Outcome of *Staphylococcus aureus* Bacteremia According to Compliance with Recommendations of Infectious Diseases Specialists: Experience with 244 Patients


To determine whether recommendations of infectious diseases specialists affect outcome for patients, we evaluated 244 hospitalized patients with *Staphylococcus aureus* bacteremia. We offered our management recommendations to each patient’s physicians and then assessed the clinical outcome for both patients for whom our consultative advice was followed and those for whom our advice was not heeded. All patients were followed up for 12 weeks after their first positive blood culture. Our management advice was followed for 112 patients (45.9%) and partially or completely ignored for 132 patients (54.1%). Patients for whom our recommendations were followed were more likely to be cured of their *S. aureus* infection and less likely to relapse (P < .01), despite having significantly more metastatic infections (P < .01) at the outset of therapy, than were those for whom our recommendations were not followed. Failure to follow recommendations to remove an infected intravascular device was the most important risk for treatment failure. After controlling for other factors, logistic regression analysis revealed that patients whose intravascular device was not removed were 6.5 times more likely to relapse or die of their infection than were those whose device was removed. Our findings suggest that patient-specific management advice by infectious diseases consultants can improve the clinical outcome for patients with *S. aureus* bacteremia.

Consultation or management advice from subspecialists has been shown to improve clinical outcome for patients sustaining an acute myocardial infarction [1] and patients with AIDS [2]. However, the impact of consultation by infectious diseases specialists on the clinical outcome for hospitalized patients has been incompletely studied [3–6].

The objective of the following study was to determine whether recommendations of infectious diseases specialists affect the clinical outcome for hospitalized patients with *Staphylococcus aureus* bacteremia. During a 25-month period, we identified all hospitalized patients with *S. aureus* bacteremia, offered our management recommendations to each patient’s physicians, and then assessed the clinical outcome for patients for whom our consultative advice was and was not followed.

Methods

**Subjects and Setting**

Between September 1994 and October 1996, we received daily reports from the microbiology laboratory on all patients at Duke University Medical Center (Durham, NC) for whom one or more blood cultures were positive for *S. aureus* and for whom there was clinical evidence of infection. The clinical charts of these patients were then reviewed within 36 hours of the detection of bacteremia. Patients were excluded from the study for the following reasons: age of younger than 18 years, outpatient status, or enrollment in a simultaneous investigation randomizing patients with indwelling catheter–related bacteremia to removal or nonremoval of the catheter. To maintain the statistical assumption of independence of values, only the initial episode of bacteremia for each patient was included in the study.

**Clinical Features**

Each patient was initially evaluated by a member of the infectious diseases team for signs suggestive of infective endocarditis (IE) and for clinical evidence of a source of their bacteremia. IE was defined according to the Duke criteria [7]. Staphylococcal tissue infection was considered the source of bacteremia if clinical signs of a known or suspected soft-tissue infection antedated bacteremia. An intravascular catheter was considered to be the portal of entry for *S. aureus* bacteremia if there was evidence of inflammation at the catheter insertion site and/or a vascular catheter tip culture was positive for *S. aureus* and there was no clinical evidence of another source for bacteremia [8]. The duration of symptoms before treatment was defined as the time elapsed between the onset of symptoms...
attributable to *S. aureus* bacteremia and the initiation of effective antibiotic therapy.

*S. aureus* bacteremia was considered to be nosocomial if a blood culture was positive after >72 hours of hospitalization and clinical signs of *S. aureus* bacteremia were absent at the time of admission. *S. aureus* bacteremia was considered to be community-acquired if a blood culture was positive within 72 hours of admission and/or signs and symptoms consistent with *S. aureus* bacteremia were present before admission. *S. aureus* bacteremia was considered to be nursing home–acquired if a blood culture was positive within 72 hours of admission from a patient who was transferred from an extended-care facility because of clinical signs of active infection.

**Recommendations**

Before the study was initiated, a consensus statement on the management of *S. aureus* bacteremia was created by the investigators (table 1). The following recommendations were made for all patients with *S. aureus* bacteremia: all removable foci of infection such as catheters should be removed; blood for surveillance cultures should be obtained on days 2–4 of antibiotic therapy; transesophageal echocardiography (TEE) should be performed on days 5–7 of antibiotic therapy, or sooner if clinically indicated; and wherever possible, β-lactam antibiotic therapy should be used. Further recommendations were made on the basis of a schema outlined in table 1 [9].

A treating physician for each bacteremic patient was contacted by one of the investigators, our management recommendations were discussed, and an official consultation was offered. The decision to follow our treatment recommendations (either with or without consultation) was made by each patient’s primary physicians. Regardless of the outcome of this decision, the clinical course of each study patient was assessed during the hospital stay by periodic monitoring of the clinical chart.

Reasons for failure to follow the recommendations of the infectious diseases team were categorized as follows: failure to perform TEE, failure to remove an infected intravascular device, inappropriate vancomycin therapy, treatment for longer than the recommended duration of therapy, and failure to obtain blood for surveillance cultures.

**Treatment**

Patients were classified as having received vancomycin or β-lactam (nafcillin or cefazolin) therapy if one of these agents was prescribed for the entire treatment period or if therapy was converted to one of these agents within 2 days of initiating another antibiotic type [10]. Vancomycin (loading dose, 15–20 mg/kg of body weight) was dosed according to measured serum drug levels to maintain therapeutic levels, nafcillin was dosed at 2 g intravenously every 4–6 hours, and cefazolin was dosed at 1–2 g intravenously every 8 hours. Vancomycin therapy was categorized as appropriate if the patient was allergic to penicillin or had bacteremia due to methicillin-resistant *S. aureus* (MRSA). Combination therapy with gentamicin (3 mg/[kg·d]) or an equivalent dosage for patients with renal

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**Table 1.** Consensus recommendations for the treatment of *Staphylococcus aureus* bacteremia.

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>Therapy</th>
</tr>
</thead>
</table>
| Simple bacteremia    | All of the following:  
1. TEE on d 5–7 of therapy that was negative for both vegetations and predisposing valvular abnormalities  
2. Negative surveillance culture of blood obtained 2–4 d after beginning appropriate antibiotic therapy and removal of focus  
3. Removable focus of infection  
4. Clinical resolution (afebrile and no localizing complaints attributable to metastatic staphylococcal infection within 72 h of initiating therapy and removal of focus)  
5. No indwelling prosthetic devices | 7 d of intravenous antibiotics |
| Uncomplicated bacteremia | One or more of the following:  
1. Predisposing valvular abnormalities (more than mild regurgitation) but no vegetations shown by TEE  
2. Positive surveillance blood culture  
3. Superficial, nonremovable focus of infection  
4. Persistent signs of infection after 72 h of antibiotic therapy | 14 d of intravenous antibiotics |
| Endocarditis         | According to Duke criteria [7]                                                                                                                                                                           | 4–8 w of intravenous antibiotics with or without surgery |
| Extracardiac         | All of the following:  
1. TEE negative for vegetations  
2. Deep-tissue infection (e.g., mediastinitis and osteomyelitis)                                                                                   | 4–8 w of intravenous antibiotics with or without surgery |

NOTE. TEE = transesophageal echocardiography.
insufficiency) was administered at the discretion of each patient’s primary physician. The duration of antibiotic therapy was defined as the length of time the patient received intravenous antibiotics effective against that patient’s *S. aureus* isolate. We defined abbreviated therapy as antibiotic therapy lasting for 7 days, short-course therapy as antibiotic therapy lasting 2 weeks, and long-course therapy as antibiotic therapy lasting ≥4 weeks.

**Patient Outcome**

Follow-up of all living patients was attempted. Twelve weeks after the date of the first blood culture, one of the investigators (V.G.F.) made telephone contact with the patient, a family member, or the patient’s primary care physician and inquired about the patient’s current condition. In the event of a second hospitalization within 12 weeks of the first hospitalization, all pertinent medical records were reviewed. Four primary endpoints were defined: cure, resolution of clinical signs of infection during therapy and no evidence of recurrent staphylococcal infection at the time of follow-up 12 weeks later; relapse, clinical resolution of signs and symptoms of infection during therapy but recurrent *S. aureus* infection (as confirmed by cultures) within the 12 weeks of follow-up; death due to *S. aureus* bacteremia, clinical or microbiological evidence of infection at the time of death without an alternate explanation; and death due to underlying disease, no evidence of infection at the time of death due to a defined underlying disease.

**Pulsed-Field Gel Electrophoresis**

Pulsed-field gel electrophoresis (PFGE) was performed on both isolates from patients with a second episode of *S. aureus* bacteremia to confirm genetic similarity, as described by Kong et al. [11]. Briefly, single isolates grown overnight at 37°C on broth medium were embedded into small agarose plugs, digested with lysostaphin and lysozyme, and deproteinized with use of a reagent kit (GenePath I, Bio-Rad, Hercules, CA). Restriction enzymes digested with *SmaI* underwent electrophoresis on 1% agarose gels and were stained with ethidium bromide; results were interpreted according to previously reported guidelines [12].

**Statistical Analysis**

Descriptive statistics for continuous variables were summarized in terms of medians and interquartile ranges. Categorical variables were reported in terms of the number and percent of patients affected. Comparisons between the group for which the consultative advice was followed and the group for which it was not followed were made with Wilcoxon rank-sum tests for continuous variables and with Fisher’s exact tests for categorical variables. The outcome for patients whose physicians failed to remove an infected intravascular device was compared with the outcome for patients whose infected intravascular device was removed or patients who never had a device. The outcome for patients in whom vancomycin was used inappropriately was compared with the outcome for patients in whom vancomycin was used appropriately or not used.

Kaplan-Meier estimates were used to describe the survival distribution for time to defervescence. The logrank statistic was used to test the difference in time to defervescence between patients whose physicians did and did not follow recommendations. Relationships were considered significant when the two-sided *P* value was <.05. Logistic regression was used to evaluate the association between the reason for noncompliance with the specialist recommendations and the outcome of death or relapse. Several potential confounding variables were also evaluated for their effect on the group-outcome relationship.

**Results**

One or more cultures of blood specimens from a total of 393 adult inpatients at Duke University Medical Center were positive for *S. aureus* during the study period (figure 1). One hundred forty-eight patients (37.7%) were excluded from the

![Figure 1. Stratification of 393 patients with Staphylococcus aureus bacteremia from 1 September 1994 to 17 October 1996 according to compliance with recommendations of infectious diseases specialists. Infectious diseases specialist recommendations were followed by the physicians of 132 patients (45.9%) and were not followed by the physicians of 132 patients (54.1%). One hundred forty-eight patients were excluded from entry into the study. Reasons for study exclusion are given at the bottom of the figure.](cid-27-09-580-f01)
study because of reasons noted above, leaving 245 patients (62.3%) eligible for the study. Follow-up was performed for 244 patients (99.6%). Our management and therapeutic advice was followed by the physicians of 112 patients (45.9%). Consultation was declined and our verbal advice was completely or partially ignored by the physicians of the remaining 132 patients (54.1%).

Patient demographics and clinical characteristics are presented in tables 2 and 3. Patients for whom our recommendations were and were not followed had similar demographic characteristics and frequencies of most comorbidities; they also had similar WBC counts (12,800/mm$^3$ [interquartile range, 9,780 to 20,100/mm$^3$] vs. 13,200/mm$^3$ [interquartile range, 8,300 to 19,800/mm$^3$], respectively; $P = \text{NS}$). The two groups were cared for by a similar distribution of physician specialties, with 24%–27% of patients from a surgical service and 73%–76% of patients from a medical or obstetrical service.

Clinical characteristics of the patients whose physicians followed our recommendations differed from those of the patients whose physicians did not follow our recommendations in four aspects: the incidence of metastatic infections at the onset of therapy was higher among patients for whom recommendations were followed than among those for whom recommendations were not followed (42.9% vs. 19.7%, respectively; $P < .01$); the median duration of symptoms was longer for patients for whom recommendations were followed than for those for whom recommendations were not followed (3.0 days vs. 2.0 days, respectively; $P = .01$); rates of hospital and community-acquired bacteremia were significantly different among the two groups ($P = .02$); and patients for whom recommendations were followed were less likely to be hemodialysis-dependent than were those for whom recommendations were not followed (12.5% vs. 28.0%, respectively; $P < .01$).

### Outcome

Follow-up information was obtained 12 weeks after the onset of *S. aureus* bacteremia for >99% of study patients. Patients whose physicians followed the recommendations of infectious diseases specialists were more likely to be cured of their *S. aureus* bacteremia (79.5% vs. 64.4%, respectively; $P = .01$) and less likely to relapse (6.3% vs. 18.2%, respectively; $P < .01$) than were patients whose physicians did not follow recommendations of infectious diseases specialists (table 4). Rates of death due to *S. aureus* and death due to comorbid conditions were not significantly different among the two groups.

Thirty-one patients relapsed within the 12-week follow-up period. Recurrent *S. aureus* bacteremia was found in 24 patients. Because some episodes of recurrent *S. aureus* bacteremia may have represented reinfection rather than a true relapse of inadequately treated infection, we performed PFGE on all available isolates. Isolates from the initial and recurrent episodes of *S. aureus* bacteremia in 20 (83.3%) of 24 patients were available for PFGE. Isolates from the recurrent episode of bacteremia in 18 (90%) of these 20 patients were identical to isolates from the initial episode.

### Table 2. Characteristics of 244 patients with *Staphylococcus aureus* bacteremia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 244)</th>
<th>Patients for whom recommendations followed (n = 112)</th>
<th>Patients for whom recommendations not followed (n = 132)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in y (interquartile range)</td>
<td>57.5 (42.0–69.0)</td>
<td>59.5 (44.0–69.5)</td>
<td>55.0 (41.0–69.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>143 (58.6)</td>
<td>71 (63.4)</td>
<td>72 (54.6)</td>
<td>NS</td>
</tr>
<tr>
<td>White</td>
<td>138 (56.6)</td>
<td>66 (58.9)</td>
<td>72 (54.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Median duration of symptoms before treatment in d (interquartile range)</td>
<td>2.0 (1.0–4.0)</td>
<td>3.0 (1.0–4.0)</td>
<td>2.0 (1.0–3.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Median time to defervescence in d (interquartile range)*</td>
<td>3.0 (2.0–5.0)</td>
<td>3.0 (2.0–6.0)</td>
<td>3.0 (1.0–5.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>51 (20.9)</td>
<td>14 (12.5)</td>
<td>37 (28.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>47 (19.3)</td>
<td>16 (14.3)</td>
<td>31 (23.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Steroid therapy</td>
<td>30 (12.3)</td>
<td>11 (9.8)</td>
<td>19 (14.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>35 (14.3)</td>
<td>14 (12.5)</td>
<td>21 (15.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>21 (8.6)</td>
<td>13 (11.6)</td>
<td>8 (6.1)</td>
<td>NS</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>17 (7.0)</td>
<td>9 (8.0)</td>
<td>8 (6.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous IE</td>
<td>10 (4.1)</td>
<td>6 (5.4)</td>
<td>4 (3.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>9 (3.7)</td>
<td>7 (6.3)</td>
<td>2 (1.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Dementia</td>
<td>9 (3.7)</td>
<td>5 (4.5)</td>
<td>4 (3.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>7 (2.9)</td>
<td>5 (4.5)</td>
<td>2 (1.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NOTE. Unless stated otherwise, data are no. (%) of patients. IE = infective endocarditis; NS = not significant at an $\alpha$ of .05 (two-sided).

* Days after therapy was begun with an effective agent.
Table 3. Characteristics of infection in 244 patients with \textit{Staphylococcus aureus} bacteremia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 244)</th>
<th>Recommendations followed (n = 112)</th>
<th>Recommendations not followed (n = 132)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquisition route</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>133 (54.5)</td>
<td>65 (58.0)</td>
<td>68 (51.5)</td>
<td>.02</td>
</tr>
<tr>
<td>Community</td>
<td>103 (42.2)</td>
<td>40 (35.7)</td>
<td>63 (47.7)</td>
<td></td>
</tr>
<tr>
<td>Nursing home</td>
<td>8 (3.3)</td>
<td>7 (6.3)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Focus of infection</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Deep tissue</td>
<td>91 (37.3)</td>
<td>41 (36.6)</td>
<td>50 (37.9)</td>
<td></td>
</tr>
<tr>
<td>Intravascular device</td>
<td>136 (55.7)</td>
<td>60 (53.6)</td>
<td>76 (57.6)</td>
<td></td>
</tr>
<tr>
<td>No visible focus</td>
<td>17 (7.0)</td>
<td>11 (9.8)</td>
<td>6 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Site of metastatic complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess or other soft tissue</td>
<td>7 (2.9)</td>
<td>2 (1.8)</td>
<td>5 (3.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Arthritis</td>
<td>14 (5.7)</td>
<td>7 (6.3)</td>
<td>7 (5.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Epidural abscess</td>
<td>6 (2.5)</td>
<td>5 (4.5)</td>
<td>1 (0.8)</td>
<td>NS</td>
</tr>
<tr>
<td>IE</td>
<td>32 (13.1)</td>
<td>30 (26.8)</td>
<td>2 (1.5)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Renal embolus</td>
<td>10 (4.1)</td>
<td>6 (5.4)</td>
<td>4 (3.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2 (0.8)</td>
<td>2 (1.8)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Vertebral osteomyelitis</td>
<td>7 (2.9)</td>
<td>4 (3.6)</td>
<td>3 (2.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Nonvertebral osteomyelitis*</td>
<td>8 (3.3)</td>
<td>3 (2.7)</td>
<td>5 (3.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Psoas abscess</td>
<td>4 (1.6)</td>
<td>4 (3.6)</td>
<td>0</td>
<td>.04</td>
</tr>
<tr>
<td>Septic embolus</td>
<td>6 (2.5)</td>
<td>5 (4.5)</td>
<td>1 (0.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Any metastatic complication</td>
<td>74 (30.3)</td>
<td>48 (42.9)</td>
<td>26 (19.7)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

NOTE. IE = infective endocarditis; NS = not significant at an \( \alpha \) of .05 (two-sided).

* Acquired by the direct extension of infection.

Our recommendations were followed for seven of the 31 patients with recurrent staphylococcal infection. All seven of these patients originally had a deep-tissue infection (mediastinitis, 2 patients; psoas abscess, 1; surgical wound infection, 1; septic arthritis, 1; and IE, 2). None of these seven patients died of recurrent staphylococcal infection. Our recommendations were not followed by the physicians of 24 of the 31 patients with recurrent bacteremia. The initial site of staphylococcal infection in these 24 patients included the following: intravascular devices (14 patients), mediastinitis (4), other surgical wounds (2), entry site of chest catheter (1), diabetic foot ulcer (1), pneumonia (1), and site of injection drug use (1). Three of these 24 patients developed definite IE, and two died of recurrent staphylococccemia.

Eighteen patients (7.4%) died due to \textit{S. aureus} infection. Our recommendations were followed by the physicians of nine of these patients. Six of these nine patients had definite IE. The other three patients died of staphylococcal sepsis associated with a deep-tissue infection. Our recommendations were not followed by the physicians of the nine remaining patients who died of staphylococcal infection. Four of these nine patients died of staphylococcal sepsis associated with a removable...

Table 4. Outcome 12 weeks after the onset of \textit{Staphylococcus aureus} bacteremia in 244 patients according to adherence to recommendations of infectious diseases specialists.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total (n = 244)</th>
<th>Recommendations followed (n = 112)</th>
<th>Recommendations not followed (n = 132)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>174 (71.3)</td>
<td>89 (79.5)</td>
<td>85 (64.4)</td>
<td>.01</td>
</tr>
<tr>
<td>Relapse</td>
<td>31 (12.7)</td>
<td>7 (6.3)</td>
<td>24 (18.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>24 (9.8)</td>
<td>5 (4.5)</td>
<td>19 (14.4)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Deep-tissue infection only</td>
<td>7 (2.9)</td>
<td>2 (1.8)</td>
<td>5 (3.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Death due to \textit{S. aureus} bacteremia</td>
<td>18 (7.4)</td>
<td>9 (8.0)</td>
<td>9 (6.8)*</td>
<td>NS</td>
</tr>
<tr>
<td>Death due to other causes</td>
<td>21 (8.6)</td>
<td>7 (6.3)</td>
<td>14 (10.6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NOTE. NS = not significant (\( P > .05 \)).

* Excluding two patients who relapsed and subsequently died of \textit{S. aureus} bacteremia.
focus: three had intravascular catheter infections, and one patient had an infected peritoneal catheter. The other five patients died of staphylococcal sepsis associated with a deep-tissue infection.

Twenty-one patients (8.6%) with *S. aureus* bacteremia died of other causes during the 12-week period following onset. Causes of death for the seven patients whose physicians followed our recommendations included the following: malignancy (3 patients), sepsis due to other organisms (2), myocardial infarction (1), and pulmonary embolism (1). The causes of death for the 14 patients whose physicians did not follow our recommendations were as follows: malignancy (1 patient), sepsis due to other organisms (2), myocardial infarction (6), uncontrolled bleeding (1), pneumonia (2), burns (1), and uremia (1).

**Antimicrobial Therapy**

The median duration of antibiotic therapy was similar for patients whose physicians followed and did not follow our recommendations (21.0 days [interquartile range, 13.0–36.0 days] vs. 21.0 days [interquartile range, 14.0–28.0 days], respectively; *P* = NS). Sixty-two patients (56.4%) whose physicians followed our recommendations received β-lactam therapy, while 48 patients (43.6%) whose physicians did not follow our recommendations received β-lactam therapy.

One of the 244 patients died before receiving treatment with antistaphylococcal antibiotics. Of the 110 patients treated with β-lactam antibiotics, 92 (83.6%) were cured, 4 (3.6%) relapsed with staphylococcal infection, 6 (5.5%) died due to *S. aureus* infection, and 8 (7.3%) died of comorbidities. Of the 133 patients treated with vancomycin, 82 (61.7%) were cured, 27 (20.3%) relapsed, 12 (9.0%) died of their *S. aureus* infection, and 12 (9.0%) died of comorbidities. Vancomycin therapy was appropriately given to 96 patients. Eighteen of these patients were allergic to penicillin, and 78 patients had infection due to MRSA. Thirty-seven patients received vancomycin therapy inappropriately. There was no difference in outcome between the 68 patients who received and the 176 patients who did not receive aminoglycoside therapy.

**Logistic Regression Analysis**

Logistic regression was performed to evaluate the impact of our recommendations on the outcome for patients. Each of the reasons why our recommendations were not followed (failure to remove an intravascular device, failure to use β-lactam antibiotics when possible, failure to perform TEE, failure to obtain blood for a surveillance culture, and antibiotic therapy for longer than recommended) (table 5) were considered for the model. The small numbers of patients for whom a surveillance blood culture was not performed or who received a prolonged course of antibiotics prevented analysis of these variables. Thus, the final model contained three variables (failure to remove an intravascular device, failure to use β-lactam antibiotics when possible, and failure to perform TEE). After controlling for the other variables in the model, patients whose intravascular device was not removed were 6.5 times more likely to relapse or die of their infection than were those whose device was removed (OR, 6.5; 95% CI, 2.1–20.2; *P* < .01). Overall, 13 (56.5%) of the 23 patients whose foreign body was not removed relapsed or died due to *S. aureus* infection compared with 36 (16.3%) of the 221 patients whose infected foreign body was removed or who did not have a device (OR, 8.6; 95% CI, 2.1–34.2; *P* < .01).

Failure to perform TEE did not increase the risk of relapse or death due to infection (OR, 1.4; 95% CI, 0.7–2.9; *P* = NS). Because other aspects of our recommendations were not followed in the management of most patients who received inappropriate vancomycin therapy, we were unable to detect any independent impact of this potential variable (OR, 1.4; 95% CI, 0.5–3.6; *P* = NS). For example, the management of 33 of the 37 patients for whom vancomycin was inappropriately used also failed to comply with a second recommendation (failure to undergo TEE, 14 patients; failure to remove an infected intravascular device, 16; failure to obtain blood for surveillance cultures, 1; and treatment for longer than recommended, 2).

The impact of several potential confounding variables was evaluated with logistic regression in a model containing compliance with recommendations of infectious diseases specialists as the independent variable and death due to *S. aureus* infection or relapse as the outcome. Tested variables included infection with MRSA, diabetes mellitus, and hemodialysis dependence. There was no significant difference in outcome when each of these variables was controlled for separately in the model.

**Discussion**

We found that patients with *S. aureus* bacteremia whose physicians followed recommendations by infectious diseases specialists...
consultants were significantly more likely to be cured and less likely to relapse than were similar patients with *S. aureus* bacteremia whose physicians ignored our recommendations. This lower rate of relapse occurred despite the fact that patients whose physicians followed our recommendations had significantly more cases of metastatic infection and endocarditis at the onset of therapy than did patients whose physicians did not follow our recommendations. This difference in outcome persisted even after multiple potential confounding variables were analyzed.

**Study Strengths**

Our study design had several strengths. First, our recommendations were provided to each treating physician in the form of a previously established algorithm. This design insured that uniform advice was provided to all treating physicians. Second, the study was a large, prospective, and comprehensive investigation. All patients were evaluated by one of the infectious diseases team, thereby maximizing the likelihood for an accurate assessment of the patient. Third, a 12-week follow-up was performed for 99.6% of all our patients. Last, we used PFGE for most patients with recurrent bacteremia to address the potential confounder of reinfection.

**Algorithm Recommendations**

*Perform TEE.* Several features of our algorithm warrant further discussion. First, our management schema recommended TEE 5–7 days after diagnosis for all patients with *S. aureus* bacteremia. TEE was recommended because this modality is able to detect a significant number of cases of IE not identified by clinical examination or transthoracic echocardiography (TTE) [13–17]. In a separate study [18], we noted that IE was present in 25 of 103 consecutive patients with *S. aureus* bacteremia who underwent both TTE and TEE. All 25 of these cases of IE were detected by TEE; however, only seven were detected by TTE. In light of this surprising finding, we reasoned that identification of patients with unsuspected endocarditis is critically important before application of a treatment algorithm that includes an arm for short course therapy; thus, TEE was advised for all patients. As a result of this approach, we were able to identify 32 patients with endocarditis.

*Remove infected intravascular devices.* Our management algorithm included the recommendation that all infected intravascular devices should be removed from patients with *S. aureus* bacteremia. Our data showed that failure to comply with this recommendation was the most important risk factor for subsequent relapse or death due to *S. aureus*. Patients whose infected intravascular device was not removed were significantly more likely to relapse, thus suggesting that the removal of such infected devices should be performed in most cases.

Eighty percent of the patients in our study whose infected catheters or devices were not removed were hemodialysis-dependent. This fact reflected treating physicians’ attempts to preserve vascular access in patients with few alternate sites for life-giving hemodialysis treatment. Unfortunately, such attempted salvage of vascular access resulted in relapse in over one-half of the cases, and one of these patients died of recurrent staphylococcal sepsis.

*Perform a surveillance blood culture.* Because a surveillance blood culture was not performed for only two patients, we were unable to assess the clinical value of this test. However, our findings were consistent with those of a previous investigation [19] that persistent bacteremia was associated with complicated staphylococcal infection. Thus, many clinicians may simply wish to treat all patients for whom surveillance blood cultures are positive for *S. aureus* with a long course of intravenous antibiotics.

*Use β-lactam therapy.* Although our study was not designed to assess the comparative efficacy of vancomycin vs. β-lactam therapy, we recommended the use of β-lactam antibiotics whenever possible because the use of vancomycin as an antistaphylococcal agent has been associated with a high rate of clinical failure [10, 20–22]. Since most patients who received vancomycin treatment because of reasons we deemed inappropriate were treated in other ways that were also in noncompliance with our management recommendations (e.g., failure to remove an intravascular device), we were unable to assess the clinical impact of vancomycin therapy on outcome. However, it is notable that all 18 patients with relapsed *S. aureus* bacteremia that was confirmed by PFGE were treated with vancomycin.

**Possible Confounding Features and Limitations**

Our study has several limitations. First, this investigation did not randomize patients to groups with different management strategies. Although randomization of patients with *S. aureus* bacteremia to different treatment plans would be an ideal design, we thought that denying an infectious diseases consultation to patients with serious staphylococcal infections was not possible. Because our study was not randomized, it is possible that physicians caring for hopelessly or terminally ill patients were more likely to ignore our recommendations. Because our management recommendations involved prolonged therapy, invasive tests such as TEE, and the removal and replacement of intravascular devices, patients with a poorer prognosis might have been disproportionately represented among the group for whom these recommendations were not followed. However, we doubt that this possibility had a significant impact on outcome since the rates of death and comorbid disease were similar among the two groups.

The rates of colonization with *S. aureus* among diabetic [23] and hemodialysis-dependent [24] patients are high, and the rate of *S. aureus* bacteremia among these patients may even be
higher [25]. Because of these observations as well as the fact that hemodialysis dependence was more common among patients for whom our recommendations were not followed, these conditions were evaluated as potential confounders by using logistic regression analysis. In addition, the impact of infection with MRSA was also evaluated by logistic regression analysis. No evidence was found that any of these conditions had a significant impact on the clinical outcome for our patients.

Acute and chronic illnesses in patients were also potential confounders of our results [10, 26]. Our investigation did not assess acuity of illness by a standardized scoring system. However, three factors suggest that disease acuity did not influence the cure and relapse rates. First, there was no significant difference in the mortality rates among the two study groups. Second, the rates of comorbidities among the two groups were similar. Last, patients whose physicians followed our recommendations were often more acutely ill from their bacteremia than were patients whose physicians did not follow our recommendations. For example, 30 (93.8%) of the 32 patients with IE were in the group for whom recommendations were followed. In addition, other clinical indicators of acuity of illness (*S. aureus* pneumonia as the source of bacteremia, the presence of a rapidly fatal disease, and the presence of CNS symptoms) that were found to be independent predictors of hospital mortality [27] were also more common among patients whose physicians followed our recommendations than among those whose physicians did not follow our recommendations (17.0% vs. 14.9%, respectively).

Finally, the possibility of reinfection with a different strain of *S. aureus* represented another potential confounder. However, by means of PFGE analysis, 90% of the paired isolates from patients with recurrent *S. aureus* bacteremia were identical to isolates from the initial episode. This finding supports the explanation that most cases of recurrent *S. aureus* bacteremia were due to true relapsed infection.

**Other Considerations**

The mortality rate associated with *S. aureus* bacteremia in our study was lower than that previously reported. Although earlier investigations found that the mortality rate among patients with *S. aureus* bacteremia ranged from 20% to 30%, we found that the mortality rate attributable to *S. aureus* bacteremia was only 7.4%. There are several possible reasons for this finding. First, the median age of our study population was relatively young (57.5 years [interquartile range, 27 years]). Most studies have shown that mortality rates among elderly patients with *S. aureus* bacteremia and IE are higher than those among younger adult patients [28–32]. Second, over one-half of our patients had catheter-associated bacteremia. Catheter-associated *S. aureus* bacteremia usually is associated with a lower complication rate and better outcome when the catheter is promptly removed [33–35].

Third, the low mortality rate among our study patients may in part be related to the aggressive management of this potentially lethal disease. An infectious diseases team member saw all patients, and in each case, our management recommendations were discussed with the treating team. Even among patients for whom our recommendations were not followed, the fact that an investigator evaluated the patient’s case may have impacted upon the patient’s care. For example, only 23 patients (9.4%) with an infected intravascular device did not have it removed and at least one set of surveillance blood cultures was not performed for only two patients (1%). Furthermore, our recommendations were followed for most patients (93.8%) with IE, an observation that has been made elsewhere [4].

**Conclusions**

Thus, patients whose physicians did not follow our recommendations were more likely to relapse than were patients whose physicians did follow our recommendations. This finding persisted after consideration of host factors (acute severity of illness, comorbid diseases, and site of infection), therapeutic factors (antibiotic regimen), and pathogen factors (infection with MRSA and relapsed *S. aureus* bacteremia vs. reinfection). To our knowledge, this is the first prospective study that attempted to assess the importance of an infectious diseases consultation on the outcome for patients with *S. aureus* bacteremia.

Our finding that the rate of relapse was lower among patients with *S. aureus* bacteremia whose physicians followed the advice of infectious diseases consultants than among those whose physicians did not follow these recommendations has important implications. We believe that the benefit of our intervention was due to more than the formulation and dissemination of management guidelines. These guidelines were intended to supplement but never replace clinical judgment and are likely to be modified as more data are gathered. Implementation of our management guidelines required individual assessment (as to the likely source of infection), interpretation of clinical and laboratory findings (e.g., echocardiography), and judgment (e.g., concerning the significance of individual clinical findings in relation to the presence of metastatic disease). We believe that such a process is most likely to be successful when undertaken by infectious diseases specialists skilled in clinical medicine and knowledgeable about the myriad manifestations and complications of *S. aureus* bacteremia and its treatment.

We hope that our study will prompt other investigators to confirm these findings and undertake randomized trials of the efficacy and cost-effectiveness of intervention by infectious diseases specialists in cases of common infectious diseases. Furthermore, we hope that the results of these studies will prompt generalists and third-party payers to recognize the importance of infectious diseases consultation even in cases of *S. aureus* bacteremia, where the diagnosis is obvious. Indeed, our findings suggest that successful treatment of *S. aureus*...
bacteremia requires more knowledge than selecting the right antibiotic from a pocket reference for antimicrobial therapy.

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References