

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) - In Vitro Antibacterial Activity Against Nosocomial Pathogens in South America, 2004-2006

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REVISED ABSTRACT

Background: Tigecycline, the first member of the glycyliclins to be brought to market, has been shown to have potent activity against most Gram-negative and Gram-positive pathogens. The T.E.S.T. program reports the in vitro activity of tigecycline and comparator antimicrobials against nosocomial gram-positive and gram-negative species from South America. **Methods:** A total of 1,580 nosocomial isolates were collected from 12 hospitals across South America. MICs were determined by broth microdilution according to CLSI guidelines. **Results:** Tigecycline demonstrated a MIC₉₀ value of 8 mcg/ml against all organisms, Gram-positive and Gram-negative (excluding *Pseudomonas*). Tigecycline's activity was similar to imipenem against *Enterobacteriaceae*. It inhibited multi-resistant ESBL-producers with MIC₉₀ values equal to or less than 2 mcg/ml. Although similar to other classes of broad spectrum antimicrobials against non-fermenters, tigecycline was especially active against *Acinetobacter* spp., presenting the lowest MIC₉₀ of 1 mcg/ml, but was not active against *S. aureus* with a MIC₉₀ of 0.5 mcg/ml regardless of sensitivity or resistance to methicillin. The same phenomenon was noticed against *enterococci*, with tigecycline's MIC₉₀ less than or equal to 0.25 mcg/ml for both all strains of *enterococci* including vancomycin-resistant and -susceptible strains. **Conclusion:** Tigecycline in vitro activity was comparable to, and in some instances greater than, most commonly prescribed broad spectrum antimicrobials. Tigecycline retained potent activity against strains resistant to other antimicrobials, such as ESBL-producers, multi-resistant *Acinetobacter* spp., methicillin-resistant *S. aureus*, and vancomycin-resistant *enterococci*.

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycyliclins. 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 represents another glycyliclin 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 12 laboratories from South America. This study is part of the larger ongoing 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 and 2006 from 12 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 (0.006-8); minocycline (0.5-16); tigecycline (0.008-16); 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 both 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: ceftazidime (30 mcg), ceftazidime/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; *H. influenzae* ATCC 49786; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29212; *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].

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MATERIALS & METHODS

Table 1. In vitro activity of tigecycline and comparative agents against 840 strains of *Enterobacteriaceae*.

Organism Name	Drug	%SUS ^a	%INT	MIC		MIC range	
				MIC ₅₀	MIC ₉₀	Low	High
All <i>Enterobacteriaceae</i> (n=840)	Tigecycline	97.8	2.1	0.2	0.5	>128	8
	Amikacin	90.6	4.6	4.8	2	>16	<0.5
	AmoxClav	36.2	8.9	54.9	32	>32	0.25
	Ampicillin	10.7	5.1	84.2	>32	>32	<0.5
	Cefepime	74.4	5.2	20.4	>0.5	>32	<0.5
	Ceftazidime	70.4	5.7	23.9	>0.5	>32	<0.5
	Ceftazidime	68.4	4	29.5	0.12	>32	<0.5
	Imipenem	100	0	0	0.5	1	0.12
	Levofloxacin	73.8	3.8	22.4	0.06	>8	>0.008
	Minocycline	81.8	8.5	8.7	2	8	<0.5
PipTazo	73.2	11.4	15.4	2	128	>0.06	
<i>E. coli</i> (n=247)	Tigecycline	100	0	0	0.12	>0.008	1
	Amikacin	98	0.8	1.2	2	8	<0.5
	AmoxClav	68.4	16.2	15.4	8	32	0.25
	Ampicillin	38.4	0.8	62.8	>32	>32	<0.5
	Cefepime	88.7	2.8	8.5	>0.5	16	<0.5
	Ceftazidime	90.3	2.6	6.1	>0.5	>32	<0.5
	Ceftazidime	84.2	0.8	15	>0.06	>64	>0.06
	Imipenem	100	0	0	0.5	0.12	4
	Levofloxacin	70.9	4.5	24.7	0.03	>8	>0.008
	Minocycline	78.1	11.7	10.1	1	16	<0.5
PipTazo	82.3	4.5	3.2	1	16	>0.06	
<i>K. pneumoniae</i> (n=230)	Tigecycline	98.5	2.8	0.5	2	0.12	8
	Amikacin	87.8	3.5	8.7	2	32	<0.5
	AmoxClav	43	11.3	45.7	16	>32	0.5
	Ampicillin	0	8.3	91.7	>32	>32	16
	Cefepime	55.2	6.5	38.3	1	>32	<0.5
	Ceftazidime	57	5.7	37.4	>0.5	>32	<0.5
	Ceftazidime	50.4	3.9	45.7	1	>64	>0.06
	Imipenem	100	0	0	0.5	0.25	2
	Levofloxacin	62.9	3	33	0.25	>8	>0.008
	Minocycline	81.3	7.8	10.9	2	16	<0.5
PipTazo	64.3	16.2	30.4	8	>128	0.25	
<i>K. oxytoca</i> (n=35)	Tigecycline	95.7	3.5	0.7	0.5	0.12	8
	Amikacin	94.3	2.9	2.9	2	16	1
	AmoxClav	77.1	8.6	14.3	>32	1	>32
	Ampicillin	0	8.6	91.4	>32	16	>32
	Cefepime	94.3	5.7	0	>0.5	8	<0.5
	Ceftazidime	85.7	0	14.3	>0.5	>32	<0.5
	Ceftazidime	80	2.9	17.1	>0.06	>64	>0.06
	Imipenem	100	0	0	0.5	0.25	0.5
	Levofloxacin	84.3	0	5.7	0.06	1	0.015
	Minocycline	97.1	2.9	0	1	4	<0.5
PipTazo	68.9	9.7	6.7	1	32	>0.06	
All ESBL producers (n=141)	Tigecycline	95.7	3.5	0.7	0.5	0.12	8
	Amikacin	79.4	7.1	13.5	8	>64	<0.5
	AmoxClav	7.8	24.1	68.1	>32	>32	>32
	Ampicillin	0	6.7	93.3	>32	>32	16
	Cefepime	19.1	10.6	70.2	>32	>32	<0.5
	Ceftazidime	19.9	12.1	68.1	>32	>32	>32
	Ceftazidime	5	5.7	89.4	>64	>64	2
	Imipenem	100	0	0	0.5	0.12	2
	Levofloxacin	34	5	63	>8	>8	0.03
	Minocycline	73	13.5	13.5	2	16	<0.5
PipTazo	36.2	26.8	39	84	>128	0.5	
<i>E. aerogenes</i> (n=30)	Tigecycline	100	0	0	0.25	1	0.25
	Amikacin	86.7	3.3	10	2	32	1
	AmoxClav	3.3	0	96.7	>32	>32	8
	Ampicillin	0	3.3	96.7	>32	>32	16
	Cefepime	80	3.3	16.7	>0.5	>32	<0.5
	Ceftazidime	70	6.7	23.3	>0.5	>32	>32
	Ceftazidime	73.3	6.7	20	0.25	>64	>0.06
	Imipenem	100	0	0	1	0.5	4
	Levofloxacin	83.3	13.3	3.3	0.06	4	0.015
	Minocycline	93.3	0	6.7	2	4	<0.5
PipTazo	73.3	20	6.7	2	64	0.25	
<i>E. cloacae</i> (n=182)	Tigecycline	95.6	4.4	0	0.5	2	0.12
	Amikacin	91.8	5.5	2.7	2	16	<0.5
	AmoxClav	0.5	1.1	98.4	>32	>32	2
	Ampicillin	0	6.6	93.4	>32	>32	16
	Cefepime	73.6	6.8	19.8	>0.5	>32	<0.5
	Ceftazidime	67.7	6	36.3	>8	>32	>32
	Ceftazidime	57.1	8.2	34.6	1	>64	>0.06
	Imipenem	100	0	0	0.5	1	0.12
	Levofloxacin	78.6	2.7	18.7	0.06	>8	>0.008
	Minocycline	81.3	9.3	9.3	4	8	<0.5
PipTazo	65.9	16.5	17.6	2	128	0.12	
<i>S. marcescens</i> (n=96)	Tigecycline	97.9	2.1	0	1	2	0.25
	Amikacin	76	17.7	6.3	4	32	1
	AmoxClav	11	3.1	93.8	>32	>32	>32
	Ampicillin	0	5.2	94.8	>32	>32	16
	Cefepime	76	5.2	18.8	>0.5	>32	<0.5
	Ceftazidime	71.9	11.5	16.7	>0.5	>32	>32
	Ceftazidime	70.8	3.1	26	0.5	>64	>0.06
	Imipenem	100	0	0	0.25	4	0.25
	Levofloxacin	87.5	5.2	7.3	0.12	4	0.015
	Minocycline	88.5	10.4	1	4	8	1
PipTazo	78.1	11.5	10.4	2	128	0.5	

^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]. Species with <1% <0.06 were omitted from analysis.

RESULTS

Table 2. In vitro activity of tigecycline and comparative agents against 356 isolates of *Acinetobacter* spp. and *P. aeruginosa*.

Organism Name	Drug	%SUS ^a	%INT	MIC		MIC range		
				MIC ₅₀	MIC ₉₀	Low	High	
<i>Acinetobacter</i> spp. (n=160)	Tigecycline	na	na	na	0.5	>0.008	2	
	Cefepime	13.1	22.5	64.4	>32	>32	<0.5	
	Ceftazidime	6.3	5.6	88.1	>32	>32	>8	
	Ceftazidime	1.9	4.4	93.8	>64	>64	4	
	Imipenem	55.6	3.1	41.3	2	>16	0.25	
	Levofloxacin	6.9	25.6	67.5	8	>8	0.03	
	Minocycline	100	0	0	>0.5	1	<0.5	
	PipTazo	9.4	28.8	61.9	128	>128	>0.06	
	<i>P. aeruginosa</i> (n=196)	Tigecycline	na	na	na	8	>16	0.12
		Amikacin	68.9	15.3	15.8	8	64	<0.5
Cefepime		53.1	25	21.9	8	32	<0.5	
Ceftazidime		55.6	11.7	32.7	>8	>32	>8	
Ceftazidime		16.8	23	60.2	>64	>64	0.5	
Imipenem		65.1	21.4	13.5	2	16	0.25	
Levofloxacin		41.3	3.6	55.1	8	>8	0.06	
Minocycline		3.6	18.9	77.6	>16	>16	<0.5	
PipTazo		85.2	0	14.8	16	128	>0.06	
<i>S. aureus</i> (MRSA) (n=119)		Tigecycline	100	0	0	0.12	0.25	0.03
	AmoxClav	11.8	0	88.2	>8	>8	1	
	Ampicillin	0	0	100	>16	>16	2	
	Ceftazidime	4.2	9.2					