

Tigecycline is active against Eastern European in-patient and out-patient clinical isolates

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REVISED ABSTRACT

Background: Tigecycline has been shown to have potent 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 tigecycline compared to most commonly prescribed broad spectrum antimicrobials against gram-negative and gram-positive species collected during 2004 to 2006. **Methods:** A total of 877 clinical isolates from five Eastern European testing sites were identified to the species level. Minimum Inhibitory Concentrations (MICs) were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Selective results are presented:

Drug	In-patients (n=344)		Out-patients (n=533)	
	% SUS ^a	MIC ₅₀	% SUS ^a	MIC ₅₀
Tigecycline	98.4	1	100	1
Amikacin	96.8	8	100	4
AmoxClav	97	32	95.3	8
Ampicillin	90.1	8	87.1	16
Cefepime	100	0.5	100	0.5
Ceftazidime	100	0.5	100	0.5
Ceftriaxone	100	0.5	100	0.5
Imipenem	100	0.5	100	0.5
Levofloxacin	100	0.5	100	0.5
Linezolid	100	0.5	100	0.5
Minocycline	100	0.5	100	0.5
PipTazo	100	0.5	100	0.5

Conclusion: Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed broad spectrum antimicrobials without any demonstrable change in activity between in- and out-patient bacterial study strains. Tigecycline's inhibitory activity against *Enterobacteriaceae* was comparable to imipenem. Against *Acinetobacter* spp. tigecycline's MIC₅₀ was 16-fold lower than imipenem. Against *S. aureus* and *Enterococcus* spp., tigecycline's activity was similar to linezolid and vancomycin.

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 MIC₅₀ 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 in in-patient and out-patient isolates from Eastern European countries.

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.
- Clinical isolates (n=877) were collected from 2004 to 2006 from five Eastern European testing sites (1 study center in Poland, 1 in Hungary, 1 in Greece, and 2 in Latvia).
- 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 (0.05-32); 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 manufacturer's and CLSI guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *K. pneumoniae* ATCC 700603; *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *Pseudomonas aeruginosa* ATCC 27853.
- 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 gram-negative isolates.

Organism Name	Drug	n	In-patients				Out-patients							
			MIC (mcg/ml)		MIC range (mcg/ml)		MIC (mcg/ml)		MIC range (mcg/ml)					
			MIC ₅₀	MIC ₉₀	Low	High	MIC ₅₀	MIC ₉₀	Low	High				
<i>E. coli</i> ^b	Tigecycline	136	100	0.12	0.25	0.06	1	100	0.12	0.25	0.06	0.25		
	Amikacin		90.4	2	16	1	>64	100	2	4	<=0.5	4		
	AmoxClav		69.9	8	32	1	>32	84.2	8	16	2	16		
	Ampicillin		32.4	>32	>32	1	>32	42.1	>32	>32	1	>32		
	Cefepime		89	<=0.5	16	<=0.5	>32	94.7	<=0.5	8	<=0.5	32		
	Ceftazidime		87.5	<=8	32	<=8	>32	100	<=8	<=8	<=8	<=8		
	Ceftriaxone		81.6	<=0.6	>64	<=0.6	>64	84.2	<=0.6	64	<=0.6	>64		
	Imipenem		100	0.25	0.5	<=0.06	4	100	0.25	0.5	0.25	0.5		
	Levofloxacin		78.7	0.03	8	<=0.008	>8	68.4	0.03	>8	0.015	>8		
	Minocycline		81.6	1	8	<=0.5	>16	73.7	1	8	<=0.5	>16		
	PipTazo		91.9	1	16	0.25	>128	100	1	2	0.5	8		
	<i>Klebsiella</i> spp. ^c	Tigecycline	138	92.8	0.5	2	0.12	8	100	0.5	2	0.25	2	
Amikacin			93.5	2	16	1	>64	100	2	16	<=0.5	16		
AmoxClav			54.3	8	>32	0.5	>32	66.7	4	16	1	32		
Ampicillin			0	>32	>32	16	>32	0	>32	>32	16	>32		
Cefepime			79	<=0.5	>32	<=0.5	>32	83.3	<=0.5	16	<=0.5	16		
Ceftazidime			70.3	<=8	>32	<=8	>32	66.7	<=8	>32	<=8	>32		
Ceftriaxone			61.6	0.12	>64	<=0.06	>64	75	<=0.06	64	<=0.06	64		
Imipenem			100	0.25	0.5	<=0.06	4	100	0.5	1	0.5	1		
Levofloxacin			73.9	0.12	>8	0.015	>8	75	0.25	>8	0.03	>8		
Minocycline			77.5	2	16	<=0.5	>16	83.3	2	8	1	16		
PipTazo			69.6	2	>128	0.25	>128	66.7	2	128	0.25	>128		
ESBL-producers		Tigecycline	60	88.3	0.5	4	0.06	8	100	-	-	0.25	2	
	Amikacin		76.7	8	64	1	>64	100	-	-	1	16		
	AmoxClav		23.3	16	>32	4	>32	25	-	-	8	16		
	Ampicillin		0	>32	>32	>32	>32	0	-	-	>32	>32		
	Cefepime		61.7	8	>32	<=0.5	>32	50	-	-	8	32		
	Ceftazidime		26.7	>32	>32	78	>32	50	-	-	<=8	>32		
	Ceftriaxone		15	64	>64	1	>64	0	-	-	32	>64		
	Imipenem		100	0.25	0.5	<=0.06	4	100	-	-	0.25	0.5		
	Levofloxacin		48.3	4	>8	0.015	>8	25	-	-	0.03	>8		
	Minocycline		60	4	>16	<=0.5	>16	75	-	-	1	8		
	PipTazo		63.3	8	>128	0.5	>128	50	-	-	1	>128		
	<i>Enterobacter</i> spp. ^d	Tigecycline	143	93	0.5	2	0.12	8	100	-	-	0.25	1	
Amikacin			97.9	2	8	<=0.5	>64	87.5	-	-	1	>64		
AmoxClav			0.7	>32	>32	8	>32	0	-	-	32	>32		
Ampicillin			0	>32	>32	16	>32	0	-	-	32	>32		
Cefepime			88.8	<=0.5	16	<=0.5	>32	75	-	-	<=0.5	>32		
Ceftazidime			66.4	<=8	>32	<=8	>32	75	-	-	<=8	>32		
Ceftriaxone			66.4	0.5	>64	<=0.06	>64	62.5	-	-	0.12	>64		
Imipenem			100	0.5	1	<=0.06	4	100	-	-	0.5	1		
Levofloxacin			87.4	0.06	4	0.015	>8	75	-	-	0.03	>8		
Minocycline			81.1	2	16	<=0.5	>16	75	-	-	1	8		
PipTazo			69.9	2	128	0.5	>128	75	-	-	1	128		
<i>Serratia</i> spp. ^d		Tigecycline	51	98	1	2	0.06	4	100	1	1	0.5	1	
	Amikacin		94.1	2	8	1	>64	100	2	2	1	2		
	AmoxClav		2	>32	>32	8	>32	0	>32	>32	>32	>32		
	Ampicillin		2	>32	>32	8	>32	0	>32	>32	>32	>32		
	Cefepime		96.1	<=0.5	1	<=0.5	>32	100	<=0.5	<=0.5	<=0.5	>32		
	Ceftazidime		100	<=8	<=8	<=8	>32	100	<=8	<=8	<=8	>32		
	Ceftriaxone		92.2	0.25	4	<=0.06	>64	100	0.12	0.12	0.12	0.12		
	Imipenem		100	0.5	1	<=0.06	2	100	0.5	1	0.5	1		
	Levofloxacin		94.1	0.12	2	0.015	>8	100	0.25	0.25	0.06	0.25		
	Minocycline		86.3	4	8	1	8	100	4	4	4	4		
	PipTazo		96.1	1	8	0.25	>128	100	1	1	1	1		
	<i>Acinetobacter</i> spp. ^d	Tigecycline	94	na	0.5	1	0.06	4	4	na	-	-	0.5	2
Amikacin			56.4	4	>64	1	>64	25	-	-	16	>64		
Cefepime			44.7	16	>32	<=0.5	>32	0	-	-	16	>32		
Ceftazidime			31.9	16	>32	<=8	>32	0	-	-	32	>32		
Ceftriaxone			13.8	>64	>64	0.25	>64	0	-	-	>64	>64		
Imipenem			85.1	1	>16	<=0.06	>16	50	-	-	4	>16		
Levofloxacin			35.1	4	>8	0.03	>8	0	-	-	4	>8		
Minocycline			98.9	<=0.5	1	<=0.5	16	100	-	-	<=0.5	2		
PipTazo			35.1	64	>128	<=0.06	>128	0	-	-	128	>128		
<i>H. influenzae</i> ^e		Tigecycline	58	na	0.12	0.25	<=0.008	0.5	17	na	0.12	0.25	0.06	0.25
		AmoxClav		100	0.25	1	<=0.12	4	100	0.5	2	<=0.12	4	
		Ampicillin		89.7	<=0.5	32	<=0.5	>32	76.5	<=0.5	32	<=0.5	>32	
	Cefepime		98.3	<=0.5	<=0.5	<=0.5	4	100	<=0.5	<=0.5	<=0.5	<=0.5		
	Ceftriaxone		100	<=0.06	<=0.06</									