

## Revised Abstract

**Background:** Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent broad spectrum activity against most commonly encountered species responsible for community and hospital acquired infections. **Methods:** A total of 10,313 clinical isolates from 75 Pacific Rim testing sites in ten countries from 2004 to 2008 were identified to the species level and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Selected results are in the table as follows\*:

	<i>Enterobacter</i> spp.				<i>Acinetobacter</i> spp.			
	In-patients (n=1,017)		Out-patients (n=162)		In-patients (n=684)		Out-patients (n=85)	
	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>
Tigecycline	95.2	1	96.9	1	na	2	na	1
Amikacin	93.6	8	91.4	16	53.4	>64	74.1	>64
Cefepime	84.8	32	86.4	16	43.4	>32	58.8	>32
Ceftazidime	61.5	>32	70.4	>32	39.0	>32	51.8	>32
Ceftriaxone	63.1	>64	66.7	>64	23.0	>64	29.4	>64
Imipenem	99.7	1	100	1	63.4	>16	78.6	>16
Levofloxacin	83.7	8	80.9	8	47.4	>8	65.9	>8
Minocycline	76.7	16	74.7	16	86.5	8	92.9	4
PipTazo	70.3	128	74.7	128	43.3	>128	58.8	>128

  

	<i>S. aureus</i>				<i>Enterococcus</i> spp.			
	In-patients (n=971)		Out-patients (n=202)		In-patients (n=643)		Out-patients (n=115)	
	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>
Tigecycline	99.3	0.5	100	0.25	100	0.25	99.1	0.25
Ampicillin	34.0	>16	45.5	>16	68.3	>16	77.4	>16
Levofloxacin	62.8	16	79.2	8	37.6	>32	32.2	>32
Linezolid	100	4	100	4	100	2	100	2
Minocycline	87.7	8	97.5	2	46.5	>8	32.2	>8
Penicillin	33.3	>8	44.6	>8	68.6	>8	77.4	>8
Vancomycin	100	1	100	1	89.9	8	93.9	2

\*na = breakpoints not available

**Conclusions:** Tigecycline's *in vitro* activity was comparable to or greater than most commonly prescribed broad spectrum antimicrobials without any demonstrable change in susceptibility between in- and out-patient bacterial study strains. Tigecycline's inhibitory activity against *Enterobacteriaceae* was comparable to imipenem; vs. *Acinetobacter* spp. tigecycline's MIC<sub>50</sub> was 32-fold lower than imipenem's. Against *S. aureus* and *Enterococcus* spp., tigecycline's activity was similar to linezolid and vancomycin.

## 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 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 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 been shown to be active 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 MIC<sub>50</sub> 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].

The T.E.S.T. program determined the *in vitro* activity of tigecycline compared to most commonly prescribed broad spectrum antimicrobials against gram-negative and gram-positive species collected from 1,016 hospitals globally from 2004 to 2008. This study was designed to investigate possible differences in the *in vitro* activity of tigecycline in in-patient and out-patient isolates from Pacific Rim countries.

## Materials & Methods

- For the T.E.S.T. program 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=10,313) were collected from 2004 to 2008 from 75 Pacific Rim testing sites in ten countries (Australia, China, Hong Kong, India, Indonesia, Korea, Pakistan, the Philippines, Singapore and Taiwan).
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [12]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., Sacramento, CA, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): gram-positive panel: amoxicillin/clavulanic acid (0.03/0.015-8/4, tested using a 2:1 ratio of amoxicillin:clavulanic acid; reported concentrations refer to amoxicillin); ampicillin (0.06-16); ceftriaxone (0.03-64); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.06-32); minocycline (0.25-8); tigecycline (0.008-16); penicillin (0.06-8); piperacillin/tazobactam (0.25/4-16/4) and vancomycin (0.12-32); gram-negative panel: amikacin (0.5-64); amoxicillin/clavulanic acid (0.12/0.06-32/16, tested using a 2:1 ratio of amoxicillin:clavulanic acid; reported concentrations refer to amoxicillin); ampicillin (0.5-32); cefepime (0.5-32); ceftriaxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16) and piperacillin/tazobactam (0.06/4-128/4).
- 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 (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA). 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.
- 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].
- 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 CLSI guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *K. pneumoniae* ATCC 70603; *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, confirmation of identification, and 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).

## References

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## Results

The results are listed in the following tables.

Table 1. *In vitro* activity of tigecycline and comparative agents against gram-negative isolates.

Organism Name	Drug	In-patients					Out-patients						
		n	%SUS*	MIC <sub>50</sub>	MIC range (mcg/ml)	MIC range (mcg/ml)	n	%SUS*	MIC <sub>50</sub>	MIC range (mcg/ml)	MIC range (mcg/ml)		
<i>E. coli</i>	Tigecycline	1,015	100	0.12	0.5	0.03	2	276	100	0.25	0.5	0.03	2
		Amikacin	95.9	2	8	<0.5	>64	96.4	2	8	<0.5	>64	
		AmoxClav	56.1	8	32	0.5	>32	65.2	8	32	0.5	>32	
		Ampicillin	25.4	>32	>32	<0.5	>32	33.7	>32	>32	<0.5	>32	
		Cefepime	78.5	<0.5	>32	<0.5	>32	88.0	<0.5	16	<0.5	>32	
		Ceftazidime	83.6	<0.5	32	<0.5	>32	92.0	<0.5	16	<0.5	>32	
		Ceftriaxone	69.2	<0.06	>64	<0.06	>64	81.5	<0.06	>64	<0.06	>64	
		Imipenem	100	0.25	0.25	<0.06	2	100	0.25	0.5	<0.06	1	
		Levofloxacin	56.3	0.5	<0.008	<0.008	<0.008	68.5	0.06	<0.008	<0.008	<0.008	
		Minocycline	69.0	2	16	<0.5	>16	74.3	2	16	<0.5	>16	
PipTazo	89.2	2	32	<0.06	>128	92.8	1	16	0.12	>128			
<i>Klebsiella</i> spp.	Tigecycline	1,015	97.4	0.5	2	0.03	8	217	97.7	0.5	1	0.12	4
		Amikacin	88.8	2	64	<0.5	>64	95.4	1	4	<0.5	>64	
		AmoxClav	61.4	4	>32	0.5	>32	78.3	2	32	1	>32	
		Ampicillin	0.3	>32	>32	1	>32	0.5	>32	>32	8	>32	
		Cefepime	77.7	<0.5	>32	<0.5	>32	88.9	<0.5	16	<0.5	>32	
		Ceftazidime	73.7	<0.5	>32	<0.5	>32	88.5	<0.5	16	<0.5	>32	
		Ceftriaxone	68.5	<0.06	>64	<0.06	>64	83.9	<0.06	>64	<0.06	>64	
		Imipenem	98.7	0.25	0.5	<0.06	>16	100	0.25	0.5	<0.06	1	
		Levofloxacin	73.5	0.06	<0.008	<0.008	<0.008	85.7	0.06	<0.008	<0.008	<0.008	
		Minocycline	78.1	2	16	<0.5	>16	81.1	2	16	<0.5	>16	
PipTazo	79.1	2	>128	<0.06	>128	86.2	2	128	0.12	>128			
<b>ESBL-producing <i>E. coli</i>, <i>K. pneum.</i></b>	Tigecycline	387	97.9	0.25	1	0.06	8	50	100	0.25	2	0.12	2
		Amikacin	82.2	4	>64	<0.5	>64	82.0	4	>64	<0.5	>64	
		AmoxClav	27.4	16	>32	2	>32	32.0	16	>32	2	>32	
		Ampicillin	0.8	>32	>32	1	>32	2.0	>32	>32	8	>32	
		Cefepime	41.3	16	>32	<0.5	>32	46.0	16	>32	<0.5	>32	
		Ceftazidime	47.3	16	>32	<0.5	>32	64.0	<0.5	16	<0.5	>32	
		Ceftriaxone	10.6	>64	>64	<0.06	>64	12.0	>64	>64	0.5	>64	
		Imipenem	100	0.25	0.5	<0.06	2	100	<0.06	0.5	<0.06	1	
		Levofloxacin	25.9	8	<0.008	<0.008	<0.008	34.0	<0.008	<0.008	<0.008	<0.008	
		Minocycline	62.8	4	>16	<0.5	>16	64.0	4	>16	<0.5	>16	
PipTazo	71.6	4	>128	<0.06	>128	80.0	4	128	0.5	>128			
<i>Enterobacter</i> spp.	Tigecycline	1,017	95.2	0.5	1	0.015	8	162	96.9	0.5	1	0.03	8
		Amikacin	93.6	2	8	<0.5	>64	91.4	2	16	<0.5	>64	
		AmoxClav	2.4	>32	>32	1	>32	4.3	>32	>32	<0.12	>32	
		Ampicillin	0.8	>32	>32	1	>32	0.0	>32	>32	16	>32	
		Cefepime	84.8	<0.5	32	<0.5	>32	86.4	<0.5	16	<0.5	>32	
		Ceftazidime	61.5	<0.5	>32	<0.5	>32	70.4	<0.5	16	<0.5	>32	
		Ceftriaxone	63.1	2	>64	<0.06	>64	66.7	2	>64	<0.06	>64	
		Imipenem	99.7	0.25	1	<0.06	16	100	0.5	1	<0.06	2	
		Levofloxacin	83.7	0.06	8	<0.008	<0.008	80.9	0.12	8	<0.008	<0.008	
		Minocycline	76.7	4	16	<0.5	>16	74.7	4	16	<0.5	>16	
PipTazo	70.3	4	128	<0.06	>128	74.7	4	128	0.5	>128			
<i>Serratia</i> spp.	Tigecycline	390	97.2	1	2	<0.008	8	72	97.2	1	2	0.12	4
		Amikacin	93.1	2	16	<0.5	>64	98.6	2	8	1	>64	
		AmoxClav	1.8	>32	>32	<0.12	>32	4.2	>32	>32	1	>32	
		Ampicillin	0.8	>32	>32	4	>32	0.0	>32	>32	16	>32	
		Cefepime	89.7	<0.5	16	<0.5	>32	95.8	<0.5	2	<0.5	>32	
		Ceftazidime	88.5	<0.5	16	<0.5	>32	98.6	<0.5	8	<0.5		