

Activity of Tigecycline Against Antibiotic Resistant Clinical Isolates of *Enterobacteriaceae* from the United States - The T.E.S.T. Program

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REVISED ABSTRACT

Background: Tigecycline (TIG), 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. 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* resistant to one or more of the following antimicrobials: amoxicillin-clavulanic acid(AC), piperacillin-tazobactam(PT), levofloxacin(LV), ceftriaxone(CX), cefepime(CP), ampicillin (AMP), amikacin(AK), minocycline(MN), ceftazidime(CZ) and imipenem(IMP). The isolates were collected from 137 investigational sites in the United States during 2004-2006.

Methods: A total of 13,151 clinical isolates of *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 laboratories using broth microdilution panels. Antimicrobial resistance was interpreted according to CLSI breakpoints with TIG susceptible and resistant breakpoints defined as ≤ 2 mcg/ml and >8 mcg/ml, respectively. **Results:** Most *Enterobacteriaceae* were resistant to one or more drugs. 1% were resistant to TIG (MIC ≥ 8), compared to AMP 78%, AC 43%, CZ 9.4%, LV 11.3%, MN 6.9%, CX 5.1%, PT 4.3%, CP 1.9%, AK 0.2%, IMP 0.1%, and MER 0%. 250 strains presented phenotypes suggestive of the AmpC phenotype, of which 80.4% were susceptible and 10.0% intermediate to TIG, with an MIC₉₀ of 4 mcg/ml. TIG also showed excellent inhibitory activity against strains resistant to AK, LV, and IMP inhibiting 95.8%, 90.8%, 100%, respectively, of these isolates. **Conclusion:** These data suggest that TIG is little affected by resistance to other antimicrobials, and may be an effective and reliable therapeutic option against nosocomial or community enteric pathogens regardless of their 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 antibiotic-resistant *Enterobacteriaceae* isolates collected from study centers across the United States.

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.
- 13,151 clinical *Enterobacteriaceae* isolates from 137 centers in the United States were collected and tested from 2004 through 2006.
- 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 (0.12-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftriaxone (0.06-64); cefepime (0.5-32); ampicillin (0.5-32); amikacin (0.5-64); minocycline (0.5-16); ceftazidime (8-32); tigecycline (0.008-16); and imipenem (0.06-16) or meropenem (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: *Escherichia coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *K. 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 of tigecycline against 13,151 *Enterobacteriaceae* in the United States.

Organism	Drug	%Sus ¹	%Int	%Res	MIC (mcg/ml)	
					MIC ₅₀	MIC ₉₀
All <i>Enterobacteriaceae</i> (n=13,151)	Tigecycline	96.5	2.5	1	0.5	1
	Amikacin	99.3	0.5	0.2	2	4
	AmoxClav	50.6	6.4	43	8	>32
	Ampicillin	15.1	6.9	78	>32	>32
	Cefepime	97.1	1	1.9	≤ 0.5	2
	Ceftazidime	88.1	2.5	9.4	≤ 8	16
	Ceftriaxone	90.5	4.4	5.1	≤ 0.06	8
	Imipenem (12,098) ^a	99.9	0	0.1	0.5	1
	Levofloxacin	86.8	1.9	11.3	0.06	8
	Meropenem (1,053) ^a	100	0	0	≤ 0.06	0.25
	Minocycline	86.4	6.7	6.9	2	8
	PipTazo	91.7	4	4.3	1	16

¹ Interpretive criteria are defined by CLSI, M100-S16 (2006) and FDA package insert (Tygacil[®], 2005). ^a Meropenem was substituted for imipenem late in the study.

Table 2. In vitro activity of tigecycline against 354 ESBL-producing *Enterobacteriaceae*.

Organism	Drug	%Sus ¹	%Int	%Res	MIC (mcg/ml)	
					MIC ₅₀	MIC ₉₀
ESBL-producing <i>E. coli</i>	Tigecycline	93.2	4.8	2	0.5	2
	Amikacin	90.4	8.5	1.1	4	16
<i>K. pneumoniae</i>	AmoxClav	34.2	26.8	39	16	>32
<i>K. oxytoca</i> (n=354)	Ampicillin	1.1	0.6	98.3	>32	>32
	Cefepime	55.9	9	35	8	>32
	Ceftazidime	11.3	9	79.7	>32	>32
	Ceftriaxone	25.1	24.9	50	32	>64
	Imipenem (332) ^a	96.4	1.5	2.1	0.25	2
	Meropenem (22) ^a	100	0	0	≤ 0.06	0.25
	Levofloxacin	22.6	7.1	70.3	>8	>8
	Minocycline	67.2	10.7	22	4	>16
	PipTazo	56.8	8.5	34.7	16	>128

¹ Interpretive criteria are defined by CLSI, M100-S16 (2006) and FDA package insert (Tygacil[®], 2005). ^a Meropenem was substituted for imipenem late in the study.

Table 3. In vitro activity of tigecycline against 250 AmpC-producing *Enterobacteriaceae*.

Organism	Drug	%Sus ¹	%Int	%Res	MIC (mcg/ml)	
					MIC ₅₀	MIC ₉₀
AmpC producing <i>Enterobacter</i> spp.,	Tigecycline	80.4	10	9.6	0.5	4
	Amikacin	99.2	0.8	0	2	4
<i>S. marcescens</i> (n=250)	AmoxClav	0.4	0.8	98.8	>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 (233) ^a	100	0	0	0.5	1
	Meropenem (17) ^a	100	0	0	0.25	0.5
	Levofloxacin	71.6	8.4	20	0.25	>8
	Minocycline	64	11.2	24.8	4	>16
	PipTazo	10.4	42.4	47.2	64	>128

¹ Interpretive criteria are defined by CLSI, M100-S16 (2006) and FDA package insert (Tygacil[®], 2005). ^a Meropenem was substituted for imipenem late in the study.

Table 4. In vitro activity of tigecycline against other resistant phenotypes of *Enterobacteriaceae*.

Organism	Drug	%Sus ¹	%Int	%Res	MIC (mcg/ml)	
					MIC ₅₀	MIC ₉₀
Amikacin-Resistant <i>Enterobacteriaceae</i> (n=24)	Tigecycline	95.8	4.2	0	0.5	2
	Amikacin	0	0	100	>64	>64
	AmoxClav	25	4.2	70.8	32	>32
	Ampicillin	4.2	0	95.8	>32	>32
	Cefepime	58.3	8.3	33.3	4	>32
	Ceftazidime	37.5	25	37.5	16	>32
	Ceftriaxone	45.8	29.2	25	16	>64
	Imipenem (21) ^a	100	0	0	0.5	1
	Meropenem (3) ^a	100	0	0	0.25	4
	Levofloxacin	58.3	4.2	37.5	1	>8
	Minocycline	70.8	8.3	20.8	4	>16
	PipTazo	62.5	8.3	29.2	4	>128
Imipenem-Resistant <i>Enterobacteriaceae</i> (n=7)	Tigecycline	100	0	0	1	2
	Amikacin	42.9	57.1	0	32	32
	AmoxClav	0	0	100	>32	>32
	Ampicillin	0	0	100	>32	>32
	Cefepime	0	0	100	>32	>32
	Ceftazidime	0	0	100	>32	>32
	Ceftriaxone	0	0	100	>64	>64
	Imipenem	0	0	100	16	>16
	Levofloxacin	0	0	100	>8	>8
	Minocycline	71.4	28.6	0	4	8
	PipTazo	0	0	100	>128	>128
Levofloxacin-Resistant <i>Enterobacteriaceae</i> (n=1,486)	Tigecycline	90.8	6.3	2.8	0.25	2
	Amikacin	96	3.4	0.6	2	16
	AmoxClav	39.6	19.4	41	16	>32
	Ampicillin	6	0.8	93.2	>32	>32
	Cefepime	82.4	5.5	12.1	≤ 0.5	32
	Ceftazidime	61.9	5.7	32.4	≤ 8	>32
	Ceftriaxone	64.9	12.2	22.9	0.25	>64
	Imipenem (1371) ^a	99.1	0.4	0.5	0.25	1
	Meropenem (115) ^a	100	0	0	≤ 0.06	0.5
	Levofloxacin	0	0	100	>8	>8
	Minocycline	62.7	14.1	23.2	4	>16
	PipTazo	71.5	10.6	17.9	4	>128

¹ Interpretive criteria are defined by CLSI, M100-S16 (2006) and FDA package insert (Tygacil[®], 2005). ^a Meropenem was substituted for imipenem late in the study.

CONCLUSIONS

- Tigecycline inhibited 96.5% of all *Enterobacteriaceae* at an MIC of 2 mcg/ml, regardless of resistance phenotype.
- Tigecycline's activity against ESBL-producing *E. coli* and *Klebsiella* isolates (93.2% S) was nearly equivalent to that of imipenem (96.4%) and meropenem (100%), and was superior to all other drugs in this study.
- Against AmpC-producing strains, the most active drugs were meropenem (100%), imipenem (100%), cefepime (100%), and amikacin (99.2%), followed by tigecycline (80.4%).
- Although amikacin resistant strains were rare (0.2%, or 24 isolates), tigecycline inhibited 95.8% of them, with activity comparable to that of imipenem and meropenem.
- Imipenem resistance was very rare (0.1%, or 7 strains), but tigecycline inhibited 100% of the strains, far exceeding the activity of any other drug in this study.
- The in vitro activity of tigecycline in this report suggests that it is a very promising agent for the treatment of serious infections caused by *Enterobacteriaceae* resistant to one or more other agents.