

Stenotrophomonas maltophilia bacteremia in adults: four years' experience in a medical center in northern Taiwan

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Stenotrophomonas maltophilia has become an important nosocomial pathogen in immunocompromised patients in Taiwan. Patients with underlying diseases such as diabetes, uremia, and solid malignancy are extremely vulnerable to this organism. *S. maltophilia* bacteremia has a mortality rate of up to 62% if appropriate antibiotics are not instituted early. Knowledge of the risk factors for infection as well as local susceptibility patterns is helpful in determining which patients should receive empirical antibiotics active against *S. maltophilia*. This study assessed the characteristics of 50 episodes of *S. maltophilia* bacteremia in 48 patients admitted between March 3, 1999 and May 21, 2003. The new fluoroquinolone levofloxacin showed promising in vitro activity against *S. maltophilia* in view of the increasing resistance of isolates to trimethoprim-sulfamethoxazole. For patients at risk for *S. maltophilia* infection, such as those receiving mechanical ventilation in the ICU or those with multiple vascular access devices, the need for antimicrobial agents to which *S. maltophilia* is normally sensitive should be considered in selecting empiric therapy.

Key words: Bacteremia, microbial sensitivity tests, risk factors, *Stenotrophomonas maltophilia*

Stenotrophomonas maltophilia, previously considered a pseudomonad, was placed in the genus *Xanthomonas* in 1983, but a decade later was reclassified as the single species of the new genus *Stenotrophomonas* [1]. *S. maltophilia* is an ubiquitous bacterium found in various environments, including water, soil, plants and animals. The organism can cause clinical infections at many sites. Long-term intravenous catheter use may be a frequently overlooked portal of entry [2]. Infection due to multi-drug resistant *S. maltophilia* has emerged as an important nosocomial infection in many hospitals [3], causing bacteremia [2,4], endocarditis [5], urinary tract infections, gastrointestinal infections and pneumonia [6]. The incidence of infections caused by *S. maltophilia* is frequently high in immunocompromised patients with invasive diseases [7].

Advances in medical therapeutics and the widespread use of immunosuppressive agents, chemotherapy, mechanical life support, and broad-spectrum antibiotics have all contributed to the increasing incidence of *S. maltophilia* infection [2,7].

S. maltophilia is now classified as a opportunistic pathogen, a category shared by methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. [6]. *S. maltophilia* is inherently resistant to many antibiotics, such as β -lactams and aminoglycosides, limiting the treatment options available. Trimethoprim-sulfamethoxazole has been regarded as an agent of choice in patients with pending antimicrobial susceptibility results [2], but this appears to be changing.

We reviewed the clinical and laboratory characteristics of patients with *S. maltophilia* bacteremia treated in Mackay Memorial Hospital from March 3, 1999 to May 21, 2003. The clinical features, laboratory results, minimum inhibitory concentrations (MICs), treatment, and outcome of the patients were analyzed.

Patients and Methods

All patients with a positive blood culture for *S. maltophilia* who were admitted to Mackay Memorial Hospital between March 3, 1999 and May 21, 2003 were included in the analysis. Blood culture was performed whenever septicemia was suspected. Blood samples were inoculated into both aerobic and anaerobic

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broth media for processing with the BACTEC 9240 blood culture system (Becton Dickinson Diagnostic Instrument System, Sparks, MD, USA). Antimicrobial susceptibility testing was performed by the disk diffusion method on Mueller-Hinton agar (BBL microbiology System, Cockeysville, MD, USA) as recommended by the National Committee for Clinical Laboratory Standards (NCCLS) [8]. The MIC was determined by the agar dilution method according to the NCCLS guidelines in the 22 isolates available [9]. Overnight cultures of the isolates in tryptic soy broth were diluted with sterile normal saline to a 0.5 McFarland standard and then spotted by using a multipoint inoculator on Mueller-Hinton agar containing serial 2-fold dilutions of antimicrobial agents. Visible growth was determined after incubation at 35°C for 18 to 20 hours.

Case definition

The case definition of *S. maltophilia* bacteremia was any patient aged ≥ 18 years in whom ≥ 1 blood culture yielded *S. maltophilia* in the 4-year period from March 1999 to May 2003 and the presence of at least 2 of the following: abnormal temperature ($\geq 38^\circ\text{C}$ or $< 35.5^\circ\text{C}$); abnormal white blood cell (WBC) count ($\geq 10,000$ cells/ mm^3 or ≤ 4000 cells/ mm^3 or the presence of $\geq 10\%$ immature bands); respiratory rate $> 20/\text{min}$ or tachycardia (heart rate $> 100/\text{min}$). *S. maltophilia* bacteremia was defined as the isolation of the organism in 1 or more blood cultures by the clinical microbiology laboratory. Patients were classified as having stayed in the intensive care unit (ICU) if they were in the ICU when blood cultures were drawn and had a cumulative length of ICU stay of > 1 week. Recent surgery was defined as surgery prior to septicemia during the hospitalization in which the bacteremia occurred. Neutropenia was defined as a WBC count ≤ 1000 cells/ mm^3 or an absolute neutrophil count ≤ 500 cells/ mm^3 . Community-acquired bacteremia was defined as infection within 3 days of hospitalization or prior to admission.

Clinical parameters

Data collected from medical records included age, gender, underlying diseases or conditions, the presence of a central venous catheter, recent surgical or other invasive procedures, whether the bacteremia was monomicrobial or polymicrobial, ICU stay, empiric antibiotic therapy, and outcome. A bacteremic episode was defined as the isolation of 1 or more organisms from the same patient in 1 or more positive blood

cultures. Positive blood culture was defined by the presence of septicemia with concurrent fever and leukocytosis. The presence of contaminants in the blood cultures was defined based on a positive culture result without concurrent evidence of infection. These cases were excluded from the analysis. Empiric antibiotic therapy was defined as that given after blood cultures were drawn in the presence of fever. Appropriate antibiotic therapy was defined as 1 or more agents active against *S. maltophilia*, given an adequate dose, using an appropriate route of administration and duration of treatment. Death was considered related to bacteremia if the patient died within 14 days after positive culture results became available.

Statistical analysis

Comparisons of the groups were made using 2-tailed Fisher's exact test. A *p* value of < 0.05 was considered statistically significant in the univariate analysis.

Results

During the study period, a total of 50 *S. maltophilia* bacteremia episodes were identified in 48 patients. Among these 50 patients, 30 (60%) were men and 20 (40%) were women. The age of patients ranged from 28 to 94 (median, 66) years, with 71% (34/48) younger than 70 years. On average, a positive blood culture was obtained 36 days (range, 2-194 days) after admission. Of the 50 episodes, 42 (84%) were monomicrobial and 8 (16%) were polymicrobial. The accompanying microorganisms in the polymicrobial cases were mostly Gram-negative rods such as *Acinetobacter* spp. ($n = 3$), *Enterobacter aerogenes* ($n = 2$), and *Escherichia coli* ($n = 2$), or *Candida albicans* ($n = 1$).

Forty six (92%) of the 50 episodes were classified as nosocomial infections and the remaining 4 (8%) as community acquired. Two episodes of community-acquired *S. maltophilia* infection occurred in elderly patients (72 and 77 years, respectively) with underlying lymphoma who had frequently visited hospitals for chemotherapy. One of these patients was uremic and had received regular hemodialysis. The other patient had undergone operation for hydrocephalus 2 months before symptom onset.

Most patients (30/50) had central lines, were receiving mechanical ventilation (20/50), had had previous antibiotics treatment (50/50), and had underlying diseases (47/50) [Table 1]. Thirty one patients died during hospitalization, resulting in a case-fatality

Table 1. Risk factors for mortality in *S. maltophilia* bacteremia

Factor	No. of episodes	Fatality (%)	<i>p</i>
Gender			NS
Male	30	19 (63)	
Female	20	12 (60)	
Age			NS
<70 years	34	19 (56)	
>70 years	16	12 (75)	
Type of bacteremia			NS
Polymicrobial	8	6 (75)	
Monomicrobial	42	25 (59)	
Stay in intensive care unit			0.042
Yes	23	18 (78)	
No	27	13 (48)	
Underlying conditions			
Malignancy	14	10 (71)	NS
Congestive heart failure	3	2 (67)	NS
Diabetes mellitus	6	5 (83)	NS
COPD	6	4 (67)	NS
Central venous catheter	30	24 (80)	0.003
Recent surgery	8	6 (75)	NS
Uremia	8	7 (88)	0.134
Mechanical ventilator	20	17 (85)	0.008
Neutropenia	7	5 (71)	NS
Previous antibiotics			
Carbapenems	13	8 (61)	NS
Third-generation cephalosporins	10	6 (60)	NS
Aminoglycosides	13	9 (69)	NS
Quinolones	4	3 (75)	NS

Abbreviations: COPD = chronic obstructive pulmonary disease; NS = not significant

rate of 62%. Slightly over half of the deaths (18/31) were directly attributable to *S. maltophilia*, with the rest caused by underlying conditions. Factors significantly associated with mortality included a stay in the ICU, central venous catheter, and mechanical ventilation (Table 1). Seven of 8 patients with uremia died, although this factor did not have a significant relationship with mortality ($p=0.134$). While various antibiotics were used for initial empiric therapy, there was no difference in mortality among the specific agents used. Eight patients had had recent surgery, which was not a risk factor for mortality. Neutropenia or chemotherapy was also not significantly correlated with mortality. The in vitro antimicrobial susceptibility of blood isolates of *S. maltophilia* by disk diffusion method is listed in Table 2. Most isolates were susceptible to trimethoprim-sulfamethoxazole, levofloxacin, and ticarcillin-clavulanate but resistant to aminoglycosides, piperacillin-tazobactam, ciprofloxacin, lomefloxacin, and chloramphenicol. Empirical antibiotic therapy

Table 2. In vitro susceptibilities of *S. maltophilia* by disk diffusion

Antimicrobial agent	No. of susceptible isolates n = 50 (%)
Gentamicin	5 (10)
Netilmicin	6 (12)
Amikacin	6 (12)
Tobramycin	6 (12)
Piperacillin-tazobactam	9 (18)
Ciprofloxacin	18 (36)
Lomefloxacin	20 (40)
Chloramphenicol	21 (42)
Ceftazidime	22 (44)
Trimethoprim-sulfamethoxazole	30 (60)
Levofloxacin	13 (65) ^a
Ticarcillin-clavulanate	36 (72)

^a Levofloxacin was tested in 20 isolates.

was inappropriate in all cases after fever developed in patients with sepsis. Aminoglycosides were given in most cases, and in 28 of the 50 episodes, carbapenems, third- or fourth-generation cephalosporins or quinolones (with the exception of levofloxacin) was given. Amoxicillin-clavulanate was given in 4 episodes and the others were treated with second-generation cephalosporins.

Of the 22 isolates of *S. maltophilia* available for determination of MIC, 12 (55%) were susceptible to levofloxacin (MIC ≤ 2) and 14 (64%) to ticarcillin-clavulanate (Table 3). Almost all isolates were resistant to piperacillin-tazobactam, cefepime and ciprofloxacin. Only 1 isolate was susceptible to ceftazidime. Although ceftazidime plus sulbactam and cefepime plus sulbactam showed some synergism in 32% and 50% of the isolates, respectively, these combinations maintained MICs in the sensitive range (sensitive [S] ≤ 8 ; intermediate [I] = 16; resistant [R] ≥ 32 $\mu\text{g}/\text{mL}$) [Table 3]. Unexpectedly, the MICs for trimethoprim-sulfamethoxazole were all found to indicate resistance (>64 $\mu\text{g}/\text{mL}$). There was a significant discrepancy in the results of susceptibility testing obtained by the disk diffusion method and the MICs for ceftazidime, ciprofloxacin, and piperacillin-tazobactam, but not those for ticarcillin-clavulanate and levofloxacin.

Discussion

Few antibiotics are active against *S. maltophilia*. This is particularly worrisome because it is becoming an increasingly important pathogen. In our series, there was a crude mortality rate of 62% for *S. maltophilia* bacteremia. This is high among reported mortality rates,

Table 3. Minimum inhibitory concentrations in 22 isolates of *S. maltophilia*

Isolates no.	CAZ	CAZ + SUB	FEP	FEP + SUB	CIP	TIM	LVX	TZP	MIN	SXT	ATM	AN	GAT
1	>128 R	>128	128 R	64	4 R	128 R	1 S	>128 R	0.5 S	>64 R	>128 R	>128 R	4 I
2	>128 R	>128	>128 R	128	8 R	>128 R	2 S	>128 R	0.5 S	>64 R	>128 R	>128 R	4 I
3	>128 R	>128	>128 R	128	16 R	128 R	4 I	>128 R	1 S	>64 R	>128 R	>128 R	4 I
4	>128 R	64	64 R	32	16 R	16 S	4 I	128 R	1 S	>64 R	>128 R	>128 R	8 R
5	>128 R	>128	128 R	128	16 R	128 R	8 R	>128 R	4 S	>64 R	>128 R	>128 R	8 R
5	128 R	>128	128 R	64	128 R	>128 R	64 R	>128 R	32 R	>64 R	>128 R	>128 R	>128 R
7	>128 R	>128	>128 R	128	16 R	128 R	4 I	>128 R	4 S	>64 R	>128 R	>128 R	>128 R
8	128 R	64	128 R	64	8 R	32 S	2 S	>128 R	2 S	>64 R	>128 R	>128 R	4 I
9	128 R	128	32 R	32	8 R	64 S	2 S	>128 R	0.5 S	>64 R	>128 R	>128 R	2 S
10 (1)	32 R	64	128 R	64	8 R	32 S	2 S	>128 R	0.5 S	>64 R	>128 R	>128 R	2 S
10 (2)	32 R	64	64 R	32	4 R	32 S	2 S	>128 R	0.5 S	>64 R	>128 R	>128 R	2 S
11	>128 R	>128	128 R	128	4 R	>128 R	2 S	>128 R	8 I	>64 R	>128 R	>128 R	2 S
12	16 I	16	64 R	64	8 R	32 S	2 S	>128 R	1 S	>64 R	>128 R	>128 R	4 I
13	32 R	16	64 R	32	8 R	16 S	2 S	>128 R	1 S	>64 R	>128 R	>128 R	8 R
14	32 R	16	64 R	128	16 R	16 S	8 R	>128 R	4 S	>64 R	>128 R	>128 R	16 R
15 (1)	16 I	16	128 R	64	16 R	32 S	16 R	>128 R	1 S	>64 R	>128 R	>128 R	16 R
15 (2)	32 R	16	64 R	128	16 R	32 S	8 R	>128 R	1 S	>64 R	>128 R	>128 R	16 R
16	32 R	16	64 R	32	16 R	64 S	4 I	>128 R	1 S	>64 R	>128 R	>128 R	4 I
17	128 R	>128	64 R	64	16 R	64 S	4 I	>128 R	2 S	>64 R	>128 R	>128 R	16 R
18	32 R	16	64 R	64	4 R	16 S	2 S	>128 R	1 S	>64 R	>128 R	>128 R	4 I
19	>128 R	>128	64 R	32	2 I	128 R	1 S	>128 R	0.25 S	>64 R	>128 R	>128 R	8 R
20	8 S	8	32 R	16	16 R	8 S	2 S	64 I	0.5 S	>64 R	>128 R	>128 R	1 S

Abbreviations: CAZ = ceftazidime; SUB = sulbactam; FEP = cefepime; CIP = ciprofloxacin; TIM = ticarcillin-clavulanate; LVX = levofloxacin; TZP = piperacillin-tazobactam; MIN = minocycline; SXT = trimethoprim-sulfamethoxazole; ATM = aztreonam; AN = amikacin; GAT = gatifloxacin; R = resistant; I = intermediate; S = susceptible

which ranged from 22 to 69% [2,4,9-11]. Accurately determining the cause of death in patients with *S. maltophilia*, however, is difficult, since most patients also have serious underlying diseases. Muder et al reported a crude mortality of 38%, with 25% of patients dying within 14 days of the onset of bacteremia [2]. Underlying diseases most closely associated with acute mortality were hematological malignancy, transplantation, neutropenia, and immunosuppressive therapy [2]. Other series have found a close association between neutropenia and mortality [2,9,12]. This association was not significant in our series, but that may have been because we only had 7 neutropenic patients, of whom 5 died.

Some studies have suggested an association between inappropriate antibacterial treatment and mortality [2,9]. In our series, empiric therapy was given when fever and sepsis developed. The sensitivity results were usually not available until 3 days after the cultures were done, at which point the antibiotics were changed to agents active against *S. maltophilia*. Of the isolates in our series, 60% were susceptible to trimethoprim-sulfamethoxazole and 72% to ticarcillin-clavulanate,

but neither of these agents was used for initial empiric therapy. This may explain the relatively high crude mortality rate (62%). Univariate analysis revealed that ICU stay, central venous catheter, and mechanical ventilation were all significantly associated with mortality. As 60% of bacteremic episodes occurred in patients with a central line, the assumption that the catheter was the source of infection in these patients may be reasonable, but the actual portal of entry of *S. maltophilia* remains to be established.

Most of the risk factors we identified are similar to those identified in previous studies [2,5]. Antimicrobial therapy for *S. maltophilia* is problematic since most of the isolates are resistant to multiple agents used to treat common Gram-negative nosocomial infections. Most *S. maltophilia* strains are resistant to aminoglycosides, extended-spectrum penicillins, and third-generation cephalosporins. Krcmery et al reported 31 episodes of bacteremia and found that 80.6% of the 31 bloodstream isolates were susceptible to amikacin [12]. Tripodi et al reported that aminoglycosides were active against 42% to 50% of isolates [13]. In contrast, this study and others have shown high resistance of *S. maltophilia*

to aminoglycosides [9,14]. In a case-control study of *S. maltophilia* bacteremia, Senol et al found higher mortality among patients with a central line who had previously received aminoglycosides [4]. The intrinsic resistance to β -lactams is apparently due to 2 enzymes, L1 and L2, and an efflux system [15,16].

Many of the isolates in this study were susceptible in vitro to the combination of ticarcillin and clavulanic acid (72%) but not to piperacillin plus tazobactam, with no strains tested showing sensitivity to the latter combination. Betriu et al found that ceftazidime was the most active of the cephalosporins, with 50% of the strains susceptible [17]. However, although we found slightly improved susceptibility to β -lactams by adding a β -lactamase inhibitor, the MICs of cephalosporins in this study were still not in a clinically useful range. Levofloxacin was reasonably active, with 12 of 22 strains sensitive on agar dilution testing and 13 of 20 by disk diffusion. Results of agar dilution test suggested that levofloxacin is superior to gatifloxacin (susceptible in 12/22 and 5/22, respectively). We also found that although 20 of 22 strains were sensitive to minocycline, none of our patients received minocycline as an empirical therapeutic agent.

The interpretation of antimicrobial sensitivity testing results for *S. maltophilia* remains somewhat problematic. In vitro determination of susceptibility is not well standardized, and there is poor correlation between disk diffusion and agar dilution results for some agents. Trimethoprim-sulfamethoxazole is still a reasonable choice if the isolates are susceptible to this combination [18,19] even if the MICs are in the resistant range, as was unexpectedly found in our study (R >64 μ g/mL). Use of ticarcillin-clavulanate alone or combination therapy with aminoglycosides for *S. maltophilia* bacteremia after susceptibility results became available was common in this series (80%). Krueger et al reported that the addition of aztreonam to ticarcillin-clavulanate increases activity against *S. maltophilia* [20]. Combination therapy with trimethoprim-sulfamethoxazole, minocycline, and ticarcillin-clavulanate at or close to the maximum dose has been suggested for severe cases [21]. Muder et al reported that adding either ticarcillin-clavulanate or a third-generation cephalosporin to trimethoprim-sulfamethoxazole may be more effective than monotherapy when patients are neutropenic or seriously ill [2]. Lemmen et al reported improved bactericidal activity with high-dose ceftazidime and ciprofloxacin [22].

In this series, empirical therapy for *S. maltophilia* bacteremia in ICU patients with multiple underlying diseases rarely included any agent that was active against this pathogen. Aminoglycosides were often administered concurrently with β -lactams in critically ill patients, but the former are inactive against *S. maltophilia*. This combination did not result in clinical improvement in this series. Some authors have recommended trimethoprim-sulfamethoxazole as the initial treatment of choice for *S. maltophilia* bacteremia pending susceptibility testing [2]. Resistance of *S. maltophilia* to trimethoprim-sulfamethoxazole in our hospital (40%) was higher than in previous studies [22]. Based on susceptibility testing, most of our patients received ticarcillin-clavulanate (80%), but the mortality rate was still high (62%). The high rate of treatment failure may have been due to the lack of coverage of *S. maltophilia* in our initial empirical therapy. By the time the sensitivity results became available and treatment was switched to a better antibiotic, it was probably already too late for many of our patients, especially those with comorbidities.

The question of whether combined treatment rather than monotherapy should be used remains controversial. The combination of trimethoprim-sulfamethoxazole and ticarcillin-clavulanate was not administered in our series. Ceftazidime plus sulbactam had a synergistic effect on the MIC but not to a clinically significant extent. The addition of clavulanate to imipenem and to aztreonam also failed to improve the activity against *S. maltophilia* [10]. Tripodi et al found the combination of ciprofloxacin with either β -lactams or trimethoprim-sulfamethoxazole was ineffective [13]. Based on our sensitivity results, however, the combination of levofloxacin with trimethoprim-sulfamethoxazole or ticarcillin-clavulanate appears to show promise and deserves further study. Weiss et al suggested that the problem of emerging resistance could be potentially avoided by using combination therapy [23]. In this study, 5 patients had multi-resistant *S. maltophilia*, of whom 2 died. Tsiodras et al reported that trimethoprim/sulfamethoxazole resistance or even panresistance had minimal effect on mortality from a variety of *S. maltophilia* infections [24]. Bonfiglio et al showed that levofloxacin exhibited good in vitro activity against a large inoculum and against ciprofloxacin-resistant strains [14]. Valdezate et al also concluded that new fluoroquinolones have a potential role in the treatment of *S. maltophilia* infection [25]. However, the ideal antibiotic treatment of central line infections caused

by *S. maltophilia* remains unknown [26]. We found that the in vitro susceptibility of *S. maltophilia* to levofloxacin was similar to that of trimethoprim-sulfamethoxazole and ticarcillin-clavulanate by the disk diffusion or agar dilution method. Empiric therapy for patients at risk of *S. maltophilia* bacteremia should include antimicrobial agents active against this organism. Levofloxacin may be a potentially useful alternative compared with gatifloxacin, and further clinical trials of this agent are warranted.

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