Review

Clinical Management of *Staphylococcus aureus* Bacteremia
A Review

Thomas L. Holland, MD; Christopher Arnold, MD; Vance G. Fowler Jr, MD, MHS

IMPORTANCE Several management strategies may improve outcomes in patients with *Staphylococcus aureus* bacteremia.

OBJECTIVES To review evidence of management strategies for *S aureus* bacteremia to determine whether transesophageal echocardiography is necessary in all adult cases and what is the optimal antibiotic therapy for methicillin-resistant *S aureus* (MRSA) bacteremia.

EVIDENCE REVIEW A PubMed search from inception through May 2014 was performed to identify studies addressing the role of transesophageal echocardiography in *S aureus* bacteremia. A second search of PubMed, EMBASE, and the Cochrane Library from January 1990 through May 2014 was performed to find studies addressing antibiotic treatment for MRSA bacteremia. Studies reporting outcomes from antibiotic therapy for MRSA bacteremia were included. All searches, which were limited to English and focused on adults, were augmented by review of bibliographic references from included studies. The quality of evidence was assessed using the Grades of Recommendation, Assessment, Development and Evaluation system with consensus of independent evaluations by at least 2 of the authors.

FINDINGS In 9 studies with a total of 4050 patients, use of transesophageal echocardiography was associated with higher rates of a diagnosis of endocarditis (14%-28%) compared with transthoracic echocardiography (2%-15%). In 4 studies, clinical or transthoracic echocardiography findings did not predict subsequent transesophageal echocardiography findings of endocarditis. Five studies identified clinical or transthoracic echocardiography characteristics associated with low risk of endocarditis (negative predictive values from 93% to 100%). Characteristics associated with a low risk of endocarditis include absence of a permanent intracardiac device, sterile follow-up blood cultures within 4 days after the initial set, no hemodialysis dependence, nosocomial acquisition of *S aureus* bacteremia, absence of secondary foci of infection, and no clinical signs of infective endocarditis. Of 81 studies of antibiotic therapy for MRSA bacteremia, only 1 high-quality trial was identified. In that study of 246 patients with *S aureus* bacteremia, daptomycin was not inferior to vancomycin or an antistaphylococcal penicillin, each in combination with low-dose, short-course gentamicin (clinical success rate, 44.2% [53/120] vs 41.7% [48/115]; absolute difference, 2.4% [95% CI, −10.2% to 15.1%]).

CONCLUSIONS AND RELEVANCE All adult patients with *S aureus* bacteremia should undergo echocardiography. Characteristics of low-risk patients with *S aureus* bacteremia for whom transesophageal echocardiography can be safely avoided have been identified. Vancomycin and daptomycin are the first-line antibiotic choices for MRSA bacteremia. Well-designed studies to address the management of *S aureus* bacteremia are needed.

JAMA. 2014;312(13):1330-1341. doi:10.1001/jama.2014.9743

Supplemental content at jama.com

Author Affiliations: Division of Infectious Diseases and International Health, Department of Medicine, Duke University School of Medicine, Durham, North Carolina (Holland, Arnold, Fowler); Duke Clinical Research Institute, Duke University, Durham, North Carolina (Holland, Fowler).

Corresponding Author: Vance G. Fowler Jr, MD, MHS, Division of Infectious Diseases and International Health, Department of Medicine, Duke University School of Medicine, PO Box 102359, Durham, NC 27710 (vance.fowler@duke.edu).

Section Editor: Mary McGrae McDermott, MD, Senior Editor.

Annual incidence of *Staphylococcus aureus* bacteremia is 4.3[1] to 38.2[2] per 100 000 person-years in the United States. The 30-day all-cause mortality of *S aureus* bacteremia is 20% and has not changed since the 1990s.[3] Methicillin resistance is an independent risk factor for mortality in *S aureus* bacteremia.[4,5]

Several management strategies for *S aureus* bacteremia are well established,[6-8] including (1) performing a thorough history and physical examination, (2) obtaining follow-up blood cultures to document resolution of bacteremia after initiation of treatment, and (3) draining abscesses and removing infected prosthetic material. Other strategies remain controversial. Despite 20 years of research and 3 treatment guidelines,[6-8] the optimal role of transesophageal echocardiography in the evaluation of *S aureus* bacteremia remains unclear. *Staphylococcus aureus* infective endocarditis is common, often clinically indistinguishable from *S aureus* bacteremia, and may be fatal if inadequately treated.[9,10] Because the diagnosis of infective endocarditis determines prognosis, monitoring, and treatment, the presence of infective endocarditis should be considered in all patients with *S aureus* bacteremia.[6,7] It is unclear whether transthoracic echocardiography is sufficient to determine the presence of infective endocarditis or whether transesophageal echocardiography is required.

Optimal antibiotic therapy for methicillin-resistant *S aureus* (MRSA) bacteremia is also unclear. Even though vancomycin has been considered the standard treatment, there are concerns that its efficacy may be waning and that other agents might be preferable.[11] Thus, we performed a systematic review of the evidence addressing whether all patients with *S aureus* bacteremia require transesophageal echocardiography and what is the optimal antibiotic therapy for MRSA bacteremia.

Clinical Bottom Line

- All patients with *Staphylococcus aureus* bacteremia should be evaluated with echocardiography, preferably by transesophageal echocardiography unless the patient meets criteria for being at low risk.
- For low-risk patients, transthoracic echocardiography is adequate.
- Low-risk patients meet all of the following criteria: (1) nosocomial acquisition of bacteremia, (2) sterile follow-up blood cultures within 4 days after the initial positive blood culture, (3) no permanent intracardiac device, (4) no hemodialysis dependence, and (5) no clinical signs of endocarditis or secondary foci of infection.
- Vancomycin and daptomycin are first-line antibiotic therapies for methicillin-resistant *S aureus* (MRSA) bacteremia.
- For patients with uncomplicated MRSA bacteremia, at least 14 days of antibiotic therapy from the first negative culture may be adequate. For all others, a longer course (eg, 4-6 weeks) is recommended.

Methods

Transesophageal Echocardiography

To assess whether all patients with *S aureus* bacteremia require transesophageal echocardiography, PubMed was searched from inception through May 2014 using the following terms: *Staphylococcus aureus* or *MRSA*, *echocardiography*, and *bacteremia*. References of included studies were also searched. The abstracts of studies being considered for inclusion were reviewed independently by 2 of the authors (T.L.H., C.A.). To be included for full-text review, studies had to specifically address the role of transesophageal echocardiography in *S aureus* bacteremia and provide echocardiography results by organism.

Optimal Antibiotic Therapy for MRSA Bacteremia

To determine what is the optimal antibiotic therapy for MRSA bacteremia, PubMed, EMBASE, and the Cochrane Library were searched from January 1990 through May 2014 using the following terms: *Staphylococcus aureus* or *MRSA*; *bacteremia* or *bloodstream infection*; *antibiotic* or *antimicrobial; vancomycin, daptomycin, linezolid, teicoplanin, trimethoprim-sulfamethoxazole, clindamycin, quinupristin-dalfopristin, tigecycline, ceftaroline, telavancin, dalbavancin, oritavancin,* or *tedizolid*. The ClinicalTrials.gov website was searched for *bacteremia* and *methicillin-resistant Staphylococcus aureus* or *MRSA*. References of included studies were also reviewed. Studies that reported outcomes of antibiotic therapy for MRSA bacteremia were included for review.

Both search strategies were limited to studies published in the English language of adults and excluded case reports, review articles, editorials, guidelines, and studies reporting duplicate data or subgroup analyses of earlier published studies.

Grading the Quality of Included Studies

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system[12] was used to rate the evidence quality of reviewed studies. Each study was assigned a score of high, moderate, low, or very low. Studies were graded by independent reviews conducted by 2 of the authors (T.L.H., C.A.). Studies for which the 2 original ratings disagreed underwent a resolution review by a third author (V.G.F.). For the antibiotic therapy question, studies in which only a subset of included patients had MRSA bacteremia were graded based on the quality of evidence for participants with MRSA bacteremia specifically.

Results of Evidence Review

Transesophageal Echocardiography

Of the 79 identified publications, 14 met inclusion criteria. Five were subsequently excluded based on full-text review (eFigure 1 in the Supplement), leaving 9 studies (4050 patients) that underwent quality assessment. The independent quality assessments were in agreement in all 9 cases (4 low[13-16] and 5 very low[17-21]). All studies were observational (**Table 1**). Sample sizes of included studies ranged from 98 to 877 patients. Transesophageal echocardiography was performed in 12% to 82% of these patients. All studies were susceptible to sampling bias because patients undergoing transesophageal echocardiography had a higher pretest probability of infective endocarditis than patients in whom transesophageal echocardiography was not performed. Infective endocarditis was defined in all studies via either the original[22] or modified[23] Duke criteria. Among the 6 studies[13,14,17-19,21] that evaluated infective endocarditis rates by both transthoracic echocardiography and transesophageal echocardiography, detection of infective endocarditis was higher with

Table 1. Role of Transesophageal Echocardiography in *Staphylococcus aureus* Bacteremia (SAB)

Source (Study Design)	GRADE Category	Age of Study Population With SAB	No. of Cases	Patients, No./Total (%)		Key Outcomes (KO)	Strengths (S)
				TEE or TTE	With IE	Risk Stratification (RS)	Weaknesses (W)
Studies Suggesting TEE Should Be Required for All SAB Cases							
Fowler et al,[13] 1997 (prospective cohort)	Low	Mean (SD), 56 (15) y; underwent both TTE and TEE	SAB: 176 (5 PV, 4 CD) IE: 26	TEE: 103/176 (58) TTE: 103/176 (58)	TEE: 26/103 (25) TTE: 7/103 (7)	KO: Positive TEE in 15 of 77 patients (19%) with negative TTE RS: Clinical findings and TTE results did not predict TEE results	S: Physical examination performed by study investigators, blinded repeat reading of all TEEs, 3-mo follow-up W: Single-center study
Sullenberger et al,[17] 2005 (retrospective cohort)	Very low	Mean (SD), 56.5 (19.1) y; underwent TEE	SAB: 176 (1 PV, 0 CD) IE: 11	TEE: 64/176 (36) TTE: 48/176 (27)	TEE: 9/64 (14) TTE: 1/48 (2)	KO: Positive TTE in 0 of 9 patients with positive TEE; negative TEE and positive TTE in 1 of 64 patients (2%) RS: Clinical findings and TTE results did not predict TEE results	W: Single-center study, low rate of TEE, high incidence (42.2%) of polymicrobial bacteremia
Incani et al,[14] 2013 (prospective cohort)	Low	Median (IQR), 68 (53-76) y; underwent TEE	SAB: 175 (9 PV, 7 CD) IE: 41	TEE: 144/175 (82) TTE: 144/175 (82)	TEE: 41/144 (28) TTE: 22/144 (15)	KO: Nineteen IE cases (46%) not suspected clinically; 22 of 144 cases (15%) reclassified as definite or possible IE after TEE RS: Clinical findings did not predict TEE results	S: High inclusion rate of 83%, 3-mo follow-up W: Single-center study
Holden et al,[18] 2014 (prospective cohort)	Very low	Median (IQR), 62 (19-100) y	SAB: 98 (1 PV, 4 CD) IE: 13	TEE: 58/98 (59) TTE: 32/98 (33)	TEE: 9/58 (16) TTE: 3/32 (9)	KO: Six of 13 IE cases (46%) had no risk factors; 1 of 10 patients (10%) who underwent both modalities had negative TTE and positive TEE RS: Clinical findings did not predict TEE findings	S: Follow-up of 3 mo W: Single-center study, small sample size, only 10 patients underwent both imaging modalities
Studies Suggesting TEE May Be Unnecessary in Some SAB Cases							
Van Hal et al,[19] 2005 (retrospective cohort)	Very low	Median (IQR), 61.4 (22-92) y without IE and 56.3 (28-84) y with IE; without cardiac prostheses; underwent both TTE and TEE	SAB: 808 (0 PV, 0 CD) IE: 22	TEE: 125/808 (15) TTE: 125/808 (15)	TEE: 20/125 (16) TTE: 18/125 (14)	KO: Two IE cases had both negative TTE and TEE; 2 of 125 patients had negative TTE and positive TEE RS: Criteria for proposed low-risk group: (1) no permanent intracardiac device, which was a study exclusion criterion; (2) no embolic phenomena (had NPV of 99/104 [95.2%]); (3) ≤trivial left-sided regurgitation on TTE in the absence of stenosis (had NPV of 55/59 [93%])	S: TTE data assessed by blinded independent observer W: Single-center study, low TEE rate of 15%, only assessed valvular regurgitation
Kaasch et al,[15] 2011 (2 separate prospective cohorts)	Low	Median (IQR), 67 (21-91) y for INSTINCT cohort and 65 (15-95) y for SAB cohort; hospitalized patients with nosocomial infection	SABG: 736 (43 PV, 92 CD) IE: 53	TEE: 175/736 (24) TTE: 298/736 (40)	TEE: 31/175 (18) TTE: NA	KO: Low-risk criteria: only 1 of 208 patients (0.5%) had IE in INSTINCT cohort; 52 of 53 patients (98%) with IE fulfilled at least 1 high-risk criteria in SABG cohort RS: Criteria for proposed low-risk group with an NPV of 207/208 (99.5%): (1) no permanent intracardiac device; (2) no prolonged bacteremia (>4 d); (3) no hemodialysis dependency; (4) no spinal infection; (5) no nonvertebral osteomyelitis	S: Multicenter study, large sample size, 3-mo follow-up W: Low rate of echocardiography overall (50%)
Rasmussen et al,[16] 2011 (prospective cohort)	Low	Mean (SD), 65 (16) y with IE and 64 (16) y without IE; underwent echocardiography	SAB: 336 (20 PV, 14 CD) IE: 53	TEE: 152/336 (45) TTE: NA	NA	KO: Forty-seven of 53 IE cases (89%) predicted by high-risk criteria; 6 of 53 IE cases (11%) missed by high-risk criteria: 4 of 6 had both positive TTE and TEE; 2 of 6 had negative TTE and positive TEE RS: Criteria for proposed low-risk group with an NPV of 114/120 (95%): (1) no permanent intracardiac device; (2) no previous IE; (3) no known heart valve disease; (4) no heart murmur; (5) no embolic events; (6) no vascular or immunologic phenomena suggesting IE; (7) known SAB source; (8) not community-acquired infection; (9) no intravenous drug use	S: Multicenter study, strict definition of IE W: High rate of TTE (38%) without TEE

(continued)

Table 1. Role of Transesophageal Echocardiography in *Staphylococcus aureus* Bacteremia (SAB) (continued)

Source (Study Design)	GRADE Category	Age of Study Population With SAB	No. of Cases	Patients, No./Total (%)		Key Outcomes (KO)	Strengths (S)
				TEE or TTE	With IE	Risk Stratification (RS)	Weaknesses (W)
Joseph et al,[20] 2013 (retrospective cohort)	Very low	Mean (SD), 50.7 (3.6) y with IE and 61.1 (1.1) y without IE; hospitalized patients	SAB: 668 (20 PV, 14 CD) IE: 31	TEE: 82/668 (12) TTE: 270/668 (40)	NA	KO: Prosthetic valve in 10 of 31 patients with IE (32%) vs 10 of 275 patients without IE (4%); cardiac device: 5 of 31 (16%) vs 9/275 (3%), respectively; no IE in low-risk group RS: Criteria for proposed low-risk group with an NPV of 105/105 (100%): (1) no permanent intracardiac device; (2) line-related bacteremia; (3) ≤mild valvular regurgitation on TTE	S: Large sample size W: Single-center study, low TEE rate of 12%
Khatib and Sharma,[21] 2013 (retrospective cohort)	Very low	NA	SAB: 877 (104 CD)[a] IE: 64	TEE: 177/877 (20) TTE: 321/877 (37)	TEE: 42/177 (24) TTE: 25/321 (8)	KO: Low-risk group: only 1 patient with positive TEE RS: Criteria for proposed low-risk group with an NPV of 30/31 (96.8%): (1) no permanent intracardiac device; (2) bacteremia duration <3 d; (3) current bacteremia episode not a relapse from a prior episode within past 100 d; (4) no secondary foci of infection	S: Large sample size W: Low TEE rate of 20%, no standardized timing of echocardiography, high rate of loss to follow-up

Abbreviations: CD, cardiac device; GRADE, Grades of Recommendation, Assessment, Development and Evaluation; IE, infective endocarditis; IQR, interquartile range; NA, data not available; NPV, negative predictive value; PV, prosthetic valve; TEE; transesophageal echocardiogram; TTE, transthoracic echocardiogram.

[a] Included prosthetic valves, pacemakers, defibrillators.

transesophageal echocardiography (14%-28%) than with transthoracic echocardiography (2%-15%).

Two low-quality studies[13,14] reported that clinical findings and transthoracic echocardiography results were poorly predictive of subsequent transesophageal echocardiography findings. In the study by Fowler et al,[13] transesophageal echocardiography detected endocarditis in 15 of 77 patients (19%) with negative transthoracic echocardiography results. Strengths of this study included blinded reinterpretation of transesophageal echocardiography results with high interobserver agreement (100/103 [97%]). In a study of 144 Australian adults with *S aureus* bacteremia who underwent transesophageal echocardiography, 15% of patients without clinical evidence of infective endocarditis were reclassified by transesophageal echocardiography.[14] The quality of the study was increased by the high transesophageal echocardiography rate among all patients with *S aureus* bacteremia (82%). Both studies were limited by relatively small sample size and single-center design.

Five studies[15,16,19-21] proposed that transesophageal echocardiography might be avoided safely in patients with *S aureus* bacteremia who lacked several infective endocarditis risk factors. Factors associated with low risk of infective endocarditis included absence of a permanent intracardiac device,[15,16,19-21] sterile follow-up blood cultures within 4 days after the initial set,[15,21] no hemodialysis dependence,[15] nosocomial acquisition of *S aureus* bacteremia,[16] absence of secondary foci of infection,[15,21] and no clinical signs of infective endocarditis.[16,19] Negative predictive values for the proposed low-risk criteria were 93% to 100% in the individual studies (Table 1).

In summary, all patients with *S aureus* bacteremia should undergo echocardiography. Transesophageal echocardiography is preferred for most patients because *S aureus* infective endocarditis is associated with high mortality risk and transesophageal echocardiography has better detection rates for infective endocarditis. Transthoracic echocardiography may be adequate for patients without identified risk factors for infective endocarditis (as described in previous paragraph). However, these recommendations are based on low-quality evidence.

Optimal Antibiotic Therapy for MRSA Bacteremia

Of 1876 publications identified, 105 met inclusion criteria. Of these, 24 were subsequently excluded after full-text review (eFigure 2 in the Supplement), leaving 81 studies that underwent quality assessment review. The sample sizes of included studies ranged from 6 to 337 patients. The independent quality assessments were in agreement in 68 of 81 cases (84%). All 13 discrepancies in assessment varied by 1 level of evidence, and 11 of the 13 were rated either very low or low quality by reviewers.

Overall, data quality was poor. Only 1 study[28] met GRADE criteria for high-quality evidence. Three were categorized as moderate,[43,45,48] 22 as low,[24-27,29-42,44,46,47,49] and 55 as very low. Studies with a grade of high, moderate, or low are summarized in **Table 2**. Study outcomes were variable and included mortality, clinical success (variably defined), microbiological success, duration of *S aureus* bacteremia, and recurrence.

Evidence for Vancomycin

Vancomycin was the standard therapy in most MRSA bacteremia treatment studies. In the only high-quality trial,[28] vancomycin was compared with daptomycin for patients with *S aureus* bacteremia. Treatment success was assessed 42 days after completion of therapy, with failure defined as a composite outcome of clinical failure, microbiological failure, death, failure to obtain blood culture, receipt of potentially effective nonstudy antibiotics, or premature discontinuation of the study medication because of clinical failure, microbiological failure, or an adverse event. Daptomycin was not inferior

Table 2. Studies of Antibiotic Therapy in Methicillin-Resistant *Staphylococcus aureus* Bacteremia (MRSAB)

Source (Study Design)	GRADE Category	No. of Patients	Population With MRSAB[a] and Treatment Regimen	Primary End Points	Results
Vancomycin Dosing Studies					
Kullar et al,[24] 2011 (retrospective cohort)	Low	320	Median (IQR) age of 53 (45-64) y with vancomycin success and 54 (46-61) y with vancomycin failure (attention to dosing regimens)	Treatment failure (30-d mortality, persistent infection, or bacteremia ≥7 d)	Treatment failure rate of 168/320 (52.5%); in those experiencing failure: 30-d mortality, 35/168 (21%); persistent infection, 93/168 (56%); bacteremia ≥7 d, 127/168 (76%) Independent predictors of failure included: vancomycin trough <15 mg/L (AOR, 2.0 [95% CI, 1.3 to 3.2]); MIC >1 (AOR, 1.5 [95% CI, 1.1 to 2.5])
Moore et al,[25] 2011 (retrospective cohort)	Low	200	Mean (SD) age of 57 (17) y with vancomycin use	Predictors of clinical failure (30-d mortality, persistent bacteremia ≥7 d while receiving therapy, bacteremia recurrence within 30 d)	Overall clinical failure at 30 d in 48/200 (24%); 30-d mortality: 30/200 (15%); microbiological failure rate: 14/200 (7%); recurrence rate: 10/200 (5%) Predictors of failure: severity of illness at onset (10/93 [11%] with APACHE score <14 vs 37/107 [35%] with APACHE score >14); vancomycin MIC in those with low APACHE score (7/88 [8%] with MIC ≤1 vs 3/5 [60%] with MIC = 2); bacteremia source in those with high APACHE score (5/37 [14%] with low-risk source vs 32/70 [46%] with high-risk source); MRSA strain type in those with low-risk source of bloodstream infections (4/11 [36%] for USA300 vs 1/26 [4%] for other infection)
Hall et al,[26] 2012 (retrospective cohort)	Low	337	Median (IQR) age of 53 (42-63) y for survivors and 65 (56-77) y for nonsurvivors; vancomycin dosing of ≥15 mg/kg vs <15 mg/kg	In-hospital mortality	Dosing not significantly associated with mortality (16% for ≥15 mg/kg vs 13% for <15 mg/kg; OR, 1.26 [95% CI, 0.67 to 2.39])
Forstner et al,[27] 2013 (retrospective cohort)	Low	124	Median (range) age of 64.5 (18-96) y; treatment with vancomycin (n = 63), teicoplanin (n = 28), linezolid (n = 7), tigecycline (n = 2), other (n = 24)	Persistent bacteremia ≥7 d, 28-d mortality, treatment failure	Vancomycin trough levels of 15-20 mg/L associated with lower odds of persistent bacteremia (AOR, 0.16; *P* = .01) and treatment failure (AOR, 0.29 [95% CI, 0.10 to 0.79])
Daptomycin					
Fowler et al,[28] 2006 (open-label RCT)	High	246	Median (range) age of 50.5 (21-87) y for adults with SAB and use of daptomycin (6 mg/kg/d; n = 120) and 55 (25-91) y with use of standard therapy (n = 115; low-dose gentamicin plus either an antistaphylococcal penicillin or vancomycin)	Treatment success 42 d after the end of therapy	Daptomycin not inferior to standard therapy for SAB (treatment success: 53/120 [44%] for daptomycin vs 48/115 [42%] for standard therapy; absolute difference, 2.4% [95% CI, −10.2% to 15.1%) and right-sided endocarditis (treatment success: 41/90 [46%] for daptomycin vs 37/91 [41%] for standard therapy; absolute difference, 4.9% [95% CI, −9.5% to 19.3%])
Kullar et al,[29] 2011 (retrospective cohort)	Low	250 (126 MRSAB)	Median (IQR) age of 55 (45-65) y with complicated gram-positive infections; treatment with median dose of 8.9 mg/kg/d of daptomycin	Clinical response (cure, improvement, or failure); adverse events	Clinical success rate for all patients was 209/250 (83.6%) with 119/250 (47.6%) representing clinical cure; Microbiologic success rate for all bacteremic patients was 175/218 (80.3%); 13/250 patients (5.2%) developed non-susceptibility to daptomycin; 3/250 patients (1.2%) experienced adverse event attributed to high-dose daptomycin
Moore et al,[30] 2012 (retrospective case-control)	Low	177	Mean (SD) age of 52 (14) y with use of vancomycin (n = 118) and 51 (14) y with daptomycin (n = 59); vancomycin MIC of 1.5 or 2	Clinical failure (composite of 60-d mortality, persistent bacteremia ≥7 d, or recurrence within 30 d)	No difference in clinical failure rate for daptomycin (10/59 [17%]) vs vancomycin (37/118 [31%]) (*P* = .08); mortality: 5/59 (8%) vs 24/118 (20%), respectively (*P* = .046); persistent bacteremia: 6/59 (10%) vs 11/118 (9%) (*P* = .86); recurrence: 2/59 (3%) vs 6/118 (5%) (*P* = .62)
Falcone et al,[31] 2012 (retrospective case-control)	Low	106 (57 bacteremia, 35 MRSAB)	All staphylococcal invasive infections; mean age of 67.2 y with daptomycin use (n = 23) and 66.7 y with vancomycin use (n = 34)	Duration of antibiotic therapy, length of stay, attributable mortality	No significant difference in mortality (7/23 [30%] with daptomycin vs 17/34 [50%] with vancomycin, *P* = .27) or length of hospital stay (32.5 d vs 34.9 d, respectively; *P* = .49); duration of therapy shorter with daptomycin (18 d vs 25.6 d with vancomycin, *P* = .004)
Murray et al,[32] 2013 (retrospective matched cohort)	Low	170	Median (IQR) age of 57 (51-65) y with daptomycin use (n = 85) and 56 (51-64) y with vancomycin use (n = 85); vancomycin MIC >1	Clinical failure (composite of all-cause 30-d mortality or persistent bacteremia ≥7 d)	Higher risk of failure with vancomycin (OR, 4.5 [95% CI, 2.1 to 9.8]); both components of composite lower with daptomycin: mortality (3/85 [3.5%] vs 11/85 [12.9%] with vancomycin, *P* = .047) and persistent bacteremia (16/85 [18.8%] vs 36/85 [42.4%], respectively; *P* = .001)
Cheng et al,[33] 2013 (retrospective case-control)	Low	78	Age, NA; treatment with daptomycin (8-10 mg/kg; n = 26) or vancomycin (n = 52); vancomycin MIC ≥1.5	Clinical outcome at 14 and 30 d (cure or improvement vs failure or death)	Early daptomycin treatment associated with favorable outcome (OR, 0.27 [95% CI, 0.08 to 0.86]); 14-d favorable outcome: 16/26 (61.5%) with daptomycin vs 19/52 (36.5%) with vancomycin (*P* = .04); 30-d favorable outcome: 20/26 (76.9%) vs 28/52 (53.8%), respectively (*P* = .048); no difference in 30-d mortality (4/26 [15.4%] vs 10/52 [19.2%], *P* = .76) or microbiological failure (4/26 [15.4%] vs 11/52 [21.2%], *P* = .54)

(continued)

Table 2. Studies of Antibiotic Therapy in Methicillin-Resistant *Staphylococcus aureus* Bacteremia (MRSAB) (continued)

Source (Study Design)	GRADE Category	No. of Patients	Population With MRSAB[a] and Treatment Regimen	Primary End Points	Results
Carugati et al,[34] 2013 (prospective cohort)	Low	178 (86 SAB, 25 MRSAB)	Gram-positive left-sided endocarditis; median (IQR) age of 62.5 (54-72.5) y with daptomycin use (n = 29) and 60.5 (44-73) y with standard therapy (n = 149)	In-hospital mortality	Daptomycin (mean dose of 9.2 mg/kg/d) not associated with mortality (RR, 0.8 [95% CI, 0.4 to 1.3], *P* = .35)
Weston et al,[35] 2014 (retrospective matched cohort)	Low	150	Mean age of 61 y; treatment with daptomycin (n = 50) vs vancomycin (n = 100)	Treatment failure (composite of in-hospital mortality, 30-d recurrence, or persistent bacteremia ≥5 d)	Daptomycin use not associated with treatment failure in patients with preserved (OR, 0.45 [95% CI, 0.11 to 1.79]) or impaired renal function (OR, 0.46 [95% CI, 0.11 to 1.94]); lower rate of composite outcome with daptomycin (17/50 [34%]) vs vancomycin (51/100 [51%]) (*P* = .048); mortality: 8/50 (16%) vs 35/100 (35%), respectively (*P* = .02); persistent bacteremia: 7/50 (14%) vs 21/100 (21%) (*P* = .30); recurrence: 6/50 (12%) vs 5/100 (5%) (*P* = .12)
Teicoplanin					
Menichetti et al,[36] 1994 (open-label RCT)	Low	635 (527 evaluable, 102 gram-positive bacteremia,12 MRSAB)	Febrile neutropenia; mean (range) age of 44 (14-78) y with teicoplanin use and 42 (14-72) y with vancomycin use (each in combination with amikacin and ceftazidime)	Treatment success (resolution of signs of infection, eradication of organism)	No difference in rates of treatment success in those with gram-positive bacteremia (45/52 [87%] with vancomycin vs 46/50 [92%] with teicoplanin, *P* = .28) and among those with SAB (11/13 [85%] vs 14/15 [93%], respectively; *P* = .40)
Yoon et al,[37] 2014 (prospective cohort)	Low	190	Health care–associated MRSAB; median (IQR) age of 66 (51-73) y; treatment with vancomycin (n = 134) vs teicoplanin (n = 56)	Clinical failure (composite of MRSAB-attributed mortality, bacteremia duration ≥7 d, and fever duration ≥7 d)	Choice of antibiotic not associated with clinical failure (OR, 0.73 [95% CI, 0.18 to 2.98]); MRSAB mortality: 18/134 (13.4%) with vancomycin vs 10/56 (17.9%) with teicoplanin (*P* = .43); persistent bacteremia: 15/134 (11.2%) vs 5/56 (9.1%), respectively (*P* = .60); persistent fever: 29/134 (22%) vs 22/56 (39.3%) (*P* = .02)
Linezolid					
Birmingham et al,[38] 2003 (open-label compassionate-use cohort)	Low	796 (378 bacteremia, 14 evaluable MRSAB)	Patients with signs and symptoms of a serious infection; median (IQR) ages of 55.8 (18-93) y and 8.7 (0.1-17) y; treatment with linezolid	Clinical and microbiological outcome (cure, failure, or indeterminate)	Patients with evaluable MRSAB: 10/14 (71.4%) cured
Shorr et al,[39] 2005 (Retrospective pooled analysis of subgroups with bacteremia in 5 RCTs)	Low	3228 in parent studies (144 SAB, 64 MRSAB)	Nosocomial pneumonia, complicated SSTI, or general MRSA infections plus bacteremia; mean (SD) age of 63.5 (17.1) y with linezolid use (n = 36) and 59.3 (18.9) y with vancomycin use (n = 28)	Clinical cure, microbiological success, survival	No significant differences in clinical cure for MRSA bacteremia: 13/28 (46%) with vancomycin vs 14/25 (56%) with linezolid (OR, 1.47 [95% CI, 0.50 to 4.34]); other primary end points only reported for SAB as a whole (ie, included MSSA); microbiological success: 41/56 (73%) with vancomycin vs 41/59 (69%) with linezolid (OR, 0.83 [95% CI, 0.37 to 1.87); survival: 52/70 (74%) vs 55/74 (74%), respectively (OR, 1.08 [95% CI, 0.41 to 2.85])
Gómez et al,[40] 2007 (prospective cohort)	Low	100	Median (IQR) age of 60 (14-95) y; treatment with vancomycin (n = 49), teicoplanin (n = 20), linezolid (n = 17), other (n = 14)	Influence of empirical antibiotic choice on mortality	Empirical therapy with linezolid yielded lower mortality than glycopeptides in bivariate analysis (OR, 7.7 [95% CI, 1.1 to 53.0])
Wilcox et al,[41] 2009 (open-label RCT)	Low	739 (47 MRSAB in microbiologically evaluable population)	Suspected catheter-related infection; mean (SD) age of 53.7 (18.1) y with linezolid use and 53.8 (17.6) y with vancomycin use; β-lactam for methicillin-susceptible pathogens	Microbiological outcome at test of cure	For microbiologically evaluable bacteremic patients, linezolid (82/95 [86.3%]) not inferior to vancomycin (67/74 [90.5%]) (absolute difference, 4.2% [95% CI, −7.1% to 6.4%]); however, increased mortality (78/363 [21.5%] in linezolid group vs 58/363 [16%] with vancomycin) led to FDA warning (see text)
Park et al,[42] 2012 (prospective cohort)	Low	90	Persistent MRSAB; mean (SD) age of 63.7 (11.6) y with linezolid-based salvage therapy (n = 38) (with or without carbapenem) and 62.4 (14.2) y with continued glycopeptide use (n = 52)	Early microbiological response, duration of bacteremia, salvage success	Shorter duration of bacteremia in glycopeptide group (10 d vs 16 d with linezolid-based salvage therapy, *P* = .008); no significant difference in early microbiological response (17/38 [45%] vs 32/52 [62%], respectively, *P* = .11) or mortality (4/38 [11%] vs 13/52 [25%], *P* = .08)
Trimethoprim-Sulfamethoxazole					
Markowitz et al,[43] 1992 (double-blind RCT)	Moderate	228 (65 SAB, 38 MRSAB)	Intravenous drug use with suspected SAB without left-sided infective endocarditis; median (IQR) age of 32.6 (31.1-34.1) y with use of trimethoprim (320 mg/d) and sulfamethoxazole (1600 mg/d) and 32.5 (30.7-34.3) y with vancomycin (1 g every 12 h)	Cure rate in those with *S aureus* infection (not limited to bacteremia)	Cure rate: 37/43 (86%) with trimethoprim-sulfamethoxazole vs 57/58 (98%) with vancomycin (*P* = .01); all treatment failures were in patients with MSSA

(continued)

Table 2. Studies of Antibiotic Therapy in Methicillin-Resistant *Staphylococcus aureus* Bacteremia (MRSAB) (continued)

Source (Study Design)	GRADE Category	No. of Patients	Population With MRSAB[a] and Treatment Regimen	Primary End Points	Results
Goldberg et al,[44] 2010 (retrospective matched cohort)	Low	114	Mean (SD) age of 74.7 (15.9) y with use of trimethoprim-sulfamethoxazole (n = 38) and 75.8 (13.7) y with vancomycin (n = 76)	Persistent bacteremia >14 d, relapse, 30-d mortality, adverse events	No significant differences in any of the outcomes; mortality: 13/38 (34.2%) with trimethoprim-sulfamethoxazole vs 31/76 (40.8%) with vancomycin (OR, 0.76 [95% CI, 0.34 to 1.70]); relapse and persistent bacteremia: 3/38 (7.9%) vs 13/76 (17.1%), respectively (*P* = .18); renal failure: 11/38 (28.9%) vs 21/76 (27.6%)
Combination Therapy					
Levine et al,[45] 1991 (open-label RCT)	Moderate	42	MRSA endocarditis (median [range] age of 32 [23-61] y); treatment with vancomycin alone (1 g every 12 h; n = 22) vs vancomycin (1 g every 12 h) plus rifampin (600 mg/d) (n = 20)	Duration of bacteremia	Median duration of 9 d for bacteremia for all patients; 7 (95% CI, 5 to 11) d for vancomycin vs 9 (95% CI, 6 to 13) d with combination therapy; no difference between groups with respect to therapeutic failure: 4/22 (18%) vs 2/20 (10%), respectively (*P* > .20)
Lemonovich et al,[46] 2011 (retrospective cohort)	Low	87 (48 MRSAB)	Persistent SAB, *S aureus* endocarditis, or both; median (range) age of 58 (50-70) y with β-lactam or vancomycin with concomitant aminoglycoside use (n = 49) and 57 (53-71) y without concomitant aminoglycoside use (n = 38)	Incidence of recurrent SAB within 6 mo, duration of bacteremia, 6-mo mortality, incidence of bacteremia complications, incidence of renal failure	Aminoglycoside use associated with lower incidence of recurrence (RR, 0.51 [95% CI, 0.22 to 1.17]; *P* = .04); other outcomes not significantly different; mortality: 51% for aminoglycoside use vs 42.1% for no aminoglycoside use (*P* = .41); complication rate: 71.4% vs 73.7%, respectively (*P* = .82); renal failure: 54.5% vs 46.9% (*P* = .54)
Dilworth et al,[47] 2014 (retrospective cohort)	Low	80	Mean (SD) age of 51.6 (15) y with combination therapy of vancomycin plus β-lactam (n = 50) and 50.5 (16.8) y with vancomycin alone (n = 30); vancomycin MIC ≤2	Microbiological eradication (negative blood cultures and no relapse within 30 d of completing therapy)	Microbiological eradication more likely with combination therapy; 48/50 (96%) with combination therapy of vancomycin plus β-lactam vs 24/30 (80%) with vancomycin alone (AOR, 11.24 [95% CI, 1.72 to 144.3]; *P* = .01)
Dalbavancin					
Raad et al,[48] 2005 (open-label RCT)	Moderate	75 (14 MRSAB)	Gram-positive catheter-related bloodstream infection; mean (range) age of 54 (20-78) y with use of dalbavancin and 58 (19-85) y with vancomycin	Overall efficacy at test of cure visit in microbiological intention-to-treat population	Overall treatment success rate at test of cure was 20/23 (87%) with dalbavancin vs 14/28 (50%) with vancomycin (*P* < .05) in all study patients (not limited to MRSAB only)
Treatment Duration Study					
Chong et al,[49] 2013 (prospective cohort)	Low	111 (53 MRSAB)	Uncomplicated SAB; median (IQR) age of 60 (49.5-68) y; treatment duration <14 d (n = 38) vs ≥14 d (n = 73)	Relapse, crude mortality, and 12-wk treatment failure	Higher relapse with short-course therapy (3/38 [7.9%]) vs ≥14 d (0/73) (*P* = .04); no difference in crude mortality (7/38 [18.4%] vs 16/73 [21.9%], respectively, *P* = .67) or treatment failure (10/38 [26.3%] vs 16/73 [21.9%], *P* = .64)

Abbreviations: AOR, adjusted odds ratio; APACHE, Acute Physiology and Chronic Health Evaluation; FDA, Food and Drug Administration; GRADE, Grades of Recommendation, Assessment, Development and Evaluation; IQR, interquartile range; OR, odds ratio; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S aureus;* MSSA, methicillin-susceptible *S aureus* bacteremia; RCT, randomized clinical trial; RR, relative risk; SSTI, skin and soft tissue infection.

[a] Unless otherwise indicated.

to standard therapy (success rate, 44.2% [53/120] vs 41.7% [48/115]; absolute difference, 2.4% [95% CI −10.2% to 15.1%]), in which standard therapy consisted of vancomycin (for MRSA bacteremia or for patients allergic to penicillin) or an antistaphylococcal penicillin (for methicillin-susceptible *S aureus* bacteremia [MSSA] bacteremia), each in combination with low-dose, short-course gentamicin. In open-label randomized trials, vancomycin also was compared with teicoplanin,[36] trimethoprim-sulfamethoxazole,[43] linezolid,[39,41] and dalbavancin.[48] None of these antibiotics performed significantly better than vancomycin.

Evidence for Daptomycin

As noted above, daptomycin was not inferior to standard therapy for *S aureus* bacteremia and right-sided infective endocarditis.[28] In the predefined subgroup of patients with MRSA bacteremia, the success rate was 20 patients among 45 recipients of daptomycin (44.4%) vs 14 patients among 44 recipients of vancomycin (31.8%). This difference was not statistically significant (absolute difference, 12.6% [95% CI −7.4% to 32.6%]; *P* = .28) for the prespecified secondary analysis. This study led to approval by the US Food and Drug Administration (FDA) of daptomycin for *S aureus* bacteremia and right-sided infective endocarditis.

Cohort[32,34,35] and case-control[30,31,33] studies tested the hypothesis that daptomycin either at[32] or above[33,34] the FDA-approved dose of 6 mg/kg/d for *S aureus* bacteremia was associated with better clinical outcomes than vancomycin in patients with bacteremia due to MRSA with high vancomycin minimum inhibitory concentration values. In a prospective cohort study of patients with left-sided infective endocarditis,[34] high-dose daptomycin (median dose, 9.2 mg/kg/d) was not significantly associated with any difference for in-hospital mortality compared with standard of care (daptomycin, 1/7 [14.3%] vs standard of care, 8/18 [44.4%];

P = .35). Antibiotic-associated adverse events (such as myositis, peripheral neuropathy, or interstitial pneumonitis) among patients receiving higher doses of daptomycin (median dose, 8.9 mg/kg/d) are low.[29] Generalizability of these results was limited by suboptimal study design, including lack of randomization to therapies.

Evidence for Linezolid

Linezolid is an oxazolidinone antibiotic with in vitro activity against a number of gram-positive pathogens, including MRSA. Observations from a compassionate-use program suggested that linezolid might be effective for treating gram-positive bacteremia.[38] Shorr et al[39] compiled data on patients with bacteremia from 5 earlier randomized trials comparing linezolid with vancomycin. Of 3228 enrolled patients in the original studies, 53 had MRSA bacteremia and were evaluable. In these 53 patients, rates of clinical cure (defined as resolution of baseline signs and symptoms of primary infection, with improvement or lack of progression of radiographic, laboratory, and other objective findings) did not differ (linezolid, 14/25 [56%] vs vancomycin, 13/28 [46%]; odds ratio [OR], 1.5 [95% CI, 0.5-4.3]).[39]

In an open-label, phase 3 study of patients with suspected catheter-related bacteremia, linezolid was not inferior to vancomycin among patients with gram-positive infections.[41] However, patients in the linezolid group had a higher rate of death than those in the comparator group. This led to an FDA black box warning advising against the empirical use of linezolid in catheter-related bacteremia if gram-negative infection is known or suspected.[50] Linezolid was evaluated as a therapy for MRSA bacteremia that persisted after 7 or more days of treatment with vancomycin or teicoplanin. Microbiological response, treatment success, and mortality were uniformly poor and were not significantly different among linezolid recipients vs vancomycin or teicoplanin recipients.[42]

Evidence for Trimethoprim-Sulfamethoxazole

Treatment with trimethoprim-sulfamethoxazole was compared with vancomycin in a randomized trial of intravenous drug users with suspected *S aureus* bacteremia.[43] Of 228 enrolled patients, 65 had *S aureus* bacteremia, of which 38 were due to MRSA. Among 101 evaluable patients, 64% of whom had *S aureus* bacteremia, vancomycin was superior to trimethoprim-sulfamethoxazole (57/58 [98%] vs 37/43 [86%] cure rate; OR, 9.2 [95% CI, 1.1-79.9]). Treatment failures in both groups occurred in patients with MSSA. More recently, 38 patients retrospectively identified and treated with trimethoprim-sulfamethoxazole for MRSA bacteremia were compared with 76 matched controls who received vancomycin. Thirty-day mortality, relapse or persistent bacteremia, and rates of renal failure were not significantly different between treatment groups.[44]

Evidence for Combination Therapy

Combination antibiotic therapy for MRSA bacteremia has generally been ineffective. Adding rifampin to vancomycin for treating MRSA-infective endocarditis was not associated with reduced bacteremia duration or improved cure rates compared with patients randomized to vancomycin alone.[45] In a randomized trial of patients with MSSA-infective endocarditis,[51] adding gentamicin to nafcillin did not improve morbidity or mortality. This finding was consistent with results from a retrospective evaluation of 87 patients with persistent *S aureus* bacteremia or infective endocarditis, 48 of whom had MRSA infection.[46] Those treated with an aminoglycoside had a lower incidence of recurrence within 6 months, although there was no significant association with other outcomes, including duration of bacteremia, 6-month all-cause mortality, incidence of complications of persistent bacteremia or infective endocarditis, and incident renal failure.[46]

Safety data from the daptomycin trial by Fowler et al[28] showed that 27 patients of 122 (22%) who received low-dose gentamicin therapy experienced a clinically significant reduction in renal function compared with 8 of 100 patients (8%) who did not receive gentamicin (*P* = .005).[52] Case reports document the use of fluoroquinolone and rifampin combination therapy for right-sided MRSA-infective endocarditis[53,54]; and for MRSA bacteremia, the addition of β-lactam antibiotics to linezolid[42,55] and daptomycin.[56]

Evidence for Other Antibiotics

Several other antibiotics have either preliminary or limited data on the treatment of MRSA bacteremia. Moderate quality data from a single randomized trial suggest that dalbavancin is a potential alternative to vancomycin for catheter-related, gram-positive bacteremia. However, only 14 patients in the trial had MRSA bacteremia.[48]

Very low–quality data from an emergency-use program suggested that quinupristin-dalfopristin may be a therapeutic option for MRSA infections, including bacteremia.[57] However, this antibiotic combination is associated with an unfavorable adverse event profile, including infusion site pain, nausea, and myalgia.

Telavancin is a lipoglycopeptide antibiotic approved for complicated skin and skin structure infections[58] and hospital-acquired and ventilator-associated bacterial pneumonia caused by *S aureus*.[59] Telavancin was not associated with a difference in cure rate compared with vancomycin in 73 patients with bacteremic pneumonia, 33 of whom had MRSA bacteremia.[60] Telavancin was compared with standard therapy for treating uncomplicated *S aureus* bacteremia in a small proof-of-concept randomized trial. All 9 evaluable patients with MRSA (of whom 5 received telavancin) were cured.[61]

In a retrospective evaluation of patients treated with ceftaroline,[62] clinical success occurred in 101 of 129 (78.3%) evaluable patients with *S aureus* bacteremia (of which 92.5% had MRSA).

Pooled results of patients with bacteremia treated with tigecycline from 8 trials have been reported; however, only 10 patients had MRSA bacteremia.[63] A subsequent analysis by the FDA of patients in 10 trials demonstrated an increased risk of death with tigecycline, leading to a black box warning that tigecycline be reserved only for situations in which alternative treatments are not suitable.[64]

Duration of Therapy for *S aureus* Bacteremia

Historically *S aureus* bacteremia was treated with 4 to 6 weeks of intravenous antibiotics.[65] Over the past 3 decades, investigators have tried to identify a subgroup of patients who can safely be treated with shorter durations of therapy. A prerequisite for shorter therapy is the ability to prospectively differentiate patients with uncomplicated *S aureus* bacteremia (who might be cured with a short treatment course) from patients with complicated *S aureus* bacteremia, for whom longer treatment is necessary. Guidelines define uncomplicated *S aureus* bacteremia as an infection in which (1) infective endocarditis has been excluded, (2) no implanted prostheses are present, (3) follow-up blood cultures drawn 2 to 4 days after the initial set are sterile, (4) the patient defervesces within 72 hours of initiation of effective antibiotic therapy, and (5) no evidence of metastatic infection is present on examination.[6]

Only a minority of all patients with MRSA bacteremia meet these criteria. In these patients, the recommended treatment duration is at least 14 days of intravenous antibiotics from time of first negative blood culture. However, there is limited evidence supporting this recommendation. One prospective study[49] reported unacceptably high relapse rates in patients meeting the guideline definition of uncomplicated *S aureus* bacteremia who were treated for less than 2 weeks. A 1993 meta-analysis of older studies evaluated the effectiveness of antibiotic therapy for 14 days or less in patients with intravascular catheter-associated *S aureus* bacteremia.[66] This study estimated a 6.1% late infectious complication rate for short-duration therapy and concluded that more than 2 weeks of intravenous antibiotics should be administered. Rosen et al[67] showed that transesophageal echocardiography was a cost-effective method to identify patients with intravascular catheter–associated *S aureus* bacteremia for whom short-course therapy was adequate. A multicenter randomized trial of treatment duration in staphylococcal bacteremia is under way.[68]

We recommend vancomycin or daptomycin as first-line therapy for MRSA bacteremia. Patients with uncomplicated *S aureus* bacteremia should be treated for at least 14 days from the first negative blood culture. Patients with complicated *S aureus* bacteremia should be treated for 4 to 6 weeks. However, these recommendations are based on low-quality evidence.

Discussion

Transesophageal Echocardiography

Transesophageal echocardiography is significantly better than either transthoracic echocardiography or physical examination in identifying infective endocarditis in patients with *S aureus* bacteremia. Three prospective cohort studies using transesophageal echocardiography identified infective endocarditis in approximately one-quarter of patients with *S aureus* bacteremia.[13,14,16] Although this prevalence is likely increased by the fact that clinicians are more likely to recommend transesophageal echocardiography in patients for whom they have a higher clinical suspicion for infective endocarditis,[69] it is clear that transesophageal echocardiography can be used to successfully diagnose infective endocarditis in a subset of patients with *S aureus* bacteremia and nondiagnostic transthoracic echocardiography.

However, transesophageal echocardiography is not recommended for all cases of *S aureus* bacteremia. First, transesophageal echocardiography has associated costs and risks. Major complications such as esophageal perforation occur in approximately 1 in 5000 transesophageal echocardiographies.[70] Second, there is no evidence demonstrating that improved detection of small valvular vegetations or oscillating targets by transesophageal echocardiography improves clinical outcome in patients with *S aureus* bacteremia. Although 1 small, single-center study[71] reported that patients with smaller vegetations discovered by transesophageal echocardiography only (after negative transthoracic echocardiography) were less likely than those with positive transthoracic echocardiography results to experience an embolic event or die of their infection, this finding was not externally validated.[10]

Third, several studies now suggest that it is possible to identify a subset of patients with *S aureus* bacteremia with a low risk of infective endocarditis for whom transesophageal echocardiography is not essential.[15,16,19-21] This low-risk subset for whom transthoracic echocardiography is sufficient could be conservatively defined as patients meeting all of the following criteria: (1) nosocomial acquisition of bacteremia,[16,20] (2) sterile follow-up blood cultures within 4 days after the initial set,[15,21] (3) absence of permanent intracardiac device,[15,16,19-21] (4) absence of hemodialysis dependence,[15] and (5) no clinical signs of infective endocarditis or secondary foci of infection.[15,16,19,21] Alternatively, patients whose *S aureus* bacteremia has resolved and who are scheduled to receive extended courses of antibiotics for other forms of complicated *S aureus* infection (for example, osteomyelitis or visceral abscess) may not require transesophageal echocardiography.

Fourth, improvements in transthoracic echocardiography image quality have narrowed the diagnostic gap between the 2 modalities, especially for the evaluation of native valves.[72] Collectively these results suggest that all patients with *S aureus* bacteremia should undergo echocardiography.[6,73] Although transesophageal echocardiography is preferred when feasible, there may be identifiable low-risk patients in whom transesophageal echocardiography is not required.

Optimal Antibiotic Therapy for MRSA Bacteremia

Vancomycin and daptomycin are the only FDA-approved agents for the treatment of MRSA bacteremia in the United States. Approval for vancomycin is based largely on historical precedent. Recently, concerns have emerged regarding clinical isolates of MRSA exhibiting increasing minimum inhibitory concentrations to vancomycin.[11] These concerns were underscored by the observation that patients with MRSA bacteremia due to isolates with higher (but still susceptible) vancomycin minimum inhibitory concentration had higher all-cause mortality than those infected with lower vancomycin minimum inhibitory concentration isolates.[74] The cause of this association is unknown.[75]

Although guidelines recommend targeting vancomycin trough levels of 15-20 mg/L to treat serious infections due to MRSA,[76] the relationship of these higher vancomycin trough levels to the outcome of patients with MRSA bacteremia is unclear.[75] Several recent observational cohort studies[30,32,33] have suggested that daptomycin might be preferred over vancomycin to treat MRSA bacteremia due to high vancomycin minimum inhibitory concentration. Randomized trials are needed. Nonetheless, an increasing number of clinicians prescribe daptomycin at doses exceeding the FDA-approved dose of 6 mg/kg once daily given intravenously for complicated MRSA bacteremia.[29] The quality of evidence for this practice is low.

Teicoplanin represents another potential alternative to vancomycin but is unavailable in the United States.[36,37] The addition of gentamicin, rifampin, or both to vancomycin for treating MRSA bacteremia and native valve infective endocarditis offers no meaningful benefit and may confer harm.[45,52] Adding a β-lactam antibiotic to vancomycin or daptomycin to treat MRSA bacteremia[56] is of unproven benefit. Low-quality evidence suggests that linezolid, trimethoprim-sulfamethoxazole, dalbavancin, ceftaroline, quinupristin-dalfopristin, and telavancin may be useful for patients who have not responded to first-line therapy. Tigecycline should be avoided. No data are yet available for tedizolid or oritavancin (both recently approved by the FDA for skin infections) or investigational compounds such as ceftobiprole to treat MRSA bacteremia.

All MRSA bacteremia should be treated with intravenous antibiotics for a minimum of 14 days from the time of blood culture clearance. For those patients not meeting the definition of uncomplicated bacteremia, 4 to 6 weeks of therapy is recommended.

Evidence for Other Components of *S aureus* Bacteremia Management

The use of antistaphylococcal β-lactam antibiotics whenever possible to treat MSSA infections is widely accepted as the standard of care. The level of evidence for this practice is poor, consisting of several observational studies,[77-83] suggesting higher treatment failure rates in patients infected with MSSA and treated with vancomycin. For example, one prospective cohort of 298 patients with MSSA bacteremia reported that the rate of microbiological failure was lower (0/18 vs 13/70 [19%]; OR, 6.5 [95% CI, 1.0-53.0]) among patients with MSSA bacteremia who were treated with nafcillin instead of vancomycin.[79] Several other prospective[78] and retrospective[81-83] cohort studies documented lower overall[81] and infection-related[82,83] mortality rates among patients infected with MSSA who were treated with β-lactam antibiotics. Although most patients with a self-reported penicillin allergy do not have a true allergy by skin testing and would tolerate β-lactam therapy,[84] patient-reported penicillin allergy constitutes a significant reason for prescribing vancomycin or other antistaphylococcal antibiotics. Skin testing appeared cost-effective in a decision analysis for treating MSSA-infective endocarditis, even after assuming equal efficacy of vancomycin and β-lactam therapy.[85]

At least 15 observational studies have evaluated the role of infectious diseases consultation (IDC) for *S aureus* bacteremia (eTable in the Supplement). All studies found clinical benefit and 11[86-96] reported improved mortality among patients with *S aureus* bacteremia who received IDC. Infectious diseases consultation is associated with increased adherence to standards of care, including β-lactam antibiotics for MSSA bacteremia,[87-91,97,98] longer durations of therapy for complicated *S aureus* bacteremia,[86-91,95,97,98] removal of infected catheters[87,97] and devices,[87,98] obtaining follow-up blood cultures[87,88,90,91,95-97] and echocardiography,[86,88,89,91,96] and draining of abscesses.[87] Although the evidence for routine IDC in patients with *S aureus* bacteremia is limited to low-quality evidence, it supports the conclusion that IDC should be considered for patients with *S aureus* bacteremia.

Conclusions

The evidence for most management strategies in *S aureus* bacteremia is poor. Evidence to guide the use of transesophageal echocardiography in adult patients with *S aureus* bacteremia is weak. It may be possible to prospectively identify a low-risk group of patients for whom transthoracic echocardiography is adequate. Vancomycin and daptomycin remain the first-line therapies for MRSA bacteremia. Treatment should consist of at least 14 days from the first negative blood culture for uncomplicated *S aureus* bacteremia and at least 4 to 6 weeks for complicated *S aureus* bacteremia. High-quality trials comparing treatment strategies, antibiotics, and treatment durations are needed to better inform the management of this common, serious infection.

ARTICLE INFORMATION

Author Contributions: Dr Fowler had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Fowler.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: All authors.
Obtained funding: Fowler.
Administrative, technical, or material support: Holland, Arnold.
Study supervision: Fowler.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Holland reported serving as a paid consultant for The Medicines Company. Dr Fowler reported serving as chair of Merck's V710 scientific advisory committee; receiving grant support and having grants pending from Cerexa, Pfizer, Advanced Liquid Logic, MedImmune, and Cubist; serving as a paid consultant for Merck, Astellas, Affinium, Theravance, Cubist, Cerexa, Debiopharm, Durata, Pfizer, NovaDigm, Novartis, Medicines Company, Biosynexus, MedImmune, and Inimex, Bayer; and receiving honoraria from Merck, Astellas, Cubist, Pfizer, Theravance, and Novartis. No other disclosures were reported.

Funding/Support: Research reported in this article was supported by award UM1-AI104681 from the National Institute of Allergy and Infectious Diseases. Dr Fowler was supported by grant K24-AI093969 from the National Institutes of Health.

Role of the Funder/Sponsor: The National Institute of Allergy and Infectious Diseases and the National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We are grateful to Megan van Noord, MSIS (Duke University Medical Center librarian), for her assistance in conducting the antibiotic therapy searches; she was not compensated for this work.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

REFERENCES

1. Landrum ML, Neumann C, Cook C, et al. Epidemiology of *Staphylococcus aureus* blood and skin and soft tissue infections in the US military health system, 2005-2010. *JAMA*. 2012;308(1):50-59.

2. El Atrouni WI, Knoll BM, Lahr BD, et al. Temporal trends in the incidence of *Staphylococcus aureus* bacteremia in Olmsted County, Minnesota, 1998 to 2005. *Clin Infect Dis*. 2009;49(12):e130-e138.

3. van Hal SJ, Jensen SO, Vaska VL, et al. Predictors of mortality in *Staphylococcus aureus* bacteremia. *Clin Microbiol Rev*. 2012;25(2):362-386.

4. Cosgrove SE, Sakoulas G, Perencevich EN, et al. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2003;36(1):53-59.

5. Kaasch AJ, Barlow G, Edgeworth JD, et al. *Staphylococcus aureus* bloodstream infection. *J Infect*. 2014;68(3):242-251.

6. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52(3):e18-e55.

7. Gould FK, Brindle R, Chadwick PR, et al. Guidelines (2008) for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the United Kingdom. *J Antimicrob Chemother*. 2009;63(5):849-861.

8. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America [published correction appears in *Clin Infect Dis*. 2010;50(7):1079]. *Clin Infect Dis*. 2009;49(1):1-45.

9. Thuny F, Di Salvo G, Belliard O, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study [published correction appears in *Circulation*. 2005;112(9):e125]. *Circulation*. 2005;112(1):69-75.

10. Fowler VG Jr, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis. *JAMA*. 2005; 293(24):3012-3021.

11. Deresinski S. Counterpoint: vancomycin and *Staphylococcus aureus*—an antibiotic enters obsolescence. *Clin Infect Dis*. 2007;44(12):1543-1548.

12. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336 (7650):924-926.

13. Fowler VG Jr, Li J, Corey GR, et al. Role of echocardiography in evaluation of patients with *Staphylococcus aureus* bacteremia. *J Am Coll Cardiol*. 1997;30(4):1072-1078.

14. Incani A, Hair C, Purnell P, et al. *Staphylococcus aureus* bacteraemia. *Eur J Clin Microbiol Infect Dis*. 2013;32(8):1003-1008.

15. Kaasch AJ, Fowler VG Jr, Rieg S, et al. Use of a simple criteria set for guiding echocardiography in nosocomial *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2011;53(1):1-9.

16. Rasmussen RV, Høst U, Arpi M, et al. Prevalence of infective endocarditis in patients with *Staphylococcus aureus* bacteraemia. *Eur J Echocardiogr*. 2011;12(6):414-420.

17. Sullenberger AL, Avedissian LS, Kent SM. Importance of transesophageal echocardiography in the evaluation of *Staphylococcus aureus* bacteremia. *J Heart Valve Dis*. 2005;14(1):23-28.

18. Holden E, Bashir A, Das I, et al. *Staphylococcus aureus* bacteraemia in a UK tertiary referral centre. *J Antimicrob Chemother*. 2014;69(7):1960-1965.

19. Van Hal SJ, Mathur G, Kelly J, et al. The role of transthoracic echocardiography in excluding left sided infective endocarditis in *Staphylococcus aureus* bacteraemia. *J Infect*. 2005;51(3):218-221.

20. Joseph JP, Meddows TR, Webster DP, et al. Prioritizing echocardiography in *Staphylococcus aureus* bacteraemia. *J Antimicrob Chemother*. 2013; 68(2):444-449.

21. Khatib R, Sharma M. Echocardiography is dispensable in uncomplicated *Staphylococcus aureus* bacteremia. *Medicine (Baltimore)*. 2013;92 (3):182-188.

22. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis. *Am J Med*. 1994;96(3):200-209.

23. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30 (4):633-638.

24. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2011;52(8):975-981.

25. Moore CL, Lu M, Cheema F, et al. Prediction of failure in vancomycin-treated methicillin-resistant *Staphylococcus aureus* bloodstream infection. *Antimicrob Agents Chemother*. 2011;55(10):4581-4588.

26. Hall RG II, Giuliano CA, Haase KK, et al. Empiric guideline-recommended weight-based vancomycin dosing and mortality in methicillin-resistant *Staphylococcus aureus* bacteremia. *BMC Infect Dis*. 2012;12:104.

27. Forstner C, Dungl C, Tobudic S, et al. Predictors of clinical and microbiological treatment failure in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia. *Clin Microbiol Infect*. 2013;19(7):291-297.

28. Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med*. 2006;355(7): 653-665.

29. Kullar R, Davis SL, Levine DP, et al. High-dose daptomycin for treatment of complicated gram-positive infections. *Pharmacotherapy*. 2011;31 (6):527-536.

30. Moore CL, Osaki-Kiyan P, Haque NZ, et al. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant *Staphylococcus aureus* with a high vancomycin minimum inhibitory concentration. *Clin Infect Dis*. 2012;54(1):51-58.

31. Falcone M, Russo A, Pompeo ME, et al. Retrospective case-control analysis of patients with staphylococcal infections receiving daptomycin or glycopeptide therapy. *Int J Antimicrob Agents*. 2012; 39(1):64-68.

32. Murray KP, Zhao JJ, Davis SL, et al. Early use of daptomycin versus vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia with vancomycin minimum inhibitory concentration >1 mg/L. *Clin Infect Dis*. 2013;56(11): 1562-1569.

33. Cheng CW, Hsu PC, Yang CC, et al. Influence of early daptomycin therapy on treatment outcome of meticillin-resistant *Staphylococcus aureus* bacteraemia with high vancomycin minimum inhibitory concentrations. *Int J Antimicrob Agents*. 2013;41(3):293-294.

34. Carugati M, Bayer AS, Miró JM, et al. High-dose daptomycin therapy for left-sided infective endocarditis. *Antimicrob Agents Chemother*. 2013; 57(12):6213-6222.

35. Weston A, Golan Y, Holcroft C, Snydman DR. The efficacy of daptomycin versus vancomycin for methicillin-resistant *Staphylococcus aureus* bloodstream infection in patients with impaired renal function. *Clin Infect Dis*. 2014;58(11):1533-1539.

36. Menichetti F, Martino P, Bucaneve G, et al. Effects of teicoplanin and those of vancomycin in initial empirical antibiotic regimen for febrile, neutropenic patients with hematologic malignancies. *Antimicrob Agents Chemother*. 1994; 38(9):2041-2046.

37. Yoon YK, Park DW, Sohn JW, et al. Multicenter prospective observational study of the comparative efficacy and safety of vancomycin versus teicoplanin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2014;58 (1):317-324.

38. Birmingham MC, Rayner CR, Meagher AK, et al. Linezolid for the treatment of multidrug-resistant, gram-positive infections. *Clin Infect Dis*. 2003;36 (2):159-168.

39. Shorr AF, Kunkel MJ, Kollef M. Linezolid versus vancomycin for *Staphylococcus aureus* bacteraemia. *J Antimicrob Chemother*. 2005;56(5): 923-929.

40. Gómez J, García-Vázquez E, Baños R, et al. Predictors of mortality in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia. *Eur J Clin Microbiol Infect Dis*. 2007;26 (4):239-245.

41. Wilcox MH, Tack KJ, Bouza E, et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections. *Clin Infect Dis*. 2009;48(2):203-212.

42. Park HJ, Kim SH, Kim MJ, et al. Efficacy of linezolid-based salvage therapy compared with glycopeptide-based therapy in patients with persistent methicillin-resistant *Staphylococcus aureus* bacteremia. *J Infect*. 2012;65(6):505-512.

43. Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. *Ann Intern Med*. 1992;117(5):390-398.

44. Goldberg E, Paul M, Talker O, et al. Co-trimoxazole versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* bacteraemia. *J Antimicrob Chemother*. 2010; 65(8):1779-1783.

45. Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. *Ann Intern Med*. 1991;115(9): 674-680.

46. Lemonovich TL, Haynes K, Lautenbach E, Amorosa VK. Combination therapy with an aminoglycoside for *Staphylococcus aureus* endocarditis and/or persistent bacteremia is associated with a decreased rate of recurrent bacteremia. *Infection*. 2011;39(6):549-554.

47. Dilworth TJ, Ibrahim O, Hall P, et al. β-Lactams enhance vancomycin activity against methicillin-resistant *Staphylococcus aureus* bacteremia compared to vancomycin alone. *Antimicrob Agents Chemother*. 2014;58(1):102-109.

48. Raad I, Darouiche R, Vazquez J, et al. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. *Clin Infect Dis*. 2005;40 (3):374-380.

49. Chong YP, Moon SM, Bang KM, et al. Treatment duration for uncomplicated *Staphylococcus aureus* bacteremia to prevent relapse. *Antimicrob Agents Chemother*. 2013;57(3):1150-1156.

50. Food and Drug Administration. Information for healthcare professionals: linezolid (marketed as Zyvox), 2007. http://www.fda.gov/Safety /MedWatch/SafetyInformation /SafetyAlertsforHumanMedicalProducts /ucm152993.htm. Accessed September 11, 2014.

51. Korzeniowski O, Sande MA. Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts. *Ann Intern Med*. 1982;97 (4):496-503.

52. Cosgrove SE, Vigliani GA, Fowler VG Jr, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. *Clin Infect Dis*. 2009;48(6):713-721.

53. Dworkin RJ, Lee BL, Sande MA, Chambers HF. Treatment of right-sided *Staphylococcus aureus* endocarditis in intravenous drug users with ciprofloxacin and rifampicin. *Lancet*. 1989;2(8671): 1071-1073.

54. Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users. *Am J Med*. 1996;101(1):68-76.

55. Jang HC, Kim SH, Kim KH, et al. Salvage treatment for persistent methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2009;49(3):395-401.

56. Dhand A, Bayer AS, Pogliano J, et al. Use of antistaphylococcal beta-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2011;53(2):158-163.

57. Drew RH, Perfect JR, Srinath L, et al. Treatment of methicillin-resistant *Staphylococcus aureus* infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy. *J Antimicrob Chemother*. 2000;46(5):775-784.

58. Stryjewski ME, O'Riordan WD, Lau WK, et al. Telavancin versus standard therapy for treatment of complicated skin and soft-tissue infections due to gram-positive bacteria. *Clin Infect Dis*. 2005;40(11):1601-1607.

59. Rubinstein E, Lalani T, Corey GR, et al. Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. *Clin Infect Dis*. 2011;52(1):31-40.

60. Stryjewski ME, Barriere SL, Rubinstein E, et al. Telavancin versus vancomycin for bacteraemic hospital-acquired pneumonia. *Int J Antimicrob Agents*. 2013;42(4):367-369.

61. Stryjewski ME, Lentnek A, O'Riordan W, et al. A randomized phase 2 trial of telavancin versus standard therapy in patients with uncomplicated *Staphylococcus aureus* bacteremia. *BMC Infect Dis*. 2014;14(1):289.

62. Casapao AM, Davis SL, Barr VO, et al. Large retrospective evaluation of the effectiveness and safety of ceftaroline fosamil therapy. *Antimicrob Agents Chemother*. 2014;58(5):2541-2546.

63. Gardiner D, Dukart G, Cooper A, Babinchak T. Safety and efficacy of intravenous tigecycline in subjects with secondary bacteremia. *Clin Infect Dis*. 2010;50(2):229-238.

64. Food and Drug Administration. FDA drug safety communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new boxed warning. http://www.fda.gov/drugs/drugsafety/ucm369580.htm. Accessed September 11, 2014.

65. Nolan CM, Beaty HN. *Staphylococcus aureus* bacteremia. *Am J Med*. 1976;60(4):495-500.

66. Jernigan JA, Farr BM. Short-course therapy of catheter-related *Staphylococcus aureus* bacteremia. *Ann Intern Med*. 1993;119(4):304-311.

67. Rosen AB, Fowler VG Jr, Corey GR, et al. Cost-effectiveness of transesophageal echocardiography to determine the duration of therapy for intravascular catheter-associated *Staphylococcus aureus* bacteremia. *Ann Intern Med*. 1999;130(10):810-820.

68. ClinicalTrials.gov website. Treatment algorithm to reduce the use of vancomycin in adults with blood stream infection (bacteremia). http://clinicaltrials.gov/ct2/show/NCT01191840?term=staphylococcal+bacteremia&rank=12. Accessed September 11, 2014.

69. Soriano A, Mensa J. Is transesophageal echocardiography dispensable in hospital-acquired *Staphylococcus aureus* bacteremia? *Clin Infect Dis*. 2011;53(1):10-12.

70. Khandheria BK, Seward JB, Tajik AJ. Transesophageal echocardiography. *Mayo Clin Proc*. 1994;69(9):856-863.

71. Fowler VG Jr, Sanders LL, Kong LK, et al. Infective endocarditis due to *Staphylococcus aureus*: 59 prospectively identified cases with follow-up. *Clin Infect Dis*. 1999;28(1):106-114.

72. Casella F, Rana B, Casazza G, et al. The potential impact of contemporary transthoracic echocardiography on the management of patients with native valve endocarditis. *Echocardiography*. 2009;26(8):900-906.

73. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009). *Eur Heart J*. 2009;30(19):2369-2413.

74. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections. *Clin Infect Dis*. 2012;54(6):755-771.

75. van Hal SJ, Fowler VG Jr. Is it time to replace vancomycin in the treatment of methicillin-resistant *Staphylococcus aureus* infections? *Clin Infect Dis*. 2013;56(12):1779-1788.

76. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients. *Am J Health Syst Pharm*. 2009;66(1):82-98.

77. McConeghy KW, Bleasdale SC, Rodvold KA. The empirical combination of vancomycin and a β-lactam for staphylococcal bacteremia. *Clin Infect Dis*. 2013;57(12):1760-1765.

78. Stryjewski ME, Szczech LA, Benjamin DK Jr, et al. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2007;44(2):190-196.

79. Chang FY, Peacock JE Jr, Musher DM, et al. *Staphylococcus aureus* bacteremia. *Medicine (Baltimore)*. 2003;82(5):333-339.

80. Khatib R, Saeed S, Sharma M, et al. Impact of initial antibiotic choice and delayed appropriate treatment on the outcome of *Staphylococcus aureus* bacteremia. *Eur J Clin Microbiol Infect Dis*. 2006;25(3):181-185.

81. Schweizer ML, Furuno JP, Harris AD, et al. Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible *Staphylococcus aureus* bacteremia. *BMC Infect Dis*. 2011;11:279.

82. Lodise TP Jr, McKinnon PS, Levine DP, Rybak MJ. Impact of empirical-therapy selection on outcomes of intravenous drug users with infective endocarditis caused by methicillin-susceptible *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2007;51(10):3731-3733.

83. Kim SH, Kim KH, Kim HB, et al. Outcome of vancomycin treatment in patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2008;52(1):192-197.

84. Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing. *Ann Allergy Asthma Immunol*. 2008;100(3)(suppl 3):S1-S148.

85. Dodek P, Phillips P. Questionable history of immediate-type hypersensitivity to penicillin in staphylococcal endocarditis. *Clin Infect Dis*. 1999;29(5):1251-1256.

86. Rieg S, Peyerl-Hoffmann G, de With K, et al. Mortality of *S aureus* bacteremia and infectious diseases specialist consultation—a study of 521 patients in Germany. *J Infect*. 2009;59(4):232-239.

87. Lahey T, Shah R, Gittzus J, et al. Infectious diseases consultation lowers mortality from *Staphylococcus aureus* bacteremia. *Medicine (Baltimore)*. 2009;88(5):263-267.

88. Nagao M, Iinuma Y, Saito T, et al. Close cooperation between infectious disease physicians and attending physicians can result in better management and outcome for patients with *Staphylococcus aureus* bacteraemia. *Clin Microbiol Infect*. 2010;16(12):1783-1788.

89. Honda H, Krauss MJ, Jones JC, et al. The value of infectious diseases consultation in *Staphylococcus aureus* bacteremia. *Am J Med*. 2010;123(7):631-637.

90. Choi SH, Cho SY, Park JH, Chung JW. Impact of infectious-disease specialist consultations on outcomes of *Staphylococcus aureus* bacteremia in a hospital with a low volume of patients with *S aureus* bacteremia. *J Infect*. 2011;62(2):181-185.

91. Robinson JO, Pozzi-Langhi S, Phillips M, et al. Formal infectious diseases consultation is associated with decreased mortality in *Staphylococcus aureus* bacteraemia. *Eur J Clin Microbiol Infect Dis*. 2012;31(9):2421-2428.

92. Pastagia M, Kleinman LC, Lacerda de la Cruz EG, Jenkins SG. Predicting risk for death from MRSA bacteremia. *Emerg Infect Dis*. 2012;18(7):1072-1080.

93. Isobe M, Uejima E, Seki M, et al. Methicillin-resistant *Staphylococcus aureus* bacteremia at a university hospital in Japan. *J Infect Chemother*. 2012;18(6):841-847.

94. Forsblom E, Ruotsalainen E, Ollgren J, Järvinen A. Telephone consultation cannot replace bedside infectious disease consultation in the management of *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2013;56(4):527-535.

95. Fries BL, Licitra C, Crespo A, et al. Infectious diseases consultation and the management of *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2014;58(4):598-599.

96. Tissot F, Calandra T, Prod'hom G, et al. Mandatory infectious diseases consultation for MRSA bacteremia is associated with reduced mortality. *J Infect*. 2014;69(3):226-234.

97. Jenkins TC, Price CS, Sabel AL, et al. Impact of routine infectious diseases service consultation on the evaluation, management, and outcomes of *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2008;46(7):1000-1008.

98. Pragman AA, Kuskowski MA, Abraham JM, Filice GA. Infectious disease consultation for *Staphylococcus aureus* bacteremia improves patient management and outcomes. *Infect Dis Clin Pract (Baltim Md)*. 2012;20(4):261-267.