

Patterns of Susceptibility of Gram-negatives/positives Isolated in the United Kingdom and Ireland

P 1121

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

B. Johnson¹, S. Bouchillon¹, M. Hackel¹, R. Badal¹, J. Johnson¹, D. Hoban¹, S. Lob¹, M. Dowzicky²

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

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 glycolcycline 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 1,321 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 EUCAST guidelines. **Results:** Results are in the table as follows:

<i>E. coli</i> , <i>K. oxytoca/pneumoniae</i>		<i>Acinetobacter</i> spp.		<i>P. aeruginosa</i>	
%S	MIC ₉₀	%S	MIC ₉₀	%S	MIC ₉₀
Tigecycline	95.7	1	IE	1	--
Amikacin	99.4	4	86.1	64	94.2
Cefepime	87.6	2	--	32	32
Imipenem	100	0.5	89.1	16	88.5
Levofloxacin	80.6	>8	75.2	>8	63.3

<i>S. aureus</i>		<i>Enterococcus</i> spp.		<i>S. pneumoniae</i>	
%S	MIC ₉₀	%S	MIC ₉₀	%S	MIC ₉₀
Tigecycline	100	0.25	100	12	0.5
Levofloxacin	77.2	8	--	>32	100
Linezolid	100	4	100	2	100
Minocycline	99.4*	0.5	54.3*	8	12.2*
Vancomycin	100	1	91.5	2	100

IE = There is insufficient evidence that the species in question is a good target for therapy with the drug
-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug

*CLSI breakpoints used if no EUCAST breakpoints determined yet.

Conclusion: Tigecycline was the third most active agent against *Enterobacteriaceae* spp. after imipenem and amikacin, displayed the lowest MICs against *Acinetobacter* spp., but had minimal activity against *P. aeruginosa*. Against gram-positives, tigecycline was as active as vancomycin and linezolid, and superior to levofloxacin and minocycline.

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 10⁻⁹ [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]. 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 of vanA, vanB and vanC [6].

The T.E.S.T. program determined the in vitro activity of tigecycline compared to most commonly prescribed broad spectrum antimicrobials against gram-negative and gram-positive species collected from 320 hospitals globally from 2004 to 2006. This study was designed to evaluate the in vitro activity of tigecycline against organisms collected in the United Kingdom and Ireland.

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. Only one isolate per patient was accepted. For this study 1,321 clinical isolates were collected from 2004 to 2006 from four sites in the United Kingdom and three sites in Ireland. 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 manufacturer, MicroScan (Dade Behring Inc., 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); 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 EUCAST where applicable; if no EUCAST guidelines were available [14] yet for a given antimicrobial, CLSI guidelines [13] were used instead. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution. *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftazidime 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: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922 and ATCC 35218; *K. pneumoniae* ATCC 700603; *Haemophilus influenzae* ATCC 49247 and ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *Pseudomonas aeruginosa* ATCC 27853. *K. pneumoniae* ATCC 700603 was used for ESBL confirmation by the reference lab.

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).

REFERENCES

- Sum, P.E. and P. Petersen. *Synthesis and structure-activity relationship of novel glycolcycline derivatives leading to the discovery of GAR-936*. Bioorg Med Chem Lett. 1999. 9(10): p. 1459-62.
- Abbanat, D., M. Macielag, and K. Bush. *Novel antibacterial agents for the treatment of serious Gram-positive infections*. Expert Opin Investig Drugs. 2003. 12(3): p. 379-99.
- Betriu, C., et al. *In vitro activities of tigecycline (GAR-936) against recently isolated clinical bacteria in Spain*. Antimicrob Agents Chemother. 2002. 46(3): p. 892-5.
- Gales, A.C. and R.N. Jones. *Antimicrobial activity and spectrum of the new glycolcycline, GAR-936 tested against 1,203 recent clinical bacterial isolates*. Diagn Microbiol Infect Dis. 2000. 36(1): p. 19-36.
- Henwood, C.J., et al. *Antibiotic resistance among clinical isolates of Acinetobacter in the UK, and in vitro evaluation of tigecycline (GAR-936)*. J Antimicrob Chemother. 2002. 49(3): p. 479-87.
- Chopra, I., *New developments in tetracycline antibiotics: glycolcyclines and tetracycline efflux pump inhibitors*. Drug Resist Updat. 2002. 5(3-4): p. 119-25.
- Projan, S.J. *Preclinical pharmacology of GAR-936, a novel glycolcycline antibacterial agent*. Pharmacotherapy. 2000. 20(9 Pt 2): p. 2195-2235; discussion 2245-2285.
- Biedenbach, D.J., M.L. Beach, and R.N. Jones. *In vitro antimicrobial activity of GAR-936 tested against antibiotic-resistant gram-positive blood stream infection isolates and strains producing extended-spectrum beta-lactamases*. Diagn Microbiol Infect Dis. 2001. 40(4): p. 173-7.
- 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.
- Petersen, P.J., et al. *In vitro and in vivo antibacterial activities of a novel glycolcycline, the 9-tert-butylglycylamide derivative of minocycline (GAR-936)*. Antimicrob Agents Chemother. 1999. 43(4): p. 738-44.
- Petersen, P.J., et al. *In vitro and in vivo activities of tigecycline (GAR-936), daptomycin, and comparative antimicrobial agents against glycopeptide-intermediate Staphylococcus aureus and other resistant gram-positive pathogens*. Antimicrob Agents Chemother. 2002. 46(8): p. 2595-601.
- CLSI. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*. Approved Standard-Sixth Edition, in Document M7-A6. 2005. Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing*. Sixteenth Informational Supplement. CLSI document M100-S16. Wayne, PA, 2006.
- European Committee on Antimicrobial Susceptibility Testing (EUCAST) website. <http://www.eucastr.org>. 1 August 2006.

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.

The results are listed in the following tables.

Table 1. In vitro activity of tigecycline and comparators against selected *Enterobacteriaceae* and *H. influenzae*.

Organism Name	Drug	%SUS ¹	%INT	%RES	MIC (mcg/ml)		MIC range (mcg/ml)	
					MIC ₅₀	MIC ₉₀	Low	High
<i>Enterobacteriaceae</i> (n=570)	Tigecycline	90.9	4.4	4.7	0.5	1	0.03	8
	Amikacin	99.1	0.4	0.5	2	4	≤0.5	32
	AmoxClav	47.9	9.5	42.5	16	>32	1	>32
	Ampicillin	10.7	6.3	8.3	>32	>32	1	>32
	Cefepime	82.6	12.8	4.6	≤0.5	4	≤0.5	>32
	Ceftazidime	72.8	1.9	25.3	0.12	64	≤0.06	>64
	Imipenem	99.8	0.2	0	0.5	1	0.12	8
	Levofloxacin	80	4.4	15.6	0.06	8	≤0.008	>8
	Minocycline	80.7	10.9	8.4	2	8	≤0.5	>16
	PipTazo	85.8	8.1	6.1	1	32	0.12	>128
<i>E. coli</i> ² (n=173)	Tigecycline	100	0	0	0.12	0.25	0.03	1
	Amikacin	99.4	0	0.6	2	4	1	32
	AmoxClav	73.4	17.9	8.7	8	16	1	>32
	Ampicillin	34.7	0	65.3	>32	>32	1	>32
	Cefepime	89	5.8	5.2	≤0.5	2	≤0.5	>32
	Ceftazidime	86.1	0	13.9	≤0.06	16	≤0.06	>64
	Imipenem	100	0	0	0.25	0.5	0.12	1
	Levofloxacin	72.8	0.6	26.6	0.03	>8	≤0.008	>8
	Minocycline	82.7	10.4	6.9	1	8	≤0.5	>16
	PipTazo	93.1	5.2	1.7	1	8	0.12	>128
<i>K. pneumoniae</i> ³ (n=131)	Tigecycline	89.3	5.3	5.3	0.5	2	0.12	4
	Amikacin	99.2	0	0.8	1	2	≤0.5	32
	AmoxClav	80.2	10.7	9.2	2	16	1	>32
	Amoxicillin	0	13.7	96.3	>32	>32	16	>32
	Cefepime	84	9.2	6.9	≤0.5	4	≤0.5	>32
	Ceftazidime	83.2	0.8	16	0.06	64	≤0.06	>64
	Imipenem	100	0	0	0.25	0.5	0.25	1
	Levofloxacin	85.5	2.3	12.2	0.06	4	0.03	>8
	Minocycline	80.2	7.6	12.2	2	16	≤0.5	>16
	PipTazo	90.8	3.8	5.3	2	16	0.25	>128
<i>K. oxytoca</i> ⁴ (n=42)	Tigecycline	97.6	0	2.4	0.25	1	0.12	4
	Amikacin	100	0	0	1	2	≤0.5	4
	AmoxClav	83.3	11.9	4.8	4	16	1	>32
	Ampicillin	0	16.7	83.3	>32	>32	16	>32
	Cefepime	92.9	4.8	2.4	≤0.5	1	≤0.5	>32
	Ceftazidime	85.7	7.1	7.1	≤0.06	2	≤0.06	>64
	Imipenem	100	0	0	0.25	0.5	0.25	1
	Levofloxacin	97.6	0	2.4	0.03	0.12	0.015	>8
	Minocycline	95.2	4.8	0	1	4	≤0.5	8
	PipTazo	88.1	0	11.9	1	128	0.5	>128
All ESBL producers (n=31)	Tigecycline	83.9	3.2	12.9	0.5	4	0.06	4
	Amikacin	98.8	0	3.2	4	8	1	32
	AmoxClav	32.3	45.2	22.6	16	32	4	>32
	Ampicillin	0	0	100	>32	>32	>32	>32
	Cefepime	9.7	38.7	51.6	16	>32	≤0.5	>32
	Ceftazidime	3.2	3.2	93.5	>64	>64	0.12	>64
	Imipenem	100	0	0	0.25	0.5	0.12	1
	Levofloxacin	16.1	6.5	77.4	>8	>8	0.015	>8
	Minocycline	51.6	12.9	35.5	4	>16	1	>16
	PipTazo	83.9	6.5	9.7	8	32	0.5	>128
<i>E. aerogenes</i> (n=27)	Tigecycline	77.8	14.8	7.4	0.5	2	0.12	4
	Amikacin	100	0	0	2	4	1	8
	AmoxClav	3.7	11.1	85.2	>32	>32	1	>32
	Ampicillin	0	0	100	>32	>32	>32	>32
	Cefepime	85.2	11.1	3.7	≤0.5	8	≤0.5	16
	Ceftazidime	66.7	0	33.3	0.5	64	≤0.06	>64
	Imipenem	100	0	0	1	2	0.25	2
	Levofloxacin	77.8	0	22.2	0.06	8	0.03	>8
	Minocycline	70.4	14.8	14.8	2	16	≤0.5	>16
	PipTazo	81.5	18.5	0	4	32	0.5	64
<i>E. cloacae</i> (n=125)	Tigecycline	83.2	7.2	9.6	0.5	2	0.12	8
	Amikacin	97.6	1.6	0.8	1	4	≤0.5	32
	AmoxClav	0.8	0.8	98.4	>32	>32	8	>32
	Ampicillin	0	5.6	94.4	>32	>32	16	>32
	Cefepime	64	31.2	4.8	≤0.5	8	≤0.5	>32
	Ceftazidime	46.4	2.4	51.2	4	>64	≤0.06	>64
	Imipenem	99.2	0.8	0	0.5	1	0.12	8
	Levofloxacin	73.6	12.8	13.6	0.12	4	0.015	>8
	Minocycline	76	15.2	8.8	4	8	1	>16
	PipTazo	70.4	14.4	15.2	2	128	0.5	>128
<i>S. marcescens</i> (n=61)	Tigecycline	86.9	6.6	6.6	1	2	0.25	8
	Amikacin	100	0	0	2	4	≤0.5	8
	AmoxClav	0	1.6	98.4	>32	>32	16	>32
	Ampicillin	0	3.3	96.7	>32	>32	16	>32
	Cefepime	88.5	11.5	0	≤0.5	2	≤0.5	8
	Ceftazidime	60.7	4.9	34.4	0.5	16	≤0.06	64
	Imipenem	100	0	0	0.5	1	0.25	2
	Levofloxacin	86.9	8.2	4.9	0.12	2	0.03	>8
	Minocycline	82	11.5	6.6	4	8	1	>16
	PipTazo	83.6	14.8	1.6	2	32	0.12	128
<i>H. influenzae</i> ⁶ (n=98)	Tigecycline	IE	IE	IE	0.12	0.25	0.03	1
	AmoxClav	100	0	0	0.5	1	≤0.12	4
	Ampicillin	80.6	1	18.4	≤0.5	>32	≤0.5	>32
	Cefepime	0	0	100	≤0.5	≤0.5	≤0.5	8
	Ceftazidime	98	0	2	≤0.06	≤0.06	≤0.06	2
	Imipenem	100	0	0	0.5	1	≤0.06	2
	Levofloxacin	100	0	0	0.015	0.03	≤0.008	1
	PipTazo	100	0	0	≤0.06	≤0.06	≤0.06	1

¹ Interpretive criteria as defined by EUCAST, where available; CLSI breakpoints, where available, were used where no EUCAST breakpoints exist yet. IE - there is insufficient evidence that the species in question is a good target for therapy with the drug; -- = susceptibility testing not recommended as the species is a poor target for therapy with the drug.
² Includes 12 ESBL-producing *E. coli* strains.
³ Includes 17 ESBL-producing *K. pneumoniae* strains.
⁴ Includes 1 ESBL-producing *K. oxytoca* strain.
⁵ Includes 18 beta-lactamase positive strains with the same tigecycline MIC₅₀ and MIC₉₀ as the beta-lactamase negative isolates.
⁶ Includes 18 penicillin-intermediate and 7 penicillin-resistant strains with the same susceptibility to tigecycline as the penicillin-susceptible strains.

RESULTS

Table 2. In vitro activity of tigecycline and comparative agents against *Acinetobacter* spp. and *P. aeruginosa*.

Organism Name	Drug	%SUS ¹	%INT	%RES	MIC (mcg/ml)		MIC range (mcg/ml)	
					MIC ₅₀	MIC ₉₀	Low	High
<i>A. baumannii</i> (n=76)	Tigecycline	IE	IE	IE	0.25	1	0.03	4
	Amikacin	81.6	2.6	15.8	2	>64	≤0.5	>64
	Ceftazidime	46.1	23.7	30.3	16	>64	0.5	>64
	Imipenem	85.5	0	14.5	0.5	16	0.12	>16
	Levofloxacin	68.4	9.2	22.4	0.25	>8	0.015	>8
	Minocycline	93.4	6.6	0	≤0.5	4	≤0.5	8
PipTazo	68.4	11.8	19.7	4	>128	≤0.06	>128	
<i>A. lwoffii</i> (n=21)	Tigecycline	IE	IE					