

REVISED ABSTRACT

Background: Tigecycline, a new glycolcycline, has potent expanded broad spectrum activity against commonly encountered species responsible for community and hospital acquired infections. The T.E.S.T. program determined the in vitro activity of tigecycline compared to broad spectrum antimicrobials against gram negative and gram positive species collected from hospitals within North America throughout 2004-2006. **Methods:** A total of 21,792 clinical isolates were identified to the species level. Minimum Inhibitory Concentration (MICs) were determined by the local laboratory using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Results are in the table as follows:

	ESBLs				<i>Acinetobacter spp.</i>			
	IP (n=258)		OP (n=29)		IP (n=1168)		OP (n=348)	
	%S	MIC ₉₀	%S	MIC ₉₀	%S	MIC ₉₀	%S	MIC ₉₀
Tigecycline	93	2	83	4	NA	2	NA	1
Amikacin	88	32	97	16	82	32	88	32
Cefepime	50	>32	62	>32	45	>32	65	>32
Ceftazidime	7	>32	14	>32	46	>32	65	≤8
Imipenem	86	8	100	0.5	87	8	91	4
Levofloxacin	20	>8	24	>8	48	>8	67	>8
Minocycline	67	>16	59	>16	88	8	92	≤0.5
Pip-Tazo	52	>128	59	>128	56	>128	74	1

	<i>S. aureus</i>		<i>Enterococcus spp.</i>	
	IP (n=2289)	OP (n=711)	IP (n=1429)	OP (n=308)
	%S	MIC ₉₀	%S	MIC ₉₀
Tigecycline	99	0.25	99	0.12
Levofloxacin	47	>32	60	32
Linezolid	100	2	100	2
Minocycline	99	≤0.25	99	0.5
Vancomycin	100	1	100	1

Conclusion: Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed antimicrobials. The presented data suggest that tigecycline may be an effective and reliable therapeutic option against pathogens in both inpatient and outpatient clinical settings.

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycolcyclines. This synthetic analogue of the tetracyclines exhibits significant antibacterial activity that is 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 glycolcyclines 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 North 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 study centers in North 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: ceftazidime (30-mcg), ceftazidime/clavulanic acid (30/10-mcg), ceftazidime/clavulanic acid (30/10-mcg), and ceftazidime/clavulanic acid (30/10-mcg). 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 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].

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RESULTS

The results are listed in the following tables.

Table 1. In vitro activity of tigecycline and comparator agents against *Enterobacteriaceae* isolated from inpatients and outpatients in North America.

	<i>Enterobacter spp.</i>				<i>E. coli</i>				<i>Klebsiella spp.</i>				<i>Serratia spp.</i>			
	Inpatient (n=1990)		Outpatient (n=536)		Inpatient (n=2131)		Outpatient (n=793)		Inpatient (n=2187)		Outpatient (n=595)		Inpatient (n=819)		Outpatient (n=227)	
	% S	MIC ₉₀	% S	MIC ₉₀	% S	MIC ₉₀	% S	MIC ₉₀	% S	MIC ₉₀	% S	MIC ₉₀	% S	MIC ₉₀	% S	MIC ₉₀
Tigecycline	92.6	2	93.8	2	99.5	0.25	99.5	0.25	95.2	2	95.3	1	96.6	2	97.8	2
Amikacin	99.2	4	99.4	4	99.5	4	99.7	4	98	4	99.7	2	99.6	4	100	4
Cefepime	95.9	4	97.4	2	97.3	≤0.5	99	≤0.5	94.5	4	98.3	≤0.5	97.8	1	98.7	1
Imipenem	100	1	100	1	100	0.5	100	0.5	98.4	0.5	99.8	0.5	100	1	100	2
Levofloxacin	90.4	2	93.3	1	75.4	>8	80.2	>8	87.7	8	93.9	1	94.9	1	96.1	1
Minocycline	84.8	8	86	8	86	8	86.3	8	85.7	8	85.2	8	90.5	4	91.8	4
Pip/tazo	80.2	64	90.5	16	95.9	4	97.5	4	89.7	32	95.5	4	96.5	8	96.6	8

	ESBL's			
	Inpatient (n=258)		Outpatient (n=29)	
	% S	MIC ₉₀	% S	MIC ₉₀
Tigecycline	93	2	82.8	4
Amikacin	88.4	32	96.6	16
Cefepime	49.6	>32	62.1	>32
Imipenem	86.4	8	100	0.5
Levofloxacin	19.8	>8	24.1	>8
Minocycline	67.4	>16	58.6	>16
Pip/tazo	51.6	>128	58.6	>128

Table 2. In vitro activity of tigecycline and comparator agents against *Acinetobacter spp.* isolated from inpatients and outpatients in North America.

	<i>Acinetobacter spp.</i>			
	Inpatient (n=1168)		Outpatient (n=348)	
	% S	MIC ₉₀	% S	MIC ₉₀
Tigecycline	n/a	2	n/a	1
Amikacin	81.8	32	88.2	32
Cefepime	45.2	>32	65.2	>32
Imipenem	87	8	90.8	4
Levofloxacin	47.7	>8	66.7	>8
Minocycline	88.4	8	91.7	4
Pip/tazo	56.3	>128	74.1	128

Table 3. In vitro activity of tigecycline and comparator agents against *S. aureus* and *Enterococcus spp.* isolated from inpatient and outpatients in North America.

	<i>S. aureus</i>				<i>Enterococcus spp.</i>			
	Inpatient (n=2289)		Outpatient (n=711)		Inpatient (n=1429)		Outpatient (n=308)	
	% S	MIC ₉₀	% S	MIC ₉₀	% S	MIC ₉₀	% S	MIC ₉₀
Tigecycline	99.1	0.25	99.3	0.12	99.7	0.12	99.4	0.12
Amox/clav	61.9	>8	66.5	>8	73.1	>16	83.1	>16
Ampicillin	8.5	>16	9.3	>16	40.7	>32	46.8	>32
Ceftriaxone	48.8	>64	54	>64	98.3	2	98.7	2
Imipenem	90.2	4	94.9	1	55.3	8	48.4	8
Levofloxacin	47.2	>32	59.9	32	72.6	>8	82.8	>8
Linezolid	100	2	100	2	75.9	>32	85.1	>32
Minocycline	99.4	≤0.25	99.3	0.5				
Penicillin	7.2	>8	7.7	>8				

CONCLUSIONS

- Klebsiella spp.* were the only *Enterobacteriaceae* which showed a 2 fold higher MIC₉₀ for inpatients vs. outpatients for tigecycline. *Enterobacter spp.*, *E. coli* and *Serratia spp.* showed no difference in MIC₉₀s for inpatients vs. outpatients for tigecycline.
- 287 of the 9278 *Enterobacteriaceae* were ESBL producers. Of these ESBL producers, outpatients showed a 2 fold higher MIC₉₀ than inpatients: 2mcg/ml vs. 1mcg/ml respectively.
- Enterococcus spp.* showed no difference in MIC₉₀s for inpatients vs. outpatients, both exhibiting an MIC₉₀ of 0.12 mcg/ml for tigecycline. Tigecycline exhibited the highest activity as compared to other antibiotic agents with 99% of the isolates being susceptible.
- S. aureus* showed a 2 fold increase in MIC₉₀ for inpatients vs. outpatients for tigecycline and superior activity of 99% as compared to other antibiotic agents. Linezolid was the only agent with higher activity at 100% susceptible.
- Tigecycline showed excellent activity against inpatients and outpatients, both showing MIC₉₀s of 2mcg/ml or less (equal to or below the susceptible breakpoint of tigecycline). Only ESBL isolates from outpatients had a higher MIC₉₀ (4mcg/ml) than the susceptible breakpoint for tigecycline.