

In Vitro Activity of Tigecycline and Commonly-Used Antimicrobials Against 1,559 Isolates Collected from 2004 to 2006 in Spain and Portugal

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R. Badal¹, S. Bouchillon¹, B. Johnson¹, T. Stevens¹, J. Johnson¹, D. Hoban¹, M. Dowzicky²

¹International Health Management Associates, Schaumburg, IL, USA
²Wyeth 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: Development of bacterial resistance continues to cause concern world-wide, but availability of newer agents offers clinicians options for therapy. Tigecycline (Tig) has a very broad spectrum of activity, including strains resistant to other drugs. As part of the global Tigecycline Evaluation Surveillance Trial, strains collected in Iberia from 2004 to 2006 were evaluated for susceptibility to several antimicrobials. **Methods:** Strains were collected and identified at 8 sites in Spain and Portugal. MICs were determined at each site using microdilution panels following CLSI guidelines. **Results:** The following table summarizes results for all isolates, and for specific key pathogens.

	MIC ₅₀			
	All gram pos	S. aureus	Enterococci	S. pneumoniae
	n=502	n=198	n=118	n=116
Amox/Clav	8	>8	>8	2
Ampicillin	>16	>16	>16	2
Ceftriaxone	>64	>64	>64	0.5
Imipenem	4	8	>16	0.5
Levofloxacin	16	8	>32	1
Linezolid	2	2	2	1
Minocycline	8	0.5	>8	4
Penicillin	>8	>8	>8	2
Pip/Tazo	>16	>16	>16	2
Tig	0.25	0.25	0.12	1
Vancomycin	1	2	2	0.5

	MIC ₅₀			
	All gram neg	E. coli/Klebs	Enterobacter	Acinetobacter
	n=1057	n=398	n=197	n=109
Amikacin	8	4	2	>64
Amox/Clav	>32	32	>32	>32
Ampicillin	>32	>32	>32	>32
Cefepime	16	4	2	32
Ceftazidime	32	>8	32	>32
Ceftriaxone	>64	16	32	>64
Imipenem	0.5	1	>16	>16
Levofloxacin	8	8	0.25	>8
Minocycline	16	8	4	16
Pip/Tazo	128	8	32	>128
Tig	4	0.5	1	1

Conclusion: Tig had the lowest MIC₅₀ vs. gram-positive strains (incl. MRSA, PRSP), and was essentially as active as imipenem vs. gram-negative strains (incl. ESBL+). It was also significantly more active than any comparators vs. enterococci and Acinetobacter.

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycylcyclines. 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 tetracycline and other glycylcyclines 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 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 pathogens collected in Spanish and Portuguese 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.

RESULTS

Table 1. In vitro activity of tigecycline and comparative agents against *Enterobacteriaceae*.^a

Organism Name	Drug	%SUS ^b	%INT	%RES	MIC (mcg/ml)		MIC range (mcg/ml)	
					MIC ₅₀	MIC ₉₀	Low	High
<i>E. coli</i> (n=202)	Tigecycline	100	0	0	0.12	0.25	0.03	1
	Amikacin	100	0	0	2	4	<0.5	16
	Amox/Clav	68.3	17.3	14.4	8	32	0.5	>32
	Ampicillin	24.3	0	75.7	>32	>32	<0.5	>32
	Cefepime	96	0.5	3.5	<0.5	2	<0.5	>32
	Ceftazidime	95	2.5	2.5	<8	<8	<8	>32
	Ceftriaxone	90.1	2	7.9	<0.06	8	<0.06	>64
	Imipenem	100	0	0	0.25	0.5	0.12	1
	Levofloxacin	70.8	8.4	20.8	0.03	>8	<0.008	>8
	Minocycline	90.6	5.4	4	1	4	<0.5	>16
Pip/Tazo	94.1	2	4	1	4	0.12	>128	
<i>Klebsiella</i> spp. (n=197)	Tigecycline	99	0.5	0.5	0.25	1	0.06	8
	Amikacin	99	1	0	2	4	<0.5	32
	Amox/Clav	80.7	10.7	8.6	2	16	0.5	>32
	Ampicillin	0	18.8	81.2	>32	>32	16	>32
	Cefepime	92.9	2	5.1	<0.5	4	<0.5	>32
	Ceftazidime	91.9	1	7.1	<8	<8	<8	>32
	Ceftriaxone	89.8	5.1	5.1	<0.06	16	<0.06	>64
	Imipenem	100	0	0	0.5	0.5	0.25	2
	Levofloxacin	94.4	3.6	2	0.06	0.5	<0.008	>8
	Minocycline	86.8	7.1	6.1	1	8	<0.5	>16
Pip/Tazo	89.8	2.5	7.6	1	64	0.12	>128	
All ESBL producers <i>E. coli</i> <i>K. pneumoniae</i> <i>K. oxytoca</i> (n=27)	Tigecycline	92.6	3.7	3.7	0.5	1	0.06	8
	Amikacin	96.3	3.7	0	4	16	<0.5	32
	Amox/Clav	48.1	40.7	11.1	16	32	0.5	32
	Ampicillin	3.7	0	96.3	>32	>32	1	>32
	Cefepime	44.4	11.1	44.4	16	>32	2	>32
	Ceftazidime	29.6	18.5	51.9	32	>32	<8	>32
	Ceftriaxone	22.2	29.6	48.1	32	>64	0.25	>64
	Imipenem	100	0	0	0.5	1	0.12	1
	Levofloxacin	55.6	14.8	29.6	0.5	>8	<0.008	>8
	Minocycline	74.1	7.4	18.5	2	>16	<0.5	>16
Pip/Tazo	85.2	7.4	7.4	2	64	0.5	>128	
<i>Enterobacter cloacae</i> (n=162)	Tigecycline	98.1	1.2	0.6	0.5	1	0.06	8
	Amikacin	100	0	0	1	2	<0.5	8
	Amox/Clav	0	1.2	98.8	>32	>32	16	>32
	Ampicillin	0	5.6	94.4	>32	>32	16	>32
	Cefepime	98.8	0	1.2	<0.5	2	<0.5	>32
	Ceftazidime	72.8	11.7	15.4	<8	32	<8	>32
	Ceftriaxone	77.8	16	6.2	0.25	32	<0.06	>64
	Imipenem	100	0	0	0.5	1	0.25	4
	Levofloxacin	96.9	2.5	0.6	0.03	0.12	0.015	>8
	Minocycline	96.9	0	3.1	2	4	<0.5	>16
Pip/Tazo	79.6	16	4.3	2	64	0.25	>128	
<i>E. aerogenes</i> (n=30)	Tigecycline	100	0	0	0.25	1	0.12	4
	Amikacin	100	0	0	2	4	1	4
	Amox/Clav	0	10	90	>32	>32	16	>32
	Ampicillin	0	10	90	>32	>32	16	>32
	Cefepime	100	0	0	<0.5	<0.5	<0.5	1
	Ceftazidime	86.7	3.3	10	<8	16	<8	32
	Ceftriaxone	96.7	0	3.3	0.12	4	<0.06	64
	Imipenem	100	0	0	1	2	0.25	2
	Levofloxacin	93.3	6.7	0	0.03	0.25	0.03	4
	Minocycline	100	0	0	<0.06	<0.06	<0.06	<0.06
Pip/Tazo	96.7	3.3	0	2	4	<0.5	8	
<i>Serratia</i> spp. (n=78)	Tigecycline	90	10	0	2	16	0.25	32
	Amikacin	100	0	0	2	4	<0.5	8
	Amox/Clav	2.6	2.6	94.9	>32	>32	2	>32
	Ampicillin	2.6	16.7	80.8	>32	>32	2	>32
	Cefepime	100	0	0	<0.5	<0.5	<0.5	4
	Ceftazidime	100	0	0	<8	<8	<8	<8
	Ceftriaxone	98.7	1.3	0	0.12	1	<0.06	16
	Imipenem	100	0	0	0.5	1	0.25	2
	Levofloxacin	98.7	1.3	0	0.06	0.5	<0.008	4
	Minocycline	96.2	3.8	0	2	4	<0.5	8
Pip/Tazo	98.7	1.3	0	1	8	0.12	64	

Table 2. In vitro activity of tigecycline and comparators against *Pseudomonas aeruginosa* and *Acinetobacter* spp.

Organism Name	Drug	%SUS ^b	%INT	%RES	MIC (mcg/ml)		MIC range (mcg/ml)	
					MIC ₅₀	MIC ₉₀	Low	High
<i>P. aeruginosa</i> (n=160)	Tigecycline	na	na	na	8	>16	0.06	>16
	Amikacin	97.5	2.5	0	4	8	<0.5	32
	Amox/Clav	na	na	na	>32	>32	0.5	>32
	Ampicillin	na	na	na	>32	>32	2	>32
	Cefepime	84.4	11.9	3.8	4	16	<0.5	>32
	Ceftazidime	76.3	16.3	7.5	<8	16	<8	>32
	Ceftriaxone	21.9	30	48.1	32	>64	0.12	>64
	Imipenem	83.1	11.3	5.6	1	8	0.25	>16
	Levofloxacin	73.1	3.8	23.1	1	>8	0.06	>8
	Minocycline	6.3	24.4	69.4	>16	>16	<0.5	>16
Pip/Tazo	91.3	0	8.8	4	32	0.12	>128	
<i>Acinetobacter</i> spp. (n=109)	Tigecycline	na	na	na	0.5	1	<0.008	4
	Amikacin	57.8	13.8	28.4	8	>64	<0.5	>64
	Amox/Clav	na	na	na	>32	>32	0.25	>32
	Ampicillin	na	na	na	>32	>32	<0.5	>32
	Cefepime	32.1	31.2	36.7	16	32	<0.5	>32
	Ceftazidime	27.5	10.1	62.4	32	>32	<8	>32
	Ceftriaxone	18.3	13.8	67.9	>64	>64	0.12	>64
	Imipenem	59.6	7.3	33	2	>16	<0.06	>16
	Levofloxacin	29.4	9.2	61.5	8	>8	0.015	>8
	Minocycline	63.3	25.7	11	1	16	<0.5	>16
Pip/Tazo	34.9	6.4	58.7	128	>128	<0.06	>128	

^aSpecies not tested are indicated by na. ^bSpecies not tested are indicated by na. MIC values are defined by CLSI M7-A6 (2006), when applicable. Species-specific breakpoints are according to FDA package insert (2005) when applicable (12). na = not available.

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 between 2004 to 2006 from 7 study centers in Spain and 1 in Portugal. 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 ceftriaxone 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.
- 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

- Hoellman, D.B., et al. Antipneumococcal activities of GAR-936 (a new glycylcycline) compared to those of nine other agents against penicillin-susceptible and -resistant pneumococci. *Antimicrob Agents Chemother*, 2000, 44(4): p. 1085-8.
- Labthavikul, 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. 3967-9.
- Projan, S.J., *Preclinical pharmacology of GAR-936, a novel glycylcycline antibacterial agent*. *Pharmacotherapy*, 2000, 20(9 Pt 2): p. 2195-223S; discussion 224S-228S.
- Gales, A.C. and R.N. Jones. *Antimicrobial activity and spectrum of the new glycylcycline, 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*