

Tigecycline and Comparators Susceptibility Against Enterobacteriaceae of Various Resistant Phenotypes Globally

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REVISED ABSTRACT

Background: Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent expanded broad spectrum activity against most commonly encountered species responsible for community and hospital acquired infections including GN, GP, Anaerobic and resistant strains. The T.E.S.T. program determined the in vitro activity of tigecycline compared to amoxicillin-clavulanic acid, piperacillin-tazobactam, levofloxacin, ceftriaxone, cefepime, ampicillin, amikacin, minocycline, ceftazidime and imipenem against *Enterobacteriaceae* species collected from 272 hospitals globally throughout 2004-2006. The objective of this study was to evaluate the activity of tigecycline against resistant *Enterobacteriaceae* phenotypes commonly associated with clinical infections. **Methods:** A total of 16,512 clinical *Enterobacteriaceae* were identified to the species level at each site and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. Tigecycline susceptible breakpoint was defined as ≤ 2 mcg/mL according to FDA package insert. **Results:** Various resistance patterns and phenotypes were detected among *Enterobacteriaceae* sampled in this study. As shown in the table below, tigecycline presented excellent inhibitory activity against all resistance phenotypes encountered.

Phenotype	Tigecycline	
	%Sus	MIC ₉₀
ESBL producing <i>E. coli</i> and <i>Klebsiella</i> (n=996)	94.7	2
AmpC producing <i>Enterobacter</i> and <i>Serratia</i> (n=489)	84.1	4
Fluoroquinolone resistant <i>Enterobacteriaceae</i> (n=1,791)	88.1	4
Aminoglycoside resistant <i>Enterobacteriaceae</i> (n=173)	96	2

Conclusion: Multi-drug resistance is often seen in health care acquired pathogens. The presented data suggest that tigecycline is highly potent against nosocomial or community pathogens regardless to 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, its anti-bacterial activity is significant and 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 beta-lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC₉₀ values of <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 272 study centers worldwide.

MATERIALS & METHODS

- 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.
- Clinical isolates (n=16,512) of *Enterobacteriaceae* were collected tested between January 2004 - December 2006 from 272 study centers in 34 countries.
- Custom broth microdilution panels were supplied by MicroScan (Dade MicroScan, Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/mL): amoxicillin/clavulanic acid (0.03-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-32); ceftriaxone (0.03-64); cefepime (0.5-32); ampicillin (0.06-32); amikacin (0.5-64); minocycline (0.25-16); ceftazidime (8-32); tigecycline (0.008-16); and imipenem (0.06-16).
- MIC interpretive criteria followed published guidelines established by the CLSI where applicable [12]. MIC interpretive criteria for Tigecycline followed published guidelines established by the FDA where applicable [13].
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; and *Klebsiella pneumoniae* ATCC 700603.
- 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

The results are listed in the following tables.

Table 1. In vitro activity (mcg/mL and % susceptible) 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 ^a <i>Enterobacteriaceae</i> (n=173)	Tigecycline	96	4	0	0.5	2
	Amikacin	0	0	100	>64	>64
	AmoxClav	8.1	13.9	78	32	>32
	Ampicillin	0	0	100	>32	>32
	Cefepime	29.5	10.4	60.1	32	>32
	Ceftazidime	26	8.7	65.3	>32	>32
	Ceftriaxone	9.8	9.2	80.9	>64	>64
	Imipenem	99.4	0.6	0	0.5	1
	Levofloxacin	35.3	9.2	55.5	8	>8
	Minocycline	56.6	12.7	30.6	4	>16
PipTazo	42.8	23.1	34.1	32	>128	
Fluoroquinolone -Resistant ^b <i>Enterobacteriaceae</i> (n=1,791)	Tigecycline	88.1	8.8	3.1	0.5	4
	Amikacin	90.7	4	5.4	4	16
	AmoxClav	12.4	18.3	69.3	32	>32
	Ampicillin	0.1	0.1	99.8	>32	>32
	Cefepime	60.4	10.4	29.3	8	>32
	Ceftazidime	34.8	9.5	55.7	32	>32
	Ceftriaxone	33.3	15.8	50.9	64	>64
	Imipenem	99.2	0.4	0.4	0.5	1
	Levofloxacin	0	0	100	>8	>8
	Minocycline	47.1	18.4	34.6	8	>16
PipTazo	50.6	18.3	31	16	>128	
AmpC Producing ^c <i>Enterobacter</i> and <i>Serratia</i> (n=489)	Tigecycline	84.1	9.6	6.3	0.5	4
	Amikacin	96.9	1	2	2	8
	AmoxClav	1	0.6	98.4	>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	100	0	0	0.5	1
	Levofloxacin	66.3	7	26.8	0.5	>8
	Minocycline	62.6	16.8	20.7	4	>16
PipTazo	10	40.1	49.9	64	>128	
ESBL Producing ^d <i>E. coli</i> and <i>Klebsiella</i> (n=996)	Tigecycline	94.7	3.9	1.4	0.5	2
	Amikacin	88.4	6.1	5.5	4	32
	AmoxClav	25.6	31.2	43.2	16	>32
	Ampicillin	0.7	0.3	99	>32	>32
	Cefepime	46.6	10.4	43	16	>32
	Ceftazidime	21.4	12.2	66.4	>32	>32
	Ceftriaxone	19.4	18.3	62.3	>64	>64
	Imipenem	98.8	0.5	0.7	0.5	1
	Levofloxacin	34.5	7.5	57.9	8	>8
	Minocycline	65.2	12.9	22	4	>16
PipTazo	61.1	12.7	26.2	8	>128	

* Susceptibilities are defined in CLSI document M100-S16 (2006) where applicable. Tigecycline breakpoints are defined in FDA package insert (Tygacil®, 2005).

^a Resistant to amikacin.

^b Resistant to levofloxacin.

^c Resistant to ceftazidime and ceftriaxone and susceptible to cefepime.

^d Extended-Spectrum Beta-Lactamase producing isolates.

Table 1. In vitro activity (mcg/mL and % susceptible) of tigecycline and comparative agents against 16,512 *Enterobacteriaceae* clinical isolates.

Organism	Drug	%Sus*	%Int	%Res	MIC (mcg/mL)	
					MIC ₅₀	MIC ₉₀
<i>Enterobacteriaceae</i> (n=16,512)	Tigecycline	96.5	2.7	0.9	0.5	1
	Amikacin	98.4	0.9	0.7	2	4
	AmoxClav	48	7.1	44.9	16	>32
	Ampicillin	13.7	6.9	79.4	>32	>32
	Cefepime	94.3	1.6	4.1	≤ 0.5	4
	Ceftazidime	85.2	3.1	11.7	≤ 8	32
	Ceftriaxone	86.4	5	8.6	0.12	32
	Imipenem	99.8	0.1	0.1	0.5	1
	Levofloxacin	85.2	2.5	12.4	0.06	8
	Minocycline	84.9	7.7	7.4	2	8
PipTazo	89	5	6	1	32	

* Susceptibilities are defined in CLSI document M100-S16 (2006) where applicable. Tigecycline breakpoints are defined in FDA package insert (Tygacil®, 2005).

CONCLUSIONS

➤ Tigecycline inhibited 96.5% 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, cefepime and imipenem and more potent than 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*.

➤ Tigecycline demonstrated continuing potent in vitro activity against commonly encountered resistant mechanisms within clinical isolates of *Enterobacteriaceae* during the surveillance years 2004 through 2006.