

# The Activities of Antimicrobials Against *Stenotrophomonas maltophilia* Isolates and Evaluation of Clinical Outcomes Among Treatment Regimens in Patients with *Stenotrophomonas maltophilia* Infections: A Retrospective Multicenter Cohort Study

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**Purpose:** *Stenotrophomonas maltophilia*, a multidrug-resistant pathogen can cause hospital-acquired infections such as pneumonia, or bloodstream infection. *S. maltophilia* infection is associated with high mortality rates. This retrospective study examined the antimicrobial susceptibility profile of clinical *S. maltophilia* isolates and evaluated clinical outcomes, treatment regimens, and risk factors associated with 30-day mortality or treatment failure of *S. maltophilia* infections at three tertiary care hospitals in Central Thailand.

**Patients and Methods:** The characteristics, microbiological data, and clinical treatment outcomes were derived from medical records obtained from three tertiary care hospitals in Central Thailand from January 2017 to October 2022. The primary outcomes were treatment failure and 30-day mortality. The antimicrobial susceptibility rates of trimethoprim-sulfamethoxazole (TMP-SMX), levofloxacin, and ceftazidime were determined by minimum inhibitory concentration (MIC), which were based on broth microdilution and clear zone diameters using the disk diffusion method. However, we also report the susceptibility of minocycline and tigecycline in some clinical *S. maltophilia* strains (n = 149) and determined by MIC with E-test method.

**Results:** The antimicrobial susceptibility rates to TMP-SMX, levofloxacin, and ceftazidime were 97.1%, 93%, and 55.3%, respectively. The treatment failure rate and 30-day mortality were 66.3% and 49%, respectively. Significant factors associated with treatment failure included APACHE II score  $\geq 15$  (OR 3.37, 95% confidence interval (CI) 1.46–7.76), polymicrobial infections (OR 3.20, 95% CI 1.35–7.55). The significant factors associated with reduced treatment failure was treatment with TMP-SMX-based regimen (OR 0.29, 95% CI 0.11–0.76). The 30-day mortality rate was associated with APACHE II score  $\geq 15$  (OR 3.27, 95% CI 1.45–7.39) and septic shock (OR 2.53, 95% CI 1.36–4.69).

**Conclusion:** The results indicate a high mortality rate for *S. maltophilia* infection. The predictive factors for an unfavourable outcome were severity of illness, septic shock, and non-use of TMP-SMX. Therefore, a TMP-SMX-based regimen is recommended for the treatment of *S. maltophilia* infections.

**Keywords:** co-trimoxazole, levofloxacin, mortality, *Xanthomonas*

## Introduction

*Stenotrophomonas maltophilia* (formerly *Xanthomonas maltophilia*) is a lactose non-fermenting, aerobic gram-negative bacilli that lives in an aqueous-environment. It frequently colonizes on surfaces in a hospital environment, medical equipment, dialysis solutions, and overgrows in settings of broad-spectrum antibiotic use.<sup>1–3</sup> *S. maltophilia* is a multidrug-resistant pathogen and remains problematic worldwide. It is associated with hospital-acquired infections, particularly pneumonia, followed by bloodstream infections. It is rarely associated with intraabdominal, urinary tract, or skin/soft tissue infections.<sup>4</sup> Based on a previous systematic review in 2008, the overall mortality rate of *S. maltophilia* infections ranges from 21 to 69%.<sup>5</sup>

Risk factors for *S. maltophilia* infection include broad-spectrum antibiotics, admission to the intensive care unit (ICU), mechanical ventilator use, chronic respiratory diseases, haemodialysis, indwelling prosthetic devices, such as a central venous catheter, and immunocompromised status.<sup>6–10</sup> *S. maltophilia* is difficult to treat due to it can form a biofilm which is a crucial factor in the adherence of bacteria and protection from antimicrobial agents.<sup>11</sup> It also exhibits intrinsic resistance to various classes of antimicrobial agents, particularly  $\beta$ -lactams and aminoglycosides.<sup>12–14</sup>

The mainstay treatment of *S. maltophilia* infection is trimethoprim-sulfamethoxazole (TMP-SMX), which exhibits activity in respiratory tract samples and blood cultures (>90%), based on retrospectively reviewed 10-year data.<sup>15–17</sup> According to the Infectious Disease Society of America Guidance on the Treatment of *S. maltophilia* Infections,<sup>18</sup> the general approach for treating *S. maltophilia* infection may be divided into two approaches. First, monotherapy with TMP-SMX, minocycline, tigecycline, levofloxacin, or ceftiderocol is preferred for mild infection. Second, for moderate-to-severe infection, combination therapy with at least two of the above drugs is recommended until clinical improvement or treatment with TMP-SMX and adding a second agent if no response is observed. The use of ceftazidime is not recommended for the treatment of *S. maltophilia* regardless of severity, because *S. maltophilia* exhibits intrinsic  $\beta$ -lactamase production, which inactivates ceftazidime.<sup>18</sup>

There is a limitation to using TMP-SMX if a patient has a history of severe drug hypersensitivity, including Steven's Johnson syndrome, toxic epidermal necrolysis rendering the patient intolerable, or increased drug resistance.<sup>19–22</sup> In 2020, the National Antimicrobial Resistant Surveillance Centre of Thailand (NARST) reported the resistance of *S. maltophilia* to TMP-SMX of 6.6%–7.7%.<sup>23</sup> Therefore, levofloxacin was considered as the alternative treatment. The NARST also reported increasing fluoroquinolone-resistance of 10–12%,<sup>23</sup> although several studies have shown that treatment efficacy with fluoroquinolones was similar to that of TMP-SMX.<sup>24–26</sup>

High mortality rates, clinical characteristics, and treatment outcomes of *S. maltophilia* infections have been rarely reported, including in Thailand. Moreover, the optimal treatment regimens for *S. maltophilia* infection have not been clearly elucidated. In this study, we assessed the antimicrobial susceptibility profile of clinical *S. maltophilia* isolates and evaluated clinical outcomes, treatment regimens, and risk factors associated with 30-day mortality and treatment failure.

## Materials and Methods

### Study Design and Participants

This was a multicenter retrospective study. The characteristics, microbiological data, and clinical treatment outcomes were derived from medical records available from three tertiary care hospitals in Central Thailand from January 2017 to October 2022. *S. maltophilia* isolates were collected from sterile and non-sterile sites. All patients  $\geq 20$  years old were diagnosed with infection according to the definition of the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) surveillance definitions for specific types of infections.<sup>27</sup> They also experienced a first episode of *S. maltophilia* infection with a positive culture and complete medical records were eligible.

### Ethics Approval

This study was approved by all study centres including the Institutional Review Board Royal Thai Army Medical Department at Phramongkutklao College of Medicine and Phramongkutklao Hospital (Approval number Q029h/64), Declaration of Helsinki, The Belmont Report, CIOMS Guideline International Conference on Harmonization in Good Clinical Practice at the Ratchaburi Hospital (Approval number COA-RBHEC 030/2021), and the Research and Ethics

committee of the Nopparat Rajathanee Hospital (Approval number 3/2565, 5/2566). The informed consent was waived by the Institutional Review Board, due to retrospective design and deidentification of patient data.

## Data Collection and Treatment Outcomes

The demographic and clinical variable data including age, gender, body weight, serum creatinine, serum albumin, hospitalization unit, co-morbidities, critically ill status, immunocompromised status, source of infection, antimicrobial therapy (drug, dosing regimen), invasive medical devices, treatment outcomes, and in-hospital mortality were obtained from medical records. The primary outcome was treatment failure and 30-day mortality.

## Bacterial Identification and Antimicrobial Susceptibility

All of the clinical isolates were identified as *S. maltophilia* by Microflex LT MALDITOF-MS. Antimicrobial susceptibility testing was performed using the Sensititre<sup>TM</sup> Aris HiQ System (broth microdilution method) or the Kirby-Bauer disk diffusion method. The results of minimum inhibitory concentration (MIC) were based on broth microdilution, and clear zone diameters were determined by the disk diffusion method. However, we also report the susceptibility testing of minocycline and tigecycline in some clinical *S. maltophilia* strains (n = 149) by using Epsilometer method (E-test).

The antimicrobial susceptibility was interpreted by the Clinical and Laboratory Standards Institute version 2022 (CLSI).<sup>28</sup> Isolates were interpreted as “susceptible”, “intermediate”, or “resistant” to TMP-SMX, levofloxacin, ceftazidime and minocycline, while tigecycline was reported as MIC50 and MIC90 values, respectively, due to no susceptible breakpoints in the CLSI.

## Definitions

Empirical antibiotic therapy was defined as the first agents prescribed for the initial treatment which is effective or not on *S. maltophilia*. Documented antibiotic therapy was defined as the administration of the drug corresponding to the susceptibility of *S. maltophilia* stains. Monotherapy was defined as the administration of a documented regimen of either TMP-SMX, levofloxacin, ceftazidime, or tigecycline which is susceptible for *S. maltophilia* isolates for at least 48 hours following diagnosis of an *S. maltophilia* infection. Combination therapy was defined as a patient receiving a documented regimen of either TMP-SMX or levofloxacin in combination with another active agent or susceptible, such as minocycline, ceftazidime, tigecycline or a combination of TMP-SMX with levofloxacin. Creatinine clearance was calculated by the Cockcroft–Gault equation. Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores<sup>29</sup> were assessed from the data from all patients regardless of ICU status. The Charlson comorbidity score (CCI)<sup>30</sup> was calculated from comorbidity data extracted from medical records. Chronic respiratory diseases included chronic obstructive pulmonary disease (COPD), asthma, pulmonary fibrosis, cystic fibrosis, interstitial lung disease or lung cancer.<sup>31</sup> Septic shock was defined as life-threatening organ dysfunction, serum lactate levels >2 mmol/L, persisting hypotension despite adequate volume resuscitation, which required a vasopressor to maintain mean arterial pressure >65 mmHg.<sup>32</sup> Immunocompromised status was defined as a weakened immune system including immunosuppressant use, chemotherapy treatment, active treatment with high-dose systemic corticosteroids (eg, prednisolone 20 mg per day more than or equal 2 weeks), or HIV infection.<sup>33,34</sup>

Appropriate antibiotic agent was defined as the treatment of *S. maltophilia* with at least 1 active agent corresponding to the result of antimicrobial susceptibility of *S. maltophilia* isolate. Contrarily, inappropriate antibiotic agent was defined as a patient who received inactive agents against *S. maltophilia* based on antimicrobial susceptibility report. Treatment failure was defined as all causes of in-hospital mortality required to change or add alternative antimicrobial agents with in vitro susceptibility to *S. maltophilia* during therapy or positive repeat cultures after appropriate treatment within 72 h.<sup>35,36</sup>

## Statistical Analysis

Demographics and clinical treatment outcomes were analysed using the statistical software SPSS for Windows version 27 (IBM Corp., Armonk, NY, USA). Patient data and clinical characteristics were analysed with descriptive statistics. Continuous variables were tested using a Student's *t*-test or Mann–Whitney *U*-test. Categorical variables were tested using Chi-square or Fisher's exact test. Logistic regression analysis was used to determine factors associated with

treatment failure and 30-day mortality. The Log rank test was used to analyse survival data. Variables with a *P* value <0.1 by univariate analysis were subsequently entered into logistic regression models. *P* values <0.05 were considered statistically significant.

## Results

### Baseline Characteristics of Patients and Infections

Baseline characteristics of the patients and outcomes are listed in Table 1. Patients (*n* = 208) with a positive culture from January 2017 to October 2022 who met the definition for a specific type of infection were eligible for this study.<sup>27</sup> The median age was 69 years, 60% were male, 51.9% had septic shock, 71.6% were on a mechanical ventilator, and 18.8% were immunocompromised. The median CCI score was 5. The median severity scores assessed by the APACHE II and SOFA score were 19 and 6, respectively. One-hundred and sixty-nine patients (81.3%) received documented therapy for

**Table 1** Characteristics of Patients with *S. maltophilia* Infection (*n* = 208)

Characteristics	Values
Male, number (%)	125 (60)
Age (years), median (interquartile range; IQR)	69 (26)
Body weight (kg), median (IQR)	60 (20)
BMI (kg/m <sup>2</sup> ), median (IQR)	18.7 (3)
Serum creatinine (mg/dL), median (IQR)	1.2 (1.6)
Creatinine clearance (mL/min), median (IQR)	45.3 (62.2)
Serum albumin (g/dL), median (IQR)	2.61 (0.79)
Charlson comorbidity score (CCI), median (IQR)	5 (3)
Chronic respiratory diseases, median (IQR)	24 (11.5)
APACHE II score, median, (IQR)	19 (9)
SOFA score, median (IQR)	6 (5)
Septic shock, number (%)	108 (51.9)
Intensive care unit, number (%)	87 (41.8)
Haemodialysis, number (%)	33 (15.9)
Central venous catheters, number (%)	127 (61.1)
Mechanical ventilation, number (%)	149 (71.6)
Immunocompromised status, number (%)	39 (18.8)
Primary of infections	
Pneumonia, number (%)	127 (61.1)
Bloodstream infections, number (%)	69 (33.2)
Intraabdominal infections, number (%)	4 (1.9)
Urinary tract infections, number (%)	4 (1.9)
Skin and soft tissue infections, number (%)	3 (1.4)
Lung abscess, number (%)	1 (0.5)

(Continued)

Table I (Continued).

Characteristics	Values
<b>Microbials</b>	
<b>Mono-microbial infections (<i>S. maltophilia</i> only), number (%)</b>	96 (46.2)
<b>Treatment</b>	
<b>Documented antibiotic treatment regimens, number (%)</b>	169 (81.2)
<b>TMP-SMX-based regimen, number (%)</b>	53 (25.5)
Dose (mg/kg/day), median (IQR)	10.3 (5.10)
<b>Levofloxacin-based regimen, number (%)</b>	104 (50)
Dose (mg/kg/day), median (IQR)	11.5 (5.38)
<b>Monotherapy regimen or susceptible to <i>S. maltophilia</i>, number (%)</b>	159 (94.1)
TMP-SMX	44 (27.7)
Levofloxacin	98 (61.6)
Ceftazidime	14 (8.8)
Tigecycline	3 (1.9)
<b>Combination therapy regimen for <i>S. maltophilia</i>, number (%)</b>	10 (6)
TMP-SMX + levofloxacin	5 (50)
TMP-SMX + ceftazidime	2 (20)
TMP-SMX + tigecycline	1 (10)
TMP-SMX + minocycline	1 (10)
Levofloxacin + tigecycline	1 (10)
<b>Empirical antimicrobial therapy, number (%)</b>	185 (88.9)
Beta-lactams/beta-lactamase inhibitors	32 (17.3)
3rd generation cephalosporins	22 (11.9)
Carbapenems	76 (41.1)
Colistin	5 (2.7)
Fosfomycin	2 (1.1)
Tigecycline	1 (0.5)
Vancomycin	1 (0.5)
Colistin combination regimens	37 (20)
Tigecycline combination regimens	3 (1.6)
<b>Inappropriate treatment regimen for <i>S. maltophilia</i>, number (%)</b>	39 (18.8)
Beta-lactams/beta-lactamase inhibitors	10 (25.6)
3rd generation cephalosporins	2 (5.1)
Carbapenems	21 (53.8)
Colistin	3 (7.7)
Fosfomycin	1 (2.6)
Colistin combination regimens	2 (5.1)

**Abbreviations:** APACHE II, The Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ failure Assessment; TMP-SMX, trimethoprim-sulfamethoxazole.

*S. maltophilia* infection, whereas 39 patients (18.8%) received inactive treatment regimens. The most common infections were pneumonia 61.1% followed by bloodstream infection 33.2%. Among 208 cases of *S. maltophilia* infection, 46.2% were mono-microbial infections.

## Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing of 208 *S. maltophilia* clinical isolates revealed 97.1% susceptibility to TMP-SMX, 93% susceptibility to levofloxacin, and 55.3% susceptibility to ceftazidime. About 149 clinical isolates revealed 100% susceptibility to minocycline with and MIC50 and MIC90 of tigecycline were 0.25 and 0.75 µg/mL, respectively.

## Risk Factors Associated with *S. maltophilia* Infections and Treatment Outcomes

The treatment outcomes are shown in Table 2. The treatment failure and 30-day mortality rates were 66.3% and 49%, respectively. The microbiological cure rate was 100% among patients with bloodstream infections who repeat hemoculture (n = 63 cases). Comparing survival among the patient characteristics, the significant factors associated with 30-day mortality were age ≥69 years, hypoalbuminemia (<2.5 g/dL), CCI score >5, APACHE II ≥15, mechanical ventilation, and septic shock (Table 3).

Among antimicrobial treatment regimens, for the TMP-SMX-based versus levofloxacin-based regimen, the former was associated with significant factors for reducing treatment failure (Table 3). For dose regimens of both TMP-SMX or levofloxacin, mono or combination therapy, appropriate antibiotic agent or inappropriate antibiotic agent were not significant factors associated with 30-day mortality. However, the use of appropriate antibiotic agents against *S. maltophilia* tended to reduce the treatment failure rate compared with the use of inappropriate antibiotic agents ( $p = 0.099$ ).

## Factors Associated with 30-Day Mortality and Survival Time

Based on a logistic regression analysis, the significant factors associated with treatment failure were APACHE II score ≥15 (OR 3.37, 95% CI 1.46–7.76), polymicrobial infections (OR 3.20 95% CI 1.35–7.55), whereas use of a TMP-SMX-based regimen was significant to reduce treatment failure (OR 0.29, 95% CI 0.11–0.76). The 30-day mortality rate was associated with an APACHE II score ≥15 (OR 3.27, 95% CI 1.45–7.39) and septic shock (OR 2.53, 95% CI 1.36–4.69) (Table 3).

In a comparison of the Kaplan–Meier survival curves for treatment failure among the treatment regimens, we found that a TMP-SMX-based regimen was superior to a levofloxacin-based regimen ( $p < 0.001$ ) (Figure 1).

## Discussion

The characteristics, treatment outcomes, and factors associated with 30-day mortality were few reported in Thailand. Our study included 208 isolates of *S. maltophilia*, which were collected at three tertiary care hospitals in the centre of Thailand from January 2017 to October 2022. Isolates were collected from sterile and non-sterile sites with a diagnosis of *S. maltophilia* infection.

*S. maltophilia* is challenging to eradicate because there are only a few antimicrobial treatment options. Previous studies indicated that *S. maltophilia* infection is associated with high mortality rates ranging from 21% to 69%. In this study, the 30-day mortality rate was 49%, which is consistent with the previous study.<sup>35,37–41</sup>

**Table 2** The Treatment Outcomes of *S. maltophilia* Infections (n = 208)

Treatment Outcomes	Number (%)
Treatment failure	138 (66.3)
30-day mortality	102 (49)
<b>Microbiological outcomes</b>	
Microbiological cured (n=63)*	63 (100)

**Note:** \*Microbiological cure reported among patients with bloodstream infections who repeat hemoculture.

**Table 3** Factor Associated with Treatment Failure and 30-Day in Hospital Mortality of *S. maltophilia* Infections

Variables	Treatment Failure				30-Day Mortality			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age ≥69 years (n=106)	2.33 (1.29–4.22)	0.005*			2.27 (1.30–3.96)	0.004*		
Hypoalbuminemia (<2.5 g/dL) (n=75)	2.03 (1.08–3.83)	0.027*			1.94 (1.09–3.45)	0.023*		
CCI (>5) (n=88)	2.20 (1.20–4.06)	0.011*			1.66 (0.96–2.90)	0.071*		
APACHE II (≥ 15) (n=154)	6.23 (3.19–12.29)	<0.001*	3.37 (1.46–7.76)	0.004*	5.06 (2.47–10.36)	<0.001*	3.27 (1.45–7.39)	0.004*
Mechanical ventilation (n=149)	2.82 (1.51–5.27)	<0.001*			2.00 (1.08–3.72)	0.026*		
Septic shock (n=108)	2.72 (1.50–4.93)	<0.001*			3.43 (1.94–6.08)	<0.001*	2.53 (1.36–4.69)	0.003*
Immunocompromised status (n=39)	1.18 (0.56–2.49)	0.672			1.18 (0.59–2.37)	0.641		
<b>Primary infections</b>								
Respiratory tract infections (n=128)	2.26 (1.25–4.08)	0.006*			1.34 (0.77–2.35)	0.303		
Bacteraemia (n=69)	2.09 (1.14–3.82)	0.015*			1.21 (0.68–2.15)	0.523		
<b>Microbial</b>								
Polymicrobial infections (n=112)	3.07 (1.69–5.59)	<0.001*	3.20 (1.35–7.55)	0.008*	1.42 (0.82–2.46)	0.207		
Antibiotic regimen								
TMP-SMX-based regimen (n=53)	0.21 (0.11–0.41)	<0.001*	0.29 (0.11–0.76)	0.012*	0.53 (0.28–0.99)	0.047*	0.68 (0.34–1.38)	0.283
Levofloxacin-based regimen (n=104)	2.41 (1.33–4.37)	0.003*			1.21 (0.70–2.09)	0.488		
Ceftazidime (n=14)	1.93 (0.52–7.17)	0.316			1.02 (0.35–3.02)	0.970		

(Continued)



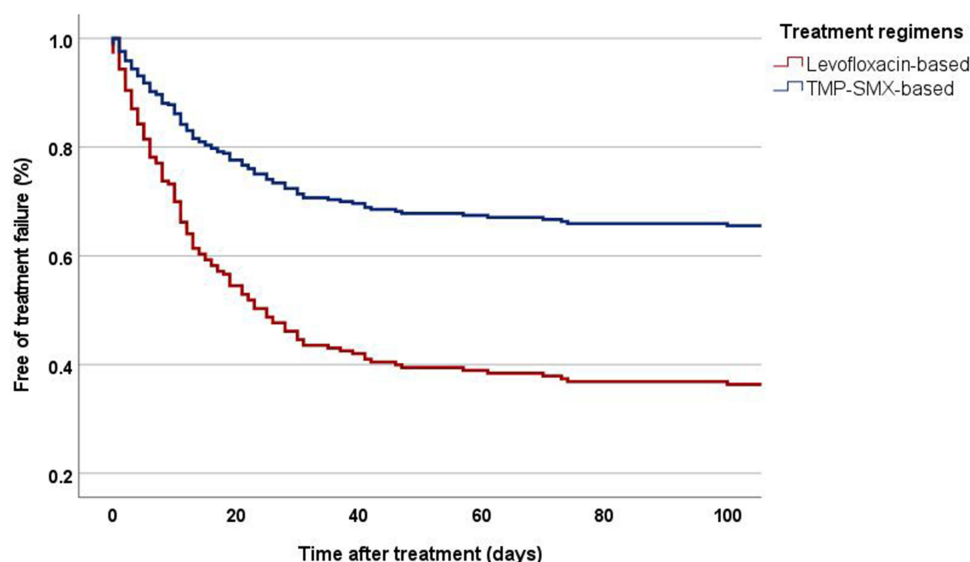
**Table 3** (Continued).

Variables	Treatment Failure				30-Day Mortality			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
<b>Between antibiotic regimen</b>								
Levofloxacin-based VS TMP-SMX-based	2.79 (1.37–5.68)	0.005*			1.75 (0.89–3.46)	0.106		
Ceftazidime VS TMP-SMX-based	3.27 (0.82–13.09)	0.093			1.65 (0.50–5.40)	0.408		
Levofloxacin-based VS ceftazidime	0.86 (0.22–3.34)	0.829			1.08 (0.35–3.30)	0.892		
Ceftazidime VS TMP-SMX-based or levofloxacin- based	1.74 (0.47–6.54)	0.409			1.14 (0.38–3.41)	0.814		
Monotherapy VS combination therapy	2.30 (2.47–11.18)	0.303			1.77 (0.48–6.50)	0.392		
Appropriate VS inappropriate antibiotic agent	0.63 (0.28–1.37)	0.243			0.55 (0.27–1.12)	0.099		
<b>Dosing regimen</b>								
TMP-SMX dosage < 10 mkd VS ≥ 10 mkd	0.86 (0.28–2.58)	0.782			1.02 (0.33–3.11)	0.974		
Levofloxacin dosage < 10 mkd VS ≥ 10 mkd	1.23 (0.45–3.29)	0.691			2.07 (0.84–5.13)	0.116		

**Notes:** Mann–Whitney U-test, logistic regression analysis. \*Defined as statistically significant test result ( $p < 0.05$ ).

**Abbreviations:** CCI, Charlson comorbidity score; APACHE II, The Acute Physiology and Chronic Health Evaluation; mkd, mg/kg/day; TMP-SMX, trimethoprim-sulfamethoxazole; OR, odds ratio; CI, confidence interval.





**Figure 1** Kaplan–Meier survival curve for treatment failure following the TMP-SMX and levofloxacin-based regimens.

Consistent with the increasing emergence of resistance described in previous reports,<sup>15–17</sup> the susceptibility rates to TMP-SMX and levofloxacin were 97.1% and 93%, respectively, in the present study. These susceptibility rates were similar to that reported by NARST in 2020, whereas the susceptibility rate of ceftazidime was low (55.3%). Thus, for the treatment of *S. maltophilia* infections in Thailand, TMP-SMX and levofloxacin are the recommended treatment options.

Among the hospitalized patients in this study, the most frequent *S. maltophilia* infections were pneumonia (61.1%) followed by bloodstream infections (33.2%). The baseline characteristics of patients in this study included chronic respiratory diseases (11.5%), immunocompromised status (18.8%) intensive care unit admission (41.8%), haemodialysis (15.9%), central venous catheters (61.1%), septic shock (51.9%), and mechanical ventilation (71.6%). The patients with severe illness had median APACHE II and SOFA scores of 19 and 6, respectively, which was similar to that of previous studies in which APACHE II and SOFA scores were 19 and 9, respectively.<sup>35,37–41</sup>

Several risk factors including ICU admission, broad-spectrum antibiotics, chronic respiratory disease, haemodialysis, central venous catheter and immunocompromised status were risk factors associated with mortality rates of *S. maltophilia* infections in previous studies.<sup>6–10</sup> However, our analysis found that these risk factors had no statistically significant association with mortality rates.

Risk factors have been associated with mortality to *S. maltophilia* infection in prior studies, including mechanical ventilator use, admission to the ICU, septic shock, high APACHE II score  $\geq 15$ , prolonged hospitalization, administration of broad-spectrum antimicrobials, and immunosuppressive status. However, there were also variables that we did not observe, such as admission to the ICU, prolonged hospitalization, immunocompromised status, and administration of broad-spectrum antibiotics.<sup>5,42</sup>

Risk factors significantly associated with 30-day mortality were APACHEII score  $\geq 15$  and septic shock. Furthermore, we found that a TMP-SMX-based regimen group was a protective factor for reduced 30-day mortality and treatment failure based on a logistic regression analysis. Kaplan–Meier survival curves showed a significant difference for the TMP-SMX-based regimen compared with levofloxacin-based regimen. From the meta-analysis and a systematic review,<sup>43</sup> there was no statistically significant difference between TMP-SMX and levofloxacin. In the present study, we defined a broader scope of treatment outcomes in terms of treatment failure, which contributed to a greater difference between regimens. However, further well-designed studies are needed to corroborate this data.

Comparison of the dosing regimens,  $\geq 10$  or  $<10$  mg/kg/day of trimethoprim was not significantly associated with mortality. We found significant treatment failure in the levofloxacin-based treatment group, which has been associated with higher mortality because of a higher severity of illness compared with a TMP-SMX-based regimen group.

Of the regimens, combination therapy has been used to improve clinical outcomes against isolates with limited therapeutic options or drug-resistant strains. In this study, only ten patients (6%) received combination therapy. Combination therapy was dependent on the severity of the illness, drug susceptibility in vitro, and designed to exhibit synergistic activity; therefore, the clinical outcome data for combination therapy were limited. However, from the results of this study, we recommend a TMP-SMX-based regimen with or without other additional agents to improve treatment outcomes for *S. maltophilia* infections. However, our study would like to support a robust data according to the Infectious Disease Society of America Guidance on the Treatment of *S. maltophilia* Infections about prefer using co-trimoxazole in mainstay of therapy either as monotherapy or preferably in combination with another active agent more than levofloxacin. Although our results for combination and monotherapy were not significantly different, there is a role for combination therapy in more favourable outcomes according to the current guidelines.<sup>18</sup>

This study had a limitation. The number of patients who received combination therapy was small, so we could not clearly assess the difference in mortality rate or treatment failure between monotherapy and combination therapy.

## Conclusion

The results indicate a high mortality rate for *S. maltophilia* infection. The predictive factors for an unfavourable outcome were severity of illness, septic shock, and non-use of TMP-SMX. Therefore, a TMP-SMX-based regimen is recommended for the treatment of *S. maltophilia* infections; however, further studies are needed to confirm these data.

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## Disclosure

The authors report no conflicts of interest.

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