

Susceptibility of Tigecycline and Comparators in Nosocomial Pathogens from South America Hospitals: T.E.S.T. program 2004-2006

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REVISED ABSTRACT

Background: One of the goals of surveillance studies is to identify and document patterns of bacterial resistance to help guide current therapy. The Tigecycline Evaluation Surveillance Trial (TEST) is an ongoing global study that can serve to help recognize current trends in resistance on many levels. This study reports on the susceptibility patterns of tigecycline and 13 antimicrobial agents against common nosocomial pathogens from 10 South American hospitals.

Methods: 1,586 strains isolated were collected and identified from 2004-2006 at 10 investigative sites. MICs for each strain were determined per CLSI guidelines at each facility using custom broth microdilution panels.

Results: Summary results for key pathogens are shown in the following table.

Organism (#)	Tigecycline		% inhibited at MIC							
	MIC ₅₀	MIC ₉₀	≤0.25	0.5	1	2	4	8		
<i>Acinetobacter</i> spp. (149)	0.5	1	26.2	70.5	94.6	100	-	-	-	-
<i>E. faecalis/E. faecium</i> (86)	0.06	0.25	100	-	-	-	-	-	-	-
VRFS (7)	*	*	100	-	-	-	-	-	-	-
<i>Enterobacteriaceae</i> (730)	0.5	1	40.8	76	92.7	98.1	99.9	100	-	-
ESBLs (67)	0.5	2	26.9	61.2	82.1	94	100	-	-	-
<i>P. aeruginosa</i> (165)	8	>16	1.2	1.8	2.4	6.7	20	61.8	-	-
<i>S. aureus</i> (230)	0.12	0.25	92.6	100	-	-	-	-	-	-
MRSAs (104)	0.12	0.25	96.2	100	-	-	-	-	-	-

* No MIC₅₀ and MIC₉₀ calculated for strains with n<10

Conclusion: TIG was shown to be a broad spectrum antimicrobial with consistent activity against *Enterobacteriaceae* including ESBL phenotypes, *S. aureus* including MR strains and both VS and VR *Enterococcus* spp. TIG's wide spectrum of activity promises to provide enhanced antimicrobial coverage of serious nosocomial pathogens.

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycylicylines. 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 tigecycline and other glycylicylines 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 restore 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 pathogens collected in 10 laboratories from South America. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, body fluids, and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested between 2004 to 2006 from 10 study centers in South America. Isolates were identified to the species level and tested at each site by the participating laboratory.
- 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 [7]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., Sacramento, CA, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amikacin (0.5-64); amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.5-32, gram-negative panel, and 0.06-16, gram-positive panel); cefepime (0.5-32); ceftazidime (0.06-64); ceftazidime (8-32); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [8] and the recent US Food and Drug Administration package insert for tigecycline [9], where applicable.

- Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftazidime 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: ceftotaxime (30-mcg), ceftotaxime/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 controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *E. coli* ATCC 25922; *E. coli* ATCC 35218; *H. influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *Pseudomonas aeruginosa* ATCC 27853; *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2005) guidelines [8].

REFERENCES

- Hoellman, D.B., et al., *Antipneumococcal activities of GAR-936 (a new glycylicyline) 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, 2003, 47(12): p. 3987-9.
- Projan, S.J., *Preclinical pharmacology of GAR-936, a novel glycylicyline 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 glycylicyline, 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. Foy, *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 Standards—Sixth Edition, in Document M7-A6. 2005: 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-S15. 2005: 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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The results are listed in the following tables.

Table 1. In vitro activity of tigecycline and comparative agents against *Enterobacteriaceae*.

Organism Name	Drug	%SUS ^a	MIC			MIC Range			
			%INT	%RES	MIC ₅₀	MIC ₉₀	Low	High	
All <i>Enterobacteriaceae</i> (n=730)	Tigecycline	98.1	1.8	0.1	0.5	1	<0.008	8	
	Amikacin	90.3	5.3	4.4	2	16	<0.5	>64	
	AmoxClav	37	8.4	54.7	>32	>32	>0.25	>32	
	Ampicillin	10.7	4.7	84.7	>32	>32	<0.5	>32	
	Cefepime	75.3	5.3	19.3	<0.5	>32	<0.5	>32	
	Ceftazidime	71.6	5.8	22.6	<8	>32	<8	>32	
	Ceftazidime	67.5	4.1	28.4	0.12	>64	<0.06	>64	
	Imipenem	100	0	0	0.5	1	0.12	4	
	Levofloxacin	74.8	4.2	21	0.06	>8	<0.008	>8	
	Minocycline	83	8.5	8.5	2	8	<0.5	>16	
	PipTazo	74.7	11.6	13.7	2	128	0.12	>128	
	<i>E. coli</i> (n=219)	Tigecycline	100	0	0	0.12	0.25	<0.008	>16
		Amikacin	97.7	0.9	1.4	2	8	<0.5	>64
AmoxClav		68.9	15.5	15.5	8	32	0.25	>32	
Ampicillin		35.6	0.5	63.9	>32	>32	<0.5	>32	
Cefepime		89	2.7	8.2	<0.5	16	<0.5	>32	
Ceftazidime		90	4.1	5.9	<8	16	<8	>32	
Ceftazidime		84.5	0.5	15.1	<0.06	>64	<0.06	>64	
Imipenem		100	0	0	0.5	0.5	0.12	4	
Levofloxacin		70.3	5	24.7	0.03	>8	<0.008	>8	
Minocycline		79	11.9	9.1	1	8	<0.5	>16	
PipTazo		92.7	4.1	3.2	1	16	0.12	>128	
<i>K. pneumoniae</i> (n=179)		Tigecycline	96.6	2.8	0.6	0.5	2	0.12	8
		Amikacin	91.6	3.4	5	2	16	<0.5	>64
	AmoxClav	43	8.4	48.6	16	>32	0.5	>32	
	Ampicillin	0	8.9	91.1	>32	>32	16	>32	
	Cefepime	57	6.1	36.9	1	>32	<0.5	>32	
	Ceftazidime	67.5	7.3	35.2	<8	>32	<8	>32	
	Ceftazidime	51.4	5	43.6	1	>64	<0.06	>64	
	Imipenem	100	0	0	0.5	0.5	0.25	2	
	Levofloxacin	64.8	3.9	31.3	0.25	>8	<0.008	>8	
	Minocycline	61.6	7.8	10.6	2	16	<0.5	>16	
	PipTazo	55.3	14.5	30.2	4	>128	0.25	>128	
	<i>K. oxytoca</i> (n=21)	Tigecycline	100	0	0	0.25	0.5	0.12	0.5
		Amikacin	95.2	4.8	0	2	16	1	32
AmoxClav		81	4.8	14.3	4	32	1	>32	
Ampicillin		0	9.5	90.5	>32	>32	16	>32	
Cefepime		95.2	4.8	0	<0.5	8	<0.5	16	
Ceftazidime		85.7	0	14.3	<8	32	<8	>32	
Ceftazidime		75.2	4.8	19	<0.06	64	<0.06	>64	
Imipenem		100	0	0	0.5	0.5	0.25	0.5	
Levofloxacin		64.8	3.9	31.3	0.25	>8	<0.008	>8	
Minocycline		61.6	7.8	10.6	2	16	<0.5	>16	
PipTazo		55.3	14.5	30.2	4	>128	0.25	>128	
All ESBL producers (n=67)		Tigecycline	94	6	0	0.5	2	0.12	>64
		Amikacin	86.6	10.4	3	8	32	1	>64
	AmoxClav	7.5	17.9	74.6	>32	>32	2	>32	
	Ampicillin	0	0	100	>32	>32	>32	>32	
	Cefepime	19.4	10.4	70.1	>32	>32	1	>32	
	Ceftazidime	19.4	14.9	65.7	>32	>32	>32	>32	
	Ceftazidime	4.5	10.4	85.1	>64	>64	2	>64	
	Imipenem	100	0	0	0.5	0.5	0.25	2	
	Levofloxacin	49.3	4.5	46.3	4	>8	0.03	>8	
	Minocycline	71.6	17.9	10.4	2	16	<0.5	>16	
	PipTazo	38.8	19.4	41.8	64	>128	1	>128	
	<i>E. aerogenes</i> (n=22)	Tigecycline	100	0	0	0.5	1	0.25	2
		Amikacin	81.8	4.5	13.6	2	64	1	>64
AmoxClav		4.5	0	95.5	>32	>32	8	>32	
Ampicillin		0	4.5	95.5	>32	>32	16	>32	
Cefepime		72.7	4.5	22.7	<0.5	32	<0.5	>32	
Ceftazidime		63.6	3.1	27.3	<8	>32	<8	>32	
Ceftazidime		68.2	4.5	27.3	>64	>0.06	>64	>64	
Imipenem		100	0	0	1	0.5	4	>32	
Levofloxacin		77.3	18.2	4.5	0.06	4	0.03	>8	
Minocycline		93.9	0	0	0	0.5	0.5	>16	
PipTazo		68.2	22.7	9.1	4	64	0.5	128	
<i>E. cloacae</i> (n=122)		Tigecycline	95.1	4.9	0	0.5	2	0.12	4
		Amikacin	90.2	7.4	2.5	2	16	<0.5	>64
	AmoxClav	0.8	0	99.2	>32	>32	16	>32	
	Ampicillin	0	7.4	92.6	>32	>32	16	>32	
	Cefepime	77.9	9	13.1	<0.5	32	<0.5	>32	
	Ceftazidime	63.1	3.3	33.6	<8	>32	<8	>32	
	Ceftazidime	61.5	9.8	27.7	0.5	>64	<0.06	>64	
	Imipenem	100	0	0	0	0.5	0.25	4	
	Levofloxacin	83.6	3.3	13.1	0.03	>8	<0.008	>8	
	Minocycline	82.8	5.7	11.5	4	16	<0.5	>16	
	PipTazo	73.8	13.1	13.1	2	128	0.12	>128	
	<i>S. marcescens</i> (n=64)	Tigecycline	98.4	1.6	0	0.5	1	0.5	4
		Amikacin	82.8	17.2	0	4	32	1	32
AmoxClav		3.1	3.1	93.8	>32	>32	8	>32	
Ampicillin		0	4.7	95.3	>32	>32	16	>32	
Cefepime		79.7	6.3	14.1	<0.5	>32	<0.5	>32	
Ceftazidime		79.7	10.9	9.4	<8	16	<8	>32	
Ceftazidime		79.7	0	20.3	0.25	>64	<0.06	>64	
Imipenem		100	0	0	0.5	2	0.5	4	
Levofloxacin		82.2	3.1	4.7	0.12	2	0.15	>8	
Minocycline		90.6	7.8	1.6	4	4	1	16	
PipTazo		81.3	10.9	7.8	1	64	0.5	>128	

^aInterpretive criteria as defined by CLSI, M100-S16 (2006), where available; tigecycline susceptibility breakpoints are according to FDA package insert (Tygacil[®], 2005), where applicable [9].

RESULTS

Table 2. In vitro activity of tigecycline and comparative agents against *Acinetobacter* spp. and *P. aeruginosa*.

Organism Name	Drug	%SUS ^a	%INT	%RES	MIC			MIC Range		
					MIC ₅₀	MIC ₉₀	Low	High		
<i>Acinetobacter</i> spp. (n=149)	Tigecycline	na	na	na	0.5	>16	0.12	>16		
	Amikacin	19.5	18.8	61.7	64	>64	1	>64		
	Cefepime	13.4	23.5	63.1	32	>32	<0.5	>32		
	Ceftazidime	6	6	87.9	>32	>32	<8	>32		
	Ceftazidime	1.3	4.7	94	>64	>64	8	>64		
	Imipenem	51.7	6.7	41.6	4	>16	0.25	>16		
	Levofloxacin	6.7	28.2	65.1	8	>8	0.03	>8		
	Minocycline	100	0	0	<0.5	2	<0.5	4		
	PipTazo	10.1	30.2	59.7	128	>128	<0.06	>128		
	<i>P. aeruginosa</i> (n=165)	Tigecycline	na	na	na	8	>16	0.12	>16	
		Amikacin	67.3	15.8	17	8	64	<0.5	>64	
		Cefepime	54.5	23.6	21.8	8	32	<0.5	>32	
		Ceftazidime	58.2	11.5	30.3	<8	>32	<8	>32	
Ceftazidime		20	21.8	58.2	64	>64	0.5	>64		
Imipenem		67.7	21.3	11	1</					