Attributable Mortality of Stenotrophomonas maltophilia Bacteremia

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A systematic evaluation of the attributable mortality of Stenotrophomonas maltophilia bacteremia was undertaken in a matched, retrospective, case-control study. We determined the attributable mortality rate (26.7%) and mortality risk ratio (an 8-fold increase) of S. maltophilia bacteremia. The attributable mortality rate for S. maltophilia bacteremia is similar to the attributable mortality rate for other nosocomial bloodstream infections.

Stenotrophomonas (formerly known as Pseudomonas or Xanthomonas) maltophilia is emerging as an opportunistic, nosocomial pathogen that primarily affects immunocompromised patients [1, 2]. Although this organism has been considered to have limited pathogenicity, reports indicate that infection with S. maltophilia can cause bacteremia and other serious infections, particularly in severely immunocompromised patients [3, 4]. Treatment of infection with this organism is also complicated by the fact that isolates are frequently resistant to many of the currently available broad-spectrum antibiotics, including those of the carbapenem class [5, 6]. Risk factors for S. maltophilia bacteremia include neutropenia, the presence of a central venous catheter (CVC), prolonged hospitalization, and previous therapy with broad-spectrum antibiotics [7, 8]. In uncontrolled clinical trials, crude mortality rates reported to be associated with S. maltophilia bacteremia have had a range of 21%–69% [9, 10]. However, many patients with S. maltophilia bacteremia have significant underlying illnesses. In addition, the organism is often recovered from mixed cultures. Therefore, the proportion of deaths directly attributable to S. maltophilia bacteremia remains unclear.

Attributable mortality is a measure of the effect of a given disease on mortality rates and provides an estimate of the contribution of one particular factor to overall mortality [11]. To improve the understanding of attributable mortality associated with S. maltophilia bacteremia, we conducted a matched, retrospective, case-control study that used stringent criteria to exclude polymicrobial bacteremia. We also assessed risk factors associated with a fatal outcome and the effect of antimicrobial therapy on survival.

Patients and methods. A case patient was defined as any patient aged ≥18 years for whom ≥1 blood culture yielded S. maltophilia in the 6.5-year period of January 1991–August 1997. A control patient was defined as a patient similar to a case patient who had been hospitalized during the same period studied but who did not have S. maltophilia bacteremia.

We identified patients by reviewing the clinical microbiology laboratory’s daily report list. To avoid any confounding, potential case patients were excluded if any other species of bacteria was isolated from the same set of blood cultures or from blood cultures performed in the 72 h before isolation of S. maltophilia. Once a patient was identified as a case patient or a control patient, a trained research nurse collected relevant clinical information by reviewing the patient’s charts. An infectious diseases fellow reviewed the discharge summaries and did a supplemental review of medical records, when necessary.

Information was obtained regarding demographic characteristics and relevant laboratory and clinical data, including underlying diseases, major surgical and other invasive procedures, length of intensive care unit and hospital stay, antibiotic exposure (by agent and day of exposure), and mortality. This information was entered into a database for statistical analysis.

Blood samples were inoculated onto aerobic and anaerobic media and processed by the ESP 384 blood culture system (Accumed International). Identification and antimicrobial susceptibility testing of isolated bacteria were performed in the Clinical Microbiology Laboratory at New England Medical Center (Boston) using the Vitek automated system for identification (bioMérieux Vitek) and Kirby-Bauer disk testing for susceptibility [12].

Each case patient was matched to the most suitable control...
patients and control patients were correctly matched for un-

egarding disease, age, and sex. Of the 60 patients (30 pairs), 40
(66.7%) had an underlying hematologic or neoplastic disorder, 20
(50%) of whom had acute myelocytic leukemia. The median
duration of hospital stay before the onset of bacteremia in the
S. maltophilia group was similar to the duration of hospitaliza-
tion for control patients.

Comparison of case patients with control patients for pre-
disposing risk factors for S. maltophilia bacteremia revealed that
case patients were more likely to have a CVC in place (P = .05) and to have received previous aminoglycoside therapy
(P = .01). Presence of neutropenia, prolonged neutropenia, and
other risk factors were not more likely to be present in case

patients.

The identified sources of bacteremia among case patients were
associated with a CVC (43.3%), were pulmonary (13.3%), were
at soft-tissue sites (6%), and were intra-abdominal (6%). Nine
case patients (30%) had no apparent primary source of infection,
but all had CVCs in place.

The mortality rate for the case patients was 30%, compared
with a mortality rate of 3.3% for control patients. The attributable
mortality was 26.7% (95% CI, 9–44), with a risk ratio of 8 for
death (95% CI, 1.3–48.5; P = .0006). The median duration of
hospitalization was slightly longer for the case patients than it
was for controls (11.5 vs. 8 days), but this difference was not
statistically significant (P = .62).

At the time of the initial case of bacteremia, 66.7% of case
patients had a temperature of ≥38°C, 43.3% had rigors, and
23.3% had leukocytosis (WBC count, >10 × 10^9 cells/L). An
acute decrease in systolic blood pressure to <90 mm Hg was
seen in 43.3% of case patients. Severity of illness at the time
of initial bacteremia, as indicated by the Acute Physiology and
Chronic Health Evaluation II (APACHE II) score, was signif-
icantly greater among case patients (mean score, 16.4 vs. 9.9;
P = .005).

All isolates were resistant in vitro to imipenem. Of the agents
tested, trimethoprim-sulfamethoxazole and ciprofloxacin had
the best in vitro activity; 89.6% and 86.2% of the isolates were
susceptible to these agents, respectively. Most isolates were re-
sistant in vitro to aminoglycoside and β-lactam antibiotics.

Once bacteremia was diagnosed, all case patients were treated
with antibiotics. The mortality rate was lower among patients
who received appropriate therapy (3 [14.3%] of 21 patients) than
it was among patients who did not (6 [75%] of 8; P = .0002). One patient could not be evaluated because the results
of susceptibility tests were not available. Most of the case pa-
tients (18 [86%] of 21) received appropriate therapy ≤48 h
after the onset of bacteremia; 3 died despite having received
early appropriate therapy. Because the number of patients re-
ceiving monotherapy with a sensitive agent was too small (2
Table 1. Comparison of 30 patients with *Stenotrophomonas maltophilia* bacteremia and control patients with regard to matching criteria and predisposing conditions.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case patients</th>
<th>Control patients</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years</td>
<td>46.1</td>
<td>47.4</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, no. male/no. female</td>
<td>17/13</td>
<td>18/12</td>
<td>NS</td>
</tr>
<tr>
<td>Underlying illness or transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic or malignancy</td>
<td>14 (46.7)</td>
<td>15 (50.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>3 (10.0)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Bone marrow transplant</td>
<td>4 (13.3)</td>
<td>4 (13.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>4 (13.3)</td>
<td>3 (10.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Solid-organ transplant</td>
<td>1 (3.3)</td>
<td>1 (3.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>3 (10.0)</td>
<td>3 (10.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (16.7)</td>
<td>5 (16.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>2 (6.7)</td>
<td>4 (13.3)</td>
<td>NS</td>
</tr>
<tr>
<td>HIV infection</td>
<td>5 (16.7)</td>
<td>4 (13.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart disease</td>
<td>3 (10.0)</td>
<td>3 (10.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of hospitalization before onset of bacteremia, median days ± IQR</td>
<td>11.5±18</td>
<td>8±27</td>
<td>.62</td>
</tr>
<tr>
<td>Major surgery</td>
<td>11 (36.7)</td>
<td>14 (46.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>24 (80.0)</td>
<td>16 (53.3)</td>
<td>.05</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>4 (13.3)</td>
<td>2 (6.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous antimicrobial therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third-generation cephalosporin</td>
<td>9 (30.0)</td>
<td>8 (26.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Imipenem</td>
<td>10 (33.3)</td>
<td>7 (23.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>8 (26.7)</td>
<td>1 (3.3)</td>
<td>.01</td>
</tr>
<tr>
<td>Quinolone</td>
<td>12 (40.0)</td>
<td>10 (33.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>10 (33.3)</td>
<td>15 (50.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment with corticosteroids</td>
<td>18 (60.0)</td>
<td>16 (53.3)</td>
<td>NS</td>
</tr>
<tr>
<td>ICU stay at time of initial bacteremia</td>
<td>3 (10.0)</td>
<td>3 (10.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>8 (26.7)</td>
<td>4 (13.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of neutropenia of &gt;10 days</td>
<td>11 (36.7)</td>
<td>9 (30.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. ICU, intensive care unit; IQR, interquartile range.

* Determined using the $\chi^2$ test for proportions and Student’s $t$ test for continuous variables.

* Defined as $<0.5 \times 10^9$ neutrophils/L.

patients), examination of outcomes comparing monotherapy to combination therapy could not be performed.

Univariate analysis of the risk factors for mortality showed that appropriate therapy was significantly protective (relative risk, 0.2; 95% CI, 0.07–0.67; $P<.01$), whereas the presence of neutropenia (relative risk, 5.5; 95% CI, 1.8–16.9; $P<.01$) increased the risk.

**Discussion.** Despite the recognition of *S. maltophilia* as a significant pathogen, to our knowledge, no study has systematically evaluated the attributable mortality of *S. maltophilia* bacteremia [9]. We found an excess mortality of 26.7% (95% CI, 9–44) attributable to *S. maltophilia* bacteremia. Although some previous studies have reported attributable mortality rates ranging from 12.5% to 41%, the criteria for attributing death to bacteremia were not specified [9, 10, 15]. The use of a well-designed, matched, historical cohort study is particularly helpful in these circumstances [11, 16]. In our study design, adequate matching between case patients and control patients eliminated the influence of comorbid conditions to control for the confounding effects of underlying disease. All case and control patients were similar with regard to the distribution of underlying disease, age, sex, and duration of exposure. Another concern raised by previous analysis of *S. maltophilia* bacteremia regarding the significance of *S. maltophilia* as a direct cause of
mortality was its frequent recovery from mixed cultures [17]. We specifically excluded all cases of polymicrobial bacteremia. Our analysis of risk factors for mortality showed that inappropriate antimicrobial therapy and neutropenia were risk factors for death. Because of the relatively small number of deaths, the independence of these associations could not be assessed.

Other studies have examined attributable mortality for other organism-specific bloodstream infections; the attributable mortality for candidemia has been estimated to be 38%; the attributable mortality for enterococcal bacteremia, 31%; the attributable mortality for Bacteroides fragilis–group bacteremia, 19%; and that associated with coagulase-negative staphylococcal bacteremia, 13.6% [12, 13, 16, 18]. These matched case-control studies used a similar study design. Thus, the mortality attributable to S. maltophilia bacteremia is higher than that for B. fragilis–group and coagulase-negative staphylococcal bacteremia, and it is lower than that for candidemia and enterococcal bacteremia. Our results indicate a mortality rate comparable with the 26%–28% attributable mortality rates reported for most nosocomial bloodstream infections from a small number of controlled studies [19, 20].

In studies published elsewhere, the factors found to be most commonly associated with S. maltophilia bacteremia were presence of malignancy, increased duration of hospitalization before bacteremia, previous receipt of broad-spectrum antibiotic therapy, presence of a CVC, and prolonged neutropenia [8, 21]. We could not analyze underlying illness and prolonged hospitalization as predisposing factors because these were matching variables in our study. However, it is noteworthy that 68% of the patients in the present study had an underlying malignancy, and one-half of those patients had acute leukemia. Duration of hospitalization before bacteremia was found to be >11.5 days for patients with S. maltophilia. Among factors that potentially predispose to infection, the presence of a CVC and previous therapy with an aminoglycoside were significantly associated with S. maltophilia.

Treatment of S. maltophilia infection is difficult because of the almost universal resistance to commonly used broad-spectrum antibiotics. Our data suggest that appropriate treatment improves almost universal resistance to commonly used broad-spectrum therapy with an aminoglycoside were significantly associated with S. maltophilia. Patients who received appropriate therapy experienced reduced likelihood of death.

References