Risk Factors for Mortality in Hospitalized Patients with *Stenotrophomonas maltophilia* Bacteremia

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**Objective:** *Stenotrophomonas maltophilia* (*S. maltophilia*) is an opportunistic and nosocomial pathogen with high mortality. And it has intrinsic resistance to a number of antibiotics classes. In this study, we investigated risk factors for death due to *S. maltophilia* bacteremia.

**Methods:** A retrospective cohort study was conducted at a tertiary-care hospital in Beijing, China. The patients from the hospital database with *S. maltophilia* bacteremia between January 2011 and December 2020 were investigated. Univariate and multivariate analyses were performed to identify factors associated with mortality.

**Results:** 51 patients with *S. maltophilia* bacteremia were identified. The mortality rate was 37.3%. Based on the univariate analysis, pulmonary disease (P=0.019), chronic kidney disease (P=0.014), shock (P=0.002), Foley catheter (P=0.011), the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (P=0.001), procalcitonin (PCT) (P=0.045) and using antifungal agent (P=0.033) were significantly related to mortality. Based on the multivariate analysis, the APACHE II score (odds ratio [OR] =1.211; 95% confidence interval [CI]: 1.061, 1.382; P=0.005) was independent factor associated with mortality. *S. maltophilia* was the most susceptible to minocycline (94.7%), followed by trimethoprim and sulfamethoxazole (TMP/SMX, 92.2%).

**Conclusion:** Our findings suggested that the APACHE II score was a significantly independent predictor in *S. maltophilia* bacteremia patients. The use of TMP/SMX or minocycline might be the first choice for the treatment of *S. maltophilia* bacteremia.

**Keywords:** risk factor, *Stenotrophomonas maltophilia*, bacteremia, drug susceptibility

**Introduction**

*Stenotrophomonas maltophilia* (*S. maltophilia*) is a multi-drug resistant (MDR) gram-negative bacillus that is widely distributed in the environment.1 *S. maltophilia* is an opportunistic pathogen for various serious nosocomial infections in humans, such as pneumonia, bacteremia, urinary tract infections, cholangitis, peritonitis, wound infections, eye infections, arthritis, meningitis, and endocarditis.2 Pneumonia and bacteremia are the most common clinical symptoms of *S. maltophilia* infection.3 And the overall mortality of *S. maltophilia* bacteremia ranges from 30 to 51% within 30 days.4–6 Intensive care unit (ICU) admission, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, central venous catheter (CVC) and mechanical ventilator were clinical characteristics associated with the mortality of *S. maltophilia* bacteremia.6,7

During the intrinsic resistance of *S. maltophilia* to a variety of antibiotics, treatment of *S. maltophilia* infection is very difficult. For *S. maltophilia* infections, trimethoprim and sulfamethoxazole (TMP/SMX) is considered as the first choice, and fluoroquinolone is the proposed alternative.8,9

The epidemiology of bacterial infections varies greatly, depending on the healthcare institution profile and geographical location. Therefore it is essential to evaluate the local data of bacterial infections to assess trends over time and initiate appropriate treatment. The purpose of this retrospective study was to identify the risk factors for *S. maltophilia* bacteremia, and the outcomes of *S. maltophilia* bacteremia in our hospital.
Materials and Methods

Study Population and Design
A retrospective cohort study was conducted to evaluate the risk factors for mortality of patients with S. maltophilia bacteremia at the Beijing Shijitan Hospital. We identified S. maltophilia-positive blood cultures from the microbiology laboratory database, and then clinical records were reviewed. Data were collected between January 2011 and December 2020 from digital medical records.

Definitions
S. maltophilia bacteremia was defined as a patient having 1 or more positive blood culture, combined with clinical symptoms of systemic inflammatory response syndromes. The source of bacteremia was determined clinically on the basis of the presence of an active site of infection as determined by isolation of the organism from other clinical specimens coincident with the episode of bacteremia. Prior antimicrobial therapy was defined as any antibiotic treatment for more than 24 hours within 1 month before the episode of bacteremia. Specific therapy was regarded as appropriate if the targeted regimen included at least 1 antibiotic agent to which S. maltophilia was susceptible in vitro. The severity of illness was assessed by APACHE II score.

Blood Culture and Drug Sensitivity Test
Bactec-9120 and Bactec-FX200 systems (Becton Dickinson, Sparks, MD) were used for blood cultures. Bacterial identification and antimicrobial susceptibility tests were performed using WalkAway 40 plus system (Beckman Coulter, Inc., Tokyo, Japan) and VITEK-2 Compact system (bioMerieux, Marcy l’Etoile, France). Some drug susceptibility tests were determined by the Kirby–Bauer disk diffusion method (filter paper purchased from Oxoid). The results were interpreted according to the Clinical and Laboratory Standards Institute guidelines.

Statistical Analysis
We conducted univariate analyses of the variables between non-survivors and survivors, using SPSS statistical software (ver. 24.0, SPSS Inc., Chicago, IL, USA). Student t-test was used for continuous variables and the Chi-square test or Fisher exact test was used for categorical variables. Multiple logistic regressions were performed to determine independent risk factors associated with mortality. All statistical tests were two-tailed and \( P \leq 0.05 \) was considered statistically significant.

Results

Clinical Characteristics of S. maltophilia Bacteremia Patients
A total of 51 bacteremia patients were enrolled in this study. The 28-day mortality rate was 37.3% (19/51). The patient baseline characteristics and the outcomes are shown in Table 1. There were 40 males and 11 females, with a mean age of 74.6 years (range, 1–93 years). The mean length of stay in the hospital before the occurrence of S. maltophilia bacteremia was 39.9±49.2 days. For main diagnosis, cardiovascular disease was the most common (44/51, 83.6%), followed by pulmonary disease (41/51, 80.4%) and diabetes mellitus (37/51, 72.5%). Central venous catheter (46/51, 90.2%) was the most common invasive procedure. The main source of bacteremia was in the respiratory tract (23/51, 45.1%). And S. maltophilia could also be identified in CVC (3/51, data not shown in the table), including two patients both in the respiratory tract and CVC. The median APACHE II score was 23.9±6.8.

Risk Factors for Mortality from S. maltophilia Bacteremia
Univariate analysis was performed to screen the risk factors for S. maltophilia bacteremia (Table 1). Pulmonary disease (\( P=0.019 \)), chronic kidney disease (\( P=0.014 \)), shock (\( P=0.002 \)), foley catheter (\( P=0.011 \)), APACHE II score (\( P<0.001 \)), PCT (\( P=0.045 \)) and using antifungal agent (\( P=0.033 \)) were significantly related to mortality.

The multivariate logistic regressions analysis revealed that high APACHE II score (odds ratio [OR] =1.211; 95% confidence interval [CI]: 1.061, 1.382; \( P=0.005 \)) was the independent factor associated with mortality (Table 2).
The antibiotic susceptibility of *S. maltophilia* isolates was summarized in Table 3. The highest antibiotic sensitivity was shown towards minocycline (94.7%), and then TMP/SMX (92.2%). The susceptibility to levofloxacin, ticarcillin-clavulanate and ceftazidime was 78.4%, 29.4% and 22.6%, respectively.

**Table 1** Overall Characteristics and Univariate Analysis of Mortality in Patients with *S. maltophilia* Bacteremia

| Variables                                      | Total n=51 (%) | Survived n=32 (%) | Death n=19 (%) | P-value |
|------------------------------------------------|----------------|-------------------|----------------|---------|
| Age, years, median, IQR                        | 74.65 (66.00–88.00) |                   |                |         |
| ≥65                                             | 11 (21.6)       | 9 (28.1)          | 2 (10.5)       | 0.260   |
| <65                                             | 40 (78.4)       | 23 (71.9)         | 17 (89.5)      |         |
| Gender                                          |                |                   |                |         |
| Male                                            | 40 (78.4)       | 26 (81.3)         | 14 (73.7)      | 0.777   |
| Female                                          | 11 (21.6)       | 6 (18.8)          | 5 (26.3)       |         |
| Hospital stay, days, mean±SD                   | 39.86±49.240    | 40.69±45.629      | 38.47±56.090   | 0.878   |
| Main diagnosis                                  |                |                   |                |         |
| Sepsis                                          | 29 (56.9)       | 15 (46.9)         | 14 (73.7)      | 0.062   |
| Pulmonary disease                               | 41 (80.4)       | 22 (68.8)         | 19 (100)       | 0.019   |
| Cardiovascular disease                          | 44 (86.3)       | 26 (81.3)         | 18 (94.7)      | 0.176   |
| Diabetes mellitus                               | 37 (72.5)       | 22 (68.8)         | 15 (78.9)      | 0.430   |
| Chronic liver disease                           | 4 (7.8)         | 2 (6.3)           | 2 (10.5)       | 0.583   |
| Chronic kidney disease                          | 21 (41.2)       | 9 (28.1)          | 12 (63.2)      | 0.014   |
| Solid tumor                                     | 15 (29.4)       | 7 (21.9)          | 8 (42.1)       | 0.125   |
| Neurologic diseases                             | 29 (56.9)       | 17 (53.1)         | 12 (63.2)      | 0.484   |
| Shock                                           | 29 (56.9)       | 13 (40.6)         | 16 (84.2)      | 0.002   |
| Invasive Procedure                              |                |                   |                |         |
| Central venous catheter                         | 46 (90.2)       | 27 (84.4)         | 19 (100)       | 0.070   |
| Mechanical ventilator                           | 32 (62.7)       | 20 (62.5)         | 12 (63.2)      | 0.963   |
| Drainage tubing                                 | 8 (15.7)        | 5 (15.6)          | 3 (15.8)       | 0.988   |
| Foley catheter                                  | 40 (78.4)       | 21 (65.6)         | 19 (100)       | 0.011   |
| Source of bacteremia                            |                |                   |                |         |
| Sputum                                          | 23 (45.1)       | 16 (50.0)         | 7 (36.8)       | 0.361   |
| APACHE II score, mean±SD                       | 23.94±6.828     | 22.41±6.633       | 28.21±4.803    | <0.001  |
| Laboratory findings                             |                |                   |                |         |
| CRP (mg/L), mean±SD                             | 98.76±57.495    | 84.18±42.121      | 114.69±70.21   | 0.076   |
| PCT(ug/L), mean±SD                              | 3.36±5.122      | 2.22±3.806        | 5.26±6.459     | 0.045   |
| Prior antimicrobial therapy                     |                |                   |                |         |
| Carbapenem                                      | 27 (52.9)       | 14 (43.8)         | 13 (68.4)      | 0.088   |
| Antifungal agent                                | 25 (49.0)       | 12 (37.5)         | 13 (68.4)      | 0.033   |
| Specific therapy                                | 29 (56.9)       | 17 (53.1)         | 12 (63.2)      | 0.484   |
| Antimicrobial therapy after bacteremia          |                |                   |                |         |
| Appropriate specific therapy                    | 40 (78.4)       | 27 (84.4)         | 13 (68.4)      | 0.324   |

**Abbreviations:** APACHE II, Acute Physiology and Chronic Health Evaluation II; CRP, C-reactive protein; PCT, Procalcitonin.

**Table 2** Multivariate Analysis of Factors Associated with 28-Day Mortality in Patients with *S. maltophilia* Bacteremia

| Factor                                      | OR (95% CI)   | P-value |
|---------------------------------------------|---------------|---------|
| APACHE II                                   | 1.211 (1.061, 1.382) | 0.005   |

**Abbreviations:** APACHE II, Acute Physiology and Chronic Health Evaluation II; OR, odds ratio; CI, confidence interval.

**Antimicrobial Susceptibilities**

The antibiotic susceptibility of *S. maltophilia* isolates was summarized in Table 3. The highest antibiotic sensitivity was shown towards minocycline (94.7%), and then TMP/SMX (92.2%). The susceptibility to levofloxacin, ticarcillin-clavulanate and ceftazidime was 78.4%, 29.4% and 22.6%, respectively.
**Discussion**

*S. maltophilia* is emerging as an opportunistic pathogen among hospitalized patients, causing significant mortality. We conducted this retrospective analysis and analyzed the risk factors for mortality as well as antibiotic susceptibility in patients with *S. maltophilia* bacteremia.

*S. maltophilia* bacteremia is associated with high mortality rates, the crude mortality estimates range from 21 to 69%. In our study, the mortality rate was 37.3%, which was similar to the studies. Previously published reviews had reported several risk factors for mortality in patients with *S. maltophilia* bacteremia, including hemodialysis, T-tube, septic shock, sequential organ failure assessment (SOFA) score, removal of the CVC, ICU admission and use of medical devices. Based on the results of our multivariate analysis, *S. maltophilia* bacteremia patients with high APACHE II scores had higher rates of mortality. In agreement with some studies, patients with severe disease and high APACHE II scores at the time of bloodstream infection had a higher mortality rate. Since the development of the APACHE II score, the prognostic value of the APACHE II score at admission to the intensive care unit had been demonstrated. It seemed that the APACHE II score could also be used to predict mortality in patients with bloodstream infection.

In addition, our results showed that appropriate specific therapy, was not associated with mortality. It was similar with the previous report. However, some studies had reported that the appropriate antibacterial therapy was significantly associated with lower mortality. So further study to evaluate the impact of appropriate antibacterial therapy in mortality should be performed.

In our study, *S. maltophilia* showed higher susceptibility rates to TMP/SMX, minocycline, and fluoroquinolones than to cefazidime and Ticarcillin clavulanate. The susceptibility to TMP/SMX was 92.2%, consistent with the reported studies. Although increasing resistance of *S. maltophilia* to TMP-SMX had been reported, the present study suggested that TMP-SMX might still be suitable as first-line drug for *S. maltophilia* infection. The susceptibility to minocycline was 94.7%, consistent with the previous studies. At the same time, the susceptibility to levofloxacin was 78.4%, similar with 83.4%. And the susceptibility to Ticarcillin clavulanate and cefazidime was 29.4% and 22.6%, respectively, similar with 27.0% in Asian-Pacific region and 25.5%. The susceptibilities to antimicrobial agents were not consistent with the previous study in china, may be due to the frequency of *S. maltophilia* infections and the region-specific level of antimicrobial consumption. These data suggested that the use of TMP/SMX or minocycline in our hospital might be the best empirical treatment for *S. maltophilia* bacteremia.

There were some limitations to this study. First, it was a single center study with a small sample size, which may not be generalizable. Second, the design of our study was retrospective, so selection and observational bias might have affected the results. Third, the cause of mortality was not consistently documented and had to be inferred in some cases.

**Conclusion**

The mortality in patients with *S. maltophilia* bacteremia was high. High APACHE II score was a significant independent predictor of *S. maltophilia* mortality in bacteremia patients. The TMP/SMX and minocycline remained high susceptibility rates and these two could be considered as an appropriate antibacterial therapy at our institution. In addition, more elaborate and multi-center study with greater patient numbers may be required in the future.

| Antibiotics                  | n  | Susceptible (%) | Intermediately Susceptible (%) | Resistant (%) |
|-----------------------------|----|-----------------|-------------------------------|--------------|
| Ticarcillin clavulanate     | 17 | 29.4            | 58.8                          | 11.8         |
| Cefazidime                   | 31 | 22.6            | 16.1                          | 61.3         |
| Levofloxacin                 | 51 | 78.4            | 5.9                           | 15.7         |
| Trimethoprim sulfamethoxazole| 51 | 92.2            | 0                             | 7.8          |
| Minocycline                  | 19 | 94.7            | 0                             | 5.3          |

Table 3 Antibiotic Susceptibility of *Stenotrophomonas maltophilia* Isolates
Abbreviations
S. Maltophilia, Stenotrophomonas maltophilia; APACHE II, Acute Physiology and Chronic Health Evaluation II; PCT, procalcitonin; OR, odds ratio; CI, confidence interval; TMP/SMX, trimethoprim and sulfamethoxazole; CVC, Central venous catheter; ICU, intensive care unit; MDR, multi-drug resistant; CRP, C-reactive protein; SOFA, sequential organ failure assessment.

Ethics Approval and Consent to Participate
The study was approved by the ethics committees of the Beijing Shijitan Hospital. The informed consent was waived, because this study was a retrospective study with review of related data through the electronic medical records.

We declare that this study is in accordance with the Helsinki Declaration and the relevant national laws and policies, and never disclose the information of all patients.

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Disclosure
The authors declare that there is no conflict of interest.

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