

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) Program - In Vitro Antibacterial Activity against Nosocomial and Community Pathogens from Asia and the Pacific Rim

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REVISED ABSTRACT

Background: Tigecycline, the representative member of the glycylycylines, a new class of antimicrobials, has been shown to have potent activity against most commonly encountered pathogens responsible for community acquired and nosocomial infections. The T.E.S.T. program determined the in vitro activity of tigecycline in comparison to several commonly prescribed antimicrobials in the treatment of nosocomial and community acquired infections. Isolates were collected from Asian and Pacific Rim hospitals throughout 2004. **Methods:** A total of 996 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 broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Tigecycline's activity was similar to imipenem against *Enterobacteriaceae* with MIC₅₀/MIC₉₀ of 0.5/1 mcg/ml. ESBL production was confirmed in 16.4 % of *E. coli* and 27.8% of *K. pneumoniae*. Tigecycline successfully inhibited >98% ESBL producers with MICs equal or less than 2 mcg/ml. Tigecycline was especially active against *Acinetobacter* spp. presenting the lowest MIC₉₀ of all study drugs at 1 mcg/ml. Tigecycline successfully inhibited *S. aureus* with a MIC₉₀ of 0.25 mcg/ml regardless of susceptibility or resistance to oxacillin. Tigecycline had the lowest MIC₉₀ against enterococci at 0.5 mcg/mL. Tigecycline inhibits all of *H. influenzae* with MICs less than 0.5 mcg/ml regardless of β-lactamase production. **Conclusion:** The data presented suggest that tigecycline may be an effective therapeutic option against nosocomial and community acquired pathogens regardless of the degree or type of resistance.

INTRODUCTION

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycylycylines. 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 β-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 a limited number of clinical isolates collected from 6 study centers in Australia, China, India, Pakistan, Philippines and Singapore.

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 996 Clinical isolates were collected tested between January 2004 – December 2004 from 6 study centers in Australia, China, India, Pakistan, Philippines and Singapore.

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RESULTS

Table 1. *In vitro* activity of tigecycline and comparative agents against 402 strains of *Enterobacteriaceae*

Organism ^a	Drug ^b	%Sus	%Int	%Res	MIC (mcg/mL)		
					MIC ₅₀	MIC ₉₀	
All <i>Enterobacteriaceae</i> (n=402)	Tigecycline	98.8	0.7	0.5	0.5	1	
	Amikacin	97.3	0	2.7	2	4	
	Amox-Clav	41	14.4	44.5	16	>32	
	Ampicillin	12.7	4.7	82.6	>32	>32	
	Cefepime	91.3	3.2	5.5	≤0.5	8	
	Ceftazidime	80.6	6	13.4	≤8	32	
	Ceftriaxone	75.4	7	17.7	0.12	>64	
	Imipenem	99.5	0.2	0.2	0.5	1	
	Levofloxacin	80.3	2.5	17.2	0.06	>8	
	Minocycline	81.3	10.2	8.5	2	8	
	Pip-Tazo	91	6.2	2.7	2	16	
	All ESBLs (n=50)	Tigecycline	98	2	0	0.5	1
		Amikacin	90	0	10	2	8
Amox-Clav		26	58	16	16	32	
Ampicillin		2	0	98	>32	>32	
Cefepime		62	18	20	8	>32	
Ceftazidime		40	20	40	16	>32	
Ceftriaxone		12	20	68	64	>64	
Imipenem		100	0	0	0.25	1	
Levofloxacin		46	2	52	8	>8	
Minocycline		72	14	14	4	16	
Pip-Tazo		94	4	2	4	8	
<i>E. aerogenes</i> (n=30)		Tigecycline	100	0	0	0.5	0.5
		Amikacin	100	0	0	2	4
	Amox-Clav	3.3	0	96.7	>32	>32	
	Ampicillin	0	0	100	>32	>32	
	Cefepime	90	0	10	≤0.5	4	
	Ceftazidime	70	10	20	≤8	>32	
	Ceftriaxone	86.7	6.7	6.7	0.12	16	
	Imipenem	96.7	0	3.3	0.5	1	
	Levofloxacin	93.3	3.3	3.3	0.06	0.5	
	Minocycline	96.7	0	3.3	2	4	
	Pip-Tazo	86.7	13.3	0	2	32	
	<i>E. cloacae</i> (n=69)	Tigecycline	97.1	0	2.9	0.5	1
		Amikacin	97.1	0	2.9	2	4
Amox-Clav		4.3	1.4	94.2	>32	>32	
Ampicillin		5.8	7.2	87	>32	>32	
Cefepime		92.8	0	7.2	≤0.5	8	
Ceftazidime		66.7	8.7	24.6	≤8	>32	
Ceftriaxone		68.1	7.2	24.6	0.25	>64	
Imipenem		98.6	1.4	0	0.5	1	
Levofloxacin		91.3	4.3	4.3	0.03	2	
Minocycline		82.6	5.8	11.6	4	>16	
Pip-Tazo		76.8	20.3	2.9	2	64	
<i>E. coli</i> (n=122)		Tigecycline	100	0	0	0.12	0.25
		Amikacin	96.7	0	3.3	2	8
	Amox-Clav	66.4	27.9	5.7	8	16	
	Ampicillin	28.7	0	71.3	>32	>32	
	Cefepime	86.9	6.6	6.6	≤0.5	16	
	Ceftazidime	88.5	5.7	5.7	≤8	16	
	Ceftriaxone	72.1	6.6	21.3	≤0.06	>64	
	Imipenem	100	0	0	0.25	0.5	
	Levofloxacin	57.4	4.1	38.5	0.5	>8	
	Minocycline	66.4	23	10.7	2	16	
	Pip-Tazo	98.4	0.8	0.8	1	4	
	<i>E. coli</i> , ESBL producers (n=20)	Tigecycline	100	0	0	0.25	0.5
		Amikacin	95	0	5	2	4
Amox-Clav		30	70	0	16	16	
Ampicillin		0	0	100	>32	>32	
Cefepime		50	30	20	8	>32	
Ceftazidime		45	30	25	16	32	
Ceftriaxone		5	20	75	>64	>64	
Imipenem		100	0	0	0.25	0.5	
Levofloxacin		20	0	80	>8	>8	
Minocycline		65	25	10	4	8	
Pip-Tazo		100	0	0	2	8	
<i>K. pneumoniae</i> (n=108)		Tigecycline	97.2	2.8	0	0.5	1
		Amikacin	95.4	0	4.6	1	4
	Amox-Clav	61.1	17.6	21.3	4	>32	
	Ampicillin	5.6	6.5	88	>32	>32	
	Cefepime	89.8	4.6	5.6	≤0.5	16	
	Ceftazidime	75.9	6.5	17.6	≤8	>32	
	Ceftriaxone	69.4	9.3	21.3	0.12	>64	
	Imipenem	100	0	0	0.5	1	
	Levofloxacin	84.3	0.9	14.8	0.06	8	
	Minocycline	84.3	5.6	10.2	2	16	
	Pip-Tazo	92.6	3.7	3.7	2	8	
	<i>K. pneumoniae</i> , ESBL producers (n=30)	Tigecycline	96.7	3.3	0	0.5	1
		Amikacin	86.7	0	13.3	2	>64
Amox-Clav		23.3	50	26.7	16	>32	
Ampicillin		3.3	0	96.7	>32	>32	
Cefepime		70	10	20	4	>32	
Ceftazidime		36.7	13.3	50	16	>32	
Ceftriaxone		16.7	20	63.3	64	>64	
Imipenem		100	0	0	0.5	1	
Levofloxacin		63.3	3.3	33.3	1	>8	
Minocycline		76.7	6.7	16.7	4	16	
Pip-Tazo		90	6.7	3.3	4	16	
<i>S. marcescens</i> (n=47)		Tigecycline	100	0	0	1	1
		Amikacin	100	0	0	2	4
	Amox-Clav	8.5	6.4	85.1	>32	>32	
	Ampicillin	12.8	8.5	78.7	>32	>32	
	Cefepime	100	0	0	≤0.5	≤0.5	
	Ceftazidime	95.7	0	4.3	≤8	≤8	
	Ceftriaxone	97.9	2.1	0	0.25	4	
	Imipenem	100	0	0	0.5	1	
	Levofloxacin	100	0	0	0.12	0.5	
	Minocycline	91.5	6.4	2.1	2	4	
	Pip-Tazo	97.9	2.1	0	1	4	

^a Only species with n ≥ 20 are represented.

^b Breakpoints as defined by NCCLS where available (M100-S14), 2004. Tigecycline breakpoints defined as: susceptible ≤ 2; intermediate = 4; and resistant ≥ 8

Table 2. *In vitro* activity of tigecycline and comparative agents against 191 Gram-negative Non-*Enterobacteriaceae*

Organism (n) ^a	Drug ^b	%Sus	%Int	%Res	MIC (mcg/mL)		
					MIC ₅₀	MIC ₉₀	
<i>A. baumannii</i> (n=74)	Tigecycline	97.3	2.7	0	0.25	1	
	Amikacin	62.2	0	37.8	8	>64	
	Amox-Clav	na	na	na	32	>32	
	Ampicillin	na	na	na	>32	>32	
	Cefepime	45.9	10.8	43.2	16	>32	
	Ceftazidime	47.3	4.1	48.6	16	>32	
	Ceftriaxone	29.7	21.6	48.6	32	>64	
	Imipenem	68.9	2.7	28.4	0.5	>16	
	Levofloxacin	58.1	23	18.9	2	8	
	Minocycline	95.9	4.1	0	≤0.5	4	
	Pip-Tazo	67.6	0	32.4	4	>128	
	<i>P. aeruginosa</i> (n=117)	Tigecycline	4.3	10.3	85.5	8	>16
		Amikacin	85.5	6	8.5	4	32
Amox-Clav		na	na	na	>32	>32	
Ampicillin		na	na	na	>32	>32	
Cefepime		71.8	10.3	17.9	8	>32	
Ceftazidime		70.9	5.1	23.9	=8	>32	
Ceftriaxone		10.3	16.2	73.5	>64	>64	
Imipenem		86.3	3.4	10.3	1	16	
Levofloxacin		62.4	6	31.6	1	>8	
Minocycline		3.4	8.5	88	>16	>16	
Pip-Tazo		88.9	0	11.1	4	128	

^a Only species with n ≥ 20 are represented.

^b Breakpoints as defined by NCCLS where available (M100-S14), 2004. na = NCCLS breakpoints not available. Tigecycline breakpoints defined as: susceptible ≤ 2; intermediate = 4; and resistant ≥ 8

Table 3. *In vitro* activity of tigecycline and comparative agents against 251 selected Gram-positive pathogens

Organism (n)	Drug ^a	%Sus	%Int	%Res	MIC (mcg/mL)		
					MIC ₅₀	MIC ₉₀	
<i>Staphylococcus aureus</i> (n=140)	Tigecycline	100	0	0	0.12	0.25	
	Amox-Clav	75.7	0	24.3	1	>8	
	Ampicillin	7.9	0	92.1	8	>16	
	Ceftriaxone	65	7.1	27.9	4	>64	
	Imipenem	80	2.1	17.9	0.25	>16	
	Levofloxacin	65	14.3	20.7	0.25	16	
	Linezolid	100	0	0	2	4	
	Minocycline	89.3	8.6	2.1	≤0.25	8	
	Penicillin	7.1	0	92.9	>8	>8	
	Pip-Tazo	75	0	25	1	>16	
	Vancomycin	100	0	0	1	1	
	Methicillin Resistant <i>S. aureus</i> (n=55)	Tigecycline	100	0	0	0.12	0.5
		Amox-Clav					