

Antimicrobial Susceptibility of a Worldwide Collection of *Stenotrophomonas maltophilia* Tested Against Tigecycline and Agents Used for *S. maltophilia* Infections

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ABSTRACT

Background: Treatment of *S. maltophilia* (SM) infections represents a significant challenge because of high levels of intrinsic antimicrobial resistance (R), difficulties in susceptibility (S) testing, and the paucity of clinical trials to determine optimal therapy.

Methods: 1,586 unique clinical SM strains were collected from 119 medical centers worldwide (2003-2008). Isolates were tested for S against tigecycline (TIG) and agents most commonly used to treat SM infections by broth microdilution methods according to CLSI guidelines and interpretative criteria. TIG breakpoints established by the USA-FDA for Enterobacteriaceae ($\leq 2/\geq 8$ $\mu\text{g/ml}$ for S/R) were applied for comparison purposes.

Results: Isolates were mainly from bloodstream infection (51%) and pneumonia (37%). TIG activity was consistent across all regions evaluated with 94.5-96.1% inhibited at ≤ 2 $\mu\text{g/ml}$; while R to other drugs were highest in the Asia-Pacific region. TIG activity was comparable to that of trimethoprim/sulfamethoxazole (T/S; 96.0% S) and greater than levofloxacin (LEV, 83.4% S) and polymyxin B (PB, 64.6% inhibited at ≤ 2 $\mu\text{g/ml}$). Minocycline showed potent activity (MIC_{90} , 2 $\mu\text{g/ml}$; 99.1% inhibited at ≤ 4 $\mu\text{g/ml}$); while S to ceftazidime and ticarcillin/clavulanate was limited (44.8 and 39.1% respectively).

Region (no. tested)	Cumulative % inhibited at TIG MIC ($\mu\text{g/ml}$) of:					MIC_{90} ($\mu\text{g/ml}$) / % S (at ≤ 2 $\mu\text{g/ml}$) ^b		
	≤ 0.25	0.5	1	2 ^a	4	LEV	PB	T/S
North America (491)	16.5	49.7	79.8	94.5	98.4	4/82.5	>4/73.2	1/97.6
Europe (447)	13.7	48.1	83.5	95.3	99.3	4/83.7	>4/72.6	1/98.9
Latin America (289)	15.2	52.3	87.5	96.5	100.0	2/91.4	>4/76.4	1/95.5
Asia-Pacific (359)	12.5	57.9	87.5	96.1	99.2	>4/78.0	>4/33.4	2/90.8
All (1,586)	14.6	51.6	84.0	95.5	99.1	4/83.4	>4/64.6	1/96.0

a. S breakpoint established by the CLSI for Enterobacteriaceae.
b. CLSI S breakpoint for these compounds.

Conclusions: Few therapeutic options are available to treat SM infections. The role of TIG in the treatment of SM infections warrants further investigations due to its in vitro activity.

INTRODUCTION

Treatment of *Stenotrophomonas maltophilia* infections represents a significant challenge because of high levels of intrinsic antimicrobial resistance, difficulties in susceptibility testing, and the paucity of clinical trials to determine optimal therapy.

S. maltophilia is a Gram-negative bacillus, inherently multidrug resistant (MDR) and is frequently recovered from the environment. 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; estimated crude mortality rates range from 20 to 70%.

Tigecycline is a semisynthetic derivative of minocycline and the first glycylcycline antibiotic licensed for clinical use. It exhibits a wide range of activity against Gram-positive and -negative organisms, including MDR strains. Tigecycline binds to the 30S ribosomal subunit which results in protein inhibition. Tigecycline is approved by the United States Food and Drug Administration (USA-FDA) for the treatment of complicated skin and skin structure infections (cSSSI), intra-abdominal infections and, more recently, community-acquired bacterial pneumonia.

MATERIALS AND METHODS

Bacterial isolates: From 2003 – 2008, a total of 1,586 unique clinical *S. maltophilia* strains were recovered and identified from 119 medical centers located across Asia-Pacific, Europe, Latin America and North America. Bacterial identification was confirmed by the central monitoring site (JMI Laboratories, North Liberty, Iowa, USA) using standard algorithms and an automated system, when needed (Vitek[®] 2; bioMerieux, Missouri, USA).

Susceptibility testing: MIC values were determined for all isolates based on the CLSI broth microdilution method using commercially prepared and validated panels (TREK Diagnostic Systems, Ohio, USA) in fresh cation-adjusted Mueller-Hinton broth (M07-A8). Tigecycline breakpoints established by the USA-FDA for Enterobacteriaceae ($\leq 2 / \geq 8$ $\mu\text{g/ml}$ for susceptibility/resistance) as well as the polymyxin B breakpoints established by the CLSI for *P. aeruginosa* ($\leq 2 / \geq 8$ $\mu\text{g/ml}$ for susceptibility/resistance), were applied for comparison purposes only. Quality control (QC) ranges and interpretive criteria for comparator compounds used the CLSI M100-S19 document; QC strains included *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853, among others.

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RESULTS

- Clinical sites of infection for *S. maltophilia* were primarily blood (51%) and respiratory (37%).
- Tigecycline activity was similar across the four geographic regions (94.5-96.5% inhibited at ≤ 2 $\mu\text{g/ml}$) and was similar to trimethoprim / sulfamethoxazole (TMP/SMX; 90.8-98.9% 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 $\mu\text{g/ml}$ and MIC_{90} , 1 $\mu\text{g/ml}$; 97.6-98.9% susceptible), followed by tigecycline (MIC_{50} , 1 $\mu\text{g/ml}$ and MIC_{90} , 2 $\mu\text{g/ml}$; 94.5-95.3% susceptible) and levofloxacin (MIC_{50} , 1 $\mu\text{g/ml}$ and MIC_{90} , 4 $\mu\text{g/ml}$; 82.5-83.7% susceptible; Table 2).

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

Region (no. tested)	Cumulative % inhibited at tigecycline MIC ($\mu\text{g/ml}$)						
	≤ 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
Asia-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	100.0
All (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.

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

Region (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	% susceptible	% resistant
North America (491)				
Tigecycline	1	2	94.5	1.6
Ceftazidime	8	>16	51.0	34.9
Levofloxacin	1	4	82.5	8.4
Polymyxin B	≤ 1	>4	73.2	17.4
Ticarcillin/clavulanate	32	128	46.1	17.6
TMP/SMX ^a	≤ 0.5	1	97.6	2.4
Europe (447)				
Tigecycline	1	2	95.3	0.7
Ceftazidime	16	>16	45.2	43.6
Levofloxacin	1	4	83.7	8.5
Polymyxin B	≤ 1	>4	72.6	16.2
Ticarcillin/clavulanate	32	>128	42.7	16.2
TMP/SMX ^a	≤ 0.5	1	98.9	1.1
APAC (359)				
Tigecycline	0.5	2	96.1	0.8
Ceftazidime	>16	>16	32.6	53.5
Levofloxacin	1	>4	78.0	11.7
Polymyxin B	>4	>4	33.4	57.7
Ticarcillin/clavulanate	64	>128	27.0	35.1
TMP/SMX ^a	≤ 0.5	1	90.8	9.2
Latin America (289)				
Tigecycline	0.5	2	96.5	-
Ceftazidime	16	>16	48.8	38.4
Levofloxacin	1	2	91.3	3.8
Polymyxin B	≤ 1	>4	76.4	14.9
Ticarcillin/clavulanate	32	128	36.7	22.5
TMP/SMX ^a	≤ 0.5	1	95.5	4.5
All Regions (1,586)				
Tigecycline	0.5	2	95.5	0.9
Ceftazidime	16	>16	4.8	42.2
Levofloxacin	1	4	83.4	8.3
Polymyxin B	≤ 1	>4	64.6	25.7
Ticarcillin/clavulanate	32	>128	39.1	24.2
TMP/SMX ^a	≤ 0.5	1	96.0	4.0

a. TMP/SMX = trimethoprim/sulfamethoxazole.

- Tigecycline was the most active compound tested against *S. maltophilia* isolates from the Asia-Pacific and Latin American regions (MIC_{50} , 0.5 $\mu\text{g/ml}$ and MIC_{90} , 2 $\mu\text{g/ml}$; 96.1-96.5% susceptible), followed by TMP/SMX (MIC_{50} , ≤ 0.5 $\mu\text{g/ml}$ and MIC_{90} , 1 $\mu\text{g/ml}$; 90.8-95.5% 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 (78.0-83.7% susceptible; Table 2).
- In general, ceftazidime (32.6-51.0% susceptible), ticarcillin/clavulanate (27.0-46.1% susceptible) and polymyxin B (33.4-76.4% susceptible) showed limited in vitro activity against *S. maltophilia*.

CONCLUSIONS

- Tigecycline exhibited similar potencies across all geographic regions and its antimicrobial activity was similar to that of trimethoprim/sulfamethoxazole.
- Overall, tigecycline showed a greater potency against *S. maltophilia* compared to levofloxacin, ceftazidime and ticarcillin/clavulanate.
- Few therapeutic options are available to treat *S. maltophilia* infections. The role of tigecycline in the treatment of *S. maltophilia* infections warrants further investigations due to its in vitro activity.