Staphylococcus aureus Bacteremia and Native Valve Endocarditis

The Role of Antimicrobial Therapy

Adolf W. Karchmer, MD

TARGET AUDIENCE

Infectious disease physicians, nurses, hospital epidemiologists, clinical microbiologists, pharmacists, public health authorities, practicing physicians, and other healthcare professionals interested in the treatment of serious infections due to methicillin-resistant *Staphylococcus aureus*.

EDUCATIONAL OBJECTIVE

Review the results of antimicrobial therapy for complicated *S. aureus* bacteremia and endocarditis, implement therapeutic options for apparent failures of standard antimicrobial therapy for *S. aureus* bacteremia and endocarditis among hospitalized patients, and reduce excessive mortality and morbidity attributable to *S. aureus* bacteremia and endocarditis by optimal antimicrobial therapy.

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From the Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, MA.

Correspondence to: Adolf W. Karchmer, MD, Division of Infectious Diseases, Beth Israel Deaconess Medical Center, 110 Francis St, Suite GB, Boston, MA 02215. E-mail: akarchme@bidmc.harvard.edu.

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Abstract: The effective management of complicated *Staphylococcus aureus* bacteremia and native valve endocarditis requires an appropriate course of antimicrobial agents (proper agent, duration, and dose) and, where possible, timely removal of foci of infection. Treatment options for methicillin-susceptible *S. aureus* (MSSA) bacteremia, methicillin-resistant *S. aureus* (MRSA) bacteremia, and MRSA complications are discussed. The use of vancomycin for the treatment of MRSA bacteremia and the challenges associated with its use are described (ie, decreased susceptibility, emergence of heteroresistant vancomycin-intermediate *S. aureus* [hVISA] isolates, and nephrotoxicity). The use of aminoglycosides or rifampin as adjunct therapy with vancomycin to treat *S. aureus* bacteremia does not appear to be supported by data in the medical literature. The optimal length of therapy for *S. aureus* infections is presented, and the need for periodic reassessment of vancomycin and daptomycin minimum inhibitory concentrations (MICs) is emphasized. The author suggests an approach to treatment of persistent MRSA bacteremia based on recent data.

Key Words: *Staphylococcus aureus*, bacteremia, endocarditis, antimicrobial

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INTRODUCTION

Given the high mortality rates with *Staphylococcus aureus* bacteremia, prompt treatment of this illness is an important issue. However, there are few prospective data that clearly define optimal antimicrobial agents and duration of therapy for complicated *S. aureus* bacteremia. The objectives of this article are to address the current status of antibiotic treatment of methicillin-susceptible *S. aureus* (MSSA) bacteremia and infectious endocarditis, methicillin-resistant *S. aureus* (MRSA) bacteremia, and endocarditis followed by a review of the causes, presentation, and treatment of persistent MRSA bacteremia.

TREATMENT OF MSSA BACTEREMIA AND NATIVE VALVE ENDOCARDITIS

The treatments of MSSA endocarditis in the absence of a prosthetic device are well established and reflected in the recommendations of the American Heart Association (Table 1).[1] Nafcillin/oxacillin or first-generation cephalosporins, with the optional addition of gentamicin, are currently recommended for treatment of MSSA bacteremia and endocarditis involving native valves. In patients who are highly allergic to penicillins and cephalosporins, vancomycin or daptomycin can be used to treat MSSA (Table 2).[1–3]

The Aminoglycoside Option

The use of short-term aminoglycosides (4–5 days) for treatment of *S. aureus* bacteremia and endocarditis was considered a treatment option that would confer bactericidal synergy and thus potentially enhance outcome and if used for an abbreviated period would avoid nephrotoxicity. However, recent data have shown that even short-term exposure to aminoglycosides is associated with nephrotoxicity.[4] Cosgrove et al[4] measured clinically significant reductions in creatinine clearance in 236 patients with *S. aureus* bacteremia or native valve infective endocarditis who were treated with antistaphylococcal penicillin plus short-course, low-dose gentamicin; vancomycin plus short-course, low-dose gentamicin; or daptomycin alone. Fewer patients treated with daptomycin alone (8%) had a reduction in creatinine clearance compared with those receiving gentamicin combined with either vancomycin (22%) or an antistaphylococcal penicillin (25%). Treatment with initial abbreviated course, low-dose gentamicin was an independent predictor of a clinically significant reduction in creatinine clearance. Because there are no data demonstrating increased cure rates or increased survival rates with the addition of an aminoglycoside, it seems prudent to reassess the option to use combination therapy.

TABLE 2. Treatment of MSSA Bacteremia or Native Valve Endocarditis in Highly Penicillin Allergic Patients With Normal Renal Function

- Vancomycin 15–20 mg/kg (actual body weight) IV every 8–12 h* (not >2 g/dose)
  - If septic, consider loading dose 25–30 mg/kg
  - Trough 15–20 μg/mL (AUC:MIC >400 if MIC <1.0)
  - If dose ≥1.5 g, infuse over 1.5–2 h
  - Monitor trough weekly
  - MIC overestimated by E-test®, MicroScan®, and BD Phoenix™; underestimated by Sensititre® and Vitek 2®
- Daptomycin 6 mg/kg IV once daily*
  - Consider if vancomycin MIC ≥1.5 μg/mL (cannot achieve AUC:MIC >400)
  - Some experts advise 8–10 mg/kg IV every day, safe in limited studies

*Doses are adjusted for impaired renal function.

β-Lactam Antibiotics Preferred for MSSA Bacteremia

The widespread use of vancomycin to treat MSSA bacteremia has led to a general belief that vancomycin is as effective as β-lactam antibiotics against this organism. However, several studies have demonstrated a greater frequency of bacteriologic failure among patients with MSSA bacteremia treated with vancomycin versus those treated with β-lactam antibiotics. In a prospective observational study in 505 consecutive patients with *S. aureus* bacteremia, among those with MSSA bacteremia, nafcillin was superior to vancomycin in preventing persistent bacteremia or relapse. Bacteriologic failure occurred after treatment

TABLE 1. Treatment of Endocarditis Due to Methicillin-Susceptible Staphylococci in the Absence of Prosthetic Material

Antibiotic	Dosage and Route	Duration
Nafcillin or oxacillin	2 g IV every 4 h	4–6 wk
With optional addition of gentamicin	1 mg/kg IM or IV every 8 h	3–5 d
Cefazolin (or other first-generation cephalosporins in equivalent doses)	2 g IV every 8 h	4–6 wk
With optional addition of gentamicin	1 mg/kg IM or IV every 8 h	3–5 d

IM indicates intramuscularly.

with vancomycin in 13 of 70 patients, whereas no failures occurred after nafcillin treatment. None of the nafcillin-treated patients had persistent bacteremia after 7 days compared with 8 of 70 patients treated with vancomycin. Multivariate analysis revealed that treatment with vancomycin predisposed patients to relapse ($P < 0.048$).[5]

Further evidence of the superiority of β-lactam antibiotics compared with vancomycin in the treatment of MSSA bacteremia is seen in the study of hemodialysis-dependent patients with MSSA bacteremia.[6] Those who were treated with vancomycin had a greater risk of treatment failure compared with those receiving cefazolin, a first-generation cephalosporin (31.2% vs 13%; $P = 0.02$) (Table 3). In a multivariate analysis, vancomycin use was also a factor that was independently associated with treatment failure in these patients (odds ratio [OR], 3.53; 95% confidence interval [CI], 1.15–13.45). The authors concluded that vancomycin should not be considered beyond empiric therapy pending culture data and that β-lactam antibiotics are preferred for the treatment of MSSA bacteremia.[6]

Vancomycin therapy was also associated with greater infection-related mortality (39.4% vs 11.4%, $P = 0.005$) compared with a regimen containing β-lactams in a retrospective study of 72 intravenous (IV) drug users with MSSA infective endocarditis. The mortality rates remained higher even among those who were started on vancomycin but switched to β-lactam therapy when compared with patients who had received β-lactam therapy upon initiation of treatment.[7]

Length of Therapy

The recommended length of therapy in patients with MSSA bacteremia and endocarditis is listed in Table 4.

Venous thrombosis may complicate central venous catheter–related *S. aureus* bacteremia. If so, the risks for relapse and death are increased. Thus, serious consideration should be given to longer courses of antimicrobial therapy than that which is standard for uncomplicated bacteremia in these patients. In a prospective observational cohort of 48 patients with central venous catheter–associated *S. aureus* bacteremia, definite or probable thrombosis was present in 71% of patients. Death or recurrent bacteremia occurred in 32% of patients with thrombosis and in 14% of patients without thrombosis.[8]

Fowler et al[9] developed a predictive model for recognition of complicated *S. aureus* bacteremia. In this model, 1 point was assigned for each of the following: community onset of infection, skin findings suggesting septic microemboli, and fever persisting at 72 hours of therapy; 4 points were given for positive blood cultures at 48 to 96 hours of treatment. Complicated bacteremia—defined as that associated with deep focal infection, systemic emboli, death, or relapse within 3 months—was noted in 30% of patients with 1 point and rose to more than 80% of those with 4 or more points. Fifteen percent of patients with no points experienced complicated bacteremia.[9] This latter observation is consistent with the findings of Jernigan and Farr,[10] who, in a meta-analysis of published reports of short-course therapy for *S. aureus* bacteremia, noted a 6.1% (95% CI, 2.0%-10.2%) rate of relapse or deep-seated infection. Thus, caution must be exercised when selecting abbreviated parenteral therapy for *S. aureus* bacteremia.

Similarly, Fowler et al[11] demonstrated that short-course therapy of antibiotics was associated with lower success rates in catheter-associated *S. aureus* bacteremia. Of 46 patients with IV catheter–associated *S. aureus* bacteremia (negative transesophageal echocardiogram, no foci of infection), short-course therapy was associated with a lower success rate compared with patients treated for 15 or more days (<14 days [64%], 14 days [90%] vs ≥15 days [100%]). Similarly, short-course therapy of non–catheter-associated *S. aureus* bacteremia resulted in a lower success rate compared with patients treated for 15 or more days (35.9% vs 77.4%).

TABLE 4. Duration of Therapy for MSSA Bacteremia and Native Valve Endocarditis

- Uncomplicated bacteremia: ≥2 wk
  - Catheter-related (with removal of catheter)
  - Infectious endocarditis ruled out with TEE
  - No device implants
  - Follow-up cultures in 2–3 d are negative
  - Defervescence in ≤72 h
  - No metastatic infection
- Complicated bacteremia: 4–6 wk
- Left-sided endocarditis: ≥6 wk

TEE indicates transesophageal echocardiogram.

TREATMENT OF MRSA BACTEREMIA OR NATIVE VALVE INFECTIOUS ENDOCARDITIS

The recommendations for treatment of MRSA bacteremia or native valve infectious endocarditis in patients with normal renal function are listed in Table 5.[1,3,12] Vancomycin is still the recommended drug of choice. The recommended trough concentration is higher than has previously been used, and actual body weight needs to be used to calculate the correct dose.[3] The area under the curve–minimum inhibitory concentration (AUC:MIC) ratio of 400 is recommended because this ratio is believed to result in greater likelihood of cure. If the dose is

TABLE 3. Cefazolin Versus Vancomycin in MSSA Bacteremia in Hemodialysis Patients[6]

	Failure (Relapse or Death)		
Variable	**Bivariate OR (95% CI)**	**Multivariate OR (95% CI)**	***P***
Age >50 y	0.79 (0.35–1.81)	—	
APACHE II >20	1.43 (0.59–3.5)	—	
Vancomycin Rx	3.02 (1.13–8.08)	3.53 (1.15–13.45)	0.04
Catheter retained	5.08 (1.95–3.24)	4.99 (1.89–13.76)	0.001

Failure vancomycin 24/77 (31.2%), cefazolin 6/46 (13%) ($P = 0.02$). Cefazolin 2–3 g after dialysis, vancomycin 15 mg/kg load, 500 mg after dialysis (MSSA-vancomycin MIC 96% <1.0; levels 13.7, 16.8).

APACHE indicates Acute Physiology and Chronic Health Evaluation.

Source: Stryjewski et al.[6]

greater than 1.5 g, the recommendation is to infuse it slowly (over 1.5–2 hours) to avoid red man syndrome.

Daptomycin 6 mg/kg administered intravenously once daily is an alternative regimen.[2,3,12] If the vancomycin MIC is 1.5 μg/mL or greater, the 400 AUC:MIC ratio cannot be achieved reliably in patients with normal renal function, and the risk of treatment failure is increased.[12–14] Some infectious disease specialists believe that this is an indication for an alternative approach to therapy.[12] Combining vancomycin or daptomycin with rifampin or an aminoglycoside is not routinely recommended for MRSA bacteremia or native valve endocarditis.[1,4,12,15,16]

Reduced Susceptibility of MRSA to Vancomycin

Although not uniformly observed, some studies have suggested that vancomycin MICs for MRSA have gradually increased ("MIC creep").[17,18] In a study of isolates from blood cultures, Rybak et al[17] noted that the percentage of MRSA with a vancomycin MIC of 0.5 μg/mL or less (E-test) had decreased from19.4% in 1986–1989 to 6.6% in 2002–2007, with a corresponding increase in isolates with an MIC of 1.0 μg/mL or greater in the later period. Heteroresistant vancomycin-intermediate *S. aureus* (hVISA) (isolates with an MIC ≤2.0 and thus susceptible, but with subpopulations of organisms surviving at vancomycin concentrations of 4–8 μg/mL) increased from 2.2% in the earlier period to 8.3% of isolates from the later period.[17] Several studies have suggested that clinical outcomes of MRSA infections are less favorable when infection is caused by isolates with MIC of 1.5 μg/mL or greater.[19–21]

Vancomycin Dosing and Nephrotoxicity

In recognition of increased vancomycin failure rates when deep-seated infection or bacteremia due to MRSA was caused by less susceptible isolates and in an effort to achieve the pharmacokinetic-pharmacodynamic ideal—the AUC:MIC of 400 or greater—increased daily vancomycin doses have been advocated with trough targets raised to 15 to 20 μg/mL.[3,12] These larger doses of vancomycin (≥4 g/d), however, have been associated with an increased incidence of nephrotoxicity. In a study of patients receiving vancomycin 4 g/d or greater (n = 26), vancomycin less than 4 g/d (n = 220), and linezolid (n = 45), a significant difference in nephrotoxicity was noted between these groups (34.6%, 10.9%, and 6.7%, respectively).[22] Vancomycin nephrotoxicity was also correlated with the initial trough concentration in a retrospective study of 166 patients with a suspected or proven gram-positive infection.[23] The rates of nephrotoxicity in this study for initial trough values of less than 10 mg/L, 10 to 15 mg/L, 15 to 20 mg/L, and greater than 20 mg/L were 5%, 21%, 20%, and 33%, respectively.

Kullar et al[14] found that increased vancomycin serum concentrations and AUC:MIC of greater than 421 were associated with a more favorable outcome of MRSA bacteremia, whereas a vancomycin trough concentration of less than 15 μg/mL, endocarditis, nosocomial bacteremia, and a vancomycin MIC of greater than 1.0 μg/mL by E-test were independently associated with an increased likelihood of failure. This provides justification for accepting (cautiously) the increased nephrotoxicity risk of more aggressive vancomycin dosing. However, others have suggested it is not feasible to achieve an AUC:MIC of greater than 400 with vancomycin therapy when the MRSA isolate has an MIC of greater than 1.0 μg/mL and that pursuing this target with increasing doses will be associated with significant nephrotoxicity.[13] They suggest alternative therapy should be strongly considered in this setting.[3,12]

TABLE 5. Treatment of MRSA Bacteremia or Native Valve Infectious Endocarditis in Patients With Normal Renal Function

- Vancomycin 15–20 mg/kg (actual body weight) IV every 8–12 h (not >2 g/dose)
  - If septic, consider loading dose 25–30 mg/kg
  - Trough concentration 15–20 μg/mL (AUC:MIC >400 if MIC <1.0)
  - If dose >1.5 g, infuse over 1.5–2 h
  - Monitor trough weekly
  - MIC overestimated by E-test®, MicroScan®, BD Phoenix™; underestimated by Sensititre® and Vitek 2®
- Daptomycin 6 mg/kg IV once daily
  - Consider if vancomycin MIC ≥1.5 μg/mL (cannot achieve AUC:MIC >400)
  - Some experts advise 8–10 mg/kg IV every day, safe in limited studies
  - FDA approved for *S. aureus* bacteremia and right-sided infective endocarditis, not left-sided infective endocarditis

Adding rifampin and/or an aminoglycoside is **not** recommended for routine therapy.

Combination Therapy

Combination therapy has been considered. Addition of an aminoglycoside to vancomycin therapy, as noted earlier, while yielding *in vitro* bactericidal synergy, has not been of demonstrable clinical benefit and is likely to be associated with further increases in nephrotoxicity, and thus, vancomycin-aminoglycoside combination therapy seems undesirable except under exceptionally urgent circumstances.

The addition of rifampin to vancomycin therapy has not been shown to improve outcomes in patients with MRSA native valve endocarditis.[15] In a study of 42 consecutive patients with MRSA native valve endocarditis treated with either vancomycin alone or vancomycin + rifampin, the median duration of bacteremia was 7 days (95% CI, 5, 11) in the vancomycin alone group and 9 days in the vancomycin + rifampin group (95% CI, 6, 13). There were 4 failures in the vancomycin treatment group and 2 failures in the vancomycin + rifampin group.[15] Furthermore, the addition of rifampin to standard therapy of native valve infective endocarditis increases the risk of hepatotoxicity, drug-drug interactions, and the emergence of rifampin-resistant *S. aureus* isolates.[16] In a retrospective study of 42 cases of *S. aureus* infective endocarditis, when comparing patients receiving rifampin combination treatment to controls, hepatic transaminase elevations occurred more frequently with rifampin (21% vs 2%; $P = 0.014$), rifampin-resistant *S. aureus* isolates developed more frequently (21% vs 0%; $P < 0.001$), and significant drug-drug interactions occurred in 52% of cases compared with none among controls. Patients treated with rifampin combination therapy had a longer duration of bacteremia (5.2 vs 2.1 days; $P < 0.001$) and lower survival rates (79% vs 95%; $P = 0.048$) compared with controls. Thus, this approach does not seem likely to address the need for more effective therapy.

Daptomycin

Daptomycin 6 mg/kg daily was similar in efficacy to standard therapy (low-dose gentamicin plus either vancomycin or semisynthetic penicillin) in a study of 246 patients with *S. aureus* bacteremia and right-sided endocarditis.[2] Overall, mortality rates were also similar between daptomycin (15%) and comparator (16%). Success rates treating left-sided endocarditis were very

low with both daptomycin (11%) and the comparator (22%) in a small subset of 18 patients. In this study, therapy with daptomycin was not inferior to vancomycin combined with low-dose abbreviated gentamicin in the treatment of MRSA bacteremia and right-sided endocarditis with tightly defined success rates of 44% (20/45) and 33% (14/43), respectively ($P > 0.05$).[2] Based on these data, some investigators have suggested daptomycin be used as primary therapy for MRSA bacteremia and endocarditis.[12] Doses of 8 to 10 mg/kg, higher than the US Food and Drug Administration (FDA)–approved 6 mg/kg dose, have been well tolerated[24] and are preferred by some investigators.[12] A retrospective case-control study comparing vancomycin to daptomycin treatment (patients commonly having been switched to daptomycin after 5 days of vancomycin because of failing therapy) for nonpneumonia bacteremic infections caused by MRSA with vancomycin MICs of 1.5 or 2.0 μg/mL (E-test) suggests improved outcomes in daptomycin-treated patients.[25] The composite (persistent bacteremia, 60–day mortality, and relapse) clinical failure rate was 31% (37/118) in vancomycin-treated patients versus 17% (10/59) among those receiving daptomycin ($P = 0.084$). Mortality at 60 days was less in the daptomycin group (8%, 5/59) than in the vancomycin-treated patients (20%, 24/118) ($P = 0.046$). In a conditional logistic regression analysis, vancomycin therapy was associated with increased mortality. These results may be undermined in part by relatively low mean initial vancomycin trough concentrations (10 μg/mL) and by frequent use of combination therapy in both groups (vancomycin 60/118 [51%] vs daptomycin 22/59 [37%]). Nevertheless, these data support switching to alternative therapy if patients are not improving during vancomycin treatment or if the MRSA has a high vancomycin MIC (≥1.5 μg/mL).

Additional agents that are bactericidal against MRSA have been approved by the FDA. These agents—telavancin and ceftaroline—while exhibiting favorable efficacy against MRSA in animal model studies and anecdotal cases, have not been studied systematically in the treatment of MRSA bacteremia or endocarditis.

PERSISTENT MRSA BACTEREMIA DURING THERAPY

Persistent MRSA bacteremia, despite "appropriate" therapy, occurs in 20% to 30% of patients in clinical series and is particularly relevant in patients with endovascular infection.

Risk Factors and Reasons for Persistent MRSA Bacteremia

The risk factors associated with persistent *S. aureus* bacteremia have not been fully identified. In a retrospective case-control study of 84 patients with persistent *S. aureus* bacteremia (>7 days) compared with 152 patients with nonpersistent *S. aureus* bacteremia (<3 days), Hawkins et al identified 5 risk factors that were independently associated with persistent *S. aureus* bacteremia.[26] These risk factors were MRSA (OR, 5.22; 95% CI, 2.63, 10.38), intravascular catheter or other foreign body use (OR, 2.37; 95% CI, 1.11, 3.96), chronic renal failure (OR, 2.08; 95% CI, 1.09, 3.96), more than 2 sites of infection (OR, 3.31; 95% CI, 1.17, 9.38), and infective endocarditis (OR, 10.30; 95% CI, 2.98, 35.64). Attributable mortality was also significantly increased in patients with persistent bacteremia (OR, 34.82; 95% CI, 4.5, 267). Yoon et al,[27] in a case-control study, found that retention of infected medical devices, multiple sites (≥2) of MRSA infection, and MRSA with an MIC 2.0 μg/mL (Vitek 2®; bioMérieux, Hazelwood, MO) were independently associated with persistent bacteremia, whereas vancomycin trough concentrations were not. Others have suggested that bacteremia persists during treatment because of the reduced susceptibility or bactericidal activity of vancomycin against the MRSA isolate. Sakoulas et al[28] found a statistically significant relationship between greater vancomycin treatment success of MRSA bacteremia and lower vancomycin MIC (≤0.5 μg/mL vs 1.0–2.0 μg/mL; $P = 0.02$) as well as greater vancomycin bactericidal activity (expressed as killing $\log_{10}$ colony-forming units/mL by vancomycin over 72 hours of incubation *in vitro*). The rate of clinical success with the lower MIC was 56% compared with 10% for the higher MIC ($P < 0.01$). Similarly, with greater vancomycin bactericidal activity, clinical success rate in the treatment of MRSA bacteremia was greater ($\log_{10}$ <4.71 [n = 9], 0%; $\log_{10}$ 4.71–6.26 [n = 13], 23.1%; $\log_{10}$ >6.27 [n = 8], 50%).[28] Lodise et al[22] confirmed these observations in a retrospective cohort study of 92 patients with MRSA bacteremia. Persistent bacteremia (>10 days) occurred more frequently when patients were infected by MRSA with a higher MIC (>1.5 μg/mL by E-test) compared with the lower MIC (<1.5 μg/mL) (6/66 9% vs 0/26).

In some studies, hVISA was associated with persistent bacteremia and vancomycin treatment failures. Charles et al[29] evaluated the clinical features of patients with hVISA bacteremia. Compared with infection caused by vancomycin-susceptible MRSA organisms, that due to hVISA was associated with higher bacterial load infections (100% vs 21%, $P = 0.001$), more vancomycin treatment failures (100% vs 31% $P = 0.006$), and greater mean/median duration of bacteremia (39/26 vs 6.4/3.5 days, $P = 0.002$). The clinical features of 27 patients with hVISA bacteremia were compared with those of 223 control patients with non-hVISA MRSA bacteremia in a case-control study. Bacteremia with hVISA was associated with a longer duration of bacteremia (12 vs 2 days, $P = 0.005$), greater prevalence of endocarditis (19% vs 4%, $P = 0.007$), osteomyelitis (26% vs 7%, $P = 0.006$), and more frequent emergence of rifampin resistance (44% vs 6%, $P < 0.001$). However, mortality related to infection with hVISA was similar to that for MRSA bacteremia.[30] To date, other studies have not confirmed all of these findings.[31,32]

Investigators have examined virulence factors and resistance mechanisms in an attempt to identify specific characteristics of MRSA isolates with persistent bacteremia. Again, studies were not conclusive but suggest that, among organisms with similar vancomycin MICs, those associated with persistent bacteremia (compared with those from patients with resolved bacteremia) are more resistant to cationic defensins, that is, human neutrophil peptide and thrombin-induced platelet microbicidal proteins, and generate increased biofilm formation. Other virulence and molecular features may also facilitate persistent bacteremia.[33–36]

The Relationship Between Reduced Vancomycin Susceptibility and Daptomycin Non-susceptibility in MRSA

The development of nonsusceptibility to daptomycin has been associated with increasing resistance to vancomycin. Pillai et al[37] demonstrated that, as vancomycin-treated patients failed therapy and vancomycin susceptibility decreased, susceptibility of the MRSA to daptomycin also deteriorated, even without prior exposure to daptomycin. Kelley et al[38] noted this phenomenon as well. The emergence of daptomycin nonsusceptibility has also been noted in patients treated with daptomycin.[2,39] In a study of 10 daptomycin-treated patients with persistent *S. aureus* bacteremia, daptomycin preexposure MIC was 0.125 to 0.5 μg/mL. During treatment with daptomycin, the MIC increased to 2.0 μg/mL in 5 patients and to 4.0 μg/mL in

1 patient. The MIC increase was noted with 5 to 14 days of exposure in 5 patients and after 21 days in 1 patient. Pulse-field gel electrophoresis of the isolates revealed genetic relatedness between the pretreatment and posttreatment isolates. The MIC increases in 5 of the isolates remained stable in the absence of daptomycin exposure. Of the 6 patients infected by MRSA that developed increased daptomycin MICs, 3 patients died with persistent bacteremia, 1 patient cleared the bacteremia but relapsed 12 days later, 1 patient cleared bacteremia after treatment with vancomycin, and 1 patient cleared after vancomycin + rifampin/trimethoprim-sulfamethoxazole (TMP/SMZ) and a mitral valve replacement.[39]

Recommended Approaches to Persistent MRSA Bacteremia

The recommended steps for treating persistent MRSA bacteremia, defined by positive blood cultures for 7 days of therapy, are summarized in Table 6. Any removable foci of infection should be removed, abscesses should be drained, and osteomyelitis should be debrided. Vancomycin MICs should be reassessed, clinicians should look for hVISA and VISA, and daptomycin MICs should be assessed. If the patient is being treated with vancomycin, confirmation of the appropriate trough serum concentration (15–20 μg/mL) should be obtained. If the patient is being treated with daptomycin, clinicians should ensure that the most effective daptomycin dose is being used. If left-sided infectious endocarditis is present, appropriately timed surgery should be considered. The patient's clinical status will determine any drug and dose changes.

Antimicrobial treatment options for persistent MRSA bacteremia in the face of optimal vancomycin dosing and effective debridement/device removal can be divided into 2 groups (Table 7): bacteremia with isolates susceptible to daptomycin and isolates not susceptible to daptomycin and vancomycin. If isolates are susceptible to daptomycin and patients are critically ill or the vancomycin MIC of the isolate is 1.5 μg/mL or greater, treatment should be changed to daptomycin 10 mg/kg per day. Support for this approach can be derived from studies indicating that daptomycin has greater activity than vancomycin against both glycopeptide-susceptible and hVISA isolates. The daptomycin MIC 50 and MIC 90 were 4 times lower, and bactericidal activity at 6 and 24 hours was significantly greater with daptomycin than with vancomycin.[40] Furthermore, the improved outcome noted in treatment of MRSA bacteremia when patients were switched from vancomycin to daptomycin

TABLE 6. Approach to Persistent MRSA Bacteremia

- Reassess around day 7 (median duration 7–9 d)
- Search for removable device or focus of infection
- Assess for vancomycin MIC, hVISA, VISA
- Assess daptomycin MIC
  - Vancomycin may select reduced daptomycin susceptibility
  - Daptomycin failure associated with reduced susceptibility
- Vancomycin trough—target attained (15–20 μg/mL)
- Check daptomycin dose
- If left-sided infective endocarditis, consider appropriately timed cardiac surgery
- Patient's clinical status informs Rx change
  - Stable clinically, isolate with vancomycin MIC <1.5 μg/mL
  - Worse regardless of susceptibility; critically ill or with vancomycin MIC ≥1.5 μg/mL

TABLE 7. Options for Antimicrobial Treatment of Persistent MRSA Bacteremia

- Susceptible to daptomycin:
  - Daptomycin 10 mg/kg per day plus optional combination with
    - Gentamicin 1 mg/kg every 8 h or 5 mg/kg/d
    - Rifampin 300 mg every 8 h or 450 every 12 h orally
    - Both gentamicin and rifampin
    - An antistaphylococcal penicillin (nafcillin/oxacillin)
- Nonsusceptible to daptomycin and vancomycin:
  - Linezolid (in combination Rx)
  - TMP/SMZ (in combination Rx)
  - Telavancin or ceftaroline
  - Daptomycin plus an antistaphylococcal penicillin (nafcillin/oxacillin)

supports this strategy.[25] Although data are scant, daptomycin can be combined with either gentamicin 1 mg/kg every 8 hours (or 5 mg/kg per day) or rifampin 300 mg every 8 hours (or 450 mg every 12 hours by mouth). If patients are clinically stable and the vancomycin MIC of the on-therapy MRSA isolate is less than 1.5 μg/mL, vancomycin could be continued with close clinical monitoring.

In patients with persistent bacteremia wherein the MRSA isolates are not fully susceptible to daptomycin or vancomycin, other antimicrobials should be considered.

Linezolid has been used in this setting as salvage therapy. In a retrospective study of persistent MRSA bacteremia, salvage therapy with linezolid or linezolid plus a carbapenem was more effective than continuing vancomycin alone or with the addition of an aminoglycoside or rifampicin (rifampin). Among patients with persistent MRSA bacteremia (≥7 days), linezolid salvage therapy resulted in a 75% cure rate, compared with a cure rate of 47% among those with continued vancomycin-based treatment.[41] Because this is a retrospective study, the 2 groups may not have had comparable infections. In another study of 25 patients with serious infections due to *S. aureus* with reduced vancomycin susceptibility, linezolid therapy with or without rifampicin and fusidic acid was effective in 14 (78%) of 18 patients.[42]

Trimethoprim-sulfamethoxazole is often active against MRSA and can be considered for therapy. It was moderately effective compared with vancomycin in treating *S. aureus* endocarditis in an earlier study.[43] In that study, TMP/SMZ appeared less effective than vancomycin in the treatment of MSSA endocarditis but appeared comparable to vancomycin in the treatment of a small group of patients with MRSA endocarditis. Experience with TMP/SMZ alone for treatment of bacteremia or endocarditis caused by current MRSA isolates is limited.

Telavancin remains active against MRSA isolates including those that have vancomycin MIC = 2.0 μg/mL, vancomycin-intermediate (MIC, 4–8 μg/mL) MRSA (VISA), and daptomycin-nonsusceptible MRSA.[44–46] It has been effective in treating MRSA endocarditis in animal models and in sporadic case reports.[47–49]

In addition, ceftaroline is also active against MRSA, including VISA, hVISA, and daptomycin non-susceptible isolates.[50] In animal models of endocarditis, ceftaroline's ability to reduce organisms in vegetations has been comparable to vancomycin versus MRSA, superior to vancomycin versus hVISA, and superior to linezolid against each organism.[51] Clinical experience is anecdotal, however.

An additional option for treatment of persistent MRSA bacteremia, despite daptomycin treatment (daptomycin non-susceptible or resistant MRSA), is to combine daptomycin with an antistaphylococcal penicillin.[52] In the presence of high concentrations of antistaphylococcal penicillins, daptomycin binding to the staphylococcal cell membrane is increased with a resulting decrease in the effective daptomycin MIC and a corresponding increase in bactericidal activity against the MRSA isolate. Among 7 patients with persistent bacteremia who were treated with daptomycin (8–10 mg/kg) plus nafcillin/oxacillin (2 g IV every 2 hours), bacteremia was promptly quenched. Five of these patients were ultimately cured.[52]

At present, the optimal choice for treating persistent bacteremia due to MRSA resistant to daptomycin and vancomycin is not clear, but these agents, none of which are FDA approved for the treatment of MRSA bacteremia or endocarditis, can be considered for treatment in desperate circumstances.

SUMMARY

In summary, nafcillin/oxacillin and first generation cephalosporins (with vancomycin and daptomycin as alternatives) are currently recommended for treatment of MSSA bacteremia and native valve endocarditis. Vancomycin is still the recommended drug of choice for MRSA bacteremia or native valve endocarditis; daptomycin is the alternative. However, reduced susceptibility among MRSA to vancomycin, emergence of hVISA isolates, and concerns about vancomycin-nephrotoxicity are challenges with vancomycin therapy. Among patients with persistent MRSA bacteremia on vancomycin, daptomycin is an alternative if the isolate remains susceptible. Improvement in outcomes with the addition of aminoglycosides or rifampin to treatment for *S. aureus* bacteremia or native valve endocarditis has not been demonstrated. Notably, linezolid has been used successfully in salvage therapy when other antibiotics have resulted in treatment failure. New antistaphylococcal antimicrobials—telavancin and ceftaroline—have promise but have yet to be studied in MRSA bacteremia. Length of treatment should be at least 2 weeks in uncomplicated bacteremia, 4 to 6 weeks in complicated bacteremia, and 6 weeks or more in left-sided endocarditis. Physicians should also be aware of the relationship between vancomycin resistance and daptomycin non-susceptibility and the need for periodic reassessment of MICs when there is breakthrough bacteremia. Approaches to treatment will continue to be revised as *S. aureus* bacteremic isolates continue to evolve and experience is gained with new antimicrobials.

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SELF-ASSESSMENT EXAMINATION

A minimum assessment score of 80% is required.

1) Which of the following treatment recommendations for MRSA bacteremia is **false**?

A. If vancomycin dose is ≥1.5 g, infuse over 1.5 to 2 h.
B. Target trough concentration should be 15 to 20 μg/mL.
C. Vancomycin 2 g IV every 8 to 12 hours should be used for treatment.
D. Daptomycin 6 mg/kg IV once daily or 8 to 10 mg/kg is an alternative to vancomycin.

2) Which of the following statements is **true** regarding the use of vancomycin in the treatment of *S. aureus* bacteremia?

A. Data suggest that the addition of aminoglycosides or rifampin to vancomycin therapy increases cure rates.
B. Some studies have shown greater bacteriologic failure with vancomycin versus treatment with β-lactam antibiotics.
C. Vancomycin resistance is not associated with daptomycin nonsusceptibility.
D. Bacteremia associated with hVISA appears to be associated with shorter duration of bacteremia and lower prevalence of endocarditis and osteomyelitis.

3) Which of the following statements are **true** regarding optimum duration of therapy for *S. aureus* bacteremia?

A. In uncomplicated bacteremia in the presence of a device implant and fever at 72 hours, duration of therapy is 2 weeks.
B. In complicated bacteremia, duration of therapy is 2 to 4 weeks.
C. In left-sided endocarditis, duration of therapy is 2 to 4 weeks.
D. In uncomplicated bacteremia, when follow-up cultures are negative, duration of therapy is 2 weeks or longer.

4) A recommended approach to persistent MRSA bacteremia includes which of the following?

A. Assess daptomycin MIC and check daptomycin dose.
B. Assess for vancomycin MIC, hVISA, and VISA.
C. Search for removal of focus of infection.
D. All of the above

5) Which of the following statements regarding treatment of persistent MRSA bacteremia during vancomycin therapy is **false**?

A. The organism is predictably susceptible to daptomycin; thus, use daptomycin 10 mg/kg per day plus possibly either gentamicin, rifampin, or both.
B. Linezolid can be considered as an alternative therapy.
C. TMP/SMZ was a moderately effective treatment for MRSA endocarditis.
D. Telavancin or ceftaroline is a potential therapy for persistent MRSA bacteremia but is not FDA approved for this indication.

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