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Antimicrobial Susceptibilities of a Worldwide Collection of *Stenotrophomonas maltophilia* Isolates Tested against Tigecycline and Agents Commonly Used for *S. maltophilia* Infections▽

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Antimicrobial susceptibilities were determined for 1,586 isolates of *Stenotrophomonas maltophilia* from globally diverse medical centers using the Clinical Laboratory Standards Institute broth microdilution method. The combination trimethoprim-sulfamethoxazole (96.0% of isolates susceptible at ≤2 μg/ml trimethoprim and 38 μg/ml sulfamethoxazole) and tigecycline (95.5% of isolates sussceptible at ≤2 μg/ml) were the only antimicrobials tested with >94% susceptibility in all regions. Susceptibility rates for other commonly used were lower than expected and varied geographically. This *in vitro* data supports tigecycline as a potential candidate for clinical investigations into *S. maltophilia* infections.

Stenotrophomonas maltophilia is a Gram-negative bacillus, inherently multidrug resistant (MDR) and frequently recovered from environmental sources. It has been associated with severe nosocomially acquired bacteremia and pneumonia, usually among immunocompromised patients, as well as meningitis, endocarditis, and urinary tract, skin/soft tissue, and ocular infections. *S. maltophilia* infections are associated with high morbidity and mortality, with estimated crude mortality rates ranging from 20 to 70% and with the risk of mortality highest among patients receiving inappropriate initial antimicrobial therapy (5). Treatment of *S. maltophilia* infections represents a significant challenge because of the organism's high levels of intrinsic resistance to many antimicrobial agents, difficulties in susceptibility testing, the development of resistance during therapy, and the paucity of clinical trials to determine optimal therapy (8, 12).

The combination trimethoprim-sulfamethoxazole (TMP/SMX) is the recognized antimicrobial of choice for the treatment of infections caused by *S. maltophilia* with ceftazidime, ticarcillin-clavulanate, minocycline, tigecycline, fluoroquinolones, and the polymyxins being described as alternative therapies. It is important to note that all recommended therapy options have been based on *in vitro* studies and anecdotal experience rather than appropriately structured clinical trials (11). Resistance to TMP/SMX has been described and varies geographically, being shown by as many as 10% of isolates in Europe (7). In addition, allergic reactions to the combination TMP/SMX are common and can be severe, which further compromises its application (1). Clearly, therapeutic alternatives are needed to treat infections caused by *S. maltophilia.*

Tigecycline is a 9-*t*-butylglycylamido derivative of minocycline and is the first glycylcycline licensed for clinical use. Tigecycline binds to the 30S ribosomal subunit, resulting in inhibition of protein synthesis (13). It exhibits a wide range of activity against Gram-positive and -negative organisms, including MDR strains. Tigecycline is approved by the United States Food and Drug Administration (USFDA) for the treatment of complicated skin and skin structure infections (cSSSI), intra-abdominal infections, and, more recently, community-acquired bacterial pneumonia. Tigecycline has demonstrated good *in vitro* activity against *S. maltophilia* in several studies (6, 9, 14). The aim of this study was to assess antimicrobial resistance in *S. maltophilia* against commonly used agents by using the largest and most geographically diverse collection of contemporary isolates available, with the rationale being the paucity of such information in the face of a clear need for clinical and research options.

From January 2003 to December 2008, a total of 1,586 unique clinical *S. maltophilia* strains were recovered and identified from 119 medical centers located across Asia and the Pacific (Asian-Pacific), Europe, Latin America, and North America. Bacterial identification was confirmed by the central monitoring site (JMI Laboratories, North Liberty, IA) using standard algorithms (microscopy, culture characteristics, and oxidase reaction) followed by an automated system (Vitek 2; bioMerieux, Hazelwood, MO). MIC values were determined for all isolates based on the Clinical Laboratory Standards Institute (CLSI) broth microdilution method using commercially prepared and validated panels (TREK Diagnostic Systems, Cleveland, OH) in fresh cation-adjusted Mueller-Hinton broth (2). Tigecycline breakpoints established by the USFDA for *Enterobacteriaceae* (≤2 μg/ml for susceptibility and ≥8 μg/ml for resistance) as well as the polymyxin B breakpoints established by the CLSI for *P. aeruginosa* (≤2 μg/ml for susceptibility and ≥8 μg/ml for resistance), were applied for comparison only (Tygacil; Wyeth Pharmaceuticals, Philadelphia, PA). CLSI quality control ranges and interpretive criteria were used for comparator compounds (3).

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TABLE 1. Regional MIC distributions for tigecycline tested against 1,586 *S. maltophilia* strains, stratified by geographic region

Region (no. of strains tested)	Cumulative % inhibited at tigecycline MIC (μg/ml) of:						
	≤0.12	0.25	0.5	1	2[a]	4	>4
North America (491)	2.2	16.5	49.7	79.8	94.5	98.4	100.0
Europe (447)	1.8	13.7	48.1	83.5	95.3	99.3	100.0
Asian-Pacific (359)	1.4	12.5	57.9	87.5	96.1	99.2	100.0
Latin America (289)	1.7	15.2	52.3	87.5	96.5	100.0	
All regions (1,586)	1.8	14.6	51.6	84.0	95.5	99.1	100.0

[a] Susceptibility breakpoint established by the CLSI for *Enterobacteriaceae* (3).

Clinical sites of infection for *S. maltophilia* were primarily bloodstream (51%) and respiratory tract (37%). Tigecycline activities were similar across the four geographic regions (94.5 to 96.5% of isolates inhibited at ≤2 μg/ml) and were most similar to those of TMP/SMX (90.8 to 98.9% of isolates susceptible) (Tables 1 and 2). When tested against *S. maltophilia* isolates from North America and Europe, TMP/SMX was the most active compound (MIC_{50}, ≤0.5 μg/ml and MIC_{90}, 1 μg/ml; 97.6 to 98.9% of isolates susceptible), followed by tigecycline (MIC_{50}, 1 μg/ml, and MIC_{90}, 2 μg/ml; 94.5 to 95.3% o isolates susceptible) and levofloxacin (MIC_{50}, 1 μg/ml, and MIC_{90}, 4 μg/ml; 82.5 to 83.7% of isolates susceptible) (Table 2). Tigecycline was the most active compound tested against *S. maltophilia* isolates from the Asian-Pacific and Latin American regions (MIC_{50}, 0.5 μg/ml, and MIC_{90}, 2 μg/ml; 96.1 to 96.5% of isolates susceptible), followed by TMP/SMX (MIC_{50}, ≤0.5 μg/ml, and MIC_{90}, 1 μg/ml; 90.8 to 95.5% of isolates susceptible) (Table 2). Levofloxacin exhibited good *in vitro* activity against *S. maltophilia* isolates from Latin America (91.3% susceptible), but its activity was more restricted when tested against isolates from other geographic regions (78.0 to 83.7% of isolates susceptible) (Table 2). In general, ceftazidime (32.6 to 51.0% of isolates susceptible), ticarcillin-clavulanate (27.0 to 46.1% of isolates susceptible), and polymyxin B (33.4 to 76.4% of isolates susceptible) showed the most limited *in vitro* activities against *S. maltophilia*.

Tigecycline exhibited similar potencies across all geographic regions, and its antimicrobial activity was similar to that of TMP/SMX. Overall, tigecycline showed a greater potency against *S. maltophilia* than levofloxacin, ceftazidime, and ticarcillin-clavulanate. Tigecycline and TMP/SMX were the only antimicrobial agents tested with susceptibility rates of >90% in all regions and overall. Prevalence of resistance to alternative therapies varied geographically and was higher than expected or previously reported for these antimicrobials in some geographic regions. There is some evidence to suggest that resistance to alternative drugs could be increasing. Ticarcillin-clavulanate susceptibility was reported as 59.1% in Brazil in 70 clinical isolates collected between 2000 and 2002 (10), compared to our data which show susceptibility at 39.1% for ticarcillin-clavulanate in several Latin American nations, including Brazil. This data highlights the need for continued antimicrobial resistance surveillance at the local level, especially for these alternative agents.

Few treatment options are available to treat *S. maltophilia* infections, and this study demonstrates that antimicrobial resistance to alternate antimicrobial agents is higher than projected and geographically varied. Infections caused by *S. mal-*

TABLE 2. Antimicrobial activity of tigecycline and comparator agents tested against *S. maltophilia* isolates from four geographic regions

Region (no. of strains tested) and antimicrobial agent	MIC (μg/ml)[a]		% of isolates	
	50%	90%	Susceptible	Resistant
North America (491)				
Tigecycline	1	2	94.5[b]	1.6[b]
Ceftazidime	8	>16	51.0	34.9
Levofloxacin	1	4	82.5	8.4
Polymyxin B	≤1	>4	73.2[c]	17.4[c]
Ticarcillin-clavulanate	32	128	46.1	17.6
TMP/SMX[d]	≤0.5	1	97.6	2.4
Europe (447)				
Tigecycline	1	2	95.3[b]	0.7[b]
Ceftazidime	16	>16	45.2	43.6
Levofloxacin	1	4	83.7	8.5
Polymyxin B	≤1	>4	72.6[c]	16.2[c]
Ticarcillin-clavulanate	32	>128	42.7	16.2
TMP/SMX	≤0.5	1	98.9	1.1
Asian-Pacific (359)				
Tigecycline	0.5	2	96.1[b]	0.8[b]
Ceftazidime	>16	>16	32.6	53.5
Levofloxacin	1	>4	78.0	11.7
Polymyxin B	>4	>4	33.4[c]	57.7[c]
Ticarcillin-clavulanate	64	>128	27.0	35.1
TMP/SMX	≤0.5	1	90.8	9.2
Latin America (289)				
Tigecycline	0.5	2	96.5[b]	0.0[b]
Ceftazidime	16	>16	48.8	38.4
Levofloxacin	1	2	91.3	3.8
Polymyxin B	≤1	>4	76.4[c]	14.9[c]
Ticarcillin-clavulanate	32	128	36.7	22.5
TMP/SMX	≤0.5	1	95.5	4.5
All regions (1,586)				
Tigecycline	0.5	2	95.5[b]	0.9[b]
Ceftazidime	16	>16	4.8	42.2
Levofloxacin	1	4	83.4	83
Polymyxin B	≤1	>4	64.6[c]	25.7[c]
Ticarcillin-clavulanate	32	>128	39.1	24.2
TMP/SMX	≤0.5	1	96.0	4.0

[a] 50% and 90%, MIC_{50} and MIC_{90}, respectively.
[b] Tigecycline breakpoints established by the USFDA (Tygacil; Wyeth Pharmaceuticals, Philadelphia, PA) for *Enterobacteriaceae* (≤2 μg/ml for susceptibility and ≥8 μg/ml for resistance) were applied for comparison only.
[c] Polymyxin B breakpoints established by the CLSI (3) (Tygacil; Wyeth Pharmaceuticals, Philadelphia, PA) for *P. aeruginosa* (≤2 μg/ml for susceptibility and ≥8 μg/ml for resistance) were applied for comparison only.
[d] TMP/SMX, trimethoprim-sulfamethoxazole.

tophilia are life threatening and have a high mortality, and the lack of evidence-based therapeutic options often forces clinicians to make difficult decisions regarding antimicrobial therapy. The role of tigecycline in the treatment of *S. maltophilia* infections warrants further investigation due to its high *in vitro* activity and potency. Synergies between tigecycline and TMP/SMX and also amikacin have been reported, and hence combination therapy would be a potential approach for clinical investigations and experimental therapy trials (4).

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