

Impact of Mandatory Infectious Diseases Consultation and Real-time Antimicrobial Stewardship Pharmacist Intervention on *Staphylococcus aureus* Bacteremia Bundle Adherence

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Background. The purpose of this study was to evaluate the impact of infectious diseases consultation (IDC) and a real-time antimicrobial stewardship (AMS) review on the management of *Staphylococcus aureus* bacteremia (SAB).

Methods. This retrospective study included adult inpatients with SAB from January 2016 to December 2018 at 7 hospitals. Outcomes were compared between 3 time periods: before mandatory IDC and AMS review (period 1), after mandatory IDC and before AMS review (period 2), and after mandatory IDC and AMS review (period 3). The primary outcome was bundle adherence, defined as appropriate intravenous antimicrobial therapy, appropriate duration of therapy, appropriate surveillance cultures, echocardiography, and removal of indwelling intravenous catheters, if applicable. Secondary end points included individual bundle components, source control, length of stay (LOS), 30-day bacteremia-related readmission, and in-hospital all-cause mortality.

Results. A total of 579 patients met inclusion criteria for analysis. Complete bundle adherence was 65% in period 1 (n = 241/371), 54% in period 2 (n = 47/87), and 76% in period 3 (n = 92/121). Relative to period 3, bundle adherence was significantly lower in period 1 (odds ratio [OR], 0.58; 95% confidence interval [CI], 0.37–0.93; P = .02) and period 2 (OR, 0.37; 95% CI, 0.20–0.67; P = .0009). No difference in bundle adherence was noted between periods 1 and 2. Significant differences were seen in obtaining echocardiography (91% vs 83% vs 100%; P < .001), source control (34% vs 45% vs 45%; P = .04), and hospital LOS (10.5 vs 8.9 vs 12.0 days; P = .01). No differences were noted for readmission or mortality.

Conclusions. The addition of AMS pharmacist review to mandatory IDC was associated with significantly improved quality care bundle adherence.

Keywords. antimicrobial stewardship; bacteremia; bundle adherence; *Staphylococcus aureus*.

Staphylococcus aureus is a leading cause of nosocomial and community-acquired bloodstream infections [1]. *S. aureus* bacteremia (SAB) is frequently complicated by metastatic infections such as osteomyelitis and endocarditis, and mortality estimates range from 13.3% to 26.0% in the United States [2]. Various strategies have been implemented to improve outcomes for SAB patients. Previous studies have demonstrated that infectious diseases consultation (IDC) improves mortality for patients with SAB [3–14]. Mandating IDC for all patients with SAB

has been shown to improve rates of guideline-recommended care, including echocardiography, source control, appropriate antimicrobial therapy, and follow-up cultures [4, 5, 15, 16].

Antimicrobial stewardship (AMS) interventions have also been investigated as a strategy to enhance SAB quality of care. AMS review has been shown to improve optimal therapy for methicillin-sensitive *S. aureus* (MSSA) bacteremia, decrease hospital length of stay, and increase adherence to quality care bundles [17–19]. A pharmacist-driven real-time AMS review with quality care bundle recommendations has also been associated with improved bundle adherence and decreased 30-day SAB-related readmission [20].

Evidence of the combined effect of IDC and AMS is limited. Smith and colleagues [21] implemented a pharmacist-driven AMS review and quality care bundle that resulted in increasing the rate of IDC from 74% to 100% and was associated with decreased readmission for SAB. However, the impact of the increased rate of IDC and AMS intervention cannot be independently evaluated. Buehrle and colleagues [22] examined

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the benefit of IDC on the management of SAB at an institution with a comprehensive AMS program already in place and found that IDC patients were more likely to receive guideline-recommended management and had reduced mortality.

The influence of real-time AMS review on SAB outcomes in the setting of preexisting mandatory IDC for SAB has not been evaluated. The objective of this study was to assess adherence to a bundle of quality care indicators for SAB before and after implementation of mandatory IDC as well as before and after subsequent implementation of real-time pharmacist-driven AMS review.

METHODS

Study Design

This was a retrospective study of all inpatients ≥ 18 years of age with at least 1 blood culture positive for *S. aureus* from January 2016 to December 2018 at 7 Advocate Aurora Health hospitals located in the Chicago, Illinois, area. Patients were excluded if they had a polymicrobial bacteremia, preexisting SAB before admission, were transferred to another institution within 72 hours of their first positive blood culture being drawn, transitioned to hospice care before completion of antimicrobial therapy, or died within 48 hours of their first positive blood culture being drawn. The study received a non-human subject research determination from the organization's institutional review board.

Interventions

Patients were divided into 3 different time periods: before mandatory IDC and AMS review (period 1), after mandatory IDC and before AMS review (period 2), and after mandatory IDC and AMS review (period 3) (Figure 1). Before the implementation of mandatory IDC and AMS review, 1 of the 7 hospitals already had a dedicated infectious diseases (ID) pharmacist, and an evidence-based practice guideline for the empiric treatment of bacteremia was available for clinicians. However, no system-wide initiatives were implemented to actively promote adherence to quality-of-care measures for SAB. On September 1, 2017, IDCs were mandated for all patients with SAB throughout the health system. A comment was added in the electronic medical record to all blood culture results positive for *S. aureus*, stating that IDC was required per system policy. In the

spring and summer of 2018, an ID pharmacist-driven AMS review program was implemented at all hospitals included in the study. When an organism from a blood culture was identified using matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI-TOF MS), microbiology sent a page in real time to the ID pharmacist providing coverage for that hospital 24 hours a day, 7 days a week. In addition to MALDI-TOF, our laboratory had the capability of testing *mecA* to differentiate between methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA). However, this test may not have been consistently utilized to inform clinical decisions. ID pharmacists made recommendations to the care team regarding optimal empiric therapy while susceptibilities are pending and, when applicable, made recommendations regarding optimization of definitive therapy once additional information was available. ID pharmacists were also responsible for enforcing the mandatory IDC policy and recommended additional interventions such as echocardiography when needed.

Outcomes

The primary outcome was complete adherence to a quality care bundle consisting of the following: appropriate intravenous antimicrobial therapy, appropriate duration of therapy, surveillance cultures obtained within 24–48 hours, echocardiography, and removal of indwelling intravenous catheters, if applicable. Antimicrobial therapy was considered appropriate if the empiric therapy selected provided coverage for MRSA and the patient was maintained on intravenous therapy for the entire duration of treatment. For patients with MSSA, therapy was considered appropriate if an antistaphylococcal beta-lactam was used for definitive therapy, unless contraindicated. Vancomycin was considered appropriate for patients with documented allergies to both penicillins and cephalosporins. Appropriate duration of therapy was defined as at least 14 days for uncomplicated SAB and at least 28 days for complicated SAB, as defined by the Infectious Diseases Society of America MRSA clinical practice guideline [23]. Either transthoracic echocardiography or transesophageal echocardiography was considered acceptable. Secondary end points were the individual bundle components, source control, time to IDC, time to definitive antimicrobial therapy, time to blood culture clearance, hospital LOS, intensive

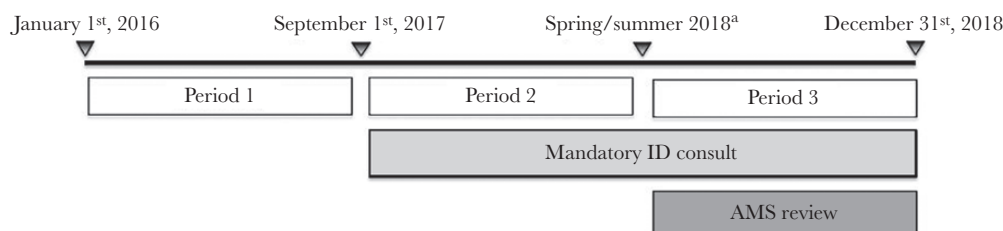


Figure 1. Timeline of study. ^aExact date of AMS review implementation varied by hospital. Abbreviations: AMS, antimicrobial stewardship; ID, infectious disease.

care unit LOS, 30-day bacteremia-related readmission, and in-hospital all-cause mortality. Source control was defined as abscess drainage or surgical removal of an infection source such as indwelling prosthetic devices or pacemakers.

Statistical Analysis

Descriptive statistics were performed for all continuous and categorical data. The chi-square or Fisher exact test was used to evaluate categorical data, as appropriate. A 3-way analysis of variance was used to evaluate continuous data. If a statistically significant difference was detected between the 3 groups, the post hoc Tukey, chi-square, or Fisher exact test was used to compare groups 1 and 2, groups 2 and 3, and groups 1 and 3 to determine which pair of groups was driving the difference. A chi-square test with odds ratio (OR) or a Fisher exact test was used for categorical data, and *t* tests were used for continuous data. Analyses were performed with SAS, version 9.4 (SAS Institute, Cary, NC, USA), and a 2-tailed *P* value of <.05 was considered statistically significant.

RESULTS

A total of 810 patients were screened, with 579 patients meeting inclusion criteria (period 1: *n* = 137; period 2: *n* = 82; period 3: *n* = 121). The most common reason for exclusion was transition to hospice care before completion of antimicrobial therapy (Figure 2). Demographics and baseline characteristics were similar between the 3 groups (Table 1), though significant statistical differences were observed between groups 1, 2, and 3 with regard to MRSA vs MSSA infection (40% vs 45% vs 27%, respectively; *P* = .01) and in patients with IDC (95% vs 98% vs 99%, respectively; *P* = .05). A majority of patients were male (*n* = 353, 61%) and had community-acquired bacteremia (*n* = 523, 90%), which we defined as first positive culture drawn within 48 hours of hospital admission. The most common source of SAB was acute bacterial skin and

skin structure infection (*n* = 168, 29%), followed by intravenous catheter (*n* = 112, 19%). Although not statistically significant, a lower rate of uncomplicated bacteremia was seen in period 3 (32%) compared with periods 1 (43%) and 2 (44%; *P* = .09). A lower proportion of patients in period 1 (29%) had metastatic sites of infection compared with period 3 (39%; OR, 0.63; 95% confidence interval [CI], 0.41–0.97; *P* = .03), although the rate of metastatic infection was not statistically significant when comparing periods 1, 2, and 3 (29% vs 26% vs 39%, respectively; *P* = .07). Empiric and definitive therapy for all patients is described in Table 2. All patients in period 3 were given an intravenous agent for empiric and definitive treatment.

Complete bundle adherence was statistically significant across periods 1, 2, and 3 (65% vs 54% vs 76%, respectively; *P* = .004) (Table 3). Relative to period 3, bundle adherence was significantly lower in period 1 (OR, 0.58; 95% CI, 0.37–0.93; *P* = .02) and period 2 (OR, 0.37; 95% CI, 0.20–0.67; *P* = .0009). For the individual bundle elements, a significant difference was seen in obtaining echocardiography, with patients in period 3 (100%) being more likely to have an echocardiogram compared with periods 1 (91%) and 2 (83%; *P* < .001). The highest rate of compliance across all remaining bundle elements was seen in period 3, though no statistically significant differences were noted (Table 3).

Patients in periods 2 and 3 were more likely to have a procedure done for source control compared with period 1 (45% vs 45% vs 34%, respectively; *P* = .04), reflecting a statistically significantly lower rate of source control observed in period 1 relative to period 3 (OR, 0.64; 95% CI, 0.42–0.97; *P* = .03). Hospital LOS also varied significantly between periods 1, 2, and 3 (10.5 vs 8.85 vs 12.0 days, respectively; *P* = .01). Although not statistically significant, 30-day bacteremia-related readmission was higher in period 1 (2.7%) compared with periods 2 (0%) and 3 (0%; *P* = .07). No statistically significant differences were noted for other secondary outcomes (Table 3).

DISCUSSION

Our study uniquely evaluated the combined effect of implementing a system-wide policy mandating IDC for SAB and real-time AMS ID pharmacist review. The integration of these 2 strategies was associated with improvement in optimal care of SAB. Specifically, mandatory IDC and AMS ID pharmacist review was associated with increased adherence to SAB quality care bundle and achievement of source control. These interventions were also associated with a numerically lower rate of 30-day readmission for SAB, and all patients in the combined intervention period received intravenous empiric and definitive therapy. This was not the case for a small number of patients in periods 1 and 2 who were either discharged on no therapy before blood culture results were available or were given oral therapy.

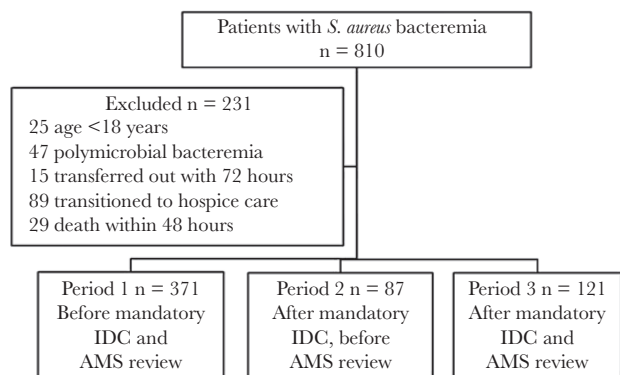


Figure 2. Development of study cohort. Abbreviations: AMS, antimicrobial stewardship; IDC, infectious diseases consult.

Table 1. Demographics and Baseline Characteristics

Characteristic	Period 1 (n = 371)	Period 2 (n = 87)	Period 3 (n = 121)	P Value
Age, mean ± SD, y	64.5 ± 16.5	67.4 ± 16.8	62.9 ± 16.0	.1
Male sex, No. (%)	233 (62.8)	51 (58.6)	69 (57.0)	.5
Charlson comorbidity index, mean ± SD	5.3 ± 3.0	5.1 ± 2.8	4.9 ± 2.7	.5
Pitt bacteremia score, mean ± SD	1.3 ± 1.8	1.1 ± 1.5	1.5 ± 2.3	.2
History of IV drug abuse, No. (%)	17 (4.6)	3 (3.4)	4 (3.3)	.9
History of SAB, No. (%)	48 (12.9)	7 (8.0)	15 (12.4)	.4
Hardware or prosthetic material, No. (%)	138 (37.2)	27 (31.0)	38 (31.4)	.2
Community-acquired, No. (%)	334 (90.0)	80 (92.0)	109 (90.0)	.9
MRSA, No. (%)	149 (40.2)	39 (44.8)	33 (27.3)	.02
ID consult, No. (%)	351 (94.6)	85 (97.7)	120 (99.2)	.05
Uncomplicated bacteremia, No. (%)	160 (43.1)	38 (43.7)	39 (32.2)	.09
Metastatic site of infection, No. (%)	106 (28.6)	23 (26.4)	47 (38.8)	.07
Source of bacteremia, No. (%)				
Bone and joint	48 (12.9)	15 (17.2)	26 (21.5)	.1
ABSSSI	102 (27.5)	34 (39.1)	32 (26.4)	
Respiratory	20 (5.4)	8 (9.2)	6 (5.0)	
Endocarditis	20 (5.4)	1 (1.1)	6 (5.0)	
Urinary	15 (4.0)	1 (1.1)	3 (2.5)	
Intravenous catheter	79 (21.3)	12 (13.8)	21 (17.4)	
Unknown	53 (14.3)	8 (9.2)	19 (15.7)	
Other	34 (9.2)	8 (9.2)	8 (6.6)	
ICU admission, No. (%)	140 (37.7)	25 (28.7)	45 (37.2)	.3

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; ICU, intensive care unit; ID, infectious disease; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; SAB, *Staphylococcus aureus* bacteremia.

The results of this study suggest that there is additional benefit to AMS review for SAB patients at an institution with mandatory IDC for SAB already in place. This is consistent with findings from Buehrle and colleagues [22], who evaluated the effect of IDC on the management of SAB at an institution with a comprehensive AMS program already in place. These authors demonstrated that patients with IDC were more likely to receive guideline-recommended management and had reduced mortality. However, improvements in antimicrobial choice or dosing were not seen, perhaps due to the preexisting AMS review. Around-the-clock AMS review of patients with positive blood cultures may provide additional benefit, as delayed appropriate SAB treatment is associated with increased mortality [24]. Real-time AMS review has been shown to decrease time to optimal antimicrobial therapy for bacteremia patients [25].

Specific to SAB, Nguyen and colleagues [20] implemented a pharmacist-driven real-time AMS review with quality care bundle recommendations that was associated with improved bundle adherence and decreased 30-day SAB-related readmission even though a majority of patients had IDC. Therefore, a multidisciplinary approach achieved by combining IDC and AMS review may garner additional benefit for patients with SAB.

IDC remains an integral part of this multidisciplinary approach for improving SAB care. ID physician-led bundled interventions for SAB have also been shown to improve adherence to quality care indicators and decrease mortality [4, 16, 26, 27]. Bedside IDC has been shown to be more effective than a telephone consult for SAB [13, 28]. An AMS intervention that recommends IDC for SAB patients may not be as

Table 2. Empiric and Definitive Intravenous Therapy

	Empiric Therapy			Definitive Therapy		
	Period 1 (n = 371)	Period 2 (n = 87)	Period 3 (n = 121)	Period 1 (n = 371)	Period 2 (n = 87)	Period 3 (n = 121)
Vancomycin, No. (%)	331 (89)	75 (86)	94 (78)	143 (39)	38 (44)	29 (24)
Daptomycin, No. (%)	16 (4.3)	1 (1.1)	10 (8.3)	19 (5.1)	4 (4.6)	8 (6.6)
Oxacillin, No. (%)	2 (0.54)	0 (0)	0 (0)	50 (13)	4 (4.6)	26 (21)
Cefazolin, No. (%)	1 (0.27)	2 (2.3)	0 (0)	127 (34)	34 (39)	45 (37)
Other, ^a No. (%)	17 (4.6)	7 (8.0)	17 (14)	23 (6.2)	5 (5.7)	13 (11)
None, No. (%)	4 (1.1)	2 (2.3)	0 (0)	9 (2.4)	2 (2.3)	0 (0)

^aOther agents included cefepime, ceftriaxone, clindamycin, doxycycline, ertapenem, levofloxacin, linezolid, meropenem, piperacillin/tazobactam, and telavancin.

Table 3. Primary and Secondary Outcomes

Outcome	Period 1 (n = 371)	Period 2 (n = 87)	Period 3 (n = 121)	PValue
Complete bundle adherence, ^a No. (%)	241 (65)	47 (54)	92 (76)	.004
Repeat blood cultures, No. (%)	291 (78)	66 (76)	105 (87)	.09
Echocardiography, No. (%)	339 (91)	72 (83)	121 (100)	<.0001
Removal of indwelling lines or nonapplicable, No. (%)	357 (96)	81 (93)	117 (97)	.4
Appropriate antimicrobial therapy, No. (%)	354 (95)	83 (95)	120 (99)	.1
Appropriate antimicrobial duration, No. (%)	324 (87)	76 (87)	112 (93)	.3
Source control, No. (%)	126 (34)	39 (45)	54 (45)	.04
Time to IDC, mean ± SD, d	1.06 ± 1.42	0.99 ± 0.85	0.83 ± 0.69	.2
Time to definitive therapy if change in therapy required, mean ± SD, d	2.49 ± 1.58	2.41 ± 1.35	2.77 ± 5.67	.7
Time to blood culture clearance, mean ± SD, h	52.6 ± 44.0	54.2 ± 63.3	41.9 ± 25.8	.06
Hospital LOS, mean ± SD, d	10.5 ± 6.96	8.85 ± 6.17	12.0 ± 10.7	.01
ICU LOS, mean ± SD, d	5.34 ± 6.10	5.33 ± 5.72	6.34 ± 6.28	.6
In-hospital all-cause mortality, No. (%)	16 (4.3)	2 (2.3)	6 (5.0)	.6
30-d SAB-related readmission, No. (%)	10 (2.7)	0 (0)	0 (0)	.07

Abbreviations: ICU, intensive care unit; IDC, infectious diseases consult; LOS, length of stay; SAB, *Staphylococcus aureus* bacteremia.

^aPrimary end point.

effective as mandating IDC. Previous studies of pharmacist-led AMS bundles for SAB have included recommending IDC as a component of the intervention, with varied success. Smith and colleagues [21] achieved 100% IDC in their postintervention group. However, other similar studies have shown an IDC rate ranging from 60% to 93.4%; all these results were lower than the IDC rate of 95% seen in our cohort before IDC was mandated [18–20].

We observed a longer average hospital LOS in period 3, our combined intervention group, compared with periods 1 and 2. Because more patients in period 3 had complicated bacteremia and metastatic sites of infection, they may have required a longer hospital stay in order to obtain source control. Remtulla and colleagues [19] observed a similar increase in LOS and decrease in patients with uncomplicated bacteremia in their study of a successful AMS intervention for SAB. We observed a nonsignificant decrease in 30-day SAB-related readmission from 10 patients in period 1 to 0 patients in periods 2 and 3, which was consistent with findings from previous studies [19, 27, 29]. We did not see a mortality benefit, possibly due to the already low 4.3% mortality in period 1. The high rate of IDC before IDC was mandated for all patients may have also contributed. Previous studies that demonstrated a mortality benefit with IDC had a much lower baseline rate of IDC, ranging from 33% to 67% [8–10]. This likely made differences in mortality easier to detect. The mortality rate seen in our study was similar to the postintervention 3% mortality found in a similar study by Smith and colleagues [21], which also excluded patients who transitioned to hospice care and those who died or transferred to another institution shortly after admission.

Other novel interventions for SAB care have been investigated. Djelic and colleagues [30] implemented a process to notify ID physicians of blood cultures positive for *S. aureus* in real time, which was similar to our real-time notification of AMS

pharmacists. This intervention was associated with decreased time to IDC and improved adherence to quality care indicators. Real-time notification of SAB detection for ID physicians may be an effective method for ensuring prompt IDC, especially for institutions like ours that mandate IDC for SAB patients. Wenzler and colleagues [29] developed an automated scoring tool for SAB within their EMR for use by frontline pharmacists working all shifts. The intervention was associated with improved adherence to quality care indicators and a decrease in mortality. Similarly, Brotherton and colleagues [31] created a best practice advisory alert within their EMR that provided physicians with recommendations for SAB management and was associated with improved bundle adherence. It is unclear how these types of interventions compare to involvement of physicians and pharmacists specially trained in infectious diseases. Utilization of rapid diagnostic testing may also have a role in improving outcomes, particularly by shortening time to definitive therapy [32]. After the completion of data collection for this study, our institution began using a new FDA-approved polymerase chain reaction testing for all blood culture isolates with a gram stain of gram-positive cocci in clusters. This technology can rapidly identify *S. aureus* and detect MRSA resistance genes, and its impact on patient outcomes may warrant further investigation.

The limitations of our study include its retrospective design and reliance on manual chart review for data collection. There were a limited number of patients eligible to be included in period 2, owing to the timing of the implementation of the 2 interventions examined in this study. This may have hindered our ability to detect statistical differences between our 3 periods. Another important limitation of our analysis is the already high rate of IDC in period 1, which may account for the lack of improvement seen from period 1 to period 2. Additionally, there was an ID pharmacist employed at 1 of the 7 hospitals

included in this study before the implementation of the real-time AMS review who provided recommendations for SAB patients, which may have also confounded the results of our study. The strengths of this study include the multisite design and the unique combination of mandatory IDC followed by the implementation of a real-time AMS review.

In conclusion, this study describes an effective real-time, pharmacist-driven AMS review that was associated with improved management of SAB in the setting of preexisting mandatory IDC. Combining mandatory IDC and AMS review was associated with increased adherence to a bundle of quality care indicators and improvement in the rate of source control. Our study is unique in that it demonstrates the benefit of AMS review in addition to IDC for optimizing SAB care.

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Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Prior presentation. This work was previously presented as a poster at IDWeek 2019 in Washington, DC.

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