

Tigecycline and Comparator Agents In Vitro Activity Against Recently Collected Extended Spectrum Beta-Lactamase Isolates - TEST 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 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 (CTX), cefepime, amikacin (AK), minocycline (MIN), ceftazidime, and imipenem (IMP) against ESBL isolates collected from 205 hospitals globally throughout 2004-2006. **Methods:** A total of 996 ESBL-producing clinical isolates were identified to the species level from participating site and confirmed by the central laboratory. Minimum Inhibitory Concentrations (MICs) were determined by the local laboratory using supplied broth microdilution panels and interpreted according to CLSI guidelines. Tigecycline used the susceptible breakpoint of ≤ 2 mcg/ml for *Enterobacteriaceae* as defined in the FDA package insert. **Results:** %S for all ESBL-producing isolates vs. TIG, IMP, and AK was 94.7, 98.8, and 88.4%, respectively; %S for other comparators ranged from a high of 65.2% (MIN) to a low of 19.4% (CTX). MIC_{50/90} for TIG, IMP, and AK were 0.5/2, 0.5/1, and 4/32 mcg/ml; the MIC₉₀ for all other drugs was in the resistant range. There were some regional differences in levels of activity, with IMP being the most active compound in this study, with TIG MIC₉₀ values within 1-2 doubling dilutions of IMP. **Conclusion:** TIG has in vitro activity similar to IMP against ESBL strains. Its expanded broad spectrum of activity, including gram-negative and -positive strains resistant or multiply-resistant to other agents, should make it a very useful treatment option for difficult to treat ESBL producing *Enterobacteriaceae*.

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].

The T.E.S.T. program determined the in vitro activity of tigecycline compared to most commonly prescribed broad spectrum antimicrobials against gram-negative and gram-positive species collected from 205 hospitals globally from 2004 to 2006. This study was designed to evaluate the in vitro activity of tigecycline against globally collected ESBL-producing strains.

MATERIALS & METHODS

- For the T.E.S.T. program 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.
- For this study, clinical isolates (n=966) were collected from 2004 to 2006 from hospitals in Africa, Asia/Pacific Rim, Europe, the Middle East, Latin America, and North America.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring, West 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.
- Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftriaxone were > 1 mcg/ml using broth microdilution panels. ESBL activity was confirmed using the CLSI (2006) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2006) 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 and *Pseudomonas aeruginosa* ATCC 27853; *K. pneumoniae* ATCC 700603 was used for ESBL confirmation by the reference lab. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2006) guidelines [12].
- The collection and transportation of organisms, confirmation of identification, and 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 and comparative agents against global ESBL-producing *Enterobacteriaceae*.

Organism Name	Drug	%SUS ^a	%INT	%RES	MIC (mcg/ml)		MIC range (mcg/ml)	
					MIC ₅₀	MIC ₉₀	Low	High
All ESBL (n=996)	Tigecycline	94.7	3.9	1.4	0.5	2	0.03	8
	Amikacin	88.4	6.1	5.5	4	32	≤ 0.5	> 64
	AmoxClav	25.6	31.2	43.2	16	> 32	0.5	> 32
	Cefepime	46.6	10.4	43	16	> 32	≤ 0.5	> 32
	Ceftazidime	21.4	12.2	66.4	> 32	> 32	≤ 8	> 32
	Ceftriaxone	19.4	18.3	62.3	> 64	> 64	≤ 0.06	> 64
	Imipenem	98.8	0.5	0.7	0.5	1	≤ 0.06	> 16
	Levofloxacin	34.5	7.5	57.9	8	> 8	≤ 0.008	> 8
	Minocycline	65.2	12.9	22	4	> 16	≤ 0.5	> 16
	PipTazo	61.1	12.7	26.2	8	> 128	≤ 0.06	> 128
ESBL-producing <i>E. coli</i> (n=324)	Tigecycline	100	0	0	0.25	0.5	0.03	2
	Amikacin	93.2	3.7	3.1	4	16	≤ 0.5	> 64
	AmoxClav	25.9	35.2	38.9	16	32	0.5	> 32
	Cefepime	34.6	9.9	55.6	32	> 32	≤ 0.5	> 32
	Ceftazidime	38	20.1	42	16	> 32	≤ 8	> 32
	Ceftriaxone	14.2	8	77.8	> 64	> 64	≤ 0.06	> 64
	Imipenem	100	0	0	0.25	0.5	≤ 0.06	4
	Levofloxacin	19.1	5.2	75.6	> 8	> 8	≤ 0.008	> 8
	Minocycline	66.4	12	21.6	4	16	≤ 0.5	> 16
	PipTazo	83.6	9	7.4	4	64	≤ 0.06	> 128
ESBL-producing <i>K. pneumoniae</i> (n=626)	Tigecycline	91.9	5.9	2.2	0.5	2	0.12	8
	Amikacin	85.6	7.5	6.9	8	32	≤ 0.5	> 64
	AmoxClav	24.1	30	45.8	16	> 32	2	> 32
	Cefepime	51	10.9	38.2	8	> 32	≤ 0.5	> 32
	Ceftazidime	12.8	8.1	79.1	> 32	> 32	≤ 8	> 32
	Ceftriaxone	20.4	22.8	56.7	64	> 64	0.12	> 64
	Imipenem	98	0.8	1.1	0.5	1	≤ 0.06	> 16
	Levofloxacin	40.1	7.8	52.1	8	> 8	0.03	> 8
	Minocycline	64.1	13.3	22.7	4	> 16	≤ 0.5	> 16
	PipTazo	48.7	14.9	36.4	32	> 128	0.12	> 128
ESBL-producing <i>K. oxytoca</i> (n=46)	Tigecycline	95.7	4.3	0	0.5	2	0.12	4
	Amikacin	91.3	4.3	4.3	2	16	≤ 0.5	> 64
	AmoxClav	43.5	19.6	37	16	32	2	> 32
	Cefepime	71.7	8.7	19.6	8	> 32	≤ 0.5	> 32
	Ceftazidime	21.7	13	65.2	32	> 32	≤ 8	> 32
	Ceftriaxone	41.3	28.3	30.4	16	> 64	0.12	> 64
	Imipenem	100	0	0	0.5	0.5	≤ 0.06	1
	Levofloxacin	67.4	19.6	13	1	> 8	0.03	> 8
	Minocycline	71.7	13	15.2	4	16	≤ 0.5	> 16
	PipTazo	71.7	8.7	19.6	4	> 128	0.25	> 128

^a Interpretive criteria as defined by CLSI, M100-S16 (2006) [12], where available; tigecycline susceptibility breakpoints are according to FDA package insert (Tygacil®, 2005), where available [13].

Table 2. In vitro activity of tigecycline and comparative agents against all ESBL-producing *Enterobacteriaceae*, by region.

Organism Name	Drug	%SUS ^a	%INT	%RES	MIC (mcg/ml)		MIC range (mcg/ml)	
					MIC ₅₀	MIC ₉₀	Low	High
Africa (n=35)	Tigecycline	94.3	5.7	0	0.5	2	0.12	4
	Amikacin	100	0	0	4	16	1	16
	AmoxClav	22.9	51.4	25.7	16	> 32	4	> 32
	Cefepime	54.3	17.1	28.6	8	> 32	≤ 0.5	> 32
	Ceftazidime	20	20	60	32	> 32	≤ 8	> 32
	Ceftriaxone	25.7	25.7	48.6	32	> 64	1	> 64
	Imipenem	100	0	0	0.5	1	0.25	4
	Levofloxacin	74.3	5.7	20	1	> 8	0.03	> 8
	Minocycline	51.4	22.9	25.7	4	16	≤ 0.5	> 16
	PipTazo	74.3	11.4	14.3	8	> 128	0.25	> 128
Asia/Pacific Rim (n=104)	Tigecycline	98.1	1.9	0	0.5	1	0.06	4
	Amikacin	88.5	0	11.5	4	> 64	≤ 0.5	> 64
	AmoxClav	26.9	51	22.1	16	32	2	> 32
	Cefepime	51	11.5	37.5	8	> 32	≤ 0.5	> 32
	Ceftazidime	42.3	16.3	41.3	16	> 32	≤ 8	> 32
	Ceftriaxone	18.3	10.6	71.2	> 64	> 64	≤ 0.06	> 64
	Imipenem	100	0	0	0.25	0.5	≤ 0.06	2
	Levofloxacin	45.2	6.7	48.1	4	> 8	0.015	> 8
	Minocycline	67.3	11.5	21.2	4	16	≤ 0.5	> 16
	PipTazo	86.5	10.6	2.9	4	32	0.12	> 128
Europe (n=276)	Tigecycline	93.1	4.7	2.2	0.5	2	0.03	8
	Amikacin	88.4	5.8	5.8	4	32	≤ 0.5	> 64
	AmoxClav	28.6	35.1	36.2	16	> 32	0.5	> 32
	Cefepime	49.3	12	38.8	16	> 32	≤ 0.5	> 32
	Ceftazidime	28.6	10.5	60.9	32	> 32	≤ 8	> 32
	Ceftriaxone	18.8	19.6	61.6	64	> 64	≤ 0.06	> 64
	Imipenem	100	0	0	0.25	0.5	≤ 0.06	4
	Levofloxacin	41.3	11.6	47.1	4	> 8	≤ 0.008	> 8
	Minocycline	60.5	13.4	26.1	4	16	≤ 0.5	> 16
	PipTazo	67	12.7	20.3	8	> 128	0.25	> 128
Middle East (n=42)	Tigecycline	100	0	0	0.5	1	0.25	2
	Amikacin	88.1	11.9	0	4	32	2	32
	AmoxClav	0	4.8	95.2	32	> 32	16	> 32
	Cefepime	23.8	2.4	73.8	> 32	> 32	2	> 32
	Ceftazidime	16.7	19	64.3	32	> 32	≤ 8	> 32
	Ceftriaxone	7.1	14.3	78.6	> 64	> 64	4	> 64
	Imipenem	100	0	0	0.5	1	0.25	2
	Levofloxacin	45.2	0	54.8	8	> 8	0.03	> 8
	Minocycline	52.4	14.3	33.3	4	> 16	≤ 0.5	> 16
	PipTazo	61.9	9.5	28.6	16	> 128	0.12	> 128
Latin America (n=154)	Tigecycline	96.1	3.2	0.6	0.5	2	0.06	8
	Amikacin	79.9	6.5	13.6	8	> 64	≤ 0.5	> 64
	AmoxClav	7.8	24	68.2	32	> 32	2	> 32
	Cefepime	18.8	11.7	69.5	> 32	> 32	\le	