

# Tigecycline Evaluation Surveillance Trial (T.E.S.T.) - In Vitro Antibacterial Activity against Gram-positive and Gram-negative Pathogens in Asia

#P 807

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## REVISED ABSTRACT

**Background:** Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent expanded 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 tigecycline compared to amikacin, ampicillin, imipenem, cefepime, ceftazidime, ceftriaxone, levofloxacin, minocycline and piperacillin/tazobactam against Gram-negative strains in addition to linezolid, penicillin and vancomycin for the Gram-positive species. Isolates were collected from 3 centers in Asia throughout 2004. **Methods:** A total of 671 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by the local laboratory using supplied broth microdilution panels from Dade Behring MicroScan and interpreted according to CLSI guidelines. **Results:** Tigecycline's activity was similar to imipenem against most Enterobacteriaceae with MIC<sub>50</sub>/MIC<sub>90</sub> of 0.25/1 mcg/ml. Resistance to third generation cephalosporin was found in 23% of *E. coli* and 38.5% of *K. pneumoniae* of the ESBL phenotype. Tigecycline inhibited majority of ESBL producers with MICs equal or lesser than 1 mcg/mL. Although similar to other classes of broad spectrum antimicrobial agents against glucose non-fermenters, tigecycline was especially active against *Acinetobacter* spp. presenting the lowest MIC<sub>90</sub> at 0.5 mcg/ml. Methicillin-resistance (oxacillin) was detected in 47.4% of *S. aureus*. Tigecycline had a MIC<sub>90</sub> of 0.25 mcg/mL against all strains of *S. aureus* without regard to methicillin susceptibility phenotype. Similar results were noticed against enterococci with a tigecycline MIC<sub>90</sub> of 0.25 mcg/mL. **Conclusion:** Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed antimicrobials against a broad spectrum of aerobic clinical pathogens. The presented data suggest that tigecycline may be an effective and reliable therapeutic option against both aerobic Gram-positive and aerobic Gram-negative bacteria, including problematic strains with ESBL and MRSA resistance phenotypes.

## INTRODUCTION

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycylcyclines. 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<sup>-9</sup> [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 MIC<sub>90</sub> 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 3 hospitals in China, India and the Philippines.

## 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.
- There were 671 clinical isolates were collected tested between January 2004 - December 2004 from 3 study centers in China, India and the Philippines.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring, 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 NCCLS where applicable [12]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined as susceptible  $\leq$  2; intermediate = 4; and resistant  $\geq$  8.
- 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 manufacture'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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## RESULTS

Table 1. In vitro activity of tigecycline and comparative agents against 369 strains of *Enterobacteriaceae*.

Organism Name <sup>a</sup>	Drug <sup>b</sup>	MICs (mcg/mL)				
		%SUS	%INT	%RES	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Enterobacteriaceae</i> (n=369)	Tigecycline	98.9	1.1	0	0.25	1
	Amikacin	94.6	0	5.4	2	8
	Amox-Clav	44.4	26	29.6	16	>32
	Ampicillin	11.9	5.1	83	>32	>32
	Cefepime	87.3	6.5	6.2	$\leq$ 0.5	16
	Ceftazidime	89.8	6.7	10.5	$\leq$ 8	32
	Ceftriaxone	66.7	7.3	26	0.25	>64
	Imipenem	100	0	0	0.25	0.5
	Levofloxacin	66.7	2.7	30.6	0.25	>8
	Minocycline	77.2	11.9	10.9	2	16
Pip-Tazo	95.7	2.7	1.6	2	4	
<i>E. coli</i> (n=74)	Tigecycline	100	0	0	0.12	0.25
	Amikacin	94.6	0	5.4	2	8
	Amox-Clav	55.4	29.2	5.4	8	16
	Ampicillin	20.3	0	79.7	>32	>32
	Cefepime	83.8	10.8	5.4	$\leq$ 0.5	16
	Ceftazidime	89.2	6.7	4.1	$\leq$ 8	16
	Ceftriaxone	62.2	6.1	29.7	$\leq$ 0.06	>64
	Imipenem	100	0	0	0.25	0.5
	Levofloxacin	39.2	5.4	56.4	8	>8
	Minocycline	63.5	21.6	14.9	4	16
Pip-Tazo	98.6	1.4	0	0.5	2	
<i>K. pneumoniae</i> (n=65)	Tigecycline	99.9	3.1	0	0.5	4
	Amikacin	92.3	0	7.7	2	8
	Amox-Clav	49.2	26.2	24.6	16	>32
	Ampicillin	4.6	6.2	89.2	>32	>32
	Cefepime	84.6	6.2	9.2	$\leq$ 0.5	16
	Ceftazidime	69.2	9.2	21.6	16	>32
	Ceftriaxone	60	7.7	32.3	0.5	>64
	Imipenem	100	0	0	0.5	1
	Levofloxacin	80	0	20	0.12	8
	Minocycline	81.5	7.7	10.8	2	16
Pip-Tazo	93.8	3.1	3.1	2	8	
<i>K. oxytoca</i> (n=8)	Tigecycline	100	0	0	0.25	2
	Amikacin	100	0	0	1	8
	Amox-Clav	75	0	25	4	>32
	Ampicillin	0	25	75	>32	>32
	Cefepime	100	0	0	$\leq$ 0.5	$\leq$ 0.5
	Ceftazidime	100	0	0	$\leq$ 8	$\leq$ 8
	Ceftriaxone	87.5	12.5	0	$\leq$ 0.06	32
	Imipenem	100	0	0	0.5	0.5
	Levofloxacin	75	0	25	0.06	>8
	Minocycline	100	0	0	1	2
Pip-Tazo	100	0	0	1	4	
ESBL producers (E. coli, K. pneumoniae, K. oxytoca) (n=42)	Tigecycline	97.6	2.4	0	0.5	1
	Amikacin	96.1	0	11.9	2	>64
	Amox-Clav	26.2	59.5	14.3	16	32
	Ampicillin	2.4	0	97.6	>32	>32
	Cefepime	84.3	19	16.7	8	>32
	Ceftazidime	45.2	19	35.8	16	>32
	Ceftriaxone	11.9	19	69.1	64	>64
	Imipenem	100	0	0	0.25	1
	Levofloxacin	45.2	0	54.8	8	>8
	Minocycline	71.4	14.3	14.3	4	16
Pip-Tazo	95.2	4.8	0	2	8	
<i>E. aerogenes</i> (n=13)	Tigecycline	100	0	0	0.5	1
	Amikacin	100	0	0	2	4
	Amox-Clav	7.7	0	92.3	>32	>32
	Ampicillin	0	0	100	>32	>32
	Cefepime	100	0	0	$\leq$ 0.5	$\leq$ 0.5
	Ceftazidime	92.3	0	7.7	$\leq$ 8	$\leq$ 8
	Ceftriaxone	92.3	7.7	0	0.12	4
	Imipenem	100	0	0	1	1
	Levofloxacin	100	0	0	0.06	2.5
	Minocycline	100	0	0	2	16
Pip-Tazo	92.3	7.7	0	2	4	
<i>E. cloacae</i> (n=28)	Tigecycline	100	0	0	0.5	1
	Amikacin	92.9	0	7.1	1	16
	Amox-Clav	7.1	3.6	89.3	>32	>32
	Ampicillin	100	0	71.8	>32	>32
	Cefepime	89.3	0	10.7	$\leq$ 0.5	32
	Ceftazidime	71.4	7.1	21.5	0.03	4
	Ceftriaxone	71.4	3.6	25	0.25	>64
	Imipenem	100	0	0	0.5	1
	Levofloxacin	89.3	7.1	3.6	0.03	4
	Minocycline	82.1	7.1	10.8	4	>16
Pip-Tazo	89	7.1	7.2	2	16	
<i>S. marcescens</i> (n=28)	Tigecycline	100	0	0	0.5	1
	Amikacin	100	0	0	2	4
	Amox-Clav	10.7	10.7	78.6	>32	>32
	Ampicillin	17.9	14.2	67.9	>32	>32
	Cefepime	100	0	0	$\leq$ 0.5	1
	Ceftazidime	92.9	0	7.1	$\leq$ 8	$\leq$ 8
	Ceftriaxone	96.4	3.6	0	0.12	4
	Imipenem	100	0	0	0.5	1
	Levofloxacin	100	0	0	0.12	0.5
	Minocycline	96.4	0	3.6	2	4
Pip-Tazo	100	0	0	1	2	

<sup>a</sup>Only species with n  $\geq$  20 are represented.  
<sup>b</sup>Breakpoints as defined by NCCLS where available (M100-S14), 2004. Tigecycline breakpoints defined as: susceptible  $\leq$  2; intermediate = 4; and resistant  $\geq$  8.

Table 2. In vitro activity of tigecycline and comparative agents against 98 gram-negative Non-*Enterobacteriaceae*.

Organism Name <sup>a</sup>	Drug <sup>b</sup>	MICs (mcg/mL)				
		%SUS	%INT	%RES	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Acinetobacter</i> spp (n=38)	Tigecycline	97.4	2.6	0	0.12	0.5
	Amikacin	71.1	0	28.9	2	>64
	Amox-Clav	na	na	na	16	>32
	Ampicillin	na	na	na	16	>32
	Cefepime	65.8	7.9	26.3	4	>32
	Ceftazidime	68.4	2.6	29	$\leq$ 8	>32
	Ceftriaxone	55.3	18.4	26.3	8	>64
	Imipenem	89.5	0	10.5	0.25	16
	Levofloxacin	78.9	13.2	7.9	0.12	4
	Minocycline	84.7	5.3	0	$\leq$ 0.5	0.5
Pip-Tazo	89.5	0	10.5	0.12	>16	
<i>A. baumannii</i> (n=36)	Tigecycline	97.2	2.8	0	0.12	0.5
	Amikacin	69.4	0	30.6	4	>64
	Amox-Clav	na	na	na	16	>32
	Ampicillin	na	na	na	16	>32
	Cefepime	63.9	8.3	27.8	4	>32
	Ceftazidime	66.7	2.7	30.6	$\leq$ 8	>32
	Ceftriaxone	52.8	18.4	27.8	8	>64
	Imipenem	89.9	0	11.1	0.25	16
	Levofloxacin	77.8	13.9	8.3	0.12	4
	Minocycline	84.4	5.6	0	$\leq$ 0.5	4
Pip-Tazo	88.9	0	11.1	0.12	>16	
<i>P. aeruginosa</i> (n=60)	Tigecycline	5	3.3	91.7	8	>16
	Amikacin	81.7	8.3	10	4	32
	Amox-Clav	na	na	na	>32	>32
	Ampicillin	na	na	na	>32	>32
	Cefepime	70	8.3	21.7	8	>32
	Ceftazidime	65	3.3	31.7	$\leq$ 8	>32
	Ceftriaxone	13	13.3	73	>64	>64
	Imipenem	83.3	5	11.7	1	16
	Levofloxacin	58.3	3.3	38.4	1	>8
	Minocycline	3.3	11.7	85	>16	>16
Pip-Tazo	86.7	0	13.3	4	128	

<sup>a</sup>Only species with n  $\geq$  20 are represented.  
<sup>b</sup>Breakpoints as defined by NCCLS where available (M100-S14), 2004. Tigecycline breakpoints defined as: susceptible  $\leq$  2; intermediate = 4; and resistant  $\geq$  8.

Table 3. In vitro activity of tigecycline and comparative agents against 136 selected Gram-positive pathogens.

Organism Name <sup>a</sup>	Drug <sup>b</sup>	MICs (mcg/mL)				
		%SUS	%INT	%RES	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>S. aureus</i> (n=76)	Tigecycline	100	0	0	0.12	0.25