Staphylococcus aureus Bacteremia: Predictors of 30-Day Mortality in a Large Cohort

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We performed a retrospective study of a large cohort of patients who had episodes of Staphylococcus aureus bacteremia (SAB) from January 1995 through February 1999 at 1 medical center to identify predictors of 30-day mortality in SAB. Among 293 patients with episodes of SAB, 68 died (23.2%) within 30 days of onset. There was no significant difference in 30-day mortality associated with treatment with vancomycin, a β-lactam, or a miscellaneous group of antimicrobial agents (P = .180). By logistic regression, an acute physiology score (a component of the acute physiology and chronic health evaluation [APACHE III]) ≥60 at onset of SAB was the most important predictor of 30-day mortality (odds ratio [OR], 15.7). Other significant predictors were lung (OR, 5.8) or unknown (OR, 4.1) focus of SAB, age ≥65 years (OR, 2.0), and diabetes mellitus (OR, 2.4). Future investigators of SAB should take into consideration acute severity of illness at onset as well as other factors when evaluating or comparing outcomes.

Staphylococcus aureus bacteremia (SAB) continues to be a major problem related to both community-acquired and nosocomial infection [1, 2]. In the community setting, S. aureus has a propensity to cause serious invasive infection in normal hosts as well as those with debilitating illnesses. In the hospital setting, both methicillin-resistant S. aureus (MRSA) and methicillin-susceptible S. aureus (MSSA) are major causes of bloodstream infection [1–3]. In particular, iv catheter–related SAB has emerged as a major nosocomial infection problem [1]. In addition, S. aureus has a propensity to produce metastatic infection when it invades the bloodstream [4]. Osteomyelitis, endocarditis, and septic arthritis are the most common metastatic infections related to SAB.

In the past decade studies of SAB have focused primarily on 3 areas: iv catheter–related SAB [1, 5–9], the risk of infectious endocarditis among various populations with SAB [10–15], and factors predictive of mortality [16–24]. The study presented in this report focused on factors predictive of mortality among patients with SAB. Among previously published studies [16–24], there has been considerable variation in the factors found to be predictive of mortality related to SAB.

In a previous study [20] one of us (Joseph M. Mylotte) found that acute severity of illness at onset of SAB was an important predictor of in-hospital death. However, the cohort of patients evaluated was small (n = 89). Therefore, we undertook an evaluation of a large cohort of patients with SAB at the same hospital, with the objective of carefully reassessing the variables previously identified as important predictors of mortality related to this infection, including acute severity of illness at onset of SAB. Status (dead or alive) 30 days after onset of SAB, or 30-day mortality, was chosen as the dependent variable for this analysis.

Patients and Methods

Setting. This study was done at the Erie County Medical Center (ECMC), in Buffalo, New York, a 300-bed public, university-affiliated hospital. This hospital provides both primary and tertiary care to patients in the Buffalo area. ECMC has the only level I trauma unit, burn treatment unit, spinal cord unit, and AIDS treatment center in the region. There are also separate medical and coronary intensive care units. There are no obstetrical or pediatric inpatient services at this hospital.

Study population. Patients with SAB were identified by review of results of blood cultures from the microbiology laboratory of the hospital. Every patient with ≥1 blood culture positive for S. aureus from January 1995 through February 1999 was initially considered for inclusion in this study (n = 337). A patient was excluded if the SAB was part of a polymicrobial bacteremia (n = 5), if death occurred before a positive blood culture result was known (n = 2), if the patient had true SAB but received no treatment or outpatient treatment (n = 12), or if the criteria for true SAB were not met (n = 25). Thus, 293 patients with episodes of true SAB were included in this study. During the study period, no outbreaks of MRSA infection were identified at the study facility.

Design. This study consisted of a retrospective analysis of charts of patients with SAB. Data were abstracted from charts with
use of a data collection form specifically designed for this study. Data collected included age, sex, hospital service, underlying diseases, focus of infection, complications developing during hospitalization, acute physiology and chronic health evaluation (APACHE III) score at onset of SAB [25], antibiotic treatment, and outcome.

**Definitions.** A patient was considered to have true SAB if ≥1 blood cultures were positive within 24 h, in association with clinical evidence of infection (fever, leukocytosis, and localizing signs and symptoms) [26]. A localized focus of staphylococcal infection was considered to be the source or primary focus of SAB if signs and symptoms of infection or confirmatory physical findings antedated the bacteremia. SAB was considered to be community-acquired if the first positive blood culture specimen was obtained within the first 72 h of admission or if there was clinical and cultural evidence of *S. aureus* infection at the time of admission.

SAB was considered to be nosocomial if the first positive blood culture specimen was obtained ≥72 h after admission and there was no clinical evidence of infection on admission. Endocarditis was identified according to the Duke criteria [27]. Staphylococcal infection of the CNS or joints was always considered a secondary (metastatic) focus unless there was evidence of direct inoculation (associated with surgery or trauma). An intravascular catheter was considered the focus of SAB if there was no other focus of SAB identified and ≥1 of the following conditions was noted: inflammation at the site of catheter insertion, purulent drainage from the insertion site that on culture yielded *S. aureus*, or an *S. aureus*-positive semiquantitative culture of the catheter tip [9]. Pneumonia was considered the source of the SAB if the following conditions were met: a new or progressive infiltrate was noted on a chest radiograph within 24 h of the first *S. aureus*-positive blood culture result, *S. aureus* was cultured from the sputum or endotracheal aspirate on the same day or within 3 days before the blood culture positivity, and there was no other source of SAB.

**Antimicrobial treatment.** All episodes of SAB in the study cohort were treated with appropriate antibiotic(s) (i.e., the organism was susceptible to ≥1 of the antibiotics prescribed), either on the day that the first positive blood culture was drawn, or within 24 h of when the first positive blood culture was drawn. Treatment regimens were stratified into 3 groups (vancomycin, β-lactam, or other) for analysis with use of previously published definitions [20]. Treatment with vancomycin or a β-lactam plus an aminoglycoside or rifampin was considered combination antistaphylococcal therapy only if the second agent was prescribed for ≥5 days concomitantly. There was no significant difference (*P* = .21) in the proportion of episodes treated with combination therapy among the 3 treatment groups (vancomycin, 71%; β-lactam, 65%; and other regimens, 77%).

**Outcome.** The dependent variable in this study was whether the patient was dead or alive 30 days after the onset of SAB (30-day mortality). No follow-up was done after hospital discharge unless the discharge occurred before the 30-day time limit. For case patients who were discharged before the 30-day limit, status was determined by review of outpatient records or by contacting the patient directly; no patients in this group were lost to follow-up.

No attempt was made to determine if death was directly attributable to SAB. It is our view [20] that this determination is difficult in many instances, especially when evaluated in retrospect. In addition, investigators who are aware of study objectives and attempting to identify the cause of death among patients with SAB may be biased in their decisions. This latter situation often results in several categories of death (e.g., definite and probable [21]) that can be confusing when study findings are interpreted.

**Statistical analysis.** Univariate predictors of 30-day mortality were identified by means of Pearson’s χ² analysis or Fisher’s exact test, where appropriate, for categorical variables, and Student’s *t*-test for continuous variables. Significant univariate predictors of 30-day mortality were entered into a logistic regression analysis with use of maximum likelihood to define independent predictors of 30-day mortality. Continuous independent variables were dichotomized before being included in the multivariate analysis. *P* < .05 was considered significant.

## Results

### Clinical characteristics.

From January 1995 through February 1999, 293 patients with episodes of SAB were identified, and the medical records of all 293 patients were available for review. Demographic and clinical characteristics of these patients are listed in table 1.

**Foci of SAB.** The primary foci of SAB are listed in table 2.

### Table 1. Demographic and clinical characteristics of 293 patients with *Staphylococcus aureus* bacteremia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56 ± 19</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>55</td>
</tr>
<tr>
<td>Median</td>
<td>64.8</td>
</tr>
<tr>
<td>Male sex</td>
<td>30.4</td>
</tr>
<tr>
<td>Bacteremia</td>
<td></td>
</tr>
<tr>
<td>Community-acquired</td>
<td>58</td>
</tr>
<tr>
<td>Due to MRSA</td>
<td>32.1</td>
</tr>
<tr>
<td>Underlying condition</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>53.6</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>24.6</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>8.5</td>
</tr>
<tr>
<td>HIV infection/AIDS</td>
<td>11.3</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>11.3</td>
</tr>
<tr>
<td>Malignancy</td>
<td>11.3</td>
</tr>
<tr>
<td>Transplantation</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Note. Data are % of total unless otherwise indicated. MRSA, methicillin-resistant *S. aureus*.
Focus of SAB

Acute severity of illness at onset of SAB

Infectious disease consultation

Complication

Treatment group

Type of bacteremia

Acquisition of SAB

Race

Sex

Underlying disease

Diabetes

Age, y

Characteristic 30-Day mortality\(^a\) \(P\)

Age, y

<65 31/179 (17.3) .003

≥65 37/114 (32.5)

Sex

Male 41/190 (21.6) .37

Female 27/103 (26.2)

Race

White 42/179 (23.5) .90

Black 26/114 (22.8)

Acquisition of SAB

Community-acquired 39/170 (22.9) .90

Nosocomial 29/123 (23.6)

Type of bacteremia

MRSA 21/89 (23.6) .91

MSSA 47/204 (23)

Underlying disease

Diabetes

Yes 38/92 (41.3) .001

No 38/197 (19.8)

HIV infection

Yes 4/25 (16) .46

No 64/268 (23.9)

Cancer

Yes 6/33 (18.2) .66

No 62/260 (23.6)

End-stage renal disease

Yes 7/17 (41.2) .46

No 32/131 (24.4)

Treatment group

Vancomycin 24/123 (19.5) .180

β-lactam 18/86 (20.9)

Other 25/83 (30.1)

Acute severity of illness at onset of SAB

APACHE III score ≥ 60

Yes 38/92 (41.3) .001

No 32/141 (22.7)

APS ≥ 60

Yes 23/29 (79.3) .001

No 45/264 (17)

Complication

Any metastatic infection

Yes 8/45 (17.8) .35

No 60/240 (24.2)

Endocarditis

Yes 6/18 (33.3) .38

No 62/75 (22.6)

Infectious disease consultation

Yes 16/100 (16) .04

No 48/181 (26.5)

Focus of SAB

Unknown

Yes 39/125 (31.2) .005

No 29/168 (17.3)

Respiratory

Yes 16/41 (39) .01

No 52/225 (23.6)

\(^a\) Number of patients dying within 30 days of onset of bacteremia/number of patients with the indicated characteristic (%).

NOTE. APACHE III, acute physiology and chronic health evaluation III; APS, acute physiology score component of the APACHE III scoring system, minus age and chronic illness; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

2. There was no significant difference in the frequency of various foci of SAB and acquisition of infection.

**Endocarditis.** Definite endocarditis, as defined by the Duke criteria [27], was identified in 10 (3.4%) of 293 patients with SAB, and possible endocarditis was identified in 8 (2.7%). Echocardiography (tranesophageal or transtracheal) was performed for 134 patients (45.7%); transesophageal echocardiography was performed for only 36 (12.3%). Fifteen (83.3%) of the 18 cases of endocarditis were associated with community-acquired SAB, whereas, of the 275 episodes of SAB without endocarditis, 56.4% (\(P = .03\)) were community-acquired. For 10 (55.6%) of 18 episodes of endocarditis there was an unknown focus of SAB, whereas, of the 275 episodes of SAB without endocarditis, 41.8% (\(P = .33\)) had an unknown focus.

**Antimicrobial treatment.** The frequency distribution of treatment regimens for SAB in the study cohort was as follows: vancomycin, 123 patients; a β-lactam, 86; and other regimens, 83. There was no significant difference between the 3 treatment groups in the mean (± SD) days of treatment for those who were alive 30 days after the onset of SAB (vancomycin, 22 ± 11 [\(n = 87\)]; β-lactam, 23 ± 11 [\(n = 68\)]; other regimens: 21 ± 10 [\(n = 58\)]; \(P = .534\)).

**Outcome.** Overall, 82 (28%) of the 293 patients with episodes of SAB died during hospitalization. Sixty-eight (83%) of the 82 patients died during the first 30 days after the onset of SAB. Among the 68 patients who died within 30 days of onset of SAB, the mean (± SD) number of days to death was 10.1 ± 7.0 (median, 9 days; 90th percentile, 20 days). Among the 14 patients who died in the hospital >30 days after the onset of SAB, the mean (± SD) number of days to death was 59.4 ± 33.9 (median, 48 days; 90th percentile, 123 days). None of the 14 patients who died >30 days after onset of SAB had recurrent SAB or metastatic infection before death.

**Predictors of mortality.** Table 3 shows the results of the univariate analysis to identify predictors of 30-day mortality in the study cohort. Table 3 does not show that the 30-day mortality rate for patients treated with a combination antibiotic regimen (48 [23.3% of 203] was not significantly different from the mortality rate for patients treated with a single antibiotic agent (19 [22.4% of 85]; \(P = .861\)). Significant univariate predictors of 30-day mortality were included in a logistic regression model to define independent predictors (table 4). The acute physiology score (APS) of the APACHE III score was used in the model, rather than the total APACHE III score, because the APACHE III system [25] accounts for age and certain underlying diseases. However, we wished to enter age and diabetes into the model as separate independent variables because of their significance in previous studies. An APS ≥ 60 at onset of SAB, an unknown focus, and a respiratory focus were the most important predictors of 30-day mortality.

**Discussion**

Using a 30-day mortality end point, we identified factors predictive of this outcome among patients with SAB at our facility. Acute severity of illness at onset of SAB, a respiratory focus of SAB, and unknown focus of SAB were the most important predictors. Our findings verify those of previous studies [19, 20], which determined that acute severity of illness at onset of SAB is an important predictor of death related to this in-
Table 4. Results of the logistic regression analysis to identify predictors of 30-day mortality among patients with *Staphylococcus aureus* bacteremia.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Reg. coefficient</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>APS &gt;60</td>
<td>1.366</td>
<td>15.7 (5.8–49.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Respiratory source</td>
<td>0.956</td>
<td>5.8 (2.1–16.5)</td>
<td>.0007</td>
</tr>
<tr>
<td>Unknown source</td>
<td>0.692</td>
<td>4.1 (1.9–9.4)</td>
<td>.0005</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.455</td>
<td>2.4 (1.2–4.7)</td>
<td>.014</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>0.372</td>
<td>2.0 (1.0–3.8)</td>
<td>.048</td>
</tr>
<tr>
<td>No infectious disease consultation</td>
<td>0.169</td>
<td>1.4 (0.7–3.0)</td>
<td>.325</td>
</tr>
</tbody>
</table>

**NOTE.** APS, acute physiology score of the acute physiology and chronic health evaluation III scoring system.

fection. We also verified that greater age significantly influenced the outcome of SAB even after acute severity of illness was accounted for; this is in agreement with the findings of other studies [17, 23] that did not control for acute severity of illness.

Several studies [16–24] published in the 1990s have identified risk factors for mortality among patients with SAB. Factors previously found to be significantly associated with mortality include older age [17, 23], source of SAB [17, 22], presence of shock [17, 22], SAB caused by MRSA [18, 22], presence of meningitis [18], inadequate treatment [18], acute severity of illness at onset of SAB [19, 20], and underlying disease status [20, 24]. What is striking is the variability in risk factors identified among these studies [16–24]. In our opinion this variability is primarily due to 3 factors. First, the populations studied have varied. Second, the definition of mortality has not been consistent. Third, the sample size of some studies was small.

The effect of variation in study population on the risk factors identified is illustrated by studies that have specifically addressed MRSA bacteremia as a risk factor for death ([16–18, 20–22] and the present study). Of the 2 studies [18, 22] that identified MRSA as a significant independent predictor of death, 1 [18] was done during an outbreak of MRSA infection, and in the other [22] there was a high prevalence of MRSA in the hospital. In the epidemic setting MRSA may be more virulent. For example, Pujol et al. [28] prospectively studied nasal carriage of *S. aureus* as a risk factor for SAB in an intensive care unit during an outbreak of MRSA infection. They found that nasal carriers of *S. aureus* were at higher risk for SAB than noncarriers. However, using multivariate analysis, they found that the risk of SAB was almost 4-fold higher among nasal carriers of MRSA than among MSSA carriers. In contrast, in settings where MRSA is endemic, it has not been found to be an independent predictor of death ([16, 19–21] and the present study).

Possibly the most important reason for the difference in the findings regarding predictors of mortality related to SAB in various studies [16–24] is variation in the definition of mortality: studies have defined mortality as deaths that occur from times of <48 h of the onset of SAB to deaths that occur as long as 12 weeks after onset. In the present study, 83% of all deaths in the hospital occurred within 21 days of onset of SAB. Harbarth et al. [21] also found that the majority of hospital deaths among patients with SAB occurred within this same time frame. Deaths >30 days after onset of SAB were infrequent in the present study and were most likely due to underlying disease or other complications rather than to SAB. Thus, 21-day or 30-day mortality should be given consideration as a standard end point for assessing the outcome of first episodes of SAB.

The source of SAB (specifically, lung or an unknown source) has been identified as an independent predictor of mortality for patients with SAB [17, 22, 24]. In the present study we found that these sources of SAB were also important predictors of 30-day mortality, even after accounting for acute severity of illness and age in the multivariate model.

There are several potential limitations of the present study that should be mentioned. First, the study was retrospective, a design which can make identifying the source of SAB difficult at times. Second, some have criticized the use of the APACHE scoring system to measure acute severity of illness at onset of SAB [21] because it was developed for use in the intensive care setting [25]. However, the present study is the third one in which the APACHE score (II or III) has been found to be an important independent predictor of mortality among patients with SAB [19, 20]. The APACHE score has also been found to be useful in predicting outcome of enterococcal bacteremia [29, 30]. These findings provide sufficient support for use of the APACHE system to measure acute severity of illness in future studies of SAB.

A third potential limitation is that echocardiography was performed in <50% of cases of SAB and transesophageal echocardiography in only 12% of cases. Therefore, it is possible that the rate of endocarditis was underestimated in the present study. Endocarditis occurred predominantly among patients with community-acquired SAB without an identifiable focus. Recent studies at the Duke Medical Center have shown a much higher rate of endocarditis overall among patients with SAB and a relatively high rate among patients with nosocomial SAB [11, 12]. In these latter studies, the diagnosis of endocarditis was based most often on the presence of SAB plus the presence of a well-defined vegetation identified by transesophageal echocardiography, without other signs or symptoms of endocarditis. The findings by the Duke investigators, although they have yet to be verified at other medical centers, raise the important issue of which patients with SAB should be evaluated with transesophageal echocardiography. The present study does not shed any light on this issue.

In conclusion, in a large cohort of patients with SAB at one medical center, acute severity of illness at onset of SAB was the most important predictor of 30-day mortality among a group of significant predictors (older age, lung source, unknown source, and diabetes mellitus). Review of recent studies of SAB revealed differences in the definition of mortality, which may have been a factor in the variation in clinical factors identified as predictive of outcome related to this infection. This suggests...
the need to standardize the mortality end point in studies of SAB. Finally, in addition to standardizing the mortality end point, future investigators need to take into consideration acute severity of illness at onset of SAB, along with other factors, when assessing outcome.

References
