

Tigecycline In-Vitro Antibacterial Activity from a Global Perspective - The T.E.S.T. Program 2005

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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 107 hospital sites in 25 countries throughout 2005. **Methods:** A total of 25,134 clinically significant isolates 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 global pathogens tested against tigecycline are shown in the table below:

Organism (#)	Tigecycline		% inhibited at					%S
	50%	90%	≤0.5	1	2	4	8	
<i>Acinetobacter baumannii</i> (1,618)	0.5	1	69.8	92.8	98.6	99.9	100	98.6*
<i>E. faecalis/faecium</i> (1,891)	0.06	0.12	99.7	100				99.8**
<i>Enterobacteriaceae</i> (10,791)	0.5	1	79.6	92.3	96.4	99.2	100	96.4
ESBLs (441)	0.5	2	66	83.4	93	98.4	100	93
<i>P. aeruginosa</i> (2,716)	8	>16	1.5	2.7	5.3	18.4	55.3	5.3*
<i>S. aureus</i> (3,228)	0.12	0.25	99.1	99.4	99.9	100		99.1*
<i>S. pneumoniae</i> (1,879)	0.06	0.5	92.7	100				100*
<i>H. influenzae</i> (1,588)	0.12	0.25	98	99.8	100			100*

Breakpoints defined by FDA Tygacil® Package Insert unless otherwise noted.

*TIG susceptible breakpoint defined as 2 µg/mL.

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

Conclusion: TIG has been described an expanded broad spectrum antimicrobial because of its consistent activity against *Enterobacteriaceae* including extended spectrum beta-lactamase producers, *S. aureus* including methicillin-resistant strains, *S. pneumoniae* including penicillin-resistant strains, both vancomycin-sensitive and -resistant *Enterococcus* spp., and *H. influenzae* including beta-lactamase producers. 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 beta-lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC₉₀ values of ≤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 selected clinical isolates collected from 150 study centers worldwide.

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=25,134) 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 pneumoniae* 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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RESULTS

The results are listed in the following Tables and Graph.

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

Organism	Drug	%Sus	%Int	%Res	MIC (mcg/mL)	
					MIC ₅₀	MIC ₉₀
All <i>Enterobacteriaceae</i> (n=10,791)	Tigecycline	96.4	2.9	0.8	0.5	1
	Amikacin	98.9	0.6	0.5	2	4
	Amox-Clav	48.5	7.1	44.3	16	>32
	Ampicillin	14.3	6.8	78.9	>32	>32
	Cefepime	95.5	1.4	3.1	≤0.5	2
	Ceftazidime	86	2.9	11.1	≤8	32
	Ceftriaxone	87.5	5	7.5	0.12	16
	Imipenem	100	0	0	0.5	1
	Levofloxacin	86.7	2.4	10.8	0.06	8
	Minocycline	85	7.5	7.5	2	8
	Pip/Tazo	90.2	4.4	5.4	1	16
<i>Enterobacter aerogenes</i> (n=746)	Tigecycline	95.2	3.9	0.9	0.5	1
	Amikacin	98.9	1.1	0	2	4
	Amox/Clav	3.5	4.2	95	>32	>32
	Ampicillin	0	4.6	95.4	>32	>32
	Cefepime	95.6	1.7	2.7	≤0.5	2
	Ceftazidime	74.5	6.4	19	≤8	>32
	Ceftriaxone	87.1	8.4	4.4	0.12	16
	Imipenem	100	0	0	1	1
	Levofloxacin	89.9	2.7	7.4	0.06	4
	Minocycline	87.5	6.6	5.9	2	8
	Pip/Tazo	87	9.1	3.9	2	32
<i>Enterobacter cloacae</i> (n=2,126)	Tigecycline	92.8	5.1	2.1	0.5	2
	Amikacin	99.2	0.3	0.6	2	4
	Amox/Clav	1.6	1	97.4	>32	>32
	Ampicillin	0	5.6	94.4	>32	>32
	Cefepime	94.9	2	3.1	≤0.5	4
	Ceftazidime	70.8	5.6	23.6	≤8	>32
	Ceftriaxone	74.6	10.4	15	0.25	64
	Imipenem	100	0	0	0.5	1
	Levofloxacin	90.5	2.9	6.7	0.03	2
	Minocycline	83.3	7.6	9.2	2	8
	Pip/Tazo	78.9	11.2	9.9	2	64
<i>Escherichia coli</i> (n=3,403)	Tigecycline	99.8	0.2	0	0.12	0.25
	Amikacin	99.5	0.3	0.2	2	4
	Amox/Clav	74.6	13.3	12.1	8	32
	Ampicillin	44.9	0.8	54.3	>32	>32
	Cefepime	96.4	0.7	2.9	≤0.5	8
	Ceftazidime	94	2.3	3.7	≤8	≤8
	Ceftriaxone	92.7	2.2	5.1	≤0.06	1
	Imipenem	100	0	0	0.25	0.5
	Levofloxacin	77.3	2.3	20.4	0.03	>8
	Minocycline	84.5	8.4	7.1	1	8
	Pip/Tazo	95.7	2.1	2.2	1	4
<i>Klebsiella pneumoniae</i> (n=2,557)	Tigecycline	94.3	4.8	0.9	0.5	2
	Amikacin	98	1.2	0.9	2	4
	Amox/Clav	81.9	7.8	10.3	2	32
	Ampicillin	0	16	94	>32	>32
	Cefepime	93.5	2.1	4.3	≤0.5	4
	Ceftazidime	86.6	1.7	11.7	≤8	32
	Ceftriaxone	88.2	3.8	8.1	≤0.06	16
	Imipenem	100	0	0	0.5	0.5
	Levofloxacin	89.2	2.6	8.5	0.06	4
	Minocycline	82.2	7	10.8	2	16
	Pip/Tazo	91	2.4	6.5	2	16
<i>Klebsiella oxytoca</i> (n=606)	Tigecycline	98.5	1.5	0	0.25	1
	Amikacin	99	0.5	0.5	2	4
	Amox/Clav	82.8	5.9	11.2	2	32
	Ampicillin	0	10.7	89.3	>32	>32
	Cefepime	97.2	0.8	2	≤0.5	2
	Ceftazidime	92.9	1	6.1	≤8	≤8
	Ceftriaxone	92.2	4.8	3	≤0.06	8
	Imipenem	100	0	0	0.5	0.5
	Levofloxacin	94.1	2.1	3.8	0.03	1
	Minocycline	93.2	4.8	2	1	4
	Pip/Tazo	87.5	0.8	11.7	1	128
<i>S. marcescens</i> (n=1,225)	Tigecycline	97.3	2.2	0.5	1	2
	Amikacin	99	0.3	0.7	2	4
	Amox/Clav	0.7	1.6	97.7	>32	>32
	Ampicillin	0	5.1	94.9	>32	>32
	Cefepime	97.5	0.5	2	≤0.5	1
	Ceftazidime	93.4	1.5	5.1	≤8	8
	Ceftriaxone	93.1	3.6	3.3	0.25	4
	Imipenem	100	0	0	0.5	2
	Levofloxacin	95.3	2	2.7	0.12	1
	Minocycline	90.1	7.2	2.7	4	4
	Pip/Tazo	95.8	2.6	1.6	8	8
All ESBL producers <i>E. coli</i> , <i>K. pneumoniae</i> , <i>K. oxytoca</i> (n=441)	Tigecycline	93	5.4	1.6	0.5	2
	Amikacin	89.8	5.7	4.5	4	32
	Amox/Clav	27.2	34.7	38.1	16	>32
	Ampicillin	0.7	0.5	98.9	>32	>32
	Cefepime	51.9	10.7	37.4	8	>32
	Ceftazidime	22.2	10.7	67.1	>32	>32
	Ceftriaxone	20.6	20.9	58.5	64	>64
	Imipenem	100	0	0	0.5	0.5
	Levofloxacin	38.1	7.7	54.2	8	>8
	Minocycline	61	12	27	4	>16
	Pip/Tazo	68	8.8	23.1	8	>8

* Tigecycline breakpoints are defined as Sus ≤ 2, Int = 4 and Res ≥ 8 mcg/mL for comparative purposes only.

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

Organism	Drug	%SUS*	%INT	%RES	MIC (mcg/mL)		
					MIC ₅₀	MIC ₉₀	
<i>Acinetobacter baumannii</i> (n=1,618)	Tigecycline	96.6	1.3	0.1	0.5	1	
	Amikacin	77.4	7.4	15.2	4	64	
	Cefepime	47.2	16.4	36.3	16	>32	
	Ceftazidime	47	6.4	46.6	16	>32	
	Ceftriaxone	29.8	23.2	47	32	>64	
	Imipenem	82.9	5.4	11.7	0.5	16	
	Levofloxacin	49.4	8.7	41.9	4	>8	
	Minocycline	88.8	8.6	2.6	≤0.5	8	
	Pip/Tazo	57.2	14	28.9	8	>128	
	<i>Pseudomonas aeruginosa</i> (n=2,716)	Tigecycline	5.3	13.1	81.6	8	>16
		Amikacin	95.2	2	2.8	4	8
Cefepime		75.7	12.7	11.6	4	32	
Ceftazidime		79.9	6.6	13.5	≤8	32	
Ceftriaxone		16.2	23.9	59.9	64	>64	
Imipenem		82.1	8.2	9.6	1	8	
Levofloxacin		63.9	6.6	29.5	1	>8	
Minocycline		4.9	13.3	81.8	>16	>16	
Pip/Tazo		88.3	0	11.7	4	128	

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

Organism	Drug	%SUS*	%INT	%RES	MIC (mcg/mL)	
					MIC ₅₀	MIC ₉₀
<i>S. aureus</i> (n=3,228)	Tigecycline	99.1	0	0.0	0.12	0.25
	Amox-Clav	69	0	31	1	>8
	Ampicillin	9.7	0	90.3	16	>16
	Ceftriaxone	57.8	22.4	19.8	4	>64
	Imipenem	89.8	1.5			