Clinical Infectious Diseases

STATE-OF-THE-ART REVIEW

Contemporary Management of *Staphylococcus aureus* Bacteremia—Controversies in Clinical Practice

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Staphylococcus aureus bacteremia (SAB) carries a high risk for excess morbidity and mortality. Despite its prevalence, significant practice variation continues to permeate clinical management of this syndrome. Since the publication of the 2011 Infectious Diseases Society of America (IDSA) guidelines on management of methicillin-resistant *Staphylococcus aureus* infections, the field of SAB has evolved with the emergence of newer diagnostic strategies and therapeutic options. In this review, we seek to provide a comprehensive overview of the evaluation and management of SAB, with special focus on areas where the highest level of evidence is lacking to inform best practices.

Keywords. *Staphylococcus aureus* bacteremia.

Staphylococcus aureus bacteremia (SAB) is one of the most morbid infectious syndromes and is a leading bacterial cause of death worldwide [1–3]. Complicating its evaluation is the remarkable heterogeneity in disease severity; certain patients may recover quickly with therapy, whereas others develop multiple hematogenous complications and/or endocarditis.

Traditionally, SAB has been described as "complicated" or "uncomplicated" (Table 1) [4]. Such terminology uses host factors and clinical course to direct treatment decisions but may not fully account for the range of SAB presentations. More recently, experts have argued for a shift towards classifying patients by "risk" for complications, using this distinction to guide further diagnostic evaluation and, ultimately, treatment decisions (Figure 1) [5].

Despite published consensus guidelines [4, 6], there continues to be significant discrepancy in how adult infectious diseases (ID) providers manage SAB [7, 8]. In this review, we seek to provide an overview of the evaluation and management of SAB, with special focus on areas where the highest level of evidence is lacking to inform best practices (Table 2).

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EVALUATION

Case: A 35-Year-Old Woman With a History of Injection Drug Use Presents With Fever and Blood Cultures Growing *Staphylococcus aureus*. How Would You Evaluate This Patient?

It is generally accepted (even if not rigorously studied) that the minimum evaluation of the patient with SAB should include the following:

- A thorough history and physical examination, evaluating for the source (eg, onset of symptoms, injection drug use, presence of indwelling lines, evidence of a skin/soft tissue infection), and potential sites of metastatic involvement (eg, cardiac, skin, osteoarticular) [9]
- Infectious diseases consultation [10]
- Follow-up blood cultures [9, 11, 12]
- Echocardiography [9]

Below, we outline multiple areas of uncertainty in the evaluation of patients with SAB.

In What Situations Should Transesophageal Echocardiography be Pursued?

The sensitivity of transthoracic echocardiography (TTE) for the detection of infective endocarditis (IE) in patients with SAB varies across studies (32–82%), which have consistently demonstrated greater sensitivity of transesophageal echocardiography (TEE) over TTE [13, 14]. The added benefit of TEE, where available, historically has included superior detection of small vegetations, intracardiac abscesses, leaflet perforations, and prosthetic valve involvement [13].

Of note, many of the seminal studies comparing TTE and TEE in SAB were from the 1990s or early 2000s, and other

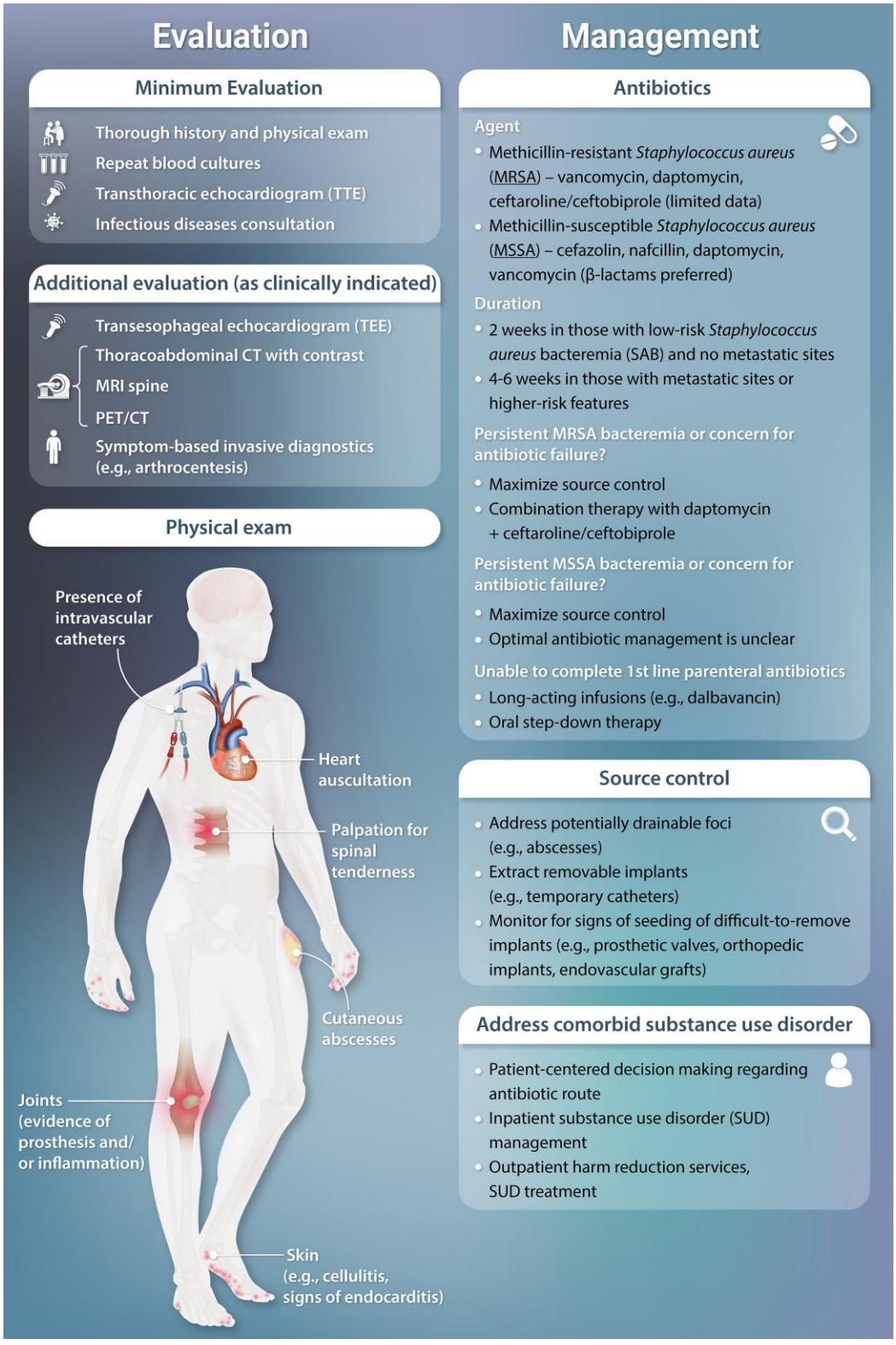

Table 1. Definitions and Differences Between the Conventional Classification (ie, Uncomplicated vs Complicated SAB) Detailed in the 2011 MRSA Guidelines [4] and the Risk-Informed Model for Guiding the Evaluation and Management of SAB Proposed by Kouijzer et al [5]

Conventional Classification	Risk-Informed Evaluation and Treatment
"Uncomplicated SAB" • Exclusion of endocarditis • No implanted prostheses • Negative follow-up cultures at 2–4 d • Defervescence within 72 h of antibiotics • No evidence of metastatic sites of infection	Predisposing host factors • Implanted prostheses • IDU • History of endocarditis Features of bacteremia • Duration • Community acquisition • Time to positivity • Treatment delay Clinical Course • Persistent fever • Unknown source of infection • Signs of metastatic infection
"Complicated SAB" • Not meeting criteria for uncomplicated SAB	

Abbreviations: IDU, injection drug use; MRSA, methicillin-resistant *Staphylococcus aureus*; SAB, *Staphylococcus aureus* bacteremia.

authors have questioned whether more modern TTE probes that utilize harmonic imaging have improved sensitivity. Casella and colleagues [15] evaluated the sensitivity of harmonic imaging and digital processing associated with more contemporary TTE technology in 75 patients with suspected IE (percentage with SAB not reported). When using TEE as a reference standard, they found that TTE had a sensitivity of 81.8%, which was improved (89.3%) if image quality was "good." Similarly, a prospective cohort of 139 patients diagnosed with definite IE (microbiology not reported) by Duke criteria (incorporating endocardial involvement demonstrated by surgery, autopsy, or subsequent clinical or echocardiographic follow-up) found higher levels of agreement between TEE and harmonic imaging TTE compared with TEE and fundamental imaging TTE (89.9% agreement vs 61.8%) [16]. However, both of these studies are more than 10 years old and contemporary studies in SAB are lacking.

The choice to pursue TEE in the face of an unrevealing TTE should be related to the pretest probability of IE, quality of TTE, and host risk factors. Transthoracic echocardiography alone may be sufficient in a subset of patients with SAB at relatively lower risk of IE, specifically those with nosocomial acquisition of bacteremia, sterile follow-up blood cultures, no permanent intracardiac device, no hemodialysis dependence, and no clinical signs of IE or a secondary focus of infection [17]. Positive follow-up blood cultures should serve as a warning sign. For example, a patient with SAB who has a single positive blood culture bottle may be expected to have a relatively lower risk (3.8% in 1 study) for IE, whereas the overall risk for complications and IE increases with any subsequent positive cultures [11, 12, 18–20].

Work in recent years has focused on more accurately stratifying the risk of endocarditis in SAB. The POSITIVE, PREDICT, and VIRSTA prediction rules were evaluated in a prospective cohort of patients with SAB, and the VIRSTA score performed best with a negative-predictive value of 99.3% for IE, although its relatively stringent criteria may result in overclassifying IE risk [21]. In patients at very low risk for endocarditis, the echocardiogram strategy is unlikely to impact the outcome [22].

The choice to pursue TEE in the face of a positive TTE is similarly nuanced. In this scenario, the primary question is how a TEE may affect management if the TTE is already consistent with IE, with the identification of an occult surgical indication being the most relevant consideration. Fowler and colleagues [13] compared the performance of TTE with TEE in 103 patients with SAB and found that all instances (n = 3) of cardiac abscess or leaflet perforation were initially missed on TTE; these findings were published in 1997 and updated studies are warranted.

When and How Frequently Should Follow-up Blood Cultures Be Obtained?

Even a single positive culture after starting therapy is a poor prognostic sign, with attributable mortality increasing with each day of culture positivity [4, 12, 20]. Some experts argue that failure to immediately clear one's cultures should serve as a "worry point" to guide further investigations [11]. The 2011 guidelines recommended obtaining additional blood cultures at 2–4 days and as needed thereafter, although studies delineating the optimal timing and frequency of follow-up blood cultures have not been done. General practice is to stop obtaining blood cultures once they clear, yet some patients will have intermittently negative blood cultures prior to complete clearance (termed the "skip phenomenon"), which may have implications for the timing of reimplantation of cardiac devices or intravascular catheters [23].

What Is the Benefit of Molecular Testing for Diagnosis and Management of SAB?

Many institutions integrate rapid multiplex polymerase chain reaction (rmPCR) testing platforms that provide pathogen identification and genotypic resistance prediction directly from the positive blood culture bottle, prior to traditional methods [24]. As it pertains to SAB, rmPCR can accurately identify *S. aureus* and the presence or absence of relevant resistance genes (eg, *mecA*) [24]. In a recent randomized controlled trial (RCT), the use of rmPCR compared with standard blood culture processing was associated with shorter time to narrow-spectrum beta-lactam therapy in patients with methicillin-susceptible *S. aureus* (MSSA), especially when coupled with an antibiotic stewardship intervention in which the primary service was contacted if a modification to antimicrobial therapy was felt to be appropriate [25]. Discrepancies between genotypic and phenotypic determination of resistance are rare but possible; in such cases, the Clinical and Laboratory Standards Institute recommends treating the isolate as methicillin-

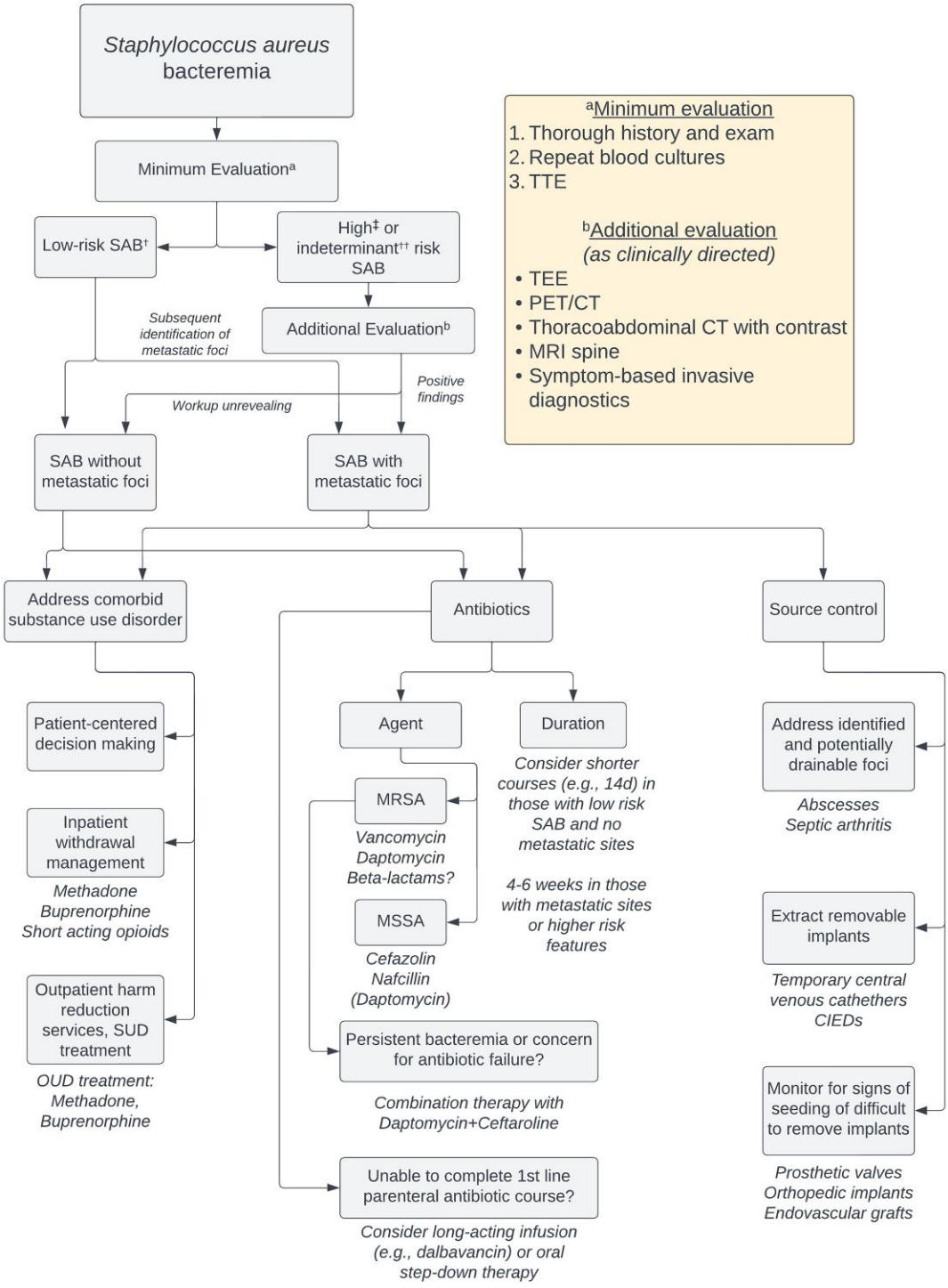

Figure 1. Proposed algorithm for the evaluation and management of SAB, modified with permission from Kouijzer et al [5]. All patients should undergo a standardized minimum evaluation[a] (thorough history and examination, repeat blood cultures, and TTE) that serves to stratify risk of metastatic foci. In those determined to have low-risk SAB (see below), additional workup can potentially be deferred. In those with indeterminant or high-risk SAB, additional evaluation[b] (guided by the patient's clinical features) is recommended. Classification of patients as having SAB with or without metastatic foci assists in guiding treatment decisions, which should include antibiotics, source control, and (when applicable) substance-use treatment. [†]Low-risk SAB: no predisposing host factors, negative TTE; blood cultures clear in <48 hours, bacteremia is hospital-acquired; no persistent fever, timely antibiotic start, and no clinical signs of metastatic infection. [‡]High-risk SAB: risk factors and/or suspicion for IE; clinical signs of metastatic infection, implanted prostheses, history of IDU and/or IE; blood cultures are positive >48 hours of therapy, delayed start in antibiotics, persistent fever. [††]Indeterminant-risk SAB: not meeting criteria for low- or high-risk SAB. Abbreviations: CIED, cardiac implantable electronic device; CT, computed tomography; MRI, magnetic resonance imaging; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; OUD, opioid use disorder; PET/CT, positron emission tomography/computed tomography; SAB, *Staphylococcus aureus* bacteremia; SUD, substance-use disorder; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

Table 2. Patient-Centered Discussion Guide for Areas of SAB Evaluation and Management That Lack the Highest-Quality Evidence

Area of Controversy	Points of Consideration
Evaluation	
TEE	Rationale: • TEE has superior detection of vegetations and intracardiac complications of IE • Positive findings on TEE can help inform decisions around antibiotic duration and need for cardiac surgery Potential drawbacks: • Acquiring a TEE can be time and resource intensive • TEE may not be universally available at every hospital • Potential procedural complications
PET/CT	Rationale: • May help diagnose infective endocarditis (especially in the setting of a prosthetic valve) and other metastatic sites of involvement Potential drawbacks: • Availability and/or insurance coverage may be limited • Risk of identifying incidental findings • Benefit of PET/CT in the management of SAB remains to be delineated
Management	
Removal of prosthetic material that is not suspected to be the source of SAB	Rationale: • High rate of seeding of intravascular and extravascular prosthetic material during the course of SAB • Removal of prosthetic material may reduce the risk of SAB recurrence Potential drawbacks: • Removal of certain types of implants (ie, CIED or articular prosthesis) may incur significant morbidity
Long-acting agents	Rationale: • Long-acting agents (eg, dalbavancin) offer the ability to achieve therapeutic drug levels with periodic infusions and expand access to effective antibiotics for at-risk patients Potential drawbacks: • Limited prospective data to support the use of long-acting agents currently exist for patients with SAB • Risk of treatment-emergent cross-resistance developing to vancomycin and daptomycin, potentially limiting subsequent therapeutic options
Oral agents for step-down	Rationale: • Oral antibiotics as step-down therapy can help expand access to effective antibiotics for at risk patients Potential drawbacks: • Limited prospective data exist regarding the use of oral antibiotics as step-down therapy in high-risk SAB • Oral options may not have favorable pharmacokinetic or adverse effect profiles, potentially hindering their efficacy

Abbreviations: CIED, cardiovascular implantable electronic device; IE, infective endocarditis; PET/CT, positron emission tomography/computed tomography; SAB, *Staphylococcus aureus* bacteremia; TEE, transesophageal echocardiogram.

resistant, and there have been cases of *mecA*-positive isolates reverting from phenotypic methicillin susceptibility to methicillin resistance during treatment [26–28].

More recently, investigators have evaluated whether newer diagnostic modalities, such as next-generation sequencing of microbial cell-free DNA (mcfDNA) or serum biomarkers, have added utility in the evaluation of patients with bloodstream infections (eg, through prediction of cases with metastatic involvement or more complicated courses) [29–31]. More research, however, is warranted before routine use.

When Should Imaging Other Than Echocardiography Be Pursued?

In cases of SAB with suspected spinal involvement, contrast-enhanced magnetic resonance imaging (MRI) is regarded as the gold-standard imaging modality [32, 33]. Which patients should undergo MRI remains an open question and is largely triggered by clinical findings. Practice variation exists regarding whether to pursue imaging of the total spine versus at a focal level in cases of suspected focal osteomyelitis (OM). In a retrospective single-center study of patients with suspected single-level OM who, per institutional protocol, underwent screening total spine MRI, 23% had noncontiguous sites of infection identified [34].

Positron emission tomography/computed tomography (PET/CT) is an emerging imaging modality being incorporated into the diagnostic evaluation for SAB and IE [35]. In a recent study of patients with SAB, PET/CT revealed a metastatic focus of infection in 70.8% of uses and was associated with lower

mortality [36]. A recent review of 7 observational studies suggested that the numbers needed to treat for receipt of PET/CT were 7–9 to change antimicrobial therapy, 10–27 to lead to an additional source control procedure, and 4–8 to prevent death [37]. Such findings, however, have recently been questioned due to the "immortal time bias" in observational studies of PET/CT, as patients who survive long enough to undergo additional imaging may systematically bias such results. van der Vaart and colleagues [38] found that the apparent mortality benefit (adjusted hazard ratio [aHR]: .5; 95% confidence interval [CI]: .34–.74) of PET/CT in their prospective cohort disappeared when adjusted for immortal time bias (aHR: 1.0; 95% CI: .68–1.48). An RCT evaluating the use of PET/CT in the diagnostic workup of SAB is currently recruiting, with an estimated completion date in 2024, although the primary outcome of this study is the identification of deep foci of infection rather than mortality, the clinical importance of which is debatable [39].

TREATMENT

Case: The Patient's Blood Cultures Speciate to Methicillin-Resistant *S. aureus* and Remain Positive After 5 Days of Therapy. TTE and TEE Did Not Demonstrate Evidence of Infective Endocarditis. What Treatment Decisions Might You Consider in Her Case?

Evidence-based and guideline-supported practices in the treatment of SAB include the following [4, 9]:

- Use of cefazolin or an anti-staphylococcal penicillin (ASP) for MSSA
- Use and appropriate dosing of vancomycin or daptomycin for methicillin-resistant *S. aureus* (MRSA)
- Early source control
- Using a treatment duration of 4–6 weeks for bacteremia with high-risk features

In this section, we will address antibiotic choice, source control, long-acting agents, oral step-down therapy, and issues affecting persons who use drugs (PWUDs).

Antibiotic Choice

Should Beta-lactam Therapy Be Added Empirically to MRSA Coverage in Areas With High MRSA Prevalence?. A critical branch point in the choice of antibiotic therapy for SAB is whether the isolate is methicillin-susceptible or -resistant, as studies have shown superior outcomes of beta-lactams for MSSA bloodstream infections when compared with vancomycin [9, 40]. Based on these findings, some have argued for an empiric combination approach (eg, vancomycin or daptomycin and a beta-lactam) in the period prior to discovering if the isolate is MSSA or MRSA to provide optimal upfront therapy for both [41]. Retrospective data from the VA healthcare system, however, found that early incorporation of beta-lactams during the empiric treatment of SAB (ie, during the first 4 d of bacteremia) performed similarly to vancomycin monotherapy [40]. Furthermore, this approach may cause harm in light of data from the CAMERA-2 trial, which demonstrated a significant increase in acute kidney injury (AKI) in the group receiving combination therapy for definitive treatment of MRSA bacteremia compared with those receiving monotherapy, although AKI became apparent after approximately 5 days and shorter empiric durations of combination therapy may be safer [42]. The impetus to utilize empiric combination therapy for undifferentiated SAB may be lower in the modern era with increasing access to molecular rapid diagnostic tests.

When Are ASPs Preferred Compared With Cefazolin for Definitive Treatment of MSSA?. Whether ASPs versus cefazolin should be selected for the treatment of MSSA bacteremia is controversial. The American Heart Association (AHA) endocarditis guidelines suggest ASPs as first-line treatment for MSSA endocarditis, with cefazolin listed as an alternative [6]. Anti-staphylococcal penicillins have historically been preferred in patients with central nervous system (CNS) involvement due to concerns about penetration of the blood–brain barrier, although newer studies have called this dogma into question [43–45]. Anti-staphylococcal penicillins are associated with higher rates of treatment-limiting toxicity and more frequent dosing schedules, making alternative therapeutic options appealing [46].

There has been concern about decreased efficacy of cefazolin in isolates noted to have the cefazolin inoculum effect (CzIE), an observed increase in minimum inhibitory concentrations (MICs) to 16 micrograms per mililiter or greater when drug susceptibility testing is performed with a 100-fold higher than standard inoculum of MSSA in vitro [47]. In an observation study performed in Argentine hospitals where ASPs were not available, higher 30-day mortality (39.5% vs 15.2%) was seen in isolates positive for the CzIE, and multivariate logistic regression identified the CzIE as an independent predictor of mortality in their cohort, although it is unclear whether antibiotic selection (eg, with an ASP) would ameliorate this association [48]. Recent observational data suggest similar efficacy, or even a trend towards superiority of cefazolin over ASPs [46, 49, 50]. A French RCT is recruiting and seeks to investigate whether cefazolin is noninferior to cloxacillin for the treatment of MSSA bacteremia, yet the small sample size and wide noninferiority margin may limit the generalizability of their results [51]. Given the current uncertainty about the clinical implications of the CzIE, the preferable safety profile of cefazolin compared with ASPs, and the availability of large-scale observational data supporting the efficacy of cefazolin, the authors feel comfortable using cefazolin in most patients with MSSA bacteremia. The use of penicillin for the subset of MSSA that is

penicillin-susceptible is currently not recommended but is the subject of an ongoing RCT [52].

Which Agent and What Dosing Strategy Should Be Used for Definitive Therapy of MRSA Bacteremia?. Vancomycin continues to be standard of care for most patients with MRSA bacteremia, despite being suboptimal for a variety of reasons. Revised consensus guidelines on the therapeutic monitoring of vancomycin for serious MRSA infections published in 2020 sought to help clinicians and pharmacists better navigate vancomycin's narrow therapeutic index by recommending that dosing be optimized through the use of individualized area under the curve (AUC) monitoring with Bayesian software programs, thereby abandoning the use of trough-only pharmacokinetic monitoring as a surrogate for daily AUC values [53]. Observational data suggest that day-2 AUCs over MIC values of 515 or less are associated with lower rates of AKI without increasing the incidence of treatment failure, although rigorous comparative effectiveness studies of AUC versus trough-based vancomycin dosing have not been completed [54].

Aside from vancomycin, daptomycin, a lipopeptide antibiotic that is bactericidal against both MSSA and MRSA and does not require therapeutic drug monitoring, is the only other antibiotic with a Food and Drug Administration (FDA) indication for the treatment of MRSA bacteremia. In an open-label RCT evaluating the efficacy of daptomycin at a dose of 6 mg/kg versus standard of care, daptomycin met the criteria for noninferiority [55]. However, there were numerically more microbiologic failures in the daptomycin arm, some of which had documented increasing daptomycin MICs. Many experts argue that, while the FDA approved a dose of 6 mg/kg, higher doses (eg, 8–12 mg/kg) of daptomycin are warranted in the treatment of SAB, due to its concentration-dependent bactericidal activity and pharmacokinetic studies suggesting inadequate drug exposure in certain populations at a dose of 6 mg/kg [4, 56]. An analysis from the European Cubicin Outcomes Registry and Experience Study (in which 43% of infections were caused by *S. aureus*) found that use of doses 8 mg/kg/day or higher demonstrated numerically higher cure rates for patients with IE, were an independent predictor of clinical success, and did not have higher rates of adverse effects when compared with doses of 6 mg/kg/day or less [57]. Prospective studies comparing different doses of daptomycin, however, are lacking; given clinical experience with doses of up to 12 mg/kg/day (in enterococcal infections) and the relatively low rates of treatment-limiting toxicity, targeting a dose of 8–12 mg/kg/day is reasonable for SAB [58, 59]. Daptomycin should not be used for primary pulmonary infections due to inactivation by surfactant.

Ceftaroline is an advanced-generation cephalosporin that is FDA-approved for the treatment of acute bacterial skin and skin-structure infection (ABSSI) as well as community-acquired bacterial pneumonia. While not approved for MRSA bacteremia, this antibiotic at clinically relevant concentrations inactivates PBP2a (the molecular determinant of methicillin resistance), and there is considerable interest in using it for this indication. A 2017 systematic review of ceftaroline use for indications outside of its FDA approval identified 22 studies that included case series of ceftaroline use in MRSA bacteremia or endocarditis, CNS infection, and nosocomial pneumonia, with many instances using ceftaroline as salvage therapy at a variety of dosing schedules and often in combination with other antibiotics [60]. Similarly, a retrospective cohort study of adults with MRSA bacteremia described outcomes of 83 patients treated with ceftaroline for at least 72 hours and found similar rates of failure when compared with those receiving daptomycin (32.5% vs 39%, respectively) [61]. In the absence of more compelling clinical data, however, we do not recommend using ceftaroline as initial monotherapy for SAB at this time, although we encourage further research into this question given the superiority of beta-lactam therapy for MSSA.

Ceftobiprole is a novel advanced-generation cephalosporin antibiotic that, like ceftaroline, is active against MSSA and MRSA. Results of the ERADICATE trial, a phase 3, randomized, double-blind trial comparing ceftobiprole with daptomycin for the treatment of high-risk/complicated SAB, including right-sided endocarditis, were recently published [62]. The trial evaluated 387 patients with SAB (94 with MRSA). Ceftobiprole met the prespecified noninferiority margin (15%) with regard to the primary outcome of overall clinical success at 70 days post-randomization, although it performed numerically, but nonsignificantly, worse than daptomycin in the MRSA subgroup. Taken collectively, these results are encouraging and suggest that ceftobiprole can be considered in the treatment of SAB in countries where it is available, although its role in initial therapy remains uncertain.

Linezolid and trimethoprim-sulfamethoxazole (TMP-SMX) are occasionally considered in the treatment of MRSA bacteremia but have not been directly studied for this indication in prospective RCTs. Linezolid had similar rates of clinical cure to vancomycin in a pooled meta-analysis of bacteremic patients from 5 RCTs of infections due to *S. aureus* (not limited to SAB), although the number of patients with MRSA bacteremia was low (52 of 3228 enrolled patients) [63]. Similarly, TMP-SMX was studied in 252 patients with MRSA infections (36% of whom had bacteremia) but did not meet prespecified noninferiority criteria when compared with vancomycin [64]. Given a lack of well-conducted clinical trial data and concerns about tolerability, we do not recommend these agents as first-line treatment of SAB.

The available evidence does not support the routine addition of rifampin or gentamicin for SAB or native valve IE due to *S. aureus* [65–67]. Controversy remains regarding their inclusion in antibiotic regimens for staphylococcal prosthetic valve endocarditis, which is outside the scope of this review [6, 68].

When Should Clinicians Change Antibiotic Therapy for Lack of Response, and Which Agents Should Be Selected?. While the 2011 MRSA guidelines suggest 7 days as the cutoff for persistent bacteremia, others propose considering any positive follow-up blood culture after starting appropriate antibiotic therapy as a concerning feature [4, 11, 12, 20]. Clinicians use of a variety of antibiotic switches and combination regimens in patients with persistently positive blood cultures [30, 69].

In vitro studies suggest synergistic activity between high-dose daptomycin and either ceftaroline or ASPs [70]. The combination of daptomycin and ceftaroline has been evaluated in a retrospective cohort of 58 patients with MRSA bacteremia, where it was associated with numerically lower 30-day mortality compared with a matched cohort receiving standard-of-care antimicrobials (8.3% [2/24] vs 14.2% [16/113]; $P > .05$) in those receiving combination therapy within 72 hours of the index blood culture [71]. An unblinded, pilot RCT comparing daptomycin + ceftaroline with vancomycin or daptomycin monotherapy was terminated early due to a disproportionate amount of deaths in the control arm, although this trial was small, not well matched between groups, and lacked a formal data and safety monitoring board, making extrapolation challenging [72, 73].

While robust clinical trial data to support the combination of daptomycin and ceftaroline are lacking, we favor this approach for use as salvage therapy for MRSA bacteremia due to in vitro demonstration of synergy and the growing body of observational studies (utilizing an every-8-h dosing interval for ceftaroline). This strategy may be preferable to switching from vancomycin to high-dose daptomycin monotherapy due to the observation that such a switch confers risk for treatment-emergent daptomycin resistance [74, 75]. When to make the switch, how long after culture clearance to continue combination therapy, and what monotherapy to use for therapy completion remain open questions.

The field of persistent MSSA bacteremia is less well studied and the optimal strategy is unclear. Some experts consider switching to an ASP (if on cefazolin) or high-dose daptomycin. Other investigators have proposed novel antibiotic combinations (eg, cefazolin + ertapenem, nafcillin + ceftaroline), although there are insufficient clinical data to recommend such an approach at present [76, 77]. While not directly studied for persistent MSSA bacteremia, a recent RCT found that daptomycin added to an anti-staphylococcal beta-lactam did not result in faster culture clearance or mortality [78].

What Controversies Exist Regarding Source Control for SAB?

Delays in source control have been associated with persistent bacteremia, metastatic foci, and worse outcomes [12, 79]. This recommendation is reflected in the 2009 Infectious Diseases Society of America (IDSA) guidelines on the management of catheter-related bloodstream infections, which advocate for line removal with *S. aureus* [80].

What is less clear is whether prosthetic material that is definitively not the source of bacteremia (ie, if there is a clear alternative source) needs to be removed in a case of SAB. In many cases, this is challenging or unfeasible, especially for devices/material where removal is associated with higher morbidity (eg, pacemakers, prosthetic valves, prosthetic joints). While hematogenous involvement of some devices may be clinically apparent (eg, cardiovascular implantable electronic device [CIED] pocket infection, knee arthroplasty), others may be less obvious. For example, in a retrospective study of patients with SAB and indwelling CIEDs without clinical evidence of a pocket infection, 34% of participants developed a CIED infection during their SAB episode [81]. The 2010 AHA update on CIED infections and their management suggests complete device removal in the setting of occult SAB due to high rates of bacterial seeding [82].

The high prevalence of patients having previously undergone placement of orthopedic prostheses poses additional challenges. Murdoch and colleagues [83] found that 34% of patients with a prosthetic joint subsequently developed a periprosthetic joint infection (PJI). Manifestations of PJIs are often subtle and clinicians should have a low threshold for diagnostic arthrocentesis in patients with SAB and joint pain when a prosthesis is present [84].

The use of PET/CT to assess for involvement of indwelling protheses (eg, prosthetic valves, orthopedic implants) is an intriguing concept and may prove to have utility in cases where device infection is unclear; further research is needed [35, 37].

Can Oral or Long-Acting Intravenous Agents Be Used for Step-Down Treatment of SAB?

Receiving prolonged courses of intravenous (IV) antibiotics carries risks of vascular and medication-related adverse consequences [85, 86]. Less burdensome alternative strategies are of great interest.

Dalbavancin is a long-acting lipoglycopeptide with an activity spectrum against both MSSA and MRSA and has gained interest as a patient-centered regimen for SAB in PWUDs [87, 88]. It has a terminal half-life of more than 14 days, allowing for infrequent dosing [89]. In a recent retrospective study, 45 patients with SAB treated with dalbavancin following an initial IV therapy of at least 7 days were compared with a matched group of controls. In the dalbavancin group, 13.3% (6/45) experienced clinical failure compared to 18.3% (33/180) of the control group ($P = .4$) [90]. Until further studies are conducted, caution should be used due to emerging evidence of the possibility of treatment-emergent dalbavancin resistance as well as cross-resistance to daptomycin and vancomycin [91]. While the FDA approved dalbavancin as either a single dose (1500 mg) or 2-dose regimen (1000 mg on day 1 followed by 500 mg on day 8) for the treatment of ABSSI, the optimal dosing regimen in SAB is unclear and a variety of dosing schedules have been suggested [87, 92]. An RCT (utilizing 1500 mg on days 1 and 8) is currently recruiting and will hopefully shine further light on this practice [93].

There has been increasing interest in the use of partial oral therapy for a variety of serious infectious syndromes [94, 95]. The results of the SABATO trial were recently presented in which the authors reported noninferiority of early oral step-down compared with conventional IV therapy for patients with uncomplicated SAB (both MRSA and MSSA) in a select population at lower risk of complications [96]. For patients with high-risk SAB, practitioners frequently encounter the scenario of patients who are unable to complete parenteral therapy and are utilizing oral antibiotics as a harm-reduction measure. Increasing evidence suggests that partial oral treatment of SAB is effective at reducing clinical failure rates in PWUDs, leading to outcomes similar to those who complete IV therapy [97–100]. The AHA statement on the management of IE in PWUDs proposes a variety of oral regimens (including dicloxacillin/rifampin, ciprofloxacin/rifampin, linezolid/rifampin, and TMP-SMX), although the optimal agents are uncertain and additional research is needed [87, 101].

There are few data to suggest whether oral or long-acting agents are preferred for patients unable to complete parenteral treatment courses. We suspect that this will need to be evaluated on an individual patient basis, taking into account their preferences and personal characteristics. Regardless, we urge providers to consider these alternate step-down strategies for vulnerable patients, as any antibiotic treatment is better than none at all.

What Duration of Treatment Should Patients With SAB Receive?

While the guidelines recommend a 4–6-week duration of therapy for patients with complicated SAB and 2 weeks for uncomplicated SAB [4], the optimal duration is open to debate. The minimum duration of 2 weeks is based on observational studies suggesting that shorter courses were associated with relapse and late complications, although contemporary data question this finding [102–104]. The SAB7 trial aims to better delineate whether 7 days of antibiotic treatment is noninferior to 14 days of antibiotic treatment for patients with low-risk SAB [105].

The recommendation that patients with higher risk profiles receive 4–6 weeks is largely based on expert opinion, with 6 weeks often being utilized in cases of endovascular infections or those with osteomyelitis [4, 6]. The SAFE trial is enrolling adult patients with complicated MSSA bacteremia (including native valve endocarditis) and is randomizing them to receive either 4 or 6 weeks of IV therapy [106]. We hope that the results of the SAB7 and SAFE trials can provide further clarity on choosing an optimal duration.

What Additional Management Strategies Should Be Used for Patients With SAB Who Use Drugs?

Persons who use drugs with SAB have distinct demographic and clinical characteristics compared with others with SAB (eg, younger, more likely to experience homelessness, higher rates of substance-use disorders in need of treatment), and as such, need management tailored accordingly [107, 108].

Early recognition of withdrawal syndromes and treatment of opioid withdrawal with medications for opioid use disorder (eg, buprenorphine, methadone) and/or short-acting opioids (in addition to nonopioid adjuncts) is critical. Alleviating the suffering related to opioid withdrawal may allow for greater engagement in SAB treatment, and undertreated withdrawal and pain are commonly cited reasons for patient-directed discharges [109]. Moreover, the treatment of opioid use disorder with buprenorphine or methadone is associated with an approximately 5 times reduced risk of fatal overdose [110]. This is particularly relevant, as the risk of opioid overdose may be higher immediately following hospitalization (postulated to be due to a loss of opioid tolerance) [111]. In a sample of PWUDs with serious *S. aureus* infections, overdose deaths were more common than infection-related deaths among patients who self-discharged before antibiotic completion [112].

Involving PWUDs in shared decision making about SAB treatment options is essential. A compelling body of literature challenges the notions that outpatient parenteral antibiotic therapy is unsafe for PWUDs or that PWUDs will not be able to adhere to oral antibiotics [97, 113]. The recent AHA scientific statement regarding the management of IE in people who inject drugs contains guidance for ID physicians seeking to balance optimally effective antibiotics with patient-centered, achievable treatment [87]. The writing group recommends a multidisciplinary approach that includes consultation from addiction-trained clinicians as well as a compassionate and flexible approach to antimicrobial therapy.

FUTURE DIRECTIONS

As highlighted in this review, there are many open questions regarding the optimal management of SAB. Designing RCTs for SAB is challenging due, in part, to the requirements for antimicrobial registration trials, costs, and inherent heterogeneity and complexity of this syndrome [114]. Additional work has focused on utilizing novel outcome measures (eg, desirability of outcome ranking) and quality-of-life metrics to help add nuance to trial results as well as incorporate elements of the patient experience [2, 115].

The "*Staphylococcus aureus* Network Adaptive Platform" (SNAP) was recently launched and aims to tackle many open questions in SAB utilizing an innovative, adaptive trial design. This incorporates standard entry criteria and outcomes to facilitate enrollment and comparison; enrollment commenced in February 2022 and 829 participants have been recruited as of May 2023, making it the largest trial in SAB to date [52, 116]. Additional areas of study that may be relevant include the efficacy of shorter durations of therapy for select patients, approach and timing to antibiotic changes/additions for persistent bacteremia, integration of PET/CT into the diagnostic workup, and the use of biomarkers to personalize management decisions [30, 39, 117, 118].

Case: No Metastatic Sites Were Identified. The Patient was Initially Switched to Combination Therapy With Daptomycin and Ceftaroline and Her Blood Cultures Cleared Shortly Thereafter. Her Hospitalization Was Complicated by Opioid Withdrawal, Treated With Short-Acting Opioids. She Was Offered Therapy for Her Opioid Use Disorder But Declined at This Time. On Hospital Day 11, She Pursued a Self-Directed Discharge and Agreed to Receive Dalbavancin as a Harm-Reduction Measure. She Received 1 Infusion in the Hospital and a Second 1 Week After Discharge

CONCLUSIONS

In summary, SAB is a syndrome frequently encountered by ID practitioners and continues to be associated with significant morbidity and mortality. We provide evidence-informed recommendations throughout this review regarding the evaluation and management of SAB, highlighting areas of ongoing uncertainty. Innovative efforts to conduct novel clinical trials are currently underway and hold the promise to shine light on many of the unanswered questions in this field. In the interim, however, we urge clinicians to approach this condition with humility, concern, and compassion.

Notes

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