

A Multi-year Update of *In Vitro* Activity of Tigecycline and Commonly Used Antimicrobials Against Significant Clinical Isolates Collected from 2004 to 2008 in Belgium

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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 2008 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:

	<i>S. aureus</i> n=234	Enterococci n=147	<i>S. pneumo</i> n=116
Tigecycline	0.25	0.25	0.12
Amox/Clav	8	1	0.5
Ampicillin	>16	2	1
Ceftriaxone	32	>64	0.5
Imipenem	1	8	0.25
Levofloxacin	16	>32	1
Linezolid	4	2	1
Minocycline	0.5	>8	4
Penicillin	>8	8	1
Pip/Tazo	16	16	2
Vancomycin	1	2	0.5
	<i>E. coli/Kleb</i> n=484	<i>Enterobacter spp.</i> n=239	<i>Acinetobacter</i> n=134
Tigecycline	1	2	1
Amikacin	8	8	>64
Amox/Clav	32	>32	>32
Ampicillin	>32	>32	>32
Cefepime	4	4	>32
Ceftazidime	<8	>32	>32
Ceftriaxone	32	>64	>64
Imipenem	0.5	1	2
Levofloxacin	>8	>8	>8
Minocycline	16	16	2
Pip/Tazo	128	128	>128

Conclusions: 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 is a member of a new class of antimicrobial agents, the glycyclines. This synthetic analogue of the tetracyclines exhibits 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 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 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 mg/L, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum β -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 and 2008 from 20 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.
- MIC interpretive criteria followed published breakpoints established by EUCAST where applicable [10]; if no EUCAST guidelines were available for a given antimicrobial, CLSI breakpoints [8] were used or the recent US Food and Drug Administration package insert for tigecycline [9], where applicable.
- 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 mg/L): 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).
- Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftriaxone were >1 mg/L using broth microdilution panels. ESBL presence was confirmed using the CLSI (2009) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2009) 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 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 (2009) guidelines [8].

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Results

The results are listed in the following tables:

Table 1. *In vitro* activity of tigecycline and comparative agents against 815 strains of *Enterobacteriaceae*.

Organism Name	Drug	%SUS*	%INT	%RES	MIC (mg/L)			
					MIC ₅₀	MIC ₉₀	Low	High
<i>E. coli</i> (n=247)	Tigecycline	96.4	3.6	0.0	0.25	1	0.06	2
	Amikacin	98.8	0.8	0.4	2	8	<0.5	32
	Amox/Clav	40.1	26.3	33.6	8	32	1	>32
	Ampicillin	28.2	1.4	70.4	>32	>32	1	>32
	Cefepime	89.5	4.5	6.1	<0.5	2	<0.5	>32
	Ceftazidime	0.0	93.9	6.1	<8	<8	<8	>32
	Ceftriaxone	89.1	0.8	10.1	<0.06	4	<0.06	>64
	Imipenem	100.0	0.0	0.0	0.25	0.5	<0.06	0.5
	Levofloxacin	73.7	0.8	25.5	0.06	>8	<0.008	>8
	Minocycline	74.5	12.6	13.0	2	16	<0.5	>16
	Pip/Tazo	87.9	1.6	10.5	2	32	0.25	>128
<i>K. pneumoniae</i> (n=153)	Tigecycline	83.0	11.1	5.9	0.5	2	0.12	8
	Amikacin	94.1	3.9	2.0	1	8	<0.5	32
	Amox/Clav	60.1	12.4	27.5	4	32	1	>32
	Ampicillin	0.0	0.0	100.0	>32	>32	16	>32
	Cefepime	79.7	11.8	8.5	<0.5	8	<0.5	>32
	Ceftazidime	0.0	85.0	15.0	<8	32	<8	>32
	Ceftriaxone	79.1	0.7	20.3	<0.06	64	<0.06	>64
	Imipenem	100.0	0.0	0.0	0.25	0.5	<0.06	2
	Levofloxacin	81.0	2.6	16.3	0.06	8	0.015	>8
	Minocycline	69.3	12.4	18.3	2	16	<0.5	>16
	Pip/Tazo	75.8	5.9	18.3	2	128	0.25	>128
<i>K. oxytoca</i> (n=84)	Tigecycline	88.1	10.7	1.2	0.5	2	0.12	4
	Amikacin	95.2	2.4	2.4	2	4	<0.5	32
	Amox/Clav	56.0	9.5	34.5	4	>32	0.5	>32
	Ampicillin	0.0	0.0	100.0	>32	>32	16	>32
	Cefepime	70.2	21.4	8.3	<0.5	4	<0.5	>32
	Ceftazidime	0.0	94.0	6.0	<8	<8	<8	>32
	Ceftriaxone	69.0	0.0	31.0	<0.06	64	<0.06	>64
	Imipenem	97.8	2.2	0.0	0.25	0.5	<0.06	4
	Levofloxacin	77.4	7.1	15.5	0.06	8	0.015	>8
	Minocycline	81.0	11.9	7.1	2	8	<0.5	>16
	Pip/Tazo	63.1	2.4	34.5	2	>128	0.25	>128
All ESBL Producers	Tigecycline	76.1	17.4	6.5	0.5	2	0.12	8
Amikacin	84.8	6.5	8.7	4	16	1	32	
Amox/Clav	2.2	28.3	69.6	16	32	4	>32	
Ampicillin	0.0	0.0	100.0	>32	>32	>32	>32	
Cefepime	10.9	34.8	54.3	16	>32	<0.5	>32	
Ceftazidime	0.0	45.7	54.3	16	>32	<8	>32	
Ceftriaxone	6.5	2.2	91.3	>64	>64	0.25	>64	
Imipenem	96.8	3.2	0.0	0.25	0.5	<0.06	4	
Levofloxacin	39.1	2.2	58.7	4	>8	0.03	>8	
Minocycline	50.0	23.9	26.1	4	>16	<0.5	>16	
Pip/Tazo	56.5	8.7	34.8	8	>128	0.5	>128	
<i>E. aerogenes</i> (n=112)	Tigecycline	77.7	17.0	5.4	0.5	2	0.06	8
	Amikacin	95.5	2.7	1.8	2	8	<0.5	>64
	Amox/Clav	0.9	0.9	98.2	>32	>32	<0.12	>32
	Ampicillin	0.0	0.0	100.0	>32	>32	16	>32
	Cefepime	72.3	20.5	7.1	<0.5	4	<0.5	>32
	Ceftazidime	0.0	40.2	59.8	16	>32	<8	>32
	Ceftriaxone	33.9	7.1	58.9	4	>64	<0.06	>64
	Imipenem	91.7	8.3	0.0	0.5	2	<0.06	4
	Levofloxacin	34.8	4.5	60.7	8	>8	0.015	>8
	Minocycline	58.9	24.1	17.0	4	16	<0.5	>16
	Pip/Tazo	44.6	9.8	45.5	16	64	0.5	>128
<i>E. cloacae</i> (n=125)	Tigecycline	86.4	8.8	4.8	0.5	2	0.25	8
	Amikacin	97.6	2.4	0.0	2	8	1	16
	Amox/Clav	0.0	0.0	100.0	>32	>32	32	>32
	Ampicillin	0.0	0.0	100.0	>32	>32	16	>32
	Cefepime	74.4	20.8	4.8	<0.5	4	<0.5	>32
	Ceftazidime	0.0	72.8	27.2	<8	>32	<8	>32
	Ceftriaxone	62.4	3.2	34.4	0.5	>64	<0.06	>64
	Imipenem	100.0	0.0	0.0	0.5	1	<0.06	2
	Levofloxacin	80.8	6.4	12.8	0.06	8	0.015	>8
	Minocycline	75.2	15.2	9.6	4	8	1	>16
	Pip/Tazo	73.6	4.0	22.4	2	128	0.25	>128
<i>S. marcescens</i> (n=94)	Tigecycline	72.3	20.2	7.4	1	2	0.25	8
	Amikacin	94.7	0.0	5.3	2	8	1	>64
	Amox/Clav	0.0	1.1	98.9	>32	>32	8	>32
	Ampicillin	0.0	0.0	100.0	>32	>32	16	>32
	Cefepime	88.3	8.5	3.2	<0.5	2	<0.5	16
	Ceftazidime	0.0	93.6	6.4	<8	<8	<8	>32
	Ceftriaxone	78.7	4.3	17.0	0.25	16	<0.06	>64
	Imipenem	95.7	4.3	0.0	0.5	1	<0.06	4
	Levofloxacin	89.4	4.3	6.4	0.12	2	<0.008	>8
	Minocycline	62.8	25.5	11.7	4	16	<0.5	>16
	Pip/Tazo	90.4	4.3	5.3	2	8	0.5	>128

* Interpretive criteria as defined by EUCAST, where available; and CLSI breakpoints, where available, if no EUCAST breakpoints exist, na = not available.

Table 2. *In vitro* activity of tigecycline and comparative agents against 332 strains of *Acinetobacter* spp. and *P. aeruginosa*.

Organism Name	Drug	%SUS*	%INT	%RES	MIC (mg/L)			
					MIC ₅₀	MIC ₉₀	Low	High
<i>Acinetobacter</i> spp. (n=134)	Tigecycline	na	na	na	0.25	1	0.03	4
	Amikacin	73.9	6.7	19.4	4	>64	<0.5	>64
	Cefepime	64.9	14.2	20.9	8	>32	<0.5	>32
	Ceftazidime	64.9	6.7	28.4	<8	>32	<8	>32
	Ceftriaxone	34.3	35.1	30.6	16	>64	<0.06	>64
	Imipenem	90.8	6.2	3.1	0.5	2	<0.06	>16
	Levofloxacin	55.2	1.5	43.3	0.25	>8	0.03	>8
	Minocycline	95.5	4.5	0.0	<0.5	2	<0.5	8
	Pip/Tazo							