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MAJOR ARTICLE

Stenotrophomonas Bacteremia Antibiotic Susceptibility and Prognostic Determinants: Mayo Clinic 10-Year Experience

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Background. *Stenotrophomonas maltophilia* is a gram-negative, opportunistic infection that is usually hospital-acquired and associated with high morbidity and mortality. The reported increase in *S. maltophilia* infections is presumed to be due to an increase in the population at risk.

Methods. We retrospectively reviewed 10-year data for *S. maltophilia* bacteremia in hospitalized adults at our institution to determine the population at risk, sources of infection, common complications, antimicrobial susceptibility profiles, and clinical outcome trends over the past decade.

Results. Among the 98 patients analyzed, the most common source of infection was catheter-related (62, 63.3%). Most isolates (61, 65%) were resistant to ceftazidime; fewer were resistant to trimethoprim-sulfamethoxazole (TMP-SMX; 2, 2.1%) and levofloxacin (22, 23.4%). All-cause in-hospital mortality was 29.6% (29 patients). The highest mortality, 53.8%, was observed in pulmonary sources of bacteremia.

Conclusions. Although TMP-SMX continues to have reliable activity in our cohort, we noted resistance to TMP-SMX in patients with recent TMP-SMX exposure, including a case with developing resistance to TMP-SMX while on therapy.

Keywords. bacteremia; multidrug resistance; *Stenotrophomonas*.

Stenotrophomonas maltophilia is a gram-negative, multidrug-resistant organism that is typically hospital-acquired and associated with high morbidity and mortality [1, 2]. It is a free-living organism present in most aquatic and humid environments. It is not considered part of normal human flora. It is generally considered a low-virulence, opportunistic pathogen, can survive in humid surfaces, and has been isolated from a wide variety of aquatic nosocomial sources (such as exposure to nebulizers, endoscopes, hemodialysis dialysate sample, sink drains, and shower heads) [3]. Worldwide, the rate of *S. maltophilia* infections has increased in past decades, likely attributable to the increase in the population at risk as a result of advances in the care of immunocompromised patients, also driven by use of invasive devices and broad-spectrum antibiotics [2]. The population at risk includes those who are critically ill, patients with chronic obstructive pulmonary disease, HIV, an organ transplant, prolonged therapy with broad-spectrum antibiotics, extended need for assisted ventilation, respiratory tract *S. maltophilia* colonization, and prolonged neutropenia [2].

S. maltophilia can cause a wide variety of clinical syndromes, including pneumonia, bloodstream- and catheter-related infection, and, less commonly, skin and soft tissue infection, endocarditis, meningitis, bone and joint infections, and endophthalmitis [2–4]. The organism is inherently resistant to multiple classes of antibiotics, and trimethoprim-sulfamethoxazole (TMP-SMX) remains the main agent for treatment [5, 6].

Data regarding the optimal treatment, however, are still limited, and *S. maltophilia* bacteremia mortality continues to be high, 16% to 61% in the literature [5–10].

The aim of this study was to review the current epidemiology of *S. maltophilia* and updated data on contemporary susceptibility profiles on this hard-to-manage organism. We aimed to describe morbidity, complications, recurrence, and mortality outcomes.

METHODS

We conducted a retrospective review at Mayo Clinic Hospital in Rochester, Minnesota. After obtaining Mayo Clinic Institutional Review Board approval, we used Advanced Cohort Explorer to identify patients who had blood cultures positive for *S. maltophilia* from January 1, 2008, through December 31, 2017. Patients were included if they were age 18 years or older, had blood specimens for cultures for *S. maltophilia* collected either peripherally or from intravenous catheters (or both), and received treatment at Mayo Clinic Hospital, Rochester, Minnesota. Those whose culture was deemed a contaminant and did not receive treatment were excluded from the

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study. Classification of the source of bacteremia was clinically determined from review of physician notes and associated microbiology data.

Patient demographic data collected included age, sex, body mass index, antibiotic allergies, vital signs including fever (defined as temperature >38°C), and hemodynamic instability at the time of *S. maltophilia* infection. In addition, hospitalization episode data were collected: duration of hospitalization, duration of bacteremia, complications of bacteremia (including endocarditis, acute respiratory distress syndrome, and central nervous system impairment), concomitant positive cultures from a respiratory, gastrointestinal, or urinary source, need for admission to the intensive care unit, and need for mechanical ventilation. High-risk characteristics, including organ transplant, malignancy, and neutropenia (defined as an absolute neutrophilic count <500 cells/μL) and antibiotic susceptibility data were also recorded.

Minimum Inhibitory Concentrations

Minimum inhibitory concentrations (MICs) to define susceptibility were determined according to Clinical and Laboratory Standards Institute guidelines (CLSI). Isolates with "intermediate" and "resistant" susceptibility during our descriptive analysis were grouped as "nonsusceptible" isolates. Agar broth dilution was used, and our lab routinely reports *S. maltophilia* susceptibilities to ceftazidime, levofloxacin, and TMP-SMX.

Statistical Analysis

We analyzed data using the Fisher exact test or χ^2 analysis for nominal data and the median test and interquartile ranges for nonparametric continuous data. We considered *P* values of <.05 significant. We performed all statistical analysis using JMP software, version 14.1.0 (SAS Institute Inc.). Mortality was determined from the onset of *S. maltophilia* bacteremia to death.

RESULTS

We identified 105 individual patients who had blood cultures positive for *S. maltophilia* during the 10-year study period. Of these, 7 patients were excluded because a culture was deemed a contaminant and no antimicrobial treatment was given and patients had no evidence of relapse (Supplementary Table 1). Characteristics for the 98 study patients are summarized in Table 1.

Blood for culture was positive peripherally in 63 patients (64.3%) and from intravenous catheters only in 35 (35.7%). The median duration of bacteremia (interquartile range [IQR]) was 3 (2–4) days. Concomitant cultures of specimens from sources other than blood were positive in 31 patients (31.6%). These sources included pulmonary (n = 20), gastrointestinal (n = 9), urine (n = 2), pleural fluids (n = 3), bone marrow (n = 1), and paranasal sinuses (n = 1).

Table 1. Characteristics of 98 Patients With *Stenotrophomonas maltophilia* Infection

Characteristics	No. (%) or Median (IQR)
Age, y	56 (40–65.75)
Sex	
Male	54 (55.1)
Female	44 (44.9)
BMI, kg/m^2	24.4 (22–30.44)
Antibiotic allergy	
Penicillin	8 (8.2)
Quinolones	4 (4.1)
Sulfa	11 (11.2)
Cephalosporin	10 (10.2)
Hospitalization in the 60 d before bacteremia	83 (84.7)
Immunocompromised host	73 (74.5)
Malignancy	61 (62.2)
Neutropenia	36 (36.7)
Transplant	31 (31.6)
Fever[a]	59 (60.2)
Charlson Comorbidity Index	
0–2	16 16.3)
≥3	82 (83.6)

Abbreviations: BMI, body mass index; IQR, interquartile range.

[a]Temperature of ≥38°C (≥100.4°F).

Catheter-associated infection was the most common source of *S. maltophilia* bacteremia (n = 62, 63.3%), followed by gastrointestinal (n = 15, 15.3%) and pulmonary (n = 14, 14.3%). Blood cultures were polymicrobial in 40 patients (40.8%). These included *Enterococcus* species (n = 11), coagulase-negative *Staphylococcus* (n = 8), *Escherichia coli* (n = 3), *Candida* species (n = 3), *Acinetobacter* (n = 3), *Pseudomonas putida* (n = 3), *Pseudomonas aeruginosa* (n = 2), *Klebsiella* species (n = 2), *Enterobacter cloacae* (n = 2), *Clostridium innocuum* (n = 2), *Lactobacillus rhamnosus* (n = 1), and *Fusarium* species (n = 1). Documentation of negative follow-up blood culture was done in 80 (81.6%) of the cases.

Among the 98 study patients, 73 (74.5%) were immunocompromised: active malignancy in 61 (62.2%), history of organ transplant in 31 (31.6%), and neutropenia in 36 (36.7%). In addition, 82 (83.6%) patients had high Charlson Comorbidity Index scores (≥3), 50 patients (51%) required admission to the intensive care unit, and 27 (27.6%) required mechanical ventilation. Complications of *S. maltophilia* bacteremia included infective endocarditis in 2 patients (2%) and acute respiratory distress syndrome in 8 (8.2%).

On blood culture susceptibility testing, 61 (65%) of the isolates were resistant to ceftazidime, 22 (23.4%) were resistant to levofloxacin, and only 2 (2.1%) were resistant to TMP-SMX. Minocycline susceptibility testing was performed in only 12 isolates, and all 12 were susceptible, with MICs of ≤4 μg/mL. Susceptibility to tigecycline was tested in 17 isolates, and 10 were susceptible, with MICs ≤2 μg/mL. MICs used to define susceptibility and resistance are outlined in Table 2.

Table 2. *Stenotrophomonas maltophilia* Antimicrobial Susceptibility MIC Interpretation for 94 of 98 Samples[a, b]

		MIC Interpretive Criteria, μg/mL (No. of Isolates, %)		
Antimicrobial Agent	Total No. of Isolates	Susceptible	Intermediate	Resistant
Ceftazidime	94	≤8 (33, 35)	16 (1, 1)	>16 (60, 63.8)
Levofloxacin	94	≤2 (71, 75.5)	4 (2, 2.1)	>4 (21, 22.3)
Trimethoprim-sulfamethoxazole	94	≤2/38 (92, 97.8)	-	>2/38 (2, 2.1)
Ticarcillin-clavulanate	63	≤16/2 (31, 49.2)	32/2 (16, 2.5), 64/2 (4, 6.3)	>64/2 (12, 1.9)
Minocycline	12	≤4 (12, 100)	-	-
		No defined breakpoints		
Tigecycline	17	≤2 (10, 58.8)	4 (5, 29.4)	>4 (2, 11)
Colistin	7	≤4 (1, 14)	>4 (6, 85.7)	

Abbreviation: MIC, minimum inhibitory concentration.

[a]Determined according to Clinical and Laboratory Standards Institute guidelines.

[b]Susceptibilities were not performed on 4 samples.

The median duration from the time of first positive blood culture to starting effective therapy (susceptible antimicrobial agent) for *S. maltophilia* (IQR) was 2 (2–3) days. Exposure to a quinolone in the 30 days before presentation did not affect fluoroquinolone resistance. A total of 5 patients were exposed to TMP-SMX in the 30 days before presentation, and we noted 1/5 with TMP-SMX resistance. The total number of isolates with TMP-SMX resistance in our cohort was 2.

We compared our susceptibility data from blood cultures with the susceptibility data from 1954 cultures from all sources collected during a similar time frame at the Mayo Clinic. The resistance patterns were similar for levofloxacin (18%) and ceftazidime (69%) but higher for TMP-SMX (4.7%). Minocycline susceptibility was tested in 483 of the 1954 samples, and 478 (99%) of the tested isolates were susceptible. Two of the isolates (from sputum) were resistant (MICs > 8), whereas 3 isolated (from sputum) were categorized as intermediate susceptibility (MICs = 8).

Treatment regimens included combination therapy, and TMP-SMX was the primary agent used in most patients (58, 60.4%). The median duration of therapy (IQR) was 14 (14–14) days. TMP-SMX was discontinued in 11 of 58 patients (18.9%). The most common reason for change in TMP-SMX-based therapy was concern for renal dysfunction in 7 patients (63.6%), increased liver enzyme value in 2, increased sulfamethoxazole peak level in 1, and rash in 1.

The prognosis for patients with *S. maltophilia* infection was generally poor, and all-cause in-hospital 30-day mortality was 29.6% (29 patients) (Table 3). Mortality ranged from 9/58 (21%) in line-associated *S. maltophilia* infections to 8/14 (57.1%) in *S. maltophilia* bacteremia from a pulmonary source.

Even though the mortality rates were variable and were dependent on the source of bacteremia as well as the clinical and immunologic characteristics of the patients, overall these remained poor. Even in patients with presumed isolated line colonization, the mortality rate was as high as 22.8%, which was attributed to infection in 50% and to other causes (multiorgan failure, metastatic malignancy, or acute respiratory distress syndrome) in the other half of patients.

DISCUSSION

S. maltophilia is a challenging infection that affects patients who are critically ill and receiving broad-spectrum antimicrobials. Optimal empiric therapy can be lifesaving for numerous infectious complications. However, there remains a substantial delay to effective antimicrobial therapy for *S. maltophilia* bacteremia (median [IQR], 2 [2–3] days), as confirmed by our study.

Table 3. Thirty-Day Mortality in 98 Patients With *Stenotrophomonas maltophilia* Infection

Characteristics	No. (%)	Death, No. (%)	*P* Value
Patients with positive peripheral blood culture vs positive line–only culture	63 (64.2)	21 (33.3)	.27
Patients with line-associated infections	62 (63.3)	13 (20.9)	.01
Patients requiring ICU admission	50 (51)	24 (48)	<.001
Patients with neutropenia	36 (36.7)	16 (44.4)	.01
Patients with pulmonary source	14 (14.2)	8 (57.1)	.01
Patients with monomicrobial infection	58 (59)	22 (37.9)	.029
Patients with polymicrobial infection	40 (40.8)	7 (17.5)	.029

Abbreviation: ICU, intensive care unit.

Although catheter-related infections and pulmonary infections remain the most common sources of *S. maltophilia* bacteremia in the literature, we were surprised to find a substantial minority of our cases linked to a gastrointestinal source (15% of the patients), likely driven by complex gastrointestinal operations in high-risk hosts and previous broad-spectrum antimicrobial therapy [5, 7, 9].

Our study is limited by its inherent retrospective nature and exclusion of cases who were deemed to have "contaminants" on blood cultures and had no active therapy for the findings.

TMP-SMX remains the most appropriate empiric agent for treatment of *S. maltophilia* infection because of its favorable susceptibility profile (98% isolates susceptible). In our cohort, we noted a concerning finding of increasing TMP-SMX MICs in a patient with recurrent bacteremia. As such, susceptibility to this drug needs to be confirmed, and not assumed, for such patients.

Therapeutic options for *S. maltophilia* infections are limited, due to intrinsic multidrug resistance, and other less toxic antimicrobial options are poorly studied. We confirm that nearly a fifth of the patients (11 of 58, 18.9%) required a change in TMP-SMX therapy. Small reports have suggested that minocycline is a promising option [11, 12]. Among 12 blood culture isolates that were tested for minocycline susceptibility in our study, all were susceptible. Data from all sources also showed susceptibility rates up to 99%. Minocycline is showing promising in vitro susceptibility [13], and data from recent retrospective studies have shown that it is not inferior to TMP-SMX in the management of some infections [11, 12]. Similarly, in our study, for those who were not able to tolerate TMP-SMX, minocycline was utilized as an alternative therapy, even for cases of bacteremia. Larger studies are needed before minocycline can be considered a firstline agent; however, our findings support that this should be a routinely tested and reported alternative, given that 1 in 5 patients may not be able to complete therapy with TMP/SMX.

We also noted worse mortality in patients with monomicrobial *S. maltophilia* bacteremia compared with polymicrobial bloodstream infections. However, this difference may be driven by the underlying host characteristics resulting in increasing mortality in the monomicrobial infection population, rather than the influence of *S. maltophilia* alone.

CONCLUSIONS

Infections with *S. maltophilia* should be considered in critically ill patients with prolonged hospitalization who are receiving broad-spectrum antibiotics. A high degree of clinical suspicion and prompt microbiologic identification are imperative for initiation of appropriate empiric therapy. Although TMP-SMX remains the treatment of choice, alternative therapy might be needed in those with previous exposure to TMP-SMX due to higher rates of resistance. Minocycline can be considered as an alternative option in those with documented or suspected resistance or intolerance to TMP-SMX due to its excellent susceptibility profile.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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