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Clinical Management of *Staphylococcus aureus* Bacteremia

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Abstract

Importance—Several management strategies may improve outcomes in patients with *Staphylococcus aureus* bacteremia (SAB). The strength of evidence supporting these management strategies, however, varies widely.

Objective—To perform a systematic review of the evidence for two unresolved questions involving management strategies for SAB: 1) is transesophageal echocardiography (TEE) necessary in all cases of SAB; and 2) what is the optimal antibiotic therapy for methicillin resistant *Staphylococcus aureus* (MRSA) bacteremia?

Evidence acquisition—A PubMed search from inception through May 2014 was performed to find studies that addressed the role of TEE in SAB. A second search of PubMed, EMBASE, and The Cochrane Library from 1/1/1990 to 5/28/2014 was performed to find studies that addressed antibiotic treatment of MRSA bacteremia. Studies that reported outcomes of systemic antibiotic therapy for MRSA bacteremia were included. All searches were augmented by review of bibliographic references from included studies. The quality of evidence was assessed using the GRADE system by consensus of independent evaluations by at least two authors.

Results—In 9 studies with a total of 3513 patients, use of TEE was associated with higher rates of diagnosis of endocarditis (14–25%) when compared with TTE (2–14%). Five studies proposed criteria to identify patients in whom TEE might safely be avoided. Only one high-quality trial of antibiotic therapy for MRSA bacteremia was identified from the 83 studies considered.

Conclusions and relevance—Most contemporary management strategies for SAB are based upon low quality evidence. TEE is indicated in most patients with SAB. It may be possible to identify a subset of SAB patients for whom TEE can be safely avoided. Vancomycin and

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daptomycin are the first-line antibiotic choices for MRSA bacteremia. Well-designed studies to address the management of SAB are desperately needed.

Introduction

Case fatality rates for *Staphylococcus aureus* bacteremia (SAB) have improved only modestly in recent decades. The emergence of methicillin resistance in *S. aureus* complicates therapy and is an independent risk factor for mortality in SAB.[1,2] Several management strategies for SAB are accepted as standard of care,[3–5] including a) performing a thorough history and physical examination; b) obtaining follow-up blood cultures to document resolution of bacteremia; and c) draining abscesses and removing infected prosthetic material.

Other SAB management strategies are unresolved. Despite almost 20 years of deliberation and at least three major treatment guidelines,[3–5] the ideal role of transesophageal echocardiography (TEE) in the management of SAB remains unresolved. The optimal antibiotic therapy of MRSA bacteremia is also unresolved, particularly for infections due to MRSA isolates with high, but still susceptible minimum inhibitory concentrations to vancomycin.[6] Thus, this manuscript systematically reviews the evidence informing two key questions:

1. Do all patients with SAB require transesophageal echocardiography (TEE)?
2. What is the optimal antibiotic therapy for MRSA bacteremia?

Methods

Do all patients with SAB require transesophageal echocardiography (TEE)?

To evaluate the evidence surrounding this question, PubMed was queried from inception to May 2014 for the following terms: *Staphylococcus aureus* or *MRSA*, *echocardiography*, and *bacteremia*. Queries were limited to English language studies that involved adults only. References of included studies were also searched. The abstracts of studies being considered for inclusion were reviewed independently by two authors (TH, CA). To be included, studies had to specifically address the role of TEE in SAB. Reviews, editorials, case reports, studies reporting data that were included in part within previous publications, and studies not reporting echocardiography results by organism were excluded. Those remaining were selected for full text review.

What is the optimal antibiotic therapy for MRSA bacteremia?

To evaluate the final question, searches were performed on PubMed, EMBASE, and The Cochrane Library from January 1990 to May 2014 for the following terms: *Staphylococcus aureus* or *MRSA; bacteremia* or *bloodstream infection; antibiotic* or *antimicrobial; vancomycin, daptomycin, linezolid, teicoplanin, trimethoprim-sulfamethoxazole (TMP/SMX), clindamycin, quinupristin-dalfopristin, tigecycline, ceftaroline, telavancin, dalbavancin, oritavancin,* or *tedizolid*. In addition, www.ClinicalTrials.gov was queried for *bacteremia* and *methicillin-resistant Staphylococcus aureus* or *MRSA*. Search results were limited to English-language studies in adults. Finally, the references of included studies

were also reviewed. Studies that reported outcomes of systemic antibiotic therapy for MRSA bacteremia were included for review. Case reports involving fewer than 5 patients with MRSA bacteremia, review articles, editorials, guidelines, and studies reporting duplicate data or subgroup analyses of earlier published studies were excluded.

Grading and review of studies

The level of evidence of reviewed studies was assigned a score of *high*, *moderate*, *low*, or *very low* based upon the GRADE system.[7] Studies were graded by consensus of independent reviews by two authors (TH, CA). Studies for which the two original scores disagreed underwent a resolution review by a third author (VGF). For the antibiotic therapy question, studies in which only a subset of included patients had MRSA bacteremia were graded upon the quality of evidence for MRSA bacteremia specifically.

Results of Evidence Review

Do all patients with SAB require transesophageal echocardiography (TEE)?

Of the 79 publications identified by search definitions, 14 met inclusion criteria. Five were subsequently excluded based on the full-text review (Figure 1), yielding 9 studies that underwent quality assessment review. The independent quality assessments agreed in all 9 cases. All studies were observational (Table 1). Sample sizes of included studies ranged from 98 to 877 patients. TEE was performed in 12–63% of these patients. Endocarditis was defined in all studies via either the original[8] or modified[9] Duke criteria. Among the 4 studies[10–13] that evaluated endocarditis rates by both transthoracic (TTE) and TEE, detection of infective endocarditis (IE) was higher with TEE (14–25%) than with TTE (2–14%).

Two studies[10,11] reported that clinical findings and TTE results were poorly predictive of subsequent TEE findings. In Fowler et al, TEE detected endocarditis in 19% of patients with a negative TTE.[10] Among 230 Australian patients with SAB, 144 of whom underwent TEE, 46% of IE cases were not suspected on clinical grounds, and 15% of patients without clinical evidence of IE were reclassified by TEE.[14] Most recently, 13 of 98 SAB patients (16%) were found to have IE in a “mandatory TEE” approach.[15]

Five studies[12,13,16–18] to date have proposed that TEE might safely be avoided in SAB patients without any of several specific IE risk factors. Identified low risk factors include: a) absence of a permanent intracardiac device (e.g. prosthetic valve, pacemaker, cardioverter defibrillator),[12,13,16–18] short duration of bacteremia, [13,16] no hemodialysis dependence,[16] nosocomial acquisition of infection,[17] absence of secondary foci of infection,[13,16] and no evidence of embolic or immunologic phenomena. [12,17]

Recommendation—Obtain an echocardiogram for all patients with SAB. TEE is preferred for most patients. TTE may be adequate for patients without identified risk factors for IE. (***weak recommendation based on low quality evidence***).

What is the optimal antibiotic therapy for MRSA bacteremia?

Of the 1876 publications identified by search definitions, 105 met inclusion criteria. Of these, 24 were subsequently excluded based on the full-text review (Figure 2), yielding 81 studies that underwent quality assessment review. The sample size of included studies ranged from 6 to 337. The independent quality assessments agreed in 68 of 81 cases (84%). All 13 discrepancies in assessment varied by one level of evidence, and 11 of the 13 differed between scores of *very low* and *low*. These 13 studies underwent resolution review to determine their final evidence grade.

Overall, data quality was poor. Only one met GRADE criteria for *high* quality evidence.[19] Three were categorized as *moderate*,[20–22] 22 as *low*,[23–44] 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 SAB, and recurrence.

Evidence for Vancomycin—Vancomycin was the comparator in most MRSA bacteremia antibiotic studies. In the sole high quality randomized control trial, vancomycin was part of standard therapy compared to daptomycin for patients with SAB with or without endocarditis.[19] In that open-label clinical trial, for which the primary outcome was treatment success in the modified intention-to-treat population 42 days after completion of therapy, daptomycin was non-inferior (44.2% [53/120] vs 41.7% [48/115], absolute difference 2.4%, 95% CI −10.2 to 15.1%) to low-dose, short course gentamicin plus either an antistaphylcoccal penicillin (for MSSA bacteremia) or vancomycin (for MRSA bacteremia or penicillin-allergic patients). Vancomycin was also compared in open-label randomized trials to teicoplanin,[31] TMP/SMX,[21] linezolid,[34,36] and dalbavancin.[22] None of these antibiotics performed significantly better than vancomycin.

Evidence for Daptomycin—As noted above, daptomycin at a dose of 6mg/kg/day was not inferior to standard therapy for SAB and right-sided endocarditis.[19] In the pre-defined subgroup of patients with MRSA bacteremia, the success rate was 20/45 (44.4%) among daptomycin recipients vs. 14/44 (31.8%) in patients who were randomized to receive standard therapy; this difference was not statistically significant (absolute difference 12.6%, 95% CI −7.4% to 32.6%, p=0.28). This study led to FDA approval of daptomycin for SAB and right-sided endocarditis. Presently, vancomycin and daptomycin are the only two agents approved for MRSA bacteremia.

Subsequent investigators have employed cohort [28,30] or case-control [27,29,42] studies to test the hypothesis that daptomycin, either at [28] or above [29,30] the FDA-approved dose of 6mg/kg daily, was associated with better clinical outcomes than vancomycin in patients with bacteremia due to MRSA with high vancomycin minimum inhibitory concentrations (MIC) values. In infections caused by MRSA with vancomycin MIC >1mg/dl, outcomes generally appeared better with daptomycin. In a prospective cohort study of patients with left-sided endocarditis, use of high-dose daptomycin (mean dose 9.2mg/kg/day) was not significantly associated with in-hospital mortality when compared to standard of care (daptomycin: 1/7 [14.3%] vs. standard of care: 8/18 [44.4%], p=0.35).[30] Among a retrospective cohort of 250

patients with complicated Gram-positive infections, 126 of which were MRSA bacteremia, daptomycin at a mean dose of 8.9mg/kg/day was associated with a very low adverse event rate.[43] Generalizability of these results was limited by suboptimal trial design and non-random receipt of antibiotics and Infectious Diseases consultation.

Evidence for Linezolid—Observations from a compassionate-use program suggested that linezolid might have utility for bacteremia.[33] Shorr et al compiled data on patients with bacteremia from five earlier randomized trials comparing linezolid to vancomycin. Of 3228 enrolled patients in the original studies, 53 had MRSA bacteremia and were evaluable. Among these 53 patients, rates of clinical cure were not significantly different (14/25 [56%]) linezolid recipients vs.13/28 (46%) vancomycin recipients; OR 1.47, 95% CI 0.50–4.34).[34] Linezolid was also compared to vancomycin in an open-label phase 3 non-inferiority study involving patients with suspected catheter-related bacteremia.[36] Linezolid was non-inferior among patients with Gram-positive infections. However, patients in the linezolid group had a higher chance of death than did those in the comparator group. This led to an FDA "black box" warning advising against the empiric use of linezolid in catheter-related bacteremia, if Gram-negative infection is known or suspected.[45] Linezolid was evaluated as a salvage agent for MRSA bacteremia persisting ≥7 days despite glycopeptide (e.g. vancomycin or teicoplanin) therapy. Outcomes including microbiologic response, treatment success, and mortality were not significantly different among those switched to linezolid versus those continued on glycopeptide therapy.[37]

Evidence for TMP/SMX—TMP/SMX was compared to vancomycin in a randomized trial of intravenous drug users with suspected SAB.[21] Of 228 enrolled patients, 65 had SAB, of which 38 were due to MRSA. Overall, vancomycin was superior to TMP/SMX (98% vs. 86% cure rate; p=0.014). All failures in both groups were in patients with MSSA. More recently, 38 retrospectively-identified patients treated with TMP/SMX for MRSA bacteremia were compared to 76 matched controls who received vancomycin for the same diagnosis. Thirty-day mortality, relapse or persistent bacteremia, and rates of renal failure were not significantly different between groups.[38]

Evidence for Combination therapy—Results of combination therapy for MRSA bacteremia have been largely disappointing. In a small randomized trial, addition of rifampin to vancomycin for treatment of MRSA IE was not associated with improved duration of bacteremia or rates of treatment failure, as compared to patients randomized to vancomycin alone.[20] In a classic randomized trial of patients with MSSA IE, addition of gentamicin to nafcillin did not alter morbidity or mortality.[46] This concept was revisited in a retrospective evaluation of 87 patients with persistent SAB or IE, 48 of whom had MRSA infection. Those treated with an aminoglycoside had lower incidence of recurrence within 6 months, though there was no significant association with other outcomes.[39] In an analysis of the safety data from the Fowler et al daptomycin trial, [19] Cosgrove et al noted that 27/122 (22%) of patients who received initial low-dose gentamicin therapy experienced a clinically significant decrease in renal function, compared to 8/100 (8%) of those who did not receive gentamicin.[47] There are case reports of the successful use of fluoroquinolone/rifampin combination therapy for right-sided MRSA IE.[48,49] Last, there have been small case series

of successful treatment of MRSA bacteremia with the addition of β-lactam antibiotics to linezolid[37,50] and daptomycin.[51]

Evidence for other antibiotics—Several other antibiotics have either preliminary or limited data in treatment of MRSA bacteremia. Moderate quality data from a single randomized trial suggested that dalbavancin is a potential alternative to vancomycin for catheter-related Gram-positive bacteremia. However, only 14 patients in the trial had MRSA bacteremia. [22]

Very low quality data from an emergency-use program suggested that quinupristin-dalfopristin could be a treatment option for MRSA infections, including bacteremia.[52] Use of this antibiotic, however, has been limited by its unfavorable adverse event profile.

Telavancin is a lipoglycopeptide antibiotic approved for MRSA soft tissue infection [53] and hospital acquired pneumonia.[54] In subgroup analysis of the 73 patients with bacteremic pneumonia, 33 of whom had MRSA bacteremia, telavancin therapy, when compared to vancomycin, was not associated with a difference in cure rate.[55] Additionally, telavancin was compared to standard therapy for the treatment of uncomplicated SAB in a small "proof-of-concept" randomized trial. All 9 clinically evaluable patients with MRSA, of whom 5 received telavancin, were cured.[56]

In a retrospective evaluation of patients treated with ceftaroline, clinical success was reported in 101/129 (78.3%) of patients with SAB (of which 92.5% had MRSA).[57]

Pooled results of patients with secondary bacteremia from 8 trials with tigecycline have been reported; however, only 10 patients had MRSA bacteremia.[58] A subsequent analysis by the FDA of patients in 10 trials demonstrated increased risk of death with tigecycline.[59] This led to an FDA "black box" warning recommending that tigecycline be reserved only for situations in which alternative treatments are not suitable.

Evidence for duration of therapy—In addition to selecting an antibiotic to treat MRSA bacteremia, clinicians must also decide how long to treat. Historically, SAB was treated with 4–6 weeks of intravenous antibiotics.[60] Over the past 3 decades, clinicians have repeatedly tried to identify a subgroup of patient with SAB who could safely be treated with shorter durations of therapy. A prerequisite for short course therapy is the ability to prospectively differentiate patients with uncomplicated SAB, who might be cured with a short treatment course, from complicated SAB, for whom longer treatment is necessary. MRSA treatment guidelines define uncomplicated SAB as infection in which: a) endocarditis has been excluded; b) no implanted prostheses are present; c) follow-up blood cultures drawn 2–4 days after the initial set are sterile; d) the patient defervesces within 72 hours of initiation of effective antibiotic therapy; and e) no evidence of metastatic infection is present on exam.[3] Generally, only a minority of all cases of MRSA bacteremia meet these guideline-based criteria for uncomplicated infection. In these cases, the recommended treatment duration is at least ≤14 days of intravenous (IV) antibiotics from time of first negative blood culture. There is limited evidence supporting this recommendation. One prospective cohort study reported unacceptably high relapse rates in patients meeting the guideline definition of

uncomplicated bacteremia who were treated for less than 2 weeks.[41] A 1993 meta-analysis of older studies evaluated the effectiveness of 14 days of antibiotic therapy for intravascular catheter-associated SAB.[61] This study estimated a 6.1% late complication rate (such as relapse and metastatic infections) for short-course therapy, albeit with low statistical precision, and concluded that until a means exists to identify patients who may safely receive short course therapy, more than 2 weeks of IV antibiotics should be administered. In an attempt to provide a means of identifying patients with catheter-associated SAB who might safely receive 14 days of IV therapy, Rosen et al used outcomes data from a prospective cohort of patients with uncomplicated SAB to show that a TEE-guided approach to identify patients in whom short courses of antibiotics are adequate was cost-effective.[62] A multicenter randomized trial of treatment duration in staphylococcal bacteremia is currently recruiting participants.[63]

Recommendation: Use vancomycin or daptomycin as first-line therapy for MRSA bacteremia. Treat for at least 14 days from the first negative blood culture. (**weak recommendation based on low quality evidence**).

Discussion

Do all patients with SAB require transesophageal echocardiography (TEE)?

S. aureus IE is common, often clinically indistinguishable from SAB, and lethal if inadequately treated.[64,65] Thus, it is important to consider the possibility of underlying IE, which will impact management and prognosis, in all patients found to have *S. aureus* in their blood. TEE is significantly better than either TTE or physical examination in identifying findings of IE in patients with SAB. For example, three prospective cohort studies evaluating TEE in patients with SAB conducted on different continents all identified IE in ~ one-quarter of patients.[10,14,17] While this prevalence is almost certainly enriched by a heightened clinical suspicion for IE in patients whose clinicians refer them for TEE, [66] it is clear that TEE will diagnose IE in a subset of SAB patients with a non-diagnostic TTE.

Several points argue against a universal recommendation for TEE in all cases of SAB. First, TEE has associated cost and risks. Major complications such as esophageal perforation occur in approximately 1 in 5000 TEEs performed.[67] Second, there is virtually no evidence to suggest that the improved detection of small valvular vegetations or oscillating targets by TEE actually improves clinical outcome in patients with SAB. Although one small, single center study reported that patients with smaller vegetations discovered by TEE only (after negative TTE) were less likely than those with positive TTE to suffer an embolic event or die of their infection, [68] this finding was not externally validated.[65] Third, several studies now suggest that it is possible to identify a subset of patients with SAB at low risk of IE in whom TEE is not essential. [12,13,16–18] This low-risk subset could be conservatively defined as patients meeting all of the following criteria: a) a negative TTE,[12,18] b) nosocomial acquisition of bacteremia,[17,18] c) sterile follow-up blood cultures,[13,16] d) absence of permanent intracardiac device,[12,13,16–18] e) absence of hemodialysis dependence,[16] and f) no clinical signs of endocarditis or secondary foci of infection.[12,13,16,17] Alternatively, patients whose SAB has resolved and who are already scheduled to receive extended courses

of antibiotics for other forms of complicated *S. aureus* infection may not always require TEE. Fourth, imaging technology in echocardiography is not static. Indeed, improvements in TTE image quality have already narrowed the diagnostic gap between the two modalities, especially for the evaluation of native valves.[69] Collectively, these results suggest that all patients with SAB should undergo echocardiography.[3,70] Although TEE is preferred when feasible, there may be identifiable low-risk patients in whom TEE is not required. A trial comparing a strategy of universal versus targeted TEE, with attention to clinical outcomes, would be a pivotal contribution to the literature.

What is the 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 rising MIC to vancomycin.[6] These concerns were underscored by the observation that patients with MRSA bacteremia due to isolates with higher (but still susceptible) vancomycin MIC had significantly higher all-cause mortality than those infected with lower vancomycin MIC isolates.[71] The cause of this association is unknown, and the subject has been recently reviewed.[72] One response to the perceived threat of rising vancomycin MICs in clinical MRSA isolates is to target higher vancomycin trough levels of 15–20mg/L for serious infections, an approach that was recommended in consensus guidelines.[73] The relationship of these higher vancomycin trough levels to the outcome of patients with MRSA bacteremia, however, is also unresolved.[72]

Daptomycin is FDA-approved for SAB and right-sided IE based upon a pivotal randomized trial. [19] Observational data from patients with MRSA bacteremia due to high-vancomycin MIC isolates suggest the possibility that daptomycin might be preferred in this setting.[28,29,42] Randomized trials are required to confirm this possibility. Increasingly, clinicians employ daptomycin at doses exceeding the FDA-approved dose of 6mg/kg IV once daily for MRSA bacteremia;[43] the quality of evidence for this practice is low.

Teicoplanin represents another potential alternative to vancomycin but is unavailable in the US.[31,32] The addition of gentamicin and/or rifampin to vancomycin for the treatment of MRSA bacteremia and native valve endocarditis appears to offer no meaningful benefit and to confer significant risk for harm. Addition of a β-lactam antibiotic to vancomycin or daptomycin for the treatment of MRSA bacteremia is interesting but unproven. Options for salvage therapy, based on low-quality data, include linezolid, TMP/SMX, dalbavancin, ceftaroline, quinupristin/dalfopristin, and telavancin. Tigecycline should be avoided. No data in MRSA bacteremia are yet available for other recently approved (e.g., tedizolid) or late-stage investigational compounds (e.g., oritavancin, ceftobiprole).

All cases of MRSA bacteremia should be treated with IV antibiotics for a minimum of 14 days from the time of blood culture clearance. For those patients not meeting the stringent definition of uncomplicated bacteremia, 4–6 weeks of therapy is recommended. Readers are additionally directed to current guidelines for more detailed discussion of treatment issues.[3–5]

Evidence for other Components of SAB management

The use of anti-staphylococcal β-lactam antibiotics whenever possible to treat methicillin-susceptible *S. aureus* (MSSA) infections is widely accepted as standard of care. The level of evidence for this practice is poor, consisting of several observational studies suggesting higher treatment failure rates in MSSA-infected patients treated with vancomycin.[74–80] For example, one prospective cohort of 298 patients with MSSA bacteremia reported that the rate of microbiologic failure was lower (0/18 [0%] vs. 13/70 [19%], OR 6.5, 95% CI 1.0–53) among patients with MSSA bacteremia who were treated with nafcillin instead of vancomycin.[76] Several other prospective[75] and retrospective[78–80] cohort studies documented lower overall[78] and infection-related[79,80] mortality rates among MSSA-infected patients who were treated with β-lactam antibiotics. The importance of using β-lactam antibiotics when possible is a crucial message, as patients often receive vancomycin or other alternative antibiotics due to a reported penicillin allergy. However, most patients with a self-reported penicillin allergy do not have a true allergy by skin testing and would tolerate β-lactam therapy.[81] While clinical data is scarce, skin testing appeared cost-effective in a decision analysis for treatment of MSSA IE, even assuming equal efficacy of vancomycin and β-lactam therapy.[82]

At least 15 studies have now evaluated the role of Infectious Diseases consultation (IDC) for SAB (Table 3). All found clinical benefit; 11 reported improved mortality among patients who received IDC.[83–93] IDC was also associated with increased adherence to standards of care, including selection of a β-lactam for MSSA infections,[84–88,94,95] longer duration of therapy for complicated infection,[83–88,92,94,95] removal of intravenous catheters,[84,94] obtaining follow-up blood cultures to assess for clearance of bacteremia,[84,85,87,88,92–94] obtaining echocardiography,[83,85,86,88,93,96] draining abscesses,[84] and removing infected prosthetic material. [84,95] Thus, while the evidence for routine IDC in patients with SAB is limited to observational studies, it supports the conclusion that IDC should be considered for every case of SAB at institutions where such expertise is available.

Conclusion

The evidence for most management strategies in SAB is poor. The overall evidence guiding the use of TEE in patients with SAB is weak. It may be possible to prospectively identify a low-risk group of patients for whom TTE is adequate. Vancomycin and daptomycin remain the first-line therapies for MRSA bacteremia. Treatment should extend for at least 14 days from the first negative blood culture, and it should be longer in those with complicated disease. High quality trials comparing treatment strategies, antibiotics, and treatment durations are needed to optimize the management of this common, serious infection.

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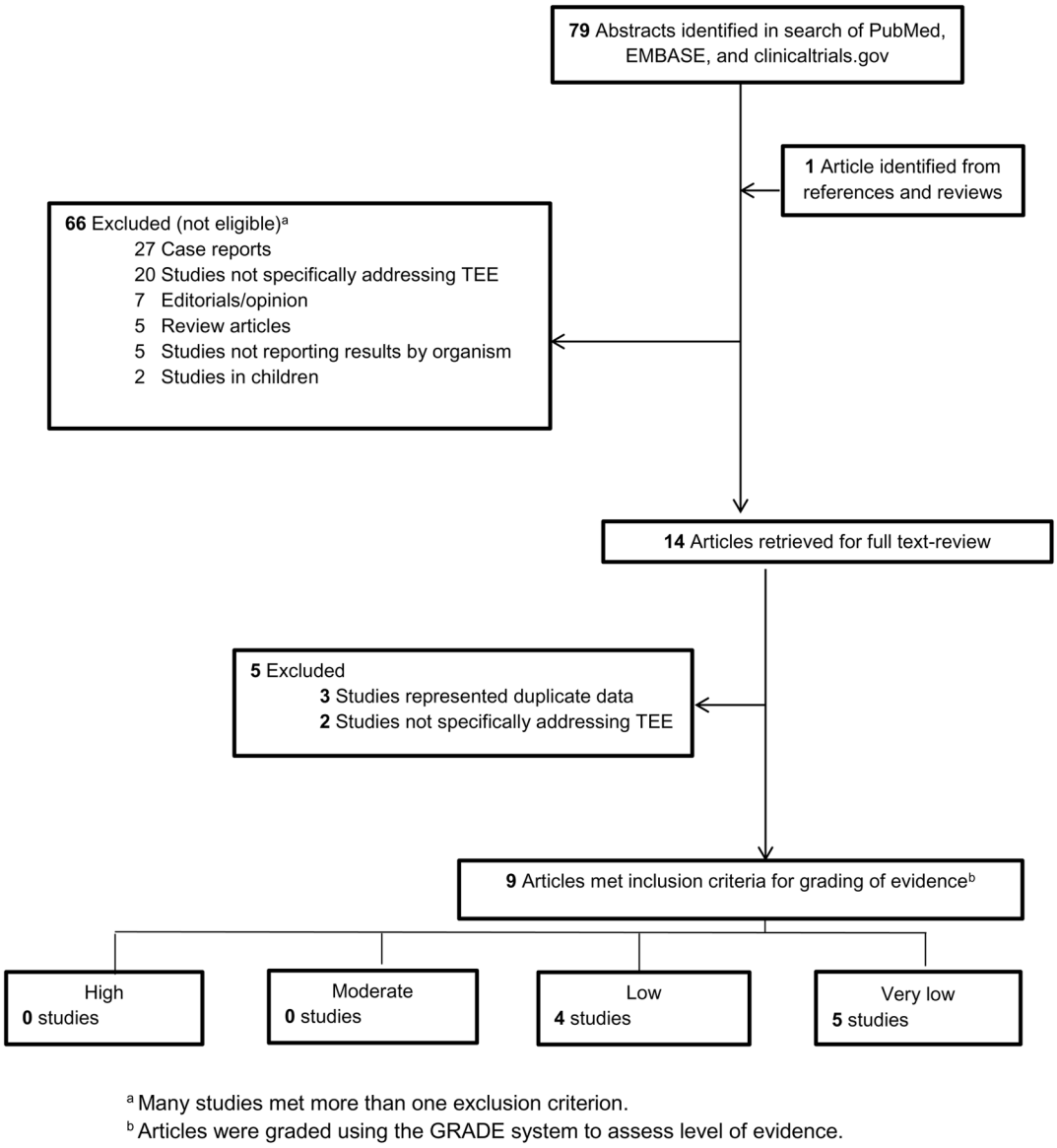
Key Take-Home Messages

All patients with *S. aureus* bacteremia should be evaluated with echocardiography. Transesophageal echocardiography is preferred, but it may be possible to identify a low-risk group of patients for whom transthoracic echocardiography is adequate. This low-risk group could include all of the following: a) nosocomial acquisition of bacteremia; b) sterile follow-up blood cultures; c) no permanent intracardiac device; d) no hemodialysis dependence; and e) no clinical signs of endocarditis or secondary foci of infection.

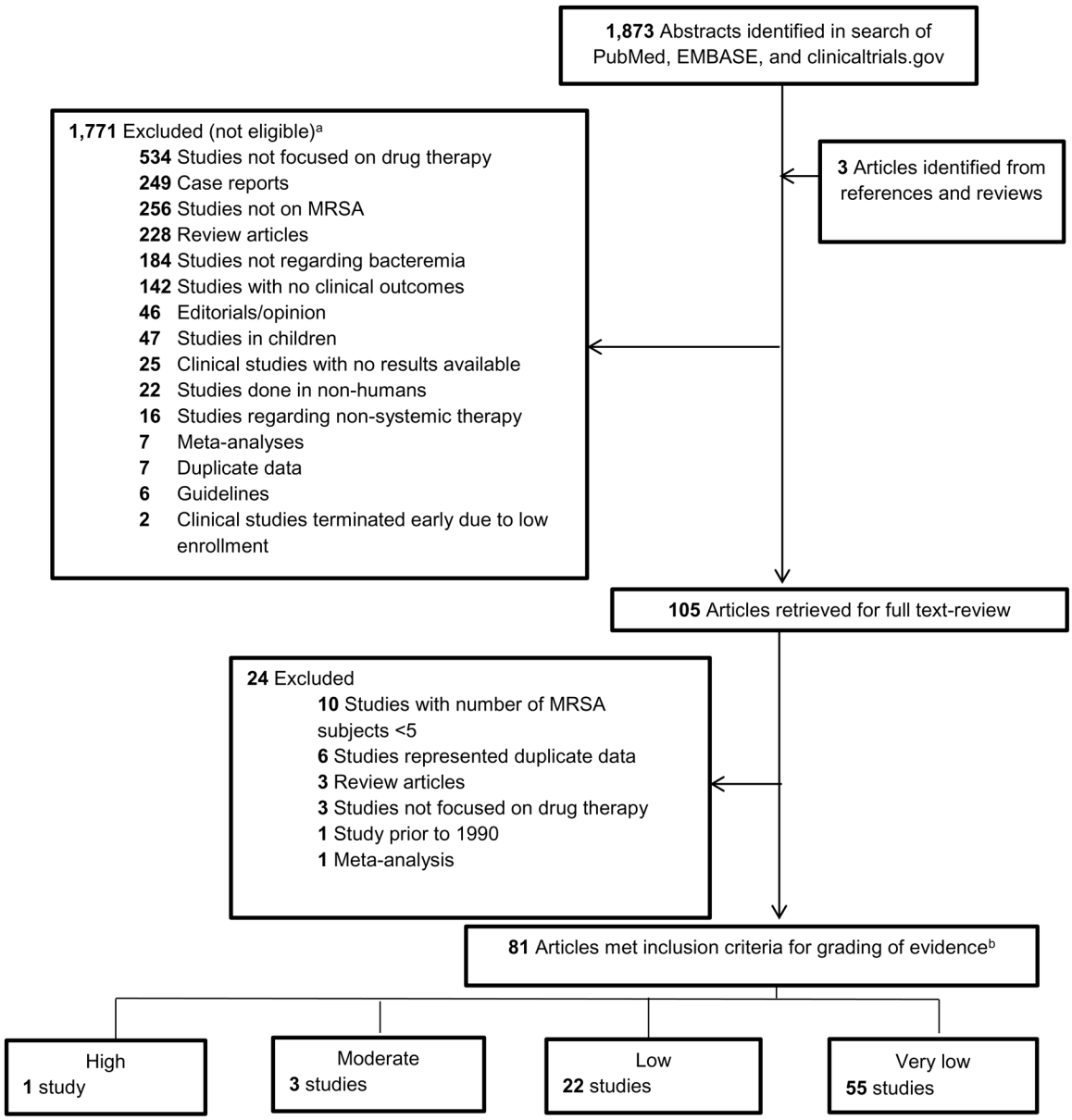
Vancomycin and daptomycin are first-line antibiotic options for MRSA bacteremia.

For patients meeting a stringent definition of uncomplicated MRSA bacteremia, at least 14 days of antibiotic therapy from the first negative culture may be adequate. For all others, a longer course (e.g. 4–6 weeks) is recommended.



[a] Many studies met more than one exclusion criterion.
[b] Articles were graded using the GRADE system to assess level of evidence.

Figure 1.
Identification of Manuscripts for Systematic Review of the Role of Transesophageal Echocardiogram for Patients with *S. aureus* Bacteremia.



[a] Many studies met more than one exclusion criterion.

[b] Articles were graded using the GRADE system to assess level of evidence.

Figure 2.

Identification of Manuscripts for Systematic Review of Antibiotic Therapy for Patients with MRSA Bacteremia.

Table 1

Role of Transesophageal Echocardiography in *S. aureus* Bacteremia

Author, year	GRADE category	Study Design	Study population	Total # SAB cases	# IE cases	# with TEE (%)	IE # and rate by TTE	IE # and rate by TEE	Key Outcomes	Risk stratification
Studies which suggest that TEE should be required for all SAB cases										
Fowler, 1997[10]	Low	Prospective cohort	Adults with SAB (age 56 ± 15) who underwent both TTE and TEE PV=5, CD=4	176	26	103 (58%)	7 (7%)	26 (25%)	TEE(+) in 19 (19%) of TTE(−)patients	Clinical findings and TTE results did not predict TEE results
Sullenberger, 2005[11]	Very low	Retrospective cohort	Adults with SAB (age 56.5 ± 19.1) who underwent TEE PV=1, CD=0	176	11	64 (36%)	1 (2%)	9 (14%)	0/9 TEE (+)patients had (+)TTE 1 TTE(+)/ TEE(−)patient	Clinical findings and TTE results did not predict TEE results
Incani, 2013[14]	Low	Prospective cohort	Adults with SAB (age 68, IQR 53–76) who underwent TEE PV=9, CD=7	230	41	144 (63%)	N/A	41 (29%)	19 (46%) IE cases not suspected clinically	Clinical findings did not predict TEE results
Holden, 2014[15]	Very low	Prospective cohort	Adults with SAB (age 62 [19–100]) PV=0, CD=4	98	13	58 (59%)	3 (14%)	9 (16%)	6/13 (46%) IE cases had no risk factors	Clinical findings did not predict TEE findings
Studies which suggest that TEE may be unnecessary in some SAB cases										
Van Hal, 2005[12]	Very low	Retrospective cohort	Adults without cardiac prostheses with SAB (age: non-IE 61.4 [22–92], IE 56.3 [28–84]) who underwent both TTE and TEE PV=0, CD=0	808	22	125 (15%)	18 (14%)	20 (16%)	2 IE cases had both (−)TTE and (−)TEE 2/125 patients had (−)TTE, (+)TEE	Proposed low-risk group: • no permanent intracardiac device (a study exclusion criterion) • no embolic phenomena • ≤ trivial left sided regurgitation on TTE in the absence of stenosis

Author, year	GRADE category	Study Design	Study population	Total # SAB cases	# IE cases	# with TEE (%)	IE # and rate by TTE	IE # and rate by TEE	Key Outcomes	Risk stratification
Kaasch, 2011[16]	Low	Prospective cohorts (2 separate cohorts)	Hospitalized patients (age: INSTINCT cohort 67 [21–91], SABG cohort 65 [15–95]) with nosocomial SAB PV=43, CD=92	736	53	175 (24%)	N/A	N/A	Low-risk criteria patients: only 1/208 had IE 52/53 patients with IE fulfilled at least one “high risk criteria”	Proposed low-risk group: • no permanent intracardiac device • no prolonged bacteremia (>4d) • no hemodialysis dependency • no spinal infection • no non-vertebral osteomyelitis
Rasmussen, 2011[17]	Low	Prospective cohort	Adults with SAB (age: IE 65 ± 16, non-IE 64 ± 16) who underwent echocardiography PV=20, CD=14	244	53	152 (62%)	N/A	N/A	47 (87%) IE cases: predicted by “high risk” criteria 6 IE cases missed by “high-risk” criteria: 4: (+)TTE/ (+)TEE 2: (−)TTE/ (+)TEE	Proposed low-risk group: • no permanent intracardiac device • no previous IE • no known heart valve disease • no heart murmur • no embolic events • no vascular or immunologic phenomena suggesting IE • known SAB source

Author, year	GRADE category	Study Design	Study population	Total # SAB cases	# IE cases	# with TEE (%)	IE # and rate by TTE	IE # and rate by TEE	Key Outcomes	Risk stratification
										• infection is not community-acquired • no intravenous drug use
Joseph, 2013[18]	Very low	Retrospective cohort	Hospitalized patients (age: IE 50.7 ± 3.6, non-IE 61.1 ± 1.1) with SAB PV=20, CD=14	668	31	82 (12%)	N/A	N/A	Highest rate IE in: • prosthetic valve: 10/31 (32%) vs 10/274 (4%) • cardiac device: 5/31 (16%) vs 9/275 (3%) No IE in "low-risk group"	Proposed low-risk group: • no permanent intracardiac device • line-related bacteremia • ≤ mild valvular regurgitation on TTE
Khatib, 2013[13]	Very low	Retrospective cohort	Adults (age N/A) with SAB CD=104[a]	877	64	177 (20%)	25 (8%)	42 (24%)	"Low-risk" group: only 1 patient with (+) TEE	Proposed low-risk group: • no permanent intracardiac device • bacteremia duration <3 days • current bacteremia episode not a relapse from a prior episode within past 100 days

Author, year	GRADE category	Study Design	Study population	Total # SAB cases	# IE cases	# with TEE (%)	IE # and rate by TTE	IE # and rate by TEE	Key Outcomes	Risk stratification
										• no secondary foci of infection

Abbreviations: SAB, *Staphylococcus aureus* bacteremia; IE, infective endocarditis; TTE, transthoracic echocardiogram; TEE; transesophageal echocardiogram; IQR, interquartile range; PV, prosthetic valve; CD, cardiac device

[a] Included prosthetic valves, pacemakers, defibrillators

Table 2

Studies of Antibiotic Therapy in MRSA Bacteremia.

Author, year	GRADE category	Population	Study design	Number of patients	Treatment	Primary Endpoints	Results
VANCOMYCIN DOSING STUDIES							
Kullar, 2011[23]	Low	Adults with MRSAB (age: vancomycin success 53 [45–64]; vancomycin failure 54 [46–61]) who received vancomycin >3 days as initial therapy	Retrospective cohort	320	Vancomycin, (attention to dosing regimens)	Treatment failure (30-day mortality, persistent infection or bacteremia ≥7 days)	168/320 (52.5%) failure rate Independent predictors of failure: Vancomycin trough <15mg/L and MIC>1
Moore, 2011[24]	Low	Adults with MRSAB (age 57 ± 17) treated with vancomycin	Retrospective cohort	200	Vancomycin	Predictors of clinical failure (30-day mortality, persistent bacteremia ≥7 days while on therapy, bacteremia recurrence within 30 days)	Predictors of failure: • Severity of illness at onset • vancomycin MIC • bacteremia source • MRSA strain type
Hall, 2012[25]	Low	Adults with MRSAB (age: survivors 53 [42–63]; non-survivors 65 [56–77])	Retrospective cohort	337	Vancomycin, (dosing of ≥15mg/kg vs <15mg/kg)	In-hospital mortality	Dosing not significantly associated with mortality
Forstner, 2013[26]	Low	Adults with MRSAB (age 64.5 [18–96])	Retrospective cohort	124	Vancomycin (N=63), teicoplanin (N=28), linezolid (N=7), tigecycline (N=2), other (N=24)	28-day mortality, persistent bacteremia ≥7 days, treatment failure	Vancomycin trough levels 15–20mg/L associated with lower odds of persistent bacteremia and treatment failure
DAPTOMYCIN							
Fowler, 2006[19]	High	Adults with SAB (age: daptomycin 50.5 [21–87]; standard therapy 55 [25–91])	Open-label RCT	246	Daptomycin 6mg/kg/day vs. initial low-dose gentamicin plus either an anti-staphylococcal penicillin or vancomycin	Treatment success 42 days after the end of therapy	Daptomycin non-inferior to vancomycin for SAB and right-sided endocarditis
Kullar, 2011[43]	Low	Adults with complicated Gram-positive infections (age 55 [45–65]) who received high-dose daptomycin	Retrospective cohort	250 (126 MRSAB)	Daptomycin, (median dose 8.9mg/kg/day)	Clinical response (cure, improvement, or failure) Adverse events	Cure rate for bacteremic patients was 175/218 (80.3%) 3/250 (1.2%) experienced adverse event attributed to high dose daptomycin
Moore, 2012[42]	Low	Adults with MRSAB (age: vancomycin 52 ± 14; daptomycin 51 ± 14) and vancomycin MIC 1.5 or 2	Retrospective case-control	177	Daptomycin (N=59) vs. vancomycin (N=118)	Clinical failure (composite of 60-day mortality, persistent bacteremia ≥7 days, or recurrence within 30 days)	Non-significant trend toward lower failure rate with daptomycin (10/59 [17%] vs. 37/118 [31%], p=0.084)
Falcone, 2012[27]	Low	All staphylococcal invasive infections (age: daptomycin 67.2; vancomycin 66.7)	Retrospective case-control	106 (57 bacteremia, 35 MRSAB)	Daptomycin (N=23), glycopeptide (N=34)	Duration of antibiotic therapy, length of stay, attributable mortality	• No significant difference in mortality or length of hospital stay • Duration of therapy shorter with daptomycin

Author, year	GRADE category	Population	Study design	Number of patients	Treatment	Primary Endpoints	Results
Murray, 2013[28]	Low	Adults with MRSAB and vancomycin MIC>1 (age: daptomycin 57 [51–65]; vancomycin 56 [51–64])	Retrospective matched cohort	170	Daptomycin or vancomycin	Clinical failure (composite of all-cause 30-day mortality or persistent bacteremia ≥7 days)	Higher risk of failure with vancomycin (OR 4.5, 95% CI 2.1–9.8)
Cheng, 2013[29]	Low	Adults with MRSAB (age N/A) and vancomycin MIC≥1.5	Retrospective case-control	78	Daptomycin 8–10mg/kg or vancomycin	14-day and 30-day clinical outcome (cure or improvement vs failure or death)	Daptomycin associated with favorable outcome (OR 0.27, 95% CI 0.084–0.857)
Carugati, 2013[30]	Low	Adults with Gram-positive left-sided endocarditis (age: daptomycin 62.5 [54–72.5]; standard therapy 60.5 [44–73])	Prospective cohort	178 (86 SAB, 25 MRSAB)	Daptomycin (N=29) vs. standard of care (N=149)	In-hospital mortality	Daptomycin (mean dose 9.2mg/kg/day) not associated with mortality (RR 0.8, 95% CI 0.4–1.3, p=0.35)
Weston, 2014	Low	Adults with MRSAB (mean age 61)	Retrospective matched cohort	150	Daptomycin (N=50) vs. vancomycin (N=100)	Treatment failure (composite of in-hospital mortality, 30-day recurrence, or persistent bacteremia ≥ 5 days)	Daptomycin use not associated with treatment failure in patients with preserved (OR 0.45, 95% CI 0.11–1.79) or with impaired renal function (OR 0.46, 95% CI 0.11–1.94)
TEICOPLANIN							
Menichetti, 1994[31]	Low	Adults with febrile neutropenia (age: teicoplanin 44 (14–78); vancomycin 42 (14–72))	Open-label RCT	635 (527 evaluable, 102 Gram-positive bacteremia, 12 MRSAB)	Vancomycin vs. teicoplanin, (each in combination with amikacin/ceftazidime)	Success (resolution of signs of infection, eradication of organism)	No difference in rates of treatment success: both overall and among those with Gram-positive bacteremia
Yoon, 2014[32]	Low	Adults with healthcare-associated MRSAB (age 66 [51–73])	Prospective cohort	190	Vancomycin (N=134) vs. teicoplanin (N=56)	Clinical failure (composite of MRSAB-attributed mortality, bacteremia duration ≥7 days, and/or fever duration ≥7 days)	Choice of antibiotic not associated with clinical failure
LINEZOLID							
Birmingham, 2003[33]	Low	Patients with signs and symptoms of a serious infection (age: adults 55.8 [18–93]; children 8.7 [0.1–17])	Open-label compassionate-use cohort	796 (378 bacteremia, 14 evaluable MRSAB)	Linezolid	Clinical and microbiological outcome (cure, failure, or indeterminate)	• Patients with evaluable MRSAB: • Clinical cure: 12/14 • Microbiological cure: 10/14
Shorr, 2005[34]	Low	Adults with nosocomial pneumonia, cSSTI, or general MRSA infections who also had bacteremia (age: linezolid 63.5 ± 17.1; vancomycin 59.3 ± 18.9)	Retrospective pooled analysis of subgroups with bacteremia in 5 RCTs	3228 in parent studies (144 SAB, 64 MRSAB)	Vancomycin 1g q12h vs. linezolid	Clinical cure, microbiologic success, survival	No significant differences in clinical cure, microbiologic success, or survival
Gomez, 2007[35]	Low	Patients with MRSAB (mean age: 60 [14–95])	Prospective cohort	100	Vancomycin (N=49), teicoplanin (N=20), linezolid (N=17), other (N=14)	Influence of empiric antibiotic choice on mortality	Empiric therapy with linezolid: lower mortality than glycopeptides in bivariate analysis
Wilcox, 2009[36]	Low	Adults with suspected catheter-related infection (age: linezolid 53.7 ± 18.1; vancomycin 53.8 ± 17.6)	Open-label RCT	739 (49 MRSAB in evaluable population)	Linezolid or vancomycin (or β-lactam for methicillin-susceptible pathogens)	Microbiologic outcome at test-of-cure	• Linezolid non-inferior to vancomycin

Author, year	GRADE category	Population	Study design	Number of patients	Treatment	Primary Endpoints	Results
							• However, increased mortality in linezolid group led to FDA warning (see text)
Park, 2012[37]	Low	Adults with persistent MRSAB (age: linezolid 63.7 ± 11.6; glycopeptide 62.4 ± 14.2)	Prospective cohort	90	Linezolid-based salvage therapy (with or without carbapenem) vs. continued glycopeptide	Early microbiologic response, duration of bacteremia, salvage success	• Shorter duration of bacteremia in glycopeptide group • No significant difference in treatment success or mortality
TRIMETHOPRIM/SULFAMETHOXAZOLE							
Markowitz, 1992[21]	Moderate	Adult IVDU with suspected SAB, without left-sided IE (age: TMP/SMX 32.6 [31.1–34.1]; vancoymcin 32.5 [30.7–34.3])	Double-blind RCT	228 (65 SAB, 38 MRSAB)	TMP/SMX 320/1600 q12h vs. vancomycin 1g q12h	Cure rate in those with *S. aureus* infection (not limited to bacteremia)	• Cure rate: TMP/SMX 37/43 (86%) vs. Vancomycin 57/58 (98%) • All treatment failures were in patients with MSSA
Goldberg, 2010[38]	Low	Adults with MRSAB (age: TMP/SMX 74.7 ± 15.9; vancomycin 75.8 ± 13.7)	Retrospective matched cohort	114	TMP/SMX (N=38) vs. vancomycin (N=76)	30-day mortality, persistent bacteremia >14 days, relapse, adverse events	No significant differences in any of the outcomes
COMBINATION THERAPY							
Levine, 1991[20]	Moderate	Adults with MRSA endocarditis (age 32 [23–61])	Open-label RCT	42	Vancomycin 1g q12h vs. vancomycin 1g q12h + rifampin 600mg daily	Duration of bacteremia	• Median duration bacteremia 9 days for all patients • No difference between groups
Lemonovich, 2011[39]	Low	Adults with persistent SAB and/or *S. aureus* endocarditis (median age: aminoglycoside 58 [50–70]; no aminoglycoside 57 [53–71])	Retrospective cohort	87 (48 MRSAB)	Aminoglycoside use (N=49) vs. no aminoglycoside (N=38)	Incidence of recurrent SAB within 6 months, duration of bacteremia, 6-month mortality, incidence of complications of bacteremia, incidence of renal failure	• Aminoglycoside use associated with lower incidence of recurrence (RR 0.51, 95% CI 0.22–1.17, p=0.04) • Other outcomes not significantly different
Dilworth, 2014[40]	Low	Adults with MRSAB with vancomycin MIC≤2 (age: combination 51.6 ± 15; vancomycin 50.5 ± 16.8)	Retrospective cohort	80	Vancomycin vs. vancomycin/β-lactam combination therapy	Microbiological eradication (negative blood cultures and no relapse within 30 days of completing therapy)	Microbiological eradication more likely with combination therapy (AOR 11.24, 95% CI 1.72–144.34, p=0.01)
DALBAVANCIN							
Raad, 2005[22]	Moderate	Adults with Gram(+) catheter-related bloodstream infection (age: dalbavancin 54 [20–78]; vancomycin 58 [19–85])	Open-label RCT	75 (14 MRSAB)	Dalbavancin vs. vancomycin	Overall efficacy at test-of-cure visit in microITT population	Overall success higher with dalbavancin (21/23 [87%] vs 14/28 [50%], p<0.05), in all study patients (not limited to MRSAB only)
TREATMENT DURATION							

Author, year	GRADE category	Population	Study design	Number of patients	Treatment	Primary Endpoints	Results
Chong, 2013[41]	Low	Adults with uncomplicated SAB (age: 60 [49.5–68])	Prospective cohort	111 (53 MRSAB)	Treatment duration <14 days vs. ≥14 days	Relapse, crude mortality, and 12-week treatment failure	Higher relapse (3/38 [7.9%] vs. 0/73 [0%], p=0.036) and non-significant trend toward increased treatment failure with short-course therapy

Abbreviations: SAB; *Staphylococcus aureus* bacteremia; MSSA, methicillin susceptible *Staphylococcus aureus* bacteremia; MRSA, methicillin resistant *Staphylococcus aureus;* MRSAB, methicillin resistant *Staphylococcus aureus* bacteremia; MIC, minimum inhibitory concentration; RCT, randomized controlled trial; cSSTI, complicated skin and soft tissue infection; TMP/SMX, trimethoprim/sulfamethoxazole; microITT, microbiological intention-to-treat

Table 3

Impact of Infectious Diseases Consultation on Outcomes in *S. aureus* Bacteremia

Author, year	Study Design	SAB cases	Patients with IDC (%)	Outcome Measures	Key Results	Adherence to Standards of Care
Fowler, 1998[97]	Prospective cohort	244	244/244 (100%)	12-week outcome according to whether or not IDC recommendations were followed	Following IDC advice associated with higher cure rate (89/112 [79.5%] vs. 85/132 [64.4%], p=0.01) and lower relapse rate (7/112 [6.3%] vs 24/132 [18.2%], p<0.01). Rates of death were not significantly different	N/A
Kaech, 2006[98]	Retrospective cohort	308	253/308 (82%)	In-hospital complications and all-cause mortality	IDC associated with better outcome in univariate, but not multivariate, analysis	N/A
Jenkins, 2008[94]	Retrospective cohort	234	161/234 (69%) overall, increase from 71/134 (53%) to 90/100 (90%) after policy of routine IDC enacted	12-week outcome, comparing groups before (N=134) and after (N=100) a policy of mandatory IDC for SAB was enacted, and adherence to 4 pre-identified standards of care	Rates of failure and death were not significantly different between groups.	Higher adherence to standards of care with mandatory IDC (74/100 [74%] vs.53/134 [40%], p<0.001): removal of IV catheters, obtaining follow-up blood cultures, using β-lactam for MSSA, appropriate duration of therapy for complicated infection
Rieg, 2009[83]	Retrospective cohort/prospective cohort	521	350/521 (67%) overall, increase from 33% to 81% after policy of routine IDC enacted	In-hospital mortality based on patient characteristics and whether IDC was performed	IDC associated with lower in-hospital mortality (66/350 [19%] vs. 47/171 [28%], OR 0.6, CI 0.4–1.0, p=0.045) and 90-day mortality (28% vs. 43%, OR 0.5, CI 0.3–0.9, p=0.02).	Patients with IDC more likely to have echocardiography, bone scan, and ≥14 days parenteral therapy
Lahey, 2009[84]	Retrospective cohort	240	122/240 (51%)	Clinical management and in-hospital mortality	IDC associated with lower mortality (13.9% vs. 23.7%, OR 0.45, CI 0.22–0.93, p=0.03).	Patients with IDC more likely to have follow-up blood cultures, appropriate antibiotic selection, longer duration of therapy, interventions to drain abscesses and remove prosthetic material
Nagao, 2010[85]	Retrospective cohort	346	N/A	Comparison of outcomes between initial (N=194) and latter (N=152) halves of observation period after mandatory IDC policy enacted	Mortality rate decreased (25.8% to 16.4%, p=0.04) during the study period	Adherence to standards of care improved: follow-up blood cultures, obtaining echocardiogram, appropriate duration of therapy and antibiotic choice

Author, year	Study Design	SAB cases	Patients with IDC (%)	Outcome Measures	Key Results	Adherence to Standards of Care
Honda, 2010[86]	Prospective cohort	341	111/341 (33%)	28-day and 365-day all-cause mortality	IDC associated with 56% reduction in 28-day mortality (adjusted HR, 0.44; 95% CI, 0.22–0.89), but not 365-daymortality (HR 0.88, CI 0.56–1.38 p=0.579).	Patients with IDC more likely to have appropriate antibiotic choice and duration of therapy, TEE performed
Choi, 2011[87]	Retrospective cohort	100	42/100 (42%)	Unfavorable outcome (30-day mortality or relapse)	IDC associated with lower rate of unfavorable outcome (31.0% vs. 53.4%, p=0.025).	Patients with IDC more likely to have selection of optimal antimicrobials, appropriate duration of therapy, and follow-up blood cultures performed
Robinson, 2012[88]	Retrospective cohort	599	162/599 (27%)	7-day, 30-day, and 1-year mortality	In univariate analysis, 7-day (3.1% vs 16.5%, p<0.001), 30-day (8.0% vs. 27%, p<0.001), and 1-year mortality (22.2% vs 44.9%, p<0.001) all lower with IDC.	Patients with IDC more likely to receive appropriate empiric antibiotics, have TEE performed, have follow-up blood cultures, and had longer duration of therapy
Pragman, 2012[95]	Retrospective cohort	233	179/233 (77%)	Conformance to standards of care (use of β-lactam for MSSA, at least 28 days' treatment for complicated infection, removal of infected prosthetic device)	IDC associated with lower risk of 12-week relapse but not with mortality	IDC associated with increased conformance to standards of care (adjusted OR 5.9, 95% CI 2.5–13.8).
Pastagia, 2012[89]	Retrospective cohort	699	(461/699) 66%	Predictors of 90-day all-cause mortality in MRSA bacteremia	IDC associated with lower adjusted risk ratio (0.69, 95% CI 0.57–0.86) and adjusted risk difference (−0.11, 95% CI −0.16 to −0.04) of 90-day mortality	N/A
Isobe, 2012 [90]	Retrospective cohort	115	28/115 (24%)	30-day mortality	IDC associated with lower 30-day mortality (6/28 [21.4%] vs. 40/87 [46.0%], p=0.02)	N/A
Forsblom, 2013[91]	Retrospective cohort	342	245/342 (72%) bedside IDC, 62/342 (18%) telephone IDC	Primary: 28-day and 90-day mortality. Secondary: number of deep infection foci, time to defervescence, inadequate antibiotic therapy, duration of hospitalization, 90-day relapse	Bedside IDC, compared to telephone IDC, associated with lower 28-day (12/245 [5%] vs 10/62 [16%], OR 0.27; 95% CI 0.11–0.65), and 90-day mortality (23/245 [9%] vs 18/62 [29%], OR 0.25; 95% CI 0.13–0.51).	Patients with bedside IDC more likely to have deep focus of infection identified, compared to telephone IDC
Fries, 2014[92]	Retrospective cohort	177	142/177 (80%)	Crude and attributable mortality	IDC associated with lower crude mortality (10/142 [7%] vs. 7/35 [20%],	Patients with IDC more likely to have follow-up blood cultures, focal source

Author, year	Study Design	SAB cases	Patients with IDC (%)	Outcome Measures	Key Results	Adherence to Standards of Care
					p=0.02) and attributable mortality (9/142 [6%] vs. 4/35 [11%], p=0.3	removed, echocardiography
					p=0.02) and attributable mortality (9/142 [6%] vs. 4/35 [11%], p=0.3	and blood culture duration
					p=0.02) and attributable mortality (9/142 [6%] vs. 4/35 [11%], p=0.3	therapy
Tissot, 2014[93]	Retrospective cohort	148, all MRSA	124/148 (80%) overall, increase from 58% to 91% after policy of routine IDC enacted	Primary: 7-day, 30-day, and in-hospital mortality. Secondary: appropriateness of antibiotic therapy, performance of follow-up cultures and echocardiography, eradication of removable foci	IDC associated with lower 7-day (6/124 [5%] vs. 7/32 [22%], OR 0.18, 95% CI 0.06–0.59, p<0.01), 30-day, 23/114 [20%] vs. 12/30 [40%], OR 0.38, 95% CI 0.16–0.90, p=0.03) and in-hospital mortality (36/124 [29%] vs. 17/32 [53%], HR 0.38, 95% CI 0.20–0.74, p<0.01).	IDC associated with longer duration of therapy.

Abbreviations: SAB; *Staphylococcus aureus* bacteremia; MSSA, methicillin susceptible *Staphylococcus aureus* bacteremia; MRSA, methicillin resistant *Staphylococcus aureus*; IDC, infectious diseases consultation; IVDU, intravenous drug use; IE, infective endocarditis; TEE, transesophageal echocardiogram; ICU, intensive care unit