

# In Vitro Activity of Tigecycline Against 24,278 Pathogens Isolated from Common Body Sites and Tissues in North America

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## REVISED ABSTRACT

**Background:** Tigecycline, as a parenteral agent, exhibits linear pharmacokinetics, has a long terminal half-life and is extensively distributed into the tissues. The TEST program has surveyed a large number of isolates to determine the variability, if any, of tigecycline in vitro activity against clinical pathogens taken from various tissues and body sources. **Methods:** More than 24,000 clinically significant isolates from North American testing sites (Canada, Mexico and the United States) were analyzed. 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 uniform broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Tigecycline was the only study drug that demonstrated consistent activity against both Gram-negative and Gram-positive pathogens across all body sources, sites, and tissues. Summary data of tigecycline activity against selected pathogens and body sources are shown in the table below:

Organism	Tigecycline MIC <sub>90</sub> (n)			
	Blood	Genitourinary	Respiratory	Skin and Soft Tissues
<i>Acinetobacter</i> spp	1 (403)	1 (226)	2 (781)	1 (468)
<i>EcKpnKox</i> <sup>a</sup>	1 (2346)	1 (2636)	1 (1238)	1 (975)
All ESBLs	2 (92)	2 (103)	2 (97)	2 (50)
<i>Enterobacter</i> spp	2 (668)	2 (867)	2 (996)	1 (723)
<i>Enterococcus</i> spp	0.12 (866)	0.12 (810)	0.12 (81)	0.12 (561)
VREs	0.12 (205)	0.06 (121)	0.12 (9)	0.12 (112)
<i>S. aureus</i>	0.25 (814)	0.25 (141)	0.25 (803)	0.12 (1354)
MRSA	0.25 (413)	0.25 (83)	0.25 (491)	0.25 (732)
<i>S. pneumoniae</i>	0.5 (654)	0.5 (8)	0.25 (1305)	0.25 (24)
PRSP-SP	0.25 (52)	0.5 (1)	0.25 (164)	0.12 (2)

EcKpnKox = *E. coli*, *K. pneumoniae* and *K. oxytoca*.

**Conclusion:** Tigecycline showed excellent inhibitory activity against all groups of pathogens regardless of isolation site. Tigecycline's MIC<sub>90</sub> of  $\leq 0.12$  mcg/ml against Gram-positive pathogens (including resistant phenotypes) and MIC<sub>90</sub> of  $\leq 1$  mcg/ml against *Enterobacteriaceae* and *Acinetobacter* spp. validate the potent inhibitory activity of TIG against North American community/hospital pathogens.

## INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycoacyclines. This synthetic of tetracycline analogue has significant antibacterial activity that is bacteriostatic, but in certain instances is bactericidal with killing activity that is up to four times better than vancomycin and daptomycin [1, 2]. Tigecycline and other glycoacyclines are active against bacteria possessing 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]. Thus far, resistance to tigecycline is difficult to produce, even in the laboratory.

Many previous studies have demonstrated tigecycline's excellent in vitro activity against gram-positive and -negative bacteria with MIC<sub>90</sub>  $\leq 2$  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, part of the global Tigecycline Evaluation Surveillance Trial (TEST), was undertaken to document the in vitro activity of tigecycline against large numbers of clinical pathogens collected in North American laboratories.

## 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. More than 24,000 clinical isolates were collected and tested from 2004 through 2006 from 177 investigative sites in the U.S.A., Canada and Mexico. 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., 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); ceftriaxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16) or meropenem (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: ceftazidime (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.
- 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 49786; *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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The results are listed in the following table and figures.

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

Organism (n)	Drug	MIC (mg/ml)				Range
		MIC <sub>50</sub>	MIC <sub>90</sub>	Low	High %Sus <sup>a</sup>	
<i>Enterobacteriaceae</i> spp (865)	Tigecycline	0.12	0.12	0.12	0.12	0.008-0.5
	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
(impipenem n=181)	Impipenem	0.12	0.12	0.12	0.12	na
	Linezolid	0.5	0.5	0.5	0.5	na
	Meropenem	0.06	0.06	0.06	0.06	na
	Levofloxacin	0.06	0.06	0.06	0.06	na
	Vancomycin	0.12	0.12	0.12	0.12	na
(meropenem n=47)	Meropenem	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
	Levofloxacin	0.06	0.06	0.06	0.06	na
	Vancomycin	0.12	0.12	0.12	0.12	na
	PipTazo	0.12	0.12	0.12	0.12	na
<i>S. aureus</i> (814)	Tigecycline	0.12	0.12	0.12	0.12	0.008-0.5
	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
(impipenem n=79)	Impipenem	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
	Meropenem	0.06	0.06	0.06	0.06	na
	Levofloxacin	0.06	0.06	0.06	0.06	na
	Vancomycin	0.12	0.12	0.12	0.12	na
(meropenem n=23)	Meropenem	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
	Levofloxacin	0.06	0.06	0.06	0.06	na
	Vancomycin	0.12	0.12	0.12	0.12	na
	PipTazo	0.12	0.12	0.12	0.12	na
<i>S. pneumoniae</i> (44)	Tigecycline	0.12	0.12	0.12	0.12	0.008-0.5
	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
(impipenem n=17)	Impipenem	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
	Meropenem	0.06	0.06	0.06	0.06	na
	Levofloxacin	0.06	0.06	0.06	0.06	na
	Vancomycin	0.12	0.12	0.12	0.12	na
<i>S. pneumoniae</i> (17)	Tigecycline	0.12	0.12	0.12	0.12	0.008-0.5
	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
<i>S. pneumoniae</i> (17)	Tigecycline	0.12	0.12	0.12	0.12	0.008-0.5
	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
<i>Acinetobacter</i> spp (24)	Tigecycline	0.25	0.25	0.25	0.25	0.008-0.5
	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
<i>Acinetobacter</i> spp (24)	Tigecycline	0.25	0.25	0.25	0.25	0.008-0.5
	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
<i>Acinetobacter</i> spp (24)	Tigecycline	0.25	0.25	0.25	0.25	0.008-0.5
	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
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	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
<i>Acinetobacter</i> spp (24)	Tigecycline	0.25	0.25	0.25	0.25	0.008-0.5
	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
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	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
<i>Acinetobacter</i> spp (24)	Tigecycline	0.25	0.25	0.25	0.25	0.008-0.5
	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
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	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
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	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
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	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
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	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
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	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5	0.5	0.5	na
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	Amoxiclav	0.5	0.5	0.5	0.5	na
	Ampicillin	0.06	0.06	0.06	0.06	na
	Ceftazidime	0.06	0.06	0.06	0.06	na
	Linezolid	0.5	0.5			