Tigecycline Activity Tested against Infrequently Recovered Clinical Species of Non-enteric Gram-negative Bacilli

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ABSTRACT

Objectives: To assess tigecycline activity and potency against non-enteric Gram-negative bacilli (NEGNB) clinical isolates. NEGNB usually display multidrug-resistance (MDR) phenotype due to upregulated efflux and chromosomal β-lactamases belonging to Classes A, B, C or D, limiting the therapeutic options for treating infections caused by these organisms. Tigecycline has demonstrated a broad spectrum of activity against Gram-positive and -negative bacterial pathogens, including many MDR isolates.

Methods: A total of 2,996 clinically-significant isolates of NEGNB (23 species) were collected from 142 hospitals in 32 countries as part of the SENTRY Antimicrobial Surveillance Program over a seven year sampling period (2003-2009; North America [32.1%], Europe [26.8%], Asia-Pacific region [23.4%] and Latin America [17.7%]). Isolates were submitted to a coordinator laboratory where species identifications were confirmed using standard algorithms and Vitek 2, and tested for susceptibility against tigecycline and comparators by reference CLSI methods (M07-A8, 2009). CLSI interpretative criteria were applied when available.

Results: Isolates were recovered mostly from bacteremia (58.1%), pneumonia (29.7%) or skin and skin structure infections (10.4%). Tigecycline was most active against *Pasteurella multocida* (MIC_{90}, 0.12 mg/L) and various *Acinetobacter* spp. (MIC_{90}, 0.5 mg/L). *Aeromonas* spp., *Rhizobium radiobacter*, *Ralstonia pickettii* and *Sphingomonas paucimobilis* were also very susceptible to tigecycline (MIC_{90}, 0.5 mg/L). In contrast, *Burkholderia cepacia*, *P. fluorescens/putida, Chryseobacterium* spp. and *Elizabethkingia* spp. (MIC_{90}, 4 – >4 mg/L) generally exhibited elevated tigecycline MIC values. Tigecycline ($MIC_{50/90}$, 0.5/2 mg/L; 95.5% inhibited at ≤2 mg/L) and trimethoprim/sulfamethoxazole (TMP/SMX) ($MIC_{50/90}$, ≤0.5/1 mg/L; 96.1% susceptible) were the most active compounds tested against *Stenotrophomonas maltophilia*; while ceftazidime ($MIC_{50/90}$, 16/>16 mg/L; 45.1% susceptible), levofloxacin ($MIC_{50/90}$, 1/4 mg/L; 83.3% susceptible) and ticarcillin/clavulanate ($MIC_{50/90}$, 32/>128 mg/L; 38.7% susceptible) showed more limited activity against this organism.

Organism (no. tested)	MIC (mg/L) 50%	90%	Organism (no. tested)	MIC (mg/L) 50%	90%
Achromobacter xylosoxidans (130)	0.5	2	*Ochrobactrum anthropi* (14)	0.5	1
Acinetobacter haemolyticus (13)	0.12	0.5	*Pasteurella multocida* (53)	0.06	0.12
A. junii (47)	0.12	0.5	*Pseudomonas* spp. (83)[b]	0.25	2
A. lwoffii (216)	0.25	0.5	*P. fluorescens/putida* (191)	2	>4
Aeromonas spp. (211)[a]	0.25	0.5	*Ralstonia pickettii* (17)	0.25	0.5
Alcaligenes faecalis (23)	0.5	2	*Rhizobium radiobacter* (18)	0.12	0.5
Burkholderia cepacia (198)	1	4	*Sphingomonas paucimobilis* (32)	0.12	0.5
Chryseobacterium indologenes (26)	4	>4	*Stenotrophomonas maltophilia* (1685)	0.5	2
Elizabethkingia meningosepticum (39)	2	>4			

a. Includes *A. caviae* (34), *A. hydrophila* (118), *A. salmonicida* (1), *A. sobria* (15), *A. veronii* (6) and *Aeromonas* spp. (37).
b. Includes *P. mendocina* (14), *P. oryzihabitans* (27) and *P. stutzeri* (42).

Conclusions: Tigecycline showed potent in vitro activity against many NEGNB for which there are very limited therapeutic options and susceptibility data to guide therapy. Against *S. maltophilia,* tigecycline activity was comparable to that of TMP/SMX. The results of this study indicated that tigecycline may have an important role in the treatment of infections caused by these species.

INTRODUCTION

Non-enteric Gram-negative bacilli (NEGNB) occur in moist environments and are ubiquitous in nature, particular in soil and water. These bacterial species can contaminate the hospital environment and spread horizontally through fomites or healthcare workers, and frequently cause hospital outbreaks. As nosocomial opportunists, these organisms rarely affect healthy persons, but cause infections in immunocompromised hosts and those with severe underlying medical conditions.

Pseudomonas spp., *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* are the most important NEGNB responsible for bacteremia in hospitalized patients. In addition, *P. aeruginosa* and *Burkholderia cepacia* complex are important pathogens in cystic fibrosis patients. Infections caused by NEGNB have significant morbidity and mortality, owing to the compromised nature of the patients rather than the inherent pathogenicity of the organisms. Moreover, many NEGNB species are intrinsically resistant to multiple antimicrobial agents (MDR) and capable of acquiring additional resistance mechanisms, affecting drugs that are usually active.

Given the compromised affected patient population, intrinsic resistance and that susceptibility testing methodologies are not standardized for some of these organisms, appropriate broad-spectrum empiric therapy strategies are crucial. Tigecycline is approved in the United States (USA) and Europe for the treatment of complicated skin and skin structure infections (SSSI) and intra-abdominal infections (IAI). Tigecycline possesses a proven broad-spectrum of activity against numerous bacterial pathogens, including aerobic and anaerobic species. In this study, we evaluated the activity and potency of tigecycline tested against a clinically-significant and worldwide collection of several infrequently recovered NEGNB.

MATERIALS AND METHODS

Bacterial isolates. A total of 2,996 isolates of NEGNB (23 species) were collected from patients in 142 hospitals in 32 countries as part of the SENTRY Antimicrobial Surveillance Program over a seven year sampling period (2003-2009). Isolates were collected in a prevalence mode and mostly from bacteremia (58.1%), pneumonia (29.7%) or SSSI (10.4%) in hospitalized patients in North America (USA; 32.1%), Europe (26.8%), Asia-Pacific region (23.4%) and Latin America (17.7%). Bacterial species identifications were confirmed using standard algorithms and the automated Vitek 2 system (bioMérieux, Hazelwood, Missouri, USA).

Antimicrobial susceptibility testing. All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical Laboratory Standards Institute recommendations (CLSI; M07-A8, 2009). Susceptibility testing was performed by using validated broth microdilution panels manufactured by TREK Diagnostics Systems/Sensititre (Cleveland, Ohio, USA) and freshly prepared Mueller-Hinton broth (MHB), which is necessary for testing tigecycline. Comparator agents included meropenem, ceftazidime, piperacillin/tazobactam, ticarcillin/clavulanate, amikacin, tobramycin, levofloxacin, trimethoprim/sulfamethoxazole (TMP/SMX) and polymyxin B.

Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20, 2010) quality control (QC) strains: *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853.

Categorical interpretation of comparator MIC values were performed according to CLSI (M100-S20, 2010) criteria, when available. Tigecycline breakpoints approved by the USA-FDA for Enterobacteriaceae (≤2 mg/L for susceptible and ≥8 mg/L for resistant) were applied for comparison purposes only. MIC ranges for tigecycline and comparator agents tested against ATCC QC strains were those published in the CLSI M100-S20 (2010) document.

RESULTS

- *S. maltophilia* represented the majority of isolates in this investigation (56.2%). Other organisms tested included non-*baumannii Acinetobacter* spp. (9.2%), *Aeromonas* spp. (7.0%), *B. cepacia* (6.6%), *Pseudomonas fluorescens/putida* (6.4%) and *Achromobacter xylosoxidans* (4.3%) among others (Table 1).
- Tigecycline ($MIC_{50/90}$, 0.5/2 mg/L; 95.5% inhibited at ≤2 mg/L) and TMP/SMX ($MIC_{50/90}$, ≤0.5/1 mg/L; 96.1% susceptible) were very active against *S. maltophilia* (Tables 1 and 2). Levofloxacin ($MIC_{50/90}$, 1/4 mg/L; 83.3% susceptible) was two- and four-fold less active than tigecycline and TMP/SMX against *S. maltophilia*, respectively (Table 2).
- Tigecycline ($MIC_{50/90}$, 0.12/0.5 mg/L; 99.6% inhibited at ≤2 mg/L) was the most active compound tested against non-*baumannii Acinetobacter* spp., followed by polymyxin B ($MIC_{50/90}$, ≤0.5/1 mg/L; 98.2% susceptible), meropenem ($MIC_{50/90}$, 0.25/2 mg/L; 94.6% susceptible) and amikacin ($MIC_{50/90}$, 2/8 mg/L; 92.0% susceptible; Tables 1 and 2).
- Tigecycline ($MIC_{50/90}$, 0.25/0.5 mg/L) and levofloxacin ($MIC_{50/90}$, ≤0.5/≤0.5 mg/L) were the most active compounds tested against *Aeromonas* spp., inhibiting 99.5 and 98.6% of isolates at ≤2 mg/L, respectively (Tables 1 and 2).
- Only meropenem ($MIC_{50/90}$, 2/4 mg/L; 93.9% susceptible) and TMP/SMX ($MIC_{50/90}$, ≤0.5/2 mg/L 93.9% susceptible) exhibited good coverage (>90% susceptibility) against *B. cepacia*. Tigecycline ($MIC_{50/90}$, 1/4 mg/L; 84.8% inhibited at ≤2 mg/L) and ceftazidime ($MIC_{50/90}$, 4/16 mg/L; 88.4% susceptible) were less activity against this species (Tables 1 and 2).
- Tigecycline ($MIC_{50/90}$, 0.5/2 mg/L; 95.4% inhibited at ≤2 mg/L), meropenem ($MIC_{50/90}$, 0.25/4 mg/L; 93.8% susceptible), piperacillin/tazobactam ($MIC_{50/90}$, 1/8 mg/L; 95.4% susceptible) and TMP/SMX ($MIC_{50/90}$, ≤0.5/1 mg/L; 91.5% susceptible) were the most active compounds tested against *A. xylosoxidans* (Tables 1 and 2).
- High in vitro potency was noted for tigecycline and most comparator agents when tested against *Pasteurella multocida* and *Pseudomonas* spp. (*P. mendocina*, *P. oryzihabitans* and *P. stutzeri*; Table 2).
- Among *Alcaligenes faecalis*, the highest tigecycline MIC value was 4 mg/L, and 91.3% of strains were inhibited at ≤2 mg/L (Table 1).
- The highest MIC value observed for tigecycline when tested against *Rhizobium radiobacter* was 0.5 mg/L. Furthermore, tigecycline inhibited all tested *Ochrobactrum anthropi, Ralstonia pickettii*, and *Sphingomonas paucimobilis* isolates at ≤1 mg/L (Table 1).
- Tigecycline demonstrated limited activity against *Chryseobacterium indologenes* ($MIC_{50/90}$, 4/>4 mg/L), *Elizabethkingia meningosepticum* ($MIC_{50/90}$, 2/>4 mg/L) and *P. fluorescens/putida* ($MIC_{50/90}$, 2/>4 mg/L; Table 1).

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Table 1. MIC distribution of tigecycline tested against non-enteric Gram-negative bacilli clinical isolates collected as part of the SENTRY Antimicrobial Surveillance Program (2003-2009).

Organism group (number tested; % of total)	Number (cumulative %) inhibited at tigecycline MIC value (mg/L) of: ≤0.06	0.12	0.25	0.5	1	2	4	>4
Stenotrophomonas maltophilia (1685; 56.2)	2(0.12)	29(1.8)	211(14.4)	626(51.5)	547(84.0)	195(95.5)	61(99.2)	14(100.0)
Acinetobacter spp.[a] (276; 9.2)	42(15.2)	97(50.4)	94(84.4)	27(94.2)	12(98.6)	3(99.6)	0(99.6)	1(100.0)
Aeromonas spp.[b] (211; 7.0)	1(0.5)	37(18.0)	108(69.2)	52(93.8)	11(99.0)	1(99.5)	1(100.0)	–
Burkholderia cepacia (198; 6.6)	2(1.0)	2(2.0)	12(8.1)	53(34.8)	64(67.2)	35(84.8)	19(94.4)	11(100.0)
Pseudomonas fluorescens/putida (191; 6.4)	1(0.5)	9(5.2)	14(12.6)	22(24.1)	44(47.1)	54(75.4)	20(85.9)	27(100.0)
Achromobacter xylosoxidans (130; 4.3)	4(3.1)	5(6.9)	13(16.9)	67(68.5)	25(87.7)	10(95.4)	6(100.0)	–
Pseudomonas spp.[c] (83; 2.8)	7(8.4)	25(38.5)	22(65.1)	9(75.9)	7(84.3)	9(95.2)	4(100.0)	–
Pasteurella multocida (53; 1.8)	44(83.0)	6(94.3)	2(98.1)	0(98.1)	0(98.1)	1(100.0)	–	–
Elizabethkingia meningosepticum (39; 1.3)	0(0.0)	0(0.0)	0(0.0)	1(2.6)	8(23.1)	17(66.7)	8(87.2)	5(100.0)
Sphingomonas paucimobilis (32; 1.1)	12(37.5)	8(62.5)	8(87.5)	1(90.3)	3(100.0)	–	–	–
Chryseobacterium indologenes (26; 0.9)	0(0.0)	0(0.0)	2(7.7)	3(19.2)	5(38.5)	2(46.1)	9(80.8)	5(100.0)
Alcaligenes faecalis (23; 0.8)	1(4.3)	4(21.7)	4(39.1)	3(52.2)	8(87.0)	1(91.3)	2(100.0)	–
Rhizobium radiobacter (18; 0.6)	2(11.1)	7(50.0)	6(83.3)	3(100.0)	–	–	–	–
Ralstonia pickettii (17; 0.6)	0(0.0)	2(11.8)	9(64.7)	5(94.1)	1(100.0)	–	–	–
Ochrobactrum anthropi (14; 0.5)	0(0.0)	0(0.0)	3(21.4)	7(71.4)	4(100.0)	–	–	–

a. Includes *A. haemolyticus* (13), *A. junii* (47) and *A. lwoffii* (216).
b. Includes *A. caviae* (34), *A. hydrophila* (118), *A. salmonicida* (1), *A. sobria* (15), *A. veronii* (6) and *Aeromonas* spp. (37).
c. Includes *P. mendocina* (14), *P. oryzihabitans* (27), and *P. stutzeri* (42).

Table 2. Activity of tigecycline and comparators tested against most common non-enteric Gram-negative bacilli clinical isolates collected as part of the SENTRY Antimicrobial Surveillance Program over a seven year sampling period (2003-2009).

Organism / Antimicrobial agent	MIC (mg/L) 50%	90%	% Susceptible[a]	% Resistant[a]
Stenotrophomonas maltophilia (1,685)				
Tigecycline	0.5	2	95.5[b]	0.8[b]
Meropenem	>8	>8	–[c]	–
Ceftazidime	16	>16	45.1	42.1
Ticarcillin/clavulanate	32	>128	38.7	24.8
Amikacin	>32	>32	–	–
Levofloxacin	1	4	83.3	8.2
TMP/SMX[d]	≤0.5	1	96.1	3.9
Polymyxin B	≤1	>4	–	–
Acinetobacter spp. (276)[e]				
Tigecycline	0.12	0.5	99.6[b]	0.4[b]
Meropenem	0.25	2	94.6	2.5
Ceftazidime	4	>16	79.7	15.2
Piperacillin/tazobactam	≤0.5	>64	83.7	13.8
Ampicillin/sulbactam	≤2	>16	83.0	11.6
Amikacin	2	8	92.0	5.8
Levofloxacin	≤0.5	4	88.8	7.2
TMP/SMX	≤0.5	>2	84.8	15.2
Polymyxin B	≤0.5	1	98.2	1.8
Aeromonas spp. (211)[f]				
Tigecycline	0.25	0.5	99.5[b]	0.0[b]
Meropenem	0.25	1	97.2	2.8
Ceftazidime	≤1	8	91.9	5.2
Piperacillin/tazobactam	8	>64	63.8	16.7
Amikacin	≤4	8	96.7	2.4
Levofloxacin	≤0.5	≤0.5	98.6	1.4
TMP/SMX	≤0.5	>2	86.3	13.7
Polymyxin B	≤1	>4	66.8	30.3
Burkholderia cepacia (198)				
Tigecycline	1	4	84.8[b]	5.6[b]
Meropenem	2	4	93.9	3.5
Ceftazidime	4	16	88.4	5.6
Ticarcillin/clavulanate	>128	>128	4.5	89.9
Amikacin	>32	>32	–	-
Levofloxacin	2	>4	74.7	12.6
TMP/SMX	≤0.5	2	93.9	6.1
Polymyxin B	>4	>4	–	-
Pseudomonas fluorescens/putida (191)				
Tigecycline	2	>4	75.4[b]	14.1[b]
Meropenem	2	8	89.5	0.0
Ceftazidime	2	8	100.0	0.0
Piperacillin/tazobactam	16	32	73.7	8.9
Amikacin	≤4	≤4	100.0	0.0
Levofloxacin	≤0.5	2	100.0	0.0
TMP/SMX	>2	>2	21.1	78.9
Polymyxin B	≤0.5	>4	89.5	10.5
Pseudomonas spp. (83)[g]				
Tigecycline	0.25	2	95.2[b]	0.0[b]
Meropenem	≤0.12	2	91.6	3.6
Ceftazidime	≤1	4	94.0	4.8
Piperacillin/tazobactam	2	16	95.2	2.4
Amikacin	≤4	≤4	97.6	2.4
Levofloxacin	≤0.5	4	88.0	8.4
TMP/SMX	≤0.5	>2	74.7	25.3
Polymyxin B	≤1	≤1	95.2	4.8
Pasteurella multocida (53)				
Tigecycline	≤0.06	0.12	100.0[b]	0.0[b]
Meropenem	≤0.12	≤0.12	100.0	0.0
Ceftazidime	≤1	2	100.0	0.0
Piperacillin/tazobactam	≤0.5	≤0.5	100.0	0.0
Amikacin	8	16	98.1	0.0
Levofloxacin	≤0.5	≤0.5	100.0	0.0
TMP/SMX	≤0.5	≤0.5	100.0	0.0
Polymyxin B	≤1	2	92.5	3.8
Elizabethkingia meningosepticum (39)				
Tigecycline	2	>4	66.7[b]	12.8[b]
Meropenem	>8	>8	2.6	97.4
Ceftazidime	>16	>16	5.1	94.9
Piperacillin/tazobactam	4	32	89.7	0.0
Amikacin	>32	>32	12.8	59.0
Tobramycin	>16	>16	0.0	100.0
Levofloxacin	≤0.5	4	87.2	7.7
TMP/SMX	1	>2	64.1	35.9
Polymyxin B	>4	>4	0.0	100.0
Sphingomonas paucimobilis (32)				
Tigecycline	0.12	0.5	100.0[b]	0.0[b]
Meropenem	≤0.12	2	93.5	3.2
Ceftazidime	4	>16	62.5	21.9
Piperacillin/tazobactam	2	64	75.0	6.3
Amikacin	≤4	32	84.4	3.1
Levofloxacin	≤0.5	4	84.4	6.3
TMP/SMX	≤0.5	≤0.5	93.8	6.3
Polymyxin B	2	>4	59.4	37.5
Chryseobacterium indologenes (26)				
Tigecycline	4	>4	46.1[b]	19.2[b]
Meropenem	>8	>8	19.2	73.1
Ceftazidime	4	>16	80.8	11.5
Piperacillin/tazobactam	4	8	96.2	0.0
Amikacin	>32	>32	11.5	57.7
Levofloxacin	≤0.5	>4	73.1	23.1
TMP/SMX	≤0.5	2	96.2	3.8
Polymyxin B	>4	>4	7.7	92.3
Alcaligenes faecalis (23)				
Tigecycline	0.5	2	91.3[b]	0.0[b]
Meropenem	≤0.12	>8	82.6	13.0
Ceftazidime	2	>16	78.3	21.7
Piperacillin/tazobactam	≤0.5	>64	82.6	13.0
Amikacin	≤4	>32	78.3	21.7
Levofloxacin	≤0.5	>4	69.6	13.0
TMP/SMX	≤0.5	>2	87.0	13.0
Polymyxin B	≤0.5	4	87.0	4.3
Rhizobium radiobacter (18)				
Tigecycline	0.12	0.5	100.0[b]	0.0[b]
Meropenem	≤0.12	0.25	100.0	0.0
Ceftazidime	16	>16	44.4	16.7
Piperacillin/tazobactam	8	16	94.4	0.0
Amikacin	16	16	100.0	0.0
Levofloxacin	≤0.5	1	100.0	0.0
TMP/SMX	≤0.5	>2	83.3	16.7
Polymyxin B	≤1	>4	72.2	16.7
Ralstonia pickettii (17)				
Tigecycline	0.25	0.5	100.0[b]	0.0[b]
Meropenem	>8	>8	29.4	52.9
Ceftazidime	8	>16	52.9	11.8
Piperacillin/tazobactam	8	>64	70.6	11.8
Amikacin	>32	>32	41.2	58.8
Levofloxacin	≤0.5	≤0.5	100.0	0.0
TMP/SMX	≤0.5	>2	83.3	16.7
Polymyxin B	≤1	>4	5.9	94.1
Ochrobactrum anthropi (14)				
Tigecycline	0.5	1	100.0[b]	0.0[b]
Meropenem	0.5	2	100.0	0.0
Ceftazidime	>16	>16	7.1	92.9
Piperacillin/tazobactam	>64	>64	7.1	85.7
Amikacin	8	32	85.7	7.1
Levofloxacin	≤0.5	≤0.5	92.9	7.1
TMP/SMX	≤0.5	≤0.5	92.9	7.1
Polymyxin B	2	>4	71.4	14.3

a. Breakpoint susceptibility criteria as published by the CLSI M100-S20 document (2010).
b. Tigecycline susceptible breakpoints for Enterobacteriaceae (≤2 mg/L for susceptible and ≥8 mg/L for resistant) approved by the US-FDA were applied for comparison purposes only.
c. –, indicates no breakpoint criteria are available for the respective drug/organism combination.
d. TMP/SMX, trimethoprim/sulfamethoxazole.
e. Includes *A. haemolyticus* (13), *A. junii* (47) and *A. lwoffii* (216).
f. Includes *A. caviae* (34), *A. hydrophila* (118), *A. salmonicida* (1), *A. sobria* (15), *A. veronii* (6) and *Aeromonas* spp. (37).
g. Includes *P. mendocina* (14), *P. oryzihabitans* (27) and *P. stutzeri* (42).

CONCLUSIONS

- Tigecycline showed potent in vitro activity against many NEGNB for which there are very limited therapeutic options and susceptibility testing data to guide therapy.
- Against *S. maltophilia,* tigecycline activity was comparable to that of trimethoprim/sulfamethoxazole.
- The results of this study indicated that tigecycline may have an important role in the treatment of infections caused by these NEGNB species.