

# Determining In Vitro Activity of 14 Antimicrobials in Asia/Pacific Rim from 2004-2006

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## REVISED ABSTRACT

**Background:** Tigecycline, the first member of the glycylicyclines, was marketed in mid 2005 and has demonstrated success against multiple-resistant species and phenotypes. Due to its chemical structure, resistance to tigecycline is reportedly difficult to produce even in the laboratory. The T.E.S.T. program is an ongoing global surveillance with the first post-marketing prospective report of tigecycline and comparator in vitro activity for the years 2004 through 2006. **Methods:** 3,884 clinical isolates were collected from 23 investigative sites in 9 countries in Asia and the Pacific Rim (A/P). MICs were determined by broth microdilution according to CLSI guidelines using identical panels. **Results:** Results are given by year for all pathogens and antimicrobials. Summary data for tigecycline and key species are as follows:

Organism	N (04/05/06)	2004		2005		2006	
		MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Acinetobacter</i> spp	97/50/155	0.12	1	0.5	1	0.5	2
<i>Enterobacteriaceae</i>	536/344/872	0.5	1	0.5	1	0.5	1
ESBL producers*	68/35/47	0.5	2	0.5	2	0.25	2
<i>Enterococcus</i> spp	81/69/157	0.12	0.12	0.12	0.12	0.06	0.12
VRE	0/6/17	-	-	0.03	0.06	0.06	0.12
<i>S. aureus</i>	153/84/222	0.12	0.25	0.12	0.25	0.12	0.5
MRSA	58/42/92	0.25	0.5	0.25	0.5	0.25	0.5
<i>S. pneumoniae</i>	75/57/109	0.03	0.12	0.03	0.06	0.03	0.03
<i>P. aeruginosa</i>	132/87/228	8	>16	8	16	8	>16

**Conclusion:** Tigecycline demonstrated no shift in MIC values in A/P over three years from its pre-marketing baseline values. Tigecycline activity was retained even against strains resistant to other antimicrobials, such as ESBL-producers, multi-resistant *Acinetobacter* spp., methicillin-resistant *S. aureus*, vancomycin-resistant *enterococci*, and penicillin-resistant *S. pneumoniae*.

## INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycylicyclines. 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 glycylicyclines 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 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 and comparators against significant numbers of clinical pathogens collected from Asia/Pacific Rim over three years time. This study is part of the 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. 3,881 clinical isolates were collected and tested between 2004 to 2006 from 23 investigative sites in 9 countries in Asia/Pacific Rim. 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 [6]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers, MicroScan (Dade Behring Inc., West Sacramento, CA, USA) and Trek (TREK Diagnostic Systems, Cleveland, OH). The following antimicrobial agents and dilution ranges (expressed in mcg/mL) were included on the panels: tigecycline (0.008-16), imipenem (0.06-16), levofloxacin (0.008-8), minocycline (0.5-16), piperacillin/tazobactam (0.06/4-128/4), amikacin (0.5-32), ceftazidime (8-32), ceftriaxone (0.06-64) and cefepime (0.5-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [7], where applicable. There are currently no breakpoints defined for tigecycline against *Acinetobacter* species.
- Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftriaxone 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: cefotaxime (30-mcg), cefotaxime/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; *E. coli* ATCC 35218; *K. pneumoniae* ATCC 700603 (positive ESBL control); *Haemophilus influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *Pseudomonas aeruginosa* ATCC 27853; *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2006) guidelines [8].

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The results are listed in the following table and figures.

Table 1. In vitro activity of tigecycline and comparators against *Acinetobacter* spp. by year of isolation.

Antimicrobial	2004 n=97		2005 n=50		2006 n=155	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	0.12	1	0.5	1	0.5	2
Amikacin	4	>64	4	>64	8	>64
Amoxicillin/Clavulanate	16	>32	16	>32	>32	>32
Ampicillin	>32	>32	32	>32	>32	>32
Cefepime	8	>32	32	>32	16	>32
Ceftazidime	<8	>32	<8	>32	32	>32
Ceftriaxone	32	>64	64	>64	64	>64
Imipenem	0.5	>16	0.5	>16	4	>16
Levofloxacin	0.5	8	0.25	8	4	>8
Minocycline	<0.5	8	<0.5	4	<0.5	8
Piperacillin/Tazobactam	4	>128	16	>128	16	>128

Table 2. In vitro activity of tigecycline and comparators against *Enterobacteriaceae* by year of isolation.

Antimicrobial	2004 n=536		2005 n=344		2006 n=872	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	0.5	1	0.5	1	0.5	1
Amikacin	2	4	2	8	2	8
Amoxicillin/Clavulanate	16	>32	16	>32	32	>32
Ampicillin	>32	>32	>32	>32	>32	>32
Cefepime	<0.5	16	<0.5	16	<0.5	32
Ceftazidime	<8	>32	<8	>32	<8	>32
Ceftriaxone	0.12	>64	0.12	>64	0.12	>64
Imipenem	0.5	1	0.25	1	<0.06	0.25
Levofloxacin	0.06	>8	0.06	>8	0.12	>8
Minocycline	2	8	2	16	2	16
Piperacillin/Tazobactam	2	16	2	32	2	32

Table 3. In vitro activity of tigecycline and comparators against ESBL producers by year of isolation.

Antimicrobial	2004 n=68		2005 n=35		2006 n=47	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	0.5	2	0.5	2	0.25	2
Amikacin	4	>64	4	>64	4	>64
Amoxicillin/Clavulanate	16	>32	16	>32	32	>32
Ampicillin	>32	>32	>32	>32	>32	>32
Cefepime	8	>32	8	>32	>32	>32
Ceftazidime	16	>32	16	>32	16	>32
Ceftriaxone	>64	>64	>64	>64	>64	>64
Imipenem	0.25	0.5	0.25	0.5	0.12	0.5
Levofloxacin	4	>8	4	>8	>8	>8
Minocycline	4	16	4	>16	2	>16
Piperacillin/Tazobactam	4	32	4	64	8	>128

Table 4. In vitro activity of tigecycline and comparators against *P. aeruginosa* by year of isolation.

Antimicrobial	2004 n=132		2005 n=87		2006 n=228	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	8	>16	8	16	8	>16
Amikacin	4	32	4	16	4	32
Amoxicillin/Clavulanate	>32	>32	>32	>32	>32	>32
Ampicillin	>32	>32	>32	>32	>32	>32
Cefepime	4	32	4	16	4	32
Ceftazidime	<8	>32	<8	32	<8	>32
Ceftriaxone	>64	>64	32	>64	64	>64
Imipenem	1	8	1	8	1	16
Levofloxacin	1	>8	0.5	>8	1	>8
Minocycline	>16	>16	16	>16	16	>16
Piperacillin/Tazobactam	4	64	4	64	4	128

## RESULTS

Table 5. In vitro activity of tigecycline and comparators against *Enterococcus* spp. by year of isolation.

Antimicrobial	2004 n=81		2005 n=69		2006 n=157	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	0.12	0.12	0.12	0.12	0.06	0.12
Amoxicillin/Clavulanate	1	>8	0.5	>8	1	>8
Ampicillin	1	>16	1	>16	1	>16
Ceftriaxone	>64	>64	>64	>64	>64	>64
Imipenem	1	>16	1	>16	8	>16
Levofloxacin	1	>32	1	>32	4	>32
Linezolid	2	2	2	2	2	2
Minocycline	8	>8	8	>8	8	>8
Penicillin	2	>8	2	>8	4	>8
Piperacillin/Tazobactam	4	>16	2	>16	4	>16
Vancomycin	1	2	1	>32	1	32

Table 6. In vitro activity of tigecycline and comparators against vancomycin-resistant *enterococci* (VRE) by year of isolation.

Antimicrobial	2004 n=0		2005 n=6		2006 n=17	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	na	na	0.03	0.06	0.06	0.12
Amoxicillin/Clavulanate	na	na	>8	>8	>8	>8
Ampicillin	na	na	>16	>16	>16	>16
Ceftriaxone	na	na	>64	>64	>64	>64
Imipenem	na	na	>16	>16	>16	>16
Levofloxacin	na	na	>32	>32	>32	>32
Linezolid	na	na	1	2	2	2
Minocycline	na	na	<0.25	4	0.5	8
Penicillin	na	na	>8	>8	>8	>8
Piperacillin/Tazobactam	na	na	>16	>16	>16	>16
Vancomycin	na	na	>32	>32	>32	>32

na = not applicable; MIC<sub>90</sub> values not calculated if n<10.

Table 7. In vitro activity of tigecycline and comparators against *Staphylococcus aureus* by year of isolation.

Antimicrobial	2004 n=153		2005 n=84		2006 n=222	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	0.12	0.25	0.12	0.25	0.12	0.5
Amoxicillin/Clavulanate	1	>8	2	>8	2	>8
Ampicillin	8	>16	16	>16	16	>16
Ceftriaxone	4	>64	8	>64	4	>64
Imipenem	0.25	>16	0.25	>16	0.25	>16
Levofloxacin	0.25	16	0.25	>32	0.25	16
Linezolid	2	4	2	2	2	4
Minocycline	<0.25	8	<0.25	4	<0.25	4
Penicillin	<8	>8	>8	>8	>8	>8
Piperacillin/Tazobactam	1	>16	2	>16	1	>16
Vancomycin	1	1	0.5	1	1	1

Table 8. In vitro activity of tigecycline and comparators against methicillin-resistant *Staphylococcus aureus* by year of isolation.

Antimicrobial	2004 n=58		2005 n=42		2006 n=92	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	0.25	0.5	0.25	0.5	0.25	0.5
Amoxicillin/Clavulanate	>8	>8				