Outcomes Analysis of Delayed Antibiotic Treatment for Hospital-Acquired *Staphylococcus aureus* Bacteremia

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The objective of this study was to determine the effect of delayed therapy on morbidity and mortality associated with nosocomial *Staphylococcus aureus* bacteremia. The study included all episodes of *S. aureus* bacteremia that developed >2 days after hospital admission during 1999 to 2001. Classification and regression tree analysis (CART) was used to select the mortality breakpoint between early and delayed treatment. During the 25-month study period, 167 patients met the inclusion criteria. The breakpoint between delayed and early treatment derived using CART was 44.75 hours. On multivariate analysis, delayed treatment was found to be an independent predictor of infection-related mortality (odds ratio, 3.8; 95% confidence interval, 1.3–11.0; \( P = .01 \)) and was associated with a longer hospital stay than was early treatment (20.2 days versus 14.3 days; \( P = .05 \)). These findings support the notion that delay of therapy has deleterious effects on clinical outcomes, and efforts should be made to ensure that appropriate therapy is initiated promptly.

The widespread use of vancomycin to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infection has coincided with an increased incidence of vancomycin-resistant enterococci (VRE) infections, and numerous studies have suggested an association between vancomycin use and the emergence of VRE [1–5]. In response to the increased prevalence of VRE and its implications for public health, the Hospital Infection Control Practices Advisory Committee (HICPAC) ratified recommendations for preventing and limiting the spread of infections caused by vancomycin-resistant organisms. The guidelines for prudent use of vancomycin are a major component of the HICPAC recommendations [6, 7]. Recent emergence of clinical isolates of *S. aureus* with vancomycin resistance further underscores the need to control vancomycin use [8].

A consequence of the increasing prevalence of MRSA and of vancomycin restriction policies is that patients may not receive empirical therapy with antimicrobials that have in vitro activity against the *S. aureus* isolate. Delay in the initiation of appropriate antimicrobial therapy has been identified as an important determinant of clinical outcomes in various patient care settings [9–11]. However, the impact of delaying antimicrobial therapy for patients with *S. aureus* bacteremia (SAB) has not been extensively evaluated [12–14]. At our institution, empirical use of vancomycin is restricted to patient populations deemed to be at high risk for MRSA infection (i.e., patients who have burns, chronic decubitus ulcers, catheter infection, prosthetic valve endocarditis, or CNS infections with ventriculostomies or who have undergone total hip/knee arthroplasty). Empirical vancomycin use outside the policy must be approved by a clinician specializing in infectious diseases. Therefore, the objective of this study was to determine
the impact of delayed therapy on the clinical outcomes associated with hospital-acquired SAB.

PATIENTS AND METHODS

Study Population

We performed the study at Detroit Receiving Hospital and University Health Center, which is a 279-bed, level 1 trauma center in Detroit, Michigan. The study included consecutive episodes of SAB identified from 1 January 1999 through 31 January 2001. Only cases of SAB that occurred ≥2 days after hospital admission and that met the Centers for Disease Control and Prevention (CDC) criteria for bloodstream infection were included in the analysis [15]. If a patient had ≥1 episode of SAB during a hospitalization, only the first episode was considered.

Study Design

To evaluate the effect of delayed treatment on clinical outcomes associated with SAB, a retrospective cohort analysis was performed. Classification and regression tree analysis (CART) was used to select the time interval that partitioned infection-related mortality (IRM) on the basis of the duration, in hours, from the time that the first S. aureus–positive blood culture result was attained until administration of appropriate treatment. With use of this method, the hour breakpoint that maximized the difference in the IRM was identified, and the entire population of study patients was divided into 2 groups: those who had a high likelihood of IRM, and those who had a low risk of IRM [16]. The time identified by CART served as the breakpoint between early and delayed treatment, and patients were stratified accordingly. Clinical characteristics associated with the delayed treatment group selected by CART were also examined to identify potentially modifiable predictors of delayed therapy.

Data Collection

Clinical data. Data regarding the following characteristics were obtained for each patient from medical records: age, sex, comorbidities present, hospitalizations within 180 days before admission, receipt of prior antibiotic therapy, length of hospitalization before the onset of SAB (total hospitalization and hospitalization in the intensive care unit [ICU]), hospital unit at the onset of SAB (ICU vs. non-ICU), presence of a central venous catheter, receipt of total parenteral nutrition (TPN) or mechanical ventilation at the onset of SAB, source of bacteremia, and severity of illness at the onset of SAB (as calculated on the basis of the APACHE II score [17]).

The presence of the following comorbid conditions was documented: diabetes mellitus, heart failure, chronic obstructive pulmonary disease (COPD), hepatic dysfunction, renal failure (as indicated by the necessity for dialysis), history of cerebrovascular accident, malignancy, HIV infection, alcoholism, presence of decubitus ulcers (stage II–IV), administration of immunosuppressive drugs (receipt of ≥20 mg of prednisone per day or of an equivalent corticosteroid for ≥14 days before the onset of SAB, or receipt of any antineoplastic chemotherapy in the 3 months before the onset of SAB), surgery requiring >48 h of hospitalization in the 30 days before the onset of SAB, and presence of burns on >30% of the body surface area.

Prior antibiotic use was defined as the administration of antimicrobials for >48 h in the 30 days before the onset of SAB. The source of SAB was determined by assessment of other S. aureus–positive cultures at the time of onset of SAB and/or clinical description by the physician in the medical record. For the purpose of analysis, sources of SAB were divided into 2 categories on the basis of the mortality risk associated with the origin of SAB. Low-risk sources (i.e., those associated with a mortality rate of <10%) included intravenous catheters, the urinary tract, and several manipulation-related sources (including endoscopy, arterial catheterization, and sclerosis of esophageal varices). High-risk sources (i.e., those associated with a mortality rate of ≥10%) included osteoarticular sources, skin and soft tissue, pressure ulcers, endovascular sources, the lower respiratory tract, abdominal sources, CNS foci, and primary sources. Patients with >1 possible source of bacteremia (e.g., 1 low-risk source and 1 high-risk source) were considered to have a high-risk source [14, 18].

Microbiological data. Microbiologic data collected included all data on S. aureus–positive cultures. Susceptibility testing was performed using the microtiter-well method, and the results were interpreted according to NCCLS guidelines [19].

Treatment data. All antimicrobials administered in response to SAB were noted. Treatment was considered to be appropriate on the basis of 2 factors: (1) the timing of treatment relative to the time of the first positive blood culture result, and (2) the susceptibility of the blood isolate. If a patient received ≥1 intravenous antibiotic to which the S. aureus blood isolate was susceptible, and if the antibiotic was administered within the CART defined breakpoint, it was considered to be appropriate early treatment. For example, if an individual had MRSA bacteremia and received vancomycin within the CART defined breakpoint, the patient would be classified as having received early treatment. An example of a recipient of delayed treatment would be a patient with MRSA bacteremia who was initially treated with a β-lactam but who did not receive vancomycin until some time after the CART defined breakpoint.

Outcome Assessment

We assessed the outcomes death related to SAB and length of hospital stay after the onset of SAB (LOS-SAB). Calculation of LOS-SAB excluded patients who died secondary to SAB. To
prevent bias, investigators involved in the outcomes assessments were blinded to both susceptibility data and treatment data, including time to receipt of treatment.

Death was considered to be related to SAB if ≥1 of the following criteria were present: (1) blood cultures were positive for SAB at the time of death, (2) death occurred before resolution of signs and symptoms of SAB, (3) death occurred ≤14 days after the onset of SAB without another explanation, (4) autopsy findings indicated SAB as a cause of death, and (5) SAB was indicated as a cause of death on the death certificate. LOS-SAB was defined as the time from the first S. aureus–positive culture until discharge or death.

Statistical Analysis
Qualitative variables were compared by Pearson χ² test or Fisher’s exact test, and quantitative variables were compared by Student’s t test or the Mann-Whitney U test. LOS-SAB was log-transformed to more closely approximate a normal distribution. CART was used to select the time interval that partitioned IRM on the basis of the number of hours to receipt of appropriate treatment (i.e., the identified breakpoint between early treatment and delayed treatment).

Multivariate analyses were performed to determine the independent association of delayed treatment with the clinical outcome of interest while adjusting for confounding variables. All variables that were significantly associated with the outcome on univariate analysis were included in the explanatory multivariate model. Standard logistic regression was used to analyze IRM. CART, which included optimal tree selection based on pruning and 10-fold cross-validation, was also used to identify subsets of patients at greatest risk for IRM and to determine the influence of delayed treatment in these subsets of patients. Pruning and cross-validation were used in the CART analysis to select the optimal nested subtree with the smallest misclassification cost based on the predefined parameters for sensitivity and specificity [16].

LOS-SAB was evaluated with analysis of covariance (ANCOVA). ANCOVA was selected to analyze LOS-SAB because it measures mean group differences while adjusted for confounding variables (in this case, adjusted mean LOS-SAB). For 2-tailed tests, P < .05 was considered to be statistically significant. SPSS software, version 10.0 (SPSS), and CART software (Salford Systems) were used for all calculations.

RESULTS
During the study period, 458 episodes of SAB were identified. Of the 458 cases of SAB, 167 fulfilled the inclusion criteria. Reasons that cases of SAB were excluded are as follows: 285 cases of SAB developed <2 days after the patient’s hospital admission, 3 cases did not meet the CDC criteria for bloodstream infection, and, for 3 cases, the patients died ≤48 h after onset of SAB. Overall, the mean age (±SD) was 54.2 ± 16.6 years, and the cohort was predominantly male (62.9% of patients). Most patients were receiving care at an internal medicine service (58.7%) and were admitted to an ICU (61.1%). The MRSA infection rate was 61.7% of cases.

Fifty-three patients (31.7%) died during hospitalization. Of these deaths, 39 met the definition of death related to SAB; for 14 patients, there was an alternative explanation of death. The causes of death in these 14 patients are as follows: 3 died secondary to non–infection-related cerebral hemorrhages, 1 patient died of terminal lung cancer, 1 died secondary to hepatic encephalopathy and bleeding esophageal varices, 1 died of a myocardial infarction (which was not infection related), and 1 died of fungemia that developed 10 days after completion of SAB treatment; 7 patients died >30 days after the onset of SAB. It should be noted that the results of additional blood cultures were negative for all 14 patients.

The time breakpoint derived by CART analysis that partitioned IRM was 44.75 h. Forty-eight patients did not receive appropriate treatment before the CART-derived breakpoint (the delayed treatment group), and 119 patients received appropriate treatment within 44.75 h (the early treatment group). Comparison of the IRM rate between the groups revealed there was a 1.7-fold increase in the IRM rate in the delayed treatment group compared with the early treatment group (33.3% vs. 20.2%, respectively; P = .05). No significant differences in the mean LOS-SAB were observed between the treatment groups (table 1).

To determine the independent association between delayed treatment and the clinical end points, multivariate analyses were performed that controlled for the significant univariate predictors for each outcome of interest. After controlling for the clinical characteristics associated with IRM (i.e., APACHE II score, high-risk source of infection, receipt of mechanical ventilation, and presence of decubitus ulcers), delayed treatment was still found to be an independent predictor of IRM (OR, 3.8; 95% CI, 1.3–11.0; P = .01). As determined by ANCOVA

Table 1. Univariate analysis of outcomes of the phase I cohort analysis.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Delayed treatment group (n = 48)</th>
<th>Early treatment group (n = 119)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection-related death, no. (%) of patients</td>
<td>16 (33.3)</td>
<td>23 (19.3)</td>
<td>.05</td>
</tr>
<tr>
<td>LOS-SAB, mean days a</td>
<td>17.6</td>
<td>14.9</td>
<td>.4</td>
</tr>
</tbody>
</table>

NOTE. LOS-SAB, length of hospital stay after the onset of Staphylococcus aureus bacteremia.

a Continuous variable, log transformed, expressed as mean value. Includes data for 128 patients (32 in the delayed treatment group and 96 in the early treatment group) who did not die secondary to bacteremia.
analysis that controlled for clinical characteristics associated with a longer mean LOS-SAB (i.e., APACHE II score, presence of burns, receipt of mechanical ventilation, and stay in an ICU at onset of SAB), the adjusted mean LOS-SAB was longer in the delayed group than in the early treatment group (20.2 days vs. 14.3 days; \( P = .05 \)).

CART was also used to identify subsets of the cohort at greatest risk for IRM and to determine the influence of delayed treatment in these subsets (figure 1). This analysis resulted in a tree containing 3 terminal nodes. An APACHE II score of \( \geq 15.5 \) was the most important predictor of IRM. Patients who had an APACHE II score of \( < 15.5 \) had an extremely low probability of mortality (6.7%). Within the population of patients who had an APACHE-II score of \( \geq 15.5 \), patients with a high-risk source of infection had 56.6% probability of IRM, compared with a 12.5% probability of IRM for patients with a low-risk source. Assessment of the impact of delayed treatment revealed no difference in the mortality rate when the APACHE II score was \( < 15.5 \). Among patients with an APACHE II score of \( \geq 15.5 \) and a high-risk source of infection, the mortality rate was significantly higher in the delayed treatment group than it was in the early treatment group (86.7% vs. 44.7%, respectively; \( P = .006 \)).

On univariate analysis, MRSA infection was the most significant predictor of delayed treatment (\( P < .001 \)). Of the 48 episodes of delayed treatment, 42 involved MRSA infection; the patients were initially treated with an antibiotic that lacked activity against the MRSA strain, and they did not receive appropriate therapy within 44.75 h of the initial positive blood culture result. Non-ICU hospital stay at the onset of SAB and COPD were also significantly associated with delayed treatment, compared with early treatment (33.3% vs. 16.0% \( [P = .01] \) and 64.6% vs. 39.5% \( [P = .003] \), respectively). On logistic regression analysis, MRSA infection was found to be the most significant predictor of delayed treatment (OR, 8.3; 95% CI, 2.6–16.8). Non-ICU stay at the onset of SAB (OR, 3.7; 95% CI, 1.7–7.8) and COPD (OR, 3.0; 95% CI, 1.3–7.3) were also found to be independent predictors of delayed treatment.

**DISCUSSION**

The deleterious effects of delayed antimicrobial therapy are well documented in various patient care settings [9–11]. In an analysis by Kollef et al. [10], inadequate antimicrobial treatment was found to be the most important independent determinant of in-hospital mortality among critically ill patients. Similarly, Ibrahim et al. [11] reported that patients who received inappropriate empirical therapy for bloodstream infections in the ICU were at an almost 7-fold higher risk of mortality, compared with patients who received adequate antimicrobial therapy.

Patients with nosocomial SAB are at an increased risk of receiving delayed therapy because of the increasing prevalence of \( S. aureus \) isolates with multidrug resistance [20]. In a study that examined the benefit of appropriate empirical antibiotic treatment for bloodstream infection, 141 (35.4%) of 398 patients with SAB did not receive appropriate therapy \( \geq 48 \) h after the first positive blood culture result was obtained [9]. Similarly, Ibrahim et al. [11] reported that 46 patients (32.6%) with

Figure 1. Classification and regression tree analysis of predictors of infection-related mortality due to hospital-acquired \( Staphylococcus aureus \) bacteremia (SAB). D-Tx, delayed treatment group; E-Tx, early treatment group. Data are percentage of patients.
MRSA bacteremia did not receive appropriate therapy. Despite the high rates of inadequate therapy associated with SAB, the clinical implications of delayed therapy have not been extensively evaluated [12–14]. In addition, the specific time delay to receipt of appropriate antibiotics that increases the risk of clinical failure has not been investigated.

This study demonstrated that delaying therapy for >44.75 h substantially increases the risk of IRM in patients with hospital-acquired SAB. Patients who developed SAB outside of the hospital were excluded, because the time of onset of bacteremia in relation to the time of treatment initiation is difficult to assess accurately in these patients. The 44.75-h breakpoint was derived using CART. CART is a useful analytical tool to identify breakpoints for continuous variables in which the outcome of interest is distinctly different between the resulting groups. Different methodologies to control for confounding variables were used for optimum determination of the intrinsic impact of delayed therapy. Consistency in the results of the analyses strongly supports the hypothesis that delayed appropriate therapy for hospital-acquired SAB is independently associated with IRM. Furthermore, the influence of delayed treatment on mortality was most evident in critically ill patient populations, particularly for patients with an APACHE II score of ≥15.5 and a high-risk source of infection.

The results of previous analyses that have examined the impact of delayed treatment on outcomes for patients with SAB are conflicting [12–14]. This may be the result of methodological differences between studies—specifically, the definition of inappropriate therapy and the mortality end point selected. In an analysis by Soriano et al. [14], inappropriate empirical therapy was identified as an independent predictor of IRM. Similarly, in an evaluation of nosocomial SAB, Romero-Vivas et al. [13] reported that inadequate treatment was independently associated with IRM. In each of these studies, the first regimen that the patient received was assessed for appropriateness, regardless of the time from onset of SAB to initiation of therapy. Analysis by Roghmann [12] failed to find a relationship between survival and the administration of effective antibiotic therapy within 48 h after SAB onset; the primary end point in that study was 30-day, all-cause mortality. This is in contrast to the end point of IRM, which was used in our analysis and in the aforementioned studies [13, 14]. Some investigators have suggested examining the mortality rate at some predefined time point after blood culture results are positive, because this end point is objective and reproducible [21]. We elected to exclude non–infection-related deaths, because we were specifically interested in the causal relationship between delayed treatment and mortality. Inclusion of non–infection-related deaths would diminish the strength of this association.

We also evaluated risk factors for delayed therapy and found that MRSA infection was the most important determinant of delayed therapy. Forty-two of the 48 episodes of delayed treatment involved MRSA infection. This observation is not surprising, because MRSA strains often express resistance to numerous antimicrobials [20]. Therefore, knowledge of institution-specific risk factors for acquisition of MRSA should be considered when initiating empirical antimicrobial therapy. Patients in non-ICU settings and patients with COPD were also found to be at an increased risk of receiving delayed therapy. Efforts should be made to ensure that these patients are evaluated thoroughly and receive timely and adequate empirical therapy.

There are additional outcome measurements that are of importance in assessing the implications of delayed treatment. In the cohort analysis, delayed treatment was also independently associated with a longer LOS-SAB than was early treatment. These results suggest that delaying appropriate treatment not only impacts mortality but is also associated with considerable morbidity and increased cost due to greater resource use and prolonged hospitalization.

There are several limitations to our study that should be noted. First, the results of this study may be unique to our patient population. Detroit Receiving Hospital is a level 1 urban trauma center that rarely provides care for pediatric or immunosuppressed patients. Second, it must be considered that institution-specific antibiotic practices may impact the likelihood of patients receiving delayed treatment. Finally, we did not examine the relationship between the specific antimicrobial agents administered and patient outcomes. The potential difference between empirical agents that can be used for SAB merits further evaluation.

In conclusion, the observations made in this study support the notion that delaying appropriate treatment for >44.75 h is detrimental to patient outcomes. Delayed treatment is not only a predictor of IRM, but it is also associated with a longer duration of hospitalization. Efforts should be made to ensure that appropriate therapy that has a spectrum of activity consistent with likely resistance patterns is initiated promptly. This is most crucial in critically ill patients and in populations with a high likelihood of acquiring MRSA infection. When developing antibiotic-restriction policies, the potential adverse outcomes resulting from delayed treatment must be balanced with the potential ecological benefit of limiting excessive antibiotic use.

References