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Original Article

# Appropriate antibiotic therapy is a predictor of outcome in patients with *Stenotrophomonas maltophilia* blood stream infection in the intensive care unit

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Trimethoprim—sulfamethoxazole;
Antibiotic therapy;
Intensive care

**Abstract** *Background/purpose:* The study was to assess the relationship between antibiotic therapy and the outcome in intensive care unit (ICU) patients with *Stenotrophomonas maltophilia* bloodstream infection (BSI).
*Methods:* ICU patients with monomicrobial *S. maltophilia* BSI from January 2004 to December 2019 were included and divided into two groups—those with- and without appropriate antibiotic therapy after BSI—for comparison. The primary outcome was the relationship between appropriate antibiotic therapy and 14-day mortality. The secondary outcome was the influence of different antibiotic therapies: levofloxacin- and trimethoprim—sulfamethoxazole (TMP/SMX)-containing regimens, on 14-day mortality.
*Results:* A total of 214 ICU patients were included. Patients received appropriate antibiotic therapy (n = 133) after BSI had a lower 14-day mortality than those ($n = 81$) without appropriate antibiotic therapy (10.5% vs. 46.9%, $p < 0.001$). No difference on 14-day mortality between groups of patients by time of appropriate antibiotic therapy was observed ($p > 0.05$). After a propensity score matching, the results is consistent that 14-day mortality were lower

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in patients with appropriate antibiotic therapy than those without appropriate antibiotic therapy (11.5% vs. 39.3%, $p < 0.001$). Among patients with *S. maltophilia* BSI receiving appropriate antibiotic therapy, there was a trend levofloxacin-containing regimens is associated with lower mortality than TMP/SMX-containing regimens (HR 0.233, 95% CI 0.050—1.084, $p = 0.063$).
*Conclusion:* Appropriate antibiotic therapy was associated with decreased 14-day mortality in ICU patients with *S. maltophilia* BSI regardless of time. Levofloxacin-containing regimens may be better choice than TMP/SMX -containing regimens in treating ICU patients with *S. maltophilia* BSI.


## Introduction

*Stenotrophomonas maltophilia*, a non-fermentative gram-negative bacillus that is found in aquatic or humid environments, has emerged as an important nosocomial pathogen in recent years.[1,2] The organism is considered an opportunistic pathogen and primarily causes invasive infections among immunocompromised patients.[3,4] A wide variety of clinical infectious syndromes caused by *S. maltophilia* has been reported; these mainly include pneumonia, bloodstream infection (BSI) and, less commonly, skin and soft tissue infection, endocarditis, meningitis, intra-abdomen infections, bone and joint infections, and endophthalmitis.[4]

For BSI, a more serious type of *S. maltophilia* infection, the crude mortality rate of infected patients varies across studies, ranging from 18% to 69%.[5] The reported risk factors for mortality in patients with *S. maltophilia* BSI include disease severity, intensive care unit (ICU) stay, and neutropenia.[6—11] Catheter-related BSI, however, was reported to be a protective factor if the infected catheter was removed immediately.[7,9]

Owing to inherent multiple drug resistance properties of *S. maltophilia*, treatment of *S. maltophilia* infection is difficult.[12,13] Among the limited effective antibiotics currently available, trimethoprim—sulfamethoxazole (TMP/SMX) has remained the drug of choice for BSI due to *S. maltophilia* for years.[14] Levofloxacin has been considered an alternative based upon recent clinical studies.[15,16] The efficacy of other antibiotics with potential in vitro-activity against *S. maltophilia* has not yet been validated in clinical studies.[17]

Patients admitted in the ICU are at risk for invasive infection by *S. maltophilia* because of frequent associated conditions, such as multiple underlying comorbidities, high disease severity, exposure to broad-spectrum antibiotics, and indwelling invasive medical devices.[18—20] Respiratory tract infections, including healthcare-associated pneumonia and ventilator-associated pneumonia, caused by *S. maltophilia* are frequently reported and substantial mortality, despite antibiotic treatment, have also been noted.[21—23] BSI, another common manifestation of *S. maltophilia* infection, has rarely been specifically described in ICU patients. In the published studies on *S. maltophilia* BSI, the study population is mainly from the hospitalized patients with a small portion of those in the ICU. Occurrence of *S. maltophilia* BSI in ICU patients usually associated with severe disease conditions may influence the outcome more drastically. Moreover, patients in the ICU with severe disease conditions may likely have kidney or liver function impairment and more often be exposed to a potential drug—drug interaction, which may interfere with the pharmacodynamics of the antibiotic administered against organisms. Therefore, the effects of antibiotics on BSI due to *S. maltophilia* in ICU patients might be different from those in the general ward.

In the abovementioned context, the present study was designed to specifically assess the efficacy of antibiotic therapy on the clinical outcomes in ICU patients with BSI due to *S. maltophilia*. Responses to two different effective antibiotic regimens for *S. maltophilia*, namely levofloxacin or TMP/SMX, were also evaluated.

## Methods

### Study design and data collection

This observational retrospective study was conducted from January 2004 to December 2019 at the Tri-Service General Hospital, which is a university-affiliated tertiary care hospital with 1800 general beds and 140 ICU beds located in northern Taiwan. All patients aged over 18 years with BSI due to *S. maltophilia* in the ICU were considered for inclusion. Each patient was only included once, using the first positive culture result of *S. maltophilia* during hospitalization. Admitted ICU patients with polymicrobial BSI or age <18 years were excluded.

Clinical data were extracted from the medical records of patients via hospital computerized databases. The following data were collected: demographics, baseline clinical characteristics related to ICU admission, comorbidities, and clinical outcomes. The Charlson Comorbidity Index (CCI) was used as an aggregate measure for comorbidities.[24] At the onset of BSI, severity assessment of diseases with APACHE II score, requirement of mechanical ventilation, acute kidney injury defined using the Kidney Disease Improving Global Outcomes (KDIGO) criteria, and septic shock defined previously were recorded.[25,26] The antibiotic therapy used for at least 48 h from the onset until 14 days after BSI or death were documented.

### Diagnosis of BSI due to *S. maltophilia* and microbiological tests

BACTEC FX automatic blood culture detection system (Becton Dickinson, Sparks, MD, USA) was used to detect microorganisms in the blood. From 2004 to 2015,

identification of BSI pathogens was done using the Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France). Since 2016, matrix-assisted laser desorption/ionization—time of flight mass spectrometry (VITEK MS; bioMerieux) and a rapid identification protocol has been adopted for identification of pathogens in positive blood culture in our hospital.[27] A *S. maltophilia* BSI was defined as blood culture positivity for *S. maltophilia* as determined using the Vitek 2 automated system (bioMérieux) or VITEK MS. The source of BSI was assessed according to the available clinical and microbiological information and classified according to described guidelines.[28] Primary BSI was defined in the absence of an identified source of infection growing in the same organism as from blood. Minimum inhibitory concentrations (MICs) of the tested antibiotics against *S. maltophilia* were determined using the Vitek 2 automated system (bioMérieux). Antibiotic susceptibility assessments were according to the Clinical and Laboratory Standards Institute (CLSI) standard. Only the susceptibility to levofloxacin and TMP/SMX were tested in our hospital during the study period.

## Antibiotic therapy for BSI due to *S. maltophilia*

All patients with sepsis were evaluated by an on-duty infectious disease specialist during their ICU hospitalization. Antibiotic therapies for BSI due to *S. maltophilia* were classified as empiric and definitive, as described.[29] Empiric antibiotic therapy was defined as treatment with antibiotics prescribed from the time of BSI onset to the obtaining of final blood culture results. Empiric antimicrobial agents were selected according to clinical assessment by infectious disease specialists, which could be subsequently modified according to clinical responses during the next few days after BSI and depending on final blood culture results. Definitive therapy was defined as the use of antibiotics after obtaining microbiology results indicating etiologic pathogen and antibiotic susceptibility data. In our study, antibiotic therapy was classified as appropriate if *S. maltophilia* displayed documented in vitro susceptibility to at least one administered antibiotic. To compare the efficacy of levofloxacin and TMP/SMX in treating BSI due to *S. maltophilia*, subgroup analysis was performed for patients with appropriate antibiotic therapy receiving TMP/SMX- or levofloxacin-containing regimen. Patients were excluded if they received both TMP/SMX and levofloxacin simultaneously.

## Outcome assessment

The primary outcome of the study was the effect of appropriate antibiotic therapy on the mortality rate at day 14. The 14-day mortality is defined as death from any cause within 14 days after the BSI onset. We also categorized patients with appropriate antibiotic therapy into groups according to antibiotic administration time (<48 h, 49—96 h, 97 h—7 days, and >7 days after BSI onset) to see whether timing of appropriate antibiotic use influence outcomes. The secondary outcome was the evaluation of the influence of different treatment regimens, TMP/SMX or levofloxacin, on the 14-day mortality. To this end, we identified two groups of patients treated with TMP/SMX-containing or levofloxacin-containing regimens from those with appropriate antibiotic therapy and made a comparison.

## Statistical analysis

All results were analyzed using a commercially available software package (SPSS, version 25.0; SPSS Inc., Chicago, IL, USA). Statistical significance was established at $p < 0.05$. All reported $p$ values are two-tailed. Continuous variables are presented as medians and interquartile ranges (IQRs), and categorical variables are expressed as numbers and percentages. The differences in continuous and categorical variables between included patients with and without appropriate antibiotic therapy were compared using the Mann—Whitney *U* test, chi-square test, or Fisher's exact test. We also used chi-square test to compared 14-day mortality rates between groups of patients with different antibiotic administration time. Moreover, a more formal causal analysis was conducted based on propensity scores. The variables used for the estimation of propensity score were age, sex, length of stay before BSI, the presence of comorbidities (heart failure, old cerebrovascular accident, chronic obstructive pulmonary disease, diabetes mellitus, liver cirrhosis, chronic kidney disease, malignancy, Charlson Comorbidity Index), source of BSI (respiratory tract, urinary tract, catheter related, intra-abdominal, primary and skin/soft tissue), disease severity at BSI onset including APACHE score, acute kidney injury, shock, and mechanical ventilation. The propensity score-matched analysis was performed by matching patients in the two groups at a 1:1 ratio, without replacement, using the nearest neighbor technique, using a caliper of 0.2 of the standard deviation of the propensity score on the logit scale.[30] The standardized difference was further used to assess whether this matching technique properly balanced the baseline characteristics between the groups. A standardized difference less than 0.1 was considered as evidence of balance in the variables.[31] Cox proportional hazards modeling was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of potential risk factors including appropriate antibiotic therapy associated with the overall 14-day mortality due to BSI. Baseline prognostic factors, namely age, length of hospital stay before BSI, CCI, source of BSI, disease severity, and appropriate antibiotic therapy were entered in the model as time-dependent variables. Baseline time-dependent variables associated ($p < 0.05$) with the outcome in the univariate analysis were included for the multivariate model to find the independent factors for 14-day mortality. The Cox proportional hazards model, with a robust variance estimator to take into account the correlation induced by the matching, was also used for propensity-based matched cohort to check if the results were consistent with those for the original unmatched cohort.[32] Besides, Cox proportional

hazards model was also used to evaluate the effect of different antibiotics on the clinical outcome. TMP/SMX-containing regimens was selected as a reference; levofloxacin-containing regimens was tested against the reference variable.

## Results

### Description of included patients with BSI due to *S. maltophilia*

Within the study period, a total of 1091 ICU patients with *S. maltophilia* BSI were identified and a total of 214 were included for analyses. A flowchart for the study is shown in Fig. 1. The characteristics of the ICU patients with BSI by *S. maltophilia* are shown in Table 1. The patient population was predominantly male (65.4%), with a median age of 74 years (IQR 57—83). The major reason for admission was infection (51.9%). Prolonged hospital stay and ICU stay before BSI were noted with a median of 24 days (IQR 15—38) and 15.5 days (IQR 9—24), respectively. Composite comorbidities at admission and severity at the BSI onset are illustrated by the CCI being 3 (IQR 2—6) and the APACHE score being 22 (IQR 18—28). The most common source of BSI was from respiratory tract (55.6%), followed by infection of primary origin (34.1%). The 14-day and in-hospital mortality of the included patients with BSI were 24.3% and 52.3%,

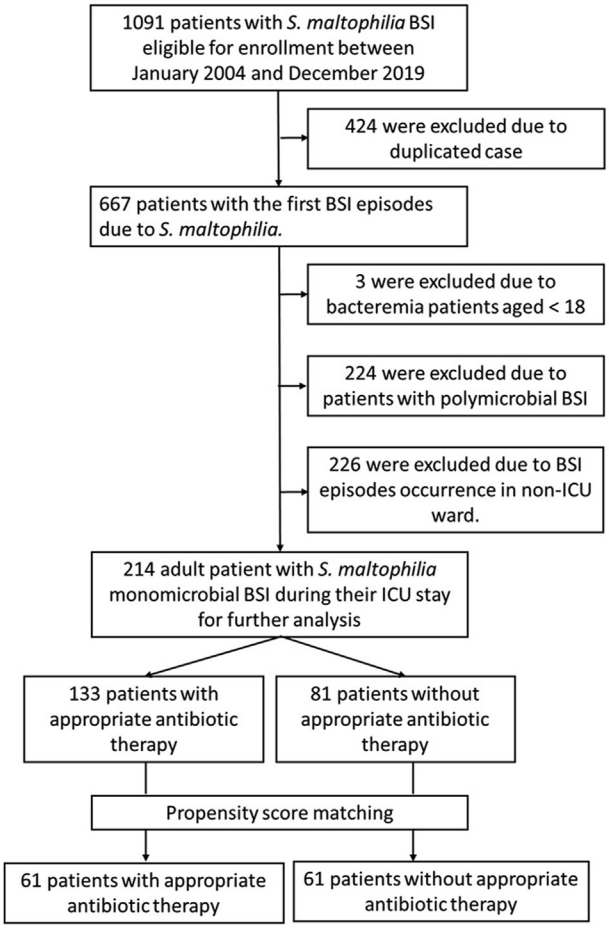


**Figure 1.** Flow chart of included patient with *Stenotrophomonas maltophilia* blood stream infection.

**Table 1** Characteristics of ICU patients with BSI by *S. maltophilia*.

| Variable | Total ($n$ = 214) |
|---|---|
| Demographics | |
| Age, years, median (IQR) | 74 (57—83) |
| Male, *n* (%) | 140 (65.4) |
| Comorbidities, *n* (%) | |
| Heart failure | 44 (20.6) |
| Old cerebrovascular accident | 42 (19.6) |
| Chronic obstructive pulmonary disease | 32 (15.0) |
| Connective tissue disease | 8 (3.7) |
| Diabetes mellitus | 78 (36.4) |
| Liver cirrhosis | 17 (7.9) |
| Chronic kidney disease | 39 (18.2) |
| Charlson Comorbidity Index, median (IQR) | 3 (2—6) |
| Setting from which patient was admitted to ICU, *n* (%) | |
| Other hospital | 17 (7.9) |
| Ward | 100 (46.7) |
| Emergency department | 97 (45.3) |
| Hospital stay before BSI onset, days, median (IQR) | 24 (15—38) |
| ICU stay before BSI onset, days, median (IQR) | 15.5 (9—24) |
| Reason for ICU admission, *n* (%) | |
| Infection | 111 (51.9) |
| Respiratory failure | 10 (4.7) |
| Cardiovascular disease | 33 (15.4) |
| Postoperative monitoring | 25 (11.7) |
| Gastrointestinal bleeding | 9 (4.2) |
| Cerebrovascular accident | 14 (6.5) |
| Trauma | 7 (3.3) |
| Others[a] | 5 (2.3) |
| Source of BSI, *n* (%) | |
| Respiratory tract | 119 (55.6) |
| Urinary tract | 3 (1.4) |
| Catheter related | 11 (5.1) |
| Intra-abdominal | 3 (1.4) |
| Primary | 73 (34.1) |
| Skin and soft tissue | 1 (0.5) |
| Disease severity at BSI onset, *n* (%) | |
| APACHE score, median (IQR) | 22 (18—28) |
| Acute kidney injury | 51 (23.8) |
| Shock | 74 (34.6) |
| Mechanical ventilation | 142 (66.4) |
| Clinical outcome, *n* (%) | |
| 14-day mortality | 52 (24.3) |
| In-hospital mortality | 112 (52.3) |
| Hospital stay after BSI among survivals, days, median (IQR) | 25.5 (14—52) |

[a] Other causes of ICU admission include 1 case of carbon monoxide poisoning, 1 case of hyperosmolar hyperglycemic state, 2 cases of acute renal failure, and 1 case of spinal shock. *S. maltophilia*, *Stenotrophomonas maltophilia*; ICU, intensive care unit; BSI, bloodstream infection; IQR, interquartile range.

**Table 2** Antibiotic therapy related to BSI due to *S. maltophilia*.

| Variable | Total ($n$ = 214) |
|---|---|
| No. of different antibiotic classes used empirically in each infected patient, median (IQR) | 2 (1–2) |
| Empiric antibiotics used after BSI due to *S. maltophilia*, *n* (%) | |
| Third-generation cephalosporin | 19 (8.9) |
| Fourth-generation cephalosporin | 41 (19.2) |
| Carbapenem | 109 (50.9) |
| Aminoglycoside | 9 (4.2) |
| Colistin | 29 (13.6) |
| Daptomycin | 5 (2.3) |
| Fluoroquinolone | 50 (23.4) |
| Glycopeptide | 60 (28.0) |
| Linezolid | 10 (4.7) |
| β-lactam/β-lactamase inhibitor | 52 (24.3) |
| Trimethoprim-sulfamethoxazole | 24 (11.2) |
| Tigecycline | 16 (7.5) |
| Colimycin | 29 (13.6) |
| Fosfomycin | 3 (1.4) |
| Appropriate antibiotic therapy after BSI, *n* (%) | 133 (62.1) |
| Empiric antibiotic therapy | 48 |
| Definite antibiotic therapy | 85 |

*S. maltophilia*, *Stenotrophomonas maltophilia*; BSI, bloodstream infection; IQR, interquartile range.

respectively. The median hospital stay after BSI was 25.5 days (IQR 14–52).

## Antibiotic therapy for BSI due to *S. maltophilia*

The prescription of antibiotic therapy is summarized in Table 2. After the onset of *S. maltophilia* BSI, the median number of classes of the antibiotic therapy empirically used in each infected patient was 2 (1–2), and 146 of 214 (68.2%) patients received at least two classes of empiric antibiotics. The most prescribed empiric antibiotic for *S. maltophilia* BSI was carbapenem (50.9%). Overall, 133 of 214 (62.1%) patients received appropriate antibiotic therapy after BSI. Only 25 of 214 (11.7%) patients received appropriate antibiotics within 48 h after BSI onset. Among 133 patients with appropriate antibiotic therapy, 62 received levofloxacin, 67 received TMP/SMX, and 4 received a combination therapy with levofloxacin and TMP/SMX. For patients receiving TMP/SMX, the median dosage of trimethoprim component was 6.2 mg/kg (IQR 4.49–8.94) regardless of renal function, and 6.6 mg/kg (IQR 5.3–12) for those with normal renal function ($n$ = 35).

## Primary outcome analysis

A comparison of clinical characteristics and clinical outcomes among patients with- and without appropriate antibiotic therapy before and after propensity score matching is shown in Table 3. For original unmatched included patients ($n$ = 214), there were no significant differences in age, sex, hospital stay before BSI, comorbidities, and source of BSI (all $p > 0.05$). With regard to disease severity, patients receiving an appropriate antibiotic therapy had a significantly lower APACHE score than those who did not receive an appropriate antibiotic therapy (22 vs. 25, $p < 0.01$). Comparison of clinical outcomes revealed that patients receiving an appropriate antibiotic therapy had a significantly lower mortality rate than those who did not receive an appropriate antibiotic therapy (10.5% vs. 46.9%, $p < 0.01$) at day 14. The median hospital stay after BSI showed no significant difference for the groups (45 days vs. 37 days, $p$ = 0.38). After propensity score matching, we were able to match 61 couples to patients who received or did not receive an appropriate antibiotic therapy after BSI (Table 3). Overall, the groups were well balanced, with standardized differences of the variables involved in PS being <0.1 after matching except for the variables, liver cirrhosis and acute kidney injury (standardized differences being 0.13 and 0.10, respectively, Table S1). Comparison of clinical outcomes between groups revealed consistent results as for the original unmatched patients. There were 7 (11.5%) and 24 (39.3%) deaths within the 14-day follow-up period in patients with and without appropriate antimicrobial therapy, respectively. Hospital stay after BSI was not significantly different for the groups (37 days vs. 36 days, $p$ = 0.430). Fig. 2 showed 14-day mortality rates of patients with appropriated antibiotic therapy categorized according to different time period from BSI onset to antibiotic therapy administration, no significant difference between groups was observed ($p > 0.05$).

In Table 4, in univariate analysis of Cox proportional hazards model for original included patients, the variables significantly associated with 14-day mortality were APACHE score (HR 1.17, 95% CI 1.10–1.24, $p < 0.01$), acute kidney injury (HR 3.15, 95% CI 1.62–6.13, $p < 0.01$), whereas appropriate antibiotic therapy was a protective factor (HR 0.50, 95% CI 0.25–0.99, $p$ = 0.047) (Table 4). In multivariate analysis, the APACHE score (HR 1.15, 95% CI 1.09–1.22, $p < 0.01$), acute kidney injury (HR 2.39, 95% CI 1.22–4.68, $p$ = 0.01), and appropriate antibiotic therapy (HR 0.48, 95% CI 0.24–0.96, $p$ = 0.04) were still significantly associated with 14-day mortality (Table 4). Similarly, for the propensity-matched cohort, the APACHE score was significant associated with 14-day mortality in univariate and multivariate analysis (HR 1.11 and 1.12, 95% CI 1.06–1.17 and 1.06–1.18, both $p < 0.01$). Appropriate antibiotic therapy remained a significant protective factor in appropriate antibiotic therapy for 14-day mortality in univariate and multivariate analysis (HR 0.24 and 0.22, 95% CI 0.10–0.56 and 0.10–0.52, both $p < 0.01$).

## Secondary outcome analysis

Table 5 showed the comparison of 14-day mortality according to treatment regimens. In univariate analysis, factors associated with 14-day mortality were acute kidney injury (HR 3.00, 95% CI 1.04–8.65, $p$ = 0.04) and APACHE score (HR 1.14, 95% CI 1.05–1.24 $p < 0.01$). Compared with the use of TMP/SMX, the use of levofloxacin was associated

**Table 3** Clinical characteristics for patients with- and without appropriate antibiotic therapy before and after propensity score matching analysis.

| Variable | Unmatched cohort | | | Propensity-matched cohort | | |
|---|---|---|---|---|---|---|
| | With appropriate antibiotic therapy ($n$ = 133) | Without appropriate antibiotic therapy ($n$ = 81) | $p$ value | With appropriate antibiotic therapy ($n$ = 61) | Without appropriate antibiotic therapy ($n$ = 61) | $p$ value |
| Age, median (IQR) | 74 (58.5—83) | 74 (56—84) | 0.99 | 73 (58—83) | 74 (56—84) | 0.89 |
| Sex, $n$ (%) | 88 (66.2) | 52 (64.2) | 0.77 | 38 (62.3) | 38 (62.3) | 1.00 |
| Length of hospital stay before BSI, median (IQR) | 23 (15—36) | 26 (15—46) | 0.61 | 24 (16—37) | 26 (16—45) | 0.54 |
| Co-morbidity, $n$ (%) | | | | | | |
| Heart failure | 26 (19.5) | 18 (22.2) | 0.64 | 18 (29.5) | 15 (24.6) | 0.54 |
| Old cerebrovascular accident | 23 (17.3) | 19 (23.5) | 0.27 | 9 (14.8) | 12 (19.7) | 0.47 |
| Chronic obstructive pulmonary disease | 15 (11.3) | 17 (21.0) | 0.05 | 9 (14.8) | 10 (16.4) | 0.80 |
| Diabetes mellitus | 49 (36.8) | 29 (35.8) | 0.88 | 24 (39.3) | 21 (34.4) | 0.57 |
| Liver cirrhosis | 8 (6.0) | 9 (11.1) | 0.18 | 5 (8.2) | 3 (4.9) | 0.72 |
| Chronic kidney disease | 24 (18.0) | 15 (18.5) | 0.93 | 12 (19.7) | 14 (23.0) | 0.66 |
| Malignancies | 34 (25.6) | 23 (28.4) | 0.65 | 13 (21.3) | 14 (23.0) | 0.83 |
| Charlson Comorbidity Index, median (IQR) | 3 (2—5) | 3 (2—6) | 0.28 | 3 (2—5) | 3 (2—5) | 0.73 |
| Source of BSI, $n$ (%) | | | | | | |
| Respiratory tract | 75 (56.4) | 44 (54.3) | 0.77 | 38 (62.3) | 37 (60.7) | 0.85 |
| Urinary tract | 2 (1.5) | 1 (1.2) | 1.00 | 1 (1.6) | 1 (1.6) | 1.00 |
| Catheter related | 6 (4.5) | 5 (6.2) | 0.75 | 2 (3.3) | 3 (4.9) | 1.00 |
| Intra-abdominal | 2 (1.5) | 1 (1.2) | 1.00 | 0 (0) | 0 (0) | — |
| Primary | 48 (36.1) | 29 (35.8) | 0.97 | 19 (31.1) | 20 (32.8) | 0.85 |
| Skin and soft tissue | 0 (0) | 1 (1.2) | 0.38 | 0 (0) | 0 (0) | — |
| Disease severity, $n$ (%) | | | | | | |
| APACHE score | 22 (16—26) | 25 (20—30) | <0.01 | 23 (19—28) | 22 (19—28) | 0.76 |
| Acute kidney injury | 28 (21.1) | 23 (28.4) | 0.22 | 17 (27.9) | 13 (21.3) | 0.40 |
| Shock | 43 (32.3) | 31 (38.3) | 0.46 | 21 (34.4) | 20 (32.8) | 0.85 |
| Mechanical ventilation | 84 (63.2) | 58 (71.6) | 0.21 | 44 (72.1) | 44 (72.1) | 1.00 |
| Clinical outcome, $n$ (%) | | | | | | |
| 14-day mortality | 14 (10.5) | 38 (46.9) | <0.01 | 7 (11.5) | 24 (39.3) | <0.01 |
| Hospital stay after BSI, median (IQR)[a] | 45 (25—67) | 37 (24.8—60) | 0.38 | 37 (22—67) | 36 (21—53) | 0.43 |

[a] The assessment of hospital stays did not include patients who died during hospitalization.
BSI, bloodstream infection; IQR, interquartile range.

with a lower mortality (HR 0.17, 95% CI 0.04—0.75, $p$ = 0.02). In the multivariable analysis after adjustment, there was a trend that the use of levofloxacin was associated with a lower mortality than TMP/SMX (HR 0.233, 95% CI 0.05—1.08, $p$ = 0.06).

## Discussion

This retrospective cohort study, focused upon ICU patients with monomicrobial BSI due to *S. maltophilia*, demonstrates that appropriate antibiotic therapy is an independent protective factor for 14-day mortality regardless of administration time. Among the ICU patients with *S. maltophilia* BSI who received appropriate antibiotic therapy, patients receiving levofloxacin-containing regimens have a trend toward better outcome than those with TMP/SMX-containing regimens.

The study population reported in published research on *S. maltophilia* BSI mainly included the overall hospitalized patients, with a small proportion of ICU patients, which may not truly reflect the situation of critical ill patients *S. maltophilia* BSI. We performed an extensive literature search and found a specific description of BSI in ICU patients in only one study.[33] In the study by *Tunger* et al.,[35] *S. maltophilia* bacteremia episodes were included and overall mortality could be up to 62.9% and appropriate antibiotic therapy was not associated with mortality. Consistently, our study showing an in-hospital mortality of 52.3% in ICU patients with *S. maltophilia* BSI suggests a serious influence of *S. maltophilia* BSI on critical ill patients. Moreover, we further described antibiotic therapy used in ICU patients after *S. maltophilia* BSI. Due to intrinsic multiple drug resistance of *S. maltophilia*, it is challenging for clinicians to prescribe proper empiric antibiotics with activity covering possible *S. maltophilia* infection in treating sepsis patients at the onset.[34] We observed that 68.2% patients received empiric antibiotic combination therapy after the BSI onset. The most frequently prescribed antibiotic was carbapenem (50.9%), which was, however, ineffective for

**Table 4** Cox regression analysis of factors associated with 14-day mortality in patients with BSI due to *S. maltophilia*.

| Variable | Unmatched cohort | | | | Propensity-matched cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Unadjusted HR (95% CI) | *p* value | Adjusted HR (95% CI) | *p* value | Unadjusted HR (95% CI) | *p* value | Adjusted HR (95% CI) | *p* value |
| Age | 0.99 (0.98–1.01) | 0.34 | | | 0.98 (0.97–1.00) | 0.07 | | |
| Length of hospital stay before BSI | 1.01 (1.00–1.02) | 0.21 | | | 1.012 (0.999–1.024) | 0.07 | | |
| Charlson Comorbidity Index | 1.05 (0.92–1.20) | 0.46 | | | 1.07 (0.93–1.23) | 0.35 | | |
| Source of BSI | | | | | | | | |
| Respiratory tract | 0.87 (0.45–1.68) | 0.67 | | | 0.74 (0.35–1.54) | 0.42 | | |
| Catheter related | 1.69 (0.53–5.45) | 0.37 | | | 2.046 (0.432–9.700) | 0.36 | | |
| Primary | 0.85 (0.42–1.72) | 0.64 | | | 0.95 (0.43–2.07) | 0.90 | | |
| Disease severity at BSI | | | | | | | | |
| APACHE score | 1.17 (1.10–1.24) | <0.01 | 1.15 (1.09–1.22) | <0.01 | 1.11 (1.06–1.17) | <0.01 | 1.12 (1.06–1.19) | <0.01 |
| Acute kidney injury | 3.15 (1.62–6.13) | <0.01 | 2.39 (1.22–4.68) | 0.01 | 1.826 (0.836–3.989) | 0.13 | | |
| Shock | 1.59 (0.81–3.12) | 0.17 | | | 1.37 (0.63–2.95) | 0.43 | | |
| Mechanical ventilation | 2.11 (0.91–4.92) | 0.08 | | | 2.59 (0.88–7.64) | 0.08 | | |
| Appropriate antibiotic therapy | 0.50 (0.25–0.99) | 0.047 | 0.48 (0.24–0.96) | 0.04 | 0.24 (0.10–0.56) | <0.01 | 0.22 (0.10–0.52) | <0.01 |

*S. maltophilia*, *Stenotrophomonas maltophilia*; HR, hazard ratio; CI, confidence interval; BSI, bloodstream infection.

**Table 5** Clinical predictors for 14-day after BSI by *S. maltophilia* among patients with appropriate antibiotic therapy.[a]

| Variable | Unadjusted HR (95% CI) | *p* value | Adjusted HR (95% CI) | *p* value |
|---|---|---|---|---|
| Age | 0.99 (0.97–1.02) | 0.66 | | |
| Length of hospital stay before BSI | 1.01 (0.99–1.02) | 0.51 | | |
| Charlson Comorbidity Index | 1.02 (0.82–1.26) | 0.88 | | |
| Source of blood stream infection | | | | |
| Respiratory tract | 1.43 (0.48–4.28) | 0.52 | | |
| Primary | 0.65 (0.20–2.07) | 0.47 | | |
| Disease severity at BSI | | | | |
| APACHE score | 1.14 (1.05–1.24) | <0.01 | 1.09 (1.00–1.20) | 0.06 |
| Acute kidney injury | 3.00 (1.04–8.65) | 0.04 | 2.19 (0.73–6.54) | 0.16 |
| Shock | 1.65 (0.57–4.76) | 0.35 | | |
| Mechanical ventilation | 1.44 (0.45–4.60) | 0.54 | | |
| Antibiotic use | | | | |
| Trimethoprim-sulfamethoxazole containing regimen | Ref variable | Ref variable | Ref variable | Ref variable |
| Levofloxacin containing regimen | 0.17 (0.04–0.75) | 0.02 | 0.23 (0.05–1.08) | 0.06 |

[a] 129 patients were analyzed.
HR, hazard ratio; CI, confidence interval; BSI, bloodstream infection.

*S. maltophilia*. Only 11.7% patients were administered appropriate antibiotic therapy within 48 h of the BSI onset. These results reflect the current dilemma in the real-world clinical settings when clinicians face *S. maltophilia* infection in the ICU.

To address the effect of an appropriate antibiotic regimen on clinical outcomes of ICU patients with BSI due to *S. maltophilia*, we used 14-day mortality as the primary endpoint to allow proper assessment of the contribution of the antibiotic therapy to clinical outcomes. We reasoned that in ICU patients, 28- or 30-day mortality may be too long a period, as there are many competing factors of death. Moreover, we excluded patients with polymicrobial *S. maltophilia* BSI to preclude potential influence from

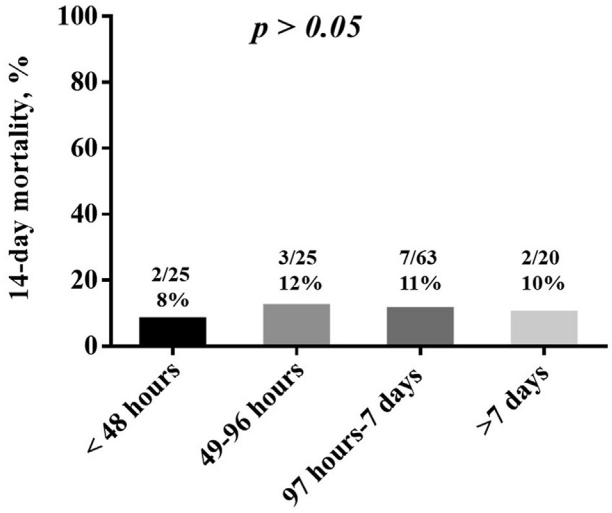


**Figure 2.** Fourteen-day mortality categorized by different time period from blood stream infection onset to appropriate antibiotic therapy.

other copathogens in blood that may bias our analysis. After analysis, we observed that patients with appropriate antibiotic therapy had a lower 14-day mortality. After propensity score matching to eliminate differences in baseline characteristics between the groups, the results were consistent. Using the cox regression model on original unmatched and matched cohorts, the appropriate antibiotic therapy remained a significant protective factor for 14-day mortality in addition to disease severity. Moreover, no effect of different appropriate antibiotic administration time on mortality was observed as shown in Fig. 2. Results from our study confirm the beneficial effects of antibiotic therapy, regardless of the time, on the outcomes of ICU patients with BSI. In a previous study involving ICU patients with *S. maltophilia* BSI, a similar trend that inappropriate antibiotic therapy was associated with poor outcomes, was reported. The relatively smaller sample size in that study (only 35 *S. maltophilia* BSI cases included), with a low statistical power, may have accounted for the insignificant effect of antibiotic therapy on the outcomes.[33] Among the studies focused on pneumonia caused by *S. maltophilia* in ICU, some studies revealed that antibiotic therapy may effect the clinical outcomes whereas others showed no such association.[21,22,35,36] The different ICU settings, respiratory copathogen diversity, and a heterogeneous population may explain the inconsistent effects of antibiotic therapy on the clinical outcomes in these studies. Considering the conflicting results observed in ICU patients with pneumonia, more research needs to be conducted in different hospitals to validate the significant results obtained in this study.

In previous clinical studies, mainly conducted on hospitalized patients with only a small proportion admitted in the ICU, levofloxacin showed similar efficacy as TMP/SMX in treating blood stream infection due to *S. maltophilia*.[15,16] Our study, however, revealed that levofloxacin based regimen may be better than TMP/SMX in treating patients with BSI due to *S. maltophilia*. Two reasons may explain the superiority of levofloxacin to TMP/SMX in our study. First, in vitro studies on bacterial killing demonstrated that the TMP/SMX therapy is bacteriostatic for *S. maltophilia* which may influence treatment efficacy on patients with severe invasive infection as BSI; Second, the average administrative dose of TMP/SMX in our study (median dosage of trimethoprim component 6.2 mg/kg) is lower than suggested dose (8—12 mg/kg) for *S. maltophilia* infection treatment, which may also impact outcomes.[37,38] Combinations with other in vitro active agents were suggested for serious *S. maltophilia* infection to achieve better efficacy of TMP/SMX.[17] In our study, only 4 patients were administered the levofloxacin and TMP/SMX combination therapy after the BSI onset, and all of them recovered, indicating promising efficacy of the combination therapy. Because of limited number of cases, further analysis could not be performed. Future prospective studies with larger number of patients to assess the beneficial outcomes of the TMP/SMX combination therapy in *S. maltophilia* BSI are warranted.

Despite the significant findings of this study, several limitations are acknowledged. First, the retrospective nature of the study may introduce selection and information bias. Moreover, with the patients admitted over a long period (from 2004 to 2019), unrecorded changes in some characteristics of the study population as well as in clinical medical practice may have biased the analyses. Second, although cases with polymicrobial *S. maltophilia* BSI were excluded and we chose 14-day mortality after BSI as the endpoint to accurately evaluate the effect of the antibiotic therapy, ICU patients usually have several concomitant medical or surgical conditions at the BSI onset. Theses co-occurring conditions, which were not considered in our study, may have impacted the clinical outcomes. Third, the effects of ceftazidime, another possible in vitro active agent against *S. maltophilia*, and other potentially effective drugs, such as tigecycline and colistin, were not evaluated due to the lack of drug susceptible data.[39,40] Combination effects of such antibiotics with TMP/SMX were also not assessed. Forth, susceptibility results for levofloxacin and TMP/SMX in this study based on commercial automated systems Vite2 have been reported inconsistent with those using reference broth microdilution method.[41] One study showed that Vite2 system may over-calling resistance in TMP/SMX susceptible isolates.[42] The categorical errors may existed in our study and might influence our analysis. Finally, our study was conducted only at a single center, which may limit the generality of the obtained results.

## Conclusion

The present study shows that appropriate antibiotic therapy is an independent predictor of 14-day mortality in patients with *S. maltophilia* BSI regardless of time. Levofloxacin may be more effective than TMP/SMX for treating ICU patients with *S. maltophilia* BSI. Our study may assist clinicians in the development of treatment strategies for ICU patients with BSI due to *S. maltophilia*.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.03.001.