

In vitro Activity of Tigecycline and Commonly-Used Antimicrobials Against 549 Isolates Collected From 2004 to 2006 in Belgium

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#E-0734

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.

	All gram pos n=179	<i>S. aureus</i> n=76	<i>Enterococci</i> n=46	<i>S. pneumoniae</i> n=42
Tigecycline	0.5	0.25	0.25	0.12
Amox/Clav	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	0.5	>8	4
Penicillin	>8	>8	4	<0.06
Pip/Tazo	8	16	8	0.5
Vancomycin	2	1	4	0.5

	All gram neg n=369	<i>E. coli/Klebs</i> n=141	<i>Enterobacter</i> spp. n=66	<i>Acinetobacter</i> n=56
Tigecycline	8	1	2	>64
Amikacin	32	8	8	>64
Amox/Clav	>32	32	>32	>32
Ampicillin	>32	>32	>32	>32
Cefepime	16	4	32	>32
Ceftazidime	>32	>8	>32	>32
Ceftriaxone	>64	16	>64	>64
Imipenem	2	0.5	2	2
Levofloxacin	>8	8	>8	>8
Minocycline	>16	16	16	1
Pip/Tazo	64	64	64	>128

Conclusion: Tigecycline's consistently low MIC₉₀ 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 it has activity against bacteria harboring genes encoding either or both 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 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., 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 (0.12-8); 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 (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), 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 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 (2005) guidelines [8].

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ACKNOWLEDGEMENTS

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation Study Trials program group. This study was sponsored by a grant from Wyeth Pharmaceuticals.

The results are listed in the following tables:

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	
					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
	Amox/Clav	63	24.7	12.3	8	32	1	>32
	Ampicillin	42.5	0	57.5	>32	>32	1	>32
	Cefepime	89	0	11	<0.5	32	<0.5	>32
	Ceftazidime	94.5	1.4	4.1	<8	<8	<8	>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
	Amox/Clav	81.4	4.7	14.4	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	<8	16	<8	>32
	Ceftriaxone	90.7	4.7	4.7	<0.06	8	<0.06	>64
	Imipenem	100	0	0	0.5	0.5	0.25	0.5
	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
	Amox/Clav	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	<8	<8	<8	>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
<i>E. coli</i> , <i>K. pneumoniae</i> , <i>K. oxytoca</i> (n=13)	Amox/Clav	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	<8	>32	<8	>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
	Amox/Clav	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	<8	>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	87.7	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
	Amox/Clav	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	<8	>32	<8	>32
	Ceftriaxone	76.5	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
	Amox/Clav	3.4	0	20.6	>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	<8	>32	<8	>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

^aInterpretive criteria as defined by CLSI, M100-S16 (2006), where available; tigecycline susceptibility breakpoints are according to FDA package insert (Tygacil[®], 2005) [9].

RESULTS

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		MIC Range	
					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	<8	>32	<8	>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	4	32	<0.5	64
	Cefepime	62.9	29	8.1	8	16	1	>32
	Ceftazidime	74.2	12.9	12.9	<8	>32	<8	>32
	Ceftriaxone	14.5	24.2	61.3	64	>64	2	>64
	Imipenem	74.2	6.5	19.4	1	>16	0.5	>16
	Levofloxacin	64.5	12.9	22.6	1	>8	0.25	>8
	Minocycline	4.8	4.8	90.3	>16	>16	2	>16
	Pip/Tazo	87.1	0	12.9	8	128	0.25	>128

^aInterpretive criteria as defined by CLSI, M100-S16 (2006), where available; tigecycline susceptible breakpoint is according to FDA package insert (2005), where applicable [9]; na = not available – breakpoints are not yet established against this species.

Table 3. In vitro activity of tigecycline and comparative agents against respiratory pathogens.

Organism Name	Drug	%SUS ^a	%INT	%RES	MIC		MIC Range	
					MIC ₅₀	MIC ₉₀	Low	High
<i>S. pneumoniae</i> (n=42)	Tigecycline	na	na	na	0.25			