

In vitro Activity of Tigecycline and Comparators in Belgium from the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.)

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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 Belgium from 2004 to 2006 were evaluated for susceptibility to several antimicrobials. **Methods:** Strains were collected and identified at 4 sites in Belgium. MICs were determined at each site using custom broth microdilution panels following CLSI guidelines. **Results:** The following table summarizes results for all isolates, and for specific key pathogens.

Organism	MIC ₅₀			
	All gram pos	S. aureus	Enterococci	S. pneumoniae
Tigecycline	n=179	n=76	n=48	n=42
Amoxiclav	2	8	1	0.12
Ampicillin	>16	>16	2	0.5
Ceftriaxone	>64	32	>64	0.12
Imipenem	1	0.5	4	0.25
Levofloxacin	8	16	>32	1
Linezolid	4	4	2	1
Minocycline	>8	>8	>8	>8
Penicillin	>8	>8	4	>0.08
Pip/Tazo	8	16	8	0.5
Vancomycin	2	4	4	0.5

Organism	MIC Range (mcg/ml)			
	All gram pos	E. coli/Klebs	Enterobacter spp.	Acinetobacter
Tigecycline	n=359	n=141	n=86	n=36
Amoxiclav	8	8	8	>64
Ampicillin	>32	>32	>32	>32
Ceftriaxone	>32	>32	>32	>32
Cefepime	16	4	32	32
Ceftazidime	>32	>32	>32	>32
Ceftazidime	>64	16	>64	>64
Imipenem	2	0.5	2	2
Levofloxacin	>8	>8	>8	>8
Minocycline	>16	16	16	1
Pip/Tazo	84	64	64	>128

Conclusion: Tigecycline's consistently low MIC₅₀ values and broad spectrum of activity, including otherwise resistant strains, should make it a useful option for difficult-to-treat infections.

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycolcyclines. 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 glycolcyclines 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 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 Belgian 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. Clinical isolates were collected and tested between 2004 to 2006 from 4 study centers in Belgium. 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: 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. *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].

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RESULTS

Table 1. In vitro activity of tigecycline and comparative agents against 238 strains of *Enterobacteriaceae*.

Organism Name	Drug	%SUS ^a	%INT	%RES	MIC (mcg/ml)		MIC Range (mcg/ml)		
					MIC ₅₀	MIC ₉₀	Low	High	
<i>E. coli</i> (n=73)	Tigecycline	100	0	0	0.25	0.5	0.06	2	
	Amikacin	98.6	1.4	0	2	8	1	>32	
	AmoxClav	63	24.7	12.3	8	32	1	>32	
	Ampicillin	42.5	0	11	<0.5	>32	1	>32	
	Cefepime	89	0	11	<0.5	32	<0.5	>32	
	Ceftazidime	94.5	1.4	4.1	<0.5	<0.5	<0.5	>32	
	Ceftriaxone	86.3	1.4	12.3	<0.06	>64	<0.06	>64	
	Imipenem	100	0	0	0.5	0.5	0.25	0.5	
	Levofloxacin	75.3	5.5	19.2	0.03	>8	0.015	>8	
	Minocycline	82.2	9.6	8.2	1	8	<0.5	16	
	Pip/Tazo	94.5	4.1	1.4	1	8	0.25	128	
	<i>K. pneumoniae</i> (n=43)	Tigecycline	86	11.6	2.3	0.5	4	0.25	8
		Amikacin	100	0	0	1	8	<0.5	16
AmoxClav		81.4	4.7	14	4	32	2	>32	
Ampicillin		0	11.6	88.4	>32	>32	16	>32	
Cefepime		93	0	7	<0.5	4	<0.5	>32	
Ceftazidime		88.4	2.3	9.3	<0.5	16	<0.5	>32	
Ceftriaxone		90.7	4.7	4.7	<0.06	8	<0.06	>64	
Imipenem		100	0	0	0.5	0.5	0.25	2	
Levofloxacin		86	9.3	4.7	0.12	4	0.03	>8	
Minocycline		67.4	11.6	20.9	4	>16	<0.5	>16	
Pip/Tazo		88.4	2.3	9.3	2	64	0.5	>128	
<i>K. oxytoca</i> (n=25)		Tigecycline	100	0	0	0.5	1	0.12	1
		Amikacin	96	4	0	2	4	1	32
	AmoxClav	64	0	36	2	32	1	>32	
	Ampicillin	0	8	92	>32	>32	16	>32	
	Cefepime	100	0	0	<0.5	4	<0.5	8	
	Ceftazidime	96	0	4	<0.5	<0.5	<0.5	32	
	Ceftriaxone	88	12	0	<0.06	16	<0.06	16	
	Imipenem	100	0	0	0.5	1	0.25	1	
	Levofloxacin	96	0	4	0.03	1	0.015	>8	
	Minocycline	84	8	8	2	8	1	16	
	Pip/Tazo	64	0	36	1	>128	0.25	>128	
	All ESBL Producers	Tigecycline	92.3	0	7.7	0.5	2	0.12	8
		Amikacin	92.3	7.7	0	2	16	2	32
AmoxClav		23.1	38.5	38.5	16	32	8	32	
Ampicillin		0	0	100	>32	>32	>32	>32	
Cefepime		38.5	0	61.5	32	>32	<0.5	>32	
Ceftazidime		61.5	7.7	30.8	<0.5	<0.5	<0.5	>32	
Ceftriaxone		23.1	15.4	61.5	>64	>64	4	>64	
Imipenem		100	0	0	0.5	0.5	0.25	1	
Levofloxacin		53.8	7.7	38.5	2	>8	0.03	>8	
Minocycline		53.8	23.1	23.1	4	16	1	>16	
Pip/Tazo		84.6	0	15.4	2	128	0.5	>128	
<i>E. aerogenes</i> (n=31)		Tigecycline	93.5	6.5	0	0.5	2	0.06	4
		Amikacin	100	0	0	2	8	1	8
	AmoxClav	3.2	9.7	87.1	>32	>32	8	>32	
	Ampicillin	0	0	100	>32	>32	32	>32	
	Cefepime	80.6	6.5	12.9	1	32	<0.5	>32	
	Ceftazidime	29	16.1	54.8	>32	>32	<0.5	>32	
	Ceftriaxone	58.1	22.6	19.4	8	>64	<0.06	>64	
	Imipenem	100	0	0	1	4	0.5	4	
	Levofloxacin	25.8	6.5	67.7	>8	>8	0.03	>8	
	Minocycline	58.1	38.7	3.2	4	8	1	>16	
	Pip/Tazo	67.7	29	3.2	16	32	0.5	>128	
	<i>E. cloacae</i> (n=34)	Tigecycline	88.2	8.8	2.9	0.5	4	0.25	8
		Amikacin	100	0	0	2	8	1	8
AmoxClav		0	0	100	>32	>32	32	>32	
Ampicillin		0	8.8	91.2	>32	>32	16	>32	
Cefepime		91.2	0	8.8	<0.5	8	<0.5	>32	
Ceftazidime		73.5	0	26.5	<0.5	32	<0.5	>32	
Ceftriaxone		75.5	2.9	20.6	0.5	>64	<0.06	>64	
Imipenem		100	0	0	1	0.5	0.5	2	
Levofloxacin		91.2	2.9	5.9	0.06	2	0.015	>8	
Minocycline		73.5	8.8	17.6	4	>16	1	>16	
Pip/Tazo		70.6	17.6	11.8	2	128	0.5	>128	
<i>S. marcescens</i> (n=29)		Tigecycline	86.2	10.3	3.4	1	4	0.25	8
		Amikacin	86.2	10.3	3.4	4	32	1	64
	AmoxClav	3.4	0	96.6	>32	>32	8	>32	
	Ampicillin	0	3.4	96.6	>32	>32	16	>32	
	Cefepime	93.1	6.9	0	<0.5	8	<0.5	16	
	Ceftazidime	86.2	0	13.8	<0.5	>32	<0.5	>32	
	Ceftriaxone	75.9	17.2	6.9	0.5	32	0.12	>64	
	Imipenem	100	0	0	0.5	2	0.25	4	
	Levofloxacin	86.2	6.9	6.9	0.12	4	0.03	>8	
	Minocycline	72.4	10.3	17.2	4	16	<0.5	>16	
	Pip/Tazo	93.1	6.9	0	2	16	0.5	32	

Table 2. In vitro activity of tigecycline and comparative agents against 98 strains of *Acinetobacter* spp. and *P. aeruginosa*.

Organism Name	Drug	%SUS ^a	%INT	%RES	MIC (mcg/ml)		MIC Range (mcg/ml)		
					MIC ₅₀	MIC ₉₀	Low	High	
<i>Acinetobacter</i> spp. (n=36)	Tigecycline	na	na	na	0.25	1	0.03	2	
	Amikacin	83.3	2.8	13.9	2	>64	<0.5	>64	
	Cefepime	66.7	11.1	22.2	4	32	<0.5	>32	
	Ceftazidime	77.8	2.8	19.4	<0.5	>32	<0.5	>32	
	Ceftriaxone	52.8	25	22.2	8	>64	1	>64	
	Imipenem	94.4	0	5.6	0.5	2	0.25	>16	
	Levofloxacin	63.9	13.9	22.2	0.25	>8	0.06	>8	
	Minocycline	94.4	5.6	0	<0.5	1	<0.5	8	
	Pip/Tazo	77.8	11.1	11.1	0.5	>128	<0.06	>128	
	<i>P. aeruginosa</i> (n=62)	Tigecycline	na	na	na	16	>16	1	>16
		Amikacin	87.1	3.2	9.7</				