

## REVISED ABSTRACT

**Background:** One of the goals of surveillance studies is to identify changing patterns of bacterial resistance to help guide current therapy. The Tigecycline Evaluation Surveillance Trial (TEST) is an ongoing global study that can serve to help recognize current trends in resistance on many levels. This report evaluates differences in susceptibility of strains from both hospital- and community-acquired infections in Asia during 2004-2006. **Methods:** 730 strains were collected and identified from 2004-2006 at 4 investigative sites in Asia. MICs for each strain were determined per CLSI guidelines at each facility using custom broth microdilution panels. **Results:** Summary results for key pathogens are shown in the following table.

	Enterobacteriaceae				Acinetobacter spp.			
	Hospital (n=222)		Community (n=30)		Hospital (n=51)		Community (n=4)	
	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>
Tigecycline	98.1	1	100	1	na	1	na	1
Amikacin	90.5	16	86.7	>64	47.1	>64	50	-
Cefepime	81.5	32	83.3	16	39.2	>32	25	-
Imipenem	100	1	100	0.5	66.7	>16	75	-
Levofloxacin	68.5	>8	78.7	>8	51	8	25	-
Minocycline	75.7	16	80	16	88	4	100	-
Pip-Tazo	89.6	32	86.7	32	51	>128	25	-

  

	S. aureus				S. pneumoniae			
	Hospital (n=62)		Community (n=10)		Hospital (n=26)		Community (n=17)	
	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>	%S	MIC <sub>50</sub>
Tigecycline	100	0.25	100	0.25	na	0.5	na	0.5
Levofloxacin	38.7	>32	40	>32	100	1	100	1
Linezolid	100	2	100	1	100	1	100	1
Minocycline	91.9	4	90	4	na	8	na	8
Vancomycin	100	1	100	1	100	0.5	100	0.5

na=breakpoints not available  
a No MIC<sub>50</sub> calculated if n<10

**Conclusion:** Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed broad spectrum antimicrobials without any demonstrable difference in activity against hospital and community bacterial study strains. Tigecycline's inhibitory activity against *Enterobacteriaceae* was comparable to imipenem; vs. *Acinetobacter* spp. tigecycline's MIC<sub>50</sub> was the lowest among all study antimicrobials. Against *S. aureus*, tigecycline's activity was comparable to linezolid and vancomycin; vs. *S. pneumoniae*, tigecycline's MIC<sub>50</sub> 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, 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>-8</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>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 205 hospitals globally from 2004 to 2006. This study was designed to evaluate the in vitro activity of tigecycline in in-patient and out-patient isolates from four Asian 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=730) were collected from 2004 to 2006 from four Asian testing sites (1 each in China, India, Korea, and Pakistan).
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring, West 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].
- 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; *Klebsiella pneumoniae* ATCC 700603; *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).

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## RESULTS

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

Organism Name	Drug	n	%SUS <sup>a</sup>	Hospital (mcg/ml)				Community (mcg/ml)					
				MIC <sub>50</sub>	MIC <sub>90</sub>	Low	High	MIC <sub>50</sub>	MIC <sub>90</sub>	Low	High		
<i>E. coli</i> <sup>b</sup>	Tigecycline	65	100	0.12	0.25	0.06	0.5	14	100	0.12	0.25	0.06	0.25
	Amikacin	93.8	2	8	≤0.5	>64	92.9	2	8	1	>64		
	AmoxClav	47.7	16	32	1	>32	64.3	8	16	2	>64		
	Ampicillin	23.1	>32	>32	1	>32	28.6	>32	>32	1	>32		
	Cefepime	75.4	2	>32	≤0.5	>32	92.9	≤0.5	8	≤0.5	>32		
	Ceftazidime	78.5	≤8	32	≤8	>32	92.9	≤8	8	≤8	>32		
	Ceftriaxone	47.7	32	>64	≤0.06	>64	78.6	≤0.06	64	≤0.06	>64		
	Imipenem	100	0.25	0.5	0.25	2	100	0.25	0.5	0.12	0.5		
	Levofloxacin	32.3	8	>8	≤0.008	>8	64.3	0.25	>8	0.015	>8		
	Minocycline	61.5	4	16	≤0.5	>16	78.6	2	16	≤0.5	16		
PipTazo	92.3	2	16	0.25	>128	85.7	1	32	0.5	32			
<i>Klebsiella</i> spp. <sup>c</sup>	Tigecycline	70	97.1	0.5	2	0.25	4	11	100	0.5	1	0.25	1
	Amikacin	88.6	2	>64	≤0.5	>64	90.9	2	4	1	>64		
	AmoxClav	52.9	8	>32	0.5	>32	72.7	2	32	1	>32		
	Ampicillin	0	>32	>32	16	>32	0	>32	>32	16	>32		
	Cefepime	81.4	1	16	≤0.5	>32	81.8	≤0.5	16	≤0.5	>32		
	Ceftazidime	61.4	≤8	>32	≤8	>32	90.9	≤8	8	≤8	>32		
	Ceftriaxone	55.7	8	>64	≤0.06	>64	72.7	≤0.06	>64	≤0.06	>64		
	Imipenem	100	0.5	0.5	0.12	1	100	0.25	0.5	0.25	0.5		
	Levofloxacin	74.3	0.25	>8	0.015	>8	100	0.03	0.25	0.03	0.5		
	Minocycline	75.7	2	16	≤0.5	>16	90.9	2	4	≤0.5	>16		
PipTazo	90	2	16	0.25	>128	90.9	1	16	0.5	128			
ESBL-producers <sup>d</sup>	Tigecycline	55	98.2	0.5	1	0.06	4	6	100	-	-	0.12	1
	Amikacin	85.5	4	>64	≤0.5	>64	66.7	-	-	1	>64		
	AmoxClav	30.9	16	32	2	>32	16.7	-	-	8	>32		
	Ampicillin	1.8	>32	>32	1	>32	0	-	-	>32	>32		
	Cefepime	58.2	8	>32	≤0.5	>32	50	-	-	2	>32		
	Ceftazidime	40	16	>32	<8	>32	66.7	-	-	<8	>32		
	Ceftriaxone	21.8	64	>64	≤0.06	>64	0	-	-	16	>64		
	Imipenem	100	0.25	1	0.25	2	100	-	-	0.25	0.5		
	Levofloxacin	47.3	4	>8	0.015	>8	50	-	-	0.12	>8		
	Minocycline	67.3	4	16	≤0.5	>16	83.3	-	-	≤0.5	>16		
PipTazo	89.1	4	32	0.25	>128	83.3	-	-	2	32			
<i>Enterobacter</i> spp. <sup>d</sup>	Tigecycline	63	100	0.5	1	0.25	2	3	100	-	-	0.25	2
	Amikacin	87.3	2	>64	1	>64	66.7	-	-	1	>64		
	AmoxClav	3.2	>32	>32	4	>32	0	-	-	32	>32		
	Ampicillin	0	>32	>32	16	>32	0	-	-	>32	>32		
	Cefepime	82.5	1	32	≤0.5	>32	66.7	-	-	≤0.5	16		
	Ceftazidime	55.6	<8	>32	≤8	>32	66.7	-	-	≤8	16		
	Ceftriaxone	57.1	4	>64	≤0.06	>64	66.7	-	-	≤0.06	>64		
	Imipenem	100	0.5	1	0.25	1	100	-	-	0.25	0.5		
	Levofloxacin	87.3	0.12	4	0.015	>8	33.3	-	-	0.03	>8		
	Minocycline	82.5	2	8	≤0.5	>16	66.7	-	-	1	8		
PipTazo	85.7	2	32	≤0.06	128	66.7	-	-	1	32			
<i>Serratia</i> spp. <sup>d</sup>	Tigecycline	24	100	1	1	0.25	2	2	100	-	-	2	2
	Amikacin	95.8	4	8	1	>64	50	-	-	2	>64		
	AmoxClav	0	>32	>32	32	>32	0	-	-	>32	>32		
	Ampicillin	0	>32	>32	16	>32	0	-	-	>32	>32		
	Cefepime	95.8	≤0.5	4	≤0.5	>32	50	-	-	≤0.5	>32		
	Ceftazidime	95.8	≤8	≤8	≤8	>32	50	-	-	≤8	>32		
	Ceftriaxone	87.5	0.5	16	≤0.06	>64	50	-	-	0.5	>64		
	Imipenem	100	0.5	1	0.25	2	100	-	-	0.5	1		
	Levofloxacin	100	0.25	1	0.03	2	100	-	-	0.06	0.25		
	Minocycline	95.8	2	4	2	>16	50	-	-	4	16		
PipTazo	91.7	2	16	0.5	128	100	-	-	2	2			
<i>Acinetobacter</i> spp. <sup>d</sup>	Tigecycline	51	na	0.25	1	0.03	4	4	na	-	-	0.12	0.5
	Amikacin	47.1	64	>64	≤0.5	>64	50	-	-	2	>64		
	AmoxClav	na	>32	>32	1	>32	na	-	-	8	>32		
	Ampicillin	na	>32	>32	1	>32	na	-	-	32	>32		
	Cefepime	39.2	16	>32	≤0.5	>32	25	-	-	4	>32		
	Ceftazidime	41.2	>32	>32	≤8	>32	25	-	-	≤8	>32		
	Ceftriaxone	31.4	>64	>64	1	>64	0	-	-	16	>64		
	Imipenem	66.7	1	>16	0.25	>16	75	-	-	0.5	>16		
	Levofloxacin	51	2	8	0.03	>8	25	-	-	0.12	8		

na = breakpoints not available.  
<sup>a</sup>Interpretive criteria as defined by CLSI, M100-S16 (2006) [12], where available; tigecycline susceptibility breakpoints are according to FDA package insert (Tygacil<sup>®</sup>, 2005), where available [13].  
<sup>b</sup>In-patient isolates include 22 ESBL-producing strains; out-patient isolates include 3 ESBL-producing strains.  
<sup>c</sup>In-patient isolates include 33 ESBL-producing *K. pneumoniae* strains; out-patient isolates include 3 ESBL-producing *K. pneumoniae* strains.  
<sup>d</sup>No MIC<sub>50</sub> and MIC<sub>90</sub> calculated if n<10; % SUS, % INT, % RES may not be statistically significant when n's are small.  
<sup>e</sup>In-patient isolates include 5 beta-lactamase positive strains and out-patient isolates include 5 beta-lactamase positive strains, with essentially the same susceptibility to tigecycline as the beta-lactam