylococcal infections, including bacteremia, among injection drug users in a randomized, double-blind, comparative trial (clinical success rates, 86% for TMP-SMX and 98% for vancomycin) [52]. However, because all patients with MRSA were cured and all treatment failures occurred among patients infected with MSSA, TMP-SMX may be considered to be an alternative therapy to vancomycin for MRSA infection [52].

CONCLUSIONS

SAB remains a considerable health care problem. The risk for patients with SAB of developing metastatic infections that constitute complications has been graded by Fowler et al. [9], using a risk-score analysis. Risk factors from the scoring system have been incorporated into a definition of complicated SAB, which effectively places many patients in this category, even in the absence of an identified metastatic focus of infection. Differentiation between complicated and uncomplicated bacteremia in this way is useful for identification of patients who require prolonged antibiotic therapy [10].

The key treatment options for MSSA bacteremia are the semisynthetic penicillins, cephalosporins, and, more recently, the cyclic lipopeptide daptomycin. Current treatment options for MRSA bacteremia include vancomycin, teicoplanin, line-

zolid, TMP-SMX, quinupristin-dalfopristin, and daptomycin. Daptomycin has demonstrated efficacy against both MSSA and MRSA infections and is thus an attractive option for the empirical therapy of suspected *S. aureus* infection [22]. It is important to reconsider the evidence base that supports the existing and sometimes long-established treatments in the context of the clinical trial data for new drugs as they enter the antimicrobial market. In this way, the standard of care may be advanced through objective assessment of both clinical data and current disease epidemiology.

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