

# An In Vitro Evaluation Of Tigecycline In An In-Patient vs. Out-Patient Population Worldwide

#E-320

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## REVISED ABSTRACT

**Background:** Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent broad spectrum activity against most 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 most commonly prescribed broad spectrum antimicrobials against gram negative and gram positive species collected from hospitals globally throughout 2004-2005. **Methods:** A total of 18,950 clinical isolates were identified to the species level at each site and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. Tigecycline's MIC  $\leq 2$  mcg/mL was defined as susceptible. **Results:** Results are in the table as follows:

Enterobacteriaceae				Acinetobacter spp.			
In patients (n=485)	Out patients (n=2458)	In patients (n=1048)	Out patients (n=194)	In patients (n=460)	Out patients (n=2448)	In patients (n=393)	Out patients (n=393)
%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>
Tigecycline 96.6	1	97.8	1	na	1	na	1
Amikacin 98.9	4	99.5	4	79	64	89.2	32
Cefepime 94.4	4	97.7	1	46	>32	64.4	>32
Ceftazidime 85.8	32	92.3	<8	46.4	>32	66	>32
Imipenem 98.5	1	99.4	1	82.8	16	94.3	2
Levofloxacin 84.2	8	87.7	8	49.5	>8	65.5	>8
Minocycline 85.4	8	84.9	8	90.4	4	90.7	4
Pip-Tazo 89.8	32	94.5	8	70.2	>128	85.1	128

  

S. aureus				Enterococcus spp.			
In patients (n=1,699)	Out patients (n=460)	In patients (n=2,248)	Out patients (n=393)	In patients (n=460)	Out patients (n=2,248)	In patients (n=393)	Out patients (n=393)
%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>
Tigecycline 99.5	0.25	100	0.25	99	0.12	99.2	0.12
Levofloxacin 55.2	>32	66.5	32	45.4	>32	50.6	>32
Linezolid 100	4	100	2	97.4	2	97.5	2
Minocycline 97.9	0.5	99.0	0.5	48.7	>8	42.2	>8
Vancomycin 100	1	100	1	83.5	>32	88.3	>32

**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 nosocomial or community pathogens regardless of resistance mechanisms.

## INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycylcyclines. 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 glycylcyclines 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 90<sup>th</sup> 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 worldwide from in-patients and Out-patients. 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, 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 January 2004 - July 2005 from 107 study centers in 25 countries (refer to Table 1). Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, as well as, development and management of a centralized database was 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 site criteria.

Table 1. Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program participating sites and microorganism contribution.

Country	Sites	Total No. of Organisms		% of Total No.
		In-Patients	Out-Patients	
Australia	1	177	0.9	
Austria	1	179	0.9	
Belgium	1	174	0.9	
Brazil	1	185	1	
Canada	1	191	1	
China	1	170	0.9	
France	4	759	4	
Germany	5	962	5.1	
Greece	1	181	1	
Hungary	1	218	1.2	
India	1	149	0.8	
Ireland	1	194	1	
Italy	3	551	2.9	
Latvia	1	177	0.9	
Pakistan	1	179	0.9	
Philippines	1	185	1	
Poland	1	142	0.8	
Portugal	1	170	0.9	
Singapore	1	197	1	
Spain	4	765	4	
Switzerland	1	183	1	
The Netherlands	1	248	1.3	
Turkey	1	198	0.8	
United Kingdom	4	747	3.9	
United States	68	11859	62.6	
<b>Total</b>	<b>107</b>	<b>18950</b>	<b>100</b>	

## Antimicrobial Susceptibility Testing

- 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 (0.12-10.0-32/16); 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 (0.064-128/4) and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [8] and recent US Food and Drug Administration packaging 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 µg/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) and ceftazidime (30 mcg), 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 29312 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 2. In Vitro Activity of Tigecycline and Comparative Antimicrobial Agents against Gram-Positive Clinical Pathogens Isolated from In-Patients and Out-Patients - Worldwide results.

Organism (N)	Drug	In-Patients			Out-Patients		
		MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus	MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus
Penicillin Susceptible <i>E. faecalis</i> In-Patient (n=806) Out-Patient (n=158)	Tigecycline	0.12	0.12	99	0.12	0.12	99.4
	Amoxiclav	0.5	1	100	0.5	1	100
	Ampicillin	1	2	100	1	2	100
	Ceftazidime	>64	>64	na	>64	>64	na
	Levofloxacin	1	>32	58.5	1	>32	58.9
	Linezolid	2	2	97.8	2	2	97.5
	Minocycline	8	>16	42.8	8	>16	36.1
	Penicillin	2	4	100	2	4	100
	Pip-tazo	2	8	na	2	4	na
	Vancomycin	1	2	95.6	1	2	94.3
Vancomycin Resistant <i>E. faecalis</i> In-Patient (n=31) Out-Patient (n=7)	Tigecycline	0.06	0.25	100	-	-	-
	Amoxiclav	>8	>8	na	-	-	-
	Ampicillin	4	8	100	-	-	-
	Ceftazidime	>64	>64	na	-	-	-
	Imipenem	>16	>16	na	-	-	-
	Levofloxacin	>32	>32	14.2	>32	>32	11.8
	Linezolid	2	2	97.3	2	2	97.1
	Minocycline	0.5	>8	68.6	>0.25	8	70.6
	Pip-tazo	>16	>16	na	>16	>16	na
	Vancomycin	16	>32	87.7	1	>32	81.8
<i>S. aureus</i> In-Patient (n=1,699) Out-Patient (n=460)	Tigecycline	0.06	0.12	100	0.06	0.12	100
	Amoxiclav	>8	>8	na	>8	>8	na
	Ampicillin	>16	>16	18.6	>16	>16	17.6
	Ceftazidime	>64	>64	na	>64	>64	na
	Imipenem	>16	>16	na	>16	>16	na
	Levofloxacin	>32	>32	14.2	>32	>32	11.8
	Linezolid	2	2	97.3	2	2	97.1
	Minocycline	0.5	8	64.8	>0.25	8	69.2
	Pip-tazo	>16	>16	na	>16	>16	na
	Vancomycin	>32	>32	0	>32	>32	0
<i>S. aureus</i> , MSSA In-Patient (n=972) Out-Patient (n=271)	Tigecycline	0.12	0.25	100	0.12	0.12	100
	Amoxiclav	1	2	98.4	1	2	98.2
	Ampicillin	4	>16	18.2	4	>16	18.5
	Ceftazidime	4	4	97.7	4	4	97.8
	Imipenem	0.25	0.25	99.6	0.25	0.25	99.6
	Levofloxacin	0.12	4	89.4	0.12	1	92.6
	Linezolid	2	2	100	2	2	100
	Minocycline	>0.25	0.5	99.5	>0.25	0.5	99.3
	Penicillin	8	>16	13.9	8	>16	14.4
	Pip-tazo	1	2	98.7	1	2	98.5
<i>S. aureus</i> , MRSA In-Patient (n=787) Out-Patient (n=189)	Tigecycline	0.12	0.25	99	0.12	0.25	100
	Amoxiclav	8	>8	23.9	8	>8	24.9
	Ampicillin	>16	>16	0	>16	>16	0
	Ceftazidime	64	>64	0.8	32	>64	0
	Imipenem	0.5	>16	71.7	0.5	>16	82.5
	Levofloxacin	16	>32	15.6	4	>32	29.1
	Linezolid	2	4	100	2	4	100
	Minocycline	>0.25	4	96.1	>0.25	1	100
	Penicillin	>8	>8	0	>8	>8	0
	Pip-tazo	>16	>16	18.6	>16	>16	18.6
<i>S. agalactiae</i> In-Patient (n=443) Out-Patient (n=308)	Tigecycline	0.03	0.12	100	0.03	0.25	100
	Amoxiclav	0.06	0.12	100	0.06	0.12	100
	Ampicillin	0.12	0.12	100	>0.06	0.12	100
	Ceftazidime	0.06	0.12	99.8	0.06	0.12	99.4
	Imipenem	>0.12	0.25	na	>0.12	0.25	na
	Levofloxacin	0.5	1	99.5	0.5	1	99.7
	Linezolid	1	1	100	1	1	100
	Minocycline	8	>16	8	>16	8	8
	Penicillin	>0.06	0.12	100	>0.06	0.12	100
	Pip-tazo	>0.25	>0.25	na	>0.25	>0.25	na
<i>S. pneumoniae</i> In-Patient (n=821) Out-Patient (n=408)	Tigecycline	0.06	0.12	99	0.06	0.12	99
	Amoxiclav	>0.03	1	97.4	>0.03	2	97.1
	Ampicillin	>0.06	2	na	>0.06	2	na

Organism (N)	Drug	In-Patients			Out-Patients		
		MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus	MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus
Penicillin Intermediate <i>S. pneumoniae</i> In-Patient (n=212) Out-Patient (n=100)	Tigecycline	0.06	0.5	na	0.06	0.5	na
	Amoxiclav	0.25	1	99.1	0.12	1	100
	Ampicillin	0.25	2	na	0.25	2	na
	Ceftazidime	0.12	1	97.6	0.12	0.5	100
	Imipenem	0.25	0.25	27.4	0.25	0.25	30
	Levofloxacin	0.5	1	99.8	0.5	1	100
	Linezolid	>0.5	1	100	>0.5	1	100
	Minocycline	>0.25	8	na	>0.25	8	na
	Penicillin	0.25	1	0	0.25	1	0
	Pip-tazo	>0.25	2	na	>0.25		