

Susceptibility Patterns of Tigecycline and Comparators in Latin America from Hospitals of Various Bed Sizes

S. Bouchillon¹, M. Hackel¹, J. Johnson¹, D. Hoban¹, B. Johnson¹, R. Badal¹, M. Dowzicky²

¹International Health Management Associates, Schaumburg, IL, USA

²Wyeth Pharmaceuticals, Collegeville, PA, USA

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REVISED ABSTRACT

Background: Drug resistance in clinical isolates can be influenced by the sources of specimens such as those isolated from large vs small hospital populations. The in vitro activity of tigecycline has been remarkably stable across multiple variables contributing to resistance in other antimicrobials. This study attempts to determine the activity of tigecycline compared to that of 13 antimicrobials against pathogens isolated from hospitals of varying population sizes. **Methods:** 10 hospital sites in 6 Latin American countries collected 1,571 clinically significant pathogens between 2004 and 2007. MICs were performed according to CLSI guidelines at each site. **Results:** MIC₉₀ of tigecycline according to bed size groups are shown in the following table:

Bed Size Group	200-500 Beds		500-1000 Beds	
	n=	MIC ₉₀	n=	MIC ₉₀
<i>Acinetobacter</i> spp	74	1	54	2
EcoKoxKpn	291	2	187	1
ESBLs	97	2	56	1
<i>Enterococcus</i> spp	83	0.12	48	0.25
VREs	12	0.06	1	0.03
<i>P. aeruginosa</i>	111	>16	79	>16
<i>S. marcescens</i>	29	2	32	1
<i>S. aureus</i>	139	0.25	72	0.25
MRSA	89	0.25	27	0.25
<i>S. pneumoniae</i>	44	0.06	28	0.06
PRSP	6	0.06	4	0.06

* *E. coli*, *K. oxytoca*, *K. pneumoniae*.

Conclusion: Although tigecycline's antimicrobial activity consistent for selected species between bed-size groups, MIC₉₀ values for other species varied +/- 1 doubling dilution according to bed sizes groups.

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycytyclines. This synthetic analogue of the tetracyclines exhibits significant antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as fourfold better than vancomycin and daptomycin [1, 2]. The development of tigecycline is important in that it and other glycytyclines are active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. Certain substituents at the 9-position of the tetracycline molecule restored activity against bacteria harboring genes encoding either or both efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible gram-positive, gram-negative, aerobic, and anaerobic bacteria [3]. Furthermore, resistance to tigecycline is difficult to produce even in the laboratory.

Previous studies have demonstrated excellent in vitro activity for tigecycline against clinical and laboratory strains of gram-positive and -negative bacteria with minimum inhibitory concentrations for the 90th percentile inhibited at or below 2 mcg/mL, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE) and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [4-6]. This study was undertaken to document the in vitro activity of tigecycline against significant numbers of clinical isolates collected from various body sites in the United States. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

MATERIALS & METHODS

- For the T.E.S.T program all isolates were derived from blood, respiratory tract, genitourinary (no more than 25% of all isolates), skin, wound, fluids, and other defined sources. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution. Only one isolate per patient was accepted.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database, were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age or gender. All sites identified each study isolate utilizing local laboratory criteria.
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [6]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers, MicroScan (Dade Behring Inc., West Sacramento, CA, USA) and Trek (TREK Diagnostic Systems, Cleveland, OH). The following antimicrobial agents and dilution ranges (expressed in mcg/mL) were included on the panels: tigecycline (0.008-16), imipenem (0.06-16), levofloxacin (0.008-8), minocycline (0.5-16), piperacillin/tazobactam (0.06/4-128/4), amikacin (0.5-32), ceftazidime (8-32), ceftioxone (0.06-64) and cefepime (0.5-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [7], where applicable. There are currently no breakpoints defined for tigecycline against *Acinetobacter* species.
- Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftioxone were >1 mcg/ml using broth microdilution panels. ESBL activity was confirmed using the CLSI (2005) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2005) guidelines. ESBL presence was confirmed by testing the following antibiotic disks: cefotaxime (30-mcg), cefotaxime/clavulanic acid (30/10-mcg), ceftazidime (30-mcg), and ceftazidime/clavulanic acid (30/10-mcg). Antimicrobial disks were manufactured by Oxoid, Inc. (Ogdensburg, NY, USA). Mueller-Hinton agar used in testing was manufactured by Remel, Inc. (Lenexa, KS, USA). An organism was interpreted as containing an ESBL if there was an increase of >5 mm in the inhibition zone of the combination disk when compared to that of the cephalosporin alone.
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains where applicable: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922 and 35218; *Haemophilus influenzae* ATCC 49247 and 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; *Pseudomonas aeruginosa* ATCC 27853 and *Klebsiella pneumoniae* ATCC 700603 (as positive ESBL control).
- Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2007) guidelines [8].

REFERENCES

- Hoellman, D.B., et al., *Antipneumococcal activities of GAR-936 (a new glycytycline) compared to those of nine other agents against penicillin-susceptible and -resistant pneumococci*. Antimicrob Agents Chemother, 2000, 44(4): p. 1085-8.
- Labthavikul, P., P.J. Petersen, and P.A. Bradford. *In vitro activity of tigecycline against Staphylococcus epidermidis growing in an adherent-cell biofilm model*. Antimicrob Agents Chemother, 2000, 47(12): p. 3967-9.
- Projan, S.J., *Preclinical pharmacology of GAR-936, a novel glycytycline antibacterial agent*. Pharmacotherapy, 2000, 20(9 Pt 2): p. 219S-223S; discussion 224S-228S.
- Gales, A.C. and R.N. Jones. *Antimicrobial activity and spectrum of the new glycytycline, GAR-936 tested against 1,203 recent clinical bacterial isolates*. Diagn Microbiol Infect Dis, 2000, 36(1): p. 19-36.
- Patel, R., et al., *In vitro activity of GAR-936 against vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus and penicillin-resistant Streptococcus pneumoniae*. Diagn Microbiol Infect Dis, 2000, 38(3): p. 177-9.
- Rupp, M.E., and P.D. Fey, *Extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae: considerations for diagnosis, prevention and drug treatment*. Drugs, 2003, 63(4): p. 353-65.
- CLSI. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Seventh Edition, in Document M7-A7*. 2007: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- CLSI. *Performance Standards for Antimicrobial Susceptibility Testing, in Document M100-S17* 2007: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- Tygacil, *Product Insert*. 2005: Wyeth Pharmaceuticals, Inc., Philadelphia, PA, USA.

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RESULTS

The results are listed in the following Tables.

Table 1. In Vitro Activity of Tigecycline and Comparative Antimicrobial Agents against Gram-Positive Clinical Pathogens Isolated from Small and Large Hospital Populations.

Organism/Phenotype (N) ^a	Significant PValue ^b	Drug	Small Hospitals (Bed Size 200 - 500)			Large Hospitals (Bed Size 500 - 1000)		
			MIC ₉₀	MIC ₅₀	%Sus ^c	MIC ₉₀	MIC ₅₀	%Sus
<i>E. faecalis</i> Small (n=49) Large (n=38)	***	Tigecycline	0.12	0.12	100	0.12	0.25	100
		Amoxicillin	1	1	100	1	1	100
		Levofloxacin	1	>32	73.5	1	>32	58.5
		Linezolid	2	2	100	2	2	95.1
		Minocycline	8	>8	14.3	8	>8	36.6
<i>E. faecium</i> Small (n=28) Large (n=6)	***	Tigecycline	0.03	0.12	100	0.06	0.12	100
		Amoxicillin	>16	>16	7.1	4	>16	50
		Levofloxacin	>32	>32	3.6	>32	>32	16.7
		Linezolid	2	4	89.3	2	4	83.3
		Minocycline	1	>8	67.9	1	>8	66.7
Vancomycin-Resistant, <i>E. faecium</i> Small (n=12) Large (n=1)	***	Tigecycline	0.03	0.12	100	0.03	0.12	100
		Amoxicillin	>16	>16	0	>16	>16	0
		Levofloxacin	>32	>32	0	>32	>32	0
		Linezolid	2	2	91.7	2	2	100
		Minocycline	2	8	83.3	1	1	100
<i>S. aureus</i> Small (n=139) Large (n=72)	***	Tigecycline	0.12	0.25	100	0.12	0.25	100
		Amoxicillin	>8	>8	41.7	1	>8	70.8
		Amoxicillin	>16	>16	4.3	8	>16	12.5
		Ceftioxone	>64	>64	38.8	4	>64	70.8
		Imipenem	>16	>16	52.5	>0.12	>0.12	91.7
<i>S. aureus</i> , MRSA Small (n=50) Large (n=45)	**	Tigecycline	0.12	0.25	100	0.12	0.25	100
		Amoxicillin	1	2	100	0.5	2	100
		Amoxicillin	4	>16	12	2	16	20
		Ceftioxone	2	4	96	2	8	100
		Imipenem	>0.12	0.25	100	>0.12	>0.12	100
<i>H. influenzae</i> Small (n=21) Large (n=30)	**	Tigecycline	0.12	0.5	98	0.12	0.5	100
		Levofloxacin	2	2	100	2	2	100
		Linezolid	2	2	100	2	2	100
		Minocycline	>0.25	1	100	>0.25	0.5	100
		Penicillin	8	>8	12	2	>8	17.8
<i>S. pneumoniae</i> Small (n=7) Large (n=2)	**	Tigecycline	0.5	1	100	1	1	100
		Amoxicillin	1	2	100	1	2	100
		Cefepime	>0.5	>0.5	100	>0.5	>0.5	100
		Ceftioxone	>8	>8	0	>8	>8	0
		Imipenem	0.25	0.5	100	>0.06	>0.06	100
<i>S. pneumoniae</i> , ESBL ⁺ Small (n=40) Large (n=4)	**	Tigecycline	0.12	0.25	na	0.25	0.5	na
		Amoxicillin	>8	>8	9	8	>8	22.2
		Amoxicillin	>16	>16	0	16	>16	0
		Ceftioxone	>64	>64	6.7	32	>64	22.2
		Imipenem	8	>16	33.3	>0.12	>0.12	37
<i>S. pneumoniae</i> , ESBL ⁻ Small (n=13) Large (n=8)	**	Tigecycline	0.12	0.25	na	0.25	0.5	na
		Amoxicillin	1	2	100	1	2	100
		Amoxicillin	1	2	100	1	2	100
		Ceftioxone	>8	>8	0	>8	>8	0
		Imipenem	0.25	0.5	100	>0.06	>0.06	100
<i>K. pneumoniae</i> Small (n=11) Large (n=5)	**	Tigecycline	0.5	1	100	1	1	100
		Amoxicillin	1	2	100	1	2	100
		Amoxicillin	1	2	100	1	2	100
		Ceftioxone	>8	>8	0	>8	>8	0
		Imipenem	0.25	0.5	100	>0.06	>0.06	100
<i>P. aeruginosa</i> Small (n=19) Large (n=8)	**	Tigecycline	0.12	0.25	na	0.12	0.25	na
		Amoxicillin	>0.03	>0.03	100	>0.03	0.06	100
		Amoxicillin	>0.03	>0.03	100	>0.03	0.06	100
		Ceftioxone	>0.03	0.12	100	>0.03	0.06	100
		Imipenem	>0.12	0.25	80	>0.12	0.25	50
Penicillin Susceptible <i>S. pneumoniae</i> Small (n=19) Large (n=16)	**	Tigecycline	0.5	1	100	1	1	100
		Amoxicillin	1	1	100	1	1	100
		Amoxicillin	1	1	100	1	1	100
		Ceftioxone	0.25	0.5	100	0.12	1	100
		Imipenem	>0.06	>0.06	100	>0.06	>0.06	100
Penicillin Resistant <i>S. pneumoniae</i> Small (n=11) Large (n=7)	**	Tigecycline	0.25	0.5	100	0.25	0.5	100
		Amoxicillin	1	2	100	1	2	100
		Amoxicillin	1	2	100	1	2	100
		Ceftioxone	0.25	0.5	100	0.12	1	100
		Imipenem	>0.12	0.25	80	>0.12	0.25	50
<i>P. aeruginosa</i> Small (n=11) Large (n=7)	**	Tigecycline	0.25	0.5	100	0.5	1	100
		Amoxicillin	2	2	100	2	2	100
		Amoxicillin	2	2	100	2	2	100
		Ceftioxone	1	1	100	0.5	1	100
		Imipenem	>0.12	0.25	80	>0.12	0.25	50
<i>P. aeruginosa</i> , ESBL ⁺ Small (n=11) Large (n=7)	**	Tigecycline	0.25	0.5	100	0.5	1	100
		Amoxicillin	2	2	100	2	2	100
		Amoxicillin	2	2	100	2	2	100
		Ceftioxone	1	1	100	0.5	1	100
		Imipenem	>0.12	0.25	80	>0.12	0.25	50
<i>P. aeruginosa</i> , ESBL ⁻ Small (n=11) Large (n=7)	**	Tigecycline	0.25	0.5	100	0.5	1	100
		Amoxicillin	2	2	100	2	2	100
		Amoxicillin	2	2	100	2	2	100
		Ceftioxone	1	1	100	0.5	1	100
		Imipenem	>0.12	0.25	80	>0.12	0.25	50

Table 2. In Vitro Activity of Tigecycline and Comparative Antimicrobial Agents against Gram-Negative Clinical Pathogens Isolated from Small and Large Hospital Populations.

Organism/Phenotype (N) ^a	Significant PValue ^b	Drug	Small Hospitals (Bed Size 200 - 500)			Large Hospitals (Bed Size 500 - 1000)		
			MIC ₉₀	MIC ₅₀	%Sus ^c	MIC ₉₀	MIC ₅₀	%Sus
<i>E. coli</i> Small (n=42) Large (n=38)	***	Tigecycline	0.5	2	94.5	0.5	1	97.4
		Amikacin	4	32	84.4	2	16	95.1
		Amoxicillin	16	>32	31.1	32	>32	27.5
		Amoxicillin	>32	>32	3.1	>32	>32	7.2
		Cefepime	1	>32	72.4	1	>32	78.4
<i>E. coli</i> , ESBL Small (n=47) Large (n=16)	***	Tigecycline	0.5	2	98	0.5	1	98.5
		Amikacin	4	>64	81.7	2	16	98.5
		Amoxicillin	>32	>32	1.2	>32	>32	7.5
		Amoxicillin	>32	>32	0	>32	>32	0
		Cefepime	1	16	85.4	>0.5	32	76.1
<i>E. coli</i> , ESBL Small (n=100) Large (n=16)	***	Tigecycline	0.25	0.5	100	0.25	0.5	100
		Amoxicillin	16	32	34.9	16	>32	48
		Amoxicillin	>32	>32	7.2	>32	>32	22
		Cefepime	2	>32	61.4	>0.5	16	85
		Ceftioxone	>8	>8	69.3	>8	>8	70
<i>H. influenzae</i> Small (n=21) Large (n=30)	**	Tigecycline	0.12	0.25	98	0.25	1	98
		Amoxicillin	1	2	100	1	2	100
		Amoxicillin	1	2	100	1	2	