Excess Mortality in Critically Ill Patients with Nosocomial Bloodstream Infections*

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and Michael S. Simberkoff, M.D.§

To determine the excess mortality attributable to hospital-acquired bloodstream infections, we applied the acute physiology and chronic health evaluation (APACHE) II classification to 34 critically ill patients with this complication. The study included primary bloodstream infections, defined by a positive blood culture at least three days after hospitalization, in the absence of any other apparent source of infection. The most frequent blood isolates included Staphylococcus aureus (39 percent), Gram-negative rods (24 percent), and Candida albicans (15 percent); the spectrum of blood isolates suggested that most infections were related to intravascular catheters. In a control group of intensive care unit patients (n = 384), the death rate predicted by APACHE II was similar to the observed death rate (35.3 vs 37.5 percent). In a subgroup of control patients (n = 34), chosen for APACHE II scores that matched the patients with bloodstream infections, predicted and observed death rates were also similar (53.1 vs 52.9 percent). For patients with bloodstream infections, however, observed mortality (82.4 percent) significantly exceeded the predicted value (54.1 percent, p = 0.025). We conclude that critically ill patients who develop nosocomial bloodstream infections are at greater risk of death than patients with comparable severity of illness without this complication. The difference between the observed and predicted death rates, 28 percent, represents the excess mortality associated with bloodstream infection in critically ill patients.

(Chest 1991; 100:164-67)

APACHE = acute physiology and chronic health evaluation

Nosocomial bloodstream infections occur in approximately 200,000 patients each year and are recognized as an important cause of excess mortality.1 Prior studies of nosocomial bloodstream infections, however, have provided only rough approximations of the excess mortality due to this complication.2 As noted by Wenzel,3 a major difficulty in such studies is the separation of mortality attributable to the nosocomial bloodstream infection from that due to the underlying disease process per se. This difficulty is compounded by studies that include patients from both general medical wards and intensive care units, thus encompassing a wide range of underlying illnesses of variable severity. Although some investigators have compared patients with bloodstream infections and control subjects matched for age, sex, clinical service, and diagnosis, the selection of a suitable control population still suffers from the variable severity of illness found in any heterogeneous group of patients.4,5 To overcome this problem, we used the acute physiology and chronic health evaluation II classification to select a control group of patients that matched, with respect to severity of illness and predicted outcome, 34 critically ill patients having nosocomial bloodstream infection.

APACHE II has been demonstrated to predict mortality accurately in various groups of patients requiring intensive care and has been validated in over 5,000 patients from a variety of critical care settings.6,7 The system stratifies patients according to severity of illness and is based on age, 12 physiologic variables, the presence of long-term disease, and 39 diagnostic category coefficients. These variables are combined in the APACHE II regression equation for the calculation of predicted death rates among groups of critically ill patients.8 Comparison of predicted and observed death rates may provide an assessment of the overall quality of care in a given ICU. When applied to specific groups of patients, comparison of predicted and observed death rates may indicate an excess mortality associated with a complication, or a lower mortality due to a new therapeutic intervention. In addition, as in the present study, APACHE II facilitates the selection of suitable control subjects in studies of critically ill patients. To determine the excess mortality attributable to nosocomial bloodstream infection, we analyzed predicted and observed death rates in 34 critically ill patients with this complication and in control patients without bloodstream infections.

METHODS

Setting

The Medical Service of the New York Veterans Administration

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Table 1—APACHE II Diagnostic Categories: Patients with Bloodstream Infections vs Control Subjects Matched for APACHE II Score

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients with Bloodstream Infections, %</th>
<th>Matched Control Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 34</td>
<td>N = 34</td>
<td></td>
</tr>
<tr>
<td>(Mean APACHE II Score, 26.3±9.8)</td>
<td>(Mean APACHE II Score, 26.3±10.0)</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>Cardiovacular failure</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>Metabolic-renal disease</td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>

Medical Center consists of 120 ward beds, six cardiac care unit beds, a 16-bed ward for care of patients with AIDS, and a 12-bed medical ICU. The medical ICU is staffed by three interns, two residents, a pulmonary fellow, and an attending physician, all of whom rotate at monthly intervals.

Data Collection

The study covered the period from July 1986, through June 1989. We identified 34 medical ICU patients from a computerized log maintained by the Infectious Disease Section, which routinely reviews every blood culture isolate recovered by the microbiology laboratory. These 34 patients were considered to have nosocomial, primary bloodstream infection based on (1) a positive blood culture at least three days after hospitalization, and (2) no clinical or laboratory evidence of infection at other tissue sites, eg, urinary tract, biliary tree, etc, that might have given rise to a secondary bacteremia. Recorded data included the organism recovered and the types of intravascular catheters present at the time of bloodstream infection. Catheters were not routinely cultured after removal. During the three-year study period, the rate of bloodstream infections in the medical ICU meeting this definition was 4.8/1,000 patient-days; no clustering of cases was noted at any time. The overall rate of bloodstream infection on the general medical wards was 1.1/1,000 patient-days during the study period.

APACHE II data were collected on all study patients, following the method of Knaus et al.1 We recorded the most abnormal value of 12 physiologic variables during the first 24 hours of a patient’s course in the ICU. Outcome endpoints were death in hospital or discharge from hospital.

Data were also collected prospectively on randomly chosen patients admitted to the medical ICU during the study period, with the following exceptions: (1) patients transferred from the ICU within 24 hours; (2) patients admitted to rule out myocardial infarction when cardiac unit beds were not available; and (3) patients transferred from the surgical ICU for further management.

Patient Groups

The 34 patients with bloodstream infections had a mean age of 60.0 years (range 31 to 86 years). The most frequent APACHE II diagnostic categories recorded for the patients with bloodstream infections are shown in Table 1. Eight (23.5 percent) of the patients had a history of intravenous drug abuse. Four patients (11.8 percent) had acquired immunodeficiency syndrome; diagnoses included respiratory failure in two (including one with Pneumocystis pneumonia), and one patient each with upper gastrointestinal hemorrhage and cardiovascular failure. From the time of entry to the ICU, the median number of days until the onset of bloodstream infection was eight (range, time of entry through 87 days after entry). Intravascular catheters included central venous lines in 60 percent of patients, peripheral intravenous lines in 53 percent, and arterial lines in 40 percent.

The overall control population consisted of 384 randomly selected ICU patients evaluated by the APACHE II system. From this group, 34 ICU patients whose APACHE II scores matched each of the patients with bloodstream infection were randomly chosen. Thus, by definition, the mean APACHE II score (±SD) of the patients with bloodstream infections and the matched control subjects was the same. The mean age of this group was 65.4 years (range, 39 to 91 years). APACHE II diagnostic categories (Table 1) were similar for patients with bloodstream infections and the matched control subjects.

Statistical Methods

Data are expressed as mean ± SD. Predicted risk of in hospital death was calculated by the APACHE II regression equation. The mortality ratio is the observed/predicted mortality; the 95 percent confidence interval of this ratio was determined by the method of Vandenbrouke.8 Differences between predicted and observed death rates were also evaluated by a two variable chi-square test. Mean APACHE II scores were compared by the unpaired Student’s t-test. Statistical significance is defined as p<0.05.

RESULTS

Microbiology Data

The frequency of blood isolates is shown in Table 2. Of the six cases of C albicans fungemia, three were associated with total parenteral nutrition, and one each with acute myelogenous leukemia, an intracranial meningioma treated with glucocorticoids, and acquired immunodeficiency syndrome. Polymicrobial bloodstream infections were found in six (14.6 percent) cases; three cases of C albicans fungemia were polymicrobial, including Enterobacter cloacae (two) and Pseudomonas cepacia (one).

Mortality Data

The predicted death rates for all patient groups are shown in Table 3. Compared to the overall ICU control subjects, the group of matched control patients had an elevated mean predicted death rate due to a higher mean APACHE II score. Although patients with bloodstream infections and the matched control subjects without bloodstream infections had the same mean APACHE II scores (26.3±9.8 vs 26.3±10.0),

Table 2—Bacterial and Fungal Blood Isolates (N = 41)*

<table>
<thead>
<tr>
<th>Organism</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>S aureus</td>
<td>16 (39)</td>
</tr>
<tr>
<td>Gram-negative rods</td>
<td>10 (24)</td>
</tr>
<tr>
<td>P aeruginosa</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>3 (8)</td>
</tr>
<tr>
<td>E cloacae</td>
<td>2 (5)</td>
</tr>
<tr>
<td>P cepacia</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>C albicans</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Streptococcus sp</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Staphylococcus sp</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

*Six patients had >1 organism isolated.
Table 3—Comparison of APACHE II Predicted Mortality and Observed Mortality

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Predicted Death Rate, %</th>
<th>Observed Death Rate, %</th>
<th>Mortality Ratio*</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ICU control subjects</td>
<td>384</td>
<td>35.3</td>
<td>37.8</td>
<td>1.07</td>
<td>0.90-1.25</td>
</tr>
<tr>
<td>Matched control subjects</td>
<td>34</td>
<td>53.1</td>
<td>52.9</td>
<td>1.00</td>
<td>0.59-1.51</td>
</tr>
<tr>
<td>Patients with bloodstream infection</td>
<td>34</td>
<td>54.1</td>
<td>82.4†</td>
<td>1.52‡</td>
<td>1.01-2.14</td>
</tr>
</tbody>
</table>

*Mortality ratio is observed/predicted death rates.
†Greater than the predicted rate for patients with bloodstream infections (p = 0.025), and greater than the observed rate for matched control subjects (p<0.025).
‡Mortality ratio is significantly greater than 1.0.

Their predicted death rates differed slightly due to minor differences in diagnostic categories of the two groups (Table 1). Within the group with bloodstream infections, the mean APACHE II score of survivors was significantly less than nonsurvivors (17.2±8.2 vs 28.2±9.1, p<0.02).

For the overall control group (n=384), predicted and observed death rates were closely matched, resulting in an observed/predicted mortality ratio not significantly different from 1 (Table 3). The group of control subjects with matched APACHE II scores (n=34) also had similar predicted and observed mortality.

In contrast, the patients with bloodstream infections had a higher observed mortality than that predicted by APACHE II, resulting in a mortality ratio significantly greater than unity (Table 3); the observed mortality also significantly exceeded the predicted mortality by the chi-square test (chi-square = 5.02, p = 0.025). Compared to the matched control subjects with comparable severity of illness and similar predicted mortality, the patients with bloodstream infections had a significantly increased observed mortality (82.4 vs 52.9 percent, p<0.025).

**DISCUSSION**

Bacteremia is the most frequently encountered nosocomial infection in critically ill patients. Prior studies have revealed that between 33 and 45 percent of nosocomial bacteremias occur in ICU patients who occupy less than 10 percent of hospital beds. This study was designed to determine the excess mortality attributable to nosocomial bloodstream infection in patients in our medical ICU. To overcome a problem found in other mortality studies, that is, the lack of an appropriate control population, we applied the APACHE II classification. APACHE II permits the selection of suitable control patients with matched severity of illness and predicted outcome. We previously validated the general use of APACHE II to predict outcome accurately in our medical ICU. Similar predicted and observed death rates (35.3 vs 37.8 percent) were also found within the overall control group of the present study.

The observed mortality of the patients with bloodstream infections in the present study, 82 percent, is higher than the rates of 25 to 49 percent reported in studies which include all hospitalized patients. The observed mortality also exceeds the 60 percent mortality reported by Forgacs and co-workers in a 15-year study of nosocomial bacteremia in an intensive care unit. Unlike our study, which was limited to cases of primary bloodstream infection, Forgacs et al. included patients with both primary and secondary bacteremia. It is noteworthy that they found a difference in mortality of 47 percent between the bacteremic patients and all other ICU patients (60 vs 13 percent). We found a similar difference, 44 percent, in the observed death rates of the patients with bloodstream infections and the overall control population (82 vs 38 percent). Importantly, since the ICU patients with bloodstream infections and the overall ICU population in our study were not comparable with respect to severity of illness and predicted outcome, this difference does not signify the excess mortality attributable to nosocomial bloodstream infection. To control for severity of illness, we separately evaluated a subgroup of patients with APACHE II scores that matched those of the patients with bloodstream infections; these control patients had a similar profile of diagnostic categories as well. Again, the predicted death rate closely corresponded to observed mortality (53.1 vs 52.9 percent), confirming the specific applicability of APACHE II to a control group with severity of illness similar to the patients with bloodstream infections. Thus, the predicted death rate for the patients with bloodstream infections, 54 percent, likely represents a reasonable estimate of underlying risk, prior to the additional risk incurred by bloodstream infection. For this group, the difference between the observed and predicted death rates, 28 percent, signifies the excess mortality attributable to nosocomial bloodstream infection.

The few studies that have attempted to match patients with nosocomial bacteremia and control subjects have combined both ICU and non-ICU patients. Nevertheless, the range of attributable mortality found in these studies, 21 to 31 percent, is similar to our
calculated value. Rose and co-workers\(^9\) noted a 38 percent mortality in cases of hospital-acquired bacteremia, compared to a rate of 10 percent in cases matched for sex, diagnosis, surgical intervention, and clinical service. Since the results of our study show a similar increment in risk among ICU patients with a greater severity of underlying illness, it may be that nosocomial bacteremia confers an excess mortality which is independent of the underlying disease process and its degree of severity. Still, severity of underlying illness does remain a major determinant of mortality. It is notable, although not surprising, that the mean APACHE II score of the nonsurvivors was significantly higher than the value calculated for survivors of bloodstream infections.

Our study was limited to cases of primary bacteremia and fungemia, defined as bloodstream infection without an identifiable source. It is likely that vascular catheters were the source of bacteremia in many of these patients. Maki\(^1\) noted that two-thirds of all primary bacteremias were due to catheter infection, based on routine surveillance at the University of Wisconsin Hospitals. Moreover, the spectrum of bacterial isolates found in the present study parallels that described in studies of catheter-related bacteremia.\(^13\)-\(^15\) Although \textit{S epidermidis} is the most common organism isolated from cultured catheters, \textit{S aureus} is the most frequent cause of catheter-related bacteremia, followed by Gram-negative organisms and fungi. Catheter-related infection in the present study is also suggested by the absence of \textit{Escherichia coli} from the 41 blood isolates reviewed; \textit{E coli} is not usually associated with primary bacteremia and is rarely cultured from catheter tips.\(^13\),\(^16\) Lastly, we found three cases of \textit{C albicans} fungemia to be polymicrobial, including \textit{E cloacae} and \textit{P cepacia}, suggesting possibly contaminated infusates as well.\(^1\)

Although suggestive of catheter-related infection, the data of the present study are limited. Vascular catheters were not routinely cultured. Also, except for the fact that all patients in our ICU have at least one peripheral intravenous line in place, more detailed catheter usage in terms of types, duration, and incidence was not systematically recorded for control patients. An alternative explanation for the observed profile of blood isolates could be endocarditis related to intravenous drug use. Endocarditis was an unlikely source of bacteremia in the eight (23.5 percent) patients at risk, however. Five of these patients were hospitalized for 20 or more days prior to the recovery of a blood isolate, and an additional patient had initially negative blood cultures.

Although the present study included a relatively small number of patients, the observed excess mortality of 28 percent in those with bloodstream infection is consistent with other mortality studies that employed different methodologies and included patients with less severe underlying illness. The APACHE II classification matched patients and control subjects by severity of illness, enabling us to assess the excess mortality attributable to bloodstream infection in critically ill patients. Further prospective studies with larger numbers of patients are needed to substantiate the present conclusions.

**References**

4. Spengler RF, Greenough WB. Hospital costs and mortality attributed to nosocomial bacteremias. JAMA 1978; 240:2455-58