

REVISED ABSTRACT

Background: Tigecycline (TIG), a new glycycline, 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 TIG and 10 comparators against respective gram positive/negative species. **Methods:** 331 cerebrospinal fluid pathogens from 42 countries were analyzed in this survey. The isolates were identified to the species level at the participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** TIG activity against pathogens isolated from cerebrospinal fluid are shown in the table below*:

Organisms (n=331)	%Sus	Tigecycline MIC (mcg/ml)		
		MIC ₅₀	MIC ₉₀	Range
<i>Acinetobacter</i> spp (n=38)	na	0.25	1	0.03 - 4
<i>P. aeruginosa</i> (n=19)	na	16	>16	4 - >16
<i>Enterobacter</i> spp (n=30)	100	0.5	1	0.25 - 2
<i>Enterococcus</i> spp (n=25)	100	0.12	0.12	0.03 - 0.25
<i>E. coli</i> (n=29)	100	0.12	0.25	0.06 - 2
<i>Klebsiella</i> spp (n=24)	95.8	0.5	1	0.12 - 4
ESBLs (n=8)	100	0.5	2	0.12 - 2
<i>H. influenzae</i> (n=11)	na	0.12	0.25	0.12 - 0.25
<i>S. aureus</i> (n=30)	100	0.12	0.25	0.15 - 0.25
MRSA (n=8)	100	0.12	0.25	0.06 - 0.25
<i>S. pneumoniae</i> (n=90)	na	0.03	0.25	≤0.008 - 0.5
<i>S. marcescens</i> (n=18)	100	1	2	0.25 - 2
<i>S. agalactiae</i> (n=17)	100	0.03	0.06	0.03 - 0.25

Conclusion: Tigecycline showed excellent inhibitory activity against all pathogens invading the cerebrospinal fluid in this study with the exception of *P. aeruginosa*. Tigecycline demonstrated MIC₅₀ values of ≤0.5mcg/ml against gram-positive pathogens (including resistant phenotypes) and MIC₉₀ values of 1 mcg/ml against the *Enterobacteriaceae* and *Acinetobacter* spp. validate the potent inhibitory activity of TIG against these invasive pathogens.

INTRODUCTION

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycyclines. 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]. Like other glycyclines, tigecycline crosses the blood-brain barrier well.

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 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].

This study was undertaken to better define the in vitro activity of tigecycline against clinical isolates from cerebrospinal fluid collected from a global population. This study is part of the larger ongoing Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

MATERIALS & METHODS

- All isolates were derived from central nervous system (CNS) specimens. Only one isolate per patient was accepted.
- Clinical isolates (n=331) were collected and tested between January 2004 and January 2006 from 42 countries throughout the world. Isolates were identified to the species level and tested using broth microdilution at each site by the participating laboratory.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring Inc., Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/ml): amikacin (0.5-64); amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.5-32, gram-negative panel, and 0.06-16, gram-positive panel); cefepime (0.5-32); ceftriaxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32).
- 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: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Escherichia coli* ATCC 35218; *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; *Klebsiella pneumoniae* ATCC 700603 and *Pseudomonas aeruginosa* ATCC 27853.
- 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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Figure 1. The distribution of 331 CNS isolates tested by organism type.

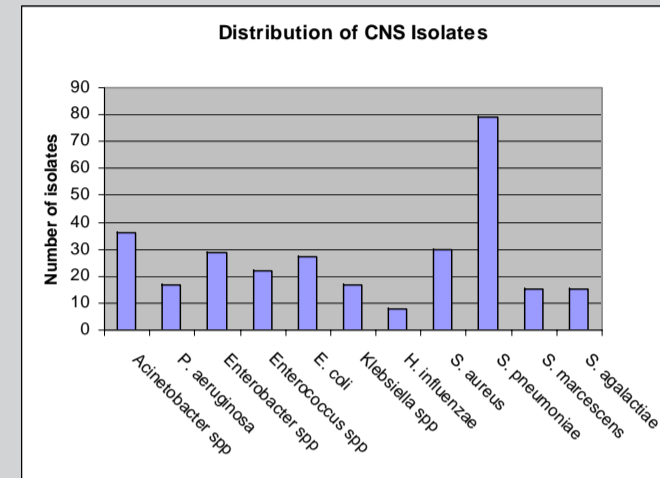


Table 1. The in vitro activity of tigecycline and comparative agents against *Enterobacteriaceae* isolated from CNS specimens.

Organism	Drug	%Sus	MIC (mcg/ml)		
			MIC ₅₀	MIC ₉₀	MIC ₉₅
<i>Enterobacter</i> spp. (n=30)	Tigecycline	100	0.5	1	
	Amikacin	96.7	2	2	
	Amox-Clav	3.3	>32	>32	
	Ampicillin	0	>32	>32	
	Cefepime	96.7	≤0.5	8	
	Ceftriaxone	70	0.25	>64	
	Imipenem	100	0.5	1	
	Levofloxacin	96.7	0.03	0.5	
	Minocycline	86.7	2	8	
	PipTazo	83.3	2	64	
<i>E. coli</i> (n=29)	Tigecycline	100	0.12	0.25	
	Amikacin	96.6	2	4	
	Amox-Clav	65.5	8	>32	
	Ampicillin	37.9	>32	>32	
	Cefepime	96.6	≤0.5	4	
	Ceftriaxone	89.7	≤0.06	64	
	Imipenem	100	0.25	0.5	
	Levofloxacin	82.8	0.03	>8	
	Minocycline	89.7	1	8	
	PipTazo	93.1	1	4	
<i>Klebsiella</i> spp. (n=24)	Tigecycline	95.8	0.5	1	
	Amikacin	91.7	1	16	
	Amox-Clav	75	4	32	
	Ampicillin	0	>32	>32	
	Cefepime	87.5	≤0.5	16	
	Ceftriaxone	75	0.12	>64	
	Imipenem	100	0.5	0.5	
	Levofloxacin	83.3	0.06	4	
All ESBL producers ^a (n=8)	Tigecycline	100	0.5	2	
	Amikacin	75	2	>64	
	Amox-Clav	50	8	>32	
	Ampicillin	0	>32	>32	
	Cefepime	75	4	>32	
	Ceftriaxone	12.5	64	>64	
	Imipenem	100	0.25	0.5	
	Levofloxacin	37.5	4	>8	
<i>S. marcescens</i> (n=18)	Tigecycline	100	1	2	
	Amikacin	94.4	2	4	
	Amox-Clav	0	>32	>32	
	Ampicillin	0	>32	>32	
	Cefepime	100	≤0.5	≤0.5	
	Ceftriaxone	94.4	0.25	8	
	Imipenem	100	0.5	1	
	Levofloxacin	100	0.12	0.25	
<i>S. agalactiae</i> (n=17)	Minocycline	94.4	4	4	
	PipTazo	100	2	4	

^a Interpretive criteria as defined by CLSI, M100-S16 (2006), where applicable; ESBL-Extended Spectrum Beta-lactamase producing strain.

RESULTS

Table 2. The in vitro activity of tigecycline and comparative agents against *Acinetobacter* spp. and *Pseudomonas aeruginosa* isolated from CNS specimens.

Organism	Drug	%SUS ^a	%INT	%RES	MIC (mcg/ml)		
					MIC ₅₀	MIC ₉₀	
<i>Acinetobacter</i> spp. (n=38)	Tigecycline	na	na	na	0.25	1	
	Amikacin	71.1	7.9	21.1	4	>64	
	Cefepime	57.9	10.5	31.6	8	>32	
	Ceftriaxone	21.1	23.7	55.3	64	>64	
	Imipenem	91.9	0	8.1	0.5	4	
	Levofloxacin	52.6	2.6	44.7	1	>8	
	Minocycline	89.5	7.9	2.6	≤0.5	8	
	PipTazo	50	18.4	31.6	16	>128	
	<i>P. aeruginosa</i> (n=19)	Tigecycline	na	na	na	16	>16
		Amikacin	100	0	0	2	16
Cefepime		78.9	5.3	15.8	4	32	
Ceftriaxone		15.8	47.4	36.8	32	>64	
Imipenem		83.3	5.6	11.1	1	16	
Levofloxacin		57.9	26.3	15.8	2	>8	
Minocycline		0	15.8	84.2	>16	>16	
PipTazo		94.7	0	5.3	4	64	

^a Interpretive criteria as defined by CLSI, M100-S16 (2006), where applicable; na = CLSI breakpoints not available.

Table 3. The in vitro activity of tigecycline and comparative agents against non-fastidious gram-positive pathogens isolated from CNS specimens.

Organism	Drug	%Sus	MIC (mcg/ml)		
			MIC ₅₀	MIC ₉₀	MIC ₉₅
<i>S. aureus</i> , MSSA (n=22)	Tigecycline	100	0.12	0.12	
	Amox-Clav	100	1	2	
	Ampicillin	13.6	4	>16	
	Ceftriaxone	100	2	4	
	Imipenem	100	≤0.12	0.25	
	Levofloxacin	95.5	0.12	0.25	
	Linezolid	100	2	2	
	Minocycline	100	≤0.25	≤0.25	
	Penicillin	13.6	8	>8	
	PipTazo	100	0.5	1	
<i>S. aureus</i> , MRSA (n=8)	Vancomycin	100	0.5	2	
	Tigecycline	100	0.12	0.25	
	Amox-Clav	0	>8	>8	
	Ampicillin	0	>16	>16	
	Ceftriaxone	0	>64	>64	
	Imipenem	0	1	>16	
	Levofloxacin	37.5	4	32	
	Linezolid	100	2	4	
	Minocycline	100	≤0.25	4	
	Penicillin	0	>8	>8	
<i>Enterococcus</i> spp ^a (n=25)	PipTazo	0	>16	>16	
	Vancomycin	100	0.5	1	
	Tigecycline	100	0.12	0.12	
	Ampicillin	92	1	1	
	Levofloxacin	76	1	>32	
	Linezolid	96	2	2	
	Minocycline	36	8	>8	
	Penicillin	92	2	4	
	Vancomycin	96	1	2	
	<i>S. agalactiae</i> (n=17)	Tigecycline	100	0.03	0.06
Ampicillin		100	0.12	0.12	
Levofloxacin		100	0.5	1	
Linezolid		100	1	1	
Penicillin		100	≤0.06	0.12	
Vancomycin		100	0.5	0.5	

^a Interpretive criteria as defined by CLSI, M100-S16 (2006), where applicable; Methicillin phenotype based upon cefoxitin 30 mcg disk results; beta-lactam susceptibilities based on methicillin phenotype. Tigecycline FDA breakpoints for enterococci are approved for vancomycin-susceptible *E. faecalis* only; interpretive criteria are expanded to include all other enterococci for comparison purposes only. [14]

Table 4. The in vitro activity of tigecycline and comparative agents against fastidious gram-positive pathogens isolated from CNS specimens.

Organism	Drug	%Sus ^a	MIC (mcg/ml)	
			MIC ₅₀	MIC ₉₀
<i>S. pneumoniae</i> (n=90)	Tigecycline	na	0.03	0.25
	Ceftriaxone	90	≤0.03	1
	Imipenem	79.2	≤0.12	0.25
	Penicillin	73.3	≤0.06	2
	Vancomycin	100	0.25	0.5
<i>S. pneumoniae</i> Susceptible to penicillin (n=66)	Tigecycline	na	0.03	0.25
	Ceftriaxone	100	≤0.03	≤0.03
	Imipenem	100	≤0.12	≤0.12
	Penicillin	100	≤0.06	≤0.06
	Vancomycin	100	0.25	0.5
<i>S. pneumoniae</i> Intermediate to penicillin (n=14)	Tigecycline	na	0.03	0.5
	Ceftriaxone	85.7	0.06	1
	Imipenem	38.5	0.25	0.25
	Penicillin	0	0.25	1
	Vancomycin	100	0.25	0.5
<i>S. pneumoniae</i> Resistant to penicillin (n=10)	Tigecycline	na	0.03	0.12
	Ceftriaxone	30	1	4
	Imipenem	0	0.5	0.5
	Penicillin	0	2	4
	Vancomycin	100	0.25	0.5
<i>Haemophilus influenzae</i> (n=11)	Tigecycline	na	0.25	0.5
	Ampicillin	100	≤0.5	≤0.5
	Ceftriaxone	100	≤0.06	≤0.06
	Imipenem	100	≤0.06	0.5

^a Breakpoints as defined by CLSI where available (M100-S16), 2006; na = CLSI breakpoints not available.

CONCLUSIONS