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ORIGINAL ARTICLE

A multicenter surveillance of antimicrobial resistance on *Stenotrophomonas maltophilia* in Taiwan

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Background: *Stenotrophomonas maltophilia* has emerged as an important opportunistic pathogen in debilitated hosts. Clinical management of *S. maltophilia* is challenging due to its intrinsic resistance to a variety of antibiotics. This study investigated the trend and prevalence of antimicrobial resistance in *S. maltophilia* from a nationwide surveillance study in Taiwan.
Methods: *S. maltophilia* isolates were collected biennially between 1998 and 2008 as part of the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program from medical centers and regional hospitals throughout Taiwan. Minimal inhibitory concentrations (MIC) were determined using the Clinical and Laboratory Standards Institute reference broth microdilution method.
Results: A total of 377 non-duplicate *S. maltophilia* isolates were collected from 38 hospitals. The majority of the isolates were from the respiratory tract (256, 67.9%), followed by blood (48, 12.7%). Overall, 376 (99.7%) isolates were susceptible to minocycline, 362 (96%) to tigecycline, 311 (82.5%) to trimethoprim/sulfamethoxazole (TMP-SMX), 300 (79.6%) to levofloxacin, 92 (24.4%) to ceftazidime, and 70 (18.6%) to ticarcillin-clavulanic acid. The MIC_{50}/MIC_{90} of minocycline, tigecycline, TMP-SMX, levofloxacin, ceftazidime, and ticarcillin-clavulanic acid, were $\leq$0.5/1 μg/mL, 0.25/1 μg/mL, $\leq$0.25/8 μg/mL, 1/4 μg/mL, 32/128 μg/mL, and 64/128 μg/mL, respectively. A trend of increased non-susceptibility to levofloxacin ($p = 0.014$) was observed over the 10-year study period. Compared to TMP-SMX-susceptible

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isolates, TMP-SMX-resistant isolates were less susceptible to levofloxacin (54.5% vs. 84.9%, $p < 0.001$).
Conclusion: In this 10-year study, minocycline and TMP-SMX remained the two antimicrobials with better *in vitro* activities against *S. maltophilia* than ceftazidime, levofloxacin, and ticarcillin-clavulanic acid. The activity of levofloxacin against *S. maltophilia* in Taiwan declined during the past 10 years.

Introduction

Stenotrophomonas maltophilia is a non-fermentative Gram-negative bacillus that could be found in almost all humid environments, including water, soil and plants.[1–3] It has emerged as an important opportunistic pathogen in debilitated hosts, including patients with cancer, chronic obstructive pulmonary disease, cystic fibrosis and prolonged mechanical ventilation.[4–7] The most common manifestations of *S. maltophilia* infection are pneumonia and blood-stream infections and, less frequently, wound and urinary tract infections.[8] Risk factors for *S. maltophilia* infection include use of indwelling devices, exposure to broad-spectrum antimicrobials, long hospital stays, chemotherapy-induced neutropenia of long duration, mucositis, and receipt of total parenteral nutrition.[5] Surveys in recent years showed an increasing isolation rate for *S. maltophilia*, probably due to increasing population of patients at risk.[8,9]

Infections caused by *S. maltophilia* are associated with high mortality rates. The crude mortality rates ranged from 18% to 69% and the attributable mortality rates ranged from 24% to 58%, especially in patients with hematological malignancies, neutropenia and intensive care unit (ICU) admission.[10–12] Fortunately, analysis of the risk factors for mortality showed that appropriate therapy was significantly protective.[12] However, *S. maltophilia* poses challenges to clinical management due to its high-level intrinsic resistance to a variety of antibiotics, especially β-lactams.[13] Of the antibiotics that are commonly investigated for *in vitro* activity against *S. maltophilia*, trimethoprim/sulfamethoxazole (TMP-SMX), fluoroquinolones, ticarcillin-clavulanic acid and minocycline appear to be the most active with lower minimal inhibitory concentrations (MICs).[14–17] Nevertheless, trends of increasing resistance to antimicrobials such as TMP-SMX and ticarcillin-clavulanic acid have been recently reported.[8,18] On the other hand, tigecycline, the new broad-spectrum glycylcycline, has been found to be active *in vitro* against TMP-SMX-resistant *S. maltophilia*.[19,20]

In Taiwan, *S. maltophilia* has also been noted as an important nosocomial pathogen. From 1999 to 2004, an 85% increase in nosocomial bloodstream infections caused by *S. maltophilia* was noted at a medical center.[9] *S. maltophilia* was the sixth leading Gram-negative nosocomial pathogen in ICUs between 2003 and 2010 (Taiwan Nosocomial Infection Surveillance, 2010, Taiwan CDC unpublished data). However, national data on the susceptibility of *S. maltophilia* in Taiwan are limited.[9,21–24] The purpose of this study was to perform nationwide surveillance to investigate the trends of antimicrobial resistance in *S. maltophilia* in Taiwan.

Methods

Isolate collection and identification

S. maltophilia isolates were collected as part of the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program from medical centers and regional hospitals throughout Taiwan. The program was conducted biennially between 1998 and 2008. The isolates were collected between October and December 1998 from 44 hospitals and between March and May 2000 from 21 hospitals. In 2002, 2004, 2006, and 2008, isolates were collected between July and September from the same 26 hospitals, except that isolates in 2006 were from 25 hospitals. The participating hospitals are located in the four geographic regions (northern, central, southern, and eastern regions) of Taiwan.

The collection process of the TSAR program has been described previously.[25] Each isolate was subcultured onto appropriate agar plates (BBL, Becton Dickinson Microbiology System, Cockeysville, MD, USA) to check for purity. The identification of each isolate was confirmed using a combination of standard conventional biochemical tests and Vitek 2 Gram-negative identification cards (bioMérieux, Maray l'Etoile, France).

Antimicrobial susceptibility testing

The MICs of seven antibiotics were determined by the reference broth microdilution method following the guidelines of the Clinical and Laboratory Standards Institute (CLSI) using freshly prepared cation-adjusted Mueller-Hinton broth.[26] The antibiotics tested included ceftazidime (1—128 μg/mL), chloramphenicol (8—32 μg/mL), levofloxacin (0.25—64 μg/mL), minocycline (0.5—64 μg/mL), ticarcillin-clavulanic acid (1/2—128/2 μg/mL), TMP-SMX (0.25—32 μg/mL) and tigecycline (0.12—4 μg/mL). Custom-designed 96 well panels (Sensititre, Trek diagnostics, West Sussex, UK) were used with a final inoculum of 5×10^5 colony forming units /mL at 100 μL per well. For tigecycline, the criteria of ≤1 μg/mL for susceptibility and ≥2.0 μg/mL for resistance were applied based on the clinical breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for *Enterobacteriaceae*.[27] CLSI interpretive criteria for *S. maltophilia* were used for other agents. Quality control was performed on each day of testing with *Escherichia coli* ATCC 25922 and *Psuedomonas aeruginosa* ATCC 27853.

Table 1 Source breakdown of 377 *S. maltophilia* isolates by year, hospital type, geographic region, specimen type, and patient location

Source category	Number (% of source category) of isolates from each year						
	1998	2000	2002	2004	2006	2008	Total
Total	49	29	77	63	69	90	377
Hospital type:							
Medical center	14 (28.6)	22 (75.9)	47 (61.0)	36 (57.1)	36 (52.2)	61 (67.8)	216 (57.3)
Regional hospital	35 (71.4)	7 (24.1)	30 (39.0)	27 (42.9)	33 (47.8)	29 (32.2)	161 (42.7)
Region of Taiwan:							
Northern	26 (53.1)	9 (31.0)	29 (37.7)	21 (33.3)	26 (37.7)	32 (35.6)	143 (37.9)
Central	11 (22.4)	7 (24.1)	17 (22.1)	17 (27.0)	17 (24.6)	38 (42.2)	107 (28.4)
Southern	11 (22.4)	12 (41.4)	27 (35.1)	20 (31.7)	21 (30.4)	16 (17.8)	107 (28.4)
Eastern	1 (2.0)	1 (3.4)	4 (5.2)	5 (7.9)	5 (7.2)	4 (4.4)	20 (5.3)
Specimen type:							
Blood	11 (22.4)	6 (20.7)	12 (15.6)	5 (7.9)	4 (5.8)	10 (11.1)	48 (12.7)
Respiratory tract	22 (44.9)	16 (55.2)	52 (67.5)	49 (77.8)	49 (71.0)	68 (75.6)	256 (67.9)
Others	16 (32.7)	7 (24.1)	13 (16.9)	9 (14.3)	16 (23.2)	12 (13.3)	73 (19.4)
Patient location:[a]							
ICU admission	19 (38.8)	15 (51.7)	35 (45.5)	34 (50.8)	36 (52.2)	35 (38.9)	174 (46.1)
Non-ICU Inpatient	11 (22.4)	8 (27.6)	36 (46.8)	21 (33.3)	28 (40.6)	39 (43.3)	143 (37.9)
OPD/ER	6 (12.2)	6 (20.7)	6 (7.8)	8 (15.9)	5 (7.2)	2 (2.2)	33 (9.3)

[a] Information on patient location of 13 isolates from 1998 and 14 isolates from 2008 was not available.
ER = emergency room; ICU = intensive care unit; OPD = outpatients department.

Statistical analysis

Susceptibility interpretation analysis was made using Whonet software (http://www.who.int/drugresistance/whonetsoftware/en/). Univariate analysis was performed using SPSS statistics 17.0 software (IBM Corporation, Somers, NY). Significance of differences in frequencies and proportions were tested by χ^2 test.

Results

During the 10-year study period, a total of 377 non-duplicate *S. maltophilia* isolates were collected. Table 1 is a breakdown of the source of these 377 clinical isolates. The majority of the isolates were from the respiratory tract (256, 67.9%) followed by blood (48, 12.7%), and most (317, 84.1%) were from inpatients including 174 (46.1%) from ICU and 143 (37.9%) from non-ICU inpatients. Among the 267 isolates whose patient age was known, 51.7% were from the ≥70 year old group.

The *in vitro* activities [MIC_{50} and MIC_{90} (MIC at which 50% and 90% of isolates were inhibited), MIC range, % resistant, % intermediate, and % susceptible] of the seven agents tested are shown in Table 2. Overall, 376 (99.7%) isolates were susceptible to minocycline, 311 (82.5%) to TMP-SMX, 300 (79.6%) to levofloxacin, 92 (24.4%) to ceftazidime, and 70 (18.6%) to ticarcillin-clavulanic acid based on the CLSI interpretive criteria. The MIC_{50}/MIC_{90} of minocycline, TMP-SMX, levofloxacin, ceftazidime, and ticarcillin-clavulanic acid were ≤0.5/1 μg/mL, ≤0.25/8 μg/mL, 1/4 μg/mL, 32/128 μg/mL, and 64/128 μg/mL, respectively. The MIC_{50} and MIC_{90} of tigecycline were 0.25 μg/mL and 1 μg/mL, respectively, and 362 (96%) isolates were susceptible (MIC ≤1 μg/mL). For better comparison of their *in vitro* activities, the MIC distribution of ceftazidime, levofloxacin, minocycline, TMP-SMX, ticarcillin-clavulanic acid and tigecycline is shown in Fig. 1.

Table 2 *In vitro* activity of seven antimicrobial agents tested against 377 *S. maltophilia* from Taiwan

Antimicrobial agent	MIC (μg/mL)			% of isolates		
	MIC_{50}	MIC_{90}	Range	Resistant	Intermediate	Susceptible
Ceftazidime	32	128	≤1—>128	69.0	6.6	24.4
Chloramphenicol	8	16	≤2—>32	8.8	22.5	68.7
Levofloxacin	1	4	≤0.25—32	8.0	12.4	79.6
Minocycline	≤0.5	1	≤0.5—8	0	0.3	99.7
Ticarcillin/Clavulanic acid	64	128	≤1—>128	25.5	55.9	18.6
Tigecycline[a]	0.25	1	≤0.12—2	4.0	0	96.0
TMP/SMX	≤0.25	8	≤0.25—>32	17.5	0	82.5

[a] Tigecycline breakpoints of EUCAST for *Enteroacteriaceae* (≤1 μg/mL for susceptible and ≥2 μg/mL for resistance) were used.
MIC = minimal inhibitory concentration; TMP/SMX = trimethoprim/sulfamethoxazole.

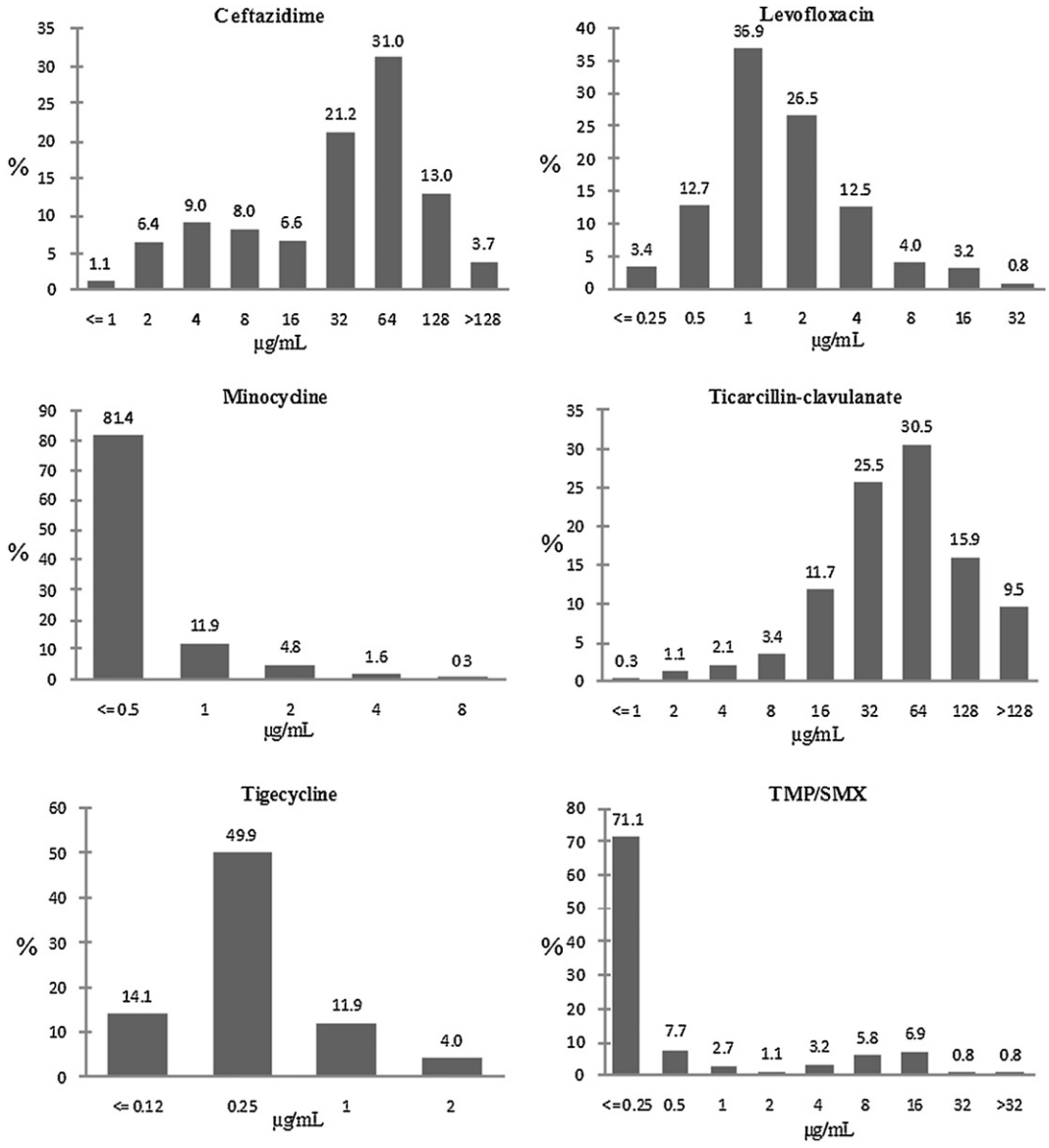

Figure 1. Minimal inhibitory concentration distribution of ceftazidime, levofloxacin, minocycline, ticarcillin-clavulanic acid, tigecycline, and trimethoprim/sulfamethoxazole against 377 isolates of *S. maltophilia*. TMP/SMX = trimethoprim/sulfamethoxazole.

The susceptibility rates of *S. maltophilia* isolates from different patient locations (ICU vs. non-ICU inpatients vs. outpatients), and specimen types (blood vs. respiratory) were compared (Table 3). Except minocycline, to which nearly all isolates were susceptible, isolates from ICUs had higher rates of nonsusceptibility than isolates from non-ICU and outpatients, but the differences were not statistically significant ($p > 0.05$ for all agents). Isolates from the respiratory tract were less susceptible than those from blood, especially to ceftazidime (45.8% vs. 18.0%, $p < 0.01$) and chloramphenicol (83.3% vs. 68.4%, $p = 0.039$). Compared to TMP/SMX-susceptible isolates, TMP/SMX-resistant isolates were less susceptible, especially to chloramphenicol (51.5% vs. 72.3%, $p = 0.001$) and levofloxacin (54.5% vs. 84.9%, $p < 0.001$; Table 3).

While the susceptibility of *S. maltophilia* to ceftazidime, minocycline, ticarcillin-clavulanic acid and TMP-SMX did not change significantly over the 10-year study period, a trend of decreased susceptibility to levofloxacin (83.7% in 1998 to 65.6% in 2008, $p = 0.014$) was observed (Fig. 2). Among all 377 isolates, there was only one isolate with multidrug resistance to ceftazidime, chloramphenicol, levofloxacin, TMP-SMX and ticarcillin-clavulanic acid.

Discussion

The present study evaluated the susceptibility of clinical *S. maltophilia* isolates collected over a 10-year period in Taiwan. We found that the activities of TMP-SMX and minocycline remained similarly high over the years. However, the activity of levofloxacin against *S. maltophilia* has declined. In addition, TMP/SMX-resistant isolates were

Table 3 Comparison of *S. maltophilia* susceptibility among isolates from different patient location and specimen types, and among trimethoprim/sulfamethoxazole-resistant versus -susceptible isolates

Antimicrobial agent	Patient location							Specimen type					TMP/SMX				
	ICU (n = 172)		Non-ICU (n = 170)		OPD (n = 33)		p[a]	Respiratory (n = 256)		Blood (n = 48)		p	Resistant (n = 66)		Susceptible (n = 311)		p
	%R	%S	%R	%S	%R	%S		%R	%S	%R	%S		%R	%S	%R	%S	
Ceftazidime	71.5	19.8	67.1	28.2	63.6	30.3	0.201	76.2	18	43.8	45.8	<0.01	77.3	18.2	67.2	25.7	0.211
Chloramphenicol	8.7	65.7	8.2	72.4	12.1	69.7	0.103	6.6	68.4	4.2	83.3	0.039	28.8	51.5	4.5	72.3	0.001
Levofloxacin	10.5	78.5	7.1	80	0	84.8	0.618	7.8	78.1	4.2	83.3	0.563	15.2	54.5	6.4	84.9	<0.001
Minocycline	0	100	0	99.4	0	100	0.748	0	100	0	100	—	0	98.5	0	100	—
Ticarcillin/ Clavulanate	22.7	21.8	27.1	15.9	30.3	15.2	0.402	24.6	18	22.9	25	0.316	22.7	27.3	26	16.7	0.175
Tigecycline	4.7	95.3	3.5	96.5	3	97	0.929	3.9	96.1	0	100	0.174	4.5	95.5	3.9	96.1	0.733
TMP/SMX	21.5	78.5	14.1	85.9	15.2	84.8	0.282	14.8	85.2	14.6	85.4	0.583	100	0	0	100	—

[a] Differences in % susceptibility among isolates within each group were compared by χ^2 test.
ICU = intensive care unit; OPD = outpatients; R = resistant; S = susceptible; TMP/SMX = trimethoprim/sulfamethoxazole.

significantly less susceptible than TMP/SMX-susceptible isolates to levofloxacin.

In a recent study by Farrell et al,[17] who evaluated susceptibilities of 1586 *S. maltophilia* clinical isolates collected worldwide between 2003 and 2008, rates of susceptibility to ceftazidime, levofloxacin, ticarcillin-clavulanic acid, and TMP-SMX were 44.8%, 83.4%, 39.1%, and 96.0%, respectively. In comparison, *S. maltophilia* isolates in our study showed significantly lower susceptibility to ceftazidime (24.4% vs. 44.8%, $p < 0.01$), ticarcillin-clavulanic acid (18.6% vs. 39.1%, $p < 0.01$) and TMP-SMX (82.5% vs. 96.0%, $p < 0.01$), while susceptibility to levofloxacin was similar between the two studies (79.6% vs. 83.4%, $p = 0.082$). Of note, the low susceptibility to ticarcillin-clavulanic acid was due in part to the large proportions of isolates in the intermediate category (55.9% vs. 36.7%) in both studies.

The differences in susceptibility rates between the two studies may be in part due to differences in specimen source. In the study by Farrell et al,[17] over half of the isolates were from blood (51%), while respiratory isolates comprised smaller proportion (37%), and no comparison was made on susceptibility from the two specimen groups. In contrast, the majority of our isolates were from the respiratory tract (67.9%). Although there were fewer blood isolates (48, 12.7%) in our study, it is worth noting that blood isolates were more susceptible to all the agents than respiratory isolates, especially ceftazidime (45.8% vs. 18%). In addition, isolates from the Asia-Pacific region in the study of Farrell et al had the lowest rates of susceptibility to ceftazidime (32.6%), levofloxacin (78.0%), ticarcillin-clavulanic acid (27.0%), and TMP-SMX (90.8%) compared to isolates from North America, Europe, and Latin America. Thus, *S. maltophilia* isolates from the Asia-Pacific region appeared to be less susceptible to these agents.

We also found a trend of decreased susceptibility to levofloxacin over the 10-year period. Although rapid emergence of resistance against fluoroquinolones has been

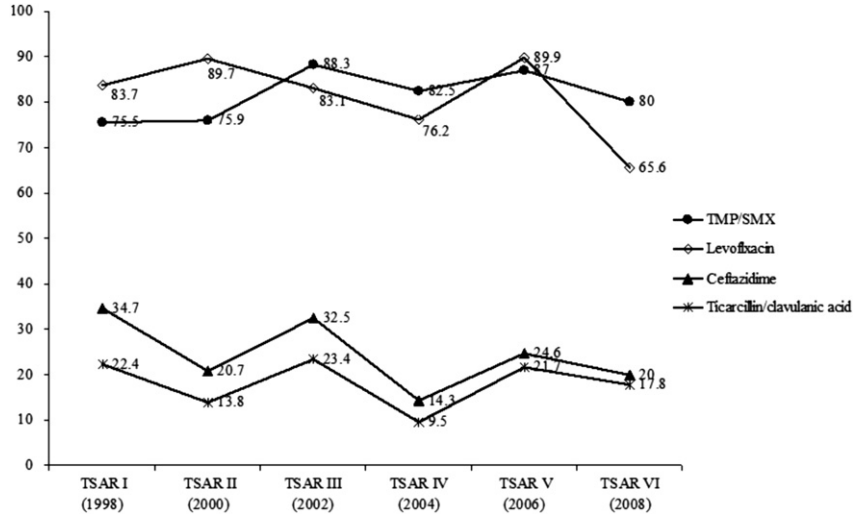

Figure 2. Trends of susceptibility of *S. maltophilia* to ceftazidime, levofloxacin, ticarcillin-clavulanic acid, and trimethoprim/sulfamethoxazole over 10 years. TMP/SMX = trimethoprim/sulfamethoxazole; TSAR = Taiwan Surveillance of Antimicrobial Resistance.

observed *in vitro* and *in vivo* for *S. maltophilia*,[8,28] this is, to our knowledge, the first study to investigate levofloxacin resistance over a long period of time. One possible explanation for this finding is that resistant mutants may have emerged following exposure to fluoroquinolones.[28,29] Increased fluoroquinolone use has been associated with decreasing susceptibility to fluoroquinolones in many Gram-negative pathogens.[30]

The present study found tigecycline to have potent *in vitro* activity against *S. maltophilia* isolates in Taiwan, with MIC_{50}/MIC_{90} of 0.25/1 μg/mL, which were one dilution lower than those reported by Farrell et al, (0.5/2 μg/mL).[17] In another study which evaluated the antimicrobial activities against isolates collected from ICUs worldwide, tigecycline also exhibited potent *in vitro* activity against *S. maltophilia*.[19] Further studies are needed to determine their clinical efficacy.

There were some limitations to this study. First, although the isolates we tested were from various clinical specimens, there was a predominance of respiratory specimens. Since isolates from the respiratory tract showed higher resistance rates than those from blood, including to ceftazidime and chloramphenicol, further studies are needed to confirm the higher susceptibilities of bloodstream isolates. Second, due to limited clinical information, we could not determine if all *S. maltophilia* isolates caused infections in the patients from whom the isolates were recovered.

In conclusion, the results of this study suggest that minocycline and TMP/SMX remain the two most potent antibiotics against *S. maltophilia* in Taiwan, although more clinical trials or observational studies are needed to confirm their efficacy. Since *S. maltophilia* demonstrated a decreasing trend of susceptibility to levofloxacin, and since TMP/SMX-resistant isolates also had lower levofloxacin susceptibility, use of higher doses of fluoroquinolone or in combination with other antibiotics with better *in vitro* activity should be considered if fluoroquinolones are to be used. Finally, this study indicated that continued surveillance of antimicrobial resistance in *S. maltophilia* to fluoroquinolones and other antibiotics is warranted.

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