**Clinical Practice Variation Among Adult Infectious Diseases Physicians in the Management of**

***Staphylococcus aureus* Bacteremia**

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**Abstract:**

Infectious disease management of *Staphylococcus aureus* bacteremia (SAB) was surveyed through the

Emerging Infections Network. While there were areas of consensus, we found substantial practice

variation in diagnostic evaluation and management of adult patients with SAB. These findings highlight

opportunities for further research and guidance to define best practices.

**Introduction**

*Staphylococcus aureus* bacteremia (SAB) is associated with high morbidity, mortality, and

healthcare costs[1]. Infectious disease (ID) consultation for SAB has been associated with significant

improvement in patient outcomes and increased adherence to best practices in SAB management such

as follow-up blood cultures, echocardiography, source identification/ control, and appropriate antibiotic

therapy[2, 3].  However, little is known about practice patterns among ID physicians in scenarios where

data are limited or inconclusive. We distributed a survey to members of the Emerging Infections

Network (EIN) to assess physician practices in the management of SAB.

**Methods**

The Infectious Diseases Society of America's (IDSA) EIN is a network of practicing ID physicians in

the United States and Canada, funded by the Centers for Disease Control and Prevention[4]. We

developed an 11-question multiple-choice survey (Supplemental Material) to assess adult ID specialist

opinions and practice patterns in the management of SAB. The EIN distributed the survey via emailed

weblink or facsimile on January 5, 2017.  Two reminders at one-week intervals were provided. Survey

responses were analyzed using SAS v9.4. A p value of < 0.05 was considered statistically significant.

**Results**

**Characteristics of Participants**

Of 1,286 active EIN physician members with an adult ID practice, 723 (56%) responded to this

survey. Respondents (220/723, 30%) were more likely than non-respondents (117/563, 21%) to have

≥25 years of ID experience (p<0.0001). No other significant differences were identified. Baseline practice characteristics including clinical experience, practice type and geographic location are provided in Supplementary Table 1. Fifty-four (7%) of respondents did not manage SAB and opted out.

**Diagnostic Evaluation of *S. aureus* Bacteremia (SAB)**

Repeat blood cultures and echocardiogram are performed by the majority of respondents (Figure 1A). Most (90%, 599/667) indicated they would always perform a transthoracic echocardiogram (TTE). Those with < 15 years of experience were more likely to always do a TTE (93% vs 86%, p=0.01). A transesophageal echocardiogram (TEE) would be performed on every patient with a negative TTE by 126 (19%) of respondents while 473 (71%) would only perform TEE under selected circumstances (Figure 1B). Those practicing in the Midwest, Northeast or South[5] regions were more likely to always perform a TEE compared to those in the West or Canada/Puerto Rico (24% vs 11%, p=0.009).

**Nafcillin or Cefazolin for MSSA Endocarditis**

For treatment of left-sided MSSA endocarditis without central nervous system involvement, 32% chose cefazolin, 29% favored nafcillin, while 32% considered the two equivalent. Among the 215 who chose cefazolin, 207 provided a rationale with most citing a combination of equal efficacy, less toxicity, dosing convenience and cost. Among the 193 who selected nafcillin, 169 provided a rationale with the most citing nafcillin as the "gold standard" while others favored it due to inoculum effect or better CNS penetration for clinically silent disease. Those with < 5 vs ≥ 5 years of experience were more likely to use cefazolin (39% vs 33%) while those with ≥ 15 vs < 15 years of experience were more likely to use nafcillin (37% vs 26%), p =0.048.

**Management of MRSA Bacteremia and Endocarditis**

When managing a patient with MRSA bacteremia and vancomycin MIC of 2 mg/L, a majority (51%, 336/665) would treat with vancomycin if clinically responding while 248 (37%) favored daptomycin and 29 (4%) chose ceftaroline. Less than 1% of respondents selected linezolid, telavancin, TMP-SMX, or daptomycin plus ceftaroline. Respondents in a university or teaching hospital were more likely to use vancomycin compared to those in a community or Veterans/Defense Department hospital (55% vs 43%, p=.03).

In a patient with MRSA endocarditis and persistent bacteremia on day 6 of vancomycin, most (75%, 504/668) would modify therapy. Alternative monotherapy was selected by 245 (37%) respondents while 215 (32%) favored combination therapy (Figure 1C). Among those who chose another single agent, 193 (78%) selected daptomycin while 36 (15%) chose ceftaroline. The specific combination of daptomycin and ceftaroline was chosen by 66 (10%). Those practicing in the Midwest were most likely to choose alternative monotherapy (62%). Those in the Northeast and West were most likely to use combination therapy with daptomycin (28%), p = 0.04, and were more likely to use daptomycin *and* ceftaroline (15%) compared to those in the Midwest (5%) and South (7%), p =0.004.

The daptomycin dose used for MRSA bacteremia varied with 38%, 43%, and 17% of respondents selecting 6 mg/kg, 8 mg/kg and 10-12 mg/kg, respectively. Doses of 10-12 mg/kg were most likely to be used in the Northeast and West (21% and 20%, respectively), while 6-8 mg/kg was most likely to be used in the Midwest (91%), p=0.0002.

**Duration of Therapy**

Most respondents managed SAB with at least 14 days of IV antibiotics in several scenarios. In a patient with MRSA bacteremia and a skin and soft tissue source, rapid clearance of blood cultures, negative TTE, and no evidence of metastatic infection, most (73%, 491/669) would treat with IV vancomycin for 14 days while 87 (13%) transitioned to oral antibiotics to complete a 14-day course. A minority (4%, 24/669) would treat for 5-7 days with either oral or IV antibiotics while 47 (7%) favored a longer duration of 21-28 days.

In a patient with one of two blood cultures positive for MSSA, no obvious signs or symptoms of infection, a normal white blood cell count, negative repeat blood cultures, negative TTE, and no evidence of metastatic infection, most (67%, 445/664) would treat with IV antibiotics for 14 days while 51 (8%) would treat for 4-6 weeks. A minority (10%) would consider the cultures a contaminant and stop antibiotics.

Most respondents would extend treatment duration to 4-6 weeks in the setting of SAB and a negative echocardiogram for patients with a prosthetic device or positive repeat blood cultures (Figure 1D).

**Management of Septic Thrombophlebitis**

Most respondents (71%, 467/657) recommended anticoagulation in the setting of SAB and PICC line-associated deep vein thrombosis after catheter removal. Duration of antimicrobial therapy varied with 52% of respondents treating for 4 weeks while 19% chose 2 weeks and 25% chose 6 weeks.

**Discussion**

SAB is a serious disease commonly managed by ID physicians. Most respondents performed repeat blood cultures, echocardiography, and treated with IV therapy for at least 14 days. While there were some areas of consensus, this survey highlights considerable practice variation among respondents representing a wide breadth of ID practitioners in North America including differences by years of experience, geographic region, and practice environment.

The IDSA MRSA Treatment Guidelines recommend echocardiography in all patients with SAB, with TEE being the preferred modality due to its greater sensitivity[6]. While the vast majority of respondents supported TTE as part of the diagnostic evaluation of SAB, only 19% of respondents indicated they would always perform a TEE. These findings are consistent with other studies that suggest routine use of TEE is infrequent[7]. TEE is an invasive procedure that has complication risks, is resource-intensive, and may not be available at all centers. Some studies suggest that TEE may not be necessary for all cases of SAB and that clinical prediction rules may help with risk stratification but these require external validation[8]. The lack of concordance between guideline recommendations and current practice indicates a need for further research and guidance on the role of TEE among patients with SAB.

There was lack of consensus regarding the treatment of MSSA endocarditis with respondents almost evenly distributed among cefazolin, nafcillin, or use of either drug suggesting the need for evidence-based guidelines to define optimal therapy. Those with fewer years of experience favored

cefazolin while more experienced clinicians preferred nafcillin. These differences may reflect a growing body of literature suggesting similar clinical outcomes and fewer drug-related adverse events with the use of cefazolin for MSSA bacteremia[9]. However, early reports of cefazolin treatment failure in setting of endocarditis have led others to caution its use in high inocula infections[10].

Although the presence of prosthetic devices or positive repeat blood cultures would prompt most to extend therapy to 4-6 weeks, a smaller proportion of respondents were influenced by immunosuppression, diabetes, or community-onset bacteremia. Further guidance is needed to identify patients who are at increased risk of relapse or serious complications in whom prolonged treatment duration may be warranted.

Consistent with guideline recommendations[6], clinical response influenced 51% of respondents to continue vancomycin in a patient with MRSA bacteremia and vancomycin MIC of 2 μg/mL, although a substantial portion would switch to daptomycin. Observational studies examining the role of daptomycin versus vancomycin in management of MRSA bacteremia with high vancomycin MICs have yielded mixed results[11, 12], and a randomized controlled trial designed to evaluate this issue was recently terminated due to slow accrual[11]. Although 8 mg/kg was the most commonly selected dose of daptomycin, a sizable minority chose the FDA-label dose of 6 mg/kg for management of MRSA bacteremia. The substantial differences in management of the above scenario and treatment of persistent bacteremia highlight the lack of high quality evidence in these areas.

Our study has several limitations. As with all voluntary surveys, selection bias could yield results not generalizable to all ID specialists. Response bias is possible and survey answers may not accurately reflect clinical practice. Although the value of ID consultation in SAB management has been established by multiple studies, this survey demonstrates there remains ample opportunity to further define best practices and optimize management of this complex disease.

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**Disclaimer**

The findings and conclusions in the manuscript are those of the authors and do not necessarily represent the official views of the US Centers for Disease Control and Prevention or the Department of Health and Human Services.

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**Potential Conflicts of Interest**

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**Figure 1. Practice patterns among survey respondents on the diagnostic evaluation and management of *Staphylococcus aureus* bacteremia (SAB).** A) Diagnostic workup routinely performed in the evaluation of a patient with SAB. B) Respondents indicating they would perform TTE on every patient but only perform TEE under these selected circumstances (N=473). *Among 222 respondents that commented on other clinical factors that would prompt TEE, common responses included: presence of cardiac device or prosthetic valve, 58(26%); clinical suspicion for IE including embolic phenomenon, metastatic infection, 43(19%); TEE results would change management (e.g. duration of therapy, surgical management), 36(16%).

C) Management of patient with MRSA endocarditis and persistent SAB on day 6 of vancomycin, therapeutic trough and vancomycin MIC of 0.5 mg/L

D) Factors influencing decision to extend duration of therapy from 2 weeks to 4-6 weeks assuming negative echocardiography (TTE and/or TEE)

A)



Legend: Almost always | Usually | Sometimes | Rarely

Repeat blood cx — N=666 — 611, 42, 5
TTE and/or TEE — N=662 — 496, 118, 48, 0
Spine MRI — N=626 — 421, 510, 95
Abd/pelvis CT — N=625 — 619, 334, 266
Dilated eye exam — N=615 — 715, 160, 330

X-axis: Number of Respondents (0–700)

B)



Positive repeat blood cultures (N=401) — 86%
Lack of clinical improvement (N=378) — 81%
Community-onset bacteremia (N=183) — 39%
Other clinical factors* (N= 209) — 45%

X-axis: Percent (0%–100%)

C)



Continue vancomycin alone — 24%
Change to another single antibiotic (N=245) — 37%
Continue vancomycin and ADD another MRSA active agent (N=120) — 18%
Change to daptomycin and ADD another MRSA active agent (N=95) — 14%
Other (N=44) — 7%

X-axis: Percent (0%–40%)

D)



Presence of prosthetic device implant (N=557) — 84%
Repeat blood cultures + at 48-96 hrs (N=517) — 78%
Persistent fevers at 72 hours (N=342) — 52%
Immunosuppressing conditions (N=316) — 48%
Community-onset bacteremia (N=230) — 35%
Diabetes (N=132) — 20%
Other (N=109) — 16%
None of the above (N=15) — 2%

X-axis: Percent (0%–90%)