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Infectious Diseases Consultation Lowers Mortality From *Staphylococcus aureus* Bacteremia

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Abstract

Staphylococcus aureus bacteremia (SAB) is a lethal and increasingly common infection in hospitalized patients. We assessed the impact of infectious diseases consultation (IDC) on clinical management and hospital mortality of SAB in 240 hospitalized patients in a retrospective cohort study. Patients who received IDC were older than those who did not (57.9 vs. 51.7 yr; $p = 0.05$), and were more likely to have a health care-associated infection (63% vs. 45%; $p < 0.01$). In patients who received IDC, there was a higher prevalence of severe complications of SAB such as central nervous system involvement (5% vs. 0%, $p = 0.01$), endocarditis (20% vs. 2%; $p < 0.01$), or osteomyelitis (15.6% vs. 3.4%; $p < 0.01$). Patients who received IDC had closer blood culture follow-up and better antibiotic selection, and were more likely to have pus or prosthetic material removed. Hospital mortality from SAB was lower in patients who received IDC than in those who did not (13.9% vs. 23.7%; $p = 0.05$). In multivariate survival analysis, IDC was associated with substantially lower hazard of hospital mortality during SAB (hazard 0.46; $p = 0.03$). This mortality benefit accrued predominantly in patients with methicillin-resistant SAB (hazard 0.3; $p < 0.01$), and in patients who did not require ICU admission (hazard 0.15; $p = 0.01$). In conclusion, IDC is associated with reduced mortality in patients with staphylococcal bacteremia.

INTRODUCTION

Staphylococcus aureus bacteremia (SAB) is lethal,⁵ and increasingly common in hospitals today.^{19,20} SAB is associated with substantial morbidity and hospital costs due to complications like endocarditis, central nervous system embolism, and septic arthritis.^{2,12,14,17}

The proper treatment of SAB is complex, involving proper antibiotic selection, drainage of pus and removal of prosthetic devices, and meticulous identification of morbid complications of SAB such as endocarditis.^{4,20} Because management is complex, it is not surprising that infectious diseases consultation (IDC) has been shown to be a critical component of the successful treatment of complicated SAB.⁹ However, to our knowledge IDC has not yet been shown to reduce mortality in patients who have SAB.^{15,16}

In light of recent trends to link health care payments with patient outcomes and increasing expectations that clinical interventions are supported by clinical evidence, it is important to demonstrate that the common (but not yet universal) practice of seeking IDC during SAB not

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only improves antibiotic use and increases the likelihood of cure of SAB,^{9,15} but also lowers mortality from SAB. Therefore, we characterized the impact of IDC on the clinical management of SAB in 240 patients with SAB at an academic tertiary care center.

METHODS

Study Design

Infection control practitioners prospectively reviewed the medical records of all patients who had blood culture isolates positive for *S. aureus* reported by the clinical microbiology laboratory at Dartmouth-Hitchcock Medical Center between 2002 and 2006, and used Centers for Disease Control definitions¹¹ to identify episodes of true infection. This study was nested within a comparison of clinical characteristics and outcomes in penicillin-sensitive and penicillin-resistant SAB,¹³ in which all patients who had penicillin-sensitive SAB during this time period were matched with the 4 most immediately contemporaneous patients who had methicillin-sensitive and methicillin-resistant SAB. Cases of SAB were selected without knowledge of IDC status or clinical outcome.

Medical Records Review

Infection control practitioners and study investigators collected additional data including IDC status, patient demographics, complications of SAB, length of stay, new intensive care unit (ICU) admission, date of death in the hospital or discharge date, cause of death, receipt and timing of IDC during the SAB episode, number of blood culture assessments and duration of bacteremia, time from first positive isolate to IDC request, IDC recommendations and adherence to them, and use of an intervention to treat focal complications of SAB, such as catheter or prosthetic joint removal or drainage of purulent collections.

Definitions

A Charlson morbidity score was assigned to each patient based on known diagnoses at the time of the first positive blood culture, as previously described.³ Cases were categorized as health care associated or community acquired according to CDC definitions.¹¹ We defined appropriate antibiotic selection as the use of an intravenous β -lactam, vancomycin, daptomycin, or linezolid for a *Staphylococcus* sensitive to the chosen agent. Specifically, we deemed as appropriate the use of non- β -lactam agents for methicillin-sensitive SAB even in the absence of an allergic contraindication to β -lactam use. SAB was defined as protracted if there were greater than 10 days between the first positive blood culture and the first negative blood culture. We deemed a death to be directly attributable to SAB if the clinicians evaluating the patient at the time of death documented SAB as a cause of death and the patient did not have another more prominent cause of death cited in the medical record.

Human Subjects Assurances

The study protocol was reviewed and approved by the Dartmouth College Committee for the Protection of Human Subjects.

Statistical Analysis

Standard descriptive statistics were used to compare demographic characteristics and complications of SAB in patients who did and did not receive IDC. A Cox proportional hazards regression model adjusting for characteristics that differed between groups in univariate comparisons was used to characterize the hazard of death during hospitalization according to whether patients received IDC. We confirmed that the proportional hazards assumption was not violated using log-log plots. Data were analyzed with STATA 9.2 (StataCorp, College Station, TX).

RESULTS

Patient Demographics

We studied 240 patients with SAB, of whom 122 (51%) received IDC. The characteristics of patients who did and did not receive IDC were similar except that patients who received IDC were older and more likely to have health care-associated SAB (Table 1). Health care-associated infections comprised 54.5% of total cases of SAB. Charlson scores did not differ between patients who had health care-associated vs. community-acquired SAB (4.8 vs. 4.3; $p = 0.21$), nor did the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA; 39.7% vs. 40.4%; $p = 0.92$). The mean Charlson score was similar between patients who did and did not receive IDC (4.8 vs. 4.4; $p = 0.40$).

Complications of SAB

Table 2 shows the complications of SAB in patients with and without IDC. Patients with severe clinical complications of SAB such as central nervous system involvement, endocarditis, and osteomyelitis were more likely to receive IDC. Three patients with endocarditis died of progressive sepsis without receiving IDC. One died within 24 hours of admission to the hospital, the second within 3 days, and the third after a month-long hospitalization. Patients with catheter-associated bacteremia were less likely to receive IDC.

Impact of IDC on the Clinical Management of SAB

Patients who received IDC were 45% more likely to have additional blood cultures obtained after the initial positive isolate (96.6% vs. 67.0%; $p < 0.01$), and the mean number of subsequent blood cultures was higher in patients who received IDC than in those who did not (2.1 vs. 1.4; $p < 0.01$). Appropriate antibiotics were selected more commonly in patients who received IDC (97.5% vs. 88.1%; $p < 0.01$). Furthermore, the mean duration of antibiotic therapy was longer in patients who received IDC (31.4 vs. 16.5 d; $p < 0.01$). Interventions to drain staphylococcal abscesses or to remove prosthetic devices were undertaken more frequently in patients who received IDC than in those who did not (35.2% vs. 19.5%; $p < 0.01$; Figure 1).

Impact of IDC on Clinical Outcomes

The mean duration of SAB was not different in patients who did or did not receive IDC (4.4 vs. 4.5 d; $p = 0.84$). However, the percentage of patients with protracted SAB was lower in patients who received IDC (2.7% vs. 10.0%; $p = 0.04$). The duration of hospitalization was similar in patients who did and did not receive IDC (25.7 vs. 28.4 d; $p = 0.58$), as was the duration of hospitalization after a positive culture result (21.3 vs. 18.6 d; $p = 0.47$). The likelihood and duration of ICU hospitalization were equivalent between groups (54.9% vs. 61.0%; $p = 0.34$; and 25.4 vs. 30.8 d; $p = 0.48$, respectively).

Impact of IDC on Hospital Mortality

Of 240 patients, 45 (19%) died during hospitalization. All-cause hospital mortality was lower in patients receiving IDC (13.9% vs. 23.7%; $p = 0.05$). The difference in all-cause hospital mortality was most pronounced in the subset of patients with endocarditis (12.0% vs. 100%; $p < 0.01$). In a Cox regression model adjusting for age and whether the infection was health care associated, all-cause hospital mortality after SAB was lower in subjects who received IDC (hazard ratio 0.5; $p = 0.02$; Figure 2). The relation between IDC and lower odds of all-cause hospital mortality remained when adjusting for multiple covariates (Table 3). Furthermore, if we excluded patients with penicillin-susceptible SAB, the relation between IDC and reduced mortality was unchanged (hazard 0.45; $p = 0.02$).

We also characterized the impact of IDC on hospital mortality attributed to SAB. Of 45 deaths, 88.9% were attributable to SAB. SAB-related hospital mortality was lower in patients who received IDC (12.4% vs. 22.1%; $p = 0.05$). When adjusting for age and health care-association in a Cox regression model, the hazard of SAB-related hospital mortality was lower in subjects who received IDC (0.4; $p = 0.01$). There was no impact of IDC on mortality that was not attributed to SAB (hazard 1.7; $p = 0.58$).

To address the possibility that some patients died so soon after admission that IDC was unfeasible, we repeated our analyses after excluding patients who died within 24 hours of admission. In the univariate analyses, IDC was still associated with lower mortality (11.6% vs. 22.5%; $p = 0.03$), a relation that persisted in our multivariate Cox regression model (hazard of death 0.4; $p = 0.01$).

The decrease in mortality associated with IDC was most pronounced in specific groups. For instance, in patients with MRSA bacteremia, the reduction in mortality associated with IDC was substantial (hazard 0.3; $p < 0.01$). Lastly, the IDC-associated reduction in mortality was most pronounced when excluding patients who were not admitted to the ICU (hazard ratio 0.15; $p = 0.01$).

DISCUSSION

Patients with SAB are often very ill, and vulnerable to lethal complications of SAB such as central nervous system emboli and endocarditis. Despite the availability of effective antibiotics and advances in supportive care, hospital mortality in patients with SAB remains high: 19% in our study. However, we found that IDC protects patients with SAB from death. This novel finding underscores how important expert consultation can be in the successful management of complex patients at high risk of death.

Our data are concordant with recent reports of lower mortality after IDC during *Candida* bloodstream infection²¹ and community-acquired pneumonia.¹⁸ However, our study is the first to show that IDC is associated with lower mortality after SAB. In addition, we have confirmed that IDC improves appropriate antibiotic selection,^{1,6–8,10} increases the likelihood of intravascular catheter removal, and also results in closer blood culture monitoring during bacteremia.¹⁵ Each intervention, driven by IDC, is likely to improve outcomes after SAB.

Other studies have not demonstrated an impact of IDC on mortality during SAB. A Swiss group¹⁶ has reported that IDC reduced mortality during SAB in univariate but not multivariate analyses. Important differences in study population may explain this discrepancy with our findings. Most notably, 49% of blood culture isolates in the current study were methicillin resistant, compared with a 2% MRSA prevalence in the Swiss study. As MRSA bacteremia has been reported to have a higher mortality rate than bacteremia with methicillin-sensitive *Staphylococcus aureus*,⁵ it is possible that patients with SAB from MRSA derived a greater benefit from IDC. Similarly, the higher proportion of MRSA blood culture isolates in the current study could have enhanced statistical power to detect a mortality benefit. Another study difference that may contribute to these discordant findings is that fully 82% of cases in the Swiss study received IDC. This more liberal consultation practice may have decreased these investigators' ability to detect a mortality impact of IDC.

In a well-conducted 2008 study, Jenkins and colleagues¹⁵ evaluated the clinical impact of routine IDC during SAB. While these authors, too, showed clear IDC-related increases in the frequency of diagnostic studies done during SAB, and an improvement in proper antimicrobial use attributable to IDC, they did not observe a significant reduction in the risk of treatment failure or mortality after routine IDC during SAB was instituted. Furthermore, they did not assess the impact of IDC on the drainage of purulent collections, an important therapeutic

intervention during staphylococcal infection. While the SAB cohort described by Jenkins et al had a similar proportion of cases from MRSA and equivalent mortality rates, there were methodologic differences that may explain the differences in our findings. First, their study was a pre- and post-intervention study, and not a direct comparison of outcomes in patients who did and did not receive IDC during the same time period. Second, because the proportion of SAB cases in which IDC was undertaken nearly doubled from 1 year to the next, the severity and associated comorbidities accompanying SAB may not be exactly comparable. For example, in their study the percentage of patients with cirrhosis was greater after routine IDC was instituted, as was the percentage of patients with endocarditis or metastatic infection. They point out that the latter difference may stem from improved detection of these complications due to an IDC-related intensification of the diagnostic workup. However, it is also possible that IDC improved outcomes during SAB in their cohort, but that this improvement was counterbalanced by consultation in sicker patients.

We acknowledge important limitations of the current study. This study was nested within a comparison of demographics and outcomes in penicillin-susceptible and penicillin-resistant SAB.¹³ As such, the 4 most immediately contemporaneous cases of SAB due to penicillin-resistant *Staphylococcus aureus* were selected as matched controls for every case due to penicillin-susceptible *Staphylococcus aureus* from 2002–2006. For this reason, selection bias has the potential to influence our results. However, as penicillin-resistant SAB cases were selected according to their timing alone, and not according to demographic or clinical characteristics, we doubt such bias would affect the association of IDC with reduced mortality during SAB. Nonetheless, in our statistical analyses we addressed the possibility of bias in 2 ways. First, we confirmed that the reduced odds of death in patients who received IDC remained when adjusting for antibiotic susceptibility in our multivariate survival analysis, and, separately, we stratified our analyses according to antibiotic susceptibility testing results, and still found a significant relation between IDC and lower mortality during SAB.

Because of the retrospective design of the current study, we cannot exclude the possibility that unmeasured differences between patients who did and did not receive IDC independently contributed to the clinical outcome differences between these groups. For instance, we did not control for illness severity when comparing outcomes between patients who did and did not receive IDC. It is theoretically possible, therefore, that unappreciated imbalances in illness severity between the 2 groups contributed to the association between lower mortality and IDC. Patients who received IDC, however, were more likely to suffer severe complications of SAB such as endocarditis and central nervous system emboli, so we doubt that any imbalance in initial illness severity biased toward lower mortality in patients who received IDC. Moreover, when adjusting for the identified demographic and clinical differences, we still saw significant clinical outcome differences that plausibly relate to the different treatment patients received with and without IDC.

Finally, retrospective reviewers were not blinded to IDC assignment. While this has the potential to bias outcome assessments, we chose quantifiable clinical outcomes such as duration of bacteremia, frequency of blood culture assessments, length of hospital stay, rate of therapeutic interventions, and in-hospital mortality in order to minimize the potential that bias could impact the assessment of clinical outcomes.

IDC was associated with significantly lower in-hospital mortality in complex patients with life-threatening SAB. Increased diagnostic evaluation, improved antibiotic selection, and more aggressive removal of purulent collections and prostheses likely explain why IDC was associated with lower mortality during SAB. IDC is thus an important component of SAB care, particularly in patients with SAB due to resistant organisms or metastatic complications of

SAB such as endocarditis. These data support the emerging concept of routine IDC during SAB,¹⁵ especially in complicated cases.

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Abbreviations

ICU	intensive care unit
IDC	infectious diseases consultation
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
SAB	<i>Staphylococcus aureus</i> bacteremia

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FIGURE 1.

Impact of infectious diseases consultation on the clinical management of *Staphylococcus aureus* bacteremia. Patients with infectious diseases consultation (IDC, black bars) were more likely to receive correct antibiotic therapy, have follow-up blood cultures, and to have an intervention aimed at draining pus or removing a prosthesis than patients who did not receive IDC (white bars).

FIGURE 2. Survival of patients who did (dotted line) or did not (solid line) receive infectious diseases consultation during *Staphylococcus aureus* bacteremia.

TABLE 1

Characteristics of Patients With *Staphylococcus aureus* Bacteremia, With and Without Infectious Diseases Consultation

Characteristic	IDC (n = 122)	No IDC (n = 118)	p Value *
	No. (%)	No. (%)	
Age, yr, mean	57.9	51.7	0.05
Male	72 (59.0)	67 (56.8)	0.73
MRSA	52 (42.6)	44 (37.3)	0.40
Health care-associated infection	77 (63.1)	54 (45.8)	<0.01
Injection drug user	3 (2.5)	1 (0.8)	0.33
Hemodialysis	22 (18.0)	28 (23.7)	0.32
HIV infected	10 (0.8)	0 (0)	0.33
Solid organ transplant recipient	2 (1.6)	7 (5.9)	0.08
Hematogenous malignancy	7 (5.7)	12 (10.2)	0.21
Diabetes mellitus	41 (33.6)	33 (28.0)	0.35
Alcohol abuse	13 (10.7)	7 (5.9)	0.19
Charlson score, mean	4.8	4.4	0.40

Abbreviations: HIV = human immunodeficiency virus.

* By t test.

TABLE 2

Clinical Characteristics of Patients With SAB, With and Without IDC

Complication	IDC (n = 122)	No IDC (n = 118)	p Value *
	No. (%)	No. (%)	
Septic arthritis	10 (8.2)	3 (2.5)	0.05
Prosthetic joint infection	4 (3.3)	1 (0.8)	0.19
Central nervous system involvement	7 (5.7)	0 (0)	<0.01
Endocarditis	25 (20.5)	3 (2.5)	<0.01
Abdominal abscess	3 (2.5)	4 (3.4)	0.67
Catheter-associated bacteremia	22 (18.0)	17 (38.1)	<0.01
Osteomyelitis	19 (15.6)	4 (3.4)	0.01
Pneumonia	13 (10.7)	23 (19.5)	0.06
Surgical site infection	8 (6.6)	4 (3.4)	0.29

* By t test.

TABLE 3

Multivariate Cox Regression Analyses of the Relation Between IDC and Mortality During SAB

	Odds of Mortality in Patients With IDC	Confidence Interval	p Value
1. Unadjusted	0.59	0.32–1.09	0.09
2. Age, health care-associated infection	0.48	0.26–0.90	0.02
3. Above + major complication	0.44	0.22–0.89	0.02
4. Above + Charlson score, antibiotic susceptibility, ICU admission	0.45	0.22–0.93	0.03