

Extended Spectrum Beta-Lactamase Producing Enterobacteriaceae Evaluated In Vitro Against Tigecycline and Comparator Agents - T.E.S.T. Program 2006

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REVISED ABSTRACT

Background: Tigecycline (TIG), 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. The T.E.S.T. program determined the in vitro activity of TIG compared to amoxicillin-clavulanic acid, piperacillin-tazobactam (PT), levofloxacin, ceftriaxone, cefepime, ampicillin (AMP), amikacin (AK), minocycline, ceftazidime and imipenem (IMP) against ESBL isolates collected from hospitals globally throughout 2004-2006. **Methods:** A total of 441 ESBL producing clinical *Enterobacteriaceae* were identified to the species level by 150 labs in 27 countries and confirmed by the central laboratory. Minimum Inhibitory Concentrations (MICs) were determined by the local laboratory using custom supplied broth microdilution panels and interpreted according to CLSI guidelines with tigecycline susceptible FDA breakpoint defined as ≤ 2 mcg/mL. **Results:** %Sus for all ESBL-producing isolates vs. TIG, IMP and AK were 93.0, 100 and 89.8%, respectively. %Sus for other comparators ranged from a high of 68% (PT) to a low of 0.7% (AMP). MIC_{50/90} values for TIG, IMP and AK were 0.5/2, 0.5/0.5 and 4/32 mcg/mL. The MIC₉₀ values for all other study drugs were in the resistant breakpoint ranges. There were minor regional differences in levels of activity, with either TIG (North America) or IMP (Europe, Asia/Pacific) being the most active. **Conclusion:** TIG's in-vitro activity is comparable to the activity of IMP against ESBL producing strains of *Enterobacteriaceae*. TIG's expanded broad spectrum of activity, including strains resistant or multiple-resistant to other agents, should make it a very useful treatment option for this difficult to treat group of gram-negative pathogens.

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 extended-spectrum beta-lactamase (ESBL) producing isolates collected from study centers representing a diverse population of clinical pathogens.

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.
- 441 Clinical isolates from 150 centers and 27 countries were collected and tested from January 2004 to January 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).
- 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].
- Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Quality control of broth microdilution panels followed manufacture's and NCCLS guidelines using the following ATCC strains: *Escherichia coli* ATCC 25922; *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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ACKNOWLEDGEMENTS

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

RESULTS

Table 1. Regional In vitro activity of Tigecycline and comparative agents against 255 ESBL producing *E. coli*.

Region/Organism *	Drug	%Sus	%Int	%Res	MIC (mcg/mL)	
					MIC ₅₀	MIC ₉₀
Global	Tigecycline	99.3	0.7	0	0.25	0.5
ESBL producing	Amikacin	96.4	1.4	2.2	4	16
<i>E. coli</i> (n=139)	AmoxClav	21.6	33.1	45.3	16	>32
	Ampicillin	2.2	0.7	97.1	>32	>32
	Cefepime	36.7	8.6	54.7	32	>32
	Ceftazidime	36	20.9	43.2	16	>32
	Ceftriaxone	12.9	10.1	77	>64	>64
	Imipenem	100	0	0	0.25	0.5
	Levofloxacin	16.5	3.6	79.9	>8	>8
	Minocycline	57.6	11.5	30.9	4	>16
	PipTazo	84.2	5.8	10.1	4	128
	North America	Tigecycline	100	0	0	0.25
ESBL producing	Amikacin	100	0	0	4	16
<i>E. coli</i> (n=37)	AmoxClav	21.6	35.1	43.2	16	32
	Ampicillin	0	2.7	97.3	>32	>32
	Cefepime	40.5	5.4	54.1	32	>32
	Ceftazidime	24.3	13.5	62.2	32	>32
	Ceftriaxone	18.9	10.8	70.3	>64	>64
	Imipenem	100	0	0	0.25	0.5
	Levofloxacin	13.5	5.4	81.1	>8	>8
	Minocycline	67.6	0	32.4	2	>16
	PipTazo	81.1	5.4	13.5	4	>128
	Europe	Tigecycline	98.1	1.9	0	0.25
ESBL producing	Amikacin	96.3	1.9	1.9	4	8
<i>E. coli</i> (n=54)	AmoxClav	29.6	31.5	38.9	16	32
	Ampicillin	3.7	0	96.3	>32	>32
	Cefepime	40.7	5.6	53.7	32	>32
	Ceftazidime	42.6	20.4	37	16	>32
	Ceftriaxone	16.7	7.4	75.9	>64	>64
	Imipenem	100	0	0	0.25	0.5
	Levofloxacin	18.5	5.6	75.9	>8	>8
	Minocycline	59.3	9.3	31.5	4	>16
	PipTazo	79.6	7.4	13	4	128
	Middle East	Tigecycline	100	0	0	0.5
ESBL producing	Amikacin	95	5	0	4	8
<i>E. coli</i> (n=20)	AmoxClav	0	0	100	32	>32
	Ampicillin	0	0	100	>32	>32
	Cefepime	5	5	90	>32	>32
	Ceftazidime	25	30	45	16	>32
	Ceftriaxone	0	5	95	>64	>64
	Imipenem	100	0	0	0.5	0.5
	Levofloxacin	5	0	95	>8	>8
	Minocycline	35	20	45	8	>16
	PipTazo	90	5	5	8	16
	Asia/Pacific Rim	Tigecycline	100	0	0	0.25
ESBL producing	Amikacin	92	0	8	4	8
<i>E. coli</i> (n=25)	AmoxClav	24	64	12	16	32
	Ampicillin	4	0	96	>32	>32
	Cefepime	48	20	32	16	>32
	Ceftazidime	48	24	28	16	>32
	Ceftriaxone	8	16	76	>64	>64
	Imipenem	100	0	0	0.25	0.5
	Levofloxacin	20	0	80	>8	>8
	Minocycline	60	20	20	4	16
	PipTazo	96	4	0	4	16

*Data from Latin America (n=3) are not individually shown, but are included in the Global results.

Table 2. Regional In vitro activity of Tigecycline and comparative agents against 277 ESBL producing *K. pneumoniae*.

Region/Organism *	Drug	%Sus	%Int	%Res	MIC (mcg/mL)	
					MIC ₅₀	MIC ₉₀
Global	Tigecycline	89.9	7.6	2.5	0.5	4
ESBL producing	Amikacin	87	7.6	5.4	8	32
<i>K. pneumoniae</i> (n=277)	AmoxClav	27.8	36.8	35.4	16	>32
	Ampicillin	0	0.4	99.6	>32	>32
	Cefepime	57.8	12.6	29.6	8	>32
	Ceftazidime	15.5	6.1	78.3	>32	>32
	Ceftriaxone	23.8	23.8	52.3	64	>64
	Imipenem	100	0	0	0.5	0.5
	Levofloxacin	45.8	8.7	45.5	4	>8
	Minocycline	62.1	11.9	26	4	>16
	PipTazo	59.2	10.8	30	8	>128
	North America	Tigecycline	90.4	6.1	3.5	1
ESBL producing	Amikacin	90.4	7.8	1.7	8	16
<i>K. pneumoniae</i> (n=115)	AmoxClav	35.7	34.8	29.6	16	32
	Ampicillin	0	0.9	99.1	>32	>32
	Cefepime	67.8	12.2	20	4	>32
	Ceftazidime	7	4.3	88.7	>32	>32
	Ceftriaxone	30.4	31.3	38.3	32	>64
	Imipenem	100	0	0	0.5	1
	Levofloxacin	30.4	3.5	66.1	8	>8
	Minocycline	66.1	8.7	25.2	4	>16
	PipTazo	53.9	7	39.1	16	>128
	Europe	Tigecycline	82.1	14.3	3.6	0.5
ESBL producing	Amikacin	89.3	6	4.8	4	32
<i>K. pneumoniae</i> (n=84)	AmoxClav	32.1	46.4	21.4	16	32
	Ampicillin	0	0	100	>32	>32
	Cefepime	54.8	16.7	28.6	8	>32
	Ceftazidime	22.6	3.6	73.8	>32	>32
	Ceftriaxone	25	20.2	54.8	64	>64
	Imipenem	100	0	0	0.5	0.5
	Levofloxacin	47.6	17.9	34.5	4	>8
	Minocycline	50	16.7	33.3	4	>16
	PipTazo	64.3	14.3	21.4	8	128
	Middle East	Tigecycline	100	0	0	0.5
ESBL producing	Amikacin	81	19	0	4	32
<i>K. pneumoniae</i> (n=21)	AmoxClav	0	9.5	90.5	32	>32
	Ampicillin	0	0	100	>32	>32
	Cefepime	42.9	0	57.1	>32	>32
	Ceftazidime	9.5	9.5	81	>32	>32
	Ceftriaxone	14.3	23.8	61.9	>64	>64
	Imipenem	100	0	0	0.5	1
	Levofloxacin	85.7	0	14.3	0.06	>8
	Minocycline	71.4	9.5	19	2	>16
	PipTazo	38.1	9.5	52.4	128	>128
	Asia/Pacific Rim	Tigecycline	95	5	0	0.5
ESBL producing	Amikacin	80	0	20	4	>64
<i>K. pneumoniae</i> (n=40)	AmoxClav	22.5	47.5	30	16	>32
	Ampicillin	0	0	100	>32	>32
	Cefepime	60	10	30	8	>32
	Ceftazidime	27.5	15	57.5	32	>32
	Ceftriaxone	15	15	70	64	>64
	Imipenem	100	0	0	0.5	1
	Levofloxacin	65	7.5	27.5	1	8
	Minocycline	62.5	12.5	25	4	>16
	PipTazo	85	12.5	2.5	4	32

*Data from Latin America (n=17) are not individually shown, but are included in the Global results.

Table 3. Regional In vitro activity of Tigecycline and comparative agents against 25 ESBL producing *K. oxytoca*.

Region/Organism ***	Drug	%Sus	%Int	%Res	MIC (mcg/mL)		
					MIC ₅₀	MIC ₉₀	
Global	Tigecycline	92	8	0	1	2	
<i>K. oxytoca</i> (n=25)	Amikacin	84	8	8	4	32	
	AmoxClav	52	20	28	8	32	
	Ampicillin	0	0	100	>32	>32	
	Cefepime	72	0	28	4	>32	
	Ceftazidime	20	4	76	4	>32	
	Ceftriaxone	28	48	24	16	>64	
	Imipenem	100	0	0	0.5	0.5	
	Levofloxacin	72	20	8	1	4	
	Minocycline	68	16	16	4	16	
	PipTazo	76	4	20	8	>128	
	North America	Tigecycline	90	10	0	1	2
	<i>K. oxytoca</i> (n=10)	Amikacin	100	0	0	1	8
AmoxClav		80	0	20	8	32	
Ampicillin		0	0	100	>32	>32	
Cefepime		100	0	0	2	8	