Tigecycline Potency and Spectrum When Tested Against Gram-negative Pathogens from North American Medical Centers (2006)

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ABSTRACT

Background:
Emerging multidrug-resistant (MDR) organisms among Gram-negative bacilli (GNB) have created therapeutic dilemmas for physicians in North America (NA). New classes of antimicrobials are needed, and tigecycline (TGC; a first in class glycylcycline) has demonstrated potent activity against GNB pathogens except *P. aeruginosa* (PSA). A TGC surveillance for 2006 reports reference MIC results from nearly 2,500 GNB isolates.

Methods:
Over 30 medical centers in NA (USA and Canada) forwarded consecutive GNB strains according to SENTRY Program objectives (2,395 strains from the 10 most common species). All GNB were susceptibility (S) tested by CLSI broth microdilution methods and the US-FDA S breakpoint for Enterobacteriaceae was applied to the MIC results (≤2 mg/L).

Results:
Among GNB summarized here, only PSA had TGC MICs at ≥8 mg/L (44.0%). TGC S rates (%) for non-indicated species *P. mirabilis* (78.7), indole-positive proteae (96.3) and *Serratia* spp. (99.1) were highly acceptable and S rates ranged from 99.2-100.0% for indicated species (see Table). ESBL screen-positive *E. coli* and *Klebsiella* (91 strains) did not have elevated TGC MIC results. MDR *Acinetobacter* were 96.1% S with no MIC at ≥8 mg/L (only polymyxins were comparably active, 98.0% S).

Organism (no.)	MIC_{50}	MIC_{90}	% ≤2 mg/L	% ≥8 mg/L
Citrobacter (41)[a]	0.25	0.5	100.0	0.0
E. coli (627)[a]	0.12	0.25	100.0	0.0
Enterobacter (251)[a]	0.25	1	99.2	0.0
Klebsiella (419)[a]	0.25	1	99.5	0.0
Acinetobacter (102)	0.5	2	96.1	0.0
Haemophilus (387)	0.5	1	100.0	0.0

a. Indicated by US-FDA

Conclusions:
TGC continues to demonstrate potent and wide spectrum activity against GNB species especially for MDR Enterobacteriaceae (ESBL-producers) and *Acinetobacters* in NA. This new glycylcycline may have a significant therapeutic role in medical centers with clonal MDR GNB, but not against PSA.

INTRODUCTION

Tigecycline is a semisynthetic glycylcycline derived from the minocycline molecule. Tigecycline has documented activity against tetracycline-resistant Gram-positive and -negative pathogens refractory by efflux and ribosomal protection mechanisms. This compound has also demonstrated excellent activity against multidrug-resistant (MDR) pathogens, including oxacillin-resistant (MRSA) and glycopeptide-intermediate *Staphylococcus aureus*, vancomycin-resistant enterococci (VRE), penicillin-resistant *Streptococcus pneumoniae*, extended-spectrum ß-lactamase (ESBL)-producing Enterobacteriaceae and some nonfermentative Gram-negative bacilli, such as *Acinetobacter* spp. and *Stenotrophomonas maltophilia*.

The introduction of a novel class of broad-spectrum agents such as the glycylcyclines is somewhat unique, in that the only other new class agent in the last decade, linezolid (an oxazolidinone), targets only Gram-positive pathogens. Although tigecycline binds to the 30S ribosomal subunit and blocks the entry of amino-acyl transfer RNA in the same manner as tetracyclines, the agent binds to the ribosomal site more avidly than the related compounds and is not removed by the common tetracycline efflux pump mechanisms.

A number of in vitro and recent clinical studies have demonstrated the broad-spectrum of tigecycline against pathogens responsible for infections of skin and skin structures and intra-abdominal infections. Recent studies also indicate that extension of these clinical indications to respiratory tract infections, specifically pneumonia in hospitalized patients, should be investigated given the documented activity of this agent against the commonly occurring respiratory tract pathogens.

This study quantitated the potency and spectrum of tigecycline tested against year 2006 clinical isolates of Gram-negative bacilli in North America (2,395 strains), each tested by the reference broth microdilution method.

MATERIALS AND METHODS

The Gram-negative bacilli isolates from the SENTRY Antimicrobial Surveillance Program (2006) were analyzed for tigecycline activity using consecutive cultures from bacteremias (3,829), community-acquired respiratory tract infections (1,071), patients with pneumonia (933) and other infection sites. The top ten most frequent Gram-negative species or genus groups (Table 1) numbered 2,395 isolates with the Enterobacteriaceae most isolated (1,540; 64.3%). All strains were processed in a central reference laboratory (JMI Laboratories, Iowa, USA).

Susceptibility testing used reference Clinical and Laboratory Standards Institute (CLSI, formerly the NCCLS) broth microdilution methods (M7-A7, 2006; M100-S17, 2007) with concurrent quality controls (QC). All QC results were within the published ranges.

Over 25 antimicrobials were tested (14 shown here) with the tigecycline results processed by suggested procedures to minimize false resistance via use of fresh Mueller-Hinton broth. *Haemophilus influenzae* testing required the application of HTM broth.

RESULTS

- Table 1 lists the tigecycline activity against 2,395 strains (top 10 pathogens) of Gram-negative bacilli. At US-FDA susceptible breakpoints for Enterobacteriaceae (≤2 mg/L), no organisms other than *P. aeruginosa* were resistant (MIC, ≥8 mg/L) to tigecycline.
- Tigecycline MIC_{90} results ranged from 0.25 to 1 mg/L for indicated species of Enterobacteriaceae. Only *P. mirabilis* and indole-positive *Proteae* species had higher MIC_{90} values (2-4 mg/L; Table 1).
- Tigecycline was not active against *P. aeruginosa* (Table 1).
- Among Enterobacteriaceae showing an extended spectrum ß-lactamase (ESBL) antibiogram phenotype, the most active agents were carbapenems, polymyxins and tigecycline. Emergence in the USA of serine carbapenemase-producing *K. pneumoniae* isolates (KPC enzymes) has compromised imipenem and meropenem use (Table 2).

Table 1. Activity of tigecycline tested against 2,395 Gram-negative bacilli (top 10 pathogens) isolated in more than 30 medical centers (North America) for 2006.

	MIC (mg/L):			% by category:[a]	
Organism (no. tested)	50%	90%	Range	Susceptible	Resistant
E. coli (627)	0.12	0.25	≤0.03-0.5	100.0	0.0
Klebsiella spp. (419)	0.25	1	0.12-4	99.5	0.0
Haemophilus spp. (387)	0.5	1	0.25-1	100.0	0.0
Enterobacter spp. (251)	0.25	1	0.12-4	99.2	0.0
Serratia spp. (114)	0.5	1	0.12-4	99.1	0.0
P. mirabilis (61)	2	4	0.5-4	78.2	0.0
Citrobacter spp. (41)	0.25	0.5	0.12-1	100.0	0.0
Indole-positive *Proteae* (27)	1	2	0.25-4	100.0	0.0
Acinetobacter spp. (102)	0.5	2	≤0.03-4	96.1	0.0
P. aeruginosa (366)	4	>4	0.5->4	13.7	44.0

a. Susceptibility criteria as found in the US-FDA tigecycline package insert for indicated Enterobacteriaceae species (2005); susceptible at ≤2 mg/L and resistant at ≥8 mg/L.

Table 2. Comparative tigecycline activity tested against *E. coli* and *Klebsiella* spp. having an ESBL-phenotype (91 strains).

	Cum. % inhibited at MIC (mg/L):								
Organism (no. tested)/ Antimicrobial	≤0.03	0.06	0.12	0.25	0.5	1	2	4	% Susceptible
E. coli (28)									
Tigecycline	0.0	17.9	50.0	96.4	100.0	-	-	-	100.0
Imipenem	-	-	21.4	67.9	85.7	92.9	96.4	100.0	100.0
Levofloxacin	-	-	-	-	3.6	3.6	3.6	14.3	3.6
Colistin	-	-	-	-	96.4	100.0	-	-	100.0
Klebsiella spp. (63)									
Tigecycline	0.0	0.0	6.3	36.5	81.0	95.2	100.0	-	100.0
Imipenem	-	-	17.5	49.2	58.7	60.3	60.3	61.9	61.9[a]
Levofloxacin	-	-	-	-	22.2	23.8	25.4	31.7	25.4
Colistin	-	-	-	-	77.8	93.7	93.7	95.2	93.7

a. A significant proportion of ESBL phenotypes possess serine carbapenemases (KPC-type) with or without an ESBL or mobilized Amp-C enzyme.

- Table 3 shows the comparative tigecycline potency tested against MDR *A. baumannii* (102 strains). The antimicrobials with the most complete coverage (% susceptible) were: polymyxins (98.0%) > tigecycline (96.1%) > imipenem (78.4%) > amikacin (76.1%) > meropenem (73.5%). All other antimicrobials had susceptibility rates of <70.0%.

Table 3. Tigecycline activity compared to 13 other antimicrobials tested against *A. baumannii* isolates (102 strains from North America).

	MIC (mg/L):			% by category:[a]	
Antimicrobial	50%	90%	Range	Susceptible	Resistant
Tigecycline	0.5	2	≤0.03-4	96.1	0.0
Amikacin	≤4	>32	<4->32	76.1	16.7
Ampicillin/sulbactam	≤2/1	>16/8	≤2/1->16/8	62.7	24.5
Cefepime	16	>16	≤0.12->16	47.1	29.4
Ceftazidime	16	>16	≤1->16	43.1	50.0
Ciprofloxacin	>4	>4	≤0.03->4	45.1	54.9
Colistin	≤0.5	≤0.5	≤0.5->4	98.0	2.0
Gentamicin	≤2	>8	≤2->8	51.0	45.1
Imipenem	0.5	>8	≤0.12->8	78.4	11.8
Levofloxacin	>4	>4	≤0.5->4	45.1	51.0
Meropenem	1	>8	≤0.12->8	73.5	19.6
Piperacillin/tazobactam	16/4	>64/4	≤0.5/4->64/4	50.0	31.4
Polymyxin B	≤0.5	1	≤0.5->4	98.0	2.0
Tobramycin	1	>16	≤0.12->16	67.6	23.5

a. Susceptibility criteria of the CLSI (M100-S17, 2007) and for tigecycline per US-FDA product package insert (2005) and Jones et al., 2007.

CONCLUSIONS

- Tigecycline was documented to be highly active (no MICs at ≥8 mg/L) against all Enterobacteriaceae screened from North American medical centers.
- Tigecycline inhibited ESBL-producing *E. coli* and *Klebsiella* spp., as well as *K. pneumoniae* noted to be resistant to carbapenems (KPC enzyme producers).
- Tigecycline was active against MDR *Acinetobacter* spp. isolates (MIC_{90}, 2 mg/L), but not *P. aeruginosa* among the non-fermentative Gram-negative bacilli isolated in 2006.
- This novel glycylcycline will be an important therapeutic alternative in North American hospitals to treat MDR strains refractory to other antimicrobial classes.

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