

The In Vitro Activity of Tigecycline Against Resistant Enterobacteriaceae Worldwide

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Revised Abstract

Objectives: Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent broad spectrum activity against most commonly encountered species responsible for hospital acquired infections. Cross-resistance to several classes of antimicrobials is often seen in nosocomial pathogens. The T.E.S.T. program determined the in vitro activity of tigecycline against strains of *Enterobacteriaceae* cross-resistant to one or more of the following antimicrobials: amoxicillin-clavulanic acid, piperacillin-tazobactam, levofloxacin, ceftriaxone, ceftazidime, ampicillin, amikacin, minocycline, ceftazidime and imipenem. The isolates were collected from 1,016 investigational sites in 53 countries throughout 2004-2008. **Methods:** A total of 51,976 clinical *Enterobacteriaceae* were identified to the species level at each site and confirmed by the central laboratory. Minimum Inhibitory Concentrations (MICs) were determined by the local laboratory using broth microdilution panels. Antimicrobial resistance was interpreted according to CLSI or FDA breakpoints, where available. **Results:** 3525/31562 (11.2%) *E. coli* and *Klebsiella spp* were ESBL producers. Of the *Enterobacteriaceae* presented, 15% were resistance to levofloxacin, 9.5% to minocycline, 1.5% to amikacin, 0.2% to imipenem, 1.4% to meropenem and 0.7% to tigecycline. Of the 17,114 *Enterobacter spp.* and *S. marcescens* collected, 1,269 (6.4%) presented resistance to ceftriaxone and ceftazidime but susceptible to ceftazidime suggestive of AmpC phenotype. Only 1554 (3.0%) of the *Enterobacteriaceae* showed any degree of non-susceptibility against tigecycline. Tigecycline also showed excellent inhibitory activity against members of *Enterobacteriaceae* that were resistant to amikacin, levofloxacin, minocycline and imipenem inhibiting 93%, 93%, 80% and 89% of isolates respectively. **Conclusions:** The presented data suggest that tigecycline is little affected by this cross-resistance phenomenon and may be an effective and reliable therapeutic option against nosocomial or community pathogens regardless of the resistance patterns.

Introduction

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycylcyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it is perceived to be bacteriostatic, it has shown some bactericidal activity against key targeted pathogens [1,2]. Tigecycline was developed to provide activity against tetracycline and multi-drug-resistant Gram-positive pathogens and has demonstrated significant broad-spectrum activity against aerobic and anaerobic Gram-positive and Gram-negative microorganisms [2-4].

Tigecycline resistance is very infrequent and is also difficult to induce in the laboratory [5, 6] with a selection frequency observed at less than 10⁻⁹ [3, 5, 7]. With the exception of *P. aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-4, 7-11]. Tigecycline has shown to be a highly effective against multi-resistant *Acinetobacter spp.*, particularly *A. baumannii* that are commonly associated with serious nosocomial infections. Similar activity has been observed against *Enterobacteriaceae*, even extended-spectrum β -lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC₉₀ values of \leq 0.5 mcg/mL against methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive organisms [2, 4-6]. Tigecycline has shown potent activity against animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4, 5] with diverse genotypes van-A, -B and -C [6].

This study was designed to better define the in vitro activity of tigecycline against *Enterobacteriaceae* clinical isolates with various resistant phenotypes collected from 1,016 study centers worldwide.

Materials & Methods

- 51,976 Clinical isolates of *Enterobacteriaceae* were collected tested between January 2004 – December 2008 from all study centers in 53 countries.
- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids and few other defined sources. Only one isolate per patient was accepted. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Custom broth microdilution panels were supplied by MicroScan (Dade MicroScan, Sacramento, CA, USA) and TREK (TREK Diagnostic Systems, West Sussex, England) with the following antimicrobial agents and concentrations (expressed in mcg/ml): amikacin (0.5-64); amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.5-32); ceftazidime (0.5-32); ceftriaxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16, MicroScan panels only); meropenem (0.06-16, MicroScan or TREK panels); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); and piperacillin/tazobactam (0.06/4-128/4).
- MIC interpretive criteria for all drugs except tigecycline followed published guidelines established by the CLSI where applicable [12]. MIC interpretive criteria for tigecycline followed criteria established by the Federal Drug Administration (FDA, United States, 2005) where applicable [13].
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *Escherichia coli* ATCC 25922; *Klebsiella pneumoniae* ATCC 700603 (positive ESBL control).
- The collection and transportation of organisms and the confirmation of identification, as well as, construction and management of a centralized database were conducted and coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA).

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Results

Results are contained in the following Tables.

Table 1. In vitro activity (mcg/mL and % susceptible) of tigecycline and comparative agents against 51,976 *Enterobacteriaceae* clinical isolates from a global population.

Organism	Drug	%Sus*	%Int	%Res	MIC (mcg/mL)	
					MIC ₅₀	MIC ₉₀
Enterobacteriaceae (n=51,976)	Tigecycline	96.9	2.3	0.7	0.5	1
	Amikacin	97.4	1.1	1.5	2	8
	AmoxClav	45.7	8.7	45.6	16	>32
	Ampicillin	13.4	6.5	80.1	>32	>32
	Cefepime	92.1	1.9	6	\leq 0.5	8
	Ceftazidime	83.9	3.5	12.5	\leq 8	32
	Ceftriaxone	83.6	5	11.4	0.12	64
	Imipenem	99.6	0.1	0.2	0.25	1
	Meropenem	98.1	0.5	1.4	\leq 0.06	0.25
	Levofloxacin	82.6	2.5	15	0.06	>8
	Minocycline	81.8	8.6	9.5	2	8
	PipTazo	87.1	5.6	7.3	2	32

* Susceptibilities are defined in CLSI document M100-S18 (2008) where applicable. Tigecycline breakpoints are defined in FDA package insert (Tygacil®, 2005).

Table 2. In vitro activity (mcg/mL and % susceptibility) of tigecycline and comparative agents against clinical isolates of *Enterobacteriaceae* with specific resistant phenotypes.

Resistant Phenotype	Drug	%Sus*	%Int	%Res	MIC (mcg/mL)	
					MIC ₅₀	MIC ₉₀
Aminoglycoside-Resistant †	Tigecycline	93.0	4.8	2.2	0.5	2
	Amikacin	0	0	100	>64	>64
Enterobacteriaceae (n=913)	AmoxClav	8.4	14.2	77.5	>32	>32
	Ampicillin	1.2	0.4	98.4	>32	>32
	Cefepime	27.8	9.4	62.8	32	>32
	Ceftazidime	23.9	9.7	66.4	>32	>32
	Ceftriaxone	11.3	10	78.7	>64	>64
	Imipenem	97.5	0.4	2.1	0.5	2
	Levofloxacin	32.4	8.4	59.3	8	>8
	Meropenem	80.2	8.2	11.6	0.25	16
	Minocycline	45.8	17.6	36.6	8	>16
	PipTazo	39.0	15.2	45.8	64	>128
Fluoroquinolone-Resistant †	Tigecycline	93.2	5	1.8	0.5	2
	Amikacin	89.7	4.3	6	4	32
	AmoxClav	28.2	23.6	48.2	16	>32
	Ampicillin	4.5	0.6	94.9	>32	>32
	Cefepime	66.2	6.7	27.1	2	>32
	Ceftazidime	53.4	8.3	38.2	\leq 8	>32
	Ceftriaxone	47.4	10	42.6	16	>64
	Imipenem	98.6	0.6	0.8	0.25	1
	Levofloxacin	0	0	100	>8	>8
	Meropenem	91.5	2	6.5	\leq 0.06	2
AmpC Producing †	Tigecycline	88.6	7.6	3.8	0.5	4
	Amikacin	94.9	2.1	3.0	2	16
	AmoxClav	0.6	1.1	98.3	>32	>32
	Ampicillin	0	0	100	>32	>32
	Cefepime	100	0	0	4	8
	Ceftazidime	0	0	100	>32	>32
	Ceftriaxone	0	0	100	64	>64
	Imipenem	99.7	0.2	0.2	0.5	1
	Levofloxacin	65.2	5.8	29.0	0.5	>8
	Meropenem	98.6	0.9	0.5	0.12	0.5
ESBL+ Producing	Tigecycline	95.2	3.4	1.4	0.5	2
	Amikacin	86.4	6.9	6.8	4	32
	AmoxClav	24	34.1	41.9	16	>32
	Ampicillin	0.5	0.2	99.3	>32	>32
	Cefepime	39.7	10.8	49.5	16	>32
	Ceftazidime	28.5	13.9	57.6	32	>32
	Ceftriaxone	14	15.2	70.7	>64	>64
	Imipenem	98.2	1	0.8	0.25	1
	Levofloxacin	29.7	6.9	63.4	8	>8
	Meropenem	91.5	1.9	6.6	\leq 0.06	2
Carbapenem †	Tigecycline	89.2	7.9	2.9	1	4
	Amikacin	60.8	20.7	18.5	16	>64
	AmoxClav	1.1	1.8	97.1	>32	>32
	Ampicillin	0.4	0.2	99.3	>32	>32
	Cefepime	17.2	9	73.8	>32	>32
	Ceftazidime	12.8	5.9	81.3	>32	>32
	Ceftriaxone	11	8.8	80.2	>64	>64
	Imipenem	0	40.7	59.3	16	>16
	Levofloxacin	23.8	5.1	71.1	>8	>8
	Meropenem	0	26.7	73.3	16	>16
Non-Susceptible	Tigecycline	54.2	19.4	26.4	4	>16
	Amikacin	13.7	7.7	78.6	>128	>128
	AmoxClav	0	0	100	>32	>32
	Ampicillin	0	0	100	>32	>32
	Cefepime	17.2	9	73.8	>32	>32
	Ceftazidime	12.8	5.9	81.3	>32	>32
	Ceftriaxone	11	8.8	80.2	>64	>64
	Imipenem	0	40.7	59.3	16	>16
	Levofloxacin	23.8	5.1	71.1	>8	>8
	Meropenem	0	26.7	73.3	16	>16
Extended-spectrum beta-lactamase producing	Tigecycline	88.6	7.6	3.8	0.5	4
	Amikacin	94.9	2.1	3.0	2	16
	AmoxClav	0.6	1.1	98.3	>32	>32
	Ampicillin	0	0	100	>32	>32
	Cefepime	100	0	0	4	8
	Ceftazidime	0	0	100	>32	>32
	Ceftriaxone	0	0	100	64	>64
	Imipenem	99.7	0.2	0.2	0.5	1
	Levofloxacin	65.2	5.8	29.0	0.5	>8
	Meropenem	98.6	0.9	0.5	0.12	0.5
Non-susceptible to either imipenem or meropenem	Tigecycline	88.6	7.6	3.8	0.5	4
	Amikacin	94.9	2.1	3.0	2	16
	AmoxClav	0.6	1.1	98.3	>32	>32
	Ampicillin	0	0	100	>32	>32
	Cefepime	100	0	0	4	8
	Ceftazidime	0	0	100	>32	>32
	Ceftriaxone	0	0	100	64	>64
	Imipenem	99.7	0.2	0.2	0.5	1
	Levofloxacin	65.2	5.8	29.0	0.5	>8
	Meropenem	98.6	0.9	0.5	0.12	0.5

* Susceptibilities are defined in CLSI document M100-S18 (2008) where applicable. Tigecycline breakpoints are defined in FDA package insert (Tygacil®, 2005).
 † Resistant to amikacin.
 ‡ Resistant to levofloxacin.
 § Resistant to both ceftazidime and ceftriaxone, and susceptible to ceftazidime.
 ¶ Extended-spectrum beta-lactamase producing isolates.
 †† Non-susceptible to either imipenem or meropenem.

Conclusions

- Tigecycline inhibited 96.9% of all *Enterobacteriaceae* at its FDA susceptible breakpoint of 2 mcg/mL. Tigecycline in vitro activity against the clinical *Enterobacteriaceae* pathogens in this study was considered equivalent to amikacin, ceftazidime, imipenem and meropenem and more potent than amoxicillin-clavulanic acid, ampicillin, ceftazidime, ceftriaxone, levofloxacin, minocycline and piperacillin-tazobactam.
- Tigecycline demonstrated potent in vitro activity against aminoglycoside-resistant strains, fluoroquinolone-resistant strains and both AmpC and ESBL producing *Enterobacteriaceae*. More than 89% of carbapenem non-susceptible (either imipenem or meropenem) *Enterobacteriaceae* were susceptible to tigecycline.
- Tigecycline demonstrated continuing potent in vitro activity during the surveillance years 2004 through 2008 of commonly encountered resistant mechanisms within clinical isolates of *Enterobacteriaceae*.