Temporal Analysis of Tigecycline in South and Central America from 2004-2008

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Revised Abstract

Background: Tigecycline, a glycylcycline antibiotic, was first marketed in the United States in 2005 and has been approved worldwide to treat serious medical conditions such as complicated skin and skin structure infections and complicated intra-abdominal infections. Bacterial resistance to antimicrobials is an on-going problem and can vary greatly geographically. The monitoring of such variation and trends is one of the goals of the Tigecycline Evaluation Surveillance Trial (TEST) program. The TEST program is an ongoing global surveillance used to generate the first post-marketing prospective report of tigecycline and comparator *in vitro* activity for the years 2004 through 2008. **Methods:** 13,744 clinical isolates were collected from 149 cumulative investigative sites in 12 countries in South and Central America. MICs were determined by broth microdilution according to CLSI guidelines using identical panels. **Results:** Results are given by year for select pathogens and antimicrobials. Summary data for tigecycline and key species are as follows:

	$MIC_{50/90}$ (mcg/ml)				
	2004	2005	2006	2007	2008
Enterobacteriaceae	0.5/1	0.5/2	0.5/1	0.5/1	0.5/2
ESBL producers	0.5/2	0.5/2	0.5/2	0.5/2	0.5/1
Acinetobacter spp.	0.5/1	0.5/1	0.5/2	0.5/2	0.5/2
P. aeruginosa	8/>16	8/>16	8/>16	8/>16	8/16
S. aureus	0.12/0.12	0.12/0.25	0.12/0.25	0.12/0.25	0.12/0.25
MRSA	0.12/0.12	0.12/0.25	0.12/0.25	0.12/0.25	0.25/0.25
Enterococcus spp.	0.06/0.12	0.12/0.12	0.12/0.12	0.12/0.25	0.12/0.25
S. pneumoniae	0.03/0.25	0.06/0.25	0.03/0.12	0.03/0.12	0.03/0.06

Conclusions: Tigecycline demonstrated no significant increases in $MIC_{50/90}$ values over five years from pre-marketing baseline values. Tigecycline's activity was retained even against strains resistant to other antimicrobials, including ESBL-producers, *Acinetobacter* spp., methicillin-resistant *S. aureus*, vancomycin-resistant enterococci, and penicillin-resistant *S. pneumoniae*.

Introduction

Tigecycline is a synthetic analogue of the tetracyclines which exhibits significant antibacterial activity against gram-negative and gram-positive bacteria [1-8]. 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 [9, 10]. The Tigecycline Evaluation Surveillance Trial (TEST), a global surveillance study, has monitored the *in vitro* activity of tigecycline and comparator agents since 2004. Tigecycline's spectrum of *in vitro* activity includes aerobic and anaerobic gram-negative and gram-positive bacteria, including antibiotic resistant strains, such as vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, extended-spectrum beta-lactamase producing members of the *Enterobacteriaceae*, and multidrug-resistant *Acinetobacter* spp. [11-13].

This study was undertaken to document the *in vitro* activity of tigecycline and comparators against significant numbers of clinical pathogens collected from Central and South America over five years time (2004 to 2008). This study is part of the ongoing global TEST 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. 13,744 clinical isolates were collected and tested between 2004 and 2008 from 149 cumulative investigative sites in 12 countries in Central and South America. 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 Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [14]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers, MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA) or Trek (TREK Diagnostic Systems, Cleveland, OH). 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); cefepime (0.5-32); ceftriaxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16, 2004-2006) meropenem (0.06-16, 2006-2008)); 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 [14] and the recent US Food and Drug Administration package insert for tigecycline [15], where applicable.
- *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 (2009) phenotypic confirmatory disk test. 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 (2009) guidelines [14].

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Results

Table 1. *In vitro* activity of tigecycline and comparators against *Acineobacter* spp. from Central and South America by year of isolation.

	2004		**2005**		**2006**		**2007**		**2008**	
	n=54		**n=136**		**n=251**		**n=288**		**n=381**	
Antimicrobial	**MIC_{50}**	**MIC_{90}**	**MIC_{50}**	**MIC_{90}**	**MIC_{50}**	**MIC_{90}**	**MIC_{50}**	**MIC_{90}**	**MIC_{50}**	**MIC_{90}**
Tigecycline	0.5	1	0.5	1	0.5	2	0.5	2	0.5	2
Amikacin	64	>64	32	>64	32	>64	>64	>64	64	>64
Amoxicillin/Clavulanate	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Ampicillin	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Cefepime	32	>32	32	>32	32	>32	32	>32	32	>32
Ceftazidime	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Ceftriaxone	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Imipenem	>16	>16	1	>16	1	>16	na	na	na	na
Levofloxacin	8	>8	8	>8	8	>8	8	>8	8	>8
Meropenem	na	na	na	na	16	>16	16	>16	16	>16
Minocycline	≤0.5	1	≤0.5	2	≤0.5	4	≤0.5	4	1	16
Piperacillin/Tazobactam	>128	>128	64	>128	128	>128	>128	>128	>128	>128

na = not available (meropenem replaced imipenem in 2006)

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

	2004		2005		2006		2007		2008	
	n=237		n=719		n=1603		n=1682		n=1941	
Antimicrobial	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Tigecycline	0.5	1	0.5	2	0.5	1	0.5	1	0.5	2
Amikacin	2	8	2	32	2	16	2	32	2	32
Amox/Clav	16	>32	32	>32	16	>32	32	>32	32	>32
Ampicillin	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Cefepime	≤0.5	32	≤0.5	>32	≤0.5	32	≤0.5	32	≤0.5	32
Ceftazidime	≤8	>32	≤8	>32	≤8	>32	≤8	>32	≤8	>32
Ceftriaxone	0.12	>64	0.25	>64	0.5	>64	0.5	>64	0.5	>64
Imipenem	0.5	0.5	0.5	1	0.25	1	na	na	na	na
Levofloxacin	0.06	4	0.12	>8	0.25	>8	0.12	>8	0.25	>8
Meropenem	na	na	na	na	≤0.06	0.5	≤0.06	0.25	≤0.06	0.5
Minocycline	2	8	2	16	2	16	4	16	4	>16
Pipe/Taz	1	128	2	128	2	128	4	>128	4	>128

na = not available (meropenem replaced imipenem in 2006)

Table 3. *In vitro* activity of tigecycline and comparators against ESBL producers* from Central and South America by year of isolation.

	2004		2005		2006		2007		2008	
	n=31		n=146		n=333		n=334		n=352	
ESBL rate	20% (31/155)		34% (146/427)		32% (333/1027)		33% (334/1026)		28% (352/1259)	
Antimicrobial	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Tigecycline	0.5	2	0.5	2	0.5	2	0.5	2	0.5	1
Amikacin	8	32	8	>64	4	32	8	>64	8	>64
Amox/Clav	32	>32	32	>32	16	>32	16	>32	32	>32
Ampicillin	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Cefepime	32	>32	32	>32	32	>32	32	>32	32	>32
Ceftazidime	>32	>32	32	>32	32	>32	32	>32	32	>32
Ceftriaxone	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Imipenem	0.5	0.5	0.5	1	0.25	1	na	na	na	na
Levofloxacin	1	>8	8	>8	>8	>8	8	>8	>8	>8
Meropenem	na	na	na	na	≤0.06	0.5	≤0.06	0.5	≤0.06	2
Minocycline	4	8	2	16	4	>16	4	>16	8	>16
Pip/Taz	64	>128	32	>128	8	>128	16	>128	32	>128

*ESBL producers include *E. coli, K. pneumoniae and K. oxytoca*; na = not tested (meropenem replaced imipenem in 2006)

Table 4 In vitro activity of tigecycline and comparators against *Pseudomonas aeruginosa* from Central and South America by year of isolation.

	2004		2005		2006		2007		2008	
	n=59		n=169		n=405		n=385		n=542	
Antimicrobial	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Tigecycline	8	>16	8	>16	8	>16	8	>16	8	16
Amikacin	4	>64	4	64	4	64	8	>64	4	64
Amox/Clav	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Ampicillin	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Cefepime	8	32	8	>32	8	>32	8	>32	8	>32
Ceftazidime	≤8	>32	≤8	>32	≤8	>32	16	>32	≤8	>32
Ceftriaxone	64	>64	64	>64	64	>64	>64	>64	>64	>64
Imipenem	1	16	2	16	1	>16	na	na	na	na
Levofloxacin	>8	>8	4	>8	2	>8	4	>8	2	>8
Meropenem	na	na	na	na	4	>16	2	>16	2	>16
Minocycline	>16	>16	>16	>16	>16	>16	16	>16	16	>16
Pip/Taz	4	128	16	128	8	>128	16	>128	16	>128

na = not available (meropenem replaced imipenem in 2006)

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

	2004		2005		2006		2007		2008	
	n=38		n=118		n=303		n=271		n=382	
Antimicrobial	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Tigecycline	0.06	0.12	0.06	0.12	0.12	0.12	0.12	0.25	0.12	0.25
Amox/Clav	0.5	>8	0.5	>8	0.5	>8	1	>8	1	>8
Ampicillin	1	>16	1	>16	1	>16	1	>16	1	>16
Imipenem	1	>16	1	>16	2	>16	na	na	na	na
Levofloxacin	1	32	1	32	1	>32	2	>32	2	>32
Linezolid	2	2	2	2	2	2	2	2	2	2
Meropenem	na	na	na	na	4	>16	8	>16	4	>16
Minocycline	≤0.25	8	≤0.25	8	8	8	8	>8	8	>8
Penicillin	2	>8	2	>8	2	>8	4	>8	4	>8
Pip/Taz	2	>16	2	>16	2	>16	4	>16	4	>16
Vancomycin	1	>32	1	>32	1	16	1	>32	1	>32

na = not available (meropenem replaced imipenem in 2006)

Table 6. *In vitro* activity of tigecycline and comparators against *Staphylococcus* from Central and South America by year of isolation.

	2004		2005		2006		2007		2008	
	n=65		n=265		n=482		n=486		n=523	
Antimicroalic	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Tigecycline	0.12	0.12	0.12	0.25	0.12	0.25	0.12	0.25	0.12	0.25
Amox/Clav	1	>8	2	>8	2	>8	2	>8	2	>8
Ampicillin	16	>16	>16	>16	16	>16	16	>16	>16	>16
Ceftriaxone	4	>64	4	>64	4	>64	4	>64	8	>64
Imipenem	≤0.12	>16	0.25	>16	0.25	>16	na	na	na	na
Levofloxacin	0.25	8	0.25	16	0.25	16	0.25	16	0.25	32
Linezolid	1	4	2	2	2	2	2	4	2	4
Meropenem	na	na	na	na	0.25	>16	0.25	>16	0.25	>16
Minocycline	≤0.25	≤0.25	≤0.25	4	≤0.25	0.5	≤0.25	0.5	≤0.25	0.5
Penicillin	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Pip/Taz	1	>16	2	>16	2	>16	2	>16	2	>16
Vancomycin	0.5	1	1	1	1	1	1	1	1	1

na = not available (meropenem replaced imipenem in 2006)

Table 7 *In vitro* activity of tigecycline and comparators against methicillin-resistance *Staphylococcus* from Central and South America by year of isolation.

	2004		2005		2006		2007		2008	
	n=29		n=131		n=227		n=212		n=235	
Antimicrobial	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	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	0.12	0.25	0.25	0.25
Amox/Clav	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Ampicillin	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16
Ceftriaxone	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Imipenem	>16	>16	>16	>16	>16	>16	na	na	na	na
Levofloxacin	4	8	4	16	8	32	8	32	8	32
Linezolid	2	2	2	2	2	2	2	4	2	4
Meropenem	na	na	na	na	16	>16	>16	>16	16	>16
Minocycline	≤0.25	4	≤0.25	4	≤0.25	1	≤0.25	1	≤0.25	1
Penicillin	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Pip/Taz	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16
Vancomycin	1	1	1	1	1	1	1	1	1	2

na = not available (meropenem replaced imipenem in 2006)

Table 8 *In vitro* activity of tigecycline and comparators against *Streptococcus pneumoniae* from Central and South America by year of isolation.

	2004		2005		2006		2007		2008	
	n=33		n=110		n=170		n=193		n=144	
Antimicrobial	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Tigecycline	0.03	0.25	0.06	0.25	0.03	0.25	0.03	0.12	0.03	0.06
Amox/Clav	≤0.03	0.12	≤0.03	0.5	≤0.03	1	≤0.03	1	≤0.03	2
Ampicillin	≤0.06	0.25	≤0.06	1	≤0.06	2	≤0.06	2	≤0.06	2
Ceftriaxone	≤0.03	0.5	≤0.03	0.5	≤0.03	1	≤0.03	1	≤0.06	1
Imipenem	≤0.12	≤0.12	≤0.12	0.25	≤0.12	1	na	na	na	na
Levofloxacin	0.5	1	0.5	1	0.5	1	0.5	1	1	1
Linezolid	≤0.5	1	≤0.5	1	≤0.5	1	1	1	1	1
Meropenem	na	na	na	na	≤0.12	0.5	≤0.12	0.5	≤0.12	0.5
Minocycline	≤0.25	1	≤0.25	2	≤0.25	4	≤0.25	8	1	8
Penicillin	≤0.06	0.5	≤0.06	1	≤0.06	2	≤0.06	2	≤0.06	2
Pip/Taz	≤0.25	≤0.25	≤0.25	2	≤0.25	2	≤0.25	2	≤0.25	4
Vancomycin	0.25	0.5	0.25	0.5	0.25	0.5	0.25	0.5	0.5	0.5

na = not available (meropenem replaced imipenem in 2006)

Table 9. *In vitro* activity of tigecycline and comparators against *Streptococcus agalactiae* from Central and South America by year of isolation.

	2004		2005		2006		2007		2008	
	n=14		n=98		n=155		n=187		n=155	
Antimicrobial	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Tigecycline	0.03	0.25	0.03	0.06	0.03	0.12	0.03	0.06	0.03	0.06
Amox/Clav	0.06	0.06	0.06	0.12	0.06	0.12	0.06	0.12	0.06	0.12
Ampicillin	≤0.06	0.12	≤0.06	0.12	≤0.06	0.12	≤0.06	0.12	≤0.06	0.12
Ceftriaxone	0.06	0.06	0.06	0.12	0.06	0.12	0.06	0.12	≤0.03	0.12
Imipenem	≤0.12	≤0.12	≤0.12	≤0.12	≤0.12	≤0.12	na	na	na	na
Levofloxacin	0.5	1	0.5	1	0.5	1	0.5	1	0.5	1
Linezolid	1	1	1	1	1	1	1	1	1	1
Meropenem	na	na	na	na	≤0.12	≤0.12	≤0.12	≤0.12	≤0.12	≤0.12
Minocycline	8	>8	4	>8	8	>8	8	>8	8	>8
Penicillin	≤0.06	≤0.06	≤0.06	0.12	≤0.06	0.12	≤0.06	0.12	≤0.06	0.12
PipTaz	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	0.5
Vancomycin	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.25	0.5

na = not available (meropenem replaced imipenem in 2006)

Table 10. *In vitro* activity of tigecycline and comparators against *Haemophilus influenzae* from Central and South America by year of isolation.

	2004		2005		2006		2007		2008	
	n=29		n=124		n=95		n=217		n=100	
Antimicrobial	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Tigecycline	0.25	0.5	0.25	0.5	0.12	0.5	0.25	0.5	0.5	0.5
Amikacin	8	8	4	8	4	8	4	8	4	8
Amox/Clav	0.5	1	0.25	0.5	0.25	2	0.5	1	0.5	2
Ampicillin	≤0.5	>32	≤0.5	4	≤0.5	16	≤0.5	32	≤0.5	32
Cefepime	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5
Ceftazidime	≤8	≤8	≤8	≤8	≤8	≤8	≤8	≤8	≤8	≤8
Ceftriaxone	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Imipenem	0.5	1	0.5	1	≤0.06	1	na	na	na	na
Levofloxacin	0.015	0.03	0.015	0.03	0.015	0.03	0.015	0.03	0.015	0.03
Meropenem	na	na	Na	na	≤0.06	0.12	≤0.06	0.25	≤0.06	0.25
Minocycline	1	2	≤0.5	1	≤0.5	1	≤0.5	1	1	1
Pip/Taz	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

na = not available (meropenem replaced imipenem in 2006)

Conclusions

- Tigecycline demonstrated no increase in $MIC_{50/90}$ values greater than a single dilution against all organism groups tested over the past five years in Central and South America.
- Tigecycline MIC_{90} values have held constant at or below 2 mcg/ml for *Enterobacteriaceae*, including those producing extended-spectrum beta-lactamases, with more than 97% of the study strains susceptible at its FDA breakpoint.
- Tigecycline has shown excellent *in vitro* activity against *Acinetobacter* spp., *S. aureus*, and *Enterococcus* spp., with the lowest MIC_{90} values of all compounds tested in this study.
- During the five years covered by this analysis, tigecycline has retained its excellent activity against a broad spectrum of bacteria, including many strains resistant to various other antimicrobials.