Original Article

Clinical characteristics and risk factors of infections caused by *Stenotrophomonas maltophilia* in a hospital in northwest China

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Abstract

Introduction: *Stenotrophomonas maltophilia* infections have recently increased in importance in China, particularly in intensive care units (ICUs). The aim of this study was to investigate the clinical characteristics and risk factors of *S. maltophilia* infection in ICU of a hospital in northwest China.

Methodology: The characteristics and outcomes of patients with any type of *S. maltophilia* infection at Shaanxi Provincial People's Hospital, Shaanxi, China, over a two-year period (from July 2011 to June 2013) were studied. *S. maltophilia* antimicrobial susceptibility was tested with the agar dilution method. The risk factors for all-cause in-hospital mortality were assessed with multivariate logistic regression.

Results: Forty patients (median age, 72 years; 77.5% males) with *S. maltophilia* infection were identified. The main type of infection was lower respiratory tract infection (97.5%); one patient had a bloodstream infection. A total of 97.5% patients were infected with two or more organisms at the same time. The main characteristics of the patients were prolonged use of mechanical ventilation, urethral catheter, and central venous catheter before the infections occurred. The case number of infection was not different in the four seasons. High *in vitro* sensitivity was observed to minocycline (91.2%), levofloxacin (85.3%), and trimethoprim-sulfamethoxazole (79.4%). Most patients received therapy with a combination of agents. The crude mortality was 50%. By multivariate analysis, low albumin content and hypotension were the independent prognostic factors for mortality.

Conclusions: Appropriate antimicrobial treatment had no positive impact on mortality. The impacts of albumin supplements and increasing blood pressure on mortality require further clinical studies.

Key words: *Stenotrophomonas maltophilia*; intensive care unit; clinical characteristics; risk factors.

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Introduction

Stenotrophomonas maltophilia (previously classified as *Pseudomonas* or *Xanthomonas maltophilia*) is an aerobic, glucose non-fermentative, Gram-negative bacillus that is widely distributed in various environments and hospital equipment [1]. This bacterium is increasingly recognized as an emerging global opportunistic pathogen of infections, causing severe infections in hospitalized patients, including bacteremia [2], biliary [3] and urinary tract infections [4], respiratory tract infections [5], skin and soft tissue infections [6], bone and joint infections [7], endocarditis [8], meningitis [9], and ocular infections [10].

These infections are particularly common in high-risk populations who are immunocompromised due to underlying illness, such as patients with cancer, chronic respiratory disease, and AIDS, and those subjected to mechanical ventilation and broad spectrum antibiotic therapy, or those requiring intensive care [11].

It is very difficult to control *S. maltophilia* infection, because this pathogen is usually resistant to multiple antimicrobials, including β-lactams, carbapenems, aminoglycosides, and quinolones. Inducible beta-lactamase activity (including L1 metallo-β-lactamase and L2 serine-β-lactamase), efflux mechanism, aminoglycoside modifying enzyme activity, biofilm formation, and production of extracellular slime or glycocalyx are responsible for its resistance [12].

S. maltophilia infection in northwest China has rarely been described. In this retrospective study, we sought to study the clinical characteristics of patients with *S. maltophilia* infection in the intensive care unit of a large tertiary care hospital located in Xi'an,

Shaanxi province, China, and to identify risk factors associated with mortality. Antibiotic susceptibilities of the isolates and antibiotic treatment and outcomes of the patients were also investigated.

Methodology

Study population

During a two-year period (From 1 July 2011 to 30 June 2013), patients who provided at least one positive culture sample for *S. maltophilia*, associated with clinical signs or symptoms of infection, in intensive care unit of Shaanxi Provincial People's Hospital, Shaanxi, China were identified retrospectively and included in this study. Shaanxi Provincial People's Hospital is a general, tertiary care center, with a 2000-bed capacity (including a 30-bed ICU) in northwest China, and is also the third affiliated hospital of the school of medicine at Xi'an Jiaotong University.

Study design

All of the available clinical and microbiological data of the patients were retrieved and reviewed. Information about patients' age, sex, race, underlying diseases, prior history of antimicrobial therapy, chemotherapy or radiation therapy and operation, use of glucocorticoids, presence or absence of a catheter, duration of hospitalization, and in-hospital mortality was recorded. Laboratory data of routine blood tests, hepatic synthetic function tests and renal function tests, and antimicrobial susceptibilities of the bacteria isolates were collected on the day of the first *S. maltophilia*-positive culture. For patients who suffered more than one episodes of *S. maltophilia* infection, only the first episode was analyzed in this study. Clinical characteristics of the patients, antibiotic treatment, and outcomes were also recorded.

Laboratory methods

Clinical *S. maltophilia* were surveyed from sputum, bronchial secretions or bronchoalveolar lavage fluid, blood, urine, and other body sites and fluids. Standard microbiological methods (microscopy, culture characteristics, and oxidase reaction), the API system (bioMérieux, Marcy l'Etoile, France), and the automated Vitek 32 system (bioMérieux Marcy l'Etoile, France) were used to identify bacteria species. Susceptibility testing was performed for the first *S. maltophilia* isolate per patient using the Kirby-Bauer disk diffusion method. The agents tested included levofloxacin, minomycin, and trimethoprim/sulfamethoxazole. The results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) criteria [13]. Quality control was performed using control strains from the ATCC as follows: *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, *Klebsiella pneumoniae* ATCC 700603, and *Pseudomonas aeruginosa* ATCC 27853.

Data analysis

Normal distribution of all measurements was tested using the Kolmogorov-Smirnov test. The correlations between characteristics of patients and mortality were tested using the *t*-test, the Mann-Whitney U test and Fisher's exact test, respectively, for normally distributed continuous variables, non-normal continuous variables, and dichotomous variables. Any variable with a significant association with mortality in the univariate analysis was entered in a multivariate forward stepwise logistic regression model to identify independent risk factors for death. The software used for statistical calculations was SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Results

Characteristics of the patients

During the study period, a total of 40 patients with *S. maltophilia* infection were identified. All patients were of Han nationality. The demographic and basic characteristics of the patients are listed in Table 1.

The characteristics of the patients at onset of *S. maltophilia* infection are presented in Table 2. A total of 77.5% (31/40) of patients received mechanical ventilation. The duration of mechanical ventilation before the onset of *S. maltophilia* infection was 16.4 ± 15.0 days. A total of 57.5% (23/40) of patients had a central venous catheter. The duration before the onset of infection was 15.6 ± 15.9 days. Finally, 85% (34/40) of patients had a urethral catheter. The duration before the onset of infection was 14.0 ± 16.8 days.

Laboratory findings of patients at the time of *S. maltophilia* infection are summarized in Table 3.

For seven patients, the first episodes of *S. maltophilia* infection were in spring (March–May). Eleven patients were found to have *S. maltophilia* infection in summer (June–August). Another eleven patients were found to have the infection in autumn (September–November). During winter (December–February), ten patients were found to be infected with *S. maltophilia*. The numbers of *S. maltophilia* infection had no significant difference in the four seasons.

Table 1. Demographic and basic characteristics of 40 patients infected with *S. maltophilia*

Characteristics	Cases
Sex	
Male	31 (77.5%)
Female	9 (22.5%)
Age (median, range)	72 (29-97) years
Average hospitalization days (mean ± SD)	34.55 ± 24.23 days
Mortality	20 (50%)
Underlying diseases	
Pneumonia	28 (70%)
Cerebral infarction or hemorrhage	17 (42.5%)
Hypertension	14 (35%)
Coronary artery disease	9 (22.5%)
Diabetes	8 (20%)
Malignancy	6 (15%)
Chronic obstructive pulmonary disease	6 (15%)
Hematonosis	6 (15%)
Cor pulmonale	4 (10%)
Pyemia	3 (7.5%)
Trauma	2 (5%)
Digestive tract inflammation	2 (5%)
Rheumatism	2 (5%)
Peptic ulcer	1 (2.5%)
Parkinson disease	1 (2.5%)
Thyropathy	1 (2.5%)

Table 2. Characteristics of patients at onset of *S. maltophilia* infection

Characteristics	Cases
Hospitalization days prior to *S. maltophilia* infection (mean, range)	17.13 (0-58) days
Body temperature (median, range)	36.8 (36-39)°C
Hypotension	19 (47.5%)
Antibiotic treatment in past 30 days	19 (47.5%)
Surgical procedure in past 30 days	5 (12.5%)
Chemotherapy in past 30 days	1 (2.5%)
Steroids or immunosuppressors in past 30 days	1 (2.5%)

Table 3. Laboratory findings of patients at onset of *S. maltophilia* infection

Laboratory findings	Mean ± SD
White blood cells	10.94 ± 6.15 ($\times 10^9$/L)
Neutrophilic granulocytes	0.803 ± 0.153 (%)
Lymphocytes (median, Q1-Q3)	0.093 (0.050-0.144) (%)
Monocytes	0.067 ± 0.038 (%)
Platelets	166.82 ± 111.52 ($\times 10^9$/L)
Red blood cells	3.24 ± 0.69 ($\times 10^{12}$/L)
Hematoglobin	98.61 ± 19.39 (g/L)
ALT alanine aminotransferase (median, Q1-Q3)	19.50 (10.00-47.25) (u/L)
AST aspartate aminotransferase (median, Q1-Q3)	31.00 (19.00-51.25) (u/L)
Total bilirubin (median, Q1-Q3)	12.20 (8.20-15.90) (imol/L)
Direct bilirubin (median, Q1-Q3)	6.60 (4.20-9.20) (imol/L)
Total protein	59.45 ± 9.32 (g/L)
Albumin	32.55 ± 5.03 (g/L)
Albumin/globulin ratio (median, Q1-Q3)	1.23 (1.00-1.43)
Urea	9.67 ± 6.64 (mmol/L)
Creatinine (median, Q1-Q3)	63 (51-109) (imol/L)
Procalcitonin (median, Q1-Q3)	0.655 (0.280-5.368) (ng/mL)

The 40 included patients provided a total of 68 *S. maltophilia*-positive culture specimens. Among them, 19 (47.5%) patients provided multiple positive culture specimens of *S. maltophilia*. Moreover, 97.5% (39/40) patients were infected with two or more organisms. The most common microorganisms co-infected with *S. maltophilia* are displayed in Table 4.

Characteristics of the S. maltophilia isolates

Most patients' *S. maltophilia* isolates were obtained from sputum (95%), while only one patient's isolate (2.5%) was obtained from blood and one (2.5%) from bronchoalveolar lavage.

S. maltophilia isolates from 34 patients were tested for *in vitro* susceptibility. The highest sensitivity was observed to minocycline (91.2%, 31/34) and levofloxacin (85.3%, 29/34), followed by trimethoprim-sulfamethoxazole (79.4%, 27/34). The detailed relevant data are presented in Table 5.

Treatment and risk factors for death

Data of antimicrobial treatment were available for 38 of the 40 included patients. Almost all patients (37/38) received combination regimes as empirical therapy. The classes of antimicrobial agents most frequently used were glycopeptide antibiotics (76.3%, 29/38), carbapenems (55.3%, 21/38), cephalosporins (42.1%, 16/38), and fluoroquinolones (21.1%, 8/38), followed by piperacillin/tazobactam (18.4%, 7/38) and tetracycline derivatives (5.3%, 2/38). After the first positive culture of *S. maltophilia* was available, the antimicrobial treatment agents was modified in 23.7% (9/38) patients. The antimicrobial agents most frequently used as targeted therapy were piperacillin/tazobactam (4/38), moxifloxacin (4/38), and minocycline (1/38). Of the 38 patients, 34 received appropriate empirical and targeted treatment. Among them, 19 patients died and 15 patients were cured. The appropriate antimicrobial treatment had no positive impact on mortality.

Twenty patients (50%) died from any cause during their hospital stay. The results of univariate analyses showed that low albumin content ($p = 0.024$) and hypotension ($p = 0.027$) were significantly associated with mortality. Compared with surviving patients, those who died had significantly lower albumin content (30.78 versus 34.32 g/L, $p < 0.05$) at the onset of *S. maltophilia* infection. In the multivariate logistic regression model, albumin content (odds ratio: 0.832, 95% confidence interval: 0.694–0.832, $p = 0.047$) and hypotension (odds ratio: 0.229, 95% confidence interval: 0.055–0.956, $p = 0.043$) were independent factors associated with mortality.

Table 4. Other microorganisms isolated from the 40 patients infected with *S. maltophilia*

Microorganisms	Cases
Acinetobacter baumannii	26 (65%)
Staphylococcus aureus	20 (50%)
Pseudomonas aeruginosa	15 (37.5%)
Klebsiella pneumoniae	9 (22.5%)
Candida albicans	9 (22.5%)
Candida glabrata	7 (17.5%)
Burkholderia cepacia	6 (15%)
Escherichia coli	5 (12.5%)
Candida krusei	5 (12.5%)
Chryseobacterium meningosepticum	4 (10%)
Aspergillus fumigatus	3 (7.5%)
Providencia rettgeri	3 (7.5%)
Staphylococcus epidermidis	2 (5%)
Enterococcus faecium	2 (5%)
Candida tropicalis	2 (5%)
Chryseobacterium indologenes	2 (5%)
Serratia marcescens	1 (2.5%)
Enterobacter cloacae	1 (2.5%)

Table 5. Susceptibility pattern of the 34 tested *S. maltophilia* isolates

Antimicrobial agents	Susceptible	Intermediate	Resistant
Minocycline	31	1	2
Levofloxacin	29	0	5
Trimethoprim-sulfamethoxazole	27	1	6

Discussion

During the last decade, *S. maltophilia* infections have increased in importance, especially in intensive care units [14]. *S. maltophilia* has become the third most common non-fermentative Gram-negative bacilli responsible for nosocomial infections, behind *P. aeruginosa* and *Acinetobacter* spp. [15]. *S. maltophilia* infections are particularly common in patients who are severely debilitated or immunocompromised due to some kind of comorbidity. In this study, 40 cases of *S. maltophilia* infection from an intensive care unit of one general tertiary care hospital in northwest China were reported. Most of the patients were elderly males. All of the patients had one or more underlying disease. The most frequently occurring diseases were pneumonia (70%), cerebral infarction or hemorrhage (42.5%), and hypertension (35%). Almost half of the patients had received antibiotic treatment in the past 30 days, before the onset of *S. maltophilia* infection. The main characteristics of the patients were prolonged use of mechanical ventilation (77.5%, average 16.4 days), urethral catheter (85%, average 14.0 days), and central venous catheter (57.5%, average 15.6 days) before the infections occurred, which were similar to findings in other studies. The main type of infection caused by *S. maltophilia* was lower respiratory tract infection; one patient had a bloodstream infection. The case number of infections was not different in the four seasons. The result shows that there is no seasonal variation in *S. maltophilia* infection.

For the treatment of *S. maltophilia* infection, trimethoprim-sulfamethoxazole is still considered as the first-line therapeutic agent of choice, but resistance (2%–25%) has also been reported as an increasing problem for this pathogen [16-18]. Alternative agents include piperacillin, fluoroquinolones (*e.g.*, levofloxacin and moxifloxacin), and tetracycline derivatives (*e.g.*, minocycline) [19]. When *S. maltophilia* is obtained from culture and a susceptibility test has been done, the treatment must be corrected as antibiogram results. In our study, the resistance to trimethoprim-sulfamethoxazole was 17.6%, higher than that to levofloxacin (14.7%) and minocycline (5.8%). Most (89.5%) patients received appropriate antimicrobial treatment; appropriate antimicrobial therapy, however, did not have a significant impact on mortality. The mortality rates were almost same between patients who received appropriate therapy and those who did not.

Previously, *S. maltophilia* was considered to be a low-virulence pathogen. Its isolation from the respiratory tract has been frequently interpreted as colonization rather than as infection [20]. However, reports of *S. maltophilia* outbreaks in patients in the intensive care unit depicted the role of *S. maltophilia* as a causative pathogen of clinically important infections [21,22]. In uncontrolled clinical trials, crude mortality rates associated with *S. maltophilia* infections ranged from 21% to 69% [23-25]. Data reviewed suggest that the independent risk factors associated with mortality are related to underlying hematological disease in cancer patients, admission to ICU, shock, organ dysfunction, thrombocytopenia, and Acute Physiological Assessment and Chronic Health Evaluation (APACHE) score > 15 [23]. In our study, the in-hospital mortality rate was 50%, regardless of the presence of underlying diseases that could potentially lead to death. The mortality rate was high and was similar to the rate reported in the literature. The univariate and multivariate analysis showed that the independent risk factors associated with mortality in patients with *S. maltophilia* infection were low albumin content and hypotension. The impacts of raising albumin levels and blood pressure on mortality require further clinical studies. It is presumed that an albumin supplement and blood pressure increase can promote a significant survival advantage.

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