

Susceptibility of Gram-negative/positive Pathogens Isolated in the United Kingdom and Ireland: A Multi-year Update

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Revised Abstract

Background: The rapid emergence of multi-drug resistant pathogens has undermined the efficacy of many widely used broad spectrum anti-bacterials 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 2004-2008. **Methods:** A total of 1,981 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 wherever possible. **Results:** *In vitro* activity on selected pathogens are shown in the table below. Data on resistant phenotypes will be presented.

	<i>E. coli, K. oxytoca/pneumoniae</i> n = 503			<i>Acinetobacter</i> spp. n = 143			<i>P. aeruginosa</i> n = 198		
	%S	MIC ₉₀	IE	%S	MIC ₉₀	IE	%S	MIC ₉₀	IE
Tigecycline	92.4	4	1	90.2	8	1	86.4	16	1
Amikacin	97.2	4	1	90.2	8	1	86.4	16	1
Cefepime	76.1	8	1	79	32	80.8	32	8	1
Imipenem	100	0.5	88.1	16	88.5	8	8	8	1
Levofloxacin	71.6	>8	79.0	8	57.6	>8	8	8	1

	<i>S. aureus</i> n = 236			<i>Enterococcus</i> spp. n = 138			<i>S. pneumoniae</i> n = 125		
	%S	MIC ₉₀	IE	%S	MIC ₉₀	IE	%S	MIC ₉₀	IE
Tigecycline	100	0.25	100	0.25	100	0.12	100	0.12	100
Levofloxacin	76.3	8	32.6	>32	100	1	100	1	1
Linezolid	100	4	100	2	100	1	100	1	1
Minocycline	97.0	0.5	47.1	>8	83.2	2	100	0.5	100
Vancomycin	100	1	87.0	>32	100	0.5	100	0.5	100

IE = There is insufficient evidence that the species in question is a good target for therapy with the drug
-- = No clinical breakpoints available
*CLSI breakpoints used if no EUCAST breakpoints determined yet.

Conclusions: Tigecycline was active against the majority of *Enterobacteriaceae* spp., 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, it 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 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 [3, 5- 7]. With the exception of *Pseudomonas aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are typically sensitive to tigecycline [2-4, 7-11]. Tigecycline has been shown to be active against multi-resistant *Acinetobacter* spp. Similar activity has been observed against *Enterobacteriaceae*, including extended-spectrum β -lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC₉₀ values of ≤ 0.5 mg/L against methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive organisms [2, 4-6]. Furthermore, tigecycline has shown potent efficacy in animal models of infection with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4,5] including 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 2008. 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 1,981 clinical isolates were collected from 2004 to 2008 from eight sites in the United Kingdom and eight 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 mg/L): 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).
- MIC interpretive criteria followed published guidelines established by EUCAST where applicable; if no EUCAST breakpoints were available yet for a given antimicrobial, CLSI breakpoints [13] or FDA breakpoints 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 ceftriaxone were >1 mg/L 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).

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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	MIC (mg/L)			MIC range (mg/L)			
		%S ¹	%INT	%RES	Low	High		
<i>Enterobacteriaceae</i> (n=828)	Tigecycline	87.0	2.7	4.3	0.5	2	0.03	8
	Amikacin	97.1	2.3	0.6	2	4	<0.5	32
	AmoxClav	28.1	13.2	58.7	16	>32	1	>32
	Ampicillin	7.4	0.9	91.7	>32	>32	1	>32
	Cefepime	75.7	17.1	7.1	<0.5	8	<0.5	>32
	Ceftriaxone	65.0	2.2	32.9	0.12	>64	<0.06	>64
	Imipenem	99.8	0.2	0.0	0.5	1	0.12	8
	Levofloxacin	73.6	5.0	21.5	0.12	>8	<0.008	>8
	Minocycline	73.4	13.6	12.9	2	16	<0.5	>16
	PipTazo	75.2	5.3	19.4	2	64	<0.2	>128
<i>E. coli</i> ² (n=249)	Tigecycline	100.0	0.0	0.0	0.12	0.5	0.03	1
	Amikacin	96.0	3.6	0.4	2	8	1	32
	AmoxClav	31.7	30.1	38.2	8	32	1	>32
	Ampicillin	24.7	0.8	74.5	>32	>32	1	>32
	Cefepime	79.1	12.4	8.4	<0.5	8	<0.5	>32
	Ceftriaxone	78.7	0.4	20.9	<0.06	>64	<0.06	>64
	Imipenem	100.0	0.0	0.0	0.25	0.5	0.12	1
	Levofloxacin	64.7	0.4	34.9	0.03	>8	<0.008	>8
	Minocycline	80.7	11.6	7.6	1	8	<0.5	>16
	PipTazo	88.0	4.4	7.6	1	16	0.12	>128
<i>K. pneumoniae</i> ³ (n=190)	Tigecycline	84.7	10.5	4.7	0.5	2	0.32	4
	Amikacin	98.4	1.1	0.5	1	4	<0.5	32
	AmoxClav	56.3	13.7	30.0	4	32	1	>32
	Ampicillin	0.0	0.5	99.5	>32	>32	8	>32
	Cefepime	70.5	18.9	10.5	<0.5	16	<0.5	>32
	Ceftriaxone	68.4	1.1	30.5	<0.06	>64	<0.06	>64
	Imipenem	100.0	0.0	0.0	0.25	0.5	0.25	1
	Levofloxacin	76.3	2.6	21.1	0.06	>8	0.03	>8
	Minocycline	68.4	13.2	18.4	2	16	<0.5	>16
	PipTazo	74.2	6.3	19.5	4	128	0.25	>128
<i>K. oxytoca</i> ⁴ (n=64)	Tigecycline	85.9	7.8	6.3	0.25	2	0.12	4
	Amikacin	98.4	1.6	0.0	1	4	<0.5	16
	AmoxClav	67.2	4.7	28.1	4	32	1	>32
	Ampicillin	0.0	4.7	95.3	>32	>32	8	>32
	Cefepime	81.3	14.1	4.7	<0.5	8	<0.5	>32
	Ceftriaxone	71.9	4.7	23.4	<0.06	16	<0.06	>64
	Imipenem	100.0	0.0	0.0	0.25	0.5	0.25	1
	Levofloxacin	84.4	3.1	12.5	0.06	8	0.015	>8
	Minocycline	79.7	7.8	12.5	2	16	<0.5	>16
	PipTazo	75.0	3.1	21.9	1	>128	0.5	>128
All ESBL producers (n=78)	Tigecycline	85.9	9.0	5.1	0.5	2	0.06	4
	Amikacin	85.9	12.8	1.3	4	16	<0.5	32
	AmoxClav	1.3	23.1	75.6	16	32	4	>32
	Ampicillin	0.0	0.0	100.0	>32	>32	>32	>32
	Cefepime	9.0	43.6	47.4	8	>32	<0.5	>32
	Ceftriaxone	1.3	13.1	97.4	>64	>64	0.12	>64
	Imipenem	100.0	0.0	0.0	0.25	0.5	0.12	>8
	Levofloxacin	19.2	3.8	76.9	>8	>8	0.015	>8
	Minocycline	52.6	17.9	29.5	4	>16	1	>16
	PipTazo	52.6	12.8	34.6	8	128	0.5	>128
<i>E. aerogenes</i> (n=37)	Tigecycline	81.1	10.8	8.1	0.5	2	0.12	4
	Amikacin	100.0	0.0	0.0	2	4	1	8
	AmoxClav	2.7	0.0	97.3	>32	>32	1	>32
	Ampicillin	0.0	0.0	100.0	>32	>32	16	>32
	Cefepime	86.5	10.8	2.7	<0.5	8	<0.5	16
	Ceftriaxone	62.2	0.0	37.8	0.5	64	<0.06	>64
	Imipenem	100.0	0.0	0.0	1	2	0.25	2
	Levofloxacin	83.8	0.0	16.2	0.06	8	0.03	>8
	Minocycline	67.6	13.5	18.9	2	16	<0.5	>16
	PipTazo	70.3	8.1	21.6	4	64	0.5	64
<i>E. cloacae</i> (n=180)	Tigecycline	83.3	8.9	7.8	0.5	2	0.12	8
	Amikacin	94.4	3.9	1.7	1	4	<0.5	32
	AmoxClav	0.0	1.1	98.9	>32	>32	8	>32
	Ampicillin	0.0	0.0	100.0	>32	>32	16	>32
	Cefepime	62.8	30.0	7.2	<0.5	8	<0.5	>32
	Ceftriaxone	47.2	2.8	50.0	2	>64	<0.06	>64
	Imipenem	99.2	0.8	0.0	0.5	1	0.12	8
	Levofloxacin	75.0	11.7	13.3	0.12	4	0.015	>8
	Minocycline	70.6	15.6	13.9	4	16	1	>16
	PipTazo	63.3	5.0	31.7	4	128	0.5	>128
<i>S. marcescens</i> (n=91)	Tigecycline	74.7	19.8	5.5	1	2	0.25	8
	Amikacin	100.0	0.0	0.0	2	4	<0.5	8
	AmoxClav	0.0	0.0	100.0	>32	>32	16	>32
	Ampicillin	0.0	0.0	100.0	>32	>32	16	>32
	Cefepime	91.2	8.8	0.0	<0.5	1	<0.5	8
	Ceftriaxone	50.5	5.5	44.0	1	16	<0.06	64
	Imipenem	100.0	0.0	0.0	0.5	1	0.25	2
	Levofloxacin	100.0	0.0	0.0	0.015	0.03	<0.008	1
	Minocycline	68.1	18.7	13.2	4	16	1	>16
	PipTazo	64.8	17.7	27.5	4	64	0.12	128
<i>H. influenzae</i> ⁵ (n=98)	Tigecycline	na	na	na	0.12	0.5	0.03	1
	AmoxClav	90.3	0.0	9.7	0.5	1	<0.12	4
	Ampicillin	76.6	0.0	23.4	<0.5	32	<0.5	>32
	Cefepime	97.9	0.0	2.1	<0.5	<0.5	<0.5	8
	Ceftriaxone	98.6	0.0	1.4	<0.06	<0.06	<0.06	2
	Imipenem	100.0	0.0	0.0	0.5	1	<0.06	2
	Levofloxacin	100.0	0.0	0.0	0.015	0.03	<0.008	1
	Minocycline	100.0	0.0	0.0	<0.06	<0.06	<0.06	1
	PipTazo	100.0	0.0	0.0	<0.06	<0.06	<0.06	1

¹ Interpretive criteria as defined by EUCAST, where available; CLSI breakpoints or FDA breakpoints, where available, were used where no EUCAST breakpoints exist yet; na, no clinical breakpoint available.

² Includes 38 ESBL-producing *E. coli* strains.

³ Includes 38 ESBL-producing *K. pneumoniae* strains.

⁴ Includes 2 ESBL-producing *K. oxytoca* strains.

⁵ Includes 30 β -lactamase positive strains with tigecycline MIC₉₀ and MIC₅₀ of 0.03 and 0.5 mg/L, respectively. For β -lactamase negative isolates tigecycline MIC₉₀ and MIC₅₀ were 0.06 and 1 mg/L, respectively.

Results

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

Organism Name	Drug	MIC (mg/L)			MIC range (mg/L)	
		%S ¹	%INT	%RES	Low	High
<i>A. baumannii</i> (n=96)	Tigecycline	na	na	na	0	