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ORIGINAL ARTICLE

Comparisons between patients with trimethoprim–sulfamethoxazole-susceptible and trimethoprim–sulfamethoxazole-resistant *Stenotrophomonas maltophilia* monomicrobial bacteremia: A 10-year retrospective study

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bacteremia;
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Background/purpose: The impact of bacteremia due to the resistance of *Stenotrophomonas maltophilia* to trimethoprim–sulfamethoxazole (TMP–SXT) is uncertain. This study compared the clinical characteristics and outcomes of patients with TMP–SXT-susceptible (TSSSM) and TMP–SXT-resistant *S. maltophilia* (TSRSM) monomicrobial bacteremia.
Methods: The medical records of adult patients with TSSSM and TSRSM monomicrobial bacteremia from January 2004 to December 2013 were reviewed and classified into two groups, namely, TSSSM and TSRSM.
Results: There were 184 patients with monomicrobial *S. maltophilia* bacteremia. The mean age was 68.3 years. Most patients were males (72.8%), had high Charlson Comorbidity Index

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scores, previously prescribed antimicrobial agents, and indwelling medical devices. The 14-day and in-hospital mortality rates were 23.9% and 47.2%, respectively. There were 128 patients (69.6%) with TSSSM and 56 (30.4%) with TSRSM. The incidence of TSSSM bacteremia increased during the study period. The TSSSM and TSRSM groups had similar demographic and clinical characteristics and no significant differences in 14-day and in-hospital mortality (24.2% vs. 23.2%, $p = 0.833$; 50.0% vs. 41.1%, $p = 0.264$, respectively). Patients with TSSSM bacteremia had an increased risk of septic shock ($p = 0.044$) and neutropenia ($p = 0.028$) at bacteremia onset. Logistic regression analysis indicated that acquisition of TMP—SXT resistance was an independent risk factor for prolonged hospitalization ($p = 0.018$) and catheter-related *S. maltophilia* bacteremia was inversely associated with prolonged hospitalization after bacteremia ($p = 0.032$).

Conclusion: There were no significant differences in mortality for patients with TSSSM and TSRSM bacteremia, but patients with TSRSM bacteremia were associated with prolonged hospitalization after bacteremia onset.

Introduction

Stenotrophomonas maltophilia is a nonfermenting Gram-negative bacillus that has emerged as an important nosocomial pathogen primarily affecting immunocompromised patients.[1] Infection with this pathogen can manifest as pneumonia, bloodstream infection, wound infection, or urinary tract infection.[1] Treatment of these infections is difficult because *S. maltophilia* is intrinsically resistant to a variety of structurally unrelated antimicrobial agents, including β-lactams, cephalosporins, carbapenems, quinolones, and aminoglycosides although ticarcillin—clavulanic acid combination, some cephalosporins (ceftazidime, cefoperazone, and cefepime), and new fluoroquinolones seem to show effective *in vitro* activity against *S. maltophilia*.[2] Antibiotic resistance is mainly due to the presence of β-lactamases, efflux pump systems, enzymatic modification, outer membrane changes, and target site modification.[3]

Trimethoprim—sulfamethoxazole (TMP—SXT) is the drug of choice for susceptible *S. maltophilia* infections based on *in vitro* activity and anecdotal reports of favorable clinical outcomes.[2,4,5] However, recent antimicrobial susceptibility studies have reported the emergence of TMP—SXT-resistant *S. maltophilia* (TSRSM), in which resistance is mediated by acquisition of class 1 integrons and insertion element common region linked to the *sul*2 genes.[6—8] TSRSM species have been reported in Taiwan since 2000.[9] Infection by TSRSM species poses a major dilemma for the clinician because of the limited treatment options available, none of which have been validated clinically.[2,10,11]

Patients with *S. maltophilia* bacteremia often have polymicrobial infections and 20—40% of such infections are catheter related.[1] The bacteria most commonly recovered concomitantly with *S. maltophilia* are coagulase-negative staphylococci and enterococci.[12,13] Few studies on *S. maltophilia* bacteremia have excluded cases with polymicrobial bacteremia in order to eliminate confounding effects from other bacteria.[14,15] There have been no comparisons of patients with *S. maltophilia* bacteremia due to TSRSM and TMP—SXT-susceptible *S. maltophilia* (TSSSM).

We conducted a 10-year retrospective cohort study on the clinical characteristics and outcomes of patients with TSSSM and TSRSM monomicrobial bacteremia in our institute.

Methods

Study design and data collection

This study was conducted at the Tri-Service General Hospital, National Defense Medical Center, a 1700-bed a tertiary referral center in northern Taiwan. This 10-year retrospective cohort study examined patients who were hospitalized from January 1, 2004, to December 31, 2013. Medical charts were reviewed after obtaining the approval of the Institutional Review Board of the hospital (TSGHIRB approval number: 2-101-05-074). All patients with monomicrobial *S. maltophilia* bacteremia and with clinical symptoms or signs of infection were included for further analysis. Patients who had polymicrobial bacteremia or who were aged <18 years were excluded. If a patient had multiple episodes of bacteremia, only data from the first episode were included.

Definitions

S. maltophilia bacteremia was defined by the presence of a blood culture that yielded *S. maltophilia* from one or more collected blood samples. Hospital-acquired bacteremia was defined by a positive blood culture obtained from patients hospitalized for >48 hours after admission. Healthcare-associated bacteremia was defined by a positive blood culture obtained from patients within 48 hours of admission and fulfilled any of the standard criteria (e.g., residence in a nursing home).[16] Community-acquired bacteremia was defined by a positive blood culture obtained within the 48

hours after admission for patients who did not fit the criteria for a healthcare-associated infection.

The severity of illness was assessed by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. The Charlson Comorbidity Index (CCI) was used as an aggregate measure for comorbidities.[17] Septic shock was defined by the presence of a systolic blood pressure <90 mmHg or <30 mmHg below the baseline value, or when inotropic agents were required to maintain blood pressure with evidence of organ hypoperfusion at bacteremia onset. Use of antimicrobial agents prior to the bacteremia after admission was recorded. The source of bacteremia was determined according to the Centers for Disease Control and Prevention definitions.[18] The duration of hospitalization after bacteremia onset was defined as the time between the date of discharge and the date of the first positive blood culture. A prolonged hospitalization after bacteremia was defined as hospitalization of at least 28 days after bacteremia onset. Appropriate empiric therapy was defined as microorganism susceptibility to one of several antimicrobial agents administered within 72 hours after the onset of bacteremia.

Microbiology

The VITEK 2 automatic system for Gram-negative rods (bioMérieux Inc., Marcy-l'Étoile, France) was used to identify blood isolates of *S. maltophilia*. Susceptibility to TMP–SXT was measured according to the updated Clinical and Laboratory Standards Institute (CLSI) 2004 guideline for *S. maltophilia*.[19] When a TSRSM isolate was identified, its susceptibility to antimicrobial agents, including ceftazidime and ciprofloxacin, was tested with the disk diffusion method and interpreted according to the CLSI 2004 guideline[19] and previous study results.[20,21] In addition, the TSSSM isolates were tested with both agents upon a physician's request.

Statistical analysis

All results were analyzed using a commercially available software package (SPSS, version 16.0; SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using the Chi-square test or Fisher's exact test as appropriate. Continuous variables were compared using Student's *t* test. All *p* values were two tailed and a $p < 0.05$ was considered statistically significant. The effect estimates are reported as odds ratios (ORs) and 95% confidence intervals (CIs). Variables with $p < 0.05$ in the univariate logistic regression were incorporated into a multivariate logistic regression model to identify independent predictors of prolonged hospitalization. In the final multivariable models, a $p < 0.05$ was considered significant. The Cochran–Armitage trend test was used to determine whether there were increasing trends in the incidence of TSSSM and TSRSM bacteremia during the study period (calculated as number of TSSSM and TSRSM bacteremia per 100,000 discharges per year).

Results

There were 277 patients with *S. maltophilia* bacteremia at our institution in the past 10 years. We excluded three patients who were aged <18 years, 86 patients because of evidence of polymicrobial bacteremia, and four patients because of incomplete medical records. The study population therefore consisted of 184 patients with *S. maltophilia* monomicrobial bacteremia. Table 1 summarizes the clinical characteristics and outcomes of these patients. The mean age was 68.3 years and 72.8% of the patients were male. Most bacteremic episodes (165/184, 89.7%) were hospital acquired. The mean CCI was 4.1. A total of 149 patients (80.9%) were given at least one class of antimicrobial agent prior to the bacteremia, and the mean number of previous antimicrobial agents was 2.2. The main infectious sources identified were the respiratory tract and central venous catheters, but 45.7% of patients had bacteremia of unknown origin.

Table 2 summarizes the clinical outcomes of the enrolled patients. The 14-day mortality and in-hospital mortality rates were 23.9% and 47.2%, respectively. The mean duration of hospitalization was 27.4 days after bacteremia onset. Nearly half of the patients (45.1%) had prolonged hospitalizations (>28 days) after bacteremia onset.

Among 184 patients with *S. maltophilia* monomicrobial bacteremia, 128 (69.6%) were caused by TSSSM and 56 (30.4%) were caused by TSRSM. There was a significant trend for increasing incidence of *S. maltophilia* bacteremia (Cochran–Armitage test for trend, $p < 0.001$) during the study period. An analysis of the incidence of TSSSM and TSRSM bacteremia indicated an increasing incidence of TSSSM bacteremia (Cochran–Armitage test for trend, $p < 0.001$) but not TSRSM bacteremia (Cochran–Armitage test for trend, $p = 0.324$, Fig. 1).

The TSRSM and TSSSM groups had similar demographic and clinical characteristics (Table 1). There was a slightly higher rate of mechanical ventilation in the TSRSM group and slightly more males in the TSSSM group, but these differences were not significant ($p = 0.073$ and $p = 0.085$, respectively). Disease severity at bacteremia onset was evaluated by the APACHE II score and the presence of thrombocytopenia, neutropenia, and septic shock. Patients in the TSSSM group had a higher risk of development of septic shock ($p = 0.044$) and neutropenia ($p = 0.028$; Table 1). The TSSSM and TSRSM groups had no significant differences in 14-day mortality and in-hospital mortality (Table 2). The duration of hospitalization after bacteremia onset was greater in the TSRSM group, but this was not significant (32.9 days vs. 24.9 days, $p = 0.126$). Patients in the TSRSM group were more likely to have prolonged hospitalization ($p = 0.030$). Among the 56 blood isolates of TSRSM, 16 (28.5%) were susceptible to ceftazidime and four isolates (7.1%) were susceptible to ciprofloxacin. The rate of appropriate empiric antimicrobial therapy was higher in the TSSSM group than in the TSRSM group (15/128 vs. 0/56, $p = 0.006$). Among the 15 patients with TSSSM bacteremia who received appropriate empiric antimicrobial therapy, four received ceftazidime and 11 received TMP–SXT. None of the TSRSM patients received appropriate empiric antimicrobial therapy.

Finally, we determined factors that were significantly associated with prolonged hospitalization and in-hospital mortality by use of logistic regression analysis (Table 3). The initial univariate analysis indicated that variables significantly associated with prolonged hospitalization were the presence of TSRSM, mechanical ventilation at bacteremia

Table 1 Demographic and clinical characteristics of patients with *Stenotrophomonas maltophilia* monomicrobial bacteremia

Variable	TSSSM (n = 128, 69.6%)	TSRSM (n = 56, 30.4%)	p[e]	All (n = 184)
General features, *n* (%)				
Age, y	68.1 (17.9)	68.8 (17.9)	0.796	68.3 (17.9)
No. (%) of males	98 (76.6)	36 (64.3)	0.085	134 (72.8)
Community-acquired	3 (2.3)	0 (0)	0.554	3 (1.6)
Healthcare-associated	13 (10.2)	3 (5.4)	0.398	16 (8.7)
Hospital-acquired	112 (87.5)	53 (94.6)	0.191	165 (89.7)
Previous surgery prior to the bacteremia episode after admission	35 (27.3)	18 (32.1)	0.508	53 (28.8)
Length of hospital stay prior to bacteremia[a]	25.2 (24.0)	30.6 (25.7)	0.173	26.8 (24.6)
Mechanical ventilation	76 (59.4)	41 (73.2)	0.073	117 (63.6)
Indwelling central venous catheters[b]	94 (73.4)	41 (73.2)	0.975	135 (73.4)
Comorbidity, *n* (%)				
Previous cerebral disease	29 (22.7)	11 (19.6)	0.648	40 (21.7)
Coronary artery disease	33 (25.8)	11 (19.6)	0.369	44 (23.9)
Renal insufficiency[c]	43 (33.6)	13 (23.2)	0.159	56 (30.4)
Chronic obstructive pulmonary disease	17 (13.3)	8 (14.3)	0.855	25 (13.6)
Liver cirrhosis	7 (5.5)	3 (5.4)	1.000	10 (5.4)
Type 2 diabetes mellitus	37 (28.9)	17 (30.4)	0.862	54 (29.3)
Malignancy	50 (39.1)	20 (35.7)	0.667	70 (38.0)
Charlson Comorbidity Index	4.08 (2.26)	4.3 (3.05)	0.634	4.1 (2.5)
Prior antimicrobial agent use, *n* (%)				
Antipseudomonal penicillin-lactamase inhibitor	42 (32.8)	23 (41.1)	0.281	65 (35.3)
3rd-generation cephalosporin	41 (32.0)	21 (37.5)	0.470	62 (33.6)
4th-generation of cephalosporin	41 (32.0)	20 (35.7)	0.625	61 (33.1)
Carbapenem	61 (47.7)	25 (44.6)	0.706	86 (46.7)
Glycopeptide	49 (38.3)	20 (35.7)	0.741	69 (37.5)
Fluoroquinolone	36 (28.1)	17 (30.4)	0.758	53 (28.8)
Trimethoprim—sulfamethoxazole	8 (6.2)	6 (10.7)	0.365	14 (7.6)
No. of antibiotics used prior to bacteremia[a]	2.2 (1.6)	2.4 (1.6)	0.479	2.2 (1.6)
Clinical condition at bacteremia onset, *n* (%)[c]				
Thrombocytopenia[c]	47 (36.7)	21 (37.5)	0.920	68 (37.0)
APACHE II score	21.6 (9.8)	21.9 (7.3)	0.859	21.7 (9.1)
Neutropenia[c]	15 (11.7)	1 (1.8)	0.028	16 (8.7)
Septic shock	33 (25.8)	7 (12.5)	0.044	40 (21.7)
Primary source of bacteremia				
Respiratory tract	49 (38.3)	23 (41.1)	0.721	72 (39.1)
Central venous catheter-related	14 (10.9)	8 (14.3)	0.520	22 (12.0)
Unknown origin	59 (46.1)	25 (44.6)	0.856	84 (45.7)
Others[d]	6 (4.7)	1 (1.8)	0.677	7 (3.8)

[a] Data are presented as mean (standard deviation).
[b] Double-lumen catheter for hemodialysis, central venous catheters, peripherally inserted central catheter included.
[c] Thrombocytopenia was diagnosed by a platelet count <100,000/mL, neutropenia by an absolute neutrophil count <1500/μL, and renal insufficiency by a serum creatinine level >2 mg/dL.
[d] Five cases had abdominal origin, two cases were from wounds.
[e] For comparison of the TMP—SXT-susceptible *S. maltophilia* and TMP—SXT-resistant *S. maltophilia* groups.
APACHE II = Acute Physiologic and Chronic Health Evaluation II score; TMP—SXT = trimethoprim—sulfamethoxazole; TSRSM = TMP—SXT-resistant *S. maltophilia*; TSSSM = TMP—SXT-susceptible *S. maltophilia*.

onset, septic shock at bacteremia onset, thrombocytopenia, and APACHE II score but catheter-related infection was inversely associated with prolonged hospitalization ($p < 0.05$ for all, Table 3). The results of multivariate analysis indicated that prolonged hospitalization was independently associated with the presence of TSRSM (OR = 2.349, $p = 0.018$) and inversely associated with catheter-related *S. maltophilia* bacteremia (OR = 0.285, $p = 0.032$).

The initial univariate analysis indicated that mechanical ventilation, septic shock, thrombocytopenia, APACHE II score, and neutropenia at bacteremia onset and *S. maltophilia* bacteremia resulting from respiratory tract infections were significantly associated with in-hospital mortality ($p < 0.05$ for all, Table 3). The results of multivariate analysis indicated that only the APACHE II score and thrombocytopenia were independently associated with in-

Table 2 Antimicrobial therapy and clinical outcomes of patients with *Stenotrophomonas maltophilia* monomicrobial bacteremia

Variable	TSSSM (n = 128)	TSRSM (n = 56)	p[b]	All (n = 184)
Antimicrobial therapy, *n* (%)				
Appropriate empiric antimicrobial therapy	15 (11.7)	0 (0)	0.006	15 (8.1)
Clinical outcome, *n* (%)				
14-d mortality	31 (24.2)	13 (23.2)	0.833	44 (23.9)
In-hospital mortality	64 (50.0)	23 (41.1)	0.264	87 (47.2)
Duration of hospitalization after bacteremia onset[a]	24.9 (23.2)	32.9 (35.3)	0.126	27.4 (27.6)
Prolonged hospital stay (≥28 d after bacteremia)	51 (39.8)	32 (57.1)	0.030	83 (45.1)

[a] Data are presented as mean (standard deviation).
[b] For comparison of the TMP–SXT-susceptible *S. maltophilia* and TMP–SXT-resistant *S. maltophilia* groups.
TMP–SXT = trimethoprim–sulfamethoxazole; TSRSM = TMP–SXT-resistant *S. maltophilia*; TSSSM = TMP–SXT-susceptible *S. maltophilia*.

hospital mortality (OR = 1.151 and OR = 4.430, and $p < 0.001$, respectively, Table 3).

Discussion

This 10-year retrospective cohort study analyzed the records of 184 patients with *S. maltophilia* monomicrobial bacteremia. To our knowledge, this is the largest retrospective observational study of *S. maltophilia* bacteremia. We compared cases with TSRSM and TSSSM bacteremia after exclusion of patients with polymicrobial bacteremia, and such a comparison has not been made in any other studies to date. In our study, the incidence of TSSSM bacteremia increased during the 10-year study period. Although there was no difference in 14-day mortality and in-hospital mortality in the TSSSM and TSRSM groups, patients with TSRSM bacteremia were associated with prolonged hospitalization than the TSSSM group after bacteremia onset.

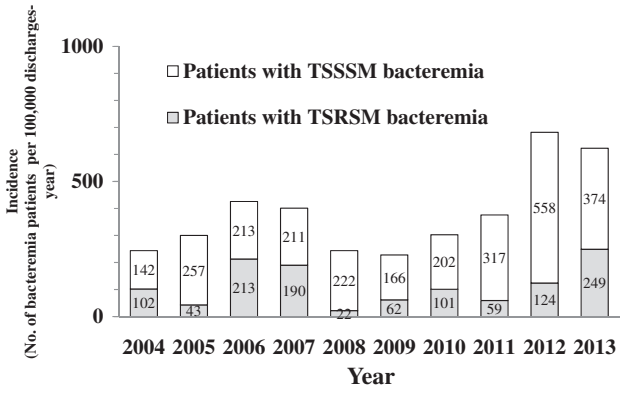

Figure 1. Incidence of TSSSM and TSRSM monomicrobial bacteremia from 2004 to 2013 at the Tri-Service General Hospital, National Defense Medical Center (Taipei, Taiwan). For each year from 2004 to 2013, there were 7, 12, 10, 10, 10, 8, 10, 16, 27, and 18 patients with TSSSM bacteremia, and 5, 2, 10, 9, 1, 3, 5, 3, 6, and 12 patients with TSRSM bacteremia. For each year from 2004 to 2013, there were 49,260, 46,620, 46,876, 47,363, 44,961, 48,189, 49,454, 50,502, 48,362, and 48,115 discharged patients. The Cochran–Armitage Trend test indicated a significant increase in TSSSM bacteremia ($p < 0.001$), but not in TSRSM bacteremia ($p = 0.324$). TMP–SXT = trimethoprim–sulfamethoxazole; TSRSM = TMP–SXT-resistant *S. maltophilia*; TSRSM = TMP–SXT-susceptible *S. maltophilia*.

The results of this study indicated that patients with *S. maltophilia* bacteremia tended to have prolonged hospitalization prior to bacteremia onset, previous use of antimicrobial agents, use of an indwelling medical device, and compromised health status (high CCI), which are in agreement with the results of previous studies.[1,22,23] Of note, most of our included cases had healthcare-associated and hospital-acquired bacteremia, suggesting that exposure to extensive healthcare system was a major risk factor for *S. maltophilia* bacteremia. Although our prevalence of hospital-acquired *S. maltophilia* bacteremia was higher than that in a tertiary hospital in southern Taiwan [165/184 (89.7%) vs. 94/153 (61.4%), respectively],[24] it was similar to those in two hospitals in northern Taiwan [64/84 (76%) and 46/50 (92%), respectively].[25,26]

The primary sources of *S. maltophilia* bacteremia were the respiratory tract and intravascular catheters, possibly because a high percentage of the included patients were ventilator dependent and had indwelling intravascular catheters. Patients with TSRSM and TSSSM bacteremia had comparable general demographic and clinical characteristics, comorbidities, sources of bacteremia, and previous use of antimicrobial agents. We observed that TSRSM bacteremia had a trend toward occurring in ventilator-dependent patients. This is consistent with a previous study claiming that patients requiring prolonged mechanical ventilation tend to become reservoirs of antimicrobial resistance.[27] The relation with environment factor (e.g., intensive care unit, respiratory care center (RCC)) should be considered in this association.

The APACHE II scores and incidence of thrombocytopenia at bacteremia onset were similar in the TSRSM and TSSSM groups. However, the rates of septic shock and neutropenia were higher in the TSSSM group than in the TSRSM group, suggesting that TSSSM is more virulent than TSRSM. Resistance acquisition in many microorganisms associated with virulence changes linked to clinical infectious diseases had been reported previously.[28] In some cases, the increased antimicrobial resistance is associated with reduced virulence, such as the acquisition of β-lactamases in *Escherichia coli* and the acquisition of vancomycin resistance in methicillin-resistant *Staphylococcus aureus*.[29,30] This may

Table 3 Logistic regression analysis of factors associated with in-hospital mortality and prolonged hospitalization (≥28 d after bacteremia onset) in patients with *Stenotrophomonas maltophilia* monomicrobial bacteremia

Variable	In-hospital mortality				Prolonged hospitalization			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Age, y	1.013 (0.996–1.030)	0.134			1.004 (0.987–1.020)	0.661		
TSRSM	0.697 (0.369–1.315)	0.265			2.013 (1.065–3.805)	0.031	2.349 (1.161–4.753)	0.018
Previous surgery	0.646 (0.338–1.236)	0.187			1.010 (0.532–1.917)	0.976		
Mechanical ventilation	8.185 (3.945–16.981)	<0.001	2.302 (0.824–6.430)	0.112	3.403 (1.773–6.530)	<0.001	1.508 (0.674–3.373)	0.317
Clinical condition								
Septic shock	5.413 (2.398–12.219)	<0.001	2.146 (0.742–6.204)	0.159	2.835 (1.365–5.885)	0.005	1.805 (0.778–4.187)	0.169
Neutropenia	3.720 (1.153–12.007)	0.028	4.345 (0.784–24.072)	0.093	2.933 (0.976–8.816)	0.055		
Thrombocytopenia	8.522 (4.237–17.141)	<0.001	4.430 (1.906–10.300)	0.001	2.201 (1.196–4.409)	0.011	1.462 (0.719–2.975)	0.295
APACHE II score (per 1-point increment)	1.204 (1.137–1.274)	<0.001	1.151 (1.074–1.233)	<0.001	1.078 (1.039–1.119)	<0.001	1.048 (0.999–1.099)	0.053
Comorbidity								
Charlson Comorbidity Index	1.016 (0.906–1.140)	0.780			0.988 (0.880–1.108)	0.831		
Source of bacteremia								
Respiratory tract	2.292 (1.252–4.195)	0.007	1.496 (0.667–3.352)	0.328	1.261 (0.696–2.286)	0.444		
Central venous catheter-related	0.478 (0.185–1.235)	0.128			0.317 (0.112–0.899)	0.031	0.285 (0.090–0.899)	0.032
Unknown origin	0.659 (0.367–1.183)	0.163			1.439 (0.802–2.582)	0.222		
Antimicrobial therapy								
Appropriate empiric antimicrobial therapy	1.302 (0.452–3.752)	0.625			0.414 (0.127–1.353)	0.144		

APACHE II = Acute Physiologic and Chronic Health Evaluation II score; CI = confidence interval; TMP–SXT = trimethoprim–sulfamethoxazole; TSRSM = TMP–SXT-resistant *S. maltophilia*.

possibly explain the different clinical presentations of patients in the two groups in our study, although we did not specifically examine the relationship between changes in virulence and acquisition of resistance in *S. maltophilia*.

Previous studies reported that the crude mortality associated with *S. maltophilia* bacteremia ranged from 23% to 69%, depending on the study population.[15,31] In our study, the 14-day and in-hospital mortality rates were 23.9% and 47.2%, respectively. There were no statistical differences in 14-day and in-hospital mortality of the TSRSM and TSSSM groups. In addition, it was also shown that the APACHE II score and thrombocytopenia were associated with in-hospital mortality. Previous studies showed that TSRSM infection was associated with serious morbidity rather than in-hospital mortality in debilitated patients, and that organ dysfunction was significantly associated with mortality in TSRSM infections.[32,33] Our study strengthened the previous conclusions that TSRSM infection was not associated with increased mortality, even in patients with bloodstream infections.

Patients with TSRSM bacteremia had a higher rate of prolonged hospitalization after bacteremia onset than those with TSSSM bacteremia. Further analysis of risk factors associated with prolonged hospitalization indicated that TSRSM bacteremia was the only factor significantly associated with prolonged hospitalization. We anticipated that prolonged hospitalization would be associated with increased morbidity and possibly higher costs of care although we did not analyze hospital costs in this study. Previous studies regarding the impact of other multiple drug-resistant Gram-negative bacterial infections indicated that multidrug resistance was associated with longer hospitalization and greater mortality.[34–37] Our study results are in agreement with existing evidence that infections caused by multidrug-resistant bacteria are associated with increased financial burdens in healthcare systems.

Our study also showed that catheter-related *S. maltophilia* bacteremia was inversely associated with prolonged hospitalization (OR = 0.285, $p = 0.032$). This finding is consistent with previous studies, which reported that catheter-related *S. maltophilia* bacteremia was associated with reduced mortality, possibly because most such cases are less complicated and respond well following removal of the infected catheter.[26,38,39] Thus, our results support the need for careful evaluation of indwelling catheters in patients who present with *S. maltophilia* bacteremia, and that early removal of infected catheters is crucial to improve the outcomes of such patients.

Among patients with *S. maltophilia* infections, the prevalence of TSRSM is 2% in medical centers in Latin America, 10% in Europe, and 8% in the Asia-Pacific region.[7] A previous study of antimicrobial resistance in blood isolates of *S. maltophilia* in Taiwan from 1998 to 2008 showed that 85.4% of isolates were susceptible to TMP–SXT.[40] Recent studies, however, reported that the TMP–SXT susceptibility of *S. maltophilia* in southern Taiwan was only 68.9%.[24] In agreement with these most recent results, we found that 69.6% of our isolates were susceptible to TMP–SXT. Based on recent antimicrobial susceptibility results of blood isolates of *S. maltophilia* and the results reported here,[24] we suggest that clinicians in Taiwan should use TMP–SXT as empirical therapy with caution for patients when *S. maltophilia* infections were suspected, because of high frequency of TMP–SXT resistance. Continued surveillance and additional research should focus on potentially effective alternatives to TMP–SXT for the treatment of *S. maltophilia* infections. Recent studies had shown that TMP–SXT in combination with other antimicrobial agents as ceftazidime or ciprofloxacin was more active than treatment with TMP–SXT alone.[41] Although clinical benefit of such combination therapy has not been validated, it may be considered a therapeutic option to TSRSM infection.[33]

Suitable methods of *S. maltophilia* susceptibility testing evolved significantly over the past decade. In the CLSI 2004 guideline, *S. maltophilia* and *Pseudomonas aeruginosa* shared the same interpretive criteria of zone diameter and minimum inhibitory concentration (MIC) of antibiotics including TMP–SXT, ceftazidime, and ciprofloxacin.[19] Although TMP–SXT is shown to exhibit good correlation between both tests,[42] broth microdilution test, instead of disk diffusion method, is preferred for determining susceptibility against ciprofloxacin and ceftazidime on *S. maltophilia*.[43,44] Therefore, the CLSI 2014 guideline recommended only MIC for ceftazidime, disk diffusion, and/or broth microdilution for TMP–SXT, and no more test for ciprofloxacin.[45]

There are a few limitations in this study. This investigation was a retrospective design, and so there may have been some selection and observational bias. In addition, not all of the isolates were available. Other potentially active agents with *in vitro* effects against *S. maltophilia*, such as levofloxacin, ticarcillin–clavulanic acid, minocycline, and chloramphenicol, were not tested in our hospital and estimates of their clinical effects are unavailable. Finally, we used standards for antimicrobial susceptibility testing of ceftazidime and ciprofloxacin according to the CLSI 2004 guideline, not according to the CLSI 2014 guideline.

In conclusion, patients with TSSSM monomicrobial bacteremia were more likely to develop septic shock and neutropenia at bacteremia onset than those with TSRSM monomicrobial bacteremia. Although there were no significant differences in 14-day and in-hospital mortality rates, patients with TSRSM were more likely to have prolonged hospitalization than those with TSSSM.

Conflicts of interest

The authors have no conflicts of interest to declare.

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