#E-288

A Comparison of the Efficacy of Tigecycline from University Hospitals in Europe and the United States

S. Bouchillon[1], B. Johnson[1], M. Hackel[1], J. Johnson[1], D. Hoban[1], R. Badal[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 is the most significant broad-spectrum injectable antimicrobial agent approved since the introduction of ticarcillin-clavulanic (1985) acid and piperacillin-tazobactam (1993). Since the approval of tigecycline in 2005, very little information is available on direct comparative activity of tigecycline among large sets of geographically diverse populations such as Europe and the United States. This study looks at the activity of tigecycline and 13 comparators in nosocomial isolates from the T.E.S.T. study for the years 2004 through 2006 in these regions. **Methods**: More than 30,000 isolates were collected from 271 investigative sites in Europe (n=6,102) and the United States (n=24,151). MICs were determined by broth microdilution according to CLSI guidelines using identical panels. **Results**: Summary data for tigecycline and key species are as follows:

	Europe		United States	
Organism	**N**	**MIC_{50}/MIC_{90}**	**N**	**MIC_{50}/MIC_{90}**
Acinetobacter spp	131	0.25 / 1	562	0.25/1
Enterobacteriaceae	915	0.25 / 1	3690	0.25/1
ESBLs	40	0.25 / 1	59	0.5/2
Enterococcus spp	101	0.12 / 0.12	523	0.06/0.12
VREs	5	0.06 / 0.12	69	0.06/0.12
P. aeruginosa	170	8/16	789	8/>16
S. aureus	304	0.12 / 0.25	1127	0.12/0.12
MRSA	58	0.12 / 0.25	571	0.12/0.25
S. pneumoniae	226	0.03 / 0.12	801	0.03/0.06

Conclusion: Tigecycline demonstrated potent in vitro activity in the majority of strains and phenotypes. Tigecycline activity was retained even against strains resistant to other antimicrobials, including ESBL-producers, *Acinetobacter* spp., methicillin-resistant *S. aureus*, vancomycin-resistant *enterococci*, and *S. pneumoniae*.

INTRODUCTION

Tigecycline is a member of a new class of antimicrobial agents, the glycylcyclines. This synthetic analogue of the tetracyclines exhibits significant antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as fourfold better than vancomycin and daptomycin [1, 2]. The development of tigecycline is important in that tigecycline and other glycylcyclines are active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. Certain substituents at the 9-position of the tetracycline molecule restored activity against bacteria harboring genes encoding either or both efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible gram-positive, gram-negative, aerobic, and anaerobic bacteria [3]. Furthermore, resistance to tigecycline is difficult to produce even in the laboratory.

Previous studies have demonstrated excellent in vitro activity for tigecycline against clinical and laboratory strains of gram-positive and -negative bacteria with minimum inhibitory concentrations for the 90[th] percentile inhibited at or below 2 mcg/mL, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE) and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [4-6]. This study was undertaken to document the in vitro activity of tigecycline against significant numbers of clinical isolates collected worldwide from Europe and United States populations. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

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 other defined sources. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution. Only one isolate per patient was accepted.
- All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age or gender. All sites identified each study isolate utilizing local laboratory site criteria.
- 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).
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [12]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers, MicroScan (Dade Behring Inc., West Sacramento, CA, USA) and Trek (TREK Diagnostic Systems, Cleveland, OH). The following antimicrobial agents were included on the panels with their dilution ranges (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); 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).
- ESBL Determination: *Escherichia coli*, *Klebsiella pneumonae* and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftriaxone were >1 mcg/ml using broth microdilution panels. ESBL activity was confirmed using the CLSI (2006) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2006) guidelines. ESBL presence was confirmed by testing the following antibiotic disks: cefotaxime (30-mcg), cefotaxime/clavulanic acid (30/10-mcg), ceftazidime (30-mcg), and ceftazidime/clavulanic acid (30/10-mcg). Antimicrobial disks were manufactured by Oxoid, Inc. (Ogdensburg, NY, USA). Mueller-Hinton agar used in testing was manufactured by Remel, Inc. (Lenexa, KS, USA). An organism was interpreted as containing an ESBL if there was an increase of >5 mm in the inhibition zone of the combination disk when compared to that of the cephalosporin alone.
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains where applicable: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922 and 35218; *Haemophilus influenzae* ATCC 49247 and 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; *Pseudomonas aeruginosa* ATCC 27853 and *Klebsiella pneumoniae* ATCC 700603 (as positive ESBL control).
- Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2005) guidelines [8].

REFERENCES

1. Hoellman, D.B., et al., *Antipneumococcal activities of GAR-936 (a new glycylcycline) compared to those of nine other agents against penicillin-susceptible and -resistant pneumococci.* Antimicrob Agents Chemother, 2000. 44(4): p. 1085-8.
2. Labthavikul, P., P.J. Petersen, and P.A. Bradford, *In vitro activity of tigecycline against Staphylococcus epidermidis growing in an adherent-cell biofilm model.* Antimicrob Agents Chemother, 2003. 47(12): p. 3967-9.
3. Projan, S.J., *Preclinical pharmacology of GAR-936, a novel glycylcycline antibacterial agent. Pharmacotherapy,* 2000. 20(9 Pt 2): p. 219S-223S; discussion 224S-228S.
4. Gales, A.C. and R.N. Jones, *Antimicrobial activity and spectrum of the new glycylcycline, GAR-936 tested against 1,203 recent clinical bacterial isolates*. Diagn Microbiol Infect Dis, 2000. 36(1): p. 19-36.
5. Patel, R., et al., *In vitro activity of GAR-936 against vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus and penicillin-resistant Streptococcus pneumoniae*. Diagn Microbiol Infect Dis, 2000. 38(3): p. 177-9.
6. Rupp, M.E. and P.D. Fey, *Extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae: considerations for diagnosis, prevention and drug treatment*. Drugs, 2003. 63(4): p. 353-65.
7. *Clinical Laboratory Standards Institute, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Seventh Edition, in Document M7-A7*. 2007: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
8. *Clinical Laboratory Standards Institute, Performance Standards for Antimicrobial Susceptibility Testing, in Document M100-S17*. 2007: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
9. Tygacil, *Product Insert*. 2005: Wyeth Pharmaceuticals, Inc., Philadelphia, PA, USA.

ACKNOWLEDGEMENTS

We gratefully acknowledge the contributions of the investigators, laboratory personnel and all members of the Tigecycline Evaluation Study Trials program group. This study was sponsored by a grant from Wyeth Pharmaceuticals.

RESULTS

The results are listed in the following Tables.

Table 1. In Vitro Activity of Tigecycline and Comparative Antimicrobial Agents against Gram-Positive Clinical Pathogens Isolated from Europe and the United States[d].

Organism/		Europe			United States		
Phenotype (N)	Drug	MIC_{50}[a,c]	MIC_{90}	%Sus[b]	MIC_{50}	MIC_{90}	%Sus
E. faecalis	Tigecycline	0.12	0.12	100	0.06	0.12	100
Europe (n=84)	Ampicillin	1	2	100	1	1	100
United States	Levofloxacin	1	32	77.4	1	>32	60.6
(n=416)	Linezolid	2	2	98.8	2	2	99.3
	Minocycline	8	>8	35.7	8	8	43.3
	Penicillin	2	4	100	2	4	100
	Vancomycin	1	2	98.8	1	2	96.9
Vancomycin-	Tigecycline	0.03	0.03	100	0.06	0.12	100
Resistant,	Ampicillin	2	2	100	1	1	100
E. faecalis	Levofloxacin	16	16	0	32	>32	0
Europe (n=1)	Linezolid	≤0.5	≤0.5	100	1	2	100
United States	Minocycline	2	2	100	4	8	63.6
(n=11)	Penicillin	8	8	100	2	4	100
	Vancomycin	>32	>32	0	>32	>32	0
E. faecium	Tigecycline	0.06	0.12	100	0.03	0.12	100
Europe (n=17)	Ampicillin	>16	>16	29.4	>16	>16	14.6
United States	Levofloxacin	>32	>32	29.4	>32	>32	9.4
(n=96)	Linezolid	2	4	88.2	2	2	97.9
	Minocycline	≤0.25	>8	70.6	≤0.25	8	75
	Penicillin	>8	>8	23.5	>8	>8	11.5
	Vancomycin	1	>32	76.5	>32	>32	38.5
Vancomycin-	Tigecycline	0.06	0.12	100	0.03	0.12	100
Resistant,	Ampicillin	>16	>16	0	>16	>16	5.2
E. faecium	Levofloxacin	>32	>32	0	>32	>32	0
Europe (n=4)	Linezolid	2	4	75	2	2	98.3
United States	Minocycline	≤0.25	>8	75	≤0.25	8	75.9
(n=58)	Penicillin	>8	>8	0	>8	>8	1.7
	Vancomycin	>32	>32	0	>32	>32	0
S. aureus	Tigecycline	0.12	0.25	100	0.12	0.12	100
Europe (n=304)	AmoxClav	1	8	87.8	2	>8	64.2
United States	Ampicillin	4	>16	22.7	16	>16	9.3
(n=1127)	Ceftriaxone	2	64	84.5	8	64	56.1
	Imipenem	≤0.12	1	93.1	0.25	2	95.3
	Levofloxacin	0.12	8	83.9	0.25	32	65.4
	Linezolid	2	4	100	2	2	100
	Minocycline	≤0.25	0.5	99	≤0.25	≤0.25	99.4
	Penicillin	8	>8	18.4	>8	>8	8.2
	PipTazo	0.5	>16	88.5	2	>16	69.3
	Vancomycin	0.5	1	100	0.5	1	100
S. aureus, MSSA	Tigecycline	0.12	0.12	100	0.12	0.12	100
Europe (n=246)	AmoxClav	0.5	2	100	1	2	100
United States	Ampicillin	2	>16	28	4	>16	18.9
(n=556)	Ceftriaxone	2	4	100	2	4	99.1
	Imipenem	≤0.12	0.25	100	≤0.12	0.25	100
	Levofloxacin	0.12	0.25	98.8	0.12	0.5	95.9
	Linezolid	2	4	100	2	2	100
	Minocycline	≤0.25	≤0.25	98.8	≤0.25	≤0.25	99.1
	Penicillin	4	>8	22.8	8	>8	16.5
	PipTazo	0.5	1	100	0.5	1	100
	Vancomycin	0.5	1	100	0.5	1	100
S. aureus, MRSA	Tigecycline	0.12	0.25	100	0.12	0.25	100
Europe (n=58)	AmoxClav	8	>8	36.2	8	>8	29.4
United States	Ampicillin	>16	>16	0	>16	>16	0
(n=571)	Ceftriaxone	64	>64	19	16	>64	14.2
	Imipenem	1	>16	62.3	0.5	4	90.8
	Levofloxacin	8	32	20.7	4	>32	35.7
	Linezolid	2	4	100	2	2	100
	Minocycline	≤0.25	4	100	≤0.25	≤0.25	99.6
	Penicillin	>8	>8	0	>8	>8	0
	PipTazo	>16	>16	39.7	16	>16	39.4
	Vancomycin	1	2	100	1	1	100
S. agalactiae	Tigecycline	0.03	0.12	100	0.03	0.12	100
Europe (n=158)	Ampicillin	0.12	0.12	2.5	0.12	0.12	2.6
United States	Ceftriaxone	0.06	0.12	2.5	0.06	0.12	2.6
(n=777)	Levofloxacin	0.5	1	1.9	0.5	1	2.6
	Linezolid	1	1	2.5	1	1	2.6
	Penicillin	≤0.06	0.12	2.5	≤0.06	0.12	2.6
	Vancomycin	0.5	0.5	2.5	0.5	0.5	2.6
S. pneumoniae	Tigecycline	0.03	0.12	na	0.03	0.06	na
Europe (n=226)	AmoxClav	≤0.03	1	97.8	≤0.03	2	92.4
United States	Ceftriaxone	≤0.03	0.5	98.2	≤0.03	1	96.6
(n=801)	Imipenem	≤0.12	0.25	85.1	≤0.12	0.5	70.8
	Levofloxacin	0.5	1	100	0.5	1	99.8
	Linezolid	≤0.5	1	100	≤0.5	1	100
	Minocycline	≤0.25	4	na	≤0.25	4	na
	Penicillin	≤0.06	1	74.8	≤0.06	2	55.3
	Vancomycin	0.25	0.5	99.6	0.25	0.5	100
Penicillin	Tigecycline	0.03	0.12	na	0.03	0.06	na
Susceptible	AmoxClav	≤0.03	≤0.03	100	≤0.03	≤0.03	100
S. pneumoniae	Ceftriaxone	≤0.03	≤0.03	100	≤0.03	0.06	100
Europe (n=169)	Imipenem	≤0.12	≤0.12	100	≤0.12	≤0.12	100
United States	Levofloxacin	0.5	1	100	0.5	1	100
(n=443)	Linezolid	≤0.5	1	100	≤0.5	1	100
	Minocycline	≤0.25	2	na	≤0.25	≤0.25	3.6
	Penicillin	≤0.06	≤0.06	100	≤0.06	≤0.06	100
	Vancomycin	0.25	0.5	100	0.25	0.5	100
Penicillin	Tigecycline	0.06	0.12	na	0.03	0.06	na
Intermediate	AmoxClav	0.12	1	100	0.12	1	99.1
S. pneumoniae	Ceftriaxone	0.12	0.5	100	0.12	0.5	99.1
Europe (n=39)	Imipenem	0.25	0.25	45.5	0.25	0.5	49.5
United States	Levofloxacin	0.5	1	100	0.5	1	99.6
(n=235)	Linezolid	≤0.5	1	100	1	1	100
	Minocycline	2	8	na	≤0.25	8	3.4
	Penicillin	0.5	1	0	0.25	1	0
	Vancomycin	0.25	0.5	100	0.25	0.5	100
Penicillin	Tigecycline	0.03	0.12	na	0.03	0.06	na
Resistant	AmoxClav	1	4	72.2	2	8	52
S. pneumoniae	Ceftriaxone	1	4	77.8	1	2	79.7
Europe (n=18)	Imipenem	0.5	1	7.7	0.5	1	6.6
United States	Levofloxacin	1	1	100	1	1	99.2
(n=123)	Linezolid	≤0.5	1	100	≤0.5	1	100
	Minocycline	2	8	na	2	4	4.9
	Penicillin	2	4	0	2	4	0
	Vancomycin	0.25	0.5	94.4	0.25	0.5	100

[a]MIC in mcg/mL
[b]Interpretive criteria are defined by CLSI, M100-S16 (2006), where available; Tigecycline susceptible breakpoint is according to FDA package insert (2005), where available [9]; Tigecycline FDA breakpoints (susceptible ≤0.25 mcg/mL) for *enterococci* are approved for vancomycin-susceptible *E. faecalis*, only; this criteria has been applied to all *enterococci* for comparison purposes only.
[c]Except for phenotypes, sample sizes <20 were not included.
na = breakpoints are not yet established for against this species.
[d]European susceptibilities do not utilize EUCAST breakpoints. FDA breakpoints are applied to both EU and US isolates.

Table 2. In Vitro Activity of Tigecycline and Comparative Antimicrobial Agents against Gram-Negative Clinical Pathogens Isolated from Europe and the United States[e].

Organism/		Europe			United States		
Phenotype (N)	Drug	MIC_{50}[a,d]	MIC_{90}	%Sus[b]	MIC_{50}	MIC_{90}	%Sus
Enterobacteriaceae	Tigecycline	0.25	1	97.9	0.25	1	97.2
Europe (n=915)	Amikacin	2	4	98.3	2	4	99.4
United States (n=3690)	AmoxClav	8	>32	52.6	8	>32	53.9
	Ampicillin	>32	>32	17.4	>32	>32	17.1
	Cefepime	≤0.5	4	93.8	≤0.5	≤0.5	97.9
	Ceftazidime	≤8	32	86.8	≤8	≤8	92.1
	Ceftriaxone	≤0.06	32	86.9	≤0.06	2	93.9
	Imipenem	0.25	1	99.5	0.25	1	99.9
	Levofloxacin	0.06	8	85.6	0.06	4	89.2
	Minocycline	2	8	86.7	2	8	86.8
	PipTazo	1	32	88.2	1	8	94.7
E. aerogenes	Tigecycline	0.5	2	96.6	0.5	1	95.9
Europe (n=58)	Amikacin	2	8	94.8	2	4	99.7
United States (n=291)	AmoxClav	>32	>32	1.7	>32	>32	1.4
	Ampicillin	>32	>32	0	>32	>32	0
	Cefepime	≤0.5	16	87.9	≤0.5	≤0.5	98.6
	Ceftazidime	≤8	>32	60.3	≤8	≤8	90
	Ceftriaxone	0.5	64	70.7	0.12	2	96.2
	Imipenem	0.5	2	98.1	1	1	100
	Levofloxacin	0.06	>8	75.9	0.06	0.25	95.9
	Minocycline	2	8	89.7	2	4	93.1
	PipTazo	4	64	75.9	2	8	93.8
E. cloacae	Tigecycline	0.5	1	96.2	0.5	2	94.3
Europe (n=130)	Amikacin	1	2	99.2	2	2	99.2
United States (n=653)	AmoxClav	>32	>32	0.8	>32	>32	2.3
	Ampicillin	>32	>32	0	>32	>32	0
	Cefepime	≤0.5	4	96.9	≤0.5	2	96.5
	Ceftazidime	≤8	>32	75.4	≤8	32	82.1
	Ceftriaxone	0.25	64	80	0.25	32	84.7
	Imipenem	0.5	1	100	0.5	1	99.8
	Levofloxacin	0.03	0.5	93.1	0.03	1	92.8
	Minocycline	2	4	90	2	8	84.4
	PipTazo	2	64	80.8	2	32	87.3
E. coli	Tigecycline	0.12	0.25	100	0.12	0.25	100
Europe (n=335)	Amikacin	2	4	99.7	2	4	99.6
United States (n=1275)	AmoxClav	4	32	73.2	4	16	79.8
	Ampicillin	>32	>32	44.2	16	>32	49.4
	Cefepime	≤0.5	4	93.5	≤0.5	≤0.5	98.3
	Ceftazidime	≤8	?8	93.8	≤8	≤8	95.5
	Ceftriaxone	≤0.06	16	89.9	≤0.06	0.12	96.5
	Imipenem	0.25	0.5	100	0.25	0.5	100
	Levofloxacin	0.03	>8	77.2	0.03	>8	80.1
	Minocycline	1	8	84.2	1	8	86.4
	PipTazo	1	8	93.5	1	2	97.6
E. coli, ESBL	Tigecycline	0.12	0.5	100	0.25	0.5	100
Europe (n=21)	Amikacin	2	8	100	4	8	95.5
United States (n=22)	AmoxClav	16	32	23.8	16	>32	36.4
	Ampicillin	>32	>32	0	>32	>32	0
	Cefepime	32	>32	23.8	32	>32	31.8
	Ceftazidime	16	>32	33.3	32	>32	22.7
	Ceftriaxone	>64	>64	14.3	>64	>64	27.3
	Imipenem	0.25	0.5	100	0.25	0.5	100
	Levofloxacin	8	>8	28.6	>8	>8	4.5
	Minocycline	2	>16	61.9	2	8	72.7
	PipTazo	2	>128	71.4	4	64	81.8
H. influenzae	Tigecycline	0.12	0.5	na	0.12	0.5	na
Europe (n=233)	AmoxClav	0.25	1	99.6	0.5	1	99.7
United States (n=746)	Ampicillin	≤0.5	4	87.1	≤0.5	>32	67.6
	Cefepime	≤0.5	≤0.5	99.6	≤0.5	≤0.5	99.2
	Ceftazidime	≤8	≤8	0	≤8	≤8	0
	Ceftriaxone	≤0.06	≤0.06	99.6	≤0.06	≤0.06	100
	Imipenem	0.25	1	100	0.5	1	100
	Levofloxacin	0.015	0.03	100	0.015	0.015	100
	PipTazo	≤0.06	≤0.06	99.6	≤0.06	≤0.06	99.9
Beta-lactamase Negative	Tigecycline	0.12	0.5	na	0.12	0.5	na
H. influenzae	AmoxClav	0.25	1	100	0.25	1	100
Europe (n=204)	Ampicillin	≤0.5	≤0.5	99.5	≤0.5	≤0.5	98.6
United States (n=511)	Cefepime	≤0.5	≤0.5	100	≤0.5	≤0.5	99
	Ceftazidime	≤8	≤8	0	≤8	≤8	0
	Ceftriaxone	≤0.06	≤0.06	100	≤0.06	≤0.06	100
	Imipenem	0.25	1	100	0.5	1	100
	Levofloxacin	0.015	0.015	100	0.015	0.015	100
	PipTazo	≤0.06	≤0.06	100	≤0.06	≤0.06	100
Beta-lactamase Positive	Tigecycline	0.12	0.25	na	0.12	0.5	na
H. influenzae	AmoxClav	0.5	2	96.6	1	2	99.1
Europe (n=29)	Ampicillin	32	>32	0	32	>32	0
United States (n=235)	Cefepime	≤0.5	≤0.5	96.6	≤0.5	≤0.5	99.6
	Ceftazidime	≤8	≤8	0	≤8	≤8	0
	Ceftriaxone	≤0.06	0.25	96.6	≤0.06	≤0.06	100
	Imipenem	0.25	0.5	100	0.5	1	100
	Levofloxacin	0.015	0.03	100	0.015	0.015	100
	PipTazo	≤0.06	0.5	96.6	≤0.06	≤0.06	99.6
K. oxytoca	Tigecycline	0.25	0.5	100	0.25	0.5	98.8
Europe (n=65)	Amikacin	1	4	100	2	4	100
United States (n=166)	AmoxClav	4	32	84.6	2	8	92.2
	Ampicillin	>32	>32	0	>32	>32	0
	Cefepime	≤0.5	1	96.9	≤0.5	≤0.5	99.4
	Ceftazidime	≤8	≤8	95.4	≤8	≤8	97
	Ceftriaxone	≤0.06	8	90.8	≤0.06	0.25	98.8
	Imipenem	0.25	0.5	100	0.25	0.5	100
	Levofloxacin	0.03	0.12	95.4	0.03	0.25	97
	Minocycline	1	2	96.9	1	2	97
	PipTazo	1	128	84.6	1	4	95.2
K. oxytoca, ESBL[c]	Tigecycline	0.5	0.5	100	1	1	100
Europe (n=1)	Amikacin	1	1	100	4	16	100
United States (n=2)	AmoxClav	8	8	100	32	32	0
	Ampicillin	>32	>32	0	>32	>32	0
	Cefepime	1	1	100	1	16	50
	Ceftazidime	≤8	≤8	100	>32	>32	0
	Ceftriaxone	64	64	0	4	>64	50
	Imipenem	0.12	0.12	100	0.5	0.5	100
	Levofloxacin	0.03	0.03	100	4	>8	0
	Minocycline	1	1	100	2	4	100
	PipTazo	1	1	100	8	>128	50
K. pneumoniae	Tigecycline	0.5	1	96.1	0.5	2	95
Europe (n=204)	Amikacin	1	8	94.6	2	2	98.7
United States (n=875)	AmoxClav	2	32	77.9	2	16	89.7
	Ampicillin	>32	>32	0	>32	>32	0
	Cefepime	≤0.5	8	91.2	≤0.5	≤0.5	97.6
	Ceftazidime	≤8	32	85.3	≤8	≤8	92.8
	Ceftriaxone	≤0.06	32	87.3	≤0.06	0.5	95.2
	Imipenem	0.25	0.5	100	0.25	0.5	99.6
	Levofloxacin	0.06	2	90.2	0.06	1	92.8
	Minocycline	2	16	83.8	2	16	82.7
	PipTazo	1	32	87.7	2	8	95.1
K. pneumoniae, ESBL[c]	Tigecycline	0.5	2	100	1	4	82.9
Europe (n=18)	Amikacin	8	>64	72.2	8	32	80
United States (n=35)	AmoxClav	16	32	22.2	16	>32	40
	Ampicillin	>32	>32	0	>32	>32	0
	Cefepime	16	>32	44.4	8	>32	68.6
	Ceftazidime	32	>32	16.7	>32	>32	8.6
	Ceftriaxone	32	>64	22.2	32	>64	25.7
	Imipenem	0.5	0.5	100	0.25	0.5	96.3
	Levofloxacin	4	>8	44.4	>8	>8	31.4
	Minocycline	2	>16	50	4	>16	60
	PipTazo	16	>128	50	16	>128	54.3
S. marcescens	Tigecycline	1	2	95.3	1	2	97.9
Europe (n=85)	Amikacin	2	4	100	2	4	99.7
United States (n=386)	AmoxClav	>32	>32	0	>32	>32	1
	Ampicillin	>32	>32	0	>32	>32	0
	Cefepime	≤0.5	2	96.5	≤0.5	1	98.2
	Ceftazidime	≤8	16	87.1	≤8	≤8	95.1
	Ceftriaxone	0.25	16	89.4	0.25	4	93.5
	Imipenem	0.5	1	96.2	0.5	1	100
	Levofloxacin	0.12	2	94.1	0.12	1	95.6
	Minocycline	2	8	88.2	2	4	92
	PipTazo	1	32	88.2	1	4	97.2
Acinetobacter spp.	Tigecycline	0.25	1	na	0.25	1	na
Europe (n=131)	Amikacin	2	>64	76.3	2	16	92.2
United States (n=562)	Cefepime	8	>32	60.3	4	>32	66.5
	Ceftazidime	≤8	>32	60.3	≤8	>32	64.1
	Ceftriaxone	16	>64	38.9	16	>64	45.9
	Imipenem	0.5	8	87.2	0.5	4	92.7
	Levofloxacin	0.12	>8	65.6	0.25	>8	66.9
	Minocycline	≤0.5	1	98.5	≤0.5	4	92.2
	PipTazo	4	>128	70.2	1	128	74.7
P. aeruginosa	Tigecycline	8	16	na	8	>16	na
Europe (n=170)	Amikacin	4	16	92.9	4	8	97.6
United States (n=789)	Cefepime	4	16	75.9	4	16	85.4
	Ceftazidime	≤8	32	79.4	≤8	16	90.4
	Ceftriaxone	32	>64	18.8	32	>64	22.4
	Imipenem	1	16	83.5	1	8	89.3
	Levofloxacin	1	>8	68.8	1	>8	68.2
	Minocycline	>16	>16	10	>16	>16	6.2
	PipTazo	4	64	83.5	4	32	88.6

[a]MIC in mcg/mL
[b]Interpretive criteria as defined by CLSI, M100-S16 (2006), where available; Tigecycline susceptible breakpoint is according to FDA package insert (2005), where available [9]
[c]Extended Spectrum Beta-Lactamase producing strains
[e]Except for phenotypes, sample sizes <20 were not included.
na = breakpoints are not established for this drug against this species.
[e]European susceptibilities do not utilize EUCAST breakpoints. FDA breakpoints are applied to both EU and US isolates.

CONCLUSIONS

- Many antimicrobial agents can and frequently do demonstrate geographic differences in activity; In this study, there were no demonstrable differences in MIC_{50} or MIC_{90} values for tigecycline against either Europe or United States strains of *Enterobacteriaceae*, *S. aureus*, *Acinetobacter* spp., *H. influenzae*, *Streptococcus* spp. or *Enterococcus* spp.
- Several study drugs demonstrated 2- to 8-fold increase in MIC_{90} values against Europe isolates compared to isolates from the United States.
- Tigecycline demonstrated comparable activity to imipenem with MIC_{90} of 1 mcg/mL against *Enterobacteriaceae*.
- The frequency of ESBL producing *Enterobacteriaceae* was higher in Europe isolates (40/624, 6.4%) than United States (59/2316, 2.5%).
- Penicillin non-susceptible rates for *S. pneumoniae* were lower in this sampling for Europe (57/226, 25.2%) vs United States (358/801, 44.7%) strains.
- Tigecycline showed potent activity against *S. pneumoniae* regardless of susceptibility to penicillin with a consistent MIC_{90} values of 0.12 mcg/ml in European centers and 0.06 mcg in centers from the United States, regardless of the penicillin phenotype.
- With MIC_{90} values of 0.25 mcg/ml tigecycline against MRSA demonstrates in vitro activity comparable in potency to commonly prescribed antimicrobial agents, linezolid and vancomycin, currently used for the treatment of serious staphylococcal infections without regard to isolate source.
- Tigecycline presented MIC_{90} of 0.12 mcg/ml against *Enterococcus* spp. regardless of vancomycin-resistant phenotype or geographic distribution.
- Tigecycline demonstrated excellent inhibitory activity against *Acinetobacter* spp. with the lowest study drug MIC_{90} of 1 mcg/ml.
- Tigecycline demonstrated potent in vitro inhibitory activity against *H. influenzae* unaffected by the presence of beta-lactamase.
- The in vitro activity of tigecycline in this study suggests that tigecycline is a suitable antimicrobial agent for consideration as empiric treatment of some of the most commonly encountered hospital and community acquired pathogens as well as many of the difficult to treat resistant phenotypes without regard to geographic considerations in this study.