

# Susceptibility to Tigecycline of 23,125 Pathogens Isolated from Common Body Sites and Tissues in North America

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S. Bouchillon<sup>1</sup>, T. Stevens<sup>1</sup>, J. Johnson<sup>1</sup>, D. Hoban<sup>1</sup>, B. Johnson<sup>1</sup>, R. Badal<sup>1</sup>, M. Dowzicky<sup>2</sup>

<sup>1</sup>International Health Management Associates, Schaumburg, IL, USA  
<sup>2</sup>Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.  
2122 Palmer Dr.  
Schaumburg, IL 60173  
Tel: (847) 303-5003  
Fax: (847) 303-5601  
www.ihmainc.com

## 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 23,000 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	Respiratory	Skin and Soft Tissues
<i>Acinetobacter spp</i>	1 (304)	2 (647)	1 (361)
EcoKpnKox*	1 (1806)	1 (893)	1 (883)
All ESBLs	2 (70)	2 (85)	2 (47)
<i>Enterobacter spp</i>	2 (509)	2 (730)	1 (613)
<i>Enterococcus spp</i>	0.12 (678)	0.12 (41)	0.12 (439)
VREs	0.12 (159)	0.12 (7)	0.12 (79)
<i>S. aureus</i>	0.25 (710)	0.25 (759)	0.12 (1308)
MRSA	0.25 (358)	0.25 (421)	0.25 (705)
<i>S. pneumoniae</i>	0.5 (531)	0.5 (979)	1 (30)
PenR-SP	0.5 (51)	0.5 (134)	0.12 (3)

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

**Conclusion:** Tigecycline showed excellent inhibitory activity against all groups of pathogens regardless of isolation site. Tigecycline MIC<sub>90</sub> of  $\leq 1$  mcg/ml against gram-positive pathogens (including resistant phenotypes) and MIC<sub>90</sub> of  $\leq 2$  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 glycylicines. 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 glycylicines 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].

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 Italian laboratories. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

## 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 23,000 clinical isolates were collected and tested between 2004 to 2006 from 140 investigative sites in the US, 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., 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); ceftriaxone (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 ceftaxone 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), 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. *K. pneumoniae* ATCC 700793 was used to QC the ESBL confirmation test. *K. pneumoniae* ATCC 700603 was used to QC the ESBL confirmation tests.
- 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].

## REFERENCES

- Hoffman, D.B., et al. Antipneumococcal activities of GAR-936 (a new glycylicine) compared to those of nine other agents against penicillin-susceptible and -resistant pneumococci. *Antimicrob Agents Chemother*, 2000, 44(4): p. 1085-9.
- Litavskii, P., P.J. Petersen, and P.A. Bradford. In vitro activity of tigecycline against *Staphylococcus epidermidis* growing in an adherent-cell biofilm model. *Antimicrob Agents Chemother*, 2003, 47(12): p. 3867-9.
- Prasad, S.J. Preclinical pharmacology of GAR-936, a novel glycylicine antibacterial agent. *Pharmacotherapy*, 2000, 20(9 Pt 2): p. 2198-223S; discussion 224S-228S.
- Giles, A.C. and R.N. Jones. Antimicrobial activity and spectrum of the new glycylicine, GAR-936 tested against 1,203 recent clinical bacterial isolates. *Diagn Microbiol Infect Dis*, 2000, 36(1): p. 19-36.
- Patel, R., et al. In vitro activity of GAR-936 against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis*, 2000, 38(3): p. 177-9.
- Rupp, M.E. and P.D. Fey. Extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae: considerations for diagnosis, prevention and drug treatment. *Drugs*, 2003, 63(4): p. 353-65.
- CLSI. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, Approved Standard-Sixth Edition, in Document M7-A6. 2006. Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- CLSI. Performance Standards for Antimicrobial Susceptibility Testing, in Document M100-S15. 2006. Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- Tygacil. Product Insert. 2005. Wyeth Pharmaceuticals, Inc., Philadelphia, PA, USA.

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## RESULTS

Table 1. Comparative *in vitro* activity of tigecycline against 15,959\* selected clinical isolates collected from blood, respiratory and skin/soft tissue sources in North American centers.

Organism	Drug	Blood		Respiratory		Skin and Soft Tissues	
		%Sus*	MIC <sub>90</sub>	%Sus	MIC <sub>90</sub>	%Sus	MIC <sub>90</sub>
<i>A. baumannii</i>	Tigecycline	na	0.5/1	na	0.5/2	na	0.25/1
	Amikacin	83.4	4/32	79.1	234/68	84.5	117/80
	Resp, n= 247						
	Cefepime	48.6	16/32	39.4	16/32	51.1	8/32
	Ceftazidime	50.2	$\leq 8/32$	41.8	32/32	50.5	$\leq 8/32$
	Ceftriaxone	31.2	32/64	23.6	64/64	32.8	32/64
	Imipenem	86.2	0.5/8	87	0.5/8	86.6	0.5/8
	Levofloxacin	52.2	1/8	43.2	8/8	49.8	4/8
	PipTazo	56.7	8/128	53.9	16/128	61.1	8/128
	<i>E. aerogenes</i>	Tigecycline	95.3	0.5/1	93.5	0.5/2	95.5
Amikacin		99.1	2/4	100	387/52	98.2	2/4
Resp, n= 106							
AmoxClav		0	$> 32/32$	2.6	$> 32/32$	3.6	$> 32/32$
Cefepime		98.1	$\leq 0.5/1$	98.7	70.5/1	97.3	$\leq 0.5/2$
Ceftazidime		78.3	$\leq 8/32$	84.1	78/32	82.7	$\leq 8/32$
Ceftriaxone		90.6	0.12/8	93.1	0.12/8	95.5	0.12/8
Imipenem		100	0.5/1	100	1/1	100	1/2
Levofloxacin		93.4	0.06/0.5	94	0.06/0.5	95.5	0.06/0.5
PipTazo		85.8	2/32	88.8	90	2/32	2/32
<i>E. cloacae</i>	Tigecycline	92.1	0.5/2	92.9	0.5/2	94.1	0.5/2
	Amikacin	98.7	2/4	99.8	2/4	99	2/2
	Blood, n= 379						
	AmoxClav	1.8	$> 32/32$	2.1	$> 32/32$	1.2	$> 32/32$
	Cefepime	95.8	$\leq 0.5/4$	95.6	$\leq 0.5/4$	96.7	$\leq 0.5/4$
	Ceftazidime	71.2	$\leq 8/32$	70.5	$\leq 8/32$	77.8	$\leq 8/32$
	Ceftriaxone	74.9	0.5/64	74.5	0.25/64	82.5	0.25/32
	Imipenem	100	0.5/1	100	0.5/1	100	0.5/1
	Levofloxacin	90	0.03/4	91.3	0.03/2	91.8	0.03/1
	PipTazo	79.9	2/64	78.8	2/128	86.8	2/32
<i>E. faecalis</i>	Tigecycline	99.6	0.06/0.12	100	0.12/0.12	99.7	0.06/0.12
	Amikacin	100	1/1	100	1/1	100	1/1
	Blood, n= 452						
	Levofloxacin	50.7	2/32	62.1	1/32	57	1/32
	Linezolid	98.2	1/2	100	2/2	98.8	2/2
	Penicillin	100	2/4	100	2/4	100	2/4
	Vancocycin	94.5	1/2	96.6	1/2	95.1	1/2
	Tigecycline	100	0.06/0.12	100	0.03/0.06	99	0.06/0.12
	Ampicillin	13	$> 16/16$	0	$> 16/16$	14.4	$> 16/16$
	Resp, n= 12						
Levofloxacin	7.9	$> 32/32$	8.3	$> 32/32$	10.3	$> 32/32$	
Linezolid	98.6	2/2	91.7	387/19	94.8	2/2	
Penicillin	10.2	$> 8/8$	0	$> 8/8$	16.5	$> 8/8$	
Vancocycin	34.9	$> 32/32$	50	2/32	33	$> 32/32$	
<i>E. coli</i>	Tigecycline	99.4	0.12/0.25	100	0.12/0.25	99.2	0.12/0.25
	Amikacin	99.7	2/4	99.2	2/8	99.4	2/4
	Blood, n= 1047						
	AmoxClav	78.9	4/32	69.8	4/32	67.9	8/32
	Cefepime	97.7	$\leq 0.5/0.5$	97.1	$\leq 0.5/1$	97.7	$\leq 0.5/1$
	Ceftazidime	94.5	$\leq 8/8$	93.4	$\leq 8/8$	93.1	$\leq 8/8$
	Ceftriaxone	94.8	$\leq 0.06/0.25$	92.6	70.06/1	94.5	$\leq 0.06/2$
	Imipenem	99.9	0.25/0.5	100	0.25/0.5	100	0.25/0.5
	Levofloxacin	79.2	0.03/8	74.8	0.03/8	72.7	0.03/8
	PipTazo	96.7	1/4	93	1/4	95	1/4
<i>H. influenzae</i>	Tigecycline	na	0.12/0.25	na	0.12/0.5	na	0.12/0.5
	Amikacin	100	0.25/1	99.8	0.5/1	100	0.5/2
	Blood, n= 66						
	AmoxClav	78.8	$\leq 0.5/32$	71.8	$\leq 0.5/32$	50	1/32
	Cefepime	92.4	$\leq 0.5/0.5$	99	$\leq 0.5/0.5$	95.5	$\leq 0.5/1$
	Ceftazidime	100	$\leq 0.06/0.25$	99.8	$\leq 0.06/0.06$	100	$\leq 0.06/0.06$
	Ceftriaxone	100	0.5/1	100	0.5/1	100	0.5/1
	Imipenem	100	0.015/0.03	100	0.015/0.03	100	0.015/0.03
	Levofloxacin	100	$\leq 0.06/0.12$	99.9	$\leq 0.06/0.06$	100	$\leq 0.06/0.06$
	PipTazo	100	$\leq 0.06/0.12$	99.9	$\leq 0.06/0.06$	100	$\leq 0.06/0.06$
<i>K. oxytoca</i>	Tigecycline	99.1	0.25/1	96.7	0.25/1	99.1	0.25/1
	Amikacin	99.1	2/2	99.2	2/4	100	2/4
	Blood, n= 116						
	AmoxClav	88.8	2/16	78.3	2/32	92.5	2/8
	Cefepime	98.3	$\leq 0.5/1$	99.2	$\leq 0.5/2$	99.1	$\leq 0.5/0.5$
	Ceftazidime	92.2	$\leq 8/8$	91.7	$\leq 8/8$	96.2	$\leq 8/8$
	Ceftriaxone	96.6	$\leq 0.06/2$	91.7	$\leq 0.06/8$	97.2	$\leq 0.06/0.25$
	Imipenem	100	0.25/0.5	100	0.5/0.5	100	0.5/0.5
	Levofloxacin	94.8	0.03/0.5	95.8	0.03/1	96.2	0.03/0.25
	PipTazo	91.4	1/8	86.7	1/128	95.3	1/4
<i>K. pneumoniae</i>	Tigecycline	94.7	0.5/2	94	0.5/2	96.3	0.5/1
	Amikacin	98.9	1/4	96.6	2/8	96.3	2/4
	Blood, n= 643						
	AmoxClav	84.8	2/16	83.4	2/32	83.3	2/32
	Cefepime	96.3	$\leq 0.5/2$	91.1	$\leq 0.5/8$	94.7	$\leq 0.5/2$
	Ceftazidime	87.6	$\leq 8/32$	84.6	$\leq 8/32$	86.3	$\leq 8/32$
	Ceftriaxone	91.1	$\leq 0.06/8$	87.2	$\leq 0.06/32$	90.3	$\leq 0.06/8$
	Imipenem	99.1	0.25/0.5	97.3	0.5/1	98	0.5/0.5
	Levofloxacin	87.7	0.06/8	84.9	0.06/8	87.7	0.06/4
	PipTazo	92.2	2/16	87.4	2/128	88.7	2/64
<i>P. aeruginosa</i>	Tigecycline	na	8/16	na	8/16	na	8/16
	Amikacin	99.4	4/8	96.5	4/8	97.6	4/8
	Blood, n= 325						
	AmoxClav	77.2	4/32	73.7	8/32	84.1	4/16
	Cefepime	83.7	$\leq 8/32$	78.4	$\leq 8/32$	86.3	$\leq 8/16$
	Ceftazidime	17.5	32/64	17.4	64/64	17.3	32/64
	Ceftriaxone	83.4	1/8	80.5	1/16	88	1/8
	Imipenem	65.2	1/8	60.7	1/8	68.2	1/8
	Levofloxacin	87.4	4/128	87.7	4/128	92.4	4/64
	PipTazo	87.4	4/128	87.7	4/128	92.4	4/64
<i>S. marcescens</i>	Tigecycline	95.5	1/2	97.2	1/2	97.8	1/2
	Amikacin	100	2/4	99.6	2/4	100</	