Bacteremia Due to *Stenotrophomonas (Xanthomonas) maltophilia*: A Prospective, Multicenter Study of 91 Episodes

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We identified 91 cases of bacteremia due to *Stenotrophomonas (Xanthomonas) maltophilia* in a prospective, multicenter observational study. The patients were highly compromised; the majority had an underlying malignancy, had received immunosuppressive therapy, and had indwelling venous catheters. Although 94% of patients received an antimicrobial agent to which the blood isolate was susceptible, the mortality among these patients 14 days after the onset of bacteremia was 21%. Mortality was significantly correlated with the presence of a hematologic malignancy or neutropenia or transplantation, immunosuppressive therapy, and a severity-of-illness score of >4. *S. maltophilia* infection is associated with substantial morbidity and mortality among highly compromised patients. The organism is typically resistant to expanded spectrum β-lactam agents and aminoglycoside antibiotics. Trimethoprim-sulfamethoxazole should be administered if the isolate is susceptible to this combination; addition of another agent to which the isolate is susceptible should be considered in treating patients who are neutropenic, immunocompromised, or critically ill.

*Stenotrophomonas (Xanthomonas) maltophilia* is a nonfermentative, gram-negative bacillus that is widespread in the environment. Although the organism is frequently isolated from clinical specimens in the absence of disease [1], it is an opportunistic pathogen in debilitated patients [2–6]. Recent reports indicate that the frequency of *S. maltophilia* infection may be increasing [5, 6]; this increase is most likely due to an increase in the patient population at risk because of advances in medical therapeutics that include aggressive treatment of malignancy and increased use of broad-spectrum antimicrobials. Treatment of invasive *S. maltophilia* infection is complicated by the debilitated state of such patients and by the fact that isolates are frequently resistant to multiple aminoglycosides and β-lactam antibiotics [2, 7, 8].

We undertook a prospective multicenter study of *S. maltophilia* infection to define the spectrum of illness in a broad patient population, to identify the clinical determinants of outcome, and to assess the impact of antimicrobial therapy on survival.

Methods

Prospective surveillance for invasive *S. maltophilia* disease was carried out at five participating centers by means of regular review of clinical microbiology laboratory reports. Identification of the isolates and determination of their antimicrobial susceptibilities were done at the respective hospital laboratories; as a consequence, a variety of susceptibility testing methods were used.

Patients whose blood cultures were positive for *S. maltophilia* were entered into the study. The portal of entry for the organism was determined clinically on the basis of the presence of an active site of infection coincident with bacteremia. An infection was considered to be catheter related if there was inflammation at the catheter insertion site or if a culture of a catheter segment was positive for *S. maltophilia*. As this was an observational study, there was no defined protocol for the culturing of vascular catheters after removal.

Clinical data included patient demographics; underlying illness(es); prior invasive procedures and the presence of indwelling devices; administration of corticosteroids, cytotoxic chemotherapy or prior antibiotics; clinical presentation; and results of laboratory studies. Severity of illness at presentation was assessed with use of a score that graded presentation on a scale of 1+ to 4+ on the basis of clinical findings at onset of bacteremia; these findings included temperature, presence of hypotension, mental status, and need for ventilatory support. This scale has been shown to correlate highly with mortality risk in prior studies of bacteremia due to a variety of organisms [9–11].

Data were collected on a clinical data form and entered into a computer data base (Prophet System, Division of Research Resources, National Institutes of Health, Bethesda, MD) for analysis. Fisher’s exact test or the χ² test (two-tailed) was used to assess the statistical significance of outcome measures.

The five centers participated in the study for different durations, depending on the availability of the investigators. During
the period of participation, however, all patients fulfilling entry criteria were enrolled. The participating institutions were as follows: University of Pittsburgh (University of Pittsburgh Medical Center and Pittsburgh Veterans Affairs Medical Center), Pittsburgh, August 1991 through June 1994; University of Iowa, Iowa City, July 1991 through January 1994; Wayne State University, Detroit, November 1991 through November 1992; Mayo Clinic and affiliates, Rochester, Minnesota, November 1991 through August 1994; and University of Texas M. D. Anderson Cancer Center, Houston, August 1991 through November 1992.

Results

We identified 91 episodes of bacteremic illness. Forty-three of these episodes were reported by the M. D. Anderson Cancer Center, 16 by the Mayo Clinic, 14 by the University of Iowa, and nine each by Wayne State University and the University of Pittsburgh. Of these episodes, 36 (40%) were polymicrobial, with one to three additional isolates recovered concurrently with *S. maltophilia*; the additional isolates included coagulase-negative staphylococci (10 isolates), other non-fermentative gram-negative bacilli (10), Enterobacteriaceae (9), Enterococcus species (7), and Candida species (3).

Predisposing conditions. The majority of patients had an underlying malignancy or other condition that caused significant immunosuppression (table 1). Seventy-one patients (78%) had a malignancy, including 41 (45%) with hematologic malignancies and 34 (37%) with solid tumors; four patients had both types of malignancy. Sixty-two patients (68%) had received cytotoxic chemotherapy, and 38 (42%) had received corticosteroids prior to the onset of bacteremia. Eleven (12%) had undergone organ transplantation, and 4 (4%) were known to be infected with HIV. The presence of other chronic diseases, including cardiac disease, pulmonary disease, hepatic disease, and renal disease, was relatively frequent. Only two patients had a history of intravenous drug abuse.

Most patients (82%) had a central venous catheter in place prior to the onset of bacteremia (table 2). Twenty patients had tunneled catheters, 53 had temporary catheters, and two had venous hemodialysis catheters; three patients had more than one type of central venous catheter. Catheters were in place before the onset of bacteremia for a mean duration of 34 days (range, 1–904 days). Thirty-seven patients (41%) had other intravascular catheters in place, and twenty-five (27%) were receiving intravenous hyperalimentation. Indwelling urinary catheters and nasogastric tubes were each present in 25% of the patients. Eighteen (20%) were receiving mechanical ventilatory assistance, and eight (9%) had undergone a surgical procedure with use of general anesthesia during the 2 weeks before the onset of bacteremia. Seventy-three patients (80%) had received systemic antimicrobial therapy within the 14 days preceding the onset of bacteremia; 23 (25%) of these patients had received imipenem.

Sixty-six patients (73%) were hospitalized at the time that bacteremia developed, and 25 (27%) were outpatients. However, all of the outpatients had significant underlying illnesses and were receiving ongoing medical care. Seventy-six percent of outpatients had an underlying malignancy, 72% had central venous catheters in place, and 68% had received systemic antibiotics within the preceding 14 days.

Portal of entry. Twenty percent of identified primary sites were central venous catheter–related, 11% were pulmonary, 6% were intra-abdominal, and 3% were soft-tissue sites (table 3). Fifty-one patients (56%) had no apparent primary source of infection; of these, 43 (84%) had central catheters in place.

Antimicrobial susceptibility of blood isolates. Most isolates were resistant in vitro to multiple aminoglycosides and β-lactam antibiotics. Of the agents tested, the combination of ticarcillin and the β-lactamase inhibitor clavulanic acid had the best in vitro activity: 94% of the 69 isolates tested were susceptible to this combination. Forty-three percent of isolates were resistant to ceftazidime. Imipenem had the least activity: 88% of the isolates were resistant. Thirty-eight percent of isolates were resistant to ciprofloxacin, and 9% were resistant in vitro to trimethoprim-sulfamethoxazole.

Therapy and outcome. Twenty-three patients (25%) died within 14 days of the onset of bacteremia (acute [14-day] mortality); an additional 12 patients died later during hospitalization after apparent resolution of the bacteremia, yielding a crude mortality rate of 38%. The acute mortality associated with polymicrobial bacteremia was not significantly different from that associated with bacteremia due to *S. maltophilia* alone. Of the patients with central venous catheter–related bacteremia, 14 of 18 had the central venous catheter removed during therapy. Two of the 14 patients who had the catheter removed died, but none of the four patients who retained the catheter died.

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**Table 1.** Underlying conditions of 91 patients with *Stenotrophomonas maltophilia* bacteremia.

<table>
<thead>
<tr>
<th>Underlying condition</th>
<th>Percent of patients with indicated condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy*</td>
<td>78</td>
</tr>
<tr>
<td>Hematologic</td>
<td>45</td>
</tr>
<tr>
<td>Other</td>
<td>37</td>
</tr>
<tr>
<td>Cytotoxic chemotherapy</td>
<td>68</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
<td>42</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>34</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>15</td>
</tr>
<tr>
<td>Receipt of a transplant</td>
<td>12</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>14</td>
</tr>
<tr>
<td>Dialysis</td>
<td>5</td>
</tr>
<tr>
<td>HIV infection</td>
<td>4</td>
</tr>
<tr>
<td>IV drug abuse</td>
<td>2</td>
</tr>
</tbody>
</table>

* Four patients had both a hematologic malignancy and a solid tumor.
Table 2. Invasive devices and/or procedures among 91 patients prior to the onset of bacteremia due to Stenotrophomonas maltophilia.

<table>
<thead>
<tr>
<th>Device or procedure</th>
<th>Percent of patients with indicated device and/or procedure</th>
</tr>
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<tbody>
<tr>
<td>Central venous catheter</td>
<td>82</td>
</tr>
<tr>
<td>Other venous catheter</td>
<td>41</td>
</tr>
<tr>
<td>Intravenous hyperalimentation</td>
<td>27</td>
</tr>
<tr>
<td>Urinary catheter</td>
<td>26</td>
</tr>
<tr>
<td>Nasogastric tube</td>
<td>24</td>
</tr>
<tr>
<td>Ventilatory assistance</td>
<td>20</td>
</tr>
<tr>
<td>Surgery</td>
<td>9</td>
</tr>
</tbody>
</table>

We analyzed the 55 cases of bacteremia due to *S. maltophilia* alone to determine the clinical correlates of acute (14-day) mortality (table 3). Cases of mixed bacteremia were excluded because of the potential confounding effects of the other pathogens. Acute mortality was significantly associated with the presence of a hematologic malignancy or neutropenia and with immunosuppressive therapy, organ transplantation, and a severity-of-illness score of $\geq 4$. There was no correlation between mortality and the presence of nonhematologic malignancy or nonmalignant underlying disease or the preceding use of invasive procedures (data not shown). There was no association between known portal of entry and mortality. However, the mortality among patients for whom the portal of entry was unknown was higher than that among patients with a defined portal of entry (14 of 36 patients vs. 2 of 18; $P < .02$).

We further analyzed the 55 cases of pure *S. maltophilia* bacteremia to determine the effect of antimicrobial therapy on outcome. Of the 49 patients who received an antimicrobial agent for which susceptibility of the blood isolate was determined, the 14-day mortality was 22% (10 of 46 patients) among those receiving an agent to which the isolate was susceptible. Only three patients received an agent to which the isolate was not susceptible; one of these patients died. Mortality was 17% (3 of 18 patients) among patients receiving an agent to which the isolate was found to be susceptible within 48 hours of blood culture, compared with 27% (8 of 30) for those receiving appropriate therapy at $\geq 48$ hours ($P > .4$).

Mortality was 24% (7 of 29) for patients treated with trimethoprim-sulfamethoxazole vs. 34% for those who did not receive this agent ($P > .3$). Treatment with a third-generation cephalosporin was associated with a 10% mortality (2 of 20 patients), whereas treatment with other agents was associated with a 40% mortality (14 of 35 patients) ($P < .02$). Mortality among patients treated with an extended-spectrum penicillin was 20% (3 of 15 patients), compared with a 32% mortality (13 of 40) among those not receiving this class of antibiotic ($P > .3$). Mortality was significantly lower among patients receiving more than one of these three classes of agents (11%; 2 of 18) than it was among those receiving one class of agents (31%; 8 of 26) or none of them (55%; 6 of 11) ($P < .05$).

**Discussion**

*S. maltophilia* is a nonfermentative gram-negative rod that is widespread in the environment. Originally included in the genus *Pseudomonas* [12], it was placed in the genus *Xanthomonas* in 1983 [13]. Recently, a new genus, *Stenotrophomonas* was proposed; *S. maltophilia* is the only recognized species [14]. The organism may be isolated in clinical material in the absence of infection [1]; its isolation in respiratory secretions or wound specimens often represents colonization rather than infection. *S. maltophilia* has been implicated in outbreaks of pseudobacteremia due to contamination of arterial pressure monitoring devices [15] and blood collection tubes [16].

Although originally considered a rare cause of infection in humans [17], recent reports indicate that this organism is being isolated with increasing frequency from highly compromised patients with invasive disease [5, 6, 8]. It is likely that the incidence of serious infection due to *S. maltophilia* will increase. Advances in medical therapeutics are likely to lead to a larger population of patients who are receiving aggressive therapies for malignancy and for the prevention of transplant rejection. In addition, the use of long-term venous access devices is becoming increasingly common.

Risk factors for *S. maltophilia* infection include malignant disease, neutropenia, prior treatment with broad-spectrum antibiotics, and indwelling vascular catheters. The majority of patients in whom this infection has been described have had underlying malignant disease. Although the largest single series of cases was reported from a cancer hospital [6], other reports from different institutions have reported that in 30%–86% of the patients with *S. maltophilia* infection had an underlying malignancy. Seventy-eight percent of our patients had an underlying malignant disease, including all of the 43 patients from the M. D. Anderson Cancer Center and 58% of 48 patients from the other facilities with a greater diversity of patients. It is likely that the higher frequency of *S. maltophilia* bacteremia reported by the M. D. Anderson Cancer Center is due in large part to the larger number of patients at risk for this infection who are treated there.

Table 3. Clinical correlates of acute (14-day) mortality for 55 patients with bacteremia due to *Stenotrophomonas maltophilia* alone.

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of patients who died/total no. with indicated factor (%)</th>
<th>No. of patients who died/total no. without indicated factor (%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic malignancy</td>
<td>14/32 (44)</td>
<td>2/23 (9)</td>
<td>.005</td>
</tr>
<tr>
<td>Organ transplantation</td>
<td>7/11 (64)</td>
<td>9/44 (20)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12/26 (46)</td>
<td>4/29 (14)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>16/45 (36)</td>
<td>0/10 (0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Severity score $\geq 4$</td>
<td>7/11 (64)</td>
<td>9/44 (20)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>
In prior series, neutropenia has been reported in 21%-86% of patients [6, 16, 18, 19]. In our series, 36% of patients had neutrophil counts of < 1,000/mm³. The presence of an indwelling central venous catheter has been previously reported for 78%-86% of patients [6, 18-20]; this range is similar to our figure of 82%. Eighty percent of our patients had received prior antibiotics, a percentage consistent with the previously reported range of 57%-86%.

The portal of entry of S. maltophilia infection is frequently unknown. In our series, central venous catheter insertion sites and pneumonia were the most frequent primary sources of infection among those patients in whom one was identified; this finding is consistent with those of other reports. Fifty-six percent of our patients did not have a clinically apparent portal of entry. As 84% of these patients had a central venous catheter in place, it is likely that the catheter was the ultimate source of infection in many of these patients. Since this was an observational study, there was no standardized protocol for catheter removal and culture.

Prior crude mortality rates among reported series have ranged from 14% to 69% [2, 8, 16, 18-20]; the attribution of death to S. maltophilia infection per se, instead of to underlying disease, is difficult. For example, Jang et al. [20] reported an overall mortality of 69%, with a 41% mortality directly attributable to bacteremia. The criteria for attributing death to the bacteremic episode were not specified, however. We prospectively chose a 14-day cutoff for attribution of death to the bacteremic episode; this cutoff eliminated the difficulty of determining a precise cause of death for a patient with multiple active comorbidities.

We found that hematologic malignancy, transplantation, neutropenia, immunosuppressive therapy, and a severity-of-illness score of ≥ 4 were significantly associated with 14-day mortality. In one other series, an association between neutropenia and mortality was reported [6]; in this study the mortality associated with S. maltophilia infection was combined with that associated with non-aeruginosa Pseudomonas species. The bacteremia severity-of-illness score has been shown to be highly predictive of mortality in previous prospective studies of bacteremia due to P. aeruginosa [9], Klebsiella species [10], and Enterobacter species [11]. Other studies of S. maltophilia have reported an association between a pulmonary source of bacteremia and mortality. Among our patients, the number of pulmonary infections was undoubtedly too small (nine cases) to permit a meaningful association.

Other studies have reported a significant association between survival and administration of appropriate antimicrobial therapy. We did not find such an association, most likely because the number of inappropriately treated patients was small.

Antimicrobial therapy for S. maltophilia infections is problematic, as many isolates are resistant to multiple agents used to treat infections due to gram-negative organisms. Most S. maltophilia strains are resistant to aminoglycosides, extended-spectrum penicillins, and third-generation cephalosporins [7, 8, 21]; nearly all strains are resistant to imipenem [21-23]. The outer membrane of S. maltophilia is relatively impermeable to a variety of antimicrobials, a property that may play a role in resistance [24, 25]. Resistance to β-lactam antibiotics is mediated by two distinct, inducible β-lactamases: a zinc-containing penicillinase [26] and a cephalosporinase [27]. Although in vitro testing shows many strains to be susceptible to the combination of ticarcillin and the β-lactamase inhibitor clavulanic acid, growth inhibition is highly dependent on testing conditions [21, 28]. Another combination, piperacillin/tazobactam, appears to be less active in vitro; only 20% of strains have been found to be susceptible by agar dilution testing [23]. The combination of ticarcillin and clavulanic acid was as effective as trimethoprim-sulfamethoxazole in a murine model of S. maltophilia pneumonia [29]; however, the clinical efficacy of available β-lactam/β-lactamase inhibitor combinations has not been tested in human trials.

S. maltophilia strains are variably susceptible to fluoroquinolones; however, spontaneous mutants resistant to multiple quinolones occur at a frequency of 10-5 to 10-7 [24], and resistant strains may emerge during therapy [30]. Historically, most strains have been susceptible in vitro to trimethoprim-sulfamethoxazole and minocycline [7, 8]. Ninety-one percent of isolates from our patients were susceptible to trimethoprim-sulfamethoxazole. Recent data suggest that the percentage of strains resistant to trimethoprim-sulfamethoxazole may be increasing [31].

It is clear, however, that the concept of “appropriate” therapy for S. maltophilia should be approached with caution. Methodology for in vitro determination of the antimicrobial susceptibility of this organism is not well standardized, and results of disk diffusion, microbroth dilution, and agar dilution assays correlate poorly for a number of agents [23]. Trimethoprim-sulfamethoxazole appears to be a reasonable choice if the infecting isolate is susceptible to this agent; susceptibilities determined by means of disk diffusion and agar dilution correlate reasonably well for this combination, and there is considerable anecdotal evidence of its efficacy. The triple combinations of gentamicin, rifampin, and carbenicillin and of trimethoprim-sulfamethoxazole, rifampin, and carbenicillin have in vitro synergy [32], but clinical experience with these combinations is lacking. Combination therapy with trimethoprim-sulfamethoxazole, minocycline, and ticarcillin/clavulanate has been suggested [31].

Our data suggest that therapy with a combination of trimethoprim-sulfamethoxazole and either ticarcillin/clavulanate or a third-generation cephalosporin may be superior to single-agent therapy. Although therapy was not controlled in our study, such combination therapy deserves serious consideration when patients are neutropenic or seriously ill. Future studies should attempt to correlate the various methods of in vitro susceptibility testing with the results of therapy in animal models and with outcomes in human infection. Randomized trials of potentially efficacious agents, singly and in combination, are warranted.
For the present, we recommend that trimethoprim-sulfamethoxazole be considered the initial agent of choice for treating bacteremia due to \textit{S. maltophilia} pending antimicrobial susceptibility studies. For patients with normal renal function, we recommend a dose of 10 mg/kg (based on the trimethoprim component) administered intravenously, as initial therapy. Addition of other antimicrobials to the initial regimen should be considered if there is a significant incidence of resistance to trimethoprim-sulfamethoxazole among isolates in a particular facility. Potentially useful agents include ticarcillin/clavulanate and minocycline. The role of combination antimicrobial therapy in treating infections due to strains that are susceptible to trimethoprim-sulfamethoxazole is uncertain, but the addition of one or more agents to which the isolate is susceptible in vitro is a reasonable consideration if the patient has an underlying hematologic malignancy or is critically ill.

References