Staphylococcus aureus Bacteremia Among Elderly vs Younger Adult Patients

Comparison of Clinical Features and Mortality

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Background: Previous studies give conflicting results regarding the effect of age on outcomes in Staphylococcus aureus bacteremia (SAB). These studies have been limited by retrospective design or small sample size.

Methods: We conducted a prospective cohort study of 385 patients with SAB aged 18 to 90 years. The setting was a large academic medical center. We observed patients from diagnosis of SAB to discharge or death. Discharged patients were contacted 12 weeks after their first positive culture findings. Data were collected on demographics, comorbid conditions, focus of infection, length of stay, and outcome. Primary outcomes were total mortality and death due to SAB.

Results: Comparisons were made between 145 patients, aged 66 to 90 years, and 240 patients, aged 18 to 60 years. Forty-three (29.7%) of the elderly patients and 36 (15%) of the younger patients died. Death directly attributable to SAB occurred in 21 (14.5%) older and 15 (6.3%) younger patients. After adjusting for confounding variables, older patients continued to have higher total mortality (odds ratio, 2.21; 95% confidence interval, 1.32-3.70), and higher mortality from SAB (odds ratio, 2.30; 95% confidence interval, 1.13-4.69). Infection with methicillin-resistant S. aureus was associated with higher total mortality in the elderly (odds ratio, 2.59; 95% confidence interval, 1.23-5.43).

Conclusions: Staphylococcus aureus bacteremia among the elderly is associated with high mortality. Both total mortality and mortality directly attributable to SAB are more than twice as likely in older patients. Infection with methicillin-resistant S. aureus carries a worse prognosis than infection with methicillin-sensitive S. aureus in the elderly.

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STAPHYLOCOCCUS AUREUS is the most common pathogen isolated from blood cultures in the United States.1 Despite antibiotic therapy, S. aureus bacteremia (SAB) remains an important source of morbidity and mortality.2-11 Reported mortality rates range from 14.7%9 to 42.0%.2

Several retrospective studies2-5,7-9 and one prospective study6 have shown higher mortality among older patients with SAB. The prospective study, however, reported only 76 cases and included pediatric as well as adult subjects. As a result, the findings may not accurately reflect the difference between older and younger adults. We are aware of only 2 prospective studies on the relationship between age and outcomes of SAB that include only adults. Neither of these showed a significant difference in mortality for the older age group.10,11

Our objective was to more clearly determine whether the clinical characteristics and outcomes of SAB are different in elderly patients as compared with younger adults. To achieve this goal, we used a prospective cohort design and the largest sample size of any study addressing this question.

RESULTS

A total of 438 patients with SAB were identified. One patient was lost to follow-up and is not included in any further analyses. Fifty-two patients aged 61 to 65 years were not included in our comparison groups, leaving 385 patients for our analysis. There were 240 patients aged 18 to 60 years and 145 patients older than 65 years. Demographic characteristics of the groups are shown in Table 1.

There were no patients with HIV infection or injection drug use in the older age group. Twenty-one (8.8%) of the younger patients were HIV positive; 29 (12.1%) used recreational injection drugs.
METHODS

PATIENT IDENTIFICATION AND DATA COLLECTION

Between September 1994 and February 1998, we received daily microbiology laboratory reports for all patients at Duke University Medical Center with one or more blood cultures positive for Staphylococcus aureus. Patients were excluded for age younger than 18 years, polymicrobial infection, neutropenia (neutrophil count lower than \(1 \times 10^9/L\)), death prior to the return of positive blood culture findings, or outpatient status. We reviewed the clinical charts and evaluated all patients for SAB within 36 hours of the initial positive blood culture findings. The hospital course was monitored by periodic review of the clinical record and re-examination of the patient. We collected demographic data including age, sex, and race of the patients. Comorbid conditions were recorded, including diabetes mellitus, renal dialysis status, corticosteroid use, neoplasm, dementia, postoperative state, history of organ transplantation, previous episodes of infective endocarditis, and presence of a pacemaker and/or prosthetic heart valve. The primary focus of infection was determined. Data related to the presence of fever prior to diagnosis, leukocyte count at diagnosis, secondary foci of infection, antibiotic sensitivities, and length of stay were collected. Follow-up was attempted for all patients surviving to discharge. Twelve weeks after the date of the first positive blood culture findings, we contacted the patient, a family member, or the patient’s primary physician. Inquiry was made regarding each patient’s condition with the goal of identifying patients who had died or suffered relapse of SAB. In the event of a second hospitalization, medical records were reviewed. Data were recorded in a computer database.

DEFINITIONS

Patients were considered to have no identifiable primary focus of infection if no such focus could be identified on the basis of physical examination and review of laboratory and radiological data. Soft tissue infection was considered to be the source if clinical signs of a soft tissue infection antedated the bacteremia. An intravascular catheter was considered to be the portal of entry if (1) there was evidence of inflammation at the catheter insertion site, and/or (2) a catheter tip culture was positive for \(S\) aureus, and (3) there was no evidence for another source of the bacteremia. Pneumonia was considered to be primary if there was evidence of an infiltrate on a chest radiograph, \(S\) aureus was cultured from the sputum, or endotracheal aspirate and no other portal of infection was apparent. Staphylococcus aureus pneumonia was considered a metastatic infection if an initial portal of entry was identified prior to development of pneumonia. Other metastatic infections were defined as infective endocarditis, or infection at a distant site in patients with infective endocarditis, or a known portal of entry. Infective endocarditis was defined using Duke criteria. Patients were considered to have no fever prior to their diagnosis if no temperature greater than 38.0°C was recorded prior to the diagnosis of SAB. A normal leukocyte count was defined as being between 3.2 \(\times\) \(10^9/L\) and 9.8 \(\times\) \(10^9/L\).

OUTCOMES

Total mortality included all patients who died within 12 weeks of the first positive blood culture findings. Death due to SAB was defined as clinical or microbiological evidence of ongoing infection at the time of death without an alternate explanation.

DATA ANALYSIS

Patients were arbitrarily grouped according to age. Similar to recent studies, our analysis compared patients aged 18 to 60 years with those older than 65 years.

Demographic characteristics were summarized in terms of the median and interquartile range (age) or by the number and percentage of patients (race, sex) in each age group. The Fisher exact test was used to evaluate age group comparisons for race and sex. Odds ratios (ORs) were calculated for elderly patients as compared with younger patients using logistic regression analysis, and are reported with 95% confidence intervals. Because there was a significant difference in race between the groups, we have reported both unadjusted ORs and ORs adjusted for race. In our analysis of length of stay, we included patients who died while in the hospital. Length of stay was also analyzed after excluding patients who died in the hospital. There was no significant difference when these patients were excluded. For our analysis of death due to SAB, we included patients who died due to other causes in the comparison group. We repeated the analysis excluding patients who died from other causes. Again, there was no significant difference in the findings. Finally, we had no cases of human immunodeficiency virus (HIV) infection or injection drug use among the older patients. As a result, it was not possible to calculate ORs for these variables. We therefore reported HIV infection and injection drug use in the younger group as the number and percentage of patients affected.

To exclude comorbid illness as the cause of the difference in mortality between the older and younger patients, we constructed main effect models including race, age, and each individual comorbid condition. We also constructed a main effect model including race, age, and the number of comorbid conditions per patient. Using these models, we examined both total mortality and death due to SAB as outcomes. None of the models significantly changed our results. We also added an interaction term between age group and each comorbid condition to determine whether the comorbidities were independent predictors of mortality regardless of age. Again, there was no change in our results. Therefore, we have not reported these models in the final analysis.

Several differences in the characteristics of SAB were seen in the elderly as compared with younger adults. Adjustment for racial variation between the groups did not account for differences in the characteristics shown in Table 2. Older patients were more likely to have a pacemaker or prosthetic heart valve. The elderly were also more likely to be afebrile prior to diagnosis and to have infections with methicillin-resistant Staphylococcus aureus.
Among the older patients, MRSA infection was associated with higher total mortality. The unadjusted OR comparing MRSA to methicillin-sensitive \textit{S. aureus} (MSSA) infection was 2.62 (95% CI, 1.26-5.44), and the adjusted OR was 2.59 (95% CI, 1.23-5.43). Death directly related to SAB was similar in elderly patients with MRSA and MSSA: unadjusted OR, 1.66 (95% CI, 0.66-4.21), adjusted OR, 1.60 (95% CI, 0.62-4.11). We also examined the relationship between primary focus of infection and outcome among elderly patients. Total mortality and mortality from SAB did not differ significantly in patients with and without an identifiable source for the bacteremia (data not shown).

This is the largest prospective study to examine the effect of age on the clinical characteristics and outcomes of SAB in adults. Older patients have higher total mortality and higher mortality directly attributable to SAB. The elderly are less likely to present with fever and more likely to have MRSA. Furthermore, MRSA bacteremia is associated with higher mortality among the elderly.

The only 2 previous prospective studies of adult patients with SAB did not show higher mortality among the elderly. The larger of these series had only 114 patients. As a result, these studies did not have sufficient power to detect the differences in outcomes that we observed. By using a much larger series, we show that older patients do have a greater risk of death with SAB. This study also suggests some reasons why older patients may have higher mortality.

One explanation is that the elderly are more likely to be infected with MRSA. Older patients with MRSA have a higher risk of death than those with MSSA. There are several factors that may contribute to this difference. First, MRSA may be a marker for patients with more severe underlying disease; our data support this hypothesis. Mortality directly attributable to SAB was not significantly influenced by antibiotic susceptibility. The increase in total mortality among patients with MRSA resulted from more deaths due to underlying disease. A second factor that might contribute to worse outcomes is the choice of empiric antibiotic therapy. The antibiotics initially selected may provide coverage only for MSSA. This would result in a comparatively longer delay to the start of effective treatment for MRSA. A third factor that may influence outcomes in patients with MRSA is that the antibiotic therapy typically used is vancomycin, which

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Age Groups, y</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>&lt;60 (n = 240)</td>
<td>≥65 (n = 145)</td>
</tr>
<tr>
<td>Median age, y</td>
<td>44 (38-53)</td>
<td>73 (68-78)</td>
</tr>
<tr>
<td>(interquartile range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men†</td>
<td>137 (57.1)</td>
<td>72 (49.7)</td>
</tr>
<tr>
<td>Blacks†</td>
<td>120 (50.0)</td>
<td>41 (28.3)</td>
</tr>
</tbody>
</table>

*Ellipses indicate not applicable.
†Data are given as number (percentage).

### Table 2. Odds Ratios for Older Group Compared With Younger Group for Selected Patient Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Odds Ratios (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Prosthetic valve or pacemaker</td>
<td>4.91 (2.11-11.41)</td>
</tr>
<tr>
<td>No primary focus identified</td>
<td>1.06 (0.52-2.14)</td>
</tr>
<tr>
<td>No fever before initial diagnosis</td>
<td>4.15 (1.56-11.06)</td>
</tr>
<tr>
<td>Abnormal WBC†</td>
<td>1.28 (0.80-2.05)</td>
</tr>
<tr>
<td>MRSA bacteremia</td>
<td>1.82 (1.19-2.82)</td>
</tr>
<tr>
<td>Metastatic infection present‡</td>
<td>1.03 (0.65-1.63)</td>
</tr>
<tr>
<td>Hospital stay greater than 15 days‡</td>
<td>1.90 (1.25-2.88)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; WBC, white blood cell count; MRSA, methicillin-resistant Staphylococcus aureus.
†White blood cell count <3.2 × 10^9/L or >9.8 × 10^9/L.
‡Metastatic infection included infectious endocarditis, epidural abscess, septic arthritis, vertebral osteomyelitis, and other metastases.
§Fifteen days was the median length of hospital stay for the combined group, including both younger and older patients.

### Table 3. Odds Ratios for Older Group Compared With Younger Group for Outcome of Staphylococcus aureus Bacteremia*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratios (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Total mortality</td>
<td>2.39 (1.45-3.95)</td>
</tr>
<tr>
<td>Mortality from SAB</td>
<td>2.54 (1.26-5.11)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; SAB, Staphylococcus aureus bacteremia.

**COMMENT**

resistant \textit{S. aureus} (MRSA). The likelihood of identifying the source of bacteremia was similar for older and younger patients. The 2 groups had a similar likelihood of abnormal leukocyte counts and metastatic infections. The unadjusted OR for dialysis (older vs younger) was 0.44 (95% confidence interval [CI], 0.27-0.72), while the adjusted OR was 0.60 (95% CI, 0.36-1.00). This adjusted OR was of borderline significance (P = .05), suggesting that an interaction between race and dialysis status may be present.

The median hospital stay for the 385 patients we analyzed was 15 days. Older patients were more likely to have a hospital stay longer than the median.

Outcomes differed significantly for the elderly. These differences remained after adjustment for race (Table 3). Models including the individual comorbid conditions and a model including the number of comorbid conditions per patient did not change the results. Forty-three older patients (29.7%) and 36 younger patients (15.0%) died. Death was more than twice as likely among the older patients (adjusted OR, 2.21). Mortality directly attributable to SAB occurred in 21 (14.5%) of the older and 15 (6.3%) of the younger patients. As with total mortality, the elderly were more than twice as likely to die as a direct consequence of SAB (adjusted OR, 2.30).
may be less effective than the β-lactams. The presence of multiple contributing factors may explain the conflicting results of previous studies looking at the relationship between MRSA and mortality.

Another factor that may contribute to the increased mortality seen among older patients with SAB is that they are more than 3 times as likely to have no fever prior to diagnosis. The absence of fever may delay diagnosis and treatment. Recent studies have shown that outcomes in bacteremic patients are related to the delay before starting treatment with effective antibiotics.1

There are some limitations to our study. We did not use a comorbidity scoring system to assess baseline health status. More severe underlying disease has been associated with worse outcomes among patients with SAB. Elderly patients are more likely to have chronic medical problems. For example, elderly patients in our analysis were more than 4 times as likely to have a cardiac pacemaker or prosthetic heart valve. Differences in baseline health status between groups of patients of different ages are anticipated. Our method allowed us to compare the clinical characteristics and outcomes of SAB between representative samples of elderly and younger patients.

Another limitation is that we may incorrectly identify the source of bacteremia or fail to identify metastatic infections. However, the prospective design of this study allowed us to make as accurate a clinical assessment as possible. Furthermore, these limitations should affect older and younger patients equally.

A final limitation is that there was a significant difference in race between our older and younger groups. This resulted primarily from the uneven distribution of dialysis patients, with significantly more of them in the younger group. Among dialysis patients in the study, 84% (70.6%) were black. Because the groups varied with respect to race, we reported both the unadjusted ORs and ORs adjusted for race. The differences in race did not account for the differences in clinical characteristics and outcomes of the groups.

Several important conclusions can be drawn from this study. First, we found that outcomes of SAB are significantly worse for elderly patients. Nearly one third of the older patients we followed died within 12 weeks of diagnosis. Total mortality and mortality directly attributable to SAB are more than twice as likely among older patients. The high mortality seen in the elderly patients highlights the need to prevent these infections whenever possible. Furthermore, elderly patients are more likely to be infected with MRSA. Consideration should be given to using vancomycin in the empiric treatment of elderly patients with possible SAB. However, the choice of empiric antibiotics in an individual patient must also be guided by knowledge of the local patterns of resistance and individual patient risk factors for infection with resistant organisms. Finally, our results demonstrate the need to adjust for age in studies looking at the outcomes of SAB. Awareness of the effect of age on mortality in SAB will be particularly important when investigating factors with an uneven age distribution such as MRSA.

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REFERENCES


