

Clinical Identifiers of Complicated *Staphylococcus aureus* Bacteremia

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Background: Complications of *Staphylococcus aureus* bacteremia (SAB) are often difficult to identify. The ability to accurately predict the likelihood of these complications would impact patient management. This investigation sought to define readily available clinical characteristics that could help identify patients at risk for complicated SAB.

Methods: A prospective, observational cohort study was conducted from September 1994 through December 1999. Patients were followed up for 12 weeks after the initial positive blood culture result. The primary end point was complicated SAB (attributable mortality, complicated infection, embolic stroke, or recurrent *S aureus* infection during the 12-week follow-up period). The predictive model was validated using bootstrap resampling.

Results: Complicated SAB was present in 43% of 724 consecutive adult hospitalized patients identified during the study period. The full predictive model had a high discriminative ability (bootstrap-corrected *c* index, 0.78). The strongest predictor of complicated SAB was a positive follow-up blood culture result at 48 to 96 hours. A scoring system based on the presence or absence of 4 risk factors (community acquisition, skin examination findings suggesting acute systemic infection, persistent fever at 72 hours, and positive follow-up blood culture results at 48-96 hours) accurately identified complicated SAB (bootstrap-corrected *c* index, 0.76).

Conclusion: Readily available clinical variables can help identify patients at risk for complicated SAB.

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STAPHYLOCOCCUS AUREUS bacteremia (SAB) is a serious, common infection.^{1,2} Complications of SAB such as infective endocarditis³⁻⁶ and vertebral osteomyelitis⁷ are also common but are often difficult to identify at the time of the initial positive blood culture result.⁸⁻¹⁶ For example, in a recent report of 260 patients with SAB due to infective endocarditis, the diagnosis of endocarditis was not clinically suspected and was first detected at autopsy in 32% of patients.¹³ Failure to identify such complications of SAB may lead to relapsing bacteremia¹⁷ or catastrophic outcomes.¹⁸ Thus, predicting the likelihood of these complications may greatly impact patient management.

Prior investigations have sought to define accurate determinants of complicated SAB using clinical,¹⁹⁻²¹ serologic,^{10,11,14,15} or microbiologic²² characteristics, but these studies were limited by retrospective design, small sample size, or the need to use all-cause mortality as an analytical end point. The goal of the present study was to define clinical charac-

teristics that can help identify the presence of complicated SAB. We prospectively evaluated the largest cohort of patients with SAB ever reported to our knowledge and limited our definition of complicated SAB to patient mortality attributable to the infection or directly related sequelae.

METHODS

SUBJECTS AND SETTING

The study was approved by the Duke University Medical Center institutional review board, Durham, NC. Between September 1994 and December 1999, one investigator (V.G.F.) received daily reports from the clinical microbiology laboratory on all hospitalized patients with 1 or more blood culture result(s) positive for *S aureus*. Patients were then evaluated within 36 hours of the detection of bacteremia with a standard protocol. Patients were excluded from the study for the following reasons: polymicrobial infection (blood culture result positive for more than 1 pathogen), age younger than 18 years, neutropenia (white blood cell count $<1.0 \times 10^3/\mu\text{L}$), or death prior

to return of positive culture result. To preserve the assumption of independence of observations, only the first episode of SAB was included in the analysis.

ASSESSMENT OF CLINICAL DATA

Investigators recorded clinical data at the time the initial blood culture specimen became positive, in most cases prior to establishing the presence or absence of complications. A full description of the methods has been previously reported.²³

Demographic Characteristics

An episode of SAB was considered to be hospital acquired if a positive blood culture result was obtained after more than 72 hours of hospitalization; health care associated if it occurred within 72 hours of hospitalization from a patient with extensive contact with the health care system (nursing home residence, organ transplantation, hemodialysis dependence, presence of an indwelling intravascular catheter, or surgery within the previous 30 days); and community acquired if it occurred within 72 hours of admission from a patient without extensive health care contact.

Indicators of Existing Complications

Clinical evidence of central nervous system involvement was defined as the presence of disorientation, coma, or documentation of a new neurological deficit at the time of initial evaluation. Clinical evidence of an embolic or autoimmune event was defined as the presence of any of the following findings on initial evaluation: septic pulmonary emboli (radiographically defined), conjunctival hemorrhage, Janeway lesion, clinically evident emboli to sites other than central nervous system, evidence of glomerulonephritis, or the documented presence of Roth spots or Osler nodes. Skin examination findings suggesting the presence of acute systemic infection was defined as the presence of petechiae, vasculitis, infarcts, ecchymoses, or pustules. Findings with a firm alternate explanation (eg, actinic keratoses, burns, or surgical wounds) were excluded. A follow-up blood culture was drawn between 48 and 96 hours of the initial blood culture result positive for *S aureus*. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were assessed on the date of the first blood culture result positive for *S aureus*.²⁴ Septic shock,²⁵ soft tissue source,²⁶ and intravascular catheter source²⁷ were defined according to standard methods.

Treatment-Related Variables

Appropriate empiric antibiotic therapy was defined as the initiation of parenteral therapy to which the organism had documented susceptibility from the day before to 2 days after the initial positive blood culture result. Both aminoglycoside and rifampin use were considered to be present if the agent was administered during the period of bacteremia. Corticosteroid use was defined as either long-term low-dose or short-term high-dose therapy.²⁴ A removable focus of infection was defined as an intravascular device (eg, intravascular catheter or synthetic hemodialysis graft) presumed to be the source of SAB.

PATIENT FOLLOW-UP

All patients were followed up 12 weeks after the date of their first positive blood culture result positive for *S aureus*. Follow-up was performed by a single investigator (V.G.F.) by telephone contact with the patient or the patient's primary care physician.

PRIMARY END POINT

Our primary end point, complicated SAB, was defined as the presence of either (1) attributable mortality, (2) complicated infection present at the time of the initial hospitalization, (3) embolic stroke, or (4) recurrent infection within the 12-week follow-up period. These variables were selected because our objective was to identify clinical features that could help identify patients at risk for complicated SAB. Care was taken to ensure that ascertainment of these end point variables was fully independent of ascertainment of the candidate predictor variables. Attributable mortality included all patients who died with persistent signs or symptoms of systemic infection, positive blood culture results, or a persistent focus of infection in the absence of another explanation for death. This outcome was determined independent of knowledge of the predictor variables.

Patients with complicated infection had a site of infection remote from the primary focus caused by (1) hematogenous seeding (eg, endocarditis or vertebral osteomyelitis) or (2) extension of infection beyond the primary focus (eg, septic thrombophlebitis or abscess). To avoid confounding caused by capturing elements of the primary dependent variable in the predictor variable, all cases of complicated infection were independently defined by radiologic imaging, culture of *S aureus* from a normally sterile site, or the use of a validated diagnostic criteria.^{28,29} Embolic stroke was defined as radiologic evidence of an acute thromboembolic event. Finally, patients with recurrent infection had *S aureus* isolated from the bloodstream or other sterile body site within 12 weeks of the initial episode of bacteremia.

Patients with uncomplicated SAB exhibited no evidence of complicated or recurrent staphylococcal infection within the 12-week follow-up period. Designation of death due to a cause other than SAB was based on investigator evaluation during hospitalization and on the judgment of the patient's primary physician or death certificate records after discharge.

STATISTICAL ANALYSIS

Two logistic regression (full and reduced) models were developed to predict the presence of the primary end point, complicated SAB. Forty independent variables were initially selected based on clinical judgment and published literature.^{15,19-21,30-39} Prior to model fitting, cluster analysis was used to reduce the number of candidate variables.⁴⁰ Highly correlated variables were either combined into a composite variable or 1 variable was chosen to represent the domain. After this process, 25 candidate variables remained. Backward selection with a type I error rate of 0.01 was used to reach a final reduced model containing 4 predictor variables. Using these 4 predictor variables, a clinical scoring system was used⁴¹ to estimate the expected probability of complicated SAB. Because of their similar coefficient values, 3 of these variables were assigned a single point (community acquisition, skin examination findings suggesting the presence of acute systemic infection, and persistent fever at 72 hours). One variable, presence of a positive follow-up blood culture, was assigned 2 points because its coefficient was approximately twice that of the other 3 variables.

Both logistic regression models were internally validated using the bootstrap resampling technique.^{42,43} Model discrimination (the model's ability to distinguish patients with and without complicated SAB) was characterized by the *c* index.⁴⁴ Calibration was assessed with calibration graphs in which the actual probability was plotted against the predicted probability of complicated SAB.⁴³ Bias-corrected *c* indexes and calibration curves for the models were obtained from the averaged bootstrapped samples. All analyses were done with S-Plus 2000 software (Insightful Inc, Seattle, Wash).

Table 1. Demographic Characteristics of 724 Patients With *Staphylococcus aureus* Bacteremia

Characteristic	Value*
Age, y	58.5 ± 16.2
Race	
White	404 (56)
Black	293 (40)
Other	27 (4)
Male	409 (56)
Hospital service	
Medical	515 (71)
Surgical	193 (27)
Other	16 (2)
Route of acquisition	
Community	124 (17)
Health care-associated	272 (38)
Hospital	328 (45)
APACHE II score	15.4 ± 6.7
Acute Physiology Score	9.2 ± 5.7
HIV positive	34 (5)
Injection drug use	44 (6)
Hemodialysis-dependent patient	187 (26)
Diabetes mellitus	225 (31)
Corticosteroid use	102 (14)
Prosthetic devices	
Orthopedic	38 (5)
Cardiac†	57 (8)
Reported symptom duration, d	3.5 ± 6.1
Persistent fever at 72 h	280 (39)
Clinical evidence of central nervous system involvement	98 (14)
Septic shock (systolic blood pressure <90 mm Hg)	153 (21)
Skin examination findings suggesting the presence of acute systemic infection	131 (18)
Clinical evidence of embolic/autoimmune event	47 (6)
Diastolic or new murmur	35 (5)
Hematocrit, %	32.0 ± 6.0
Methicillin-resistant <i>S aureus</i>	286 (40)
Presumed source of infection	
Intravascular device	363 (50)
Soft tissue infection	267 (37)
No identifiable source	94 (13)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; HIV, human immunodeficiency virus.

*Data are number (percentage) or mean ± SD.

†Includes prosthetic cardiac valve, supporting valve ring, permanent pacemaker, or implantable cardioverter defibrillator.

RESULTS

During the 64-month study period, 724 patients had at least 1 blood culture result positive for *S aureus* and met inclusion criteria (**Table 1**). Twelve-week follow-up data were obtained on 722 of the 724 patients eligible for the analysis (99.7%); 84 patients died prior to return of a positive culture result and were not included in the present analysis. The mean patient age was 58.5 years; 40% of patients were black. Of the 724 patients, 124 (17%) had community-acquired SAB. At least 1 echocardiogram was obtained in 492 patients (68%) (432 [60%] transthoracic; 303 [42%] transesophageal). Follow-up blood cultures were obtained in 571 patients (79%).

Table 2 lists the diagnoses of the 310 patients with complicated SAB (43% of study patients). The most common type of complicated SAB was a complicated infec-

Table 2. Outcomes of 724 Patients With *Staphylococcus aureus* Bacteremia

Outcome	No. (%)
Complicated <i>S aureus</i> bacteremia*	310 (43)
Complicated infection present at the time of the initial hospitalization	228 (74)†
Infective endocarditis	89 (39)
Septic arthritis	54 (24)
Deep tissue abscess	41 (18)
Vertebral osteomyelitis	22 (10)
Epidural abscess	18 (8)
Septic thrombophlebitis	17 (8)
Psoas abscess	13 (6)
Meningitis	12 (5)
Other complications‡	16 (7)
Attributable mortality	86 (28)
Recurrent <i>S aureus</i> infection§	70 (23)
Recurrent <i>S aureus</i> bacteremia	49 (16)
<i>S aureus</i> isolated only from sterile body site other than blood	21 (7)
Embolus stroke	18 (6)
No complications due to <i>S aureus</i> bacteremia	412 (57)
Uncomplicated <i>S aureus</i> bacteremia	341 (47)
Death due to causes other than <i>S aureus</i> bacteremia¶	71 (10)
Outcomes missing	2 (<1)

*Patients may have more than 1 complication. Patients with more than 1 complication were only entered into analyses for prediction once.

†Denominator is 310 for “complicated infection present at the time of the initial hospitalization” (“complicated infection”), “attributable mortality,” “recurrent *S aureus* infections,” and “embolic stroke.” Denominator for each subcategory of “complicated infection” is 228. Because more than 1 site of “complicated infection” could be present in the same patient, the sum of subcategories of “complicated infection” was 282.

‡Includes patients with mycotic aneurysm (5), empyema (5), pericarditis (3), and pneumonia (3).

§Among the 70 patients with recurrent *S aureus* infection, 19 occurred within the first month, 26 occurred within the second month, and 25 occurred within the third month.

||Includes patients with deep tissue abscesses (13), osteomyelitis (3), epidural abscesses (2), and 1 each with hematogenous brain abscess, mycotic aneurysm, and empyema.

¶Includes patients dying of malignancy (13); cardiac arrhythmia (11); congestive heart failure (6); infection with other organism (6); intracranial event sustained prior to onset of *S aureus* bacteremia (5); aspiration event (5); pulmonary embolus (4); intra-abdominal catastrophe (eg, perforation or ischemic bowel) (4); withdrawal of medical support (3); myocardial infarction (2); autoimmune disease (eg, hepatitis or pneumonitis) (2); adult respiratory distress syndrome (2); hemorrhage (gastrointestinal and postoperative) (2); and 1 each from fibrosing peritonitis, delay in hemodialysis, progressive dementia, trauma, burn, and ischemia of extremities.

tion present at the time of the initial hospitalization, which occurred in 228 patients (74%). Among the 228 patients with complicated infections, endocarditis accounted for 39% (12% of the entire 724 patients). Endocarditis was present in 20 (67%) of the 30 patients with prosthetic valves. Other complicated infections included septic arthritis (24%), deep tissue abscesses (18%), and vertebral osteomyelitis (10%).

MULTIVARIABLE MODELING

Table 3 summarizes results from the full model identifying complicated SAB. The calibration curve for this model showed a close match between predicted and actual probabilities of complicated SAB (**Figure 1**). Pa-

Table 3. Predictors of Complicated *Staphylococcus aureus* Bacteremia*

Variable	Odds Ratio (95% CI)	P Value
Demographic characteristics		
Surgical hospital service†	1.83 (1.18-2.82)	.006
Community acquired‡	3.08 (1.80-5.28)	<.001
Orthopedic or other prosthetic device	1.77 (1.01-3.11)	.05
Cardiac device	1.70 (0.82-3.51)	.16
Sex	0.84 (0.58-1.22)	.37
HIV positive or injection drug use	1.89 (0.92-3.86)	.09
Age	1.01 (1.00-1.02)	.05
Diabetes mellitus	1.10 (0.74-1.64)	.62
Race	1.15 (0.76-1.72)	.51
Indicators of existing complications		
Skin examination findings suggesting the presence of acute systemic infection	1.80 (1.10-2.95)	.02
New or diastolic murmur	2.46 (1.01-6.02)	.05
Clinical evidence of embolic/autoimmune events	2.05 (0.85-4.95)	.11
Clinical evidence of central nervous system involvement	1.30 (0.74-2.30)	.36
Reported duration of symptoms	1.04 (1.00-1.08)	.06
Septic shock	1.22 (0.77-1.94)	.40
Persistent fever at 72 h	2.00 (1.36-2.92)	<.001
Positive follow-up blood culture result	4.94 (3.37-7.25)	<.001
Treatment-related variables		
Vancomycin therapy	1.16 (0.78-1.74)	.46
Aminoglycoside use	1.42 (0.78-2.59)	.25
Rifampin use	0.87 (0.50-1.50)	.62
Appropriate empiric antibiotic therapy	0.80 (0.44-1.46)	.46
Corticosteroid use	1.63 (0.96-2.77)	.07
Removable source of <i>S aureus</i> bacteremia not removed	1.23 (0.69-2.20)	.49

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

*This analysis included 699 of the 724 patients; 2 patients were missing the outcome variable, 14 patients were missing at least 1 of the predictor variables, and 9 patients were excluded from analysis because they died before persistent fever at 72 hours could be documented or follow-up blood culture could be drawn. Original model *c* index, 0.81; bootstrap bias corrected *c* index, 0.78.

†Patient residence on a surgical or obstetric service at the time of the initial positive blood culture result.

‡“Health care or hospital associated” and “negative follow-up blood culture result or not done” are referent categories.

tients with community-acquired SAB were more likely to have complications compared with patients with health care–associated or hospital-acquired bacteremia (odds ratio [OR], 3.08; 95% confidence interval [CI], 1.80-5.28). Residence on a surgical service, presence of an orthopedic or other prosthetic device, and advancing age were also significantly associated with complicated SAB.

INDICATORS OF EXISTING COMPLICATIONS

Patients in the full prognostic model with a positive follow-up blood culture result (*n*=280, 39% of overall cohort) were significantly more likely to have complicated SAB (OR, 4.94; 95% CI, 3.37-7.25) compared with patients with a follow-up blood culture yielding no growth or patients in whom a follow-up blood culture was not drawn. Other important indicators of existing complications of SAB included persistent fever 72 hours after the initial positive blood culture result, skin examina-

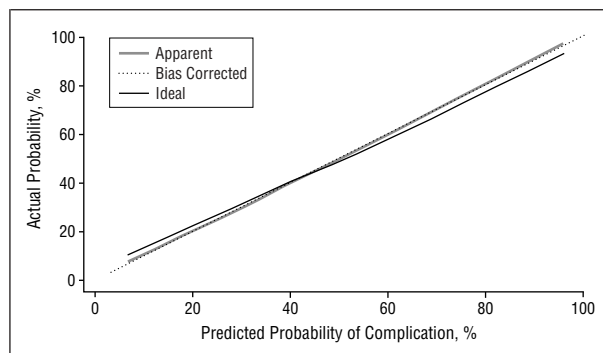


Figure 1. The calibration curve for the full model predicting the presence of complicated *Staphylococcus aureus* bacteremia. The ideal line represents perfect calibration, the apparent line represents calibration in the original full model, and the bias-corrected line represents the bootstrap-corrected calibration for the model.

tion findings suggesting the presence of acute systemic infection, and a new or diastolic murmur. Neither APACHE II score nor Acute Physiology Score were significantly associated with complicated SAB when they were added to the full predictive model.

TREATMENT VARIABLES

Several treatment variables were considered as potential predictors of subsequent complicated SAB in the final model. Because vancomycin therapy was highly correlated with methicillin-resistant *S aureus* (MRSA), only one of these variables could be simultaneously included in the final model. Vancomycin therapy was not found to be significantly associated with complicated SAB in the final model (OR, 1.16; 95% CI, 0.78-1.74). Similarly, when infection with MRSA was substituted for vancomycin therapy in the final model, it was also not significantly associated with complicated SAB (OR, 1.34; 95% CI, 0.90-1.98). Neither appropriate empiric antibiotic therapy nor adjunctive antibiotic therapy (aminoglycoside or rifampin use) were significantly associated with complicated SAB.

CALCULATING AN INDIVIDUAL PATIENT'S RISK OF COMPLICATIONS

Using a *P* value cutoff of .01, a reduced model identifying complicated SAB was generated. This reduced model provided very good discriminative ability (bootstrap-corrected *c* index, 0.76) (Table 4). Four variables remained significantly associated with complicated SAB in the reduced model. These significant variables included a positive follow-up blood culture result (OR, 5.58; 95% CI, 3.93-7.95), community acquisition (OR, 3.10; 95% CI, 1.96-4.87), persistent fever at 72 hours (OR, 2.23; 95% CI, 1.55-3.12), and skin examination findings suggesting the presence of acute systemic infection (OR, 2.04; 95% CI, 1.30-3.18). Using standard methods,⁴¹ a risk-scoring system based on the presence of these 4 risk factors was generated to estimate the likelihood of complicated SAB (Figure 2). The predicted rate of complications was 16% if no risk factors were present and rose with the presence of each risk factor.

Table 4. Reduced Prognostic Model of Complicated *Staphylococcus aureus* Bacteremia*

Variable	Odds Ratio (95% Confidence Interval)	P Value
Community acquired†	3.10 (1.96-4.87)	<.001
Skin examination findings suggesting the presence of acute systemic infection	2.04 (1.30-3.18)	.002
Positive follow-up blood culture result‡	5.58 (3.93-7.95)	<.001
Persistent fever at 72 h	2.23 (1.55-3.12)	<.001

*This analysis included 711 of the 724 patients; 2 patients were missing the outcome variable, 2 patients were missing skin examination, and 9 patients were excluded from analysis because they died before persistent fever at 72 hours could be documented or follow-up blood culture could be drawn. Original reduced model *c* index, 0.78; bootstrap corrected *c* index, 0.76.

†“Health care or hospital associated” is referent category.

‡“Negative follow-up blood culture result or not done” is referent category.

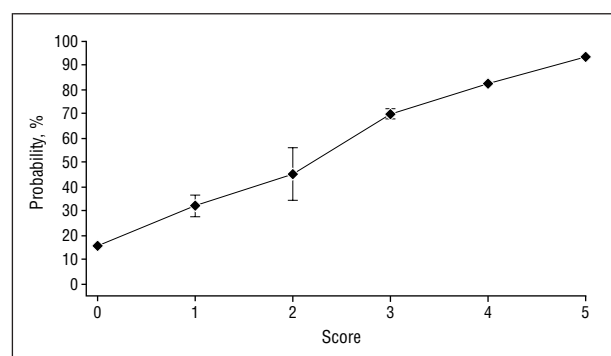


Figure 2. Association between the *Staphylococcus aureus* bacteremia (SAB) score and probability of complicated SAB. *Staphylococcus aureus* bacteremia score = sum of individual risk factor points (1 point for “community-acquired SAB,” “skin examination findings suggesting the presence of acute systemic infection,” and “persistent fever at 72 hours”; 2 points for “positive follow-up blood culture result at 48-96 hours”). The bars indicate range of predicted probabilities of complicated SAB for each corresponding risk score (only one way to achieve a score of 0, 4, or 5).

COMMENT

The presence of infectious complications of SAB alters patient management. Thus, the ability to accurately identify these complications would help clinicians make specific management decisions about a particular patient with SAB. The results of the present investigation enhance the clinician’s ability to identify complications of SAB in 2 ways. First, the large sample size and prospective design allowed us to evaluate many potential predictors of non-lethal and lethal complications of SAB and to avoid confounding issues associated with the use of all-cause mortality as a primary end point. Second, to our knowledge, this is the first investigation to develop a reduced model of 4 variables and create a clinically relevant method to estimate an individual patient’s probability for complications.

Although a variety of strategies have been attempted to identify patients with complicated SAB,^{10,11,14,15,19-22} none have produced a reliable means of making this distinction. The present study establishes 4 readily available clinical characteristics that help to identify the presence of

complicated SAB. Patients with even one of these 4 characteristics were at high risk for complicated SAB (expected probability approximately 35%). Among such patients, the use of sophisticated, invasive diagnostic tests and prolonged antibiotic treatment would be particularly important to identify and treat complications that might otherwise be clinically inapparent. In contrast, patients with none of the identified characteristics have a comparatively low risk of complications. Such patients may be suitable for shorter courses of antibiotic therapy and/or less complex testing. However, even in the absence of any of these identified characteristics, the risk of complicated SAB is still approximately 16%. Thus, clinicians should remain vigilant for complications in all patients with SAB.

One of the most important predictors of complicated SAB in both the full and reduced models was the presence of a positive follow-up blood culture result. This finding agrees with the observations of a small retrospective report.³⁵ Because follow-up blood cultures were obtained in over 75% of our large prospective cohort, the present study was able to definitively establish the association between a positive follow-up blood culture result and complicated *S aureus* infection. The results of this investigation underscore the need to obtain follow-up blood cultures in patients with SAB even if the patient’s symptoms have completely resolved.

Community acquisition was also an important risk factor of complicated SAB. Although only approximately 17% of study patients developed community-acquired SAB in the absence of recent health care contact, the risk of complicated infection among these patients was high. By contrast, most study patients developed hospital-acquired or health care-associated SAB, but the risk of complicated infection among these patients was lower. These findings agree with previous reports^{21,39} and suggest an important distinction in the risk of complicated infection according to the setting in which SAB was acquired.

Physical examination findings were also helpful in identifying complicated SAB in the reduced model. Fever persisting more than 72 hours was associated with complicated SAB in the present and a prior retrospective study.³⁵ Skin abnormalities suggesting the presence of active systemic infection were also associated with complicated SAB in the present and a previous study.²⁹ Collectively, these data suggest that readily available clinical characteristics can assist in identifying patients at risk for complicated SAB.

Patients with MRSA bacteremia had similar outcomes to patients with methicillin-susceptible SAB, a finding consistent with some^{20,32,38,45} but not all^{31,37,46,47} prior reports. Those studies finding a relationship between infection with MRSA and patient outcome may have been limited by inadequate adjustment for underlying patient comorbid conditions.^{32,38} Because patients infected with MRSA tend to be older⁴⁸ and have more comorbid conditions³⁸ than patients infected with methicillin-susceptible *S aureus*, any evaluation of the impact of MRSA on patient outcome should adjust for these confounding characteristics.^{20,32,38,48} After making such adjustments, we were unable to identify a higher rate of complications among patients infected with MRSA.

Neither APACHE II score^{15,45} nor the Acute Physiology Score^{19,20} was significantly associated with complicated SAB in our study. This may be due to the fact that the APACHE II scoring system was designed to predict all-cause mortality among patients admitted to an intensive care unit. However, the objective of the present study was to identify the presence of complicated SAB rather than to identify which patients were most likely to die of comorbid illnesses. Because most complications in this study were nonfatal, APACHE II scoring was unlikely to contribute significantly to the predictive model.

The overall prevalence of endocarditis in the present study (approximately 12%) was lower than in a prior subset investigation from this cohort (approximately 25%).⁴⁹ This difference in endocarditis prevalence is likely due to the fact that only selected patients (eg, patients undergoing both transthoracic and transesophageal echocardiography) were included in the former study.⁴⁹ The overall endocarditis prevalence rate of approximately 12% among unselected patients with SAB in the present study is similar to that reported in a recent prospective, multicenter investigation of over 500 patients with SAB.⁵⁰ Our observed rate of prosthetic valve endocarditis among patients with SAB (67%) is also consistent with a previous report.⁵¹

There are several limitations to the present investigation. Patients dying prior to return of blood culture results were not included in the current analysis because such patients have important differences from patients alive at the time of notification of a positive blood culture result.⁵² We were not fully able to model the selection of subsequent treatments in response to laboratory abnormalities or symptoms. However, because most complications (>70%) were present around the time of the initial positive blood culture result, we do not think that this would considerably change our conclusions.

It is also possible that overlap might exist between independent predictor variables and our primary end point. However, such a possible confounding influence was avoided by independently ascertaining outcome and predictor variables. In addition, other clinical features (eg, septic shock and new or diastolic murmur) are known to be independent predictors of patient morbidity and mortality. Independently, both of these clinical features were statistically significant predictors of complicated SAB (data not shown). Our multivariable model, however, shows that after adjusting for other clinical characteristics, these features do not achieve statistical significance. This may reflect the study definition of complicated bacteremia or the relative infrequency of these features in our cohort.

Because the study was conducted at a tertiary care center, referral bias or more frequent use of diagnostic tests such as transesophageal echocardiography could be present. However, because our rates of complicated SAB agree with previous reports,^{50,53,54} we do not believe that these sources of potential bias pose a significant problem. Because this was an observational cohort study, not all patients received the same diagnostic evaluation to define complications. However, we doubt that cases of complicated SAB were missed, since the mortality of untreated SAB is approximately 80%⁵⁵ and 12-week follow-up was available for over 99% of patients. Because our prog-

nostic models were developed using data from a single institution, generalizability of our results should be confirmed with independent samples of patients from other hospitals. Finally, as with any clinical instrument, the results of this investigation are intended to supplement but never replace clinical judgment.

We believe that the findings in this study establish several clinical variables that can help clinicians to identify patients with complicated SAB. Future investigations are needed to validate these findings among patients with SAB in different health care systems and countries. In addition, the impact of host and pathogen genetic characteristics on the clinical outcome of patients with SAB remains to be defined.

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