

# In Vitro Activity of Tigecycline Against South African Blood, Respiratory Tract, and Urinary Tract Isolates - T.E.S.T. Program 2006

#P1-007

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## REVISED ABSTRACT

**Background:** Tigecycline (TIG), a new glycylicycline, has been shown to have potent 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 TIG and 10 comparators against respective gram positive/negative species. **Methods:** Clinically significant isolates from two South African testing sites were analyzed in this survey. The isolates were identified to the species level at the participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to CLSI (formerly NCCLS) guidelines. **Results:** TIG activity against pathogens from selected body sites are shown in the table below\*:

	Blood				Respiratory				Urinary tract			
	n	%S <sup>a</sup>	Low	High	n	%S <sup>a</sup>	Low	High	n	%S <sup>a</sup>	Low	High
EcKpKo	6	100	0.12	0.5	18	94	0.12	4	35	100	0.06	1
ESBL producers	4	100	0.5	0.5	1	100	0.25	0.25	0	-	-	-
<i>Enterobacter</i> spp.	2	100	0.5	1	5	100	0.25	1	9	100	0.5	1
<i>Acinetobacter</i> spp.	2	na	0.25	1	7	na	0.5	1	3	na	1	1
<i>S. aureus</i>	2	100	0.12	0.25	3	100	0.12	0.12	0	-	-	-
MRSA	2	100	0.12	0.25	1	100	0.12	0.12	0	-	-	-
<i>E. faecalis</i>	1	100	0.12	0.12	2	100	0.12	0.12	3	67	0.06	0.5
<i>S. pneumoniae</i>	8	na	≤0.008	0.5	4	na	0.02	0.12	0	-	-	-
<i>H. influenzae</i>	0	-	-	-	12	na	0.03	2	0	-	-	-

\* na = breakpoints not available  
<sup>a</sup> %S may not be statistically significant when n's are small.

**Conclusion:** Tigecycline showed excellent inhibitory activity against all groups of pathogens regardless of isolation site. Tigecycline's MICs of ≤0.5mcg/ml against gram positive pathogens (including resistant phenotypes) and MICs of ≤4mcg/ml against overall *Enterobacteriaceae* and ≤1mcg/ml against *Acinetobacter* spp. validate the potent inhibitory activity of TIG against South African community/hospital pathogens.

## INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycylicyclines. This synthetic analogue of the tetracyclines exhibits significant antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as fourfold better than vancomycin and daptomycin [1, 2]. The development of tigecycline is important in that tigecycline and other glycylicyclines are active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. Certain substituents at the 9-position of the tetracycline molecule restore activity against bacteria harboring genes encoding either or both efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible gram-positive, gram-negative, aerobic, and anaerobic bacteria [3]. Furthermore, resistance to tigecycline is difficult to produce even in the laboratory.

Previous studies have demonstrated excellent in vitro activity for tigecycline against clinical and laboratory strains of gram-positive and -negative bacteria with minimum inhibitory concentrations for the 90<sup>th</sup> percentile inhibited at or below 2 mcg/ml, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE), and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [4-6]. This study was undertaken to document the in vitro activity of tigecycline against significant numbers of clinical pathogens collected in South African laboratories. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) program with isolates collected from 205 hospital sites in 30 countries from 2004 to 2006.

## MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, body fluids, and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested from 2004 to 2006 from 5 study centers in France. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database, were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age, or gender. All sites identified each study isolate utilizing local laboratory criteria.
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [7]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., West Sacramento, CA, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amikacin (0.5-64); amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.5-32, gram-negative panel) and 0.06-16, gram-positive panel; cefepime (0.5-32); ceftazidime (0.06-64); ceftazidime (8-32); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [8] and the recent US Food and Drug Administration package insert for tigecycline [9], where applicable.
- Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftazidime were >1 mcg/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), ceftazidime/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. *K. pneumoniae* ATCC 700793 was used to QC the ESBL confirmation test.
- Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *E. coli* ATCC 25922; *E. coli* ATCC 35218; *H. influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *Pseudomonas aeruginosa* ATCC 27853; *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2006) guidelines [8].

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## RESULTS

The results are listed in the following tables.

Table 1. In vitro activity of tigecycline and comparative agents against 21 blood culture isolates

Organism Name	Drug	%SUS <sup>a</sup>	%INT	%RES	MIC (mcg/ml)		MIC range (mcg/ml)		
					MIC <sub>50</sub>	MIC <sub>90</sub>	Low	High	
<i>E. coli</i> , <i>K. pneumoniae</i> <sup>b,c</sup> (n=6)	Tigecycline	100	0	0	-	-	0.12	0.5	
	Amikacin	100	0	0	-	-	≤0.5	16	
	AmoxClav	16.7	33.3	50	-	-	8	>32	
	Ampicillin	0	0	100	-	-	>32	>32	
	Cefepime	66.7	0	33.3	-	-	≤0.5	>32	
	Ceftazidime	33.3	16.7	50	-	-	≤8	>64	
	Ceftriaxone	50	16.7	33.3	-	-	≤0.06	>64	
	Imipenem	100	0	0	-	-	0.25	0.5	
	Levofloxacin	66.7	0	33.3	-	-	0.015	>8	
	Minocycline	16.7	66.7	16.7	-	-	4	>16	
PipTazo	33.3	33.3	33.3	-	-	0.5	>128		
ESBL-producers <sup>b</sup> (n=4 <i>K. pneumoniae</i> )	Tigecycline	100	0	0	-	-	0.5	0.5	
	Amikacin	100	0	0	-	-	4	16	
	AmoxClav	0	25	75	-	-	16	>32	
	Ampicillin	0	0	100	-	-	>32	>32	
	Cefepime	50	0	50	-	-	16	>32	
	Ceftazidime	0	25	75	-	-	16	>32	
	Ceftriaxone	25	25	50	-	-	8	>64	
	Imipenem	100	0	0	-	-	0.25	0.5	
	Levofloxacin	50	0	50	-	-	0.06	>8	
	Minocycline	25	50	25	-	-	4	>16	
PipTazo	0	50	50	-	-	32	>128		
<i>Enterobacter</i> spp. <sup>b</sup> (n=2)	Tigecycline	100	0	0	-	-	0.5	1	
	Amikacin	100	0	0	-	-	1	2	
	AmoxClav	0	0	100	-	-	>32	>32	
	Ampicillin	0	0	100	-	-	>32	>32	
	Cefepime	100	0	0	-	-	≤0.5	≤0.5	
	Ceftazidime	50	50	0	-	-	≤8	16	
	Ceftriaxone	100	0	0	-	-	0.12	0.12	
	Imipenem	100	0	0	-	-	0.5	2	
	Levofloxacin	100	0	0	-	-	0.03	0.03	
	Minocycline	100	0	0	-	-	2	4	
PipTazo	100	0	0	-	-	1	2		
<i>Acinetobacter</i> spp. <sup>b</sup> (n=2)	Tigecycline	na	na	na	-	-	0.25	1	
	Amikacin	100	0	0	-	-	16	16	
	AmoxClav	na	na	na	-	-	4	16	
	Ampicillin	na	na	na	-	-	32	>32	
	Cefepime	50	0	50	-	-	8	32	
	Ceftazidime	0	50	50	-	-	16	>32	
	Ceftriaxone	50	50	0	-	-	2	16	
	Imipenem	100	0	0	-	-	1	2	
	Levofloxacin	100	0	0	-	-	0.12	2	
	Minocycline	0	100	0	-	-	8	8	
PipTazo	100	0	0	-	-	1	4		
<i>S. aureus</i> (MRSA) <sup>b</sup> (n=2)	Tigecycline	100	0	0	-	-	0.12	0.25	
	AmoxClav	50	0	50	-	-	1	>8	
	Ampicillin	0	0	100	-	-	8	>16	
	Ceftriaxone	50	0	50	-	-	2	>64	
	Imipenem	50	0	50	-	-	≤0.12	>16	
	Levofloxacin	50	0	50	-	-	0.25	>32	
	Linezolid	100	0	0	-	-	2	2	
	Minocycline	100	0	0	-	-	≤0.25	4	
	Penicillin	0	0	100	-	-	>8	>8	
	PipTazo	50	0	50	-	-	1	>16	
Vancomycin	100	0	0	-	-	0.5	1		
<i>E. faecalis</i> <sup>b</sup> (n=1)	Tigecycline	100	0	0	-	-	0.12	0.12	
	Amikacin	100	0	0	-	-	0.5	0.5	
	Levofloxacin	0	0	100	-	-	>32	>32	
	Linezolid	100	0	0	-	-	1	1	
	Minocycline	0	0	100	-	-	>8	>8	
	Penicillin	100	0	0	-	-	4	4	
	Vancomycin	100	0	0	-	-	1	1	
	<i>S. pneumoniae</i> <sup>b,d</sup> (n=8)	Tigecycline	na	na	na	-	-	≤0.008	0.5
		AmoxClav	100	0	0	-	-	≤0.03	2
		Ceftriaxone	100	0	0	-	-	≤0.03	1
Imipenem		62.5	12.5	25	-	-	≤0.12	1	
Levofloxacin		100	0	0	-	-	≤0.06	1	
Linezolid		100	0	0	-	-	≤0.5	2	
Penicillin		50	37.5	12.5	-	-	≤0.06	4	
Vancomycin		100	0	0	-	-	≤0.12	1	

na = breakpoints not available.  
<sup>a</sup> Interpretive criteria as defined by CLSI M100-S16 (2006), where available; tigecycline susceptibility breakpoints are according to FDA package insert (Tygacil<sup>®</sup>, 2005), where available [9].  
<sup>b</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>c</sup> Includes 4 ESBL-producing *K. pneumoniae* strains.  
<sup>d</sup> Includes 3 penicillin-intermediate and 1 penicillin-resistant strains with tigecycline MICs of 0.06, 0.12, 0.5, and 0.015mcg/ml, respectively.

Table 2. In vitro activity of tigecycline and comparative agents against 59 respiratory isolates.

Organism Name	Drug	%SUS <sup>a</sup>	%INT	%RES	MIC (mcg/ml)		MIC range (mcg/ml)		
					MIC <sub>50</sub>	MIC <sub>90</sub>	Low	High	
<i>E. coli</i> , <i>K. pneumoniae</i> <sup>b</sup> (n=18)	Tigecycline	94.4	5.6	0	0.5	1	0.12	4	
	Amikacin	100	0	0	2	8	≤0.5	16	
	AmoxClav	94.4	5.6	0	4	8	1	16	
	Ampicillin	5.6	0	94.4	>32	>32	8	>32	
	Cefepime	100	0	0	≤0.5	2	≤0.5	4	
	Ceftazidime	94.4	0	5.6	≤8	≤8	≤8	>32	
	Ceftriaxone	88.9	5.6	5.6	≤0.06	32	≤0.06	64	
	Imipenem	100	0	0	0.5	2	0.25	2	
	Levofloxacin	100	0	0	0.03	1	0.015	1	
	Minocycline	61.1	16.7	22.2	4	16	1	>16	
	PipTazo	94.4	5.6	0	1	4	0.5	32	
	<i>Enterobacter</i> spp. <sup>b</sup> (n=5)	Tigecycline	100	0	0	-	-	0.25	1
		Amikacin	100	0	0	-	-	1	2
		AmoxClav	20	20	60	-	-	8	>32
		Ampicillin	0	0	100	-	-	32	>32
Cefepime		100	0	0	-	-	≤0.5	8	
Ceftazidime		40	0	60	-	-	≤8	>32	
Ceftriaxone		100	0	0	-	-	0.25	2	
Imipenem		100	0	0	-	-	0.5	1	
Levofloxacin		100	0	0	-	-	0.015	0.25	
Minocycline		100	0	0	-	-	4	4	
PipTazo	100	0	0	-	-	0.5	2		

## CONCLUSIONS

- Tigecycline MICs of ≤0.25mcg/ml against *S. aureus* (including MRSA) and 0.5mc