Tigecycline Evaluation Surveillance Trial (T.E.S.T.) - Global In Vitro Antibacterial Activity against 14,706 Gram-positive and Gram-negative Pathogens

S. Bouchillon[1], T. Stevens[1], B. Johnson[1], J. Johnson[1], D. Hoban[1], A. Hsiung[1], M. Hackel[1], M. Person[1], M. Dowzicky[2]

[1]International Health Management Associates, Schaumburg, IL, USA
[2]Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL 60173
Tel: (847) 303-5003
Fax: (847) 303-5601
www.ihmainc.com

REVISED ABSTRACT

Background: Tigecycline, 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 tigecycline compared to amikacin, ampicillin, imipenem, cefepime, ceftazidime, ceftriaxone, levofloxacin, minocycline, and piperacillin-tazobactam against Gram-negative strains in addition to linezolid, penicillin, and vancomycin for the Gram-positive species. Isolates were collected from hospitals in North America, Europe and Asia throughout 2004. **Methods**: A total of 14,706 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentrations (MICs) were determined by the local laboratory using supplied broth microdilution panels from Dade Behring MicroScan and interpreted according to CLSI guidelines. **Results**: Tigecycline's activity was similar to imipenem against most *Enterobacteriaceae*. Tigecycline inhibited ESBL producers with a MIC equal to or less than 2 mcg/ml. Although similar to other classes of broad spectrum antimicrobial agents against non-fermenters, tigecycline was especially active against *Acinetobacter* spp. demonstrating the lowest MIC_{90} of 1 mcg/ml. Tigecycline successfully inhibited *S. aureus* with a MIC_{90} of 0.25 mcg/ml regardless of methicillin susceptibility phenotype. Similar results were noticed against *Enterococci* with a tigecycline MIC_{90} of 0.12 mcg/ml against all strains of *Enterococci* without regard to vancomycin susceptibility. **Conclusion**: Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed antimicrobials against a broad spectrum of aerobic clinical pathogens from a diverse geographical population. The presented data suggest that tigecycline may be an effective therapeutic option against many aerobic Gram-positive and Gram-negative bacteria, including problematic strains with ESBL, VRE and MRSA resistance phenotypes.

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 activity against aerobic and anaerobic Gram-negative pathogens [2-4].

Tigecycline resistance is very infrequent and is also difficult to select for 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*, which are commonly associated with serious nosocomial infections. Similar activity has been observed against *Enterobacteriaceae*, even extended-spectrum β-lactamase and AmpC producing strains [10]. Tigecycline has demonstrated MIC_{90} 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 in 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].

This study was designed to better define the in vitro activity of tigecycline in a large diverse population of clinical isolates collected from hospitals worldwide.

MATERIALS & METHODS

- 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 were collected and tested between January 2004 – December 2004 from 80 study centers in 19 countries.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring MicroScan, 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 NCCLS where applicable [12]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined as susceptible ≤ 2; intermediate = 4; and resistant ≥ 8.
- ESBL activity was confirmed by testing the following antibiotic disks: cefotaxime (30 µg), cefotaxime/clavulanic acid (30/10µg), and ceftazidime (30µg), ceftazidime/clavulanic acid (30/10µg). Antibiotic disks were manufactured by Oxoid Inc. Ogdensburg, New York. Mueller-Hinton agar used in testing was manufactured by Remel Inc. Lenexa, Kansas.
- An organism is interpreted as producin an ESBL if there is an increase of ≥ 5mm in the inhibition zone of the combination disc when compared to that of the cephalosporin alone: cefotaxime/clavulanic acid – cefotaxime ≥ 5 mm or ceftazidime/clavulanic acid – ceftazidime ≥ 5 mm.
- Isolates were identified to the genus and species level by the local laboratory. Each site tested the isolates using broth microdilution panels.
- Quality control of broth microdilution panels followed manufacture's and NCCLS guidelines using the following ATCC strains: *Enterococcus faecalis* ATTC 29212; *Escherichia coli* ATCC 25922; *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 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).

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RESULTS

Table 1. List of Countries and Number of Investigative Sites that Contributed to T.E.S.T. Program

Country	Investigative Sites
Australia	1
Austria	1
Canada	1
China	1
France	2
Germany	5
Hungary	1
India	1
Italy	2
Latvia	1
Pakistan	1
Philippines	1
Poland	1
Singapore	1
Spain	3
Switzerland	1
The Netherlands	1
United Kingdom	2
United States	53
Total	80

Table 2. In Vitro Activity of Tigecycline and Comparative Agents against 6,279 Selected Strains of *Enterobacteriaceae*

Organism Name[a]	Drug[b]	%SUS	%INT	%RES	MIC (mcg/mL) MIC_{50}	MIC_{90}
Enterobacteriaceae (n=6,279)	Tigecycline	96.8	2.6	0.6	0.5	1
	Ampicillin	16.5	6.2	77.3	>32	>32
	Amox-Clav	48.8	7.3	43.9	16	>32
	Ceftazidime	86.6	2.7	10.7	≤8	32
	Levofloxacin	87.4	2	10.6	0.06	8
	Ceftriaxone	88.1	4.6	7.2	0.12	16
	Minocycline	85.8	7.3	6.9	2	8
	Pip-Tazo	90.9	3.9	5.2	1	16
	Cefepime	95.4	1.2	3.3	≤0.5	2
	Imipenem	98.7	0.4	0.9	0.5	1
	Amikacin	98.8	0.6	0.6	2	4
E. coli (n=1,883)	Tigecycline	99.9	0.1	0	0.12	0.25
	Amikacin	99.3	0.3	0.4	2	4
	Amox-Clav	75.5	14.6	9.9	8	16
	Ampicillin	44.7	1	54.3	>32	>32
	Cefepime	97.1	0.8	2.1	≤0.5	≤0.5
	Ceftazidime	94.4	1.7	3.9	≤8	≤8
	Ceftriaxone	93.9	1.8	4.4	≤0.06	0.5
	Imipenem	99.7	0	0.3	0.25	0.5
	Levofloxacin	77.2	2.2	20.6	0.03	>8
	Minocycline	83.6	9.6	6.8	1	8
	Pip-Tazo	96.3	1.4	2.3	1	4
K. pneumoniae (n=1,492)	Tigecycline	94.2	5	0.8	0.5	2
	Amikacin	97.9	1.2	0.9	2	4
	Amox-Clav	81.6	7.9	10.5	2	32
	Ampicillin	3.6	15	81.5	>32	>32
	Cefepime	92.7	1.5	5.8	≤0.5	4
	Ceftazidime	86.7	1.6	11.7	≤8	32
	Ceftriaxone	87.9	3.9	8.2	≤0.06	32
	Imipenem	97.3	1.2	1.5	0.5	0.5
	Levofloxacin	88.9	1.4	9.7	0.06	4
	Minocycline	83	6.6	10.3	2	16
	Pip-Tazo	91.2	1.7	7.1	2	16
K. oxytoca (n=346)	Tigecycline	98.6	1.4	0	0.25	1
	Amikacin	99.1	0.3	0.6	2	4
	Amox/Clav	85.3	4.9	9.8	2	16
	Ampicillin	4.9	10.1	85	>32	>32
	Cefepime	97.1	0.9	2	≤0.5	1
	Ceftazidime	93.6	0.9	5.5	≤8	≤8
	Ceftriaxone	92.8	4.9	2.3	≤0.06	4
	Imipenem	99.4	0	0.6	0.5	0.5
	Levofloxacin	93.6	3.2	3.2	0.03	1
	Minocycline	93.1	4.9	2	1	4
	Pip-tazo	90.5	0.6	9	1	16
ESBL producers (*E. coli*, *K. pneumoniae*, *K. oxytoca*) (n=228)	Tigecycline	93.4	5.7	0.9	0.5	2
	Amikacin	90.4	4.4	5.3	4	16
	Amox/Clav	28.9	40.4	30.7	16	>32
	Ampicillin	0.9	0.9	98.2	>32	>32
	Cefepime	52.6	9.6	37.7	8	>32
	Ceftazidime	21.9	10.1	68	>32	>32
	Ceftriaxone	20.6	24.6	54.8	64	>64
	Imipenem	92.1	4.8	3.1	0.5	1
	Levofloxacin	39.5	5.7	54.8	8	>8
	Minocycline	67.4	10.6	22	4	>16
	Pip-tazo	70.6	5.3	24.1	8	>128
E. aerogenes (n=484)	Tigecycline	96.7	2.9	0.4	0.5	1
	Amikacin	97.7	1.9	0.4	2	4
	Amox/Clav	6.4	3.5	90.1	>32	>32
	Ampicillin	4.1	3.9	91.9	>32	>32
	Cefepime	95.5	1.2	3.3	≤0.5	1
	Ceftazidime	79.5	5.6	14.9	≤8	>32
	Ceftriaxone	89.3	6	4.8	0.12	16
	Imipenem	98.8	0	1.2	1	2
	Levofloxacin	92.8	2.5	4.8	0.06	1
	Minocycline	90.3	5	4.8	2	4
	Pip-tazo	88.4	8.1	3.5	2	32
E. agglomerans (n=25)	Tigecycline	96	4	0	0.25	2
	Amikacin	100	0	0	2	8
	Amox-Clav	48	4	48	16	>32
	Ampicillin	20	12	68	>32	>32
	Cefepime	100	0	0	≤0.5	4
	Ceftazidime	72	4	24	≤8	>32
	Ceftriaxone	76	8	16	0.25	>64
	Imipenem	96	4	0	0.5	1
	Levofloxacin	88	0	12	0.06	8
	Minocycline	76	16	8	4	8
	Pip-Tazo	92	4	4	2	8
E. cloacae (n=1,260)	Tigecycline	94.4	3.9	1.7	0.5	2
	Amikacin	99	0.3	0.7	2	2
	Amox/Clav	4	1.3	94.7	>32	>32
	Ampicillin	5.1	3.9	91	>32	>32
	Cefepime	94.9	1.6	3.5	≤0.5	4
	Ceftazidime	73.3	5.3	21.4	≤8	>32
	Ceftriaxone	76.2	9.6	14.1	0.25	64
	Imipenem	99	0.2	0.9	0.5	1
	Levofloxacin	92.5	2.2	5.3	0.06	2
	Minocycline	86	6.9	7.1	2	8
	Pip-tazo	81.1	10.2	8.7	2	64
S. marcescens (n=723)	Tigecycline	97.5	2.2	0.3	1	2
	Amikacin	99.3	0.1	0.6	2	4
	Amox/Clav	2.4	1.9	95.7	>32	>32
	Ampicillin	2.9	4.6	92.5	>32	>32
	Cefepime	97.1	1	1.9	<0.5	1
	Ceftazidime	91.8	2.2	5.9	≤8	≤8
	Ceftriaxone	92.8	3.2	4	0.25	4
	Imipenem	98.9	0.3	0.8	1	2
	Levofloxacin	95.7	1.4	2.9	0.12	1
	Minocycline	90.7	6.2	3	4	4
	Pip-tazo	95.4	2.8	1.8	1	8

a Only species with n >20 are represented.
b Breakpoints as defined by NCCLS where available (M100-S14), 2004. Tigecycline breakpoints defined as: susceptible ≤ 2; intermediate = 4; and resistant ≥ 8

Table 3. In Vitro Activity of Tigecycline and Comparative Agents Selected against 2,586 *Acinetobacter* spp and *Pseudomonas aeruginosa*

Organism Name[a]	Drug[b]	%SUS	%INT	%RES	MIC (mcg/mL) MIC_{50}	MIC_{90}
Acinetobacter spp (n=1,067)	Tigecycline	98.9	1.1	0	0.25	1
	Amikacin	81.5	6.3	12.2	4	64
	Amox-Clav	na	na	na	32	>32
	Ampicillin	na	na	na	>32	>32
	Cefepime	51.4	14.9	33.7	8	>32
	Ceftazidime	51	5.6	43.5	≤8	>32
	Ceftriaxone	32.8	22.1	45.1	32	>64
	Imipenem	86.1	4.8	9.1	0.5	8
	Levofloxacin	53	7.5	39.5	2	>8
	Minocycline	90.5	6.9	2.5	≤0.5	4
	Pip-Tazo	72.9	0	27.1	8	>128
Acinetobacter anitratus (n=21)	Tigecycline	100	0	0	0.12	0.25
	Amikacin	95.2	0	4.8	2	4
	Amox-Clav	na	na	na	16	32
	Ampicillin	na	na	na	16	32
	Cefepime	95.2	4.8	0	4	8
	Ceftazidime	90.5	4.7	4.8	≤8	≤8
	Ceftriaxone	57.1	38.1	4.8	8	16
	Imipenem	100	0	0	0.5	0.5
	Levofloxacin	100	0	0	0.12	0.5
	Minocycline	100	0	0	≤0.5	≤0.5
	Pip-Tazo	100	0	0	1	8
Acinetobacter baumannii (n=940)	Tigecycline	98.7	1.3	0	0.25	1
	Amikacin	80	6.9	13.1	4	64
	Amox-Clav	na	na	na	32	>32
	Ampicillin	na	na	na	>32	>32
	Cefepime	47.3	16.2	36.5	16	>32
	Ceftazidime	47.6	5.4	46.9	16	>32
	Ceftriaxone	28.2	22.6	49.3	32	>64
	Imipenem	84.6	5.1	10.3	0.5	16
	Levofloxacin	48.9	8.2	42.9	4	>8
	Minocycline	89.4	7.8	2.9	≤0.5	8
	Pip-Tazo	71	0	29	16	>128
Acinetobacter calcoaceticus (n=22)	Tigecycline	100	0	0	0.25	2
	Amikacin	95.5	0	4.5	2	4
	Amox-Clav	na	na	na	16	>32
	Ampicillin	na	na	na	16	>32
	Cefepime	72.7	9.1	18.2	4	32
	Ceftazidime	77.3	9.1	13.6	≤8	32
	Ceftriaxone	31.8	50	18.2	16	>64
	Imipenem	100	0	0	0.25	1
	Levofloxacin	77.3	0	22.7	0.12	>8
	Minocycline	95.5	4.5	0	≤0.5	1
	Pip-Tazo	90.9	0	9.1	2	64
Acinetobacter lwoffii (n=69)	Tigecycline	100	0	0	0.06	0.25
	Amikacin	100	0	0	1	2
	Amox-Clav	na	na	na	2	16
	Ampicillin	na	na	na	4	>32
	Cefepime	95.7	2.9	1.4	1	8
	Ceftazidime	84.1	7.2	8.7	≤8	16
	Ceftriaxone	88.4	10.1	1.4	4	16
	Imipenem	100	0	0	0.25	0.5
	Levofloxacin	95.7	4.3	0	0.06	0.5
	Minocycline	100	0	0	≤0.5	≤0.5
	Pip-Tazo	98.6	0	1.4	≤0.06	2
P. aeruginosa (n=1,519)	Tigecycline	4.7	10.8	84.5	8	>16
	Amikacin	95.4	1.7	2.9	4	8
	Amox/Clav	na	na	na	>32	>32
	Ampicillin	na	na	na	>32	>32
	Cefepime	74	14	12	4	32
	Ceftazidime	78.3	7.3	14.4	?8	32
	Ceftriaxone	13.1	15.8	71.1	>64	>64
	Imipenem	81.3	8.2	10.5	1	16
	Levofloxacin	62.4	7.1	30.5	1	>8
	Minocycline	4.6	11.8	83.5	>16	>16
	Pip/Tazo	88	0	12	4	128

a Only species with n >20 are represented.
b Breakpoints as defined by NCCLS where available (M100-S14), 2004. na = not available. Tigecycline breakpoints defined as: susceptible ≤ 2; intermediate = 4; and resistant ≥ 8

Table 4. In Vitro Activity of Tigecycline and Comparative Agents against 3,862 Selected Gram-positive Pathogens

Organism Name[a]	Drug[b]	%SUS	%INT	%RES	MIC (mcg/mL) MIC_{50}	MIC_{90}
S. aureus (n=1,883)	Tigecycline	99.9	0.1	0	0.12	0.25
	Amox-Clav	68.3	0	31.7	1	>8
	Ampicillin	9.2	0	90.8	16	>16
	Ceftriaxone	57.9	20.9	21.2	4	>64
	Imipenem	88.3	1.9	9.8	0.25	8
	Levofloxacin	59.1	6.8	[illegible]	0.25	32
	Linezolid	99.6	0	0.4	2	4
	Minocycline	98.3	1.5	0.2	≤0.25	0.5
	Penicillin	8.2	0	91.8	>8	>8
	Pip-Tazo	69.8	0	30.2	1	>16
	Vancomycin	100	0	0	1	1
Methicillin-Resistant *S. aureus* (n=819)	Tigecycline	99.9	0.1	0	0.12	0.25
	Amox-Clav	34.2	0	65.8	8	>8
	Ampicillin	1.1	0	98.9	>16	>16
	Ceftriaxone	12.9	43.3	43.7	32	>64
	Imipenem	76.4	3.3	20.3	0.5	>16
	Levofloxacin	22.3	18.9	58.7	8	>32
	Linezolid	99.8	0	0.2	2	4
	Minocycline	97.1	2.5	0.4	≤0.25	2
	Pip-Tazo	37.2	0	62.8	16	>16
	Penicillin	0.9	0	99.1	>8	>8
	Vancomycin	100	0	0	1	1
E. faecalis (n=825)	Tigecycline	100	0	0	0.12	0.12
	Amox-Clav	na	na	na	0.5	1
	Ampicillin	97.7	0	2.3	1	2
	Ceftriaxone	na	na	na	>64	>64
	Imipenem	na	na	na	1	2
	Levofloxacin	57.9	1	41.1	1	>32
	Linezolid	98.1	1.6	0.4	2	2
	Minocycline	38.2	46.1	15.7	8	[illegible]
	Pip-Tazo	na	na	na	2	8
	Penicillin	96.5	0	3.5	2	4
	Vancomycin	95.9	0.4	3.8	1	2
E. faecium (n=277)	Tigecycline	100	0	0	0.06	0.12
	Amox-Clav	na	na	na	>8	>8
	Ampicillin	19.1	0	80.9	>16	>16
	Ceftriaxone	na	na	na	>64	>64
	Imipenem	na	na	na	>16	>16
	Levofloxacin	15.2	1.8	83	>32	>32
	Linezolid	94.6	2.5	2.9	2	2
	Minocycline	66.4	21.9	11.7	0.5	8
	Pip-Tazo	na	na	na	>16	>16
	Penicillin	15.5	0	84.5	>8	>8
	Vancomycin	52	1.1	46.9	2	>32
Vancomycin-resistant Enterococci (n=161)	Tigecycline	100	0	0	0.06	0.12
	Amox-Clav	na	na	na	>8	>8
	Ampicillin	14.9	0	85.1	>16	>16
	Ceftriaxone	na	na	na	>64	>64
	Imipenem	na	na	na	>16	>16
	Levofloxacin	3.1	0	96.9	>32	>32
	Linezolid	93.8	2.5	3.7	2	2
	Minocycline	54.4	35	10.6	4	8
	Pip-Tazo	na	na	na	>16	>16
	Penicillin	11.8	0	88.2	>8	>8
	Vancomycin	0	0	100	>32	>32
S. agalactiae (n=716)	Tigecycline	100	0	0	0.12	[illegible]
	Amox-Clav	na	na	na	≤0.06	0.12
	Ampicillin	100	0	0	0.12	0.12
	Ceftriaxone	95.4	0	4.5	0.06	0.12
	Imipenem	na	na	na	[illegible]	[illegible]
	Levofloxacin	96.2	0.3	3.5	0.5	1
	Linezolid	99.9	0	0.1	1	1
	Minocycline	na	na	na	8	>8
	Pip-Tazo	na	na	na	≤0.25	≤0.25
	Penicillin	100	0	0	≤0.06	≤0.06
	Vancomycin	100	0	0	0.5	0.5

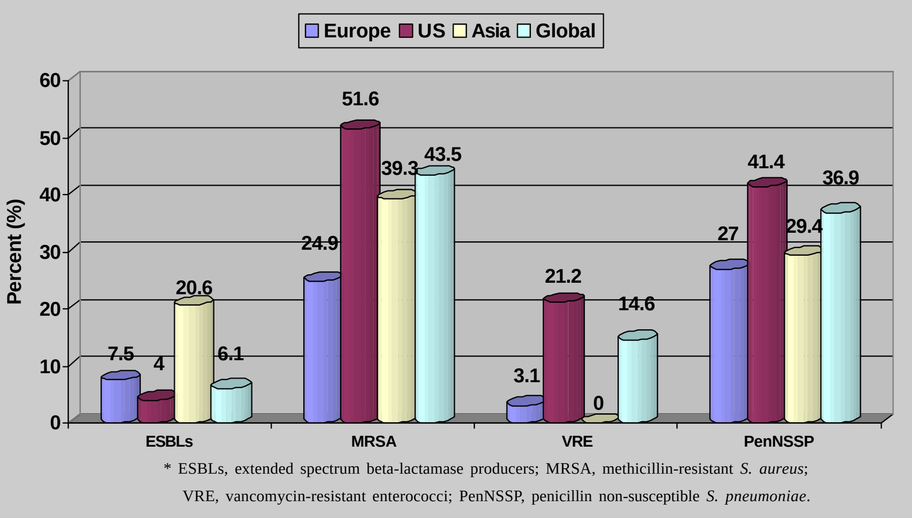
a Only species with n >20 are represented.
b Breakpoints as defined by NCCLS where available (M100-S14), 2004. na = not available. Tigecycline breakpoints defined as: susceptible ≤ 2; intermediate = 4; and resistant ≥ 8

Table 5. In Vitro Activity of Tigecycline and Comparative Agents against 2,114 Fastidious Respiratory Pathogens

Organism Name[a]	Drug[b]	%SUS	%INT	%RES	MIC (mcg/mL) MIC_{50}	MIC_{90}
S. pneumoniae (n=1,064)	Tigecycline	100	0	0	0.12	0.5
	Amox-Clav	94.6	2.4	2.9	≤0.03	2
	Ampicillin	na	na	na	≤0.06	2
	Ceftriaxone	98.1	0.9	0.9	≤0.03	1
	Imipenem	58.9	37.3	3.8	≤0.12	0.5
	Levofloxacin	98.7	0.4	0.9	0.5	1
	Linezolid	100	0	0	≤0.5	1
	Minocycline	na	na	na	≤0.25	4
	Pip-Tazo	na	na	na	≤0.25	2
	Penicillin	63.1	24.8	12.1	≤0.06	2
	Vancomycin	100	0	0	0.25	0.5
S. pneumoniae, Penicillin-Intermediate (n=264)	Tigecycline	100	0	0	0.12	0.5
	Amox-Clav	98.5	1.1	0.4	0.12	2
	Ampicillin	na	na	na	0.25	2
	Ceftriaxone	98.5	1.1	0.4	0.12	1
	Imipenem	26.1	70.8	3	0.25	0.5
	Levofloxacin	97.3	0.4	2.3	0.5	1
	Linezolid	100	0	0	≤0.5	1
	Minocycline	na	na	na	≤0.25	8
	Pip-Tazo	na	na	na	≤0.25	2
	Penicillin	0	100	0	0.25	1
	Vancomycin	100	0	0	0.25	0.5
S. pneumoniae, Penicillin-Resistant (n=129)	Tigecycline	100	0	0	0.12	0.5
	Amox-Clav	58.9	17.8	23.3	2	8
	Ampicillin	na	na	na	4	8
	Ceftriaxone	87.6	5.4	7	1	2
	Imipenem	0	75.2	24.8	0.5	1
	Levofloxacin	95.3	1.6	3.1	1	1
	Linezolid	100	0	0	≤0.5	1
	Minocycline	na	na	na	2	8
	Pip-Tazo	na	na	na	4	4
	Penicillin	0	0	100	2	4
	Vancomycin	100	0	1.6	0.25	0.5
H. influenzae (n=1,050)	Tigecycline	100	0	0	0.12	0.25
	Amikacin	na	na	na	4	8
	Amox-Clav	99.8	0	0.2	0.5	1
	Ampicillin	78	1.8	20.2	≤0.5	>32
	Cefepime	98.7	0	1.3	≤0.5	≤0.5
	Ceftazidime	0	0	100	≤8	≤8
	Ceftriaxone	99.7	0	0.3	≤0.06	≤0.06
	Imipenem	99.1	0	0.9	0.5	1
	Levofloxacin	99.1	0	0.9	0.015	0.03
	Minocycline	na	na	na	≤0.5	1
	Pip-Tazo	99.9	0	0.1	≤0.06	≤0.06
H. influenzae Beta-lactamase Positive (n=224)	Tigecycline	100	0	0	0.12	0.25
	Amikacin	na	na	na	4	8
	Amox-Clav	99.6	0	0.4	2	2
	Ampicillin	7.6	4.5	87.9	32	>32
	Cefepime	98.2	0	1.8	≤0.5	≤0.5
	Ceftazidime	0	0	100	≤8	≤8
	Ceftriaxone	99.1	0	0.9	≤0.06	≤0.06
	Imipenem	99.6	0	0.4	0.5	1
	Levofloxacin	99.6	0	0.4	0.015	0.015
	Minocycline	na	na	na	≤0.5	1
	Pip-Tazo	99.6	0	0.4	≤0.06	≤0.06

a Only species with n >20 are represented.
b Breakpoints as defined by NCCLS where available (M100-S14), 2004. na = not available. Tigecycline breakpoints defined as: susceptible ≤ 2; intermediate = 4; and resistant ≥ 8

Figure 1. Resistant Phenotype* Rates (%) by Region



* ESBLs, extended spectrum beta-lactamase producers; MRSA, methicillin-resistant *S. aureus*; VRE, vancomycin-resistant enterococci; PenNSSP, penicillin non-susceptible *S. pneumoniae*.

CONCLUSIONS

- Tigecycline inhibited 97% of all *Enterobacteriaceae* tested *in vitro* at an MIC of 2 mcg/mL.
- Tigecycline's MIC_{90} of 1 mcg/mL was equivalent to imipenem and 8 to 64 fold lower than the beta-lactams, beta-lactam/beta-lactamase inhibitor combinations and levofloxacin against all *Enterobacteriaceae* tested.
- Tigecycline demonstrated potent in vitro activity against both ESBL and non-ESBL producing *E. coli* and *K. pneumoniae* and *K. oxytoca*.
- Tigecycline inhibited >98% of *Acinetobacter* spp. tested *in vitro* at an MIC of 2 mcg/mL.
- Tigecycline's MIC_{90} of 1 mg/mL against *Acinetobacter* spp. was the lowest among all broad spectrum antimicrobials tested.
- Tigecycline's limited activity against *P. aeruginosa* is similar to other tetracyclines and their analog derivatives.
- Tigecycline inhibited the growth of 99.9% of *Staphylococcus aureus* at a MIC of 1 mcg/mL regardless of methicillin susceptibility and demonstrated *in vitro* activity against MRSA greater than levofloxacin, imipenem and the β-lactam antimicrobials and activity comparable to linezolid and vancomycin.
- Tigecycline had the lowest MIC_{90}, 0.12 mcg/mL, of all comparative agents against both *Enterococcus faecium* and *Enterococcus faecalis*.
- Tigecycline MIC_{90}s were several folds lower than linezolid, minocycline and levofloxacin against vancomycin-resistant *Enterococcus faecium* and *E. faecalis*.
- Tigecycline inhibited 100% of *Enterococcus faecium* and *Enterococcus faecalis* at MICs below the suggested breakpoint of 2 mcg/mL without regard to vancomycin susceptibility phenotype.
- Tigecycline inhibited the growth all *S. pneumoniae* and *H. influenzae* at MICs ≤ 2 mcg/mL and was unaffected, respectively, by penicillin susceptibility phenotype and the production of beta-lactamase.
- The in vitro activity of tigecycline in this study suggests that tigecycline is a promising compound in the treatment of serious nosocomial infections caused by the most commonly encountered clinical pathogens.