Published in final edited form as:
Infect Dis Clin Pract (Baltim Md). 2012 July 1; 20(4): 261–267. doi:10.1097/IPC.0b013e318255d67c.

Infectious Disease Consultation for *Staphylococcus aureus* Bacteremia Improves Patient Management and Outcomes

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Abstract

Background—*Staphylococcus aureus* bacteremia (SAB) is a common, severe infectious disease with accepted standards of care.

Methods—A retrospective cohort study of all 233 SAB cases at the Minneapolis Veterans Affairs Medical Center (MVAMC) between October 2004 and February 2008 was performed to measure the impact of Infectious Disease (ID) consultation on conformance to standards and patient outcomes. Outcomes were classified as survived without relapse, relapsed, or died without relapse. ID involvement was classified as consultation, curbside, or no involvement.

Results—ID involvement occurred in 179/233 cases (77%). Management conformed to accepted standards in 162/197 cases (82%) evaluable for conformance. ID involvement was associated with increased conformance in univariable analysis and multivariable analysis adjusted for propensity for ID consultation (OR 5.9, 95% CI 2.5 - 13.8). Relapse occurred in 14/156 cases (9%) in which therapy conformed to standards compared with 8/35 cases (23%) in which therapy did not conform to standards (p=0.045). Relapse was more common in older patients (OR 1.05, CI 1.01-1.09) and in cases without ID involvement (OR 3.02, CI 1.003-9.1). Death was associated with greater Charlson Index scores (OR 1.89, CI 1.4-2.5). Of 111 cases with definitely or possibly infected devices, relapse occurred in 9/92 cases (9.8%) in which the device was wholly or partially removed compared with 6/19 cases (32%) in which the device was left in place (p=0.02).

Conclusions—ID involvement in SAB cases was associated with increased adherence to accepted standards and fewer relapses. ID consultation should be performed for all SAB cases.

Keywords

Staphylococcus aureus; bacteremia; Referral and Consultation

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Conflicts of Interest: The authors have no conflicts of interest to disclose.

Introduction

S. aureus is the second most common cause of bacteremia in the developed world with an incidence of approximately 32/100,000 population.[1] *S. aureus* bacteremia (SAB) mortality ranges from 6-20% of cases.[2-4] Substantial clinical evidence has demonstrated that three elements of care are associated with better outcomes, and these have become widely accepted standards. First, intravenously administered β-lactam antibiotics are the best drugs for cases of methicillin susceptible *S. aureus* (MSSA).[5-9] Second, intravenous therapy must be given for minimum durations for specific types of infection.[3, 10-17] Third, devices known to be or suspected of being infected with *S. aureus* must be removed whenever possible.[5, 15, 18-21]

Six previous studies have suggested that infectious diseases (ID) consultation is associated with improved conformance to SAB management standards.[2, 4, 22-25] The impact on outcomes has been less clear. Studies have differed substantially in design, institutional setting, and outcome measures.[2-4, 22-25] For this study, we hypothesized that ID consultation would be associated with management that conformed to these widely accepted standards and would be associated with lower risk of relapse and of 12-week all-cause mortality. Here, we report our results and review the evidence of direct and indirect benefits from ID consultation for *S. aureus* bacteremia.

Materials and Methods

Samples

We identified all *S. aureus* isolates from blood cultures at the Minneapolis Veterans Affairs Medical Center (MVAMC) from October 1, 2004 to February 29, 2008. MVAMC has 279 inpatient beds including 80 in a Community Living Center (CLC) where patients receive acute rehabilitation and low-intensity medical care. CLC patients are managed by staff internists available in the hospital at all times, and access to consultative care is the same as for other inpatient locations. *S. aureus* identification and oxacillin susceptibility were performed with standard methods.[26] The MVAMC IRB considered analysis of the data for publication devoid of patient identifiers exempt under Title 38 Code of Federal Regulations 16.101 (b).

Medical Record Review

MVAMC medical records are entirely computerized. We systematically reviewed records for all patients with SAB. For each case, we extracted patient identification, age, underlying illnesses, location at onset, service making treatment decisions, acquisition, type of infection, infectious disease involvement, results of echocardiography, management, and relapse or death within 12 weeks of onset. Acquisition was classified as hospital-associated if symptoms and signs began after admission to hospital; healthcare-associated if the patient had been hospitalized, had lived in a long-term medical care facility, or had a medical procedure (such as dialysis, surgery, intravenous catheter insertion) in the preceding year;[27-29] or community-associated. SAB cases with focal infection sites were categorized as osteomyelitis; joint infection; endocarditis; intravenous catheter infection; skin, soft tissue; septic thrombophlebitis; pneumonia; UTI; wound; or other. Cases without apparent focal infection were categorized as “bacteremia.” Infections were categorized as “definite device-related” infections if the device was suspected of being infected and found to be culture-positive upon removal. Infections were categorized “possible device-related” infections if the device was suspected of being infected but was either not removed or was culture-negative upon removal. All other infections were considered not device-related.

All distinct SAB episodes in a single patient separated by at least one month without antimicrobial therapy or symptoms of infection were included. We reviewed records for 12 weeks after onset and classified patients into three categories: survived without relapse, relapsed, or died without relapse. Relapse was defined as either recurrent bacteremia or local (tissue) recurrence of infection. After initial analysis, patients who relapsed and subsequently died during the study period were included in the "relapsed" category. This did not materially affect the results or conclusions. Underlying illnesses were used to calculate Charlson co-morbidity scores.[30] The study was done in a Veterans Affairs hospital where ID consultation was not mandated and there were no direct financial incentives for ID consultation, but where the majority of patients with SAB had infectious disease involvement.

We considered that management conformed to widely accepted standards when three criteria were met. First, parenteral β-lactams were used for MSSA infections.[5-9] Vancomycin was considered appropriate when used for empirical therapy before susceptibilities were known, for cases with methicillin-resistant isolates, or when the case patient could not receive β-lactams because of allergy. Second, for cases of SAB associated with deep-seated infection or SAB cases of unknown source in which echocardiography was not done, parenteral antibiotic therapy was given for at least 28 days.[3, 10, 12, 15] Deep-seated infection included *S. aureus* infections of bone, joint, deep soft tissues, heart valves or other structures that are not easily excised or drained.[4, 29, 31, 32] Third, any infected prosthetic device (e.g., catheter, prosthetic heart valve, bone or joint prosthesis) was removed.[5, 15, 18-21] For cases with an easily removed or drained focus of infection (e.g., intravenous catheter, pneumonia, cystitis) or for SAB cases of unknown source in which echocardiography was done and did not reveal evidence of endocarditis, we considered 10 to 14 days of parenteral therapy adequate.[3, 10-13, 15-17] We did not require that echocardiography be performed.

ID involvement was classified as "consultation" if there was an ID consultation note or if a board certified ID physician was the attending physician. If there was no regular consultation, but primary team notes indicated that they discussed management with a named ID attending, the case was classified as "curbside consultation." The remainder were classified as "no ID involvement."

Exclusion Criteria

Cases were excluded from the conformance analysis if identification or antibiotic susceptibilities for the isolate were not available prior to death, or if care was withdrawn before a course of treatment was selected. Cases were excluded from the outcome analysis if care was withdrawn prior to the completion of the planned antibiotic therapy (Figure 1).

Analysis

We used Student's t test, chi-square analyses, and Fisher's exact test to determine significance of differences in baseline characteristics, conformance, and outcomes. We used binomial logistic regression to determine variables associated with improved conformance and multinomial logistic regression for patient outcome (Statistical Program for the Social Sciences [SPSS] for Windows, version 19, Chicago, Ill). Propensity scores were calculated to adjust for covariate imbalances between cases with and without ID involvement.[33, 34]

Results

During the 40-month study period, there were 233 separate episodes of SAB. Most patients were male, on the inpatient ward, and cared for by the internal medicine service (Table 1). The mean Charlson Index was 3.8. ID involvement ranged from 83 percent of patients with

onset in the CLC to 56 percent of patients in an intensive care unit (p=0.003). ID involvement occurred in 78-100% of patients with bone and joint infections, endocarditis, IV catheter related bacteremia, and skin and soft tissue infections, but only 56% of patients with primary bacteremia ($p < 0.001$). Baseline differences in percentages of ID involvement in various categories were similar, and the few differences between groups disappeared after propensity score adjustment (Table 1).

Conformance

Conformance was evaluable for 197 cases (Figure 1). Management conformed to accepted standards in 162 cases (82%). Reasons for non-conformance in the other 35 cases were that an infected device was not removed in 14 (40%); treatment duration was too short in 6 (17%); vancomycin was used to treat MSSA infections in 6 (17%); the patient received oral therapy for a portion of the treatment instead of parenteral therapy in 5 (14%), and multiple or miscellaneous reasons in four (11%).

Regular consultation occurred in 150 cases, a board certified ID physician was the attending physician in 3 cases, and curbside consultation was documented in 6 cases. In the remaining 38 cases, there was no ID involvement (Table 2). To simplify most analyses, we combined cases with regular consultation, an ID attending, and curbside consultation into the “ID involvement” category, which did not materially affect the results. Management conformed to standards in 141 of 159 cases (89%) with ID involvement, compared with 21 of 38 cases (55%) without ID involvement ($p <0.001$). Fewer cases with definite device-related infections conformed to accepted standards (58/76, 76%) compared with cases without infected devices (71/80, 89%, p=0.04).

In multivariable analysis, ID involvement was strongly associated with increased conformance to standards (OR adjusted with propensity scores 5.9, 95% CI 2.5 - 13.8). When curbside consultations were removed from the analysis, the association was nearly identical (OR 5.9, 95% CI 2.5 – 13.9). Age, Charlson Index, location at onset, service when blood culture turned positive, methicillin susceptibility, and whether the infection was device related were not significantly associated with conformance (data not shown).

Outcomes

Outcomes were evaluable for 191 cases (Figure 1). For the 12-week period after onset, *S. aureus* infection relapsed in 22 patients, and 22 patients died. In univariable analysis, relapse occurred in 14 (9%) of 156 cases in which therapy conformed to standards compared with eight (23%) of 35 cases in which therapy did not conform to standards (p=0.045). Relapse occurred in 15 (9.7%) of 155 cases with ID involvement compared with seven (19%) of 36 cases without ID involvement, but this difference was not significant (Table 2). Of 111 cases with definitely or possibly infected devices, relapse occurred in nine (9.8%) of 92 cases in which the device was wholly or partially removed compared with six (32%) of 19 cases in which the device was left in place ($p = 0.02$). Relapse rates were similar in cases with or without echocardiography (data not shown). In multivariable analysis, in which death and relapse were compared with the reference condition “survived with no relapse, ” significant associations were observed between relapse and both increasing age and lack of ID involvement (Table 3). Charlson Index was not associated with relapse. When the six curbside consultation cases were removed from multivariable analysis, the association between lack of ID involvement and relapse was weaker (OR 2.8, 95% CI 0.94 to 8.5). The other associations were slightly but not meaningfully different.

Five of the eleven patients with endocarditis died within 12 weeks, a rate which was significantly greater than for other categories of *S. aureus* infection (p=0.001). In

multivariable analysis, death was associated with greater Charlson Index scores and having bacteremia or endocarditis (Table 3). Death was less likely for patients on CLC than on other inpatient wards. Age and lack of ID involvement were not associated with death. Location at onset of infection, hospital service, origin of infection, methicillin resistance, and whether infection was device related or not were not associated with death or relapse.

Discussion

ID involvement was strongly associated with management that conformed to accepted standards, while lack of ID involvement was associated with relapse. This association was significant in multivariable analysis with or without adjustment by propensity scores. The effect of ID involvement appeared to be mediated by conformance with standards, so conformance was not included in the final model. In patients with infected devices, relapse was less likely if the infected device was removed. This confirms previous observations that devices infected with *S. aureus* must be removed whenever possible.[5, 15, 18-21]

Criteria for appropriate standards of SAB management have differed in all previous studies on the impact of ID consultation for SAB. To be conservative, we used criteria for "accepted standards" that were based on evidence that they are associated with improved outcomes and are common clinical practice. The first criterion was that intravenously administered β-lactam antibiotics were used to treat cases of MSSA.[5-9] In a recent study that supported the use of β-lactams for MSSA bacteremia, the adjusted odds ratio for treatment failure was 3.53 for those receiving vancomycin compared with those receiving cefazolin.[8] Second was that intravenous therapy was given for adequate durations. Evidence supports that deep-seated infections should be treated for 4 to 6 weeks and that bacteremia associated with minor infections or intravenous catheters should be treated for 10 to 14 days.[3, 10-13, 15-17] Third was that devices known to be or suspected of being infected were removed.[5, 15, 18-21] For example, in one recent study, relapse and death were 6.5 times more likely among patients who had an infected intravascular device left in place than among patients who had an infected device removed or those without an infected device.[3] Our study provided additional evidence that removal of an infected device decreases likelihood of relapse. Several other criteria have been proposed or used by investigators in just one or two studies, but they have not gained wide acceptance. We did not require that patients receive follow up blood cultures at defined intervals. Patients with persistently positive blood cultures often have other clinical signs or symptoms suggestive of progressive or disseminated infection.[29] No study has demonstrated that results of follow-up blood cultures affect outcomes independently of clinical signs or symptoms of infection. We did not require that echocardiography be performed. Echocardiography is often done and reveals unsuspected evidence of endocarditis or complications of endocarditis in a minority of cases, but no well-controlled study has demonstrated better outcomes for SAB cases with echocardiography compared with those without echocardiography.

Several themes have emerged from this and previous studies on the impact of ID consultation in SAB. ID consultation was associated with conformance to management standards in several studies (Table 4).[4, 22-25] Our study is the only one to demonstrate an association between ID involvement and a decreased risk of relapse. In one study, cure was more likely and relapse less likely in cases in which all ID consultation recommendations were followed.[3] In three studies, mortality was significantly lower in cases with ID consultation than in cases without ID consultation.[22, 24, 25] In two studies,[2, 35] mortality appeared lower in cases with ID consultation in univariable but not multivariable analysis. In one study, 30-day mortality decreased as the numbers of ID consultation performed increased, but no direct relationship between ID consultation and mortality in individual cases was reported.[23] Different mortality definitions were used, and in one,[22] the SAB cases

were derived from cases selected for a different study. Interestingly, the studies that showed statistically significant improvements in mortality with ID consultation were in hospitals with ID consultation in 33% to 67% of cases.[22, 24, 25] In studies (including ours) that did not observe a significant survival advantage with ID consultation, the proportion of cases with ID consultation involvement tended to be greater.[2, 4] As ID involvement increases above 50%, any statistically significant mortality benefit would be more difficult to detect. The data are also consistent with the hypothesis that frequent ID involvement led to greater awareness of appropriate SAB management among providers, which tended to improve outcomes regardless of whether ID had been consulted. While SAB is severe and common enough to be well studied, there is a growing body of literature from many countries documenting the value of ID consultation in management of other complicated infections. ID consultation has been associated with improved diagnostic workups,[36] improved antimicrobial selection,[36-40] improved patient outcomes,[37, 39] and lower costs.[38]

All studies on the value of ID consultation in SAB cases have been observational or quasiexperimental. Patient populations, definitions of what investigators considered appropriate therapy, types of consultation that were available, and outcome measurements differed considerably. Our study adds in several ways to the body of evidence. We evaluated both mortality and relapse, and our study is the first to demonstrate that ID involvement is associated with a lower risk of relapse. This is clinically significant, as relapse of SAB incurs additional risk to the patient and additional medical costs. We excluded patients in whom care was withdrawn during the study period, as treatment of their SAB was no longer a goal of care and this may have influenced whether or not ID was consulted. Furthermore, no changes in the availability of ID consultation or changes in hospital policy regarding ID consultation occurred during the study period.

This is the only study that has included cases with informal (“curbside”) consultation. Curbside consultation typically makes up a substantial percentage of the volume of infectious disease involvement.[41-45] If the ID service had less effective involvement in cases with curbside consultation than in cases with regular consultation, the effect of including them would be to weaken associations between ID consultation and outcome. In fact, conformance in cases with curbside consultation was excellent, and relapse did not occur.

Since the study was retrospective, there was no possibility that knowledge of the study could have influenced provider behavior. We chose a 12-week follow up period because it is sufficient to find disease recurrence, but it is unlikely that cases occurring in this interval represent new *S. aureus* infections. This study was done in a VA hospital where consultants had no financial incentives to provide consultation, and patients were not charged for consultations. This minimized the possibility of financial incentives influencing consultation practices.

This study had limitations. It was a retrospective observational study with 191 cases evaluable for outcome. ID involvement occurred in 77% of cases, and relapse occurred in only 12% of cases. These characteristics made it difficult for the study to detect a relationship between ID involvement and outcomes, but an association between lack of ID involvement and relapse did emerge. Twenty-three patients had more than one episode of bacteremia during the study period, and six of these patients had more than one recurrence. These cases were not completely independent. Curbside consultations may have occurred without documentation. If curbside consultations were missed, the effect would have been to dilute differences between the groups.

A growing body of evidence now strongly suggests that ID involvement increases conformance to widely accepted management standards and improves survival in SAB. In

addition, our study demonstrates that ID involvement reduces the risk of SAB relapse following treatment. We conclude that physicians should request infectious disease consultation for SAB treatment and health care organizations should consider policies that encourage or require infectious disease involvement in SAB cases.

Acknowledgments

We thank James R. Johnson, M.D., for helpful ideas and suggestions. AAP thanks the University of Minnesota Infectious Disease Fellowship Program and NIAID (T32-AI55433) for salary support. There are no other sources of financial support.

Sources of Support: AAP was supported by a National Institutes of Health training grant [T32-AI55433].

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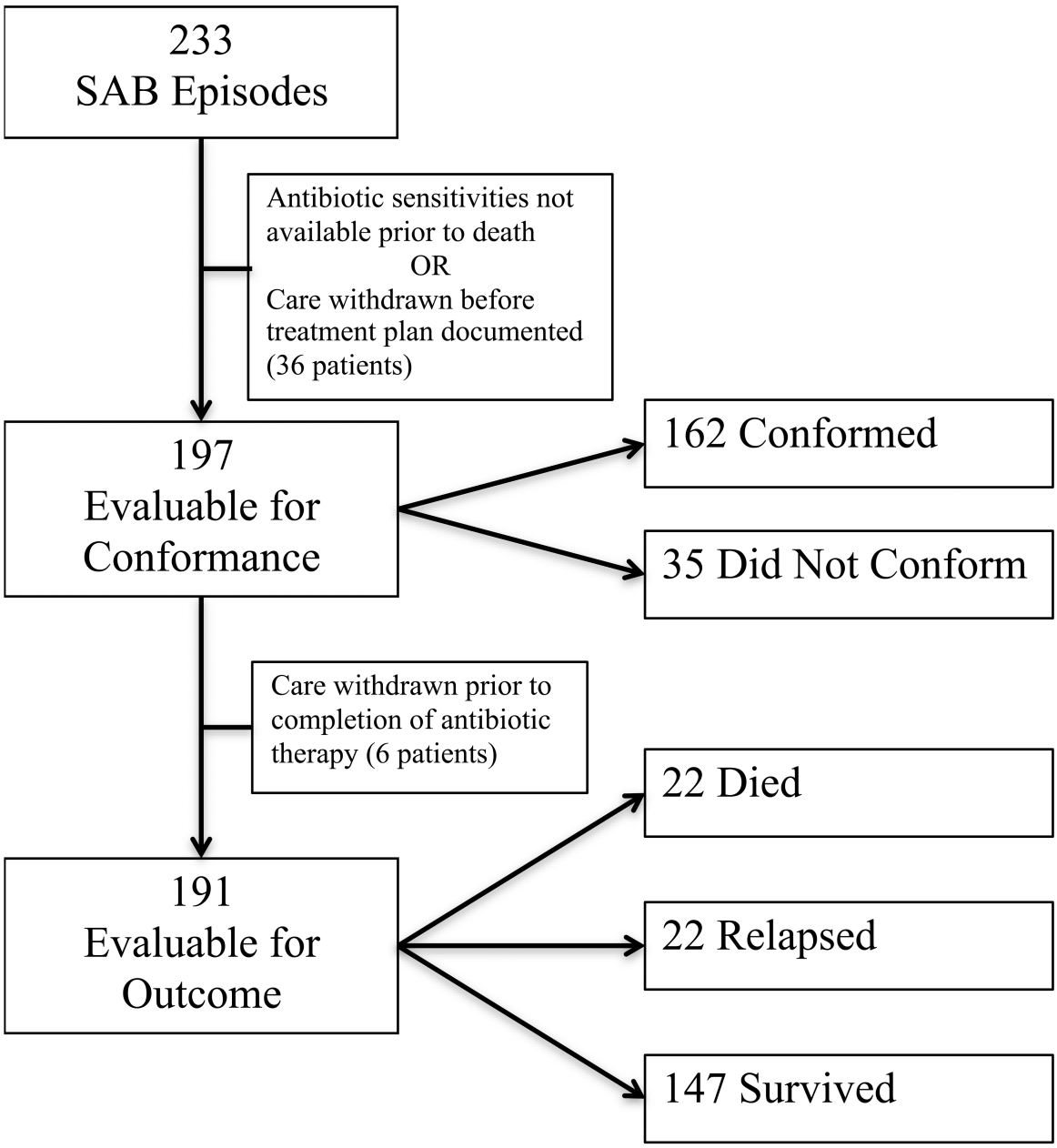

Figure 1. Study Design

Of the 233 cases, 197 were evaluable for conformance. Cases were not included in the conformance analysis if the patient died before culture results and sensitivities were available, or if care was withdrawn before a treatment plan was documented in the medical record. Six additional patients were excluded from the outcome analysis as care was withdrawn prior to the completion of the planned course of antibiotic therapy.

Table 1
Characteristics of Patients with SAB

	Infectious Diseases Involvement		
	Yes, n=179 (77%)	**No, n=54 (23%)**	**Total**
Age [years, mean ± SD, (median)]	66 ± 12 (65)	68 ± 12 (68)	
Male Gender [n]	178	52	
Charlson index (mean ± SD, median)	3.7 ± 2.5, 3	4.3 ± 2.8, 4	
Location at onset [n, (%)] *			
Community	15 (79)	4 (21)	19
Community Living Center	30 (83)	6 (17)	36
Inpatient ward	111 (81)	26 (19)	137
Intensive care	23 (56)	18 (44)	39
Management by [n, (%)]			
Internal medicine	124 (78)	36 (23)	160
Community Living Center	26 (84)	5 (16)	31
Other disciplines	29 (69)	13 (31)	42
MRSA [no (%)]	102 (75)	34 (25)	136
Acquisition [n, (%)]			
Hospital-associated	89 (73)	33 (27)	122
Healthcare-associated	72 (80)	18 (20)	90
Community-associated	18 (86)	3 (14)	21
Type of Infection [n, (%)]			
Bacteremia	27 (56)	21 (44)	48
Bone/Joint	34 (90)	4 (11)	38
Endocarditis	15 (100)	0 (0)	15
IV Catheter	40 (78)	11 (22)	51
Skin/Soft Tissue/Wound	37 (80)	9 (20)	46
Other	26 (74)	9 (26)	35
Device-Related Infections:			
Definitely Device Related	63 (80)	16 (20)	79
Possibly Device Related	38 (70)	16 (30)	54

* Number, percentages of each row with or without ID involvement.

Table 2

Conformance and Outcomes in Cases with Regular Consultations, Curbside Consultations, and No ID Involvement

	No ID Involvement	Curbside Consultation	Regular Consultation or ID Attending
Conformance with Accepted Standards *	21/38 (55%)	5/6 (83%)	136/153 (89%)
Outcomes †			
Survived, no relapse	25/36 (69%)	6/6 (100%)	116/149 (78%)
Relapse	7/36 (19%)	0/6 (0%)	15/149 (10%)
Died within 12 weeks of onset	4/36 (11%)	0/6 (0%)	18/149 (12%)

* 197 evaluable cases

† 191 evaluable cases

Infect Dis Clin Pract (Baltim Md). Author manuscript; available in PMC 2013 July 01.

Table 3

Multinomial Analysis of Outcomes*

Variable	Coefficient	SE	Wald X^2	p	Odds Ratio	95% CI
Relapse:						
Age	0.05	0.02	4.81	0.03	1.05	1.01-1.1
Charlson Index	0.08	0.11	0.45	0.5	1.08	0.9-1.3
CLC	1.7	1.0	3.0	0.09	5.4	0.8-38
Endocarditis and Bacteremia	1.3	1.0	1.7	0.2	0.3	0.04-1.9
No ID involvement	1.1	0.6	3.9	0.049	3.02	1.003-9.1
Death:						
Age	0.04	0.03	2.5	0.12	1.04	0.99-1.1
Charlson Index	0.6	0.15	17	<0.001	1.89	1.4-2.5
CLC	-2.4	1.0	5.9	0.02	0.09	0.01-0.6
Endocarditis and Bacteremia	2.2	1.1	4.3	0.04	8.8	1.1-69
No ID involvement	0.4	0.8	0.2	0.6	1.5	0.3-7.3

*Covariates included in the multinomial logistic regression model were age (continuous variable), Charlson Index (continuous variable), service (CLC, medicine, surgery), origin, type of infection, ID involvement (regular consultation, ID attending, and curbside consultation vs. no involvement), and propensity score for ID involvement. Dependent variable was relapse (top half) or death within 12 weeks (bottom half). The baseline outcome state was "survived without relapse."

[a]Variables with $p<0.1$ on univariable analysis or in preliminary models of multivariable analysis were included in the final multivariable analysis model.

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Table 4

Summary of literature on impact of ID consultation on SAB

Author, year	Study period	Study Design	SAB cases	Impact on Management	Impact on Cure, Relapse, or Mortality	Proportion with ID consultation
Fowler, 1998[3]	1994-1996	Prospective cohort	244	ID consultation advice followed in 46% of cases and partially or not followed in 54% of cases	Cure more likely and relapse less likely in cases in which ID consultation recommendations were followed. No significant mortality difference	100%
Mylotte, 2000[35]	1995-1999	Retrospective cohort	293	Not reported	Mortality benefit in cases with ID consultation in univariable but not multivariable analysis	36%
Kaech, 2006[2]	1998-2002	Retrospective cohort	308	Not reported	Mortality benefit in cases with ID consultation in univariable but not multivariable analysis	82%
Lahey, 2009[22]	2002-2006	Retrospective case control, derived from larger study	240	Follow-up blood culture, antibiotic selection, duration of therapy, and removal of pus or infected prosthetic devices improved in cases with ID consultation	Reduced in all-cause and SAB-related in hospital mortality in cases with ID consultation	51%
Reig, 2009[24]	2002-2007	Retrospective/prospective cohort	521	Echocardiography, bone scan, and ≥14 days of parenteral antimicrobial therapy more likely in cases with ID consultation	Reduced in-hospital and 90 day mortality in cases with ID consultation	Increased from 33% to >80%, 67% overall
Nagao, 2009[23]	2002-2008	Retrospective cohort	346	Echocardiography, follow-up blood cultures, ≥14 days of antimicrobial therapy, and appropriate drugs for MRSA infection improved as ID consultation numbers increased.	30-day mortality improved as ID consultation numbers increased	Not reported
Jenkins, 2008[4]	2004-2006	Retrospective cohort	234	Removal of intravascular foci (devices?), follow-up blood cultures, parenteral beta-lactam therapy, and ≥28 days of therapy more common after ID consultation became “routine”	No significant difference in cure, recurrence, or mortality	Increased from 53% to 90%, 69% overall
Honda, 2010[25]	2005-2007	Prospective cohort	341	Appropriate antimicrobial agents, transesophageal echocardiography, and appropriate planned duration of antimicrobial therapy more common in cases with ID consultation	Reduced 28-day mortality in cases with ID consultation	33%
Present Study	2004-2008	Retrospective cohort	233	Beta lactam therapy where possible, adequate duration of intravenous therapy, and drainage of pus or removal of infected devices more likely in cases with ID consultation	Greater risk of relapse in cases without ID consultation	77%

Abbreviations: ID consultation = infectious disease consultation