

# In Vitro Activity of Tigecycline Against Pathogens Isolated from Cerebrospinal Fluid - T.E.S.T. Program 2008

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IHMA, Inc.  
2122 Palmer Dr.  
Schaumburg, IL  
60173  
Tel: 847.303.5003  
Fax: 847.303.5601

S. Bouchillon<sup>1</sup>, M. Renteria<sup>1</sup>, J. Johnson<sup>1</sup>, R. Badal<sup>1</sup>, S. Hawser<sup>1</sup>, M. Hackel<sup>1</sup>, B. Johnson<sup>1</sup>, D. Hoban<sup>1</sup>, M. Dowzicky<sup>2</sup>

<sup>1</sup>International Health Management Associates, Inc., Schaumburg, IL, USA

<sup>2</sup>Wyeth Pharmaceuticals, Collegeville, PA, USA

## Revised Abstract

**Objectives:** Tigecycline (TIG), a new glycolcycline, 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:** 681 cerebrospinal fluid pathogens from 53 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=681)	Tigecycline MIC (mcg/ml)			
	%Sus	MIC <sub>50</sub>	MIC <sub>90</sub>	Range
<i>Enterobacter</i> spp (n=77)	100	0.5	1	0.25 - 2
<i>E. coli</i> (n=57)	100	0.12	0.25	0.06 - 2
<i>Klebsiella</i> spp (n=49)	93.9	0.5	1	0.12 - 4
ESBLs (n=20)	95.0	0.5	1	0.12 - 4
<i>S. marcescens</i> (n=36)	100	1	2	0.25 - 2
<i>Acinetobacter</i> spp (n=72)	na	0.5	1	0.015 - 4
<i>P. aeruginosa</i> (n=44)	na	8	>16	4 - >16
<i>H. influenzae</i> (n=32)	na	0.25	0.5	0.03 - 1
<i>Enterococcus</i> spp (n=56)	100	0.06	0.25	0.03 - 0.25
<i>S. aureus</i> (n=60)	100	0.12	0.25	0.15 - 0.5
MRSA (n=18)	100	0.12	0.25	0.06 - 0.25
<i>S. pneumoniae</i> (n=161)	na	0.03	0.12	<0.008 - 0.5
<i>S. agalactiae</i> (n=37)	100	0.03	0.12	0.015 - 0.25

\*na = breakpoints not available.

**Conclusions:** Tigecycline showed excellent inhibitory activity against all pathogens invading the cerebrospinal fluid in this study with the exception of *P. aeruginosa*. Tigecycline demonstrated MIC<sub>90</sub> values of ≤0.25 mcg/ml against gram-positive pathogens (including resistant phenotypes) and MIC<sub>90</sub> values of ≤2 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 glycolcyclines. 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<sup>-9</sup> [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 active 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 MIC<sub>90</sub> 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=681) were collected and tested between January 2004 and January 2008 from 53 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 (0.008-16); imipenem (0.06-16); meropenem (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 [14]: *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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## Results

Figure 1. The distribution of 681 isolates collected from the Central Nervous System by species.

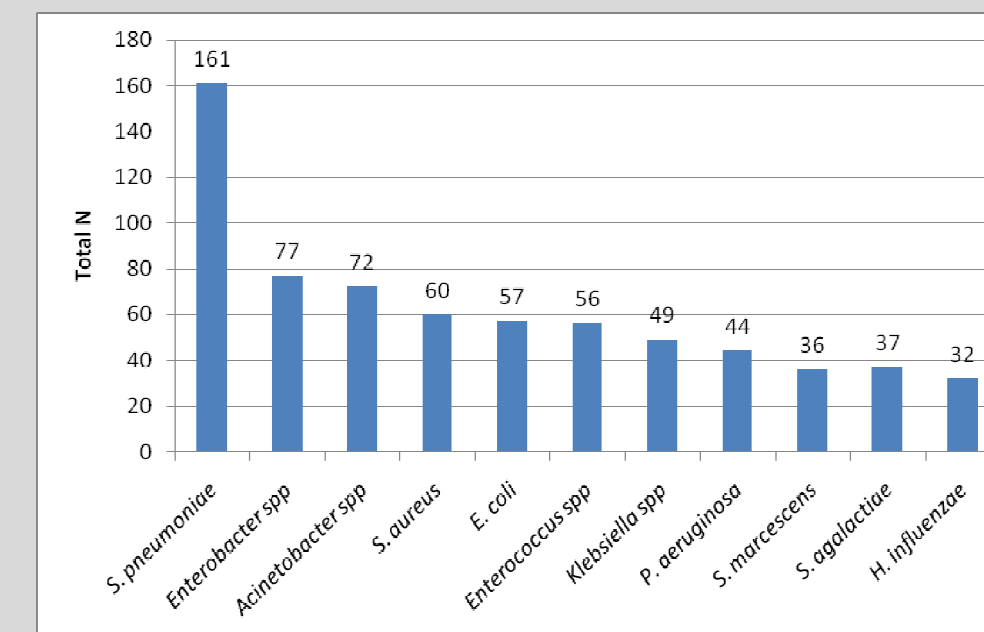


Table 1. The in vitro activity of tigecycline and comparative agents against *Enterobacteriaceae* isolated from CNS specimens.

Organism	Drug	mcg/ml			
		MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus*	%Int %Res
<i>Enterobacter</i> spp (n=77)	Tigecycline	0.5	1	100.0	0.0
	Amikacin	2	2	98.7	0.0
	AmoxClav	>32	>32	3.9	0.0
	Ampicillin	>32	>32	1.3	0.0
	Cefepime	>0.5	8	94.8	1.3
	Ceftazidime	>8	>32	72.7	2.6
	Ceftriaxone	0.25	>64	71.4	6.5
	Imipenem	0.5	1	100.0	0.0
	Levofloxacin	0.06	0.5	94.8	2.6
	Meropenem	>0.06	0.25	97.4	2.6
	Minocycline	2	16	80.5	7.8
	PipTazo	1	128	80.5	7.8
<i>Escherichia coli</i> (n=57)	Tigecycline	0.12	0.25	100.0	0.0
	Amikacin	2	8	94.7	3.5
	AmoxClav	8	32	66.7	17.5
	Ampicillin	>32	>32	26.3	1.8
	Cefepime	>0.5	2	94.7	1.8
	Ceftazidime	>8	>32	93.0	0.0
	Ceftriaxone	>0.06	32	87.7	3.5
	Imipenem	0.25	0.5	100.0	0.0
	Levofloxacin	0.03	8	82.5	3.5
	Meropenem	>0.06	>0.06	100.0	0.0
	Minocycline	1	16	77.2	12.3
	PipTazo	1	4	93.0	3.5
<i>Klebsiella</i> spp (n=49)	Tigecycline	0.5	1	93.9	6.1
	Amikacin	2	32	89.8	2.0
	AmoxClav	4	32	65.3	16.3
	Ampicillin	>32	>32	2.0	0.0
	Cefepime	>0.5	>32	81.6	4.1
	Ceftazidime	>8	>32	73.5	4.1
	Ceftriaxone	0.12	>64	71.4	6.1
	Imipenem	0.25	0.5	100.0	0.0
	Levofloxacin	0.06	>8	85.7	4.1
	Meropenem	>0.06	>0.06	100.0	0.0
	Minocycline	2	>16	75.0	8.2
	PipTazo	2	64	83.7	8.2
All ESBLs (n=20)	Tigecycline	0.5	1	95.0	5.0
	Amikacin	4	>64	75.0	10.0
	AmoxClav	16	32	35.0	35.0
	Ampicillin	>32	>32	0.0	100.0
	Cefepime	16	>32	45.0	10.0
	Ceftazidime	>32	>32	35.0	10.0
	Ceftriaxone	>64	>64	10.0	15.0
	Imipenem	0.25	0.5	100.0	0.0
	Levofloxacin	1	>8	55.0	10.0
	Meropenem	>0.06	0.25	100.0	0.0
	Minocycline	4	>16	55.0	30.0
	PipTazo	8	>128	75.0	10.0
<i>Serratia marcescens</i> (n=36)	Tigecycline	1	2	100.0	0.0
	Amikacin	2	8	91.7	5.6
	AmoxClav	>32	>32	0.0	2.8
	Ampicillin	>32	>32	0.0	2.8
	Cefepime	>0.5	4	91.7	2.8
	Ceftazidime	>8	>8	97.2	2.8
	Ceftriaxone	0.25	32	88.9	2.8
	Imipenem	0.5	1	100.0	0.0
	Levofloxacin	0.12	2	97.2	0.0
	Meropenem	0.12	0.25	100.0	0.0
	Minocycline	4	8	83.3	13.9
	PipTazo	2	4	97.2	0.0

\* Interpretive criteria as defined by CLSI, M100-S18 (2008), where applicable; na = CLSI breakpoints not available; ESBL=Extended Spectrum Beta-lactamase producing strain.

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

Organism	Drug	mcg/ml			
		MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus*	%Int %Res
<i>Acinetobacter</i> spp (n=72)	Tigecycline	0.5	1	na	na
	Amikacin	16	>64	55.6	8.3
	Cefepime	16	>32	45.8	12.5
	Ceftazidime	32	>32	31.9	9.7
	Ceftriaxone	>64	>64	19.4	18.1
	Imipenem	0.5	>16	85.7	2.4
	Levofloxacin	8	>8	40.3	8.3
	Meropenem	16	>16	36.7	0.0
	Minocycline	<=0.5	8	86.1	6.9
	PipTazo	64	>128	40.3	12.5
<i>Pseudomonas aeruginosa</i> (n=44)	Tigecycline	8	>16	na	na
	Amikacin	4	16	93.2	0.0
	Cefepime	4	32	77.3	6.8
	Ceftazidime	<=8	32	84.1	6.8
	Ceftriaxone	32	>64	18.2	38.6
	Imipenem	1	8	85.7	4.8
	Levofloxacin	1	>8	59.1	22.7
	Meropenem	1	8	87.0	4.3
	Minocycline	>16	>16	na	na
	PipTazo	4	64	90.9	0.0

\* Interpretive criteria as defined by CLSI, M100-S18 (2008), 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	mcg/ml			
		MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus*	%Int %Res
<i>Enterococcus</i> spp (n=56)	Tigecycline	0.06	0.25	100.0	0.0
	AmoxClav	0.5	>8	82.1	0.0
	Ampicillin	1	>16	83.9	0.0
	Ceftriaxone	>64	>64	1.8	0.0
	Levofloxacin	1	>32	60.7	0.0
	Linezolid	2	2	100.0	0.0
	Minocycline	8	>8	41.1	39.3
	Penicillin	2	>8	83.9	0.0
	Vancomycin	1	4	91.1	0.0
	<i>Staphylococcus aureus</i> (n=60)	Tigecycline	0.12	0.25	100.0
AmoxClav		1	>8	68.3	0.0
Ampicillin		16	>16	58.3	0.0
Ceftriaxone		4	>64	70.0	1.7
Imipenem		<=0.12	>16	74.4	0.0
Levofloxacin		0.12	8	80.0	1.7
Linezolid		2	2	100.0	0.0
Meropenem		0.25	16	66.7	0.0
Minocycline		<=0.25	0.5	100.0	0.0
Penicillin		>8	>8	58.3	0.0
Methicillin-Resistant <i>Staphylococcus aureus</i> (n=18)	Tigecycline	0.12	0.25	100.0	0.0
	AmoxClav	8	>8	0.0	0.0
	Ampicillin	>16	>16	0.0	0.0
	Ceftriaxone	64	>64	0.0	5.6
	Imipenem	1	>16	0.0	0.0
	Levofloxacin	4	>32	38.9	5.6
	Linezolid	2	2	100.0	0.0
	Meropenem	2	16	12.5	0.0
	Minocycline	<=0.25	2	100.0	0.0
	Penicillin	>8	>8	0.0	0.0
<i>Streptococcus agalactiae</i> (n=37)	Tigecycline	0.03	0.12	100.0	0.0
	Ampicillin	0.12	0.12	100.0	0.0
	Ceftriaxone	0.06	0.12	100.0	0.0
	Levofloxacin	0.5	1	100.0	0.0
	Linezolid	1	1	100.0	0.0
	Meropenem	<=0.12	<=0.12	100.0	0.0
	Minocycline	<=0.06	0.12	100.0	0.0
	Penicillin	0.5	0.5	100.0	0.0
	Vancomycin	0.5	0.5	100.0	0.0

\* Interpretive