

A Presentation of Global Data from Tigecycline Evaluation Surveillance Trials (TEST) Program, 2004 - 2006

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REVISED ABSTRACT

Background: Tigecycline (TIG), a new glycolycycline, 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 205 hospital sites in 30 countries from 2004 through 2006. **Methods:** 42,922 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 guidelines. **Results:** Tig in vitro activity on selected pathogens is shown in the table below. Data on resistant phenotypes will be presented.

Organism (n)	Tigecycline		% inhibited at MIC (mcg/mL)				
	MIC ₅₀	MIC ₉₀	≤0.5	1	2	4	8
<i>A. baumannii</i> (2,370)	0.5	1	68.9	91.9	98.1	99.8	100
<i>E. faecalis/faecium</i> (2,884)	0.12	0.12	100	-	-	-	-
<i>Enterobacteriaceae</i> (16,512)	0.5	1	79.2	92	96.5	99.1	99.9
ESBLs (692)	0.5	2	63.2	83.7	93.4	98.7	100
<i>P. aeruginosa</i> (4,031)	8	>16	1.4	2.7	6.1	19.1	56.1
<i>S. aureus</i> (5,065)	0.12	0.25	100	-	-	-	-
<i>S. pneumoniae</i> (2,651)	0.03	0.5	99.2	100	-	-	-
<i>H. influenzae</i> (2,433)	0.12	0.5	96.1	99.1	100	-	-

Conclusion: Tig is an expanded spectrum 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's 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 glycolycyclines. 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 it 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 10⁻³ [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 been shown to be 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 205 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. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Clinical isolates (n=42,922) were collected and tested between January 2004 - December 2006 from 205 study centers in 30 countries.
- 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 (0.03-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-32); ceftriaxone (0.03-64); cefepime (0.5-32); ampicillin (0.06-32); amikacin (0.5-64); minocycline (0.25-16); ceftazidime (8-32); tigecycline (0.008-16); imipenem (0.06-16); linezolid (0.5-8); penicillin (0.06-8); and vancomycin (0.12-32).
- MIC interpretive criteria for all drugs except tigecycline followed published guidelines established by the CLSI where applicable [12]. MIC interpretive criteria for tigecycline followed criteria established by the Federal Drug Administration (FDA, United States, 2005) where applicable [13].
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Klebsiella pneumoniae* ATCC 700603 (positive ESBL control); *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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RESULTS

Results are presented in the following tables and figures.

Table 1. In vitro Activity of Tigecycline and Comparative Agents against *Enterobacteriaceae* and Selected Species.*

Organism	Drug	%Sus**	%Int	%Res	MIC (mcg/mL)		
					MIC ₅₀	MIC ₉₀	
All <i>Enterobacteriaceae</i> (n=16,512)	Tigecycline	96.5	2.7	0.9	0.5	1	
	Amikacin	98.4	0.9	0.7	2	4	
	Amox-Clav	48.7	2.4	16	>32		
	Ampicillin	13.7	6.9	79.4	>32	>32	
	Cefepime	94.3	1.6	4.1	≤0.5	4	
	Ceftazidime	85.2	3.1	11.7	≤8	32	
	Ceftriaxone	86.4	5	8.6	0.12	32	
	Imipenem	99.8	0.1	0.1	0.5	1	
	Levofloxacin	85.2	2.5	12.4	0.06	8	
	Minocycline	84.9	7.7	7.4	2	8	
	Pip-Tazo	89	5	6	1	32	
	<i>Enterobacter aerogenes</i> (n=1,143)	Tigecycline	95.6	3.4	1	0.5	1
		Amikacin	98.5	1	0.5	2	4
		Amox-Clav	2.9	3.3	93.8	>32	>32
Ampicillin		0	4.7	95.3	>32	>32	
Cefepime		95.5	1.7	2.9	≤0.5	2	
Ceftazidime		75.2	6	18.7	≤8	>32	
Ceftriaxone		87.5	7.3	5.2	0.12	16	
Imipenem		100	0	0	1	1	
Levofloxacin		89.2	3.2	7.6	0.06	4	
Minocycline		88.8	6	5.2	2	8	
Pip-Tazo		85.8	10.7	3.5	2	32	
<i>Enterobacter cloacae</i> (n=3,148)		Tigecycline	93.1	4.7	2.3	0.5	2
		Amikacin	98.4	0.7	0.9	2	4
		Amox-Clav	1.5	1	97.6	>32	>32
	Ampicillin	0	5.1	94.9	>32	>32	
	Cefepime	94.2	2.1	3.7	≤0.5	8	
	Ceftazidime	69.6	5.6	24.8	≤8	>32	
	Ceftriaxone	72.8	11	16.1	0.25	64	
	Imipenem	100	0	0	0.5	1	
	Levofloxacin	89.6	2.4	7.9	0.03	4	
	Minocycline	82.8	7.5	9.7	2	8	
	Pip-Tazo	78	11.9	10.2	2	128	
	<i>Escherichia coli</i> (n=5,146)	Tigecycline	99.6	0.4	0	0.12	0.25
		Amikacin	99.3	0.4	0.3	2	4
		Amox-Clav	74.1	13.7	12.1	8	32
Ampicillin		43.6	0.8	55.6	>32	>32	
Cefepime		95.5	0.9	3.6	≤0.5	1	
Ceftazidime		93.8	2.4	3.8	≤8	≤8	
Ceftriaxone		92.2	2.1	5.8	≤0.06	2	
Imipenem		100	0	0	0.25	0.5	
Levofloxacin		75.1	2.6	22.3	0.03	>8	
Minocycline		84.3	8.9	6.8	1	8	
Pip-Tazo		95.6	2.1	2.4	1	4	
<i>Klebsiella pneumoniae</i> (n=3,935)		Tigecycline	94.7	4.1	1.2	0.5	2
		Amikacin	97.4	1.6	1	2	8
		Amox-Clav	79.7	7.4	12.9	2	32
	Ampicillin	0	16.3	83.7	>32	>32	
	Cefepime	91.3	2.3	6.4	≤0.5	8	
	Ceftazidime	84.4	2	13.6	≤8	>32	
	Ceftriaxone	86.1	3.9	10	≤0.06	64	
	Imipenem	99.1	0.6	0.3	0.5	0.5	
	Levofloxacin	86.5	2.4	11.1	0.06	8	
	Minocycline	81.9	7.4	10.7	2	16	
	Pip-Tazo	88.4	3.3	8.3	2	64	
	<i>Klebsiella oxytoca</i> (n=936)	Tigecycline	98.5	1.5	0	0.25	1
		Amikacin	99.3	0.2	0.5	2	4
		Amox-Clav	83.1	6.1	10.8	2	32
Ampicillin		0.1	12	87.9	>32	>32	
Cefepime		97.4	0.9	1.7	≤0.5	1	
Ceftazidime		93.7	1.7	4.6	≤8	≤8	
Ceftriaxone		93.4	4	2.7	≤0.06	8	
Imipenem		100	0	0	0.5	0.5	
Levofloxacin		94.9	1.8	3.3	0.03	1	
Minocycline		94.1	4.3	1.6	1	4	
Pip-Tazo		87	1.4	11.6	1	128	
<i>S. marcescens</i> (n=1,828)		Tigecycline	96.6	2.8	0.5	1	2
		Amikacin	98.4	1	0.5	2	4
		Amox-Clav	0.8	1.6	97.5	>32	>32
	Ampicillin	0	5.2	94.8	>32	>32	
	Cefepime	97	0.8	2.1	≤0.5	1	
	Ceftazidime	93.2	1.7	5.1	≤8	≤8	
	Ceftriaxone	92	4	3.9	0.25	8	
	Imipenem	100	0	0	0.5	1	
	Levofloxacin	95	2.3	2.7	0.12	1	
	Minocycline	89.3	7.7	3	2	8	
	Pip-Tazo	95	3.3	1.7	1	8	
	All ESBL producers (<i>E. coli</i> , <i>K. pneumoniae</i> , <i>K. oxytoca</i>) (n=692)	Tigecycline	93.4	5.3	1.3	0.5	2
		Amikacin	89.6	6.9	3.5	4	32
		Amox-Clav	24.6	31.2	44.2	16	>32
Ampicillin		0.9	0.3	98.8	>32	>32	
Cefepime		46.5	10.1	43.4	16	>32	
Ceftazidime		20.4	11.4	68.2	>32	>32	
Ceftriaxone		20.1	19.2	60.7	64	>64	
Imipenem		94.8	3.2	2	0.5	1	
Levofloxacin		34.5	6.6	58.8	8	>8	
Minocycline		64.7	13	22.3	4	>16	
Pip-Tazo		61.1	10.3	28.6	16	>128	

* Species with n's <20 were omitted.
** Susceptibilities are defined by CLSI document M100-S16 (2006), where available. Tigecycline breakpoints defined by the FDA (Tygacil[®], 2005).

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=2,370)	Tigecycline	na	na	na	0.5	1
	Amikacin	75.9	8.4	15.7	4	64
	Cefepime	46.1	16.2	37.7	16	>32
	Ceftazidime	45.8	6.6	47.6	16	>32
	Ceftriaxone	28.6	22.7	48.6	32	>64
	Imipenem	82.5	5.6	11.8	0.5	16
	Levofloxacin	47.4	8.9	43.7	4	>8
	Minocycline	89.2	8.1	2.7	≤0.5	8
	Pip-Tazo	54.1	17	28.9	16	>128
	<i>Pseudomonas aeruginosa</i> (n=4,031)	Tigecycline	na	na	na	8
Amikacin		94.6	2.5	2.9	4	8
Cefepime		76.2	12.7	11.2	4	32
Ceftazidime		80.2	6.8	13	≤8	32
Ceftriaxone		17	28.6	54.5	64	>64
Imipenem		82.6	8.6	8.7	1	8
Levofloxacin		63.1	6.7	30.1	1	>8
Minocycline		4.8	14.1	81	>16	>16
Pip-Tazo		89.3	0	10.7	4	128

* Susceptibilities are defined by CLSI document M100-S16 (2006), where available. na = Breakpoints have not yet been established for tigecycline against these species.

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=5,065)	Tigecycline	100	0	0	0.12	0.25
	Amox-Clav	66.6	0	33.4	2	>8
	Ampicillin	9.6	0	90.4	16	>16
	Ceftriaxone	57.4	21.8	20.8	4	>64
	Imipenem	88.8	1.7	9.4	0.25	8
	Levofloxacin	56.6	2.5	40.9	0.25	