

The In-Vitro Antibacterial Activity of Tigecycline from an Asia/Pacific Rim Population - The T.E.S.T. Program 2005

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S. Bouchillon1, T. Stevens1, J. Johnson1, D. Hoban1, B. Johnson1, A. Hsiung1, M. Dowzicky2

1International Health Management Associates, Schaumburg, IL, USA
2Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL 60173
Tel: (847) 303-5003
Fax: (847) 303-5601
www.ihmainc.com

REVISED ABSTRACT

Background: Tigecycline (TIG), a new glycolcycline, has been shown to have potent broad spectrum activity against most commonly encountered species responsible for community and hospital acquired infections. The T.E.S.T. program determined the in vitro activity of TIG and 10 comparators against respective gram positive/negative species. Isolates were collected from six study sites across Asia and Pacific Rim throughout 2005. **Methods:** Over 2,037 clinically significant infections were identified to the species level at participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to CLSI (formerly NCCLS) guidelines. **Results:** Selected pathogens tested against tigecycline are shown in the table below:

Organism (#)	Tigecycline				% inhibited at			
	50%	90%	≥0.5	1	2	4	8	16*
<i>Acinetobacter baumannii</i> (75)	0.25	1	89.3	97.3	97.3	100	98.9	-
<i>E. faecalis/faecium</i> (89)	0.12	0.25	98.9	100	-	-	95.6	-
<i>Enterobacteriaceae</i> (1,407)	0.5	1	78.7	92	98.2	99.7	98.2*	-
ESBLs (65)	0.5	2	70.8	86.2	96.9	100	96.9*	-
<i>P. aeruginosa</i> (118)	8	16	2.5	4.2	5.1	15.3	5.1	-
<i>S. aureus</i> (148)	0.12	0.25	100	-	-	-	100	-
<i>S. pneumoniae</i> (78)	0.25	0.5	94	100	-	-	100	-
<i>H. influenzae</i> (73)	0.12	0.25	100	-	-	-	100	-
<i>S. agalactiae</i> (43)	0.03	0.12	100	-	-	-	100	-

*Breakpoints are defined by FDA (Tygicel®, 2005). For all other species TIG susceptible breakpoint is defined as 2 mcg/ml for comparative purposes only.

Conclusion: TIG has been described an expanded broad spectrum antimicrobial because of its consistent activity against *Enterobacteriaceae* including ESBL producing phenotypes, *S. aureus*, including methicillin-resistant strains, *S. pneumoniae*, including penicillin-resistant strains, and both vancomycin-sensitive and vancomycin-resistant *enterococci* spp. TIG wide spectrum of activity promises to provide enhanced antimicrobial coverage of serious nosocomial/community pathogens.

INTRODUCTION

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycolcyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it is perceived to be bacteriostatic, its anti-bacterial activity is significant and has shown some bactericidal activity against key targeted pathogens [1,2]. Tigecycline was developed to provide activity against tetracycline and multi-drug-resistant Gram-positive pathogens and has demonstrated significant broad-spectrum activity against aerobic and anaerobic Gram-positive and Gram-negative microorganisms [2-4].

Tigecycline resistance is very infrequent and is also difficult to induce in the laboratory [5, 6] with a selection frequency observed at less than 10⁻⁹ [3, 5, 7]. With the exception of *P. aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-4, 7-11]. Tigecycline has shown to be a highly effective against multi-resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections. Similar activity has been observed against *Enterobacteriaceae*, even extended-spectrum β -lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC₉₀ values of \leq 0.5 mcg/mL against methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive organisms [2, 4-6]. Tigecycline has shown potent activity against animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4, 5] with diverse genotypes van-A, -B and -C [6].

This study was designed to better define the in vitro activity of tigecycline in a limited number of clinical isolates collected from study centers across Asia and Pacific Rim regions.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids and few other defined sources. Only one isolate per patient was accepted.
- Clinical isolates (n=2,037) were collected tested between January 2005 - December 2005 from six study centers across Asia and Pacific Rim.
- Custom broth microdilution panels were supplied by MicroScan (Dade MicroScan, Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/ml): amoxicillin/clavulanic acid (0.12-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftriaxone (0.06-64); cefepime (0.5-32); ampicillin (0.5-32); amikacin (0.5-64); minocycline (0.5-16); ceftazidime (8-32); tigecycline (0.008-16); and imipenem (0.06-16).
- MIC interpretive criteria followed published guidelines established by the CLSI where applicable [12].
- MIC interpretive criteria for Tigecycline followed published guidelines established by the FDA where applicable [13]. For all other species a susceptible value of 2 mcg/mL is defined for tigecycline for comparative purposes only.
- Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Quality control of broth microdilution panels followed manufacturer's and NCCLS guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *Pseudomonas aeruginosa* ATCC 27853.
- The collection and transportation of organisms and the confirmation of identification, as well as, construction and management of a centralized database were conducted and coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA).

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The results are listed in the following Tables.

Table 1. In vitro activity of Tigecycline and comparative agents against *Enterobacteriaceae*

Organism *	Drug	MIC (mcg/ml)			
		%Sus	%INT	%RES	MIC ₅₀ MIC ₉₀
All <i>Enterobacteriaceae</i> (n=1,407)	Tigecycline	98.2	1.6	0.3	0.5
	Amikacin	94.7	0	5.3	2
	Amox-Clav	45.4	17.7	36.9	16
	Ampicillin	6.8	4.7	86.7	>32
	Cefepime	85.6	4.4	10	<0.5
	Ceftazidime	75.3	6.4	18.3	>8
	Ceftioxone	68.4	7	24.6	>64
	Imipenem	100	0	0	0.5
	Levofloxacin	76	2.7	21.3	0.12
	Minocycline	76.9	11.1	12	2
	Pip/Tazo	90.4	8.2	3.4	2
All ESBLs (n=65)	Tigecycline	96.9	3.1	0	0.5
	Amikacin	84.6	0	15.4	>64
	Amox-Clav	23.1	53.9	23.1	16
	Ampicillin	1.5	0	98.5	>32
	Cefepime	55.4	13.8	30.8	8
	Ceftazidime	35.4	18.5	46.2	16
	Ceftioxone	12.3	15.2	72.3	>64
	Imipenem	100	0	0	0.25
	Levofloxacin	47.7	4.6	47.7	4
	Minocycline	91.5	15.4	23.8	>16
	Pip/Tazo	89.2	8.2	1.5	4
<i>Enterobacter aerogenes</i> (n=30)	Tigecycline	100	0	0	0.5
	Amikacin	100	0	0	2
	Amox/Clav	3.3	0	96.7	>32
	Ampicillin	0	100	>32	>32
	Cefepime	90	3.3	6.7	<0.5
	Ceftazidime	90	10	20	>8
	Ceftioxone	86.7	3.3	10	0.12
	Imipenem	100	0	0	0.5
	Levofloxacin	86.7	3.3	10	0.12
	Minocycline	93.3	0	6.7	2
	Pip/Tazo	86.7	10	3.3	2
<i>Enterobacter cloacae</i> (n=52)	Tigecycline	96.3	1.2	2.4	0.5
	Amikacin	97.6	0	2.4	2
	Amox/Clav	3.7	1.2	95.1	>32
	Ampicillin	0	61	93.9	>32
	Cefepime	85.4	1.2	13.4	>32
	Ceftazidime	58.5	8.5	32.9	>8
	Ceftioxone	62.2	7.3	30.5	0.5
	Imipenem	100	0	0	0.12
	Levofloxacin	87.8	3.7	8.5	0.06
	Minocycline	75.6	9.8	14.6	4
	Pip/Tazo	74.4	19.6	6.1	2
<i>Klebsiella pneumoniae</i> (n=122)	Tigecycline	96.7	3.3	0	0.5
	Amikacin	91.8	0	8.2	2
	Amox/Clav	58.2	18.9	23	4
	Ampicillin	0	7.4	92.6	>32
	Cefepime	83.6	5.7	10.7	<0.5
	Ceftazidime	69.7	6.6	23.8	>8
	Ceftioxone	63.9	8.2	27.8	0.12
	Imipenem	100	0	0	0.5
	Levofloxacin	83.6	2.5	13.9	0.06
	Minocycline	78.5	6.6	13.9	8
	Pip/Tazo	90.2	6.6	3.3	2
<i>Klebsiella oxytoca</i> (n=18)	Tigecycline	100	0	0	0.25
	Amikacin	100	0	0	2
	Amox/Clav	66.7	0	33.3	4
	Ampicillin	0	16.7	83.3	>32
	Cefepime	100	0	0	<0.5
	Ceftazidime	100	0	0	<0.5
	Ceftioxone	88.9	11.1	0	<0.06
	Imipenem	100	0	0	0.5
	Levofloxacin	88.9	0	11.1	0.06
	Minocycline	100	0	0	2
	Pip/Tazo	77.8	0	22.2	>128
<i>S. marcescens</i> (n=52)	Tigecycline	100	0	0	1
	Amikacin	94.2	0	5.8	2
	Amox/Clav	5.8	94.2	>32	>32
	Ampicillin	0	5.8	94.2	>32
	Cefepime	94.2	0	5.8	<0.5
	Ceftazidime	90.4	0	9.6	>8
	Ceftioxone	90.4	1.9	7.7	0.25
	Imipenem	100	0	0	1
	Levofloxacin	98.1	0	1.9	0.12
	Minocycline	90.4	7.7	1.9	4
	Pip/Tazo	98.1	1.9	0	2
All ESBL producers <i>E. coli</i> , <i>K. pneumoniae</i> (n=65)	Tigecycline	98.3	3.1	0	0.5
	Amikacin	84.6	0	15.4	>64
	Amox/Clav	16.5	39.6	44	16
	Ampicillin	1.1	0	98.9	>32
	Cefepime	51.6	12.1	36.3	8
	Ceftazidime	28.6	16.5	54.9	32
	Ceftioxone	15.4	12.1	72.5	>64
	Imipenem	100	0	0	0.5
	Levofloxacin	51.6	6.8	41.8	1
	Minocycline	59.3	17.6	23.1	4
	Pip/Tazo	87.9	8.8	3.3	4

*Species with n <20 are not shown

Table 2. In vitro activity of Tigecycline and comparative agents against *Acinetobacter baumannii* and *Pseudomonas aeruginosa*

Organism	Drug	MIC (mcg/ml)				
		%Sus	%INT	%RES	MIC ₅₀ MIC ₉₀	
<i>Acinetobacter baumannii</i> (n=75)	Tigecycline	97.3	2.7	0	0.25	
	Amikacin	60	1.3	38.7	8	
	Cefepime	45.3	12	42.7	16	
	Ceftazidime	46.7	4	49.3	16	
	Ceftioxone	28	21.3	50.7	64	
	Imipenem	69	2.7	29.3	0.5	
	Levofloxacin	57.3	2.7	20	2	
	Minocycline	96	4	0	<5	
	Pip/Tazo	56	10.7	33.3	8	
	<i>Pseudomonas aeruginosa</i> (n=118)	Tigecycline	5.1	10.2	84.7	8
		Amikacin	87.3	4.2	8.5	4
Cefepime		73.7	10.2	16.1	4	
Ceftazidime		72.9	5.1	22	8	
Ceftioxone		11	17.8	71.2	>64	
Imipenem		87.3	4.2	8.5	1	
Levofloxacin		64.4	5.9	29.7	1	
Minocycline		4.2	8.5	87.3	>16	
Pip/Tazo		90.7	0	9.3	4	

*Species with n <20 are not shown

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RESULTS

Table 3. In vitro activity of Tigecycline and comparative agents against non-fastidious Gram-positive pathogens

Organism	Drug	MIC (mcg/ml)				
		%Sus	%INT	%RES	MIC ₅₀ MIC ₉₀	
<i>S. aureus</i> (n=148)	Tigecycline	100	0	0	0.12	
	Amox-Clav	78.4	0	23.6	1	
	Ampicillin	6.8	0	91.2	>16	
	Ceftioxone	66.2	6.8	27	4	
	Imipenem	81.1	1.4	17.6	>16	
	Levofloxacin	65.5	0	34.5	0.25	
	Linezolid	100	0	0	2	
	Minocycline	87.8	10.8	1.4	<0.25	
	Penicillin	8.1	0	91.9	>8	
	Pip/Tazo	75.7	0	24.3	1	
	<i>S. aureus</i> MRSA (n=59)	Tigecycline	100	0	0	1
Amox-Clav		42.4	0	57.6	>8	
Ampicillin		0	0	100	>16	
Ceftioxone		22	11.9	66.1	>64	
Imipenem		52.5	3.4	44.1	1	
Levofloxacin		25.4	10	74.6	4	
Linezolid		100	0	0	2	
Minocycline		71.2	27.1	1.7	2	
Penicillin		0	0	100	>8	
Pip/Tazo		39	0	61	>16	
<i>E. faecalis</i> * (n=65)		Tigecycline	100	0	0	1
	Amox-Clav	96.9	0	3.1	0.12	
	Ampicillin	100	0	0	1	
	Levofloxacin	66.2	0	33.8	1	
	Linezolid	96.9	0	3.1	0	
	Minocycline	30.8	47.7	21.5	8	
	Penicillin	100	0	0	2	
	Vancomycin	100	0	0	2	
	<i>E. faecium</i> (n=22)	Tigecycline	N/A	N/A	N/A	0.06
		Ampicillin	50	0	50	4
		Levofloxacin	22.7	9.1	68.2	16
Linezolid		100	0	0	2	
Minocycline		63.6	18.2	18.2	4	
Penicillin		36.4	0	63.6	>8	
Vancomycin		90.9	0	9.1	>8	
Vancomycin resistant <i>E. faecium</i> (n=2)		Tigecycline	N/A	N/A	N/A	0.06
		Ampicillin	0	0	100	>16
		Levofloxacin	0	0	100	>32
		Linezolid	0	0	100	>32
	Minocycline	100	0	0	<0.25	
	Penicillin	0	0	100	>8	
	Vancomycin	0	0	100	>32	
	<i>S. agalactiae</i> (n=43)	Tigecycline	100	0	0	0.03
		Ampicillin	100	0	0	0.06
		Ceftioxone	97.7	0	2.3	0.06
		Levofloxacin	100	0	0	0.16
Linezolid		100	0	0	1	
Penicillin		100	0	0	<0.06	
Vancomycin		100	0	0	0.5	

* No vancomycin-resistant strains were identified.

** FDA susceptible breakpoint of 0.25 mcg/mL for vancomycin-susceptible *E. faecalis* were expanded to include all enterococci for comparative purposes only.

Table 4. In vitro activity of Tigecycline and comparative agents against fastidious respiratory pathogens

Organism (n)	Drug	MIC (mcg/ml)			
		%Sus	%INT	%RES	MIC ₅₀ MIC ₉₀