

REVISED ABSTRACT

Background: Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent broad spectrum activity against 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 from 205 hospitals globally from 2004 to 2006. **Methods:** A total of 162 clinical Enterobacteriaceae isolates from Australia were identified to the species level and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by each site using broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Results are in the table as follows*:

	Enterobacteriaceae		Enterobacteriaceae	
	In-patients (n=94)	Out-patients (n=68)	In-patients (n=94)	Out-patients (n=68)
	%S	MIC ₉₀	%S	MIC ₉₀
Tigecycline	95.7	1	100	1
Amikacin	100	4	100	4
Cefepime	97.9	2	100	0.5
Ceftazidime	76.6	32	95.6	8
Imipenem	100	1	100	1
Levofloxacin	97.9	0.25	100	0.12
Minocycline	91.5	4	94.1	4
PipTazo	76.6	64	92.6	4

*Tigecycline susceptibility defined according to FDA package insert (Tygacil®; 2005)

Conclusion: Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed broad spectrum antimicrobials without any demonstrable change between in- and out-patient bacterial study strains. Tigecycline's inhibitory activity was essentially comparable to that of most broad spectrum antimicrobials. The presented data suggest that tigecycline may be an effective and reliable therapeutic option against nosocomial or community enteric 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 10⁻⁷ [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 in in-patient and out-patient isolates from Australia.

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	In-patients					Out-patients				
		n	%SUS ^a	MIC ₅₀	MIC ₉₀	MIC range (mcg/ml)	n	%SUS ^a	MIC ₅₀	MIC ₉₀	MIC range (mcg/ml)
<i>E. coli</i>	Tigecycline	20	100	0.12	0.25	0.12 0.25	29	100	0.12	0.25	0.06 0.25
	Amikacin	100	4	8	1	8	100	2	8	2	8
	AmoxClav	90	4	8	2	32	93.1	4	8	2	16
	Ampicillin	50	4	>32	1	>32	62.1	4	>32	1	>32
	Cefepime	100	≤0.5	≤0.5	≤0.5	4	100	≤0.5	≤0.5	≤0.5	<0.5
	Ceftazidime	95	≤8	≤8	≤8	32	100	≤8	≤8	≤8	<8
	Ceftriaxone	100	≤0.06	0.12	≤0.06	2	100	≤0.06	≤0.06	≤0.06	0.12
	Imipenem	100	0.25	0.5	0.25	0.5	100	0.25	0.5	0.25	1
	Levofloxacin	100	0.03	0.12	0.015	1	100	0.03	0.06	≤0.008	0.25
	Minocycline	100	1	2	≤0.5	4	93.1	1	2	≤0.5	8
	PipTazo	95	1	4	0.5	128	100	1	2	0.25	4
<i>Klebsiella</i> spp. ^b	Tigecycline	28	96.4	0.25	1	0.25 4	19	100	0.5	1	0.25 1
	Amikacin	100	1	4	1	4	100	1	2	1	2
	AmoxClav	71.4	2	32	1	>32	89.5	2	16	1	32
	Ampicillin	0	>32	>32	32	>32	0	32	>32	16	>32
	Cefepime	96.4	≤0.5	2	≤0.5	>32	100	≤0.5	≤0.5	≤0.5	4
	Ceftazidime	96.4	≤8	≤8	≤8	16	100	≤8	≤8	≤8	<8
	Ceftriaxone	92.9	≤0.06	8	≤0.06	>64	94.7	≤0.06	1	≤0.06	16
	Imipenem	100	0.25	0.5	0.25	1	100	0.25	0.5	0.25	1
	Levofloxacin	96.4	0.06	2	0.03	>8	100	0.03	0.25	0.03	0.25
	Minocycline	96.4	1	4	≤0.5	16	100	1	2	≤0.5	4
	PipTazo	78.6	2	>128	1	>128	89.5	2	>128	0.5	>128
<i>Enterobacter</i> spp.	Tigecycline	31	93.5	0.5	1	0.25 8	16	100	0.5	1	0.25 2
	Amikacin	100	2	4	1	8	100	2	2	1	4
	AmoxClav	3.2	>32	>32	8	>32	0	>32	>32	32	>32
	Ampicillin	0	>32	>32	32	>32	0	>32	>32	32	>32
	Cefepime	96.8	1	4	≤0.5	>32	100	≤0.5	2	≤0.5	8
	Ceftazidime	35.5	16	>32	≤8	>32	81.3	≤8	32	≤8	>32
	Ceftriaxone	51.6	8	>64	≤0.06	>64	81.3	0.12	32	≤0.06	>64
	Imipenem	100	0.5	1	0.25	1	100	0.5	1	0.25	2
	Levofloxacin	96.8	0.03	0.25	0.03	8	100	0.03	0.5	0.015	1
	Minocycline	90.3	4	4	1	>16	87.5	2	8	1	8
	PipTazo	51.6	16	64	1	128	81.3	1	64	0.5	128
<i>Serratia</i> spp. ^c	Tigecycline	15	93.3	1	2	0.5 4	4	100	-	-	1 1
	Amikacin	100	4	4	2	8	100	-	-	1	2
	AmoxClav	6.7	>32	>32	8	>32	0	-	-	16	>32
	Ampicillin	0	>32	>32	32	>32	0	-	-	16	>32
	Cefepime	100	≤0.5	≤0.5	≤0.5	1	100	-	-	≤0.5	<0.5
	Ceftazidime	100	≤8	≤8	≤8	<8	100	-	-	≤8	<8
	Ceftriaxone	100	0.5	1	0.12	8	100	-	-	≤0.06	0.25
	Imipenem	100	1	2	0.5	2	100	-	-	0.5	1
	Levofloxacin	100	0.12	0.25	0.06	0.5	100	-	-	0.03	0.12
	Minocycline	73.3	4	8	2	8	100	-	-	1	4
	PipTazo	100	2	4	1	8	100	-	-	1	2

na = breakpoints not available.
^aInterpretive 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].
^bIn-patient isolates include 1 ESBL-producing tigecycline-susceptible *K. pneumoniae* strain with a tigecycline MIC of 1 mcg/ml.
^cNo MIC₅₀ and MIC₉₀ calculated if n<10; % SUS, % INT, % RES may not be statistically significant when n's are small.

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=162) were collected from 2004 to 2006 from two testing sites in Australia.
- 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 (0.5-64); 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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Figure 1: In vitro activity of tigecycline against 20 in-patient and 29 out-patient *E. coli* strains.

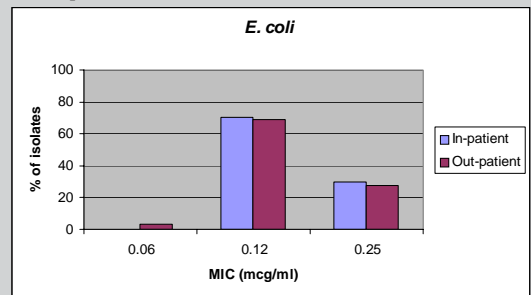


Figure 2: In vitro activity of tigecycline against 28 in-patient and 19 out-patient *K. pneumoniae* strains (including 1 in-patient ESBL-producing isolate).

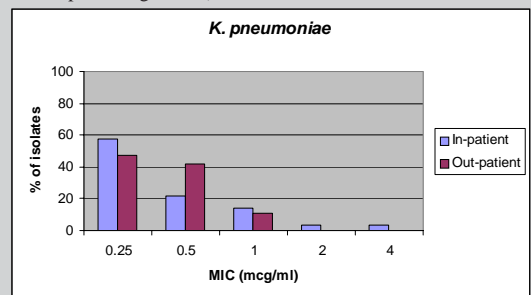


Figure 3: In vitro activity of tigecycline against 31 in-patient and 16 out-patient *Enterobacter* spp. strains.

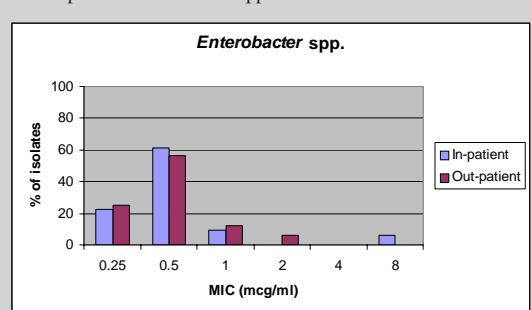
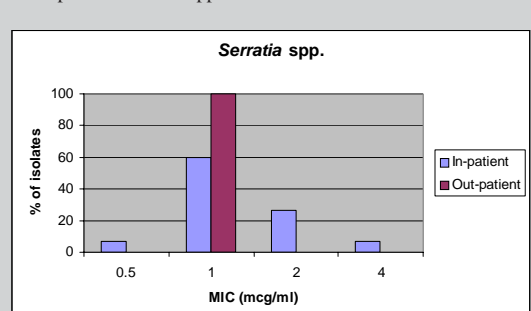


Figure 4: In vitro activity of tigecycline against 15 in-patient and 4 out-patient *Serratia* spp. strains.



CONCLUSIONS

- Tigecycline's MIC₅₀ and MIC₉₀ were remarkably similar in all Enterobacteriaceae tested when comparing in-patient and out-patient strains. In-patient isolate tigecycline MIC₅₀s and MIC₉₀s were never higher than those of out-patients.
- Even though the highs of the MIC ranges for most antimicrobials were higher for in-patient strains (as one would expect), tigecycline highs increased by only up to 2 dilutions and MIC₅₀s and MIC₉₀s were the same or lower for in-patients compared to out-patients.
- Tigecycline's inhibitory activity was essentially comparable to that of most broad spectrum antimicrobials.
- The presented data suggest that tigecycline may be an effective and reliable therapeutic option against nosocomial or community enteric pathogens.