

# Tigecycline in vitro Activity against *Staphylococcus aureus* and *Enterococcus* strains Resistant To Other Drugs In The T.E.S.T. Program - United States, 2004 - 2005

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## REVISED ABSTRACT

**Background:** Tigecycline (TIG), a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent activity against many Gram-positive and -negative organisms. The T.E.S.T. program determined the in vitro activity of TIG against *S. aureus* and enterococci resistant to 10 commonly prescribed antimicrobials: amoxicillin-clavulanic acid (AUG), piperacillin-tazobactam (PT), levofloxacin (LVX), ceftriaxone (CAX), linezolid (LZD), minocycline (MIN), vancomycin (VAN), ampicillin (AMP), penicillin (P) and imipenem (IMP). Study strains were collected from clinical laboratories in the United States during 2004-2005. **Methods:** A total of 2,434 clinical isolates (950 enterococci, 1,484 *S. aureus*) from 68 laboratories were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentrations (MICs) were determined by the local laboratory using broth microdilution panels. Antimicrobial resistance was interpreted according to CLSI breakpoints with TIG susceptible breakpoints defined as <0.5 mcg/mL for *S. aureus* and <0.25 mcg/mL for enterococci. **Results:** 590/950 (62%) enterococci and 1402/1484 (95%) *S. aureus* (including MR + MS strains) were resistant to at least one of the study drugs. Among the enterococci, resistance rates were LVX 55%, PT 23%, AMP 22%, VAN 21%, MIN 10%, and LZD 0%. Resistant rates for *S. aureus* were PT 94%, AMP 93%, AUG 41%, LVX 38%, PT 37%, CAX 22%, IMP 8%, LZD 0.0%, MIN 0.1% and VAN 0.0%. TIG inhibited 99.2% of the enterococci and 99.3% of the *S. aureus* resistant to other drugs. Modal TIG MICs ranged between 0.06 and 0.12 mcg/mL for all resistant strains. **Conclusions:** TIG retained potent activity against drug-resistant *S. aureus* and enterococcal isolates, inhibiting >99% of all resistant strains tested at the defined susceptibility breakpoints. TIG should prove to be a useful drug for therapy of infections with these resistant gram-positive pathogens.

## INTRODUCTION

Tigecycline is a broad-spectrum antimicrobial agent and first-in-class of the semisynthetic glycylcyclines to be approved for human use [1]. This synthetic analogue of the minocycline molecule 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 [2, 3]. 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 [4]. 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* [5-9]. This study was undertaken to document the in vitro activity of tigecycline against significant numbers of drug resistant *Staphylococcus aureus* and enterococci within the United States. 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. 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.

## Antimicrobial Susceptibility Testing

- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [10]. 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): amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.06-16); ceftriaxone (0.06-64); 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 [11] and recent US Food and Drug Administration packaging insert for tigecycline [12], where applicable.
- Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *S. aureus* ATCC 29213; and *Enterococcus faecalis* ATCC 29212. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2005) guidelines [11].

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## RESULTS

The results are listed in the following Tables.

Table 1. Study Organisms with Phenotypes

Genus/Species/Phenotype *	Phenotype	Total N
<b>Staphylococcus aureus</b> 1484		
<i>Staphylococcus aureus</i> , MRSA	779 (52.5%)	
<i>Staphylococcus aureus</i> , MSSA	705 (47.5%)	
<b>Enterococcus avium</b> 6		
<b>Enterococcus casseliflavus</b> 9		
<b>Enterococcus durans</b> 8		
<b>Enterococcus faecalis</b> 668		
<i>Enterococcus faecalis</i> , VRE	33 (4.9%)	
<b>Enterococcus faecium</b> 233		
<i>Enterococcus faecium</i> , VRE	159 (68.2%)	
<b>Enterococcus Group D</b> 2		
<b>Enterococcus raffinosus</b> 2		
<b>Enterococcus, non-specified</b> 22		
<b>Total</b>		<b>2434</b>

\* Phenotypes: MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; VRE = vancomycin-resistant enterococci

Table 2. In Vitro Susceptibility of Tigecycline and comparators against *Staphylococcus aureus* and *Enterococcus* species

Drug	MIC mcg/mL)			%Sus	%Res
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range		
<b>Staphylococcus aureus</b> (n=1484)					
Tigecycline	0.12	0.25	0.015 - 4	99.6	0.4
AmoxClav	4	>8	≤0.03 - 32	59.2	40.8
Ampicillin	16	>16	≤0.06 - >32	7	93
Ceftriaxone	16	>64	0.12 - >64	45.4	22.3
Imipenem	0.25	4	≤0.12 - >16	90.2	7.8
Levofloxacin	1	>32	≤0.06 - >32	52.6	38.1
Linezolid	2	4	≤0.5 - 4	100	0
Minocycline	≤0.25	0.5	≤0.25 - >8	99.3	0.1
Penicillin	>8	>8	≤0.06 - 16	6.1	93.9
PipTazo	4	>16	≤0.25 - 128	63.1	36.9
Vancomycin	1	1	≤0.12 - 4	100	0
<b>Enterococcus spp</b> (n=950)					
Tigecycline	0.06	0.12	≤0.008 - 0.5	99.6	0.4
Ampicillin	1	>16	0.12 - >32	78.2	21.8
Levofloxacin	16	>32	≤0.06 - >32	44	54.7
Linezolid	2	2	≤0.5 - 4	97.5	0
Minocycline	8	>8	≤0.25 - >8	49.6	10.2
Penicillin	2	>8	≤0.06 - >8	77.4	22.6
Vancomycin	1	>32	≤0.12 - >32	78.1	21.1

Table 3. Frequency Distribution of Drug Resistant Strains at each Tigecycline MIC (mcg/mL) for each Comparator Antimicrobial Agent against 1484 *Staphylococcus aureus* Strains Resistant to One or more Antimicrobial

Drug	Tigecycline MICs (mcg/mL)							Total
	0.015	0.03	0.06	0.12	0.25	0.5	1	
AmoxClav	1	73	400	101	24	5	1	605
Ampicillin	1	7	229	967	142	28	5	1380
Ceftriaxone	1	47	187	68	23	5	1	331
Imipenem	1	8	56	35	13	3	1	116
Levofloxacin	2	76	363	98	23	3	1	566
Linezolid								0
Minocycline					1			1
Penicillin	1	7	233	975	144	28	5	1394
PipTazo	0	2	74	348	94	26	3	547
Vancomycin								0
Total No. Drug Resistant Values	2	21	740	3296	682	166	29	4940

Table 4. Frequency Distribution of Drug Resistant Strains at each Tigecycline MIC (mcg/mL) for each Comparator Antimicrobial Agent against 590 *Enterococcus* spp Strains Resistant to One or more Antimicrobial

Drug	Tigecycline MICs (mcg/mL)						Total	
	0.015	0.03	0.06	0.12	0.25	0.5		
Ampicillin	2	90	91	21	1	2	207	
Levofloxacin	4	130	229	144	9	4	520	
Linezolid							0	
Minocycline			1	24	55	16	1	97
Penicillin	2	93	93	24	1	2	215	
Vancomycin	1	80	85	30	3	1	200	
Total No. Drug Resistant Values	9	394	522	274	30	10	1239	

Table 5. In Vitro Susceptibility of Tigecycline against Drug Resistant *Staphylococcus aureus* and *Enterococcus* spp.

Drug	Total No. of Resistant Strains/Drug	Percent (%) Resistance for each Drug	%Susceptible against Resistant Strains	%Resistant against Resistant Strains
<b>Staphylococcus aureus</b> (n=1484)				
AmoxClav	605	40.8	99.1	0.9
Ampicillin	1380	93	99.6	0.4
Ceftriaxone	331	22.3	98.5	1.5
Imipenem	116	7.8	97.4	2.6
Levofloxacin	566	38.1	99.3	0.7
Linezolid	0	0	0	0
Minocycline	1	0.1	100	0
Penicillin	1394	93.9	99.5	0.5
Pip-tazo	547	36.9	99.5	0.5
Vancomycin	0	0	0	100
Total No. Drug Resistant Values against <i>S. aureus</i>	4940	33.3	99.3	0.7
<b>Enterococcus spp</b> (n=950)				
Ampicillin	207	21.8	99	1
Levofloxacin	520	54.7	99.2	0.8
Linezolid	0	0	0	0
Minocycline	97	10.2	99	1
Penicillin	215	22.6	99.1	0.9
Vancomycin	200	21.1	99.5	0.5
Total No. Drug Resistant Values against <i>Enterococcus</i> spp	1239	21.7	99.2	0.8

## CONCLUSIONS

- Tigecycline inhibited 99.6% of all *Staphylococcus aureus* and *Enterococcus* species at the FDA susceptible breakpoints of 0.5 and 0.25 mcg/mL, respectively, without regard to either methicillin- or vancomycin resistant phenotypes.
- 1402/1484 (95%) *S. aureus* and 590/950 (62%) *Enterococcus* species were resistant to at least one of the study drugs.
- 99.3% of all drug resistant *Staphylococcus aureus* and 99.2% of all *Enterococcus* species with one or more drug resistant values were susceptible to tigecycline.
- Tigecycline demonstrated potent in vitro activity against all drug resistant *Staphylococcus aureus* and *Enterococcus* species with modal values (MIC<sub>50</sub>) ranging from 0.06 to 0.12 mcg/mL.
- Tigecycline demonstrated equivalent in vitro potency to vancomycin and linezolid against all *Staphylococcus aureus* with MIC<sub>50</sub> value of 0.25 mcg/mL and susceptibilities >99%.
- Tigecycline demonstrated equivalent in vitro potency to linezolid against all *Enterococcus* species with MIC<sub>50</sub> value of 0.12 mcg/mL and susceptibilities >99%.
- The in vitro activity of tigecycline in this study suggests that tigecycline will be a significant antimicrobial agent for the treatment of some of the most commonly encountered hospital and community acquired pathogens and is active against most drug resistant *Staphylococcus aureus* and *Enterococcus* species.