

# In Vitro Activity of Tigecycline and 10 Common Therapeutic Agents Against Methicillin-Resistant *Staphylococcus aureus* and Vancomycin-Resistant *Enterococcus* species – Global Data, 2004 - 2008

SR050

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## Revised Abstract

**Objectives:** Tigecycline (TIG), a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent activity against community and hospital acquired staphylococcal and enterococcal pathogens. The T.E.S.T. program determined the in vitro activity against methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococcus* spp. of TIG and 10 antimicrobials commonly prescribed for serious gram-positive infections: 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 1016 laboratories in 53 countries globally throughout 2004-2008. **Methods:** A total of 24,479 clinical isolates (9,024 enterococci, 15,455 *S. aureus*) were identified to the species level at each participating site and confirmed by a 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  $\leq 0.5$  mcg/ml for *S. aureus* and  $\leq 0.25$  mcg/ml for enterococci. **Results:** 13.5% (1216/9024) of enterococci were resistant to vancomycin (VRE), and 43.2% (6674/15,455) of *S. aureus* were resistant to oxacillin (MRSA). Among the *E. faecium* VRE, % resistance rates to other study drugs were LVX 99.9, P 98.7, AMP 98.3, VAN 100, and LZD 0.2. Resistance rates for MRSA were P 100, AMP 100, AUG 100, LVX 73.8, PT 100, CAX 100, IMP 100, MIN 1.0, LZD 0.0, and VAN 0.0. TIG inhibited 99.9% of the enterococci and 100% *S. aureus* resistant to other drugs. Overall, 22% of *H. influenzae* were  $\beta$ -lactamase producers and 39% of *S. pneumoniae* presented some degree to non-susceptibility to penicillin. Tigecycline demonstrated potent inhibitory activity with MIC<sub>90</sub> values of  $\leq 0.5$  mcg/ml and  $\leq 0.12$  mcg/ml against  $\beta$ -lactamase positive *H. influenzae* and penicillin non-susceptible *S. pneumoniae*, respectively. **Conclusions:** TIG retained potent activity against drug-resistant *S. aureus* and enterococci isolates, inhibiting 100% and 99.9%, respectively, of all strains tested at their defined breakpoints of 0.5 and 0.25 mcg/ml, respectively. 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 semi-synthetic 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 gram-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 *S. 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 *S. aureus* and *Enterococcus* spp. collected from 53 countries. 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 and December 2008 from 1016 study centers in 53 countries throughout the world. 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.
- 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); meropenem (0.12 -16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); 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 [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 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 (2008) guidelines [11].

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## Results

The results are listed in the following Tables.

Table 1. Study organisms with phenotypes.

Genus/Species/Phenotype <sup>a</sup>	Phenotype	Total N
<i>Staphylococcus aureus</i>		15,455
<i>Staphylococcus aureus</i> , MRSA	6,674 (43.2%)	
<i>Staphylococcus aureus</i> , MSSA	8,781 (56.8%)	
<i>Enterococcus faecalis</i>		6,638
<i>Enterococcus faecalis</i> , VRE	177 (2.7%)	
<i>Enterococcus faecium</i>		2,386
<i>Enterococcus faecium</i> , VRE	1,039 (43.6%)	
<b>Total</b>		<b>24,479</b>

<sup>a</sup> Phenotypes: MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*. Methicillin phenotype was determined by the susceptibility of *S. aureus* to cefoxitin 30 mcg disk. VRE = vancomycin-resistant enterococci.

Table 2. The in vitro activity of tigecycline and comparative agents against 15,455 clinical isolates of *Staphylococcus aureus*.

Organism / Phenotype	Drug	%	%Res	MIC (mcg/ml)		
				MIC <sub>50</sub>	MIC <sub>90</sub>	Range
Methicillin-Resistant	Tigecycline	100	0.1	0.12	0.25	$\leq 0.008$ - 0.5
<i>Staphylococcus aureus</i> (n=6,674)	Levofloxacin	23.5	73.8	8	>32	$\leq 0.06$ - >32
	Linezolid	100	0	2	4	$\leq 0.5$ - 4
	Minocycline	96.2	1.0	$\leq 0.25$	2	$\leq 0.25$ - >8
	Vancomycin	100	0	1	1	0.25 - 4
Methicillin-Susceptible <i>Staphylococcus aureus</i> (n=8,781)	Tigecycline	100	0	0.12	0.25	$\leq 0.008$ - 0.5
	AmoxClav	99.9	0.1	1	2	$\leq 0.03$ - >8
	Ampicillin	73.8	26.2	4	>16	$\leq 0.06$ - >16
	Ceftriaxone	99.5	0.1	2	4	$\leq 0.03$ - >64
	Imipenem	100	0	$\leq 0.12$	0.25	$\leq 0.12$ - >16
	Levofloxacin	95.3	2.5	0.12	0.5	$\leq 0.06$ - >32
	Linezolid	100	0	2	4	$\leq 0.5$ - 4
	Meropenem	99.9	0.1	$\leq 0.12$	0.25	$\leq 0.12$ - >16
	Minocycline	99.4	0.1	$\leq 0.25$	$\leq 0.25$	$\leq 0.25$ - >8
	Penicillin	72.7	27.3	4	>8	$\leq 0.06$ - >8
PipTazo	99.9	0.1	1	1	$\leq 0.25$ - >16	
Vancomycin	100	0	1	1	$\leq 0.12$ - 4	

<sup>a</sup> Susceptibilities are defined in CLSI document M100-S18 (2008) where applicable. Methicillin phenotype based upon cefoxitin 30 mcg disk results;  $\beta$ -lactam susceptibilities based on methicillin phenotype. Tigecycline breakpoints are defined in FDA package insert (Tygacil®, 2005) as susceptible  $\leq 0.5$  mcg/ml.

Table 3. The frequency distribution (n) and cumulative percent inhibited (%) in vitro activity of tigecycline and comparative agents against 6,674 methicillin-resistant *S. aureus*.<sup>a</sup>

N / Cum%	MIC (mcg/ml)															
	$\leq 0.008$	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64	
Tigecycline	4	3	35	997	4074	1212	349									
AmoxClav				7	83	187	411	1155	2182	2659						
Ampicillin				1	1.0	3.9	10.0	27.3	62.0	100.0						
Ceftriaxone		3	1	5	6	19	69	126	462	1935	874	452	2482			
Imipenem		0.0	0.1	0.1	0.2	0.5	1.5	3.4	13.6	42.6	93.9	67.2	100.0			
Levofloxacin			8.1	30.7	90.3	60.8	67.6	72.3	78.2	82.3	100.0					
Linezolid			77	882	416	147	46	177	1261	839	974	830	823			
Meropenem			68	126	435	796	511	297	264	288	682					
Minocycline			2.0	5.7	18.4	40.5	55.5	64.2	71.9	78.7	100.0					
Penicillin				81.2	86.9	88.8	91.2	96.2	99.0	100.0						
PipTazo					16	33	62	119	216	332	506					
Vancomycin					0.2	0.7	1.7	3.4	6.7	14.7	30.2					
					7	58	194	338	730	1110	1217	3028				
					0.1	1.0	3.8	8.8	19.8	38.4	54.6	100.0				
					14	85	2903	3806	264	2						
					0.2	1.5	39.0	96.0	99.9	100.0						

<sup>a</sup> Methicillin phenotype based upon cefoxitin 30 mcg disk results according to CLSI document M100-S18, 2008.

Table 4. The in vitro activity of tigecycline and comparative antimicrobial agents against 6,638 *Enterococcus faecalis* and 2,386 *Enterococcus faecium* isolates from a global population.

Organism / Phenotype	Drug	%	%Res	MIC (mcg/ml)		
				MIC <sub>50</sub>	MIC <sub>90</sub>	Range
<i>E. faecalis</i> (n=6,638)	Tigecycline	99.9	0.1	0.12	0.12	$\leq 0.008$ - 1
	Ampicillin	99.9	0.1	1	2	$\leq 0.06$ - >16
	Levofloxacin	58.2	41.8	1	>32	$\leq 0.06$ - >32
	Linezolid	99.9	0.1	2	2	$\leq 0.5$ - >8
	Minocycline	40.7	19.7	8	>8	$\leq 0.25$ - >8
	Penicillin	99.8	0.2	2	4	$\leq 0.06$ - >8
<i>E. faecium</i> VRE (n=177)	Vancomycin	97.0	2.7	1	2	$\leq 0.12$ - >32
	Tigecycline	99.4	0.6	0.06	0.12	0.03 - 0.5
	Ampicillin	97.7	2.3	1	2	0.25 - >16
	Levofloxacin	3.4	92.6	32	>32	1 - >32
	Linezolid	97.7	1.7	1	2	$\leq 0.5$ - >8
	Minocycline	56.5	9.6	4	8	$\leq 0.25$ - >8
<i>E. faecium</i> (n=2,386)	Penicillin	96.0	4.0	2	8	0.5 - >8
	Vancomycin	0	100	>32	>32	32 - >32
	Tigecycline	100	0	0.06	0.12	$\leq 0.008$ - 0.25
	Ampicillin	16.1	83.9	>16	>16	$\leq 0.06$ - >16
	Levofloxacin	7.2	92.8	>32	>32	0.12 - >32
	Linezolid	99.9	0.1	2	2	$\leq 0.5$ - >8
<i>E. faecium</i> VRE (n=1,039)	Minocycline	74.0	11.7	$\leq 0.25$	8	$\leq 0.25$ - >8
	Penicillin	14.7	85.3	>8	>8	$\leq 0.06$ - >8
	Vancomycin	55.1	44.2	2	>32	$\leq 0.12$ - >32
	Tigecycline	100	0	0.06	0.12	0.015 - 0.25
	Ampicillin	1.7	98.3	>16	>16	0.5 - >16
	Levofloxacin	0.1	99.9	>32	>32	1 - >32
<i>E. faecium</i> (n=1,039)	Linezolid	99.8	0.2	2	2	$\leq 0.5$ - >8
	Minocycline	71.6	10.0	$\leq 0.25$	>8	$\leq 0.25$ - >8
	Penicillin	1.3	98.7	>8	>8	$\leq 0.06$ - >8
	Vancomycin	0	100	>32	>32	16 - >32
	Tigecycline	100	0	0.06	0.12	0.015 - 0.25
	Ampicillin	1.7	98.3	>16	>16	0.5 - >16

<sup>a</sup> Interpretive criteria as defined by CLSI, M100-S18 (2008), where applicable. Tigecycline FDA breakpoints for enterococci are approved for vancomycin-susceptible *E. faecalis* only; susceptibilities for all other enterococci are entered for comparison purposes only. (16)

Table 5. The frequency distribution (n) and cumulative percent inhibited (%) in vitro activity of tigecycline and comparative agents against 177 isolates of vancomycin-resistant *Enterococcus faecalis* from a global population.

N / Cum%	MIC (mcg/ml)															
	$\leq 0.008$	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64	
Tigecycline				19	75	67	15	1								
Ampicillin				10.7	53.1	91.0	99.4	100.0								
Ceftriaxone				4	48	86	23	10	2	1	3					
Levofloxacin				0.6	1.1	1.1	1.7									
Linezolid						5										