

Susceptibilities of Hospital- and Community-Acquired Clinical Pathogens from Asian Hospitals: TEST Program in Asia 2006

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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:** 1,056 strains were collected, identified, and reported as hospital or community-acquired from 2004-2006 at 4 laboratories in Asia (1 in each of China, India, Korea, and Pakistan). 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.

	<i>E. coli/Kleb. pneumo/Kleb. Oxy</i>				<i>Acinetobacter</i> spp.			
	Hospital (n=255)		Community (n=48)		Hospital (n=85)		Community (n=7)	
	%S	MIC ₉₀	%S	MIC ₉₀	%S	MIC ₉₀	%S	MIC ₉₀
Tigecycline	98.4	1	100	0.5	na	1	na	-
Amikacin	91.4	8	93.8	8	41.2	>64	42.9	-
Cefepime	74.1	>32	87.5	32	35.3	>32	28.6	-
Imipenem	99.2	0.5	100	0.5	63.5	>16	71.4	-
Levofloxacin	55.3	>8	72.9	>8	44.7	8	28.6	-
Minocycline	73.3	16	81.3	8	97.6	4	100	-
PipTazo	90.6	16	89.6	32	44.7	>128	28.6	-

	<i>S. aureus</i>		<i>Enterococcus</i> spp.					
	Hospital (n=104)	Community (n=18)	Hospital (n=79)	Community (n=14)				
	%S	MIC ₉₀	%S	MIC ₉₀	%S	MIC ₉₀	%S	MIC ₉₀
Tigecycline	100	0.25	100	0.25	100b	0.12	100b	0.12
Levofloxacin	42.3	32	61.1	>32	30.4	>32	35.7	>32
Linezolid	100	2	100	2	98.7	2	92.9	2
Minocycline	93.3	4	94.4	4	58.2	8	35.7	8
Vancomycin	100	1	100	1	78.5	>32	85.7	>32

na=breakpoints not available
*MIC₉₀ not calculated if n<10

^bNon-VRE *Enterococcus* breakpoint applied for comparison purposes only.

Conclusion: Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed broad spectrum antimicrobials without any demonstrable change in activity between in-patient and out-patient study strains. Tigecycline's inhibitory activity against *Enterobacteriaceae* was comparable to imipenem's, and its activity vs. *Acinetobacter* spp. was superior. Against gram-positive organisms, tigecycline's activity was comparable to or better than that of linezolid and vancomycin.

INTRODUCTION

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycylicylines. 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].

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 against 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 other defined sources. Only one isolate per patient was accepted.
- For this study, 1,056 clinical isolates were collected and reported as hospital or community-acquired from 2004 to 2006 at four Asian testing sites (one in each of 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.
- Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftriaxone were >1mcg/ml using broth microdilution panels. ESBL activity was confirmed using the CLSI (2006) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2006) guidelines. 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.
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *E. faecalis* ATCC 29212; *E. coli* ATCC 25922; *K. pneumoniae* ATCC 700603; *Haemophilus influenzae* ATCC 49247; *H. influenzae* ATCC 49766; *S. 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

The results are listed in the following tables.

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

Organism Name	Drug	n	In-patients					Out-patients													
			%SUS ^a	MIC ₅₀	MIC ₉₀	Low	High	%SUS ^a	MIC ₅₀	MIC ₉₀	Low	High									
<i>E. coli</i> ^b		124																			
	Tigecycline	100	0.12	0.25	0.06	0.5	100	0.25	0.5	0.06	0.5	100	0.12	0.25	0.06	0.5	100	0.12	0.25	0.06	0.5
	Amikacin	95.2	2	8	≤0.5	>64	92	2	8	1	>64	72.2	1	>8	0.25	>8	72.2	1	>8	0.25	>8
	AmoxClav	54	8	32	0.5	>32	56	8	32	2	>32	5.6	8	>16	>0.06	>16	5.6	8	>16	>0.06	>16
	Ampicillin	18.5	>32	>32	1	>32	20	>32	>32	1	>32	41.3	64	>64	1	>64	66.7	4	>64	2	>64
	Cefepime	73.4	1	>32	≤0.5	>32	88	≤0.5	>32	≤0.5	>32	82.4	0.25	>16	≤0.12	>16	82.4	0.25	>16	≤0.12	>16
	Ceftazidime	79	≤8	32	≤8	>32	88	≤8	32	≤8	>32	42.3	4	>32	≤0.06	>32	61.1	0.25	>32	≤0.06	>32
	Ceftriaxone	54	4	>64	≤0.06	>64	80	≤0.06	>64	≤0.06	>64	100	1	2	≤0.5	4	100	1	2	≤0.5	4
	Imipenem	100	0.25	0.25	≤0.06	2	100	0.25	0.5	≤0.06	0.5	94.4	0.25	>16	≤0.06	>32	94.4	0.25	>16	≤0.06	>32
	Levofloxacin	33.9	8	>8	≤0.008	>8	56	0.25	>8	0.015	>8	0	>8	>8	≤0.06	>8	0	>8	>8	≤0.06	>8
	Minocycline	66.1	2	16	≤0.5	>16	76	2	8	≤0.5	>16	66.7	1	>16	≤0.06	>16	66.7	1	>16	≤0.06	>16
PipTazo	95.2	2	8	≤0.06	>128	88	1	32	0.25	32	100	0.5	1	0.25	2	100	0.5	1	0.5	1	
<i>Klebsiella</i> spp. ^c		132																			
	Tigecycline	97	0.5	1	0.12	4	100	0.5	1	0.12	1	100	0.5	1	0.12	1	100	0.5	1	0.12	1
	Amikacin	87.9	2	>64	≤0.5	>64	95.7	1	4	≤0.5	>64	72.2	1	>8	0.25	>8	72.2	1	>8	0.25	>8
	AmoxClav	55.3	8	>32	0.5	>32	73.9	4	32	1	>32	5.6	8	>16	>0.06	>16	5.6	8	>16	>0.06	>16
	Ampicillin	0	>32	>32	16	>32	0	>32	>32	16	>32	41.3	64	>64	1	>64	66.7	4	>64	2	>64
	Cefepime	75	1	32	≤0.5	>32	87	≤0.5	16	≤0.5	>32	82.4	0.25	>16	≤0.12	>16	82.4	0.25	>16	≤0.12	>16
	Ceftazidime	64.4	≤8	32	≤8	>32	87	≤8	32	≤8	>32	42.3	4	>32	≤0.06	>32	61.1	0.25	>32	≤0.06	>32
	Ceftriaxone	54.5	8	>64	≤0.06	>64	78.3	≤0.06	>64	≤0.06	>64	100	1	2	≤0.5	4	100	1	2	≤0.5	4
	Imipenem	98.5	0.25	0.5	≤0.06	8	100	0.25	0.5	≤0.06	0.5	94.4	0.25	>16	≤0.06	>32	94.4	0.25	>16	≤0.06	>32
	Levofloxacin	75.8	0.25	>8	≤0.008	>8	91.3	0.06	2	0.03	>8	0	>8	>8	≤0.06	>8	0	>8	>8	≤0.06	>8
	Minocycline	79.5	2	16	≤0.5	>16	87	2	8	≤0.5	>16	66.7	1	>16	≤0.06	>16	66.7	1	>16	≤0.06	>16
PipTazo	86.4	2	64	≤0.06	>128	91.3	2	16	0.12	128	100	0.5	1	0.25	2	100	0.5	1	0.5	1	
ESBL-producers ^d		66																			
	Tigecycline	98.5	0.25	1	0.06	4	100	-	-	0.12	1	100	-	-	0.12	1	100	-	-	0.12	1
	Amikacin	86.4	4	>64	≤0.5	>64	66.7	-	-	1	>64	72.2	1	>8	0.25	>8	72.2	1	>8	0.25	>8
	AmoxClav	31.8	16	32	2	>32	16.7	-	-	8	>32	5.6	8	>16	>0.06	>16	5.6	8	>16	>0.06	>16
	Ampicillin	1.5	>32	>32	1	>32	0	-	-	>32	>32	41.3	64	>64	1	>64	66.7	4	>64	2	>64
	Cefepime	53	8	>32	≤0.5	>32	50	-	-	2	>32	50	-	-	2	>32	50	-	-	2	>32
	Ceftazidime	45.5	16	>32	≤8	>32	66.7	-	-	≤8	>32	42.3	4	>32	≤0.06	>32	61.1	0.25	>32	≤0.06	>32
	Ceftriaxone	18.2	>64	>64	≤0.06	>64	0	-	-	16	>64	0	>8	>8	≤0.06	>8	0	>8	>8	≤0.06	>8
	Imipenem	100	0.25	1	≤0.06	2	100	-	-	0.25	0.5	94.4	0.25	>16	≤0.06	>32	94.4	0.25	>16	≤0.06	>32
	Levofloxacin	42.4	8	>8	0.015	>8	50	-	-	0.12	>8	0	>8	>8	≤0.06	>8	0	>8	>8	≤0.06	>8
	Minocycline	66.7	4	16	≤0.5	>16	83.3	-	-	≤0.5	>16	66.7	1	>16	≤0.06	>16	66.7	1	>16	≤0.06	>16
PipTazo	87.9	4	32	0.12	>128	83.3	-	-	2	32	100	0.5	1	0.25	2	100	0.5	1	0.5	1	
<i>Enterobacter</i> spp. ^d		113																			
	Tigecycline	97.3	0.5	1	0.25	8	80	-	-	0.25	4	80	-	-	0.25	4	80	-	-	0.25	4
	Amikacin	90.3	2	16	1	>64	80	-	-	1	>64	72.2	1	>8	0.25	>8	72.2	1	>8	0.25	>8
	AmoxClav	1.8	>32	>32	4	>32	20	-	-	≤0.12	>32	5.6	8	>16	>0.06	>16	5.6	8	>16	>0.06	>16
	Ampicillin	0	>32	>32	16	>32	0	-	-	>32	>32	41.3	64	>64	1	>64	66.7	4	>64	2	>64
	Cefepime	81.4	≤0.5	>32	≤0.5	>32	80	-	-	≤0.5	16	82.4	0.25	>16	≤0.12	>16	82.4	0.25	>16	≤0.12	>16
	Ceftazidime	57.5	≤8	>32	≤8	>32	6														