Journal of Microbiology, Immunology and Infection 55 (2022) 107—113

Available online at www.sciencedirect.com

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Original Article

Emergence of concurrent levofloxacin- and trimethoprim/sulfamethoxazole-resistant *Stenotrophomonas maltophilia*: Risk factors and antimicrobial sensitivity pattern analysis from a single medical center in Taiwan

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Received 27 September 2020; received in revised form 17 November 2020; accepted 15 December 2020
Available online 13 January 2021

KEYWORDS
Risk;
Resistance;
Stenotrophomonas maltophilia,
levofloxacin;
Trimethoprim/sulfamethoxazole

Abstract *Background:* The emergence of concurrent levofloxacin- and trimethoprim/sulfamethoxazole (TMP/SMX)-resistant *Stenotrophomonas maltophilia* (LTSRSM) in Taiwan is becoming a serious problem, but clinical data analysis on this has not been reported.
Methods: A matched case-control-control study was conducted to investigate risk factors for LTSRSM occurrence in hospitalized patients. For patients with LTSRSM infection/colonization (the case group), two matched control groups were used: control group A with levofloxacin- and TMP/SMX-susceptible *S. maltophilia* (LTSSSM) and control group B without *S. maltophilia*. Besides, tigecycline, ceftazidime, cefepime, ciprofloxacin, gentamicin, amikacin, and colistin susceptibilities in collected LTSRSM and levofloxacin- and TMP/SMX-susceptible *S. maltophilia* (LTSSSM) isolates were compared.
Results: From January 2014 to June 2016, 129 LTSRSM from cultured 1213 *S. maltophilia* isolates (10.6%) were identified. A total of 107 LTSRSM infected patients paired with 107 LTSSSM-, and 107 non-*S. maltophilia*-infected ones were included. When compared with control group A, previous fluoroquinolone and TMP/SMX use was found to be independently

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https://doi.org/10.1016/j.jmii.2020.12.012

associated with LTSRSM occurrence. When compared with control group B, mechanical ventilation, cerebrovascular disease, and previous fluoroquinolone use were risk factors for LTSRSM occurrence. Eighty-five LTSRSM and 85 LTSSSM isolates were compared for antibiotic susceptibilities; the resistance rates and minimum inhibitory concentrations of tigecycline and ceftazidime were significantly higher for LTSRSM than for LTSSSM isolates.
Conclusion: The emergence of LTSRSM showing cross resistance to tigecycline and ceftazidime would further limit current therapeutic options. Cautious fluoroquinolone and TMP/SMX use may be helpful to limit such high-level resistant strains of *S. maltophilia* occurrence.

Introduction

Stenotrophomonas maltophilia, a non-fermenting gram-negative bacterium, is an important nosocomial pathogen in hospital settings.[1] In recent years, several worldwide surveillance studies have detected increasing infection rates of this bacterium in an expanding population of patients who were immunocompromised due to advances in medical technologies and treatments.[2] Although of low virulence, *S. maltophilia* can cause a wide range of infections including the respiratory system, bloodstream, skin and soft tissue, bone and joints, biliary tract, and urinary tract in immunocompromised patients.[3] Treatment of these infections is difficult because *S. maltophilia* exhibits extensive resistance to a variety of antibiotics.[2] Different resistance mechanisms, including inducible β-lactamases L1 and L2, aminoglycoside-modifying enzymes, and overexpression of multidrug efflux pumps, render *S. maltophilia* resistant to multiple structurally unrelated antibiotics.[2] As a consequence, the World Health Organization has listed *S. maltophilia* as one of the multidrug-resistant bacteria in hospital settings.[4] Trimethoprim/sulfamethoxazole (TMP/SMX) is considered the drug of choice for treating susceptible *S. maltophilia* infections and has been widely used for many years based upon reported *in vitro* activity and favourable clinical outcomes.[5,6] As alternatives to TMP/SMX, fluoroquinolones may be considered for patients infected with TMP/SMX-resistant *S. maltophilia* or those intolerant to TMP/SMX due to adverse drug effects. Recent studies comparing treatments with fluoroquinolones and TMP/SMX have suggested that fluoroquinolones have similar efficacy but fewer adverse drug effects than TMP/SMX.[7,8] Nevertheless, the clinical efficacy of fluoroquinolones other than levofloxacin still needs to be validated due to the limited number of clinical studies reported and the current lack of clinical breakpoints.

Although the resistance rates to levofloxacin or TMP/SMX vary geographically, longitudinal global surveillance reports have revealed that this resistance has generally remained less than 10%.[9] In recent years, increased resistance rates of *S. maltophilia* to TMP/SMX or levofloxacin have been observed in several countries from local surveillance reports.[10–15] In Taiwan, a more worrisome phenomenon was noted in which resistance rates of *S. maltophilia* to both TMP/SMX and levofloxacin were elevated in nationwide surveillance reports.[16] Furthermore, analysing antibiotic susceptibilities of such resistant strains revealed that TMP/SMX-resistant *S. maltophilia* isolates often exhibited concurrent levofloxacin resistance and vice versa.[16–19] This feature of *S. maltophilia*, where mutation-driven resistance to one antibiotic results in cross-resistance to others, has also been observed in experimental evolution studies under laboratory settings.[20] The emergence of such strains showing both levofloxacin and TMP/SMX resistance would further limit therapeutic options in treating *S. maltophilia* infections, and this may become a public health concern in the future. This alarming phenomenon underscores an urgent need for effective control and prevention measures that could combat further dissemination. We therefore initiated a matched case-control-control study to identify risk factors for concurrent levofloxacin- and TMP/SMX-resistant *S. maltophilia* (LTSRSM) infections among hospitalized patients. Moreover, the antibiotic susceptibilities of resistant and susceptible strains were analysed and compared.

Methods

Study setting, design, and patient identification

This study was conducted at the Tri-Service General Hospital, which is a medical center with 1800 beds located in northern Taiwan. The study period was from January 2014 to June 2016. The approval of Institutional Review Board of the hospital (TSGHIRB approval number: 2-101-05-074). To assess risk factors for LTSRSM occurrence, a 1:1:1 matched case-control-control design was used. Adult inpatients (>18 years old) infected/colonized with LTSRSM and those infected/colonized with levofloxacin- and TMP/SMX-susceptible *S. maltophilia* (LTSSSM) were identified via a computerized medical records system and classified as the case group and control group A, respectively. Patients infected/colonized with *S. maltophilia* that showed intermediate resistance to levofloxacin were categorized in the case group for analysis. For patients with multiple episodes of *S. maltophilia* infection/colonization, only the first was included. The control group B patients were selected from the inpatient population without *S. maltophilia* during their hospital stay. Patients with *S. maltophilia* isolated less than 48 h after admission or those younger than 18 years of age were excluded. The case group was matched to control

group A by age (within 5 years), sex, and the site of isolation. The criteria for matching the case group to control group B included age (within 5 years), sex, and time at risk. Once several eligible controls were identified, they were randomly chosen using Microsoft Excel 2013® software (Microsoft Corp., Redmond, WA, USA).

Relevant clinical data and definitions

The clinical information from identified patients was retrieved from a computerized medical records system. Possible risk factors were recorded including the following: age, sex, time at risk, recent admission and intensive care unit (ICU) records, recent chemotherapy and surgery, comorbidities, previous antimicrobial exposure, and indwelling medical devices. In the case group and control group A, the time at risk was defined as the number of days elapsed from patient admission to the date of the first *S. maltophilia* isolation. In control group B, the time at risk was defined as the number of days from patient admission to discharge. Previous antibiotic exposure in the case group and control group A was defined as at least 24 h of therapy within two weeks before *S. maltophilia* isolation. In control group B, previous antibiotic exposure was defined as 24 h of therapy within two weeks prior to discharge. Recent therapeutic measures were defined as having occurred 30 days before *S. maltophilia* isolation in patients in the case group and control group A; in control group B, recent therapeutic measures were defined as having occurred 30 days before index discharge. Indwelling invasive medical devices used before *S. maltophilia* isolation in the case group and control group A were recorded. For control group B, indwelling invasive medical devices used before discharge were recorded.

Microbiologic methods

We analysed the antibiotic susceptibilities of 85 consecutive, non-duplicated preserved isolates of LTSRSM from the respiratory tract and preserved 85 LTSSSM isolates randomly chosen from the same source as LTSRSM in hospitalized patients during the study period for comparison. The identification of *S. maltophilia* isolates was performed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (bioMérieux Inc., Marcy-l'Etoile, Rhône, France). The minimum inhibitory concentrations (MICs) of identified *S. maltophilia* isolates were determined using the VITEK 2 automated system (bioMérieux Inc.). The breakpoints for TMP/SMX, levofloxacin, and ceftazidime for *S. maltophilia* were established according to 2020 Clinical and Laboratory Standards Institute (CLSI) criteria. The clinical breakpoints for tigecycline were established according to the 2020 European Committee on Antimicrobial Susceptibility Testing for Enterobacterales. The breakpoints for other tested antibiotics including ciprofloxacin, cefepime, colistin, gentamicin, and amikacin were established according to the 2020 CLSI criteria for *Pseudomonas aeruginosa*.

Statistical analysis

Continuous variables are presented as means ± standard deviations (SDs), and we used t-tests or Mann—Whitney U tests for comparisons as appropriate. Categorical variables are presented as numbers and percentages and compared using the chi-square test or Fisher's exact test. Variables with p values < 0.05 on bivariate analysis were included in a forward stepwise conditional logistic regression model for multivariate analysis. Two simultaneous multivariate models were produced from the data obtained. The first model used the pairs of the case group and matched control group A, while the second model used the pairs of the case group and matched control group B. All tests were 2-tailed, and a p value of <0.05 was considered statistically significant. All results were analysed using a commercially available software package (SPSS, version 16.0; SPSS Inc., Chicago, IL, USA).

Results

During the study period from January 2014 to June 2016, 1213 patients were identified as having cultures positive for *S. maltophilia*. Of these patients, 593 were hospitalized in the ICU and the others were admitted to the general ward. The most common isolation source was from the respiratory tract (1038/1213, 85.5%), followed by the blood (62/1213, 5.1%). One hundred and twenty-nine of the 1213 *S. maltophilia* isolates exhibited concurrent levofloxacin- and TMP/SMX resistance (10.6%). Among the 129 patients with LTSRSM, we excluded 15 patients with LTSRSM isolated within 48 h after admission, and seven unsuccessfully matched cases. Consequently, the case group consisted of 107 patients with LTSRSM. Among 107 cases in the case group with LTSRSM, the isolation source were from the respiratory tract (98/107, 91.5%), followed by the wound tissue (6/107, 5.6%), blood (2/107, 1.8%) and the urinary tract (1/107, 0.9%). After matching, control group A consisted of 107 patients with LTSSSM and control group B consisted of 107 patients randomly identified from the inpatient population without *S. maltophilia* infections were included for comparisons to determine independent risk factors for LTSRSM occurrence.

Risk factors for LTSRSM occurrence among hospitalized patients

As shown in Table 1, when the case group was compared to the control group A, there were no statistically significant between-group differences in time at risk, recent admission records, recent ICU admission, recent chemotherapy and surgery, comorbidities, and indwelling medical devices ($p > 0.05$). Previous antibiotic exposure revealed that the case group was more likely than the controls to have been exposed to fluoroquinolone and TMP/SMX (43.0% *vs.* 7.5% and 12.1% *vs.* 1.9%, $p < 0.001$ and 0.003, respectively). When the case group was compared to control group B, the

Table 1 Risk factors associated with levofloxacin- and trimethoprim/sulfamethoxazole (TMP/SMX)-resistant *Stenotrophomonas maltophilia* isolates determined by bivariate analysis.

Risk factor, n (%)	Case group (n = 107)	Control group A (n = 107)	*P*[a] value	Control group B (n = 107)	*P*[b] value
Age in years[c]	77.0 (22.0)	77.0 (22.0)	0.964	75.0 (25.0)	0.999
Male.	73 (68.2)	73 (68.2)	—	73 (68.2)	1.000
Time at risk (days)[c,d]	23 (23)	18 (19)	0.085	23 (23)	1.000
Recent admission records in the last 3 months	28 (26.2)	35 (32.7)	0.294	38 (35.5)	0.139
Prior ICU admission	89 (83.2)	87 (81.3)	0.721	32 (29.9)	<0.001
Chemotherapy in the last month	5 (4.7)	2 (1.9)	0.445	14 (13.1)	0.031
Surgery in the last month	59 (55.1)	53 (49.5)	0.412	40 (37.4)	0.009
Comorbidities					
Cerebrovascular disease	43 (40.2)	34 (31.8)	0.200	24 (22.4)	0.005
Dementia	15 (14.0)	20 (18.7)	0.355	10 (9.3)	0.287
Heart failure	19 (17.8)	17 (15.9)	0.715	11 (10.3)	0.115
Chronic renal insufficiency	40 (37.4)	29 (27.1)	0.108	28 (26.2))	0.078
Chronic lung disease	13 (12.1)	12 (11.2)	0.831	9 (8.4)	0.368
Liver cirrhosis	4 (3.7)	4 (3.7)	1.000	9 (8.4)	0.152
Diabetes mellitus	38 (35.5)	41 (38.3)	0.671	39 (36.4)	0.887
Autoimmune disease	8 (7.5)	6 (5.6)	0.580	3 (2.8)	0.122
Cancer	22 (20.6)	29 (27.1)	0.261	34 (31.8)	0.062
Peripheral vascular disease	6 (5.6)	3 (2.8)	0.498	3 (2.8)	0.498
Peptic ulcer disease	24 (22.4)	22 (20.6)	0.739	21 (19.6)	0.615
Previous antibiotics exposure					
Macrolide	11 (10.3)	12 (11.2)	0.825	4 (3.7)	0.061
Aminoglycoside	9 (8.4)	7 (6.5)	0.603	2 (1.9)	0.030
penicillin/β-lactamase inhibitor	44 (41.1)	46 (43.0)	0.782	37 (34.6)	0.324
3rd generation cephalosporin	23 (21.5)	31 (29.0)	0.208	17 (15.9)	0.293
4th generation cephalosporin	37 (34.6)	37 (34.6)	1.000	11 (10.3)	<0.001
Carbapenem	34 (31.8)	41 (38.3)	0.316	15 (14.0)	0.002
Glycopeptide	28 (26.2)	31 (29.0)	0.646	6 (5.6)	<0.001
Fluoroquinolone	46 (43.0)	8 (7.5)	<0.001	23 (21.5)	0.001
TMP/SMX	13 (12.1)	2 (1.9)	0.003	3 (2.8)	0.009
Invasive medical devices					
Central venous catheter insertion	61 (57.0)	62 (57.9)	0.890	35 (32.7)	<0.001
Nasogastric tube insertion	99 (92.5)	98 (91.6)	0.800	56 (52.3)	<0.001
Foley catheter insertion	86 (80.4)	80 (74.8)	0.325	54 (50.5)	<0.001
Percutaneous surgical wound drainage use	20 (18.7)	26 (24.3)	0.318	24 (22.4)	0.499
Mechanical ventilation	87 (81.3)	77 (72.0)	0.106	20 (18.7)	<0.001

[a] Comparison of patients in the case group and control group A.
[b] Comparison of patients in the case group and control group B.
[c] Data are presented as means (standard deviations).
[d] Days of stay prior to isolation of *S. maltophilia*.
ICU, intensive care unit.

patients in the case group had higher rates for recent ICU admission (83.2% *vs.* 29.9%, $p < 0.001$), recent surgery (55.1% *vs.* 37.4%, $p = 0.009$), cerebrovascular disease (40.2% *vs.* 22.4%, $p = 0.005$), and exposure to multiple antibiotics including aminoglycoside (8.4% *vs.* 1.9%, $P = 0.030$), fourth-generation cephalosporin (34.6% *vs.* 10.3%, $p < 0.001$), carbapenem (31.8% *vs.* 14.0%, $p = 0.002$), glycopeptide (26.2% *vs.* 5.6%, $p < 0.001$), fluoroquinolone (43.0% *vs.* 21.5%, $p < 0.001$), and TMP/SMX (12.1% vs. 2.8%, $p = 0.009$). Moreover, patients in the case group were more likely to have invasive medical devices, including a central venous catheter, nasogastric tube, Foley catheter, and ventilator, than those in control group B (57.0% *vs.* 32.7%, 92.5% *vs.* 52.3%, 80.4% *vs.* 50.5% and 81.3% *vs.* 18.7%, all $p < 0.001$).

The results of multivariate logistic regression are summarized in Table 2. In this analysis comparing the case group to control group A, previous usage of fluoroquinolone (odds ratio [OR] 22.824; 95% confidence interval [CI] 4.984—104.524) and previous usage of TMP/SMX (OR 17.724; 95% CI 1.495—210.097) were independent risk factors for LTSRSM isolation. When analysed using control group B, mechanical ventilation (OR 59.471; 95% CI 2.698—1311.079), cerebrovascular disease (OR 12.371; 95%

Table 2 Multivariate analysis (logistic regression) of risk factors for levofloxacin- and trimethoprim/sulfamethoxazole (TMP/SMX)-resistant *Stenotrophomonas maltophilia* isolates.

Risk factor, n (%)	OR (95% CI)	*P* value
Case group[a] *vs.* control group A[b]		
Fluoroquinolone	22.824 (4.984–104.524)	<0.001
Trimethoprim/sulfamethoxazole	17.724 (1.495–210.097)	0.02
Case group vs. control group B[c]		
Mechanical ventilation	59.471 (2.698–1311.079)	0.010
Cerebrovascular disease	12.371 (1.943–78.748)	0.008
Fluoroquinolone	13.075 (1.502–113.819)	0.020

CI, confidence interval; OR, odds ratio.
[a] Patients with levofloxacin- and TMP/SMX-resistant *S. maltophilia* (case group).
[b] Patients with levofloxacin- and TMP/SMX-susceptible *S. maltophilia* (control group A).
[c] Patients without *S. maltophilia* infection (control group B).

CI 1.943–78.748), and previous usage of fluoroquinolone (OR 13.075; 95% CI 1.502–113.819) were independently associated with LTSRSM isolation. Only one factor, previous antibiotic exposure to fluoroquinolone, was found to be independently associated with occurrence of LTSRSM when the case group was compared to both control groups A and B, respectively.

Antimicrobial susceptibility comparisons between LTSRSM and LTSSSM

The MIC ranges, MIC_{50}, MIC_{90} values, and the resistant percentages to the tested antibiotics of the 85 LTSRSM and 85 LTSSSM isolates are shown in Table 3. All LTSRSM isolates consistently showed resistance to ciprofloxacin, another type of fluoroquinolone, with $MIC_{50/90}$ values $>$ 4 μg/mL. Among the 170 *S. maltophilia* isolates tested, including the 85 LTSRSM and 85 LTSSSM isolates, 31% were resistant to ceftazidime, and the LTSRSM isolates were significantly more likely to exhibit resistance to ceftazidime than the LTSSSM isolates (43.5% *vs.* 25.9%, $p = 0.016$). With regard to tigecycline susceptibility, the resistance rates were significantly higher among the LTSRSM isolates than among the LTSSSM isolates (90.6% *vs.* 11.8%, $p < 0.001$). Moreover, the values of MIC_{50} and MIC_{90} were 4 μg/mL and >8 μg/mL for the LTSRSM isolates, respectively, which were at least 8-fold higher than those for the LTSSSM isolates (<0.5 μg/mL and 1 μg/mL, respectively). The other antibiotics tested (cefepime, gentamicin, amikacin, and colistin) revealed limited *in vitro* activity and resistant rates were not significantly different between the LTSRSM and LTSSSM isolates according to the CLSI MIC breakpoints for *P. aeruginosa* ($p > 0.05$).

Discussion

To our knowledge, the current study was the first to investigate risk factors and antibiotic susceptibilities for LTSRSM from hospitalized patients. A matched case-control-control design was used and compared the case group of patients with LTSRSM to two control groups of patients, one with LTSSSM and one comprised of randomly selected inpatients without *S. maltophilia* infection to eliminate the potential biased risk estimates from traditional case–control studies.[21] The main findings of our study were that previous antibiotic use of fluoroquinolone and TMP/SMX, patients with recent mechanical ventilation and cerebrovascular diseases were independent risk factors associated with subsequent LTSRSM occurrence. In addition, the MICs and resistance rates of tigecycline and ceftazidime were higher in LTSRSM than LTSSSM isolates.

Inpatients with multiple comorbidities frequently subjected to indwelling medical devices such as ventilators are

Table 3 Minimal inhibitory concentration and susceptibility comparisons of antibiotics between levofloxacin- and trimethoprim/sulfamethoxazole (TMP/SMX)-resistant *Stenotrophomonas maltophilia* (LTSRSM) and levofloxacin- and TMP/SMX-susceptible *S. maltophilia* (LTSSSM).

Antibiotic	MIC range (μg/mL)		MIC50 (μg/mL)		MIC90 (μg/mL)		No. (%) resistant isolates		
	LTSRSM (n = 85)	LTSSSM (n = 85)	LTSRSM (n = 85)	LTSSSM (n = 85)	LTSRSM (n = 85)	LTSSSM (n = 85)	LTSRSM (n = 85)	LTSSSM (n = 85)	*P* value
Ceftazidime	<1–>64	<1–>64	16	4	>64	>64	37 (43.5)	22 (25.9)	0.016
Cefepime	<1–>64	<1–>64	16	32	>64	>64	63 (74.1)	64 (75.2)	1.000
Tigecycline	<0.5–>8	<0.5–4	4	<0.5	>8	1	77 (90.6)	10 (11.8)	<0.001
Colistin	<0.5–>16	<0.5->16	<0.5	<0.5	>16	>16	34 (40.0)	24 (28.2)	0.106
Ciprofloxacin	>4	<0.12–4	>4	0.5	>4	2	85 (100)	12 (14.1)	<0.001
Gentamicin	2–>16	<1–>16	>16	8	>16	>16	43 (50.6)	41 (48.2)	0.878
Amikacin	4–>64	<2–>64	>64	>64	>64	>64	43 (50.6)	44 (51.8)	1.000

at risk of acquiring multidrug-resistant strains.[22–24] It may be that such patients with medical advices who need more nursing care during hospitalization are more likely to be infected from cross transmission and that infected resistant organisms are more difficult to be eradicated with antibiotic treatment than susceptible ones. Consistently, our study revealed that ventilator use was associated with subsequent LTSRSM occurrence. For the same reason, patients with poor functional status showing increased activities of daily living (ADL) score may need increased bedside care and are more likely to be infected with resistant bacteria.[25–27] This may explain why being a patient with cerebrovascular disease who may have a high ADL score was identified as another risk factor for LTSRSM occurrence in our study. The risk factors identified for LTSRSM occurrence mentioned above indicate that implementation of strict hand hygiene protocols in caring for inpatients may be helpful for preventing LTSRSM from spreading in the hospital. In our study, we also found that previous fluoroquinolone and TMP/SMX use were associated with subsequent LTSRSM occurrence, which was consistent with a previous study found that both antibiotics increased the likelihood of subsequent multidrug-resistant *S. maltophilia* isolation in cancer patients.[28] Besides past and our present clinical studies, we were able to observe similar results from basic studies of *S. maltophilia* in the laboratory. In experimental evolution studies reported, *S. maltophilia* exhibited simultaneous resistance to quinolone and TMP/SMX after either TMP/SMX or quinolone exposure. The resistance mechanism was resulted from overexpression of resistance-nodulation-cell division (RND) efflux pumps, mainly SmeDEF.[20,29] Since overexpression of the RND efflux pump was also reported the major resistance mechanism for tigecycline in *S. maltophilia*, cross resistance to tigecycline may be anticipated.[30] Agree with our inference, we also noted elevated MICs and higher resistance rates of tigecycline in LTSRSM than LTSSSM in our study. Tigecycline has broad activity against gram-positive and -negative organisms, including multidrug-resistant organisms. From recent global surveillance studies, tigecycline also demonstrated good *in vitro* activity against *S. maltophilia*.[31,32] Although the clinical breakpoints of tigecycline for *S. maltophilia* have not been determined, clinical studies have suggested that tigecycline has efficacy equivalent to that of TMP/SMX in treating *S. maltophilia* infections.[33] Consequently, tigecycline has been considered an alternative therapeutic option. The cross-resistance of LTSRSM to tigecycline we presented here may further restrict already limited therapeutic choices in treating *S. maltophilia* infections. The MIC_{50} values and resistance rates of ceftazidime were also higher in LTSRSM than in LTSSSM. The resistance mechanism of *S. maltophilia* for ceftazidime may generally be considered to correlate with intrinsic beta-lactamases L1 and L2 but overexpression of efflux pump transporters was also reported.[34] Whether there was difference between LTSSSM and LTSRSM on resistance mechanisms to ceftazidime warranted future investigations for further exploration. Study results on mechanisms of concurrent TMP/SMX and fluoroquinolone resistance reported before were from basic studies based on laboratory *S. maltophilia* strains under the laboratory environment, which may not be applicable to real clinical settings. Results of current study from clinical data analysis revealing consistent results strengthened findings from past basic studies but molecular mechanism characterisation using clinical *S. maltophilia* isolates to correlate clinical data results was warranted for further validation. Cautious use of TMP/SMX and fluoroquinolone to reduced selective pressure may be important to limit LTSRSM emergence in the hospital. Other antibiotics tested in our study, including colistin, all revealed limited *in vitro* activity against LTSRSM isolates. The emergence of multidrug-resistant *S. maltophilia*, as presented here, would be a great concern for current and future medical practice. New drug development would be important to provide clinicians more therapeutic options when faced with infections caused by such resistant strains.

There were some limitations to this study. First, this study was retrospective in nature; hence, our results were susceptible to potential selection biases in the study. Second, molecular epidemiology of the collected isolates was not carried out. We therefore could not assess if patient-to-patient transmission occurred during the study period, which may have influenced our results in the clinical data analysis. Third, this was a single medical center in northern Taiwan and caution was necessary when extrapolating these results to other regions in Taiwan or other countries.

Conclusion

The current study identified that mechanical ventilation use, patients with cerebrovascular disease, and previous fluoroquinolone and TMP/SMX exposure were independent risk factors for subsequent LTSRSM occurrence. LTSRSM isolates exhibited higher rates of resistance against tigecycline and ceftazidime than LTSSSM. Future multicenter studies with prospective evaluations and molecular characterizations of clinical LTSRSM isolates to corroborate our study results were necessary.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgements

This work was supported by a grant from the Tri-Service General Hospital Penghu Branch (TSGH-PH-107-02 and TSGH-PH-109-5) and the Tri-Service General Hospital, National Defense Medical Center (TSGH-C103-187, TSGH-C104-195).

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