

REVISED ABSTRACT

Background: The rapid emergence of multi-drug resistant pathogens has undermined the efficacy of many widely used broad spectrum antibacterials and prompted the development of newer antimicrobials. Tigecycline is a new glycylicycline shown to have broad spectrum activity against many hospital pathogens. The purpose of this study was to examine the activity of tigecycline and comparators to nosocomial pathogens isolated in the UK and Ireland between 2004-06. **Methods:** A total of 961 nosocomial pathogens were identified at each site and confirmed at a reference laboratory. MICs were determined at each site utilizing supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Results are in the table as follows:

	<i>E. coli</i> , <i>K. oxytoca/pneumoniae</i> n = 246		<i>Acinetobacter</i> spp. n = 71		<i>P. aeruginosa</i> n = 99		
	%S	MIC ₉₀	%S	MIC ₉₀	%S	MIC ₉₀	
Tigecycline	97	1	NA	1	NA	16	
Amikacin	99	4	88	32	96	8	
Cefepime	92	8	70	32	85	32	
Ceftazidime	90	≤8	69	>32	88	16	
Imipenem	100	0.5	90	2	89	8	
Levofloxacin	79	>8	73	>8	77	>8	
Minocycline	83	8	93	4	8	>16	
Pip/Tazo	94	8	73	>128	93	64	
		<i>S. aureus</i> n = 124		<i>Enterococcus</i> spp. n = 70		<i>S. pneumoniae</i> n = 69	
	%S	MIC ₉₀	%S	MIC ₉₀	%S	MIC ₉₀	
Tigecycline	100	0.25	97	0.12	NA	1	
Levofloxacin	78	8	36	>32	100	1	
Linezolid	100	4	96	2	100	1	
Minocycline	99	0.5	53	8	NA	2	
Vancomycin	100	1	91	2	100	0.5	

Conclusion: Tigecycline was as active as comparable agents against most *Enterobacteriaceae* spp, displayed the lowest MICs against *Acinetobacter* spp, and had minimal activity against *P. aeruginosa*. Against gram positives, tigecycline was as active as vancomycin and linezolid and superior to levofloxacin or minocycline.

INTRODUCTION

Previous studies have demonstrated excellent in vitro activity for tigecycline against clinical and laboratory strains of gram-positive and -negative bacteria. Minimum inhibitory concentrations for the 90th percentile were 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* [1-6]. This study was undertaken to document the in vitro activity of tigecycline and relevant comparators against significant numbers of nosocomial clinical pathogens isolated from hospitalized patients in 5 sites in the United Kingdom and Ireland. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, body fluids, and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested between 2004 to 2006 from 5 study centers in the United Kingdom and Ireland. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database, were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- 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 criteria.
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [7]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., West Sacramento, CA, USA). 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); ceftazidime (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 Clinical and Laboratory Standards Institute [8] and the recent US Food and Drug Administration package insert for tigecycline [9], where applicable.
- Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftaxone were >1 mcg/ml using broth microdilution panels. ESBL activity was confirmed using the CLSI (2006) phenotypic confirmatory disk test (Oxoid, Ogdenburg, 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. (Ogdenburg, 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. *K. pneumoniae* ATCC 700793 was used to QC the ESBL confirmation test.
- Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *E. coli* ATCC 25922; *E. coli* ATCC 35218; *H. influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *Pseudomonas aeruginosa* ATCC 27853; *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2006) guidelines [8].

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RESULTS

The results are listed in the following tables.

Table 1. In vitro activity of tigecycline and comparators against gram-negative pathogens.^a

Organism Name	Drug	%SUS ^b	%INT	%RES	MIC (mcg/ml)		MIC range (mcg/ml)		
					MIC ₅₀	MIC ₉₀	Low	High	
All <i>Enterobacteriaceae</i> (n=487)	Tigecycline	95.7	3.5	0.8	0.5	1	0.03	8	
	Amikacin	99.6	0.4	0	2	4	≤0.5	32	
	AmoxClav	47.4	9.7	42.9	16	>32	1	>32	
	Ampicillin	10.5	7	82.5	>32	>32	1	>32	
	Cefepime	95.3	1.4	3.3	≤0.5	4	≤0.5	>32	
	Ceftazidime	84	3.5	12.5	≤8	32	≤8	>32	
	Ceftaxone	81.1	7.6	11.3	0.12	64	≤0.06	>64	
	Imipenem	100	0	0	0.5	1	0.12	2	
	Levofloxacin	83.6	2.7	13.8	0.06	8	0.015	>8	
	Minocycline	81.3	11.1	7.6	2	8	≤0.5	>16	
	Pip/Tazo	87.9	6.4	5.7	2	32	0.12	>128	
	<i>E. coli</i> (n=124)	Tigecycline	99.2	0.8	0	0.12	0.25	0.03	4
		Amikacin	99.2	0.8	0	2	4	1	32
AmoxClav		74.2	19.4	6.5	8	16	1	>32	
Ampicillin		37.9	0	62	>32	>32	1	>32	
Cefepime		91.9	0.8	7.3	≤0.5	8	≤0.5	>32	
Ceftazidime		93.5	3.2	3.2	≤8	≤8	≤8	>32	
Ceftaxone		83.9	3.2	13	≤0.06	>64	≤0.06	>64	
Imipenem		100	0	0	0.25	0.5	0.12	1	
Levofloxacin		82.8	5.7	12	0.06	8	0.03	>8	
Minocycline		79.3	10.3	10.3	2	16	≤0.5	>16	
Pip/Tazo		93.1	3.4	3.4	2	16	0.5	>128	
<i>K. pneumoniae</i> (n=87)		Tigecycline	93.1	6.9	0	0.5	2	0.12	4
		Amikacin	100	0	0	1	2	≤0.5	8
	AmoxClav	80.5	10.3	9.2	2	16	1	>32	
	Ampicillin	0	13.8	86	>32	>32	16	>32	
	Cefepime	90.8	4.6	4.6	≤0.5	8	≤0.5	>32	
	Ceftazidime	85.1	2.3	13	≤8	32	≤8	>32	
	Ceftaxone	82.8	2.3	15	≤0.06	>64	≤0.06	>64	
	Imipenem	100	0	0	0.5	0.5	0.25	1	
	Levofloxacin	82.8	5.7	12	0.06	8	0.03	>8	
	Minocycline	79.3	10.3	10.3	2	16	≤0.5	>16	
	Pip/Tazo	93.1	3.4	3.4	2	16	0.5	>128	
	<i>K. oxytoca</i> (n=35)	Tigecycline	97.1	2.9	0	0.25	1	0.12	4
		Amikacin	100	0	0	1	4	≤0.5	4
AmoxClav		82.9	11.4	5.7	4	16	1	>32	
Ampicillin		0	17.1	83	>32	>32	16	>32	
Cefepime		97.1	0	2.9	≤0.5	1	≤0.5	>32	
Ceftazidime		91.4	2.9	5.7	≤8	≤8	≤8	>32	
Ceftaxone		97.1	0	2.9	≤0.06	2	≤0.06	>64	
Imipenem		100	0	0	0.5	0.5	0.25	1	
Levofloxacin		97.1	0	2.9	0.03	0.25	0.015	>8	
Minocycline		97.1	2.9	0	1	4	≤0.5	8	
Pip/Tazo		88.6	0	11.4	1	128	0.5	>128	
<i>E. coli/K. oxytoca/K. pneumoniae</i> (n=246)		Tigecycline	96.7	3.3	0	0.25	1	0.03	4
		Amikacin	99.6	0.4	0	2	4	≤0.5	32
	AmoxClav	77.6	15	7.3	4	16	1	>32	
	Ampicillin	19.1	7.3	74	>32	>32	1	>32	
	Cefepime	92.3	2	5.7	≤0.5	8	≤0.5	>32	
	Ceftazidime	90.2	2.8	6.9	≤8	≤8	≤8	>32	
	Ceftaxone	85.4	2.4	12	≤0.06	64	≤0.06	>64	
	Imipenem	100	0	0	0.25	0.5	0.12	1	
	Levofloxacin	79.3	2.8	18	0.06	8	0.015	>8	
	Minocycline	83.3	8.5	8.1	2	8	≤0.5	>16	
	Pip/Tazo	93.9	2.8	3.3	1	8	0.12	>128	
	All ESBL producers (n=30)	Tigecycline	83.3	16.7	0	0.5	4	0.06	4
		Amikacin	96.7	3.3	0	4	8	1	32
AmoxClav		30	50	20	16	32	4	>32	
Ampicillin		0	0	100	>32	>32	>32	>32	
Cefepime		43.3	13.3	43	16	>32	≤0.5	>32	
Ceftazidime		43.3	13.3	43	16	>32	≤8	>32	
Ceftaxone		10	6.7	83	>64	>64	0.12	>64	
Imipenem		100	0	0	0.25	0.5	0.12	1	
Levofloxacin		16.7	13.3	70	>8	>8	0.06	>8	
Minocycline		46.7	13.3	40	8	>16	1	>16	
Pip/Tazo		86.7	3.3	10	8	32	0.5	>128	
<i>E. aerogenes</i> (n=20)		Tigecycline	100	0	0	0.5	0.5	0.12	2
		Amikacin	100	0	0	2	2	1	8
	AmoxClav	5	10	85	>32	>32	1	>32	
	Ampicillin	0	0	100	>32	>32	32	>32	
	Cefepime	95	5	0	≤0.5	8	≤0.5	16	
	Ceftazidime	80	10	20	≤8	32	≤8	>32	
	Ceftaxone	80	10	10	0.5	32	≤0.06	>64	
	Imipenem	100	0	0	1	2	0.25	2	
	Levofloxacin	85	0	15	0.06	8	0.03	8	
	Minocycline	80	10	10	2	16	≤0.5	16	
	Pip/Tazo	85	15	0	2	32	0.5	64	
	<i>E. cloacae</i> (n=87)	Tigecycline	94.3	5.7	0	0.5	1	0.12	4
		Amikacin	98.9	1.1	0	2	4	≤0.5	32
AmoxClav		1.1	0	99	>32	>32	8	>32	
Ampicillin		0	5.7	94	>32	>32	16	>32	
Cefepime		95.4	1.1	3.4	≤0.5	4	≤0.5	>32	
Ceftazidime		83.2	6.9	30	≤8	>32	≤8	>32	
Ceftaxone		65.5	19.5	15	0.5	64	≤0.06	>64	
Imipenem		100	0	0	0.5	1	0.12	2	
Levofloxacin		89.7	3.4	6.9	0.06	4	0.015	>8	
Minocycline		85.1	10.3	4.6	4	8	1	>16	
Pip/Tazo		80.5	8	11.5	2	128	0.5	>128	
<i>S. marcescens</i> (n=44)		Tigecycline	95.5	4.5	0	0.5	2	0.25	4
		Amikacin	100	0	0	2	2	≤0.5	4
	AmoxClav	0	2.3	98	>32	>32	16	>32	
	Ampicillin	0	4.5	96	>32	>32	16	>32	
	Cefepime	100	0	0	≤0.5	1	≤0.5	8	
	Ceftazidime	97.7	0	2.3	≤8	≤8	≤8	32	
	Ceftaxone	84.1	15.9	0	0.25	32	≤0.06	32	
	Imipenem	100	0	0	0.5	1	0.25	1	
	Levofloxacin	95.5</							