

A Yearly Analysis of the In Vitro Activity of Tigecycline and Comparators in Asia/Pacific Rim from 2004-2008



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Revised Abstract

Objectives: Tigecycline, the first member of the glycolcyclines, was marketed in mid 2005 and has demonstrated success against multiple-resistant species and phenotypes. 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 2008. **Methods:** 10,313 clinical isolates were collected from 75 investigative sites in 10 countries in Asia and the Pacific Rim. 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	2004-2006		2007		2008	
		MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Acinetobacter</i> spp	4921/2633/312	0.25	1	0.5	2	0.5	2
<i>Enterobacteriaceae</i>	2242/1895/418	0.5	1	0.5	1	0.5	1
ESBL producers*	2052/1088/385	0.5	2	5	2	0.5	1
<i>Enterococcus</i> spp	5606/2959/963	0.06	0.12	0.12	0.25	0.12	0.25
VRE	817/309/90	0.06	0.12	0.06	0.12	0.06	0.25
<i>S. aureus</i>	9075/4860/1520	0.12	0.25	0.12	0.25	0.12	0.25
MRSA	4131/2011/532	0.12	0.25	0.12	0.25	0.12	0.5
<i>S. pneumoniae</i>	4722/1942/270	0.03	0.06	0.03	0.12	0.06	0.12
<i>H. influenzae</i>	4238/2142/96	0.12	0.5	0.25	0.5	0.5	0.5
<i>P. aeruginosa</i>	7424/4003/179	1	>16	8	>16	8	16

Conclusions: Tigecycline demonstrated no shift in MIC values in a population of Asian/Pacific Rim region over a period of 5 years from its pre-marketing baseline values. Tigecycline activity was retained even against most 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 glycolcyclines. This synthetic analogue of the tetracyclines exhibits 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 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].

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 µg/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 clinical pathogens collected from Asia/Pacific Rim over five 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. 10,313 clinical isolates were collected and tested between 2004 to 2008 from 75 investigative sites in 10 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.

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); ceftazidime (0.5-32); ceftriaxone (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.

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 (2008) guidelines [8].

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Results

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

Antimicrobial	2004-2006		2007		2008	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.25	1	0.5	2	0.5	2
Amikacin	4	>64	4	>64	8	>64
Amoxicillin/Clavulanate	32	>32	>32	>32	>32	>32
Ampicillin	>32	>32	>32	>32	>32	>32
Cefepime	8	>32	16	>32	8	>32
Ceftazidime	16	>32	16	>32	16	>32
Ceftriaxone	32	>64	64	>64	64	>64
Imipenem	16	>16	2	>16	na	na
Levofloxacin	2	>8	4	>8	1	>16
Minocycline	2	>16	2	>16	>0.5	8
Piperacillin/Tazobactam	<0.5	4	<0.5	8	64	>128

*ESBL producers include *K. pneumoniae*, *K. oxytoca* and *E. coli*.

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

Antimicrobial	2004-2006		2007		2008	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.5	1	0.5	1	0.5	1
Amikacin	2	8	2	16	2	8
Amoxicillin/Clavulanate	16	>32	16	>32	32	>32
Ampicillin	>32	>32	>32	>32	>32	>32
Cefepime	>8	>32	>8	>32	>8	>32
Ceftazidime	8	>32	8	>32	8	>32
Ceftriaxone	0.12	>64	0.25	>64	0.25	>64
Imipenem	0.25	0.5	0.12	2	na	na
Levofloxacin	0.06	>8	0.25	>8	0.12	>8
Minocycline	2	16	2	16	4	16
Piperacillin/Tazobactam	2	32	4	128	4	64

na = not available; drug was discontinued.

Table 3. In vitro activity of tigecycline and comparators against ESBL producing *E. coli* and *Klebsiella* species, by year of isolation.

Antimicrobial	2004-2006		2007		2008	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.5	2	0.5	2	0.5	1
Amikacin	4	>64	4	32	4	64
Amoxicillin/Clavulanate	32	>32	32	>32	32	>32
Ampicillin	>32	>32	>32	>32	>32	>32
Cefepime	8	>32	32	>32	32	>32
Ceftazidime	16	>32	32	>32	32	>32
Ceftriaxone	>64	>64	>64	>64	>64	>64
Imipenem	0.25	0.5	<0.06	0.12	na	na
Levofloxacin	4	>8	>8	>8	<0.06	2
Minocycline	4	16	<0.06	1	4	>16
Piperacillin/Tazobactam	4	32	4	>16	16	>128

ESBL = extended-spectrum beta-lactamase.

na = not available; drug was discontinued.

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

Antimicrobial	2004-2006		2007		2008	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.5	2	0.5	2	0.5	1
Amikacin	4	16	>32	>32	4	32
Amoxicillin/Clavulanate	>32	>32	>32	>32	>32	>32
Ampicillin	>32	>32	>32	>32	>32	>32
Cefepime	4	32	>8	>32	4	32
Ceftazidime	<8	32	64	>64	<8	>32
Ceftriaxone	64	>64	1	16	>64	>64
Imipenem	1	8	1	>8	1	>8
Levofloxacin	1	>8	1	16	1	16
Minocycline	1	16	16	>16	16	>16
Piperacillin/Tazobactam	>16	>16	4	128	16	>128

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

Antimicrobial	2004-2006		2007		2008	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.06	0.12	0.12	0.25	0.12	0.25
Amoxicillin/Clavulanate	0.5	>8	0.5	>8	1	>8
Ampicillin	1	>16	1	>16	1	>16
Ceftriaxone	>64	>64	>64	>64	>64	>64
Imipenem	>16	>16	>16	>16	>16	>16
Levofloxacin	4	>32	2	>32	2	>32
Linezolid	2	2	2	2	2	2
Minocycline	4	>8	8	>8	8	>8
Penicillin	2	>8	2	>8	4	>8
Piperacillin/Tazobactam	2	>16	4	>16	4	>16
Vancomycin	1	>32	1	>32	1	8

na = not available; drug was discontinued.

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

Antimicrobial	2004-2006		2007		2008	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.06	0.12	0.06	0.12	0.06	0.25
Amoxicillin/Clavulanate	>8	>8	>8	>8	>8	>8
Ampicillin	>16	>16	>16	>16	>16	>16
Ceftriaxone	>64	>64	>64	>64	>64	>64
Imipenem	>16	>16	>16	>16	na	na
Levofloxacin	>32	>32	>32	>32	>32	>32
Linezolid	2	2	2	2	2	2
Minocycline	<0.25	8	2	>8	1	>8
Penicillin	>8	>8	>8	>8	>8	>8
Piperacillin/Tazobactam	>16	>16	>16	>16	>16	>16
Vancomycin	>32	>32	>32	>32	>32	>32

na = not available; drug was discontinued.

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

Antimicrobial	2004-2006		2007		2008	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.12	0.25	0.12	0.25	0.12	0.25
Amoxicillin/Clavulanate	2	>8	1	>8	1	>8
Ampicillin	16	>16	16	>16	16	>16
Ceftriaxone	4	>64	4	>64	4	>64
Imipenem	0.25	16	0.25	4	na	na
Levofloxacin	0.25	32	0.25	32	0.25	16
Linezolid	2	4	0.12	0.25	2	4
Minocycline	<0.25	0.5	<0.25	0.5	<0.25	1
Penicillin	>8	>8	>8	>8	>8	>8
Piperacillin/Tazobactam	1	>16	1	>16	1	>16
Vancomycin	1	1	1	1	1	1

na = not available; drug was discontinued.

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

Antimicrobial	2004-2006		2007		2008	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	M	