J Microbiol Immunol Infect
2006;39:144-149

Original Article

Stenotrophomonas maltophilia bacteremia in pediatric patients — a 10-year analysis

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Received: March 1, 2005 Revised: June 1, 2005 Accepted: June 15, 2005

Background and Purpose: *Stenotrophomonas maltophilia* bacteremia is an important cause of mortality among immunocompromised children. However, there has been little information concerning *S. maltophilia* bacteremia in the pediatric population.

Methods: We reviewed the drug susceptibility of bloodstream isolates of *S. maltophilia* and medical charts of *S. maltophilia* bacteremia patients less than 18 years old at the Department of Pediatrics, National Taiwan University Hospital from January 1993 to June 2003. The risk factors associated with mortality of the patients with *S. maltophilia* bacteremia were analyzed.

Results: In total, 32 episodes (31 patients) of *S. maltophilia* bacteremia were reviewed. The average rate of nosocomial bloodstream infection was 8.3 episodes per 100,000 patient-days, and an average of 6.4% of them were caused by *S. maltophilia*. Malignancy was the most common underlying disease (32%). Six episodes of *S. maltophilia* bacteremia had soft tissue involvement, and only 1 of them underwent surgical intervention and survived. These 32 isolates were most susceptible to trimethoprim-sulfamethoxazole (91%), and no obvious increase in multidrug resistance was noted in the previous 10 years. The crude mortality rate was 40.6%. Malignancy, failure to remove central venous catheter, and ineffective antibiotic treatment were significant risk factors for mortality.

Conclusions: Early and effective antimicrobial therapy and removal of central venous catheter as soon as possible are vital for the successful management of *S. maltophilia* bacteremia.

Key words: Bacteremia, drug resistance, immunocompromised host, soft tissue infections, *Stenotrophomonas maltophilia*

Introduction

Stenotrophomonas maltophilia (formerly named *Pseudomonas maltophilia* or *Xanthomonas maltophilia*) is a non-fermentative Gram-negative bacillus, which is isolated from debilitated or immunocompromised patients. Due to highly antibiotic-resistant characteristics and being an important pathogen of nosocomial infection, *S. maltophilia* remains a therapeutic challenge today. Clinical manifestations of *S. maltophilia* infection include bacteremia, pneumonia, urinary tract infection, ocular infection, endocarditis, meningitis, soft tissue, wound infection, etc. [1].

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Although outbreaks of pseudobacteremia have been reported [2], bacteremia still serves as reliable evidence of true infection in susceptible hosts with the presence of compatible clinical pictures. Most articles about *S. maltophilia* infection focus on adult hematological patients [3-7]; however, there has been little information concerning *S. maltophilia* bacteremia in the pediatric population [1,8]. This article reviews *S. maltophilia* bacteremia over a 10-year-period in children. Demographic data, intervention methods and antibiotic treatment courses were analyzed for possible risk factors of mortality in bacteremic children.

Methods

From January 1993 to June 2003, the medical charts of *S. maltophilia* bacteremia patients less than 18 years

old who had been admitted to the Department of Pediatrics, National Taiwan University Hospital were reviewed. In addition, the drug susceptibility of blood isolates of *S. maltophilia* was assayed with the disk diffusion method. The National Committee for Clinical Laboratory Standards (NCCLS) criteria recommended for *Pseudomonas aeruginosa* was employed to interpret susceptibility [9].

The definitions of terms listed below follow those in published articles regarding *S. maltophilia* bacteremia [1,10]. An episode of bacteremia was defined as 1 or more positive blood isolations of *S. maltophilia* occurring within a 7-day period. Nosocomial bacteremia was defined as episodes that developed more than 72 h after admission. Nosocomial outbreak was defined as isolates with similar antibiograms found in the same ward during the admission course. Prior antibiotic therapy was defined as administration of antibiotics (including oral, intramuscular or intravenous route) within 2 weeks of positive blood cultures. Central catheter indwelling was defined as the presence of a central venous catheter, Port A catheter, Hickmann catheter or peripheral central venous catheter as the bacteremia developed. Effective antibiotic therapy was defined as usage of intravenous antibiotics to which the organism was either susceptible or intermediately susceptible within 48 h of the blood culture being collected. Outcome was recorded as either death within 7 days of the bacteremic episode or survival beyond 7 days. We estimated the crude mortality rate of *S. maltophilia* bacteremia, which was defined as death occurring within 7 days of blood isolation of *S. maltophilia*, regardless of the presence of comorbid conditions that could potentially account for death [4].

Categorical variables were analyzed by a chi-squared test with Yate's correction or a two-tailed Fisher's exact test. The numerical variables were analyzed by a Mann-Whitney *U* test. A p value <0.05 was considered statistically significant.

Results

From January 1993 to June 2003, there were 32 episodes (55 positive blood culture reports) of *S. maltophilia* bacteremia in 31 patients (12 males and 19 females) in our pediatric department (Fig. 1). One patient had 2 episodes of bacteremia separated by 7 days, while all the others had 1 episode. Eleven patients had 2 or more positive blood isolates, and the others had 1 for each episode. One to 7 episodes of *S. maltophilia* bacteremia occurred in pediatric wards per year, and the incidence of *S. maltophilia* bacteremia among the hospitalized children was 8.3 episodes per 10^5 patient-days on average (range, 2.0 to 14.0 episodes/per 10^5 patient-days), comprised of 6.4% (range, 1.7% to 11.1%) of all pediatric nosocomial bloodstream infections. During the period of study, there was no increase of *S. maltophilia* bacteremia.

All episodes involved nosocomial infection in origin; nevertheless, no nosocomial outbreak of *S. maltophilia* bacteremia was noted in our pediatric wards. The median age of our patients was 50 months old (range, 1 month to 16 years 8 months). Twenty three patients received intensive care for a median duration

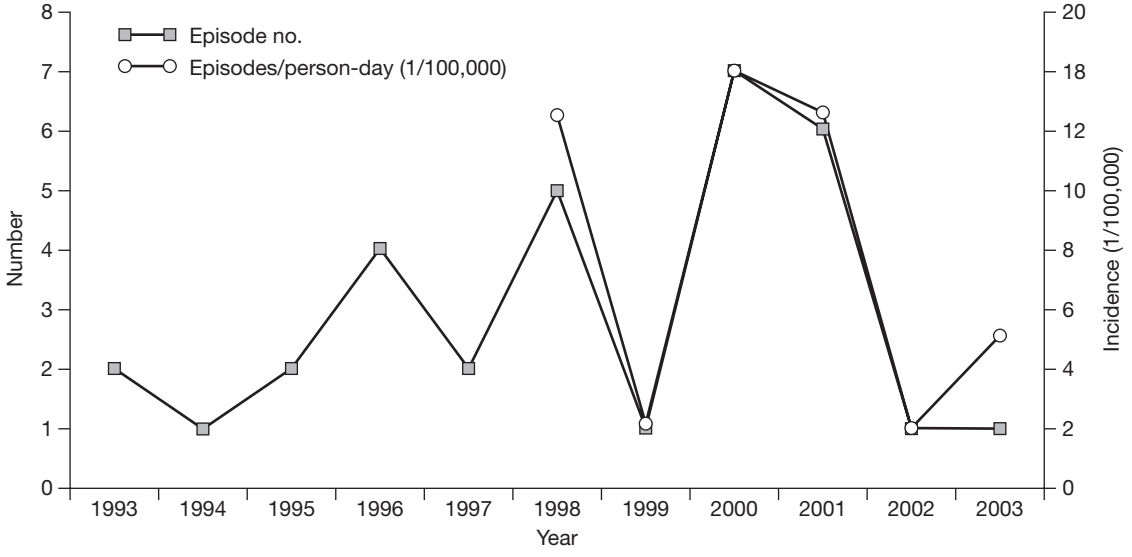

Fig. 1. Annual incidence of *Stenotrophomonas maltophilia* bacteremia at pediatric wards during the previous 10 years.

Table 1. Demographic and clinical data of patients with *Stenotrophomonas maltophilia* bacteremia and soft tissue involvement

Age	Gender	Underlying disease	Hospital days at the onset (days)	Duration of neutropenia before onset (days)	Clinical diagnosis	Tissue culture	Effective antibiotics prescription	Surgery	Outcome
5 years 10 months	Female	SAA	94	94	Necrotizing fasciitis, upper gingiva	Yes	TMP-SMX, ticarcillin-clavulanic acid	Fasciotomy	Survival
8 years 8 months	Female	ALL s/p BMT, GVHD	38	35	Necrotizing fasciitis, left thigh	Yes	No	No	Mortality
2 years 2 months	Female	SAA	129	129	Bullous fulminans, left leg	Yes	Ceftazidime, ciprofloxacin	No	Mortality
9 years 6 months	Female	ALL	31	19	Bullous gangrenosa, extremitis	No	TMP-SMX, ciprofloxacin	No	Mortality
9 years 5 months	Male	ALL	40	26	Necrotizing fasciitis, right thigh	No	No	No	Mortality
8 years 9 months	Female	AML	78	68	Myositis, left shoulder	Yes	TMP-SMX, ciprofloxacin	No	Mortality

Abbreviations: SAA = severe aplastic anemia; ALL = acute lymphoblastic leukemia; BMT = bone marrow transplantation; GVHD = graft-versus-host disease; AML = acute myelocytic leukemia; TMP-SMX = trimethoprim-sulfamethoxazole

of 22 days (range, 1 to 285 days). In 5 episodes, other bacterial pathogens were recovered concurrently (*Staphylococcus aureus*, *Enterobacter cloacae*, *Acinetobacter lwoffi*, *Staphylococcus epidermidis*, *Escherichia coli* 1 episode each).

Among the patients with *S. maltophilia* bacteremia, 30 patients had underlying diseases, including malignant (10), hematological (6), gastrointestinal (4), cardiovascular (3), prematurity (2), pulmonary (2), genetic (1, trisomy 18), neurological (1, type II spinomuscular atrophy) and renal (1, nephrotic syndrome) diseases. Fifteen episodes of bacteremia developed under severe neutropenic status, and 15 episodes developed with immunosuppressive agents prescribed in proximity. Central indwelling catheter was noted in 25 episodes (80.6%) of bacteremia; the central venous catheter was removed or replaced for sepsis control in 11 episodes. In addition, 14 episodes of bacteremia developed when patients had respiratory failure with mechanical ventilator support.

Soft tissue involvement was noted in 6 episodes of *S. maltophilia* bacteremia, manifesting as septic emboli, bullous gangrenosa, myositis or necrotizing fasciitis (Table 1). *S. maltophilia* was grown from necrotic tissue in 4 episodes. All six patients had malignancy or hematological underlying diseases, and they had been in neutropenic status from 19 to 129 days. Four cases responded to 2 kinds of effective antibiotics; however, the other 2 cases progressed so rapidly that they did not respond to any effective antibiotic treatment. The only survivor underwent fasciotomy in addition to effective antibiotic treatment.

The antibiotic susceptibility of these 32 blood isolates of *S. maltophilia* was also analyzed (Table 2). The most effective antibiotics for *S. maltophilia* in vitro were trimethoprim-sulfamethoxazole (TMP-SMX; 91%), followed by ticarcillin-clavulanic acid (76%), ofloxacin (75%), ciprofloxacin (63%) and ceftazidime (44%). Two blood isolates of *S. maltophilia* were resistant to TMP-SMX, and one of them revealed pan-antimicrobial resistance, which resulted in treatment failure and mortality in the patient. The drug susceptibility to newer fluoroquinolones was not tested in this study.

The average number of antibiotics prescribed in the preceding 2 weeks of *S. maltophilia* bacteremia was 3.2 in our patients. Carbapenem (including imipenem and meropenem) had been prescribed in 16 episodes (50%) before bacteremia; this treatment was used for broad-spectrum coverage of microorganisms in critically ill patients but is inherently ineffective for *S. maltophilia* infection. Thirteen of 32 episodes were fatal within

Table 2. Antibiotic susceptibility of 32 *Stenotrophomonas maltophilia* blood isolates from 31 children

Antibiotic	Susceptible	Intermediate susceptible	Resistant	Susceptibility rate[a] (%)
Trimethoprim-sulfamethoxazole	21	0	2[b]	91
Ticarcillin-clavulanate	16	3	6	76
Ofloxacin	11	1	4	75
Ciprofloxacin	16	4	12	63
Ceftazidime	12	2	18	44
Piperacillin-tazobactam	2	1	12	20
Meropenem-imipenem	0	0	32	0

[a]Susceptibility rate was the percentage of susceptible and intermediately susceptible strains.

[b]One blood isolation was pan-drug resistant *S. maltophilia.*

7 days of bacteremia, and the crude mortality rate was 40.6%. Effective antibiotics were given in 6 of 32 episodes (18.8%) before the blood culture results were known. Seven episodes deteriorated so rapidly that no effective antibiotics could be used during the course. One episode of *S. maltophilia* bacteremia was treated successfully with only removal of the central catheter.

A number of factors were analyzed in order to detect risk factors associated with mortality of *S. maltophilia* bacteremia (Table 3). Underlying malignancy was a significant variable contributing to mortality. Removal of the central venous catheter and effective antibiotic prescription during the course were also variables that were significantly associated with better outcomes. However, other variables, including endotracheal intubation, the prescription of carbapenem or other broad-spectrum antibiotics within the preceding 2 weeks and the neutropenic duration were not associated with a statistically significant difference in our study.

Discussion

Although uncommon, *S. maltophilia* bacteremia leads to a high mortality and treatment failure rate, especially in debilitated children. The 32 episodes in the 10-year period represents true infection rather than "pseudosepticemia" because they met the clinical criteria of infection that was defined by the Centers for Disease Control and Prevention guidelines. All cases developed bacteremia 72 h or later after admission to the general pediatric or intensive care ward, which was similar to the nosocomial acquisition rate reported previously (68-98%) [8]. However, polymicrobial isolation from blood culture was less common in this study (16%) than had been reported in previous studies (24-72%) [11].

Malignancies remained the major underlying condition in the patients with *S. maltophilia* bacteremia, which was compatible with conclusions in other

Table 3. Risk factors associated with mortality of patients with *Stenotrophomonas maltophilia* bacteremia

Risk factor	Mortality (n = 13) No. (%)	Survival (n = 19) No. (%)	*p*
Demographic data			
Age (months) [median (range)]	97 (1-200)	26 (1-260)	0.057
Male gender	5 (38)	8 (42)	0.87
Host factors			
Malignancy disease	7 (54)	3 (16)	0.049
Neutropenic status	9 (69)	6 (32)	0.083
Neutropenic days [median (range)]	41 (19-158)	81 (2-162)	0.637
Endotracheal intubation	6 (46)	8 (42)	0.892
Soft tissue involvement	4 (31)	3 (16)	0.586
Carbapenem exposure[a]	9 (69)	7 (37)	0.15
Clinical management			
Failure to remove central venous catheter	10 (83)	5 (36)	0.021
No effective antibiotic treatment during the course	11 (85)	15 (79)	0.05
No effective antibiotic treatment before blood culture result	7 (54)	1 (5)	0.954

[a]Carbapenem (including imipenem and meropenem) prescription in the previous 2 weeks before bloodstream infection.

published articles [12,13]. This host factor also contributed significantly to mortality ($p<0.05$), despite usage of effective antibiotics. In other case-control studies, risk factors for *S. maltophilia* bacteremia in oncology patients included severe mucositis, diarrhea, the number of antibiotics used, and length of hospital stay [5,14]. Other underlying illnesses such as prematurity, malnutrition, congenital heart disease and chronic lung disease unique to the pediatric population were also shown in our investigation.

Our study showed that 80.6% of bloodstream infection occurred in the presence of central catheter indwelling. This might be the most important portal of entry for *S. maltophilia* causing bacteremia. There were 17 episodes with positive sputum or endotracheal tube tip culture concurrently; however, colonization rather than true infection was involved.

Soft tissue involvement was a serious problem among the patients with *S. maltophilia* bacteremia, and the mortality rate of these patients was even higher (83.3%) than that of patients with other causes of bacteremia in our study. Several reports showed that *S. maltophilia* had a predisposition to soft tissue infection [7,15-17], which was a unique characteristic compared with the *Pseudomonas aeruginosa* bacteremia control group [6]. Some authors have suggested that *S. maltophilia* infection should be added to the differential diagnosis of mucocutaneous or soft tissue infection in patients with cancer (especially those presenting with metastatic nodular skin lesions), although the mechanism of soft tissue invasion of this microorganism is still unclear [18]. So far, almost all the reported victims in the literature have been neutropenic. Nevertheless, most of them responded to effective antibiotics, such as TMP-SMX with or without ticarcillin-clavulanic acid [18]. The outcome using antibiotics in this study was not favorable. A possible explanation is that we had more cases of more severe soft tissue involvement such as necrotizing fasciitis.

There was no specific reference for antibiotic susceptibility testing with *S. maltophilia*. NCCLS recommended testing for minimal inhibitory concentrations by use of the agar or broth microdilution methods, although the reliability is still questioned. In fact, agreement between these 2 results was poor for some antibiotics, such as ciprofloxacin and TMP-SMX [19]. Overall, the rates of resistance to TMP-SMX and ticarcillin-clavulanic acid were 3-19% and 10-29%, respectively, which were similar to our results [20]. TMP-SMX, ticarcillin-clavulanic acid, gatifloxacin and trovafloxacin were the agents with consistent therapeutic activity against *S. maltophilia* isolates in clinical practice. Unfortunately, multidrug resistant strains, which involve the multidrug efflux system, have been identified [21].

We did not witness an increasing prevalence of multidrug resistant *S. maltophilia* in recent years in our hospital; however, the crude mortality rate of patients with *S. maltophilia* bacteremia during the 10 years of this study in our hospital (40.6%) was still higher than that reported before (30%) [22]. Failure to prescribe effective empirical antibiotics before the culture report (18.8%) may in part explain why the mortality attributable to *S. maltophilia* was higher in our study. Combination therapy strategies including ticarcillin-clavulanic acid plus aztreonam for treatment of infection caused by *S. maltophilia* might be another option in improving the clinical outcome in the pediatric population, especially for treatment of those who fail TMP-SMX treatment [15,19].

Pre-existing oncology illness, failure of removal of the central venous catheter and ineffective antibiotic treatment are associated with poor outcome, which achieved statistical significance in our analysis for the risk factors of mortality of *S. maltophilia* bloodstream infection. Consistent with other reports, carbapenem exposure in the previous 2 weeks was not a significant risk factor for mortality in our study, although it was believed that broad-spectrum antibiotic exposure per se (including third-generation cephalosporins and carbapenem) appeared to be the critical factor predisposing to colonization or superinfection by *S. maltophilia* [1,23]. Because of concern about mutidrug-resistant pathogens such as *Acinetobacter baumanii* in Taiwan, the use of carbapenem was common (50%) in this series compared to previous studies (25-43%).

In conclusion, *S. maltophilia i*s an emerging nosocomial pathogen with a high rate of antibiotic resistance. In critically ill pediatric children with *S. maltophilia* bloodstream infection, especially those with immunosuppression or prolonged neutropenia, administration of effective antibiotic treatment and removal of the central venous catheter should be performed as soon as possible. The most effective antibiotics for treatment of *S. maltophilia* bacteremia in children were TMP-SMX, ticarcillin-clavulanic acid or ofloxacin. Further investigations are needed for more reliable and standardized antibiotic susceptibility testing and combination therapy strategies for selected patients.

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