

The Activity of Tigecycline and Comparators to Pathogens by Body Sites Collected in the U.S. (2004-2007)

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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 28,000 clinically significant isolates from 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*:

	Tigecycline MIC ₉₀ (n)			
	Blood	Genitourinary	Respiratory	Skin and Soft Tissues
<i>Acinetobacter</i> spp	1 (428)	1 (277)	2 (873)	1 (546)
EcoKpnKox*	1 (2684)	1 (2871)	1 (1431)	1 (1116)
All ESBLs	2 (110)	2 (110)	2 (113)	2 (55)
<i>Enterobacter</i> spp	2 (742)	2 (1009)	2 (1096)	1 (806)
<i>Enterococcus</i> spp	0.12 (958)	0.12 (678)	0.12 (56)	0.12 (658)
VREs	0.12 (228)	0.06 (134)	0.12 (9)	0.12 (125)
<i>S. aureus</i>	0.25 (927)	0.25 (162)	0.25 (1019)	0.12 (1598)
MRSA	0.25 (479)	0.25 (96)	0.25 (545)	0.25 (875)
<i>S. pneumoniae</i>	0.06 (755)	--	0.06 (1455)	0.06 (28)
PenR-SP	0.06 (73)	--	0.06 (211)	0.06 (2)

*EcoKpnKox = *E. coli*, *K. pneumoniae* and *K. oxytoca* combined.

Conclusion: Tigecycline showed excellent inhibitory activity against all groups of pathogens regardless of isolation site. Tigecycline MIC₉₀ of 0.25mcg/ml against gram positive pathogens (including resistant phenotypes) and MIC₉₀ of 2mcg/ml against *Enterobacteriaceae* and *Acinetobacter* spp. validate the potent inhibitory activity of TIG against community/hospital pathogens in the United States.

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycyclines. 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 it and other glycyclines 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 restored 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 90th 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 isolates collected from various body sites in the United States. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

MATERIALS & METHODS

- For the T.E.S.T program all isolates were derived from blood, respiratory tract, genitourinary (no more than 25% of all isolates), skin, wound, fluids, and other defined sources. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution. Only one isolate per patient was accepted.
- 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 [6]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers, MicroScan (Dade Behring Inc., West Sacramento, CA, USA) and Trek (TREK Diagnostic Systems, Cleveland, OH). The following antimicrobial agents and dilution ranges (expressed in mcg/mL) were included on the panels: tigecycline (0.008-16), imipenem (0.06-16), levofloxacin (0.008-8), minocycline (0.5-16), piperacillin/tazobactam (0.06/4-128/4), amikacin (0.5-32), ceftazidime (8-32), ceftriaxone (0.06-64) and cefepime (0.5-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [7], where applicable. There are currently no breakpoints defined for tigecycline against *Acinetobacter* species.
- Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftriaxone were >1 mcg/ml using broth microdilution panels. ESBL activity was confirmed using the CLSI (2005) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2005) 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 where applicable: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922 and 35218; *Haemophilus influenzae* ATCC 49247 and 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; *Pseudomonas aeruginosa* ATCC 27853 and *Klebsiella pneumoniae* ATCC 700603 (as positive ESBL control).
- Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2007) guidelines [8].

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RESULTS

The results are listed in the following table and figures.

Table 1. Comparative in vitro activity of tigecycline against selected clinical isolates with common resistant phenotypes collected from blood, genitourinary, respiratory and skin/soft tissue sources from centers in the United States.

Organism	Drug	MIC ₉₀ /MIC ₅₀ (%Sus)			
		Blood*	Genitourinary	Respiratory	Skin and Soft Tissues
<i>A. baumannii</i>					
Blood (344)	Tigecycline	0.12(100)	0.12(100)	0.12(100)	0.12(100)
Genitourinary (251)	Amoxiclav	4(3205.8)	4(3207.6)	4(481.2)	4(3285.2)
Respiratory (830)	Ceftriaxone	33(4435.8)	33(4435.8)	33(4435.8)	33(4435.8)
S&ST (476)	Imipenem	0.5(1697.1)	0.5(1685.2)	0.5(1685.5)	0.5(869.7)
<i>E. aerogenes</i>					
Blood (140)	Amoxiclav	2(499.3)	2(499.3)	2(410)	2(498.4)
Genitourinary (381)	Ampicillin	>32(320)	>32(320)	>32(320)	>32(320)
Respiratory (962)	Cefepime	<0.5(109)	<0.5(109.2)	<0.5(109.3)	<0.5(109.2)
S&ST (129)	Ceftriaxone	>32(327.2)	>32(327.2)	>32(327.2)	>32(327.2)
<i>E. faecalis</i>					
Blood (559)	Amoxiclav	>32(321.8)	>32(321.7)	>32(321.7)	>32(321.7)
Genitourinary (600)	Ceftriaxone	>32(321.4)	>32(321.4)	>32(321.4)	>32(321.4)
Respiratory (708)	Ceftriaxone	>32(321.4)	>32(321.4)	>32(321.4)	>32(321.4)
S&ST (650)	Imipenem	0.25(847.4)	0.25(847.4)	0.25(847.4)	0.25(847.4)
<i>E. coli</i>					
Blood (620)	Amoxiclav	1(3205.8)	1(3205.8)	1(3205.8)	1(3205.8)
Genitourinary (456)	Levofloxacin	2(209.4)	2(209.4)	2(209.4)	2(209.4)
Respiratory (43)	Imipenem	8(84.4)	8(84.4)	8(84.4)	8(84.4)
S&ST (491)	Penicillin	2(410)	2(410)	2(410)	2(410)
<i>E. faecium</i>					
Blood (100)	Tigecycline	0.03(12100)	0.03(12100)	0.03(12100)	0.03(12100)
Genitourinary (146)	Amoxiclav	>32(320.8)	>32(320.8)	>32(320.8)	>32(320.8)
Respiratory (13)	Levofloxacin	<0.25(875)	<0.25(875)	<0.25(875)	<0.25(875)
S&ST (134)	Penicillin	>32(320.8)	>32(320.8)	>32(320.8)	>32(320.8)
<i>H. influenzae</i>					
Blood (100)	Amoxiclav	0.12(25100)	0.12(25100)	0.12(25100)	0.12(25100)
Genitourinary (157)	Amoxiclav	2(1608.1)	2(1608.1)	2(1608.1)	2(1608.1)
Respiratory (1197)	Cefepime	<0.5(109.4)	<0.5(109.4)	<0.5(109.4)	<0.5(109.4)
S&ST (157)	Ceftriaxone	>32(320.8)	>32(320.8)	>32(320.8)	>32(320.8)
<i>K. pneumoniae</i>					
Blood (100)	Amoxiclav	2(1608.1)	2(1608.1)	2(1608.1)	2(1608.1)
Genitourinary (157)	Amoxiclav	2(1608.1)	2(1608.1)	2(1608.1)	2(1608.1)
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<i>S. aureus</i>					
Blood (100)	Amoxiclav	2(1608.1)	2(1608.1)	2(1608.1)	2(1608.1)
Genitourinary (157)	Amoxiclav	2(1608.1)	2(1608.1)	2(1608.1)	2(1608.1)
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