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The Value of Infectious Diseases Consultation in *Staphylococcus aureus* Bacteremia

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Abstract

Background—*Staphylococcus aureus* bacteremia results in substantial mortality. Infectious diseases specialist consultation can improve adherence to evidence-based management of *S. aureus* bacteremia, but its effect on mortality is unclear.

Methods—We performed a 2-year prospective cohort study of patients with *S. aureus* bacteremia at a large, tertiary care hospital. Patients who died within 2 days of diagnosis were excluded. Independent risk factors for 28-day mortality were determined.

Results—Among 341 patients with *S. aureus* bacteremia, 189 (55%) were male; 196 (58%) were Caucasian; 185 (54%) had methicillin-resistant *S. aureus;* 108 (32%) had nosocomial bacteremia; and 231 (68%) had a central venous catheter at the time of diagnosis. The median age was 56 years (range 22-95). One hundred eleven (33%) patients had an infectious diseases consultation. Fifty-four (16%) patients died with 28 days after diagnosis. Factors associated with mortality were intensive care unit admission ≤ 48 hours after the first positive blood culture [adjusted hazard ratio (aHR), 4.65; 95% confidence interval (CI), 2.65-8.18], cirrhosis (aHR, 4.44; 95% CI, 2.40-8.20), and advanced age (aHR, 1.27 per every 10 years of age; 95% CI, 1.08-1.50). Infectious diseases consultation was associated with a 56% reduction in 28-day mortality (aHR, 0.44; 95% CI, 0.22-0.89).

Conclusion—Only one-third of patients with *S. aureus* bacteremia in this cohort had an infectious diseases specialist consultation. Infectious diseases consultation was independently associated with a reduction in 28-day mortality. Routine infectious diseases consultation should be considered for patients with *S. aureus* bacteremia, especially those with higher severity of illness or multiple co-morbidities.

Keywords

Staphylococcus aureus bacteremia; Mortality; Infectious diseases consultation

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Staphylococcus aureus bacteremia causes significant morbidity and mortality. Mortality among patients with *S. aureus* bacteremia ranges from 20% to 50% despite the availability of effective antimicrobial therapy. [1-3] Major factors previously associated with mortality include severity of illness at the time of *S. aureus* bacteremia; inappropriate empiric antimicrobial therapy; the presence of co-morbid conditions such as diabetes mellitus; retained infectious foci; and bacteremia due to methicillin-resistant *S. aureus* (MRSA).[2, 4-6] Following an evidence-based approach is considered essential to treat *S. aureus* bacteremia, and consists of appropriate choice and duration of antimicrobial therapy, removal of infected foci, and detailed evaluation for metastatic infection or endocarditis.[7-9] Infectious diseases consultation has been associated with increasing adherence to evidence-based treatment of *S. aureus* bacteremia, [1, 10] however the impact of an infectious diseases consultation on the mortality of *S. aureus* bacteremia is uncertain. A recent German study suggested a survival benefit, however this study was performed in a healthcare delivery system different than the United States (U.S), and may have been confounded by temporal trends. The purpose of our study was to assess the effect of an infectious diseases consultation on mortality, independent of patient co-morbidities at a U.S. tertiary care center.

Methods

Participants and Setting

A prospective cohort study of patients with *S. aureus* bacteremia was performed between July 2005 and July 2007 at Barnes- Jewish Hospital, a 1252-bed, academic, tertiary care center in St. Louis, Missouri. Diagnosis of *S. aureus* bacteremia was defined as ≥ 1 blood culture positive for *S. aureus* with clinical evidence of infection. Patients who were less than 18 years old at the time of diagnosis of *S. aureus* bacteremia, had a history of *S. aureus* bacteremia in the prior 3 months, or a history of *S. aureus* endocarditis in the prior 12 months were excluded. A total of 347 patients with *S. aureus* bacteremia met these inclusion criteria. Six patients (2%) who died ≤ 2 days after their first positive blood culture were also excluded, leaving 341 patients for analysis.

Variables of interest and data collection

A 28-day all-cause mortality and 365-day all-cause mortality was used to assess the efficacy of infectious diseases consultation for *S. aureus* bacteremia. We tracked mortality for one year after the first positive blood culture of *S. aureus* by reviewing both medical records and the Social Security Death Index.[11] If there was no mortality data was available in medical chart, patients with any readmission beyond 28 days and 365 days after the initial diagnosis of *S. aureus* bacteremia were considered to be alive at 28 days and 365 days respectively. If there was no readmission data > 28 days or 365 days after diagnosis of *S. aureus* bacteremia available, Social Security Death Index was used to determine if patients died ≤ 28 days or between 29 and 365 days after the diagnosis of *S. aureus* bacteremia. Demographic characteristics, clinical data, and microbiology data were prospectively obtained from the medical record. Prolonged bacteremia was defined as the isolation of *S. aureus* from blood cultures on at least twice during the five days following the first positive culture.[12] Metastatic *S. aureus* infection was defined by microbiological or radiographic evidence of remote site of infection suggesting hematogenous spread.[10] Healthcare-associated, hospital onset bacteremia was defined by a positive blood culture obtained from patients who were hospitalized > 48 hours.[13] Healthcare-associated, community onset of bacteremia was defined as a positive blood culture ≤ 48 hours after hospitalization with the following criteria; presence of an invasive device, history of MRSA infection or colonization, surgery, hospitalization, dialysis, or residence in a long-term care facility in the 12 months preceding the culture.[13] Community-associated bacteremia was defined by a positive blood culture ≤

48 hours without meeting the criteria of healthcare associated community-onset bacteremia.[13]

During the study period, two general and one transplant infectious diseases inpatient consultation services were available. All infectious diseases consultation services were staffed by American Board of Internal Medicine (ABIM) board-certified infectious disease physicians who were Washington University faculty. Infectious diseases consultations were at the discretion of the primary care team. Acquisition of infectious diseases consultation was defined as consultation for the purpose of management for *S. aureus* bacteremia during the index hospitalization. If *S. aureus* bacteremia developed while infectious diseases consultation was already in place for another reason, the date of first positive blood culture was defined as the consult initiation date. We also assessed the following aspects of evidence-based management for *S. aureus* bacteremia: appropriateness of antimicrobial therapy, evaluation by transesophageal echocardiogram, removal or treatment of infected foci (i.e., medical devices or abscesses), and planned duration of treatment. Appropriateness of antimicrobial therapy was defined as use of parenteral antimicrobial agents [i.e., beta-lactam antimicrobials for patients with methicillin-susceptible *S. aureus* (MSSA) bacteremia, vancomycin, daptomycin, or linezolid for patients with MRSA bacteremia or *S. aureus* bacteremia with beta-lactam allergy]. Planned duration of treatment was appropriate when parenteral antimicrobial therapy was scheduled at least ≥ 2 weeks if a trans-esophageal echocardiogram showed no evidence of endocarditis, at least ≥ 4 weeks if trans-esophageal echocardiogram was not performed, at least ≥ 4 weeks if there was evidence of endocarditis, metastatic infection, or osteomyelitis.[1]

Statistical analyses

Categorical variables were compared between those with and without infectious diseases consults using Fisher's exact test, while age was compared between the two groups using the Mann-Whitney test. All tests for significance were 2-tailed, with P values <.05 considered significant.

We performed multivariable survival analyses predicting a 28-day all-cause mortality and 29-365 day all-cause mortality. For the 28-day mortality model, we used the extended Cox proportional hazards model because infectious diseases consultation was treated as a time-dependent variable, using the counting process style of input (i.e., Andersen-Gill model).[14] The value for consultation was 0 before the time of consultation and 1 after the consultation. Infectious diseases consultation was not modeled as a time-dependent variable for the 29-365 day mortality model because nearly all (108/111, 97%) consultations occurred within the first 28 days following the first positive culture. Potential risk factors were first assessed in bivariate analysis. The multivariable models were developed in forward stepwise fashion. Candidate variables with $P < .10$ in bivariate analysis were considered for inclusion in the models and variables were retained in the final models if $P < .05$. The proportional hazards assumption was assessed via –ln(-ln) survival curves, time-dependent covariates, and Shoenfeld residuals.[15, 16] The relationship of the time-dependent variable infectious diseases consultation and mortality during 365 days of follow-up was illustrated using an extended Kaplan-Meier estimator, which can be used with time-dependent covariates.[17] Extended Kaplan-Meier curves did not correspond to fixed patient cohorts, but allowed for the cohorts to be updated at each event time. Therefore, the patient without an infectious disease consultation was included in one curve, until consultation was obtained and the patient is then included in the consultation curve. The proportions illustrated should not be strictly interpreted; rather this method was intended to provide a realistic and useful graphical representation of time-varying covariate analyses. All analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, IL) and SAS version 9.1.3 (SAS Institute, Cary, NC). The Washington University Human Research Protection approved this project.

Results

Demographic characteristics and clinical data of the 341 patients with *S. aureus* bacteremia included in this study are shown in Table 1. One hundred eighty-five patients (54%) had MRSA bacteremia and 108 patients (32%) had hospital-onset of infection. One hundred-ten patients (32%) were admitted to the intensive care units (ICUs) ≤ 48 hours after the first positive blood culture.

In this cohort, 111 patients (33%) had infectious diseases consultation for management of *S. aureus* bacteremia. Factors associated with obtaining infectious diseases consultation are shown in Table 2. Eighty-seven consults (78%) were obtained within 5 days after the first positive blood culture (range 0-36 days). Patients with *S. aureus* bacteremia who received infectious diseases consultation were more likely to be Caucasian, and more likely to have congestive heart failure, orthopedic hardware, cardiac devices (i.e., implantable pacemaker/defibrillator), prosthetic valves, human immunodeficiency virus, community-associated *S. aureus* bacteremia, metastatic infection, and prolonged bacteremia. Patients who did not receive infectious diseases consultation were more likely to be chronic hemodialysis recipients, have a central venous catheter, history of smoking, or a current diagnosis of malignancy. Patients with infectious diseases consultation were more likely to receive appropriate antimicrobial agents, undergo trans-esophageal echocardiogram, and have appropriate planned duration of antimicrobial therapy (Table 3).

The overall all-cause 1-year mortality rate for patients with *S. aureus* bacteremia was 41% [140/341; 95% confidence interval (CI), 36-46 (%)]. Median length of time from diagnosis to death was 46.5 days. All-cause 28-day mortality was 16% [54/341; 95% CI, 12-20 (%)]. The extended Kaplan-Meier survival curve for patients with *S. aureus* bacteremia stratified by infectious disease consultation is shown in Figure 1. Patients with *S. aureus* bacteremia who died within 28 days of first positive blood culture were more likely to be older and treated with vancomycin, had chronic renal failure, cirrhosis, MRSA bacteremia, and have been admitted to the ICU ≤ 48 hours after the first positive blood culture (Table 4). In the multivariate model, factors independently associated with 28-day mortality among patients with *S. aureus* bacteremia were ICU admission ≤ 48 hours after the first positive blood culture [adjusted hazard ratio (aHR), 4.65; 95% confidence interval (CI), 2.65-8.18, P <. 001], cirrhosis (aHR, 4.44; 95% CI, 2.40-8.20, P <.001), and increasing age (aHR, 1.27; per every 10 years of age; 95% CI, 1.08-1.50, P =.004). Infectious diseases consultation was associated with decreased risk of 28-day mortality (aHR, 0.44; 95% CI, 0.22-0.89, P =.022) (Table 4).

For the 287 patients who survived 28 days after the initial positive culture, predictors of 1-year mortality after 28 days (i.e., 29-365 day) of the diagnosis of *S. aureus* bacteremia were elucidated. Factors independently associated with 1-year mortality for this group were malignancy at the time of bacteremia (aHR, 3.06; 95% CI, 1.97-4.74, P <.001), cirrhosis (aHR, 4.11; 95% CI, 2.02-8.33, P <.001), peripheral vascular disease (aHR, 2.58; 95% CI, 1.29-5.18, P = .008), advanced age (aHR, 1.16 per every 10 years of age, 95% CI, 1.01-1.35, P = .041), and ICU admission ≤ 48 hours after the first positive blood culture (aHR, 1.72; 95% CI, 1.09-2.73, P =.021). There was a no statistical difference in 1 year mortality after the diagnosis of *S. aureus* bacteremia between patients who received infectious diseases consultation and those who did not receive infectious diseases consultation (crude HR, 0.88; 95% CI, 0.56-1.38, P =.579).

Discussion

In this cohort of patients with *S. aureus* bacteremia, infectious diseases consultation was independently associated with a reduction in 28-day mortality, even after adjusting for preexisting co-morbidities and severity of disease. We determined 1-year mortality for the entire cohort using Social Security Death Index which has been validated for detecting deceased individuals including the date of death.[18, 19] Although previous studies conducted in US hospitals have described the positive effect of infectious diseases consultation on adherence to evidence-based management of *S. aureus* bacteremia, these studies failed to demonstrate a survival benefit.[1, 10] A recent retrospective study by Reig, et al. conducted in Germany noted a 40% reduction of in-hospital mortality of *S.aureus* bacteremia patients who received infectious diseases consultation. [20] Germany has a different healthcare delivery system compared to the United States, which may affect generalizability. Moreover, significant changes in practice might have occurred in their study period since the duration of study was longer (a 6-year period from 2002-2007). In contrast, our study demonstrated the benefit of infectious diseases consultation in mortality in a 2-year period. The German study only examined the difference in short-term mortality (i.e., in-hospital and at 90-day mortality) in combined population of retrospective and prospective subset. Our study investigated short-term and long-term mortality in an exclusively prospective cohort population.

In our study, infectious diseases consult was associated with 56% reduction in all-cause mortality among *S. aureus* bacteremic patients within 28 days of initial positive blood culture. This result may be due to improved evidence-based management after infectious diseases consultation. Patients in our cohort who had an infectious diseases consultation were significantly more likely to have received appropriate antimicrobial therapy, be evaluated by a trans-esophageal echocardiogram, and have an appropriate planned duration of antimicrobial therapy. We found patient-related factors including advanced age, cirrhosis, and ICU admission ≤ 48 hours after the first positive blood culture representing severity of illness were independently associated with 28-day mortality Our findings are consistent with previous studies. Elderly patients with *S. aureus* bacteremia are at higher risk of mortality[21, 22] A previous study demonstrated that cirrhosis has been associated with approximately a 2-fold increased risk of death in patients with *S. aureus* bacteremia.[23] Severity of illness, including septic shock, high Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and high Severity of Illness score are predictors of mortality of *S. aureus* bacteremia.[2, 5, 24] Our study is consistent with these prior reports in that patients with ICU admission ≤ 48 hours of the first positive blood culture were 4.6 times more likely to die.

In this study, the 28-day mortality rate after the diagnosis of *S. aureus* bacteremia was 15.8%, (the 28-day mortality rate reached 17.3% if 6 patients who died within 2 days of a positive blood culture being obtained were included) similar to published mortality rates (8-23%) for patients with *S. aureus* bacteremia in US tertiary care hospitals.[1, 2, 10] We found that 39 % of all deaths during the one year follow-up period occurred in the first 28 days after diagnosis of *S. aureus* bacteremia. This finding is consistent with previous studies that death after *S. aureus* bacteremia the most frequently occurred in the first month after the diagnosis.[2, 25] We found a significant difference in survival in the first 28 days between patients who had infectious diseases consultation and those who did not have infectious diseases consultation. Infectious diseases consultation did not confer additional survival benefit after 28 days, and patient comorbidities had a greater impact on mortality after the first four weeks after infection onset.

Prolonged bacteremia, metastatic infection, and the presence of prosthetic material were more likely to be associated with infectious diseases consultation in our study, suggesting that more complicated bacteremia resulted in infectious diseases consultation in our study hospital. Non-Caucasian patients with *S. aureus* bacteremia were less likely to receive infectious diseases consultation in our cohort; however, this was not significant after stratifying by receipt of chronic hemodialysis (data not shown). A previous study showed a low rate of adherence to infectious disease consultant recommendations among hemodialysis-dependent patients with *S. aureus* bacteremia.[1] Given the high frequency of central venous catheterization among cancer and hemodialysis patients, and the increased risk of complications [26, 27] due to *S. aureus* catheter-related bloodstream infections, our data suggests that theses two patients populations may benefit from infectious diseases consultation.

Our study had several limitations. Because our study was conducted at a single tertiary, academic medical center, our data may not be generalizable to other hospitals. Our result may be affected by referral bias since our institution is a tertiary academic medical center. Because our hospital serves an adult population, the survival benefit from infectious diseases consultation in this cohort may not apply to pediatric population with *S. aureus* bacteremia. Receipt of an infectious diseases consult was a non-random event among patients with *S. aureus* bacteremia in our study. Given limitation in clinical information at the time of diagnosis, we used ICU admission ≤ 48 hours at the time of diagnosis as a predictor of the severity of illness. Although this variable revealed highly correlated with mortality, more objective measures such as the APACHE II score and the Pitt bacteremia score may be more appropriate for assessing the severity of illness. [28] While we attempted to adjust for other risk factors for mortality in our study, we cannot exclude the possibility that unmeasured factors may have accounted for differences in mortality. Larger, multicenter studies in which methods such as propensity score modeling could be used to address these limitations.

Our study demonstrated a relationship between infectious diseases consultation and reduced short-term mortality. Patients who received an infectious diseases consultation in our study were more likely to receive evidence-based management. With rising prevalence of methicillin-resistant *S. aureus* and increasing use of medical devices, treatment of *S. aureus* bacteremia continues to be a challenge. Infectious diseases consultation may help guide comprehensive evaluation, adherence to evidence-based management, and improve clinical outcomes for these patients.

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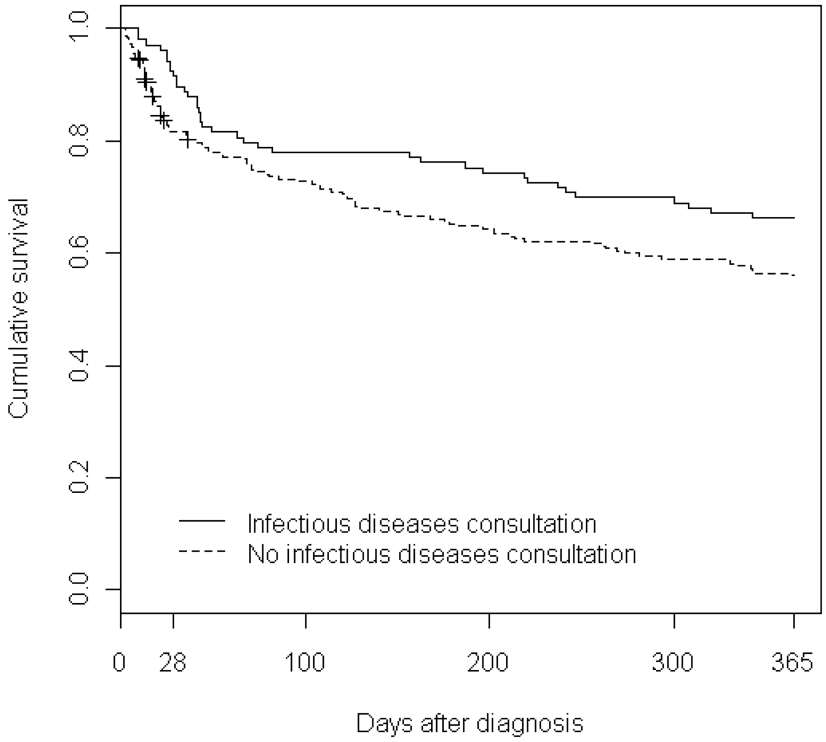

Number of patient at risk

Days after diagnosis	0	28	100	200	300	365
(+) ID consultation	111	102	87	83	77	74
(-) ID consultation	230	185	165	146	134	127

Figure 1. Extended Kaplan-Meier Curve of *S. aureus* Bacteremia Based on Infectious Diseases Consultation

Note. ID, infectious diseases.

Extended Kaplan-Meier curves did not correspond to fixed patient cohorts, but allowed for the cohorts to be updated at each event time. The patient without an infectious disease consultation was included in one curve, until consultation was obtained and the patient is then included in the consultation curve. Adjusted hazard ratio for 28-day mortality was 0.44 (P =.022) and the crude hazard ratio for 29-365 day mortality was 0.88 (P =.579).

Table 1
Demographic Characteristics of 341 Patients with *S. aureus* bacteremia

Variable	n (%)
Age, years, median (range)	56 (22-95)
Female gender	152 (45)
White race	196 (57)
Congestive heart failure	63 (18)
Coronary artery disease	80 (23)
COPD	54 (16)
Renal function	
Normal	243 (71)
CRF without dialysis	27 (8)
CRF with dialysis	71 (21)
Malignancy	85 (25)
Chronic skin disease	19 (6)
HIV	12 (4)
Peripheral vascular disease	23 (7)
Diabetes mellitus	111 (33)
Systemic corticosteroid use last 28 days	49 (14)
Cirrhosis	28 (8)
History of intravenous drug use	24 (7)
History of smoking	182 (53)
Alcohol use	95 (28)
Any transplant	26 (8)
Surgery during hospitalization	45 (13)
Prosthetic joint	29 (9)
Other orthopedic hardware	23 (7)
Vascular graft	48 (14)
Prosthetic valve	9 (3)
Cardiac device	30 (9)
ICU admission within 48 hours after the first positive blood culture	110 (32)
Central venous catheterization at the time of the first positive blood culture	231 (68)
MRSA bacteremia	185 (54)
Onset	
Community-associated	37 (11)
Healthcare-associated community onset	196 (57)
Healthcare-associated hospital onset	108 (32)
Metastatic infection *	59 (17)
Prolonged bacteremia	93 (27)
Infectious diseases consultation obtained	111 (33)
All-cause mortality ≤ 28 days after diagnosis	54 (16)
All-cause mortality ≤ 1year after diagnosis	140 (41)

Note. COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; HIV, human immunodeficiency virus; ICU, intensive care unit; MRSA, methicillin-resistant *S. aureus*.

*See methods for definition.

Table 2

Comparison of *S. aureus* Bacteremia Patients with and without Infectious Disease Consultation

Variable	Infectious diseases consultation		*P*
	Yes (n=111)	No (n=230)	
Age, years, median (range)	56 (23-95)	56 (22-92)	.67
Female gender	55 (50)	97 (42)	.20
White race	75 (68)	121 (53)	.01
Congestive heart failure	28 (25)	35 (15)	.04
Coronary artery disease	31 (28)	49 (21)	.22
COPD	17 (15)	37 (16)	.86
Renal function			
Normal	90 (81)	153 (67)	Ref
CRF without dialysis	8 (7)	19 (8)	.53
CRF with dialysis	13 (12)	58 (26)	<.01
Malignancy	18 (16)	67 (29)	.01
Chronic skin disease	7 (6)	12 (5)	.80
HIV	8 (7)	4 (2)	.02
Peripheral vascular disease	7 (6)	16 (7)	1.0
Diabetes mellitus	32 (29)	79 (34)	.33
Systemic corticosteroid use last 28 days	15 (14)	34 (15)	.87
Liver cirrhosis	6 (5)	22 (10)	.21
History of intravenous drug use	11 (10)	13 (6)	.18
History of smoking	49 (44)	133 (58)	.02
Alcohol use	33 (30)	62 (27)	.61
Any transplant	9 (8)	17 (8)	.83
Surgery during hospitalization	16 (14)	29 (13)	.73
Prosthetic joint	17 (15)	12 (4)	<.01
Other orthopedic hardware	18 (16)	5 (2)	<.01
Vascular graft	10 (9)	38 (17)	.07
Prosthetic valve	9 (8)	0	<.01
Cardiac device	16 (14)	14 (6)	.01
ICU admission within 48 hours after the first positive blood culture	35 (31)	75 (33)	.90
Central venous catheterization at the time of the first positive blood culture	63 (57)	168 (73)	<.01
MRSA	58 (52)	127 (55)	.64
Onset			
Community-associated	21 (19)	16 (7)	Ref
Healthcare-associated community onset	61 (55)	135 (59)	<.01
Healthcare-associated hospital onset	29 (26)	79 (34)	<.01
Metastatic infection	41 (37)	18 (8)	<.01
Prolonged bacteremia *	43 (39)	50 (22)	<.01

Note. COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; HIV, human immunodeficiency virus; ICU, intensive care unit; MRSA, methicillin-resistant *S. aureus*; Ref, reference.

* See methods for definition.

Table 3

Univariate Analysis of Evidence-Based Management based on Infectious Disease Consultation

Variable	Infectious diseases consultation		*P*
	Yes (n=111)	No (n=230)	
Appropriate antimicrobial choice[a]	100 (90)	182 (79)	.01
Appropriate planned duration of antimicrobial therapy (n=292)[b]	84/104 (81)	54/188 (29)	<.001
Retained infected focus present	14 (13)	34 (15)	.50
Trans-esophageal echocardiogram, performed	38 (34)	18 (8)	<.001

Note.

[a] See methods for definition.

[b] Duration of therapy was unspecified for 49 patients.

Table 4
Predictors of Mortality ≤ 28 Days after Diagnosis of *S. aureus* Bacteremia for 341 Patients

Variable	Died ≤ 28days after the diagnosis (n=54)	Survived > 28days after the diagnosis (n=287)	Crude HR (95% CI)	Adjusted HR (95% CI)
Age years, median, (range)	62 (22-91)	55 (23-95)	1.26 (1.07-1.49)	1.27 (1.08-1.50)
Female gender	27 (50)	125 (44)	1.31 (0.77-2.23)	
White race	35 (65)	161 (56)	1.39 (0.80-2.44)	
Congestive heart failure	13 (24)	50 (17)	1.41 (0.75-2.63)	
Coronary artery disease	14 (26)	66 (23)	1.15 (0.62-2.11)	
COPD	12 (22)	42 (15)	1.60 (0.84-3.04)	
Renal function				
Normal	36 (67)	207 (72)	1.00	
CRF without dialysis	11 (20)	16 (6)	3.22 (1.64-6.34)	
CRF with dialysis	7 (13)	64 (22)	0.65 (0.29-1.48)	
Malignancy	13 (24)	72 (25)	0.96 (0.51-1.79)	
Chronic skin disease	2 (4)	17 (6)	0.66 (0.16-2.65)	
HIV	1 (2)	11 (4)	0.48 (0.07-3.44)	
Peripheral vascular disease	3 (6)	20 (7)	0.80 (0.25-2.56)	
Diabetes mellitus	14 (26)	97 (34)	0.71 (0.39-1.31)	
Systemic corticosteroid use last 28 days	9 (17)	40 (14)	1.23 (0.60-2.51)	
Cirrhosis	14 (26)	14 (5)	4.72 (2.56-8.68)	4.44 (2.40-8.20)
History of intravenous drug use	4 (7)	20 (7)	1.03 (0.37-2.85)	
History of smoking	32 (59)	150 (52)	1.32 (0.77-2.28)	
Alcohol use	14 (26)	81 (28)	0.90 (0.49-1.66)	
Any transplant	4 (7)	22 (8)	0.95 (0.34-2.64)	
Surgery during hospitalization	5 (9)	40 (14)	0.66 (0.26-1.65)	
Prosthetic joint	3 (6)	26 (9)	0.60 (0.19-1.93)	
Prosthetic valve	2 (4)	7 (2)	1.33 (0.32-5.45)	
Other orthopedic hardware	4 (8)	19 (7)	1.11 (0.40-3.08)	
Vascular graft	3 (6)	45 (16)	0.34 (0.11-1.10)	
Cardiac device	8 (15)	22 (8)	1.81 (0.86-3.84)	
ICU admission ≤ 48 hours after the first positive blood culture	36 (67)	74 (26)	4.94 (2.81-8.71)	4.65 (2.65-8.18)
Central venous catheterization at the time of the first positive blood culture	41 (76)	190 (66)	1.58 (0.85-2.95)	
Vancomycin use	47 (87)	214 (75)	2.13 (0.96-4.71)	
Gentamicin use	3 (6)	28 (10)	0.55 (0.17-1.76)	
MRSA	35 (65)	150 (52)	1.61 (0.92-2.82)	
Onset				
Community-associated	3 (6)	34 (12)	1.00	
Healthcare-associated community onset	29 (54)	167 (58)	1.88 (0.57-6.16)	
Healthcare-associated hospital onset	22 (41)	86 (30)	2.63 (0.79-8.79)	

Variable	Died ≤ 28days after the diagnosis (n=54)	Survived > 28days after the diagnosis (n=287)	Crude HR (95% CI)	Adjusted HR (95% CI)
Any metastatic infection	9 (17)	50 (17)	0.95 (0.47-1.95)	
Prolonged bacteremia	13 (24)	80 (28)	0.84 (0.45-1.57)	
Infectious diseases consultation (time-dependent, covariate)	9 (17)	102 (36)	0.46 (0.23-0.93)	0.44 (0.22-0.89)

Note. CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; HIV, human immunodeficiency virus; ICU, intensive care unit; MRSA, methicillin-resistant *S. aureus*; Ref, reference.

Variables considered but not retained in the final model were chronic renal failure without dialysis, vascular graft, vancomycin use, and MRSA bacteremia.