Journal of Microbiology, Immunology and Infection (2017) 50, 646–652

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Risk factors for hospital acquisition of trimethoprim–sulfamethoxazole resistant *Stenotrophomonas maltophilia* in adults: A matched case-control study

Ching-Hsun Wang [a], Jung-Chung Lin [a], Feng-Yee Chang [a], Ching-Mei Yu [b], Wei-San Lin [c], Kuo-Ming Yeh [a,*]

[a] *Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[b] *Department of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[c] *Graduate Institute of Biomedical Informatics, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan*

Received 8 September 2016; received in revised form 15 November 2016; accepted 7 December 2016
Available online 28 June 2017

KEYWORDS
Risk;
Resistance;
Stenotrophomonas maltophilia;
Trimethoprim–sulfamethoxazole

Abstract *Background/Purpose:* The emergence of trimethoprim–sulfamethoxazole resistant *Stenotrophomonas maltophilia* (TSRSM) represents a serious threat to patients. The aim of current study was to identify risk factors associated with hospital-acquired TSRSM occurrence in adult inpatients.
Methods: We conducted a matched case-control study in Tri-Service General Hospital, Taipei, Taiwan. From January 2014 through June 2015, case patients with TSRSM and control patients with trimethoprim–sulfamethoxazole susceptible *S. maltophilia* (TSSSM) during hospitalization were identified. Control patients were matched with TSRSM cases for age (within five years), sex, and site of isolation at a ratio of 1:1.
Results: A total of 266 patients were included in our study (133 cases and 133 matched controls). Bivariable analysis showed that previous exposure to fluoroquinolone [odds ratio (OR), 2.693; 95% confidence interval (CI, 1.492–5.884; $p = 0.002$)], length of intensive care unit stay (OR, 1.015 per day; 95% CI, 1.001–1.030; $p = 0.041$), and length of hospital stay (OR, 1.012 per day; 95% CI, 1.002–1.023; $p = 0.018$) prior to *S. maltophilia* isolation were associated with TSRSM occurrence. A multivariable analysis showed that previous exposure to fluoroquinolone (OR, 3.158; 95% CI, 1.551–6.430; $p = 0.002$) was an independent risk factor for TSRSM occurrence after adjustment.

* Corresponding author. Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, No. 325, Section 2, Cheng-Kung Road, Neihu 114, Taipei, Taiwan. Fax: +886 2 87927258.
E-mail address: kmyeh@ndmctsgh.edu.tw (K.-M. Yeh).

http://dx.doi.org/10.1016/j.jmii.2016.12.007

Conclusion: Previous fluoroquinolone use was an independent risk factor for hospital-acquired TSRSM occurrence in adult inpatients, suggesting that judicious administration of fluoroquinolone may be important for limiting TSRSM occurrence.

Introduction

Stenotrophomonas maltophilia, a nonfermenting gram-negative bacillus, has emerged as a nosocomial pathogen that primarily affects immunocompromised patients.[1–3] The broad spectrum of infections that are associated with *S. maltophilia* include pneumonia and bacteremia, as well as infections of the skin and soft tissue, surgical wounds, and urinary tract.[1,4] The crude mortality rate for *S. maltophilia* infection is around 18%–69%.[5] The treatment of these infections is challenging because *S. maltophilia* is resistant to a variety of structurally unrelated antimicrobial agents.[6,7] *S. maltophilia*'s resistance to antimicrobial agents derives from intrinsic or acquired resistant mechanisms involving β-lactamases, efflux pump systems, enzymatic modification, and target site modification.[7–9]

Trimethoprim–sulfamethoxazole (TMP-SXT) has been the primary treatment for susceptible *S. maltophilia* infections, based on *in vitro* activity and anecdotal reports of favorable clinical outcomes.[6,7,10,11] Although levofloxacin and tigecycline have been considered as alternatives to TMP-SXT for the treatment of *S. maltophilia* infections, more clinical data are still needed to validate their efficacies.[12,13]

Recent antimicrobial susceptibility studies and case series, however, have demonstrated the occurrence of TMP-SXT resistant *S. maltophilia* (TSRSM) in different geographic regions.[14–16] The emergence of TSRSM limits treatment options further and it had been reported that patients with TSRAM were associated with deteriorated clinical outcome.[17,18] Studies of TMP-SXT resistance in uropathogens, mostly *Enterobacteriaceae* strains, revealed that prior TMP-SXT use was associated with TMP-SXT resistance, reflecting selective pressure of TMP-SXT.[19,20] Whether this association in *Enterobacteriaceae* strains is applicable to *S. maltophilia* has remained uncertain.

The prevalence of TSRSM in Taiwan is higher than that in other geographic regions and has been increasing.[14,15,21,22] The majority of TSRSM infections occurred in hospitalized patients, rather than those from community.[18,21,22] Our previous study reported before revealed that patients with TSRSM were associated with prolonged hospitalization indicating increased financial burdens in healthcare systems in Taiwan.[18] This alarming phenomenon in Taiwan highlights an urgent need for effective control and prevention measures that could prevent TSRSM dissemination. The first step in the design of such measures is to identify risk factors that are associated with hospital-acquired TSRSM occurrence. We therefore initiated a matched case-control study to identify risk factors for hospital-acquired TSRSM occurrence in adult hospitalized patients.

Methods

Study design and patient selection

This retrospective matched case-control study was conducted at the Tri-Service General Hospital, which is a tertiary referral center in northern Taiwan with 1700 beds. To identify the individual risk factors for inpatients having hospital-acquired TSRSM, a 1:1 matched case-control study was initiated. The study population included hospitalized adult patients from whom a clinical specimen yielded a *S. maltophilia* isolate for the first time between January 1, 2014 and June 30, 2015, as assessed via electronic records from the microbiological laboratory database. Each patient was included once only. To focus on risk factors for hospital-acquired TSRSM occurrence in adult inpatients, patients with *S. maltophilia* isolated within 48 h of admission were excluded. Patients younger than 18 years old of age were excluded. Patients with TSRSM were assigned to the case group. Patients with TSSSM were identified as potential members of the control group. Matching was performed at a ratio of 1:1 according to sex, age (within five years), and the site of isolation. When more than one control satisfied these conditions, they were randomly chosen with Microsoft Excel 2013® software (Microsoft Corp., Redmond, WA, USA).

Clinical data collections and definitions

Using a computerised data system, clinical information was systematically collected from the medical records of the patients with culture positive TSRSM and the matched controls. The collected information included demographic data, durations of intensive care unit (ICU) and hospital stays prior to *S. maltophilia* isolation, number of admission records during the previous year, comorbidities on admission, indwelling medical devices before *S. maltophilia* isolation during hospitalization, recent therapeutic measures, and previous exposure to antibiotics. The Charlson Comorbidity Index (CCI) was used as an aggregate measure for comorbidities.[23] Previous exposure to antibiotics including prescriptions in the outpatient department was defined as at least 24-h of therapy within the 14 days prior to *S. maltophilia* isolation. Recent chemotherapy within one month before *S. maltophilia* isolation was recorded. Recent surgery was defined as surgery performed in included patients after admission but before *S. maltophilia* isolation.

Microbiology test

The VITEK 2 automatic system for gram-negative rods (bioMérieux Inc., Marcy-l'Etoile, Rhône, France) was used to identify *S. maltophilia* isolates. Susceptibility of *S. maltophilia* isolates was measured by the VITEK 2 automatic system using an automated broth microdilution method. According to 2014 Clinical and Laboratory Standards Institute (CLSI) M100-S24 performance standards, *S. maltophilia* isolates resistant to TMP-SXT were defined as the minimal inhibitory concentration (MIC) to TMP-SXT $\geq$ 4/76 μg/mL. *S. maltophilia* isolates which were resistant to levofloxacin (MIC $\geq$ 8 μg/mL) or those with intermediate resistance (MIC = 4 μg/mL) to levofloxacin were defined as non-susceptible.[24]

Statistical analysis

All results were analysed using a commercially available software package (SPSS, version 16.0; SPSS Inc., Chicago, IL, USA). Continuous variables were presented as means ± standard deviations, and categorical variables were presented as numbers and percentages.

Differences in continuous variables were assessed using Student's t-test or the Mann–Whitney U-test. The Chi-square test or Fisher's exact test (when expected cell frequencies were <5) was used to assess difference in categorical variables. The odds of exposure to potential risk factors for hospital-acquired TSRSM acquisition in adult inpatients were compared for case patients and matched controls using bivariable conditional logistic regression analysis for both categorical and continuous data, conditioning on matched sets of subjects. A single multivariable conditional logistic regression model to identify independent risk factors significantly associated with hospital-acquired TSRSM occurrence was generated using regression methods on variables that yielded a *P* value < 0.05 on bivariable analysis.

Results

Study population

From January 2014 to June 2015, a total of 809 patients were identified as having cultures positive for *S. maltophilia*. Among 809 *S. maltophilia* isolates from the identified patients, 694 (85.8%) were from the respiratory tract, 38 (4.7%) were from the blood, 29 (3.6%) were from wound tissue, 18 (2.2%) were from urine, 21 (2.6%) were from abdominal ascites, and nine (1.1%) were from a central venous catheter. One hundred sixty-six of *S. maltophilia* isolates were resistant for TMP-SXT (20.5%). The rates of TSRSM isolated from the respiratory tract, the blood, wound tissue, urine, abdominal ascites, and central venous catheters were 20.4%, 21.0%, 10.3%, 16.6%, 28.6%, and 33.3%, respectively. Regarding the hospital units where TSRSM was isolated, the rate of TSRSM isolation in the medical wards, surgical wards, ICUs, and respiratory center were 13.6%, 25.9%, 21.1%, and 28.2%, respectively. No significant increase in the TSRSM isolation rate was detected in any ward.

Among 166 patients with TSRSM, we excluded two patients <18 years old, 27 patients with TSRSM isolated in 48 h after admission, and four patients because of unsuccessful matching. Therefore, a total of 133 patients with TSRSM and 133 patients with trimethoprim–sulfamethoxazole susceptible *S. maltophilia* (TSSSM) were successfully matched for the subsequent analyses.

Characteristics of matched patients with TSRSM and TSSSM

The characteristics of the patients included were shown in Table 1. The mean age was 72.5 years in the TSRSM group and 72.2 years in the matched TSSSM (control) group. The patients were predominantly male (63.9%). The most common admission diagnosis in patients with TSRSM and TSSSM was an infectious disease. Both patients with TSRSM and TSSSM had comparable CCI on admission. Clinical outcomes of patients with TSRSM and matched controls showed no statistic difference on mortality and morbidity ($p > 0.05$). The in-hospital mortality rates in TSRSM group and TSSSM group were 27.8% and 36.8%, respectively. The mean duration of hospitalization after *S. maltophilia* was 34.7 days and 32.0 days, respectively.

With regard to microbiology of identified TSRSM and TSSSM, the major hospital units in which *S. maltophilia* was isolated were ICUs (51.1%), followed by the respiratory center (21.1%). *S. maltophilia* was mostly isolated from the respiratory tract in both groups (87.2%), followed by the blood (5.2%), abdominal ascites (3.0%), wound tissue (2.2%), urine (1.5%) and central venous catheter (0.7%). The rate of TSRSM isolates which was non-susceptible to levofloxacin was higher than TSSSM isolates with significance (49.6% *vs.*11.3%, $p < 0.001$).

Risk factors for hospital-acquired TSRSM occurrence in adult inpatients

Bivariable analyses were conducted to investigate risk factors associated with TMP-SXT resistance (Table 2). Among the hospitalization-related factors, length of hospital stay [odds ratio (OR), 1.012; 95% confidence interval (CI, 1.002–1.023; $p = 0.018$)] and length of ICU stay (OR, 1.015; 95% CI, 1.001–1.030; $p = 0.041$) were associated with hospital-acquired TSRSM occurrence. In other words, each day increment of hospital and ICU stay could boost the odds ratio by 1.012 and 1.015, respectively. There were no statistically significant between-group differences in the rates of the various underlying comorbidities that were recorded. Other possible precipitating factors showed no significant association, including recent surgery and recent chemotherapy ($p > 0.05$).

With regard to previous antibiotics exposure, the mean number of antibiotics classes that patients received before *S. maltophilia* isolation were 2.26 and 2.27 in patients with TSRSM and TSSSM, respectively. Previous TMP-SXT exposure was not associated with TSRSM occurrence (OR, 1.000; 95% CI, 0.250–3.998; $p = 1.000$). Nonetheless, There was a highly significant association between previous exposure to fluoroquinolone and the subsequent occurrence of TSRSM (OR, 2.693; 95% CI, 1.492–5.884; $p = 0.002$). Among the

Table 1 Characteristics of patients with *Stenotrophomonas maltophilia*.

Variable	TSRSM (n = 133)	TSSSM (n = 133)	*p* value
Demographic			
Age in years[a]	72.5 (16.7)	72.2 (16.9)	0.879[b]
Male, n (%)	85 (63.9)	85 (63.9)	
Admission ward isolation *S. maltophilia*, n (%)			
Medical ward	17 (12.8)	31 (23.3)	
Surgical ward	17 (12.8)	9 (6.8)	
Intensive care unit	72 (54.1)	64 (48.1)	
Respiratory care center	27 (20.3)	29 (21.8)	
Primary admission diagnosis, n (%)			
Cardiovascular disease	11 (8.3)	22 (16.5)	
Gastrointestinal disease	12 (9.0)	9 (6.8)	
Hematology-oncology disease	9 (6.8)	15 (11.3)	
Infectious disease	67 (50.4)	62 (46.6)	
Neurologic disease	15 (11.3)	15 (11.3)	
Renal disease	5 (3.8)	2 (1.5)	
Trauma	11 (8.2)	8 (6.0)	
Other	3 (2.2)	0 (0)	
Charlson Comorbidity Index[a]	4.1 (2.6)	4.4 (2.7)	0.365[b]
Clinical outcome, n (%)			
Hospital stay after *S. maltophilia* isolation[a]	34.7 (40.4)	32.0 (40.7)	0.327[b]
In-hospital mortality	37 (27.8)	49 (36.8)	0.149

[a] Data are presented as means (standard deviations).
[b] *p* value were analyzed by t-test.
TSRSM = trimethoprim—sulfamethoxazole resistant *S. maltophilia*; TSSSM = trimethoprim—sulfamethoxazole susceptible *S. maltophilia*.

patients with prior exposure to fluoroquinolone in our study (n = 48), levofloxacin had mostly been used (27/48), followed by ciprofloxacin (16/48) and moxifloxacin (5/44). Patients who received prior levofloxacin were likely to develop TMP-SXT resistance (OR, 3.333; 95% CI, 1.339—8.300; $p = 0.010$), while there was no significant association between prior moxifloxacin and ciprofloxacin use and subsequent TMP-SXT resistance (OR, 0.758 and 3.000; 95% CI, 0.125—4.606 and 0.968—9.302; $p = 0.764$ and 0.057, respectively). In each group, more than a half of the patients had received mechanical ventilation before *S. maltophilia* isolation (78.2% and 75.9%, respectively). There was no significant between-group difference among the various types of indwelling medical devices ($p > 0.05$).

Further multivariable analysis showed that previous use of fluoroquinolone (adjusted OR, 3.158; 95% CI, 1.551 to 6.430; $p = 0.002$) was an independent risk factor for subsequent TSRSM occurrence after adjustment (Table 3).

Discussion

TSRSM occurrence is an emerging concern and there has been a paucity of information on risk factors for TSRSM occurrence. To the best of our knowledge, the current study was the largest to identify risk factors for hospital-acquired TSRSM occurrence in hospitalized patients using a substantial sample size and a matched case-control design. The main finding of our study was that fluoroquinolone use in the hospitalization was an independent risk factor associated with subsequent TSRSM occurrence.

There have been two related studies on risk factors for TSRSM.[18,25] In the first,[25] Ansari et al. conducted a case-control study to find out risk factors for multiple-drug resistant *S. maltophilia* on cancer patients. The results of the study suggested that previous use of TMP-SXT and recent admission were significant risk factors for multiple-drug resistant *S. maltophilia* (resistance to TMP-SXT and at least two other additional antibiotics that are often active against *S. maltophilia*). The second related study was our retrospective analysis of *S. maltophilia* bacteremia patients with TSRSM and TSSSM comparing clinical characteristics and outcomes.[18] In this study, no significant factors for TSRSM bacteraemia occurrence was identified. The sample sizes of patients with TSRSM (n = 56) in this study were relative small, which may have limited their statistic power for identifying risk factors for TMP-SXT resistance.

Because of the high prevalence of TSRSM in Taiwan, the current study was able to include more cases for the comparison of TSRSM and TSSSM. To reduce potential confounding, the study employed a matched case-control design. In addition, the periods of time at risk before *S. maltophilia* isolation were controlled in the multivariable analysis for both groups. Unlike the previous study by Ansari et al., we did not find a significant association between previous administration of TMP-SXT and TMP-SXT resistance. The discrepancy between these results could potentially be attributed to the different study populations. Ansari et al. studied cancer patients in whom TMP-SXT was commonly used as prophylactic or therapeutic agents.[25] In contrast, our study included hospitalized patients with multiple comorbidities, not only cancers.

Table 2 Bivariable analysis of risk factors associated with trimethoprim–sulfamethoxazole resistant *Stenotrophomonas maltophilia* isolation.

Variable	TSRSM (n = 133)	TSSSM (n = 133)	OR (95% CI)	*p* value
Factors related to hospitalization, n (%)				
Length of ICU stay[a,b]	18.5 (23.8)	13.2 (14.9)	1.015 (1.001–1.030)	0.041
Length of hospital stay[a,b]	34.7 (40.2)	24.4 (21.6)	1.012 (1.002–1.023)	0.018
Recent admission within 3 months	40 (30.1)	40 (30.1)	1.022 (0.618–1.689)	0.932
No. of admissions within a year[a]	1.04 (2.2)	1.06 (1.5)	0.996 (0.869–1.142)	0.954
Co-morbidity, n (%)				
Cerebrovascular disease	55 (41.4)	45 (33.8)	1.526 (0.879–2.650)	0.133
Congestive heart failure	21 (15.8)	21 (15.8)	1.000 (0.500–2.000)	1.000
Chronic obstructive pulmonary disease	21 (15.8)	19 (14.3)	1.114 (0.550–2.260)	0.764
Connective tissue disease	6 (4.5)	8 (6.0)	0.714 (0.227–2.251)	0.566
Diabetes mellitus	46 (34.6)	58 (43.6)	0.662 (0.396–1.108)	0.116
Liver cirrhosis	8 (6.0)	9 (6.8)	0.857 (0.288–2.550)	0.782
Malignancy	23 (17.3)	32 (24.1)	0.654 (0.355–1.205)	0.173
Renal insufficiency	37 (27.8)	43 (32.3)	0.799 (0.451–1.415)	0.441
Mechanical ventilation[c], n (%)	104 (78.2)	101 (75.9)	1.128 (0.600–2.121)	0.708
Recent chemotherapy, n (%)	8 (6.0)	5 (3.8)	1.750 (0.512–5.978)	0.372
Recent surgery, n (%)	42 (31.6)	35 (26.3)	1.333 (0.757–2.348)	0.319
Previous antibiotic exposure, n (%)				
Mean classes of antibiotics exposure[a]	2.26 (1.23)	2.27 (1.14)	0.988 (0.793–1.229)	0.911
3rd generation cephalosporin	29 (21.8)	33 (24.8)	0.556 (0.470–1.501)	0.840
4th generation cephalosporin	40 (30.1)	47 (35.3)	0.744 (0.439–1.259)	0.270
Aminoglycoside	12 (9.0)	10 (7.5)	1.299 (0.511–3.301)	0.582
Carbapenem	49 (36.8)	46 (34.6)	1.120 (0.653–1.921)	0.680
Colistin	15 (11.3)	8 (6.0)	2.000 (0.807–4.955)	0.134
Daptomycin	2 (1.5)	5 (3.8)	0.400 (0.078–2.062)	0.273
Fluoroquinolone	35 (26.3)	13 (9.8)	2.693 (1.492–5.884)	0.002
Glycopeptide	38 (28.6)	45 (33.8)	0.766 (0.455–1.289)	0.315
Linezolid	4 (3.0	6 (4.5)	0.667 (0.188–2.362)	0.530
Macrolide	12 (9.0)	16 (12.0)	0.688 (0.319–1.481)	0.339
Penicillin-lactamase inhibitor	55 (41.4)	64 (48.1)	0.783 (0.476–1.287)	0.334
Trimethoprim-sulfamethoxazole	5 (3.8)	4 (3.0)	1.000 (0.250–3.998)	1.000
Tigecycline	6 (4.5)	4 (3.0)	1.500 (0.423–5.315)	0.530
Indwelling medical devices, n (%)				
Central venous catheter[d]	83 (62.4)	71 (53.4)	1.425 (0.862–2.355)	0.167
Endotracheal tube	85 (63.9)	86 (64.7)	0.943 (0.560–1.587)	0.825
Nasogastric tube	119 (89.5)	120 (90.2)	0.889 (0.343–2.304)	0.808
Surgical drain	26 (19.5)	21 (15.8)	1.222 (0.656–2.279)	0.528
Tracheostomy tube	36 (27.1)	35 (26.3)	1.084 (0.621–1.890)	0.777
Urinary catheter	100 (75.2)	93 (69.9)	1.287 (0.727–2.280)	0.387

[a] Data are presented as means (standard deviations).
[b] Days of stay prior to isolation of *S. maltophilia*.
[c] Prior mechanical ventilation before *S. maltophilia*. isolation during hospitalization.
[d] Including double-lumen catheter for haemodialysis, central venous catheter, and peripherally inserted central catheter.
TSRSM = trimethoprim–sulfamethoxazole resistant *S. maltophilia*; TSSSM = trimethoprim–sulfamethoxazole susceptible *S. maltophilia*; ICU = intensive care unit; CI = confidence interval; OR = odds ratio.

Further, the majority of our patients had been exposed to broad-spectrum antibiotics before *S. maltophilia* isolation, rather than TMP-SXT. Therefore, the current study may not have included enough cases with prior TMP-SXT treatment to demonstrate a significant association between previous administration of TMP-SXT and subsequent TMP-SXT resistance. However, our study demonstrated that previous exposure to fluoroquinolone was associated with the subsequent occurrence of TSRSM, which has not been reported previously. Besides, we also observed that patients with TSRSM were more likely to be non-susceptible to fluoroquinolone than those with TSSSM in our study consisted with previous study.[26]

With regarding to resistant mechanisms in *S. maltophilia*, the *sul1* gene carried by class 1 integrons and the *sul2* gene linked to insertion sequence common region (ISCR) elements has been considered as an important role for TMP-SXT resistance in *S. maltophilia*.[16,27] In addition, overexpression of efflux pumps in *S. maltophilia* may also be considered associated with TMP-SXT resistance along

Table 3 Multivariable analysis (logistic regression) of risk factors for trimethoprim—sulfamethoxazole-resistant *Stenotrophomonas maltophilia* isolation.

Variable	TSRSM (n = 133)	TSSSM (n = 133)	OR (95% CI)	*p* value
Length of ICU stay[a,b]	18.5 (23.8)	13.2 (14.9)	1.012 (0.995—1.030)	0.170
Length of hospital stay[a,b]	34.7 (40.2)	24.4 (21.6)	1.009 (0.997—1.022)	0.156
Fluoroquinolone, n (%)	35 (26.3)	13 (9.8)	3.158 (1.551—6.430)	0.002

[a] Data are presented as means (standard deviations).
[b] Days of stay prior to isolation of *S. maltophilia*.
TSRSM = trimethoprim—sulfamethoxazole resistant *S. maltophilia*; TSSSM = trimethoprim—sulfamethoxazole susceptible *S. maltophilia*; ICU = intensive care unit; CI = confidence interval; OR = odds ratio.

with other antimicrobial agents.[28] This different resistance mechanism of TMP-SXT in *S. maltophilia* has been validated in recent reported study.[29] In the study, they demonstrated that overexpression of the efflux pump SmeDEF, which is a major determinant of quinolone resistance, may also reduce *S. maltophilia* susceptibility to TMP-SXT.[29] Our study result revealed that an association between previous fluoroquinolone exposure and TSRSM occurrence and that higher rate of fluoroquinolone resistance in TSRSM further strengthened the concept from clinical points of view. And this association might also explain the high prevalence of TSRSM in Taiwan, where fluoroquinolones have been commonly prescribed antibiotics after the implementation of national health insurance.[30]

There were some limitations to this study. Because of retrospective design, selection and observational bias may affect our analysis. More robust matching method as propensity score matching analysis may be better to further confirm our study results. The use of patients with susceptible *S. maltophilia* as the control group in our study may have led to biased estimates of risk, especially when estimating the effect of exposure to antibiotics that were active against susceptible organisms (TMP-SXT for *S. maltophilia)*.[31,32] This was a single-centre study in Taiwan and, therefore, our findings may not be generalizable.

In conclusion, this matched case-control study identified that previous fluoroquinolones exposure was an independent risk factor for hospital-acquired TSRSM occurrence in adult inpatients. Based upon our study, judicious use of fluoroquinolones might help to limit TSRSM occurrence. Future multicenter studies with a prospective evaluation to validate our findings will be necessary.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

This work was supported by a grant from the Tri-Service General Hospital, National Defense Medical Center (TSGH-C104-195), Taiwan. This work has been presented as a poster during a meeting of the Taiwan Society of Internal Medicine (Taipei, Taiwan; December 5—6, 2015).

References

1. Looney WJ, Narita M, Muhlemann K. Stenotrophomonas maltophilia: an emerging opportunist human pathogen. *Lancet Infect Dis* 2009;**9**:312—23.
2. Senol E. Stenotrophomonas maltophilia: the significance and role as a nosocomial pathogen. *J Hosp Infect* 2004;**57**:1—7.
3. Nyc O, Matejkova J. Stenotrophomonas maltophilia: significant contemporary hospital pathogen - review. *Folia Microbiol (Praha)* 2010;**55**:286—94.
4. Brooke JS. Stenotrophomonas maltophilia: an emerging global opportunistic pathogen. *Clin Microbiol Rev* 2012;**25**:2—41.
5. Paez JI, Costa SF. Risk factors associated with mortality of infections caused by Stenotrophomonas maltophilia: a systematic review. *J Hosp Infect* 2008;**70**:101—8.
6. Muder RR. Optimizing therapy for Stenotrophomonas maltophilia. *Semin Respir Crit Care Med* 2007;**28**:672—7.
7. Nicodemo AC, Paez JI. Antimicrobial therapy for Stenotrophomonas maltophilia infections. *Eur J Clin Microbiol Infect Dis* 2007;**26**:229—37.
8. Abbott IJ, Slavin MA, Turnidge JD, Thursky KA, Worth LJ. Stenotrophomonas maltophilia: emerging disease patterns and challenges for treatment. *Expert Rev Anti Infect Ther* 2011;**9**:471—88.
9. Sanchez MB. Antibiotic resistance in the opportunistic pathogen Stenotrophomonas maltophilia. *Front Microbiol* 2015;**6**:658.
10. Muder RR, Harris AP, Muller S, Edmond M, Chow JW, Papadakis K, et al. Bacteremia due to Stenotrophomonas (Xanthomonas) maltophilia: a prospective, multicenter study of 91 episodes. *Clin Infect Dis* 1996;**22**:508—12.
11. Goldberg E, Bishara J. Contemporary unconventional clinical use of co-trimoxazole. *Clin Microbiol Infect* 2012;**18**:8—17.
12. Brooke JS. New strategies against Stenotrophomonas maltophilia: a serious worldwide intrinsically drug-resistant opportunistic pathogen. *Expert Rev Anti Infect Ther* 2014;**12**:1—4.
13. Tekce YT, Erbay A, Cabadak H, Sen S. Tigecycline as a therapeutic option in Stenotrophomonas maltophilia infections. *J Chemother* 2012;**24**:150—4.
14. Farrell DJ, Sader HS, Jones RN. Antimicrobial susceptibilities of a worldwide collection of Stenotrophomonas maltophilia isolates tested against tigecycline and agents commonly used for S. maltophilia infections. *Antimicrob Agents Chemother* 2010;**54**:2735—7.
15. Gales AC, Jones RN, Forward KR, Linares J, Sader HS, Verhoef J. Emerging importance of multidrug-resistant Acinetobacter species and Stenotrophomonas maltophilia as pathogens in seriously ill patients: geographic patterns, epidemiological features, and trends in the SENTRY antimicrobial surveillance program (1997-1999). *Clin Infect Dis* 2001;**32**:S104—13.
16. Toleman MA, Bennett PM, Bennett DM, Jones RN, Walsh TR. Global emergence of trimethoprim/sulfamethoxazole

resistance in Stenotrophomonas maltophilia mediated by acquisition of sul genes. *Emerg Infect Dis* 2007;**13**:559—65.
17. Tsiodras S, Pittet D, Carmeli Y, Eliopoulos G, Boucher H, Harbarth S. Clinical implications of stenotrophomonas maltophilia resistant to trimethoprim-sulfamethoxazole: a study of 69 patients at 2 university hospitals. *Scand J Infect Dis* 2000; **32**:651—6.
18. Wang CH, Lin JC, Lin HA, Chang FY, Wang NC, Chiu SK, et al. Comparisons between patients with trimethoprim-sulfamethoxazole-susceptible and trimethoprim-sulfamethoxazole-resistant Stenotrophomonas maltophilia monomicrobial bacteremia: a 10-year retrospective study. *J Microbiol Immunol Infect* 2016;**49**:378—86.
19. Steinke DT, Seaton RA, Phillips G, MacDonald TM, Davey PG. Prior trimethoprim use and trimethoprim-resistant urinary tract infection: a nested case-control study with multivariate analysis for other risk factors. *J Antimicrob Chemother* 2001; **47**:781—7.
20. Pearson NJ, Towner KJ, McSherry AM, Cattell WR, O'Grady F. Emergence of trimethoprim-resistant enterobacteria in patients receiving long-term co-trimoxazole for the control of intractable urinary-tract infection. *Lancet* 1979;**2**:1205—8.
21. Wu H, Wang JT, Shiau YR, Wang HY, Lauderdale TL, Chang SC. A multicenter surveillance of antimicrobial resistance on Stenotrophomonas maltophilia in Taiwan. *J Microbiol Immunol Infect* 2012;**45**:120—6.
22. Tan CK, Liaw SJ, Yu CJ, Teng LJ, Hsueh PR. Extensively drug-resistant Stenotrophomonas maltophilia in a tertiary care hospital in Taiwan: microbiologic characteristics, clinical features, and outcomes. *Diagn Microbiol Infect Dis* 2008;**60**: 205—10.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373—83.
24. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing; 24th informational supplement*. Wayne: (Document M100—S24) CLSI; 2014.
25. Ansari SR, Hanna H, Hachem R, Jiang Y, Rolston K, Raad I. Risk factors for infections with multidrug-resistant Stenotrophomonas maltophilia in patients with cancer. *Cancer* 2007; **109**:2615—22.
26. Pien CJ, Kuo HY, Chang SW, Chen PR, Yeh HW, Liu CC, et al. Risk factors for levofloxacin resistance in Stenotrophomonas maltophilia from respiratory tract in a regional hospital. *J Microbiol Immunol Infect* 2015;**48**:291—5.
27. Chang LL, Lin HH, Chang CY, Lu PL. Increased incidence of class 1 integrons in trimethoprim/sulfamethoxazole-resistant clinical isolates of Stenotrophomonas maltophilia. *J Antimicrob Chemother* 2007;**59**:1038—9.
28. Chang YT, Lin CY, Chen YH, Hsueh PR. Update on infections caused by Stenotrophomonas maltophilia with particular attention to resistance mechanisms and therapeutic options. *Front Microbiol* 2015;**6**:893.
29. Sanchez MB, Martinez JL. The efflux pump SmeDEF contributes to trimethoprim-sulfamethoxazole resistance in Stenotrophomonas maltophilia. *Antimicrob Agents Chemother* 2015; **59**:4347—8.
30. Chang SC, Chen YC, Hu OY. Antibiotic use in public hospitals in Taiwan after the implementation of national health insurance. *J Formos Med Assoc* 2001;**100**:155—61.
31. Harris AD, Karchmer TB, Carmeli Y, Samore MH. Methodological principles of case-control studies that analyzed risk factors for antibiotic resistance: a systematic review. *Clin Infect Dis* 2001; **32**:1055—61.
32. Paterson DL. Looking for risk factors for the acquisition of antibiotic resistance: a 21st-century approach. *Clin Infect Dis* 2002;**34**:1564—7.