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Comparison of In Vitro Activity of Tigecycline and Comparators Against Pathogens from Intensive Care Patients in Europe – T.E.S.T. Program 2008

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Revised Abstract

Objectives: Tigecycline, a member of the glycolcyclines class of antimicrobics, has been shown to have potent broad spectrum activity against most commonly encountered species responsible for community and hospital acquired infections. The T.E.S.T. program surveyed the in vitro activity of tigecycline from ICU and non-ICU pathogens during 2004 to 2008. This report focuses on the results for ICU isolates in Europe. **Methods:** A total of 34,401 clinical isolates from 320 testing sites in 24 European countries were evaluated. Minimum Inhibitory Concentration (MICs) were determined by each site using common broth microdilution panels and interpreted according to EUCAST guidelines. Of these isolates, 6,853 (19.9%) were collected from ICU sources for evaluation. **Results:** Results are listed as follows:

Drug	Enterobacteriaceae (n=3,191)		Acinetobacter spp. (n=647)	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.5	2	0.5	1
Amikacin	2	8	4	>64
Cefepime	<0.25	8	16	>32
Imipenem	0.25	1	1	>16
Levofloxacin	0.06	8	4	>8
Minocycline	2	16	<0.5	4
PipTazo	2	128	32	>128

Drug	<i>S. aureus</i> (n=886)		Enterococcus spp. (n=553)	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.12	0.25	0.12	0.25
Levofloxacin	0.25	16	2	>32
Linezolid	2	4	2	>8
Minocycline	<0.25	0.5	4	>8
Vancomycin	1	1	1	2

Conclusions: Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed broad spectrum antimicrobics for all ICU bacterial strains encountered. Tigecycline's inhibitory activity against *Enterobacteriaceae* and *Acinetobacter* spp. was comparable to imipenem's. Against gram-positive organisms, tigecycline's activity was comparable to that of linezolid and vancomycin.

Introduction

Tigecycline is an 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 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 β -lactamase (ESBL) and AmpC-producing strains [10]. Tigecycline has demonstrated MIC₅₀ values of <0.5 mcg/ml against methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive organisms [2, 4-6]. Tigecycline has shown potential activity in animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *E. 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 2008. This report focuses specifically on the in vitro activity of tigecycline against potentially difficult-to-treat organisms collected from intensive care units (ICU) in Europe.

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.
- For this study 34,401 clinical isolates were collected from 2004 to 2008 from 320 sites in 24 European countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, The Netherlands, and the United Kingdom). Of these, 6,853 were isolated from patients in ICUs.
- 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 (Siemens Medical Solutions Diagnostics, 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 breakpoints established by EUCAST where applicable [13]; if no EUCAST guidelines were available for a given antimicrobial, CLSI breakpoints [14] were used.
- Escherichia coli*, *Klebsiella pneumoniae*, and *K. 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 (2008) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2008) 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; *E. coli* ATCC 25922; *E. coli* ATCC 35218; *K. pneumoniae* ATCC 700603 (as positive ESBL control); *Haemophilus influenzae* ATCC 49247; *H. influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *Pseudomonas aeruginosa* ATCC 27853.
- 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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Results

Table 1. In vitro activity of tigecycline and comparative agents against selected gram-negative organisms.

Organism (n)	Drug	%S*	%I	%R	MIC (mcg/ml)			
					MIC ₅₀	MIC ₉₀	Min Max	
<i>Enterobacteriaceae</i> (3,191)	Tigecycline	89.2	7.2	3.6	0.5	2	<0.008 16	
	Amikacin	94.2	3.4	2.4	2	8	<0.5 >64	
	AmoxClav	35.6	8.9	55.5	32	>32	<0.12 >32	
	Ampicillin	7.5	0.0	92.5	>32	>32	<0.5 >32	
	Cefepime	77.1	13.7	9.2	<0.5	8	<0.5 >32	
	Ceftazidime	0.0	76.3	23.7	<8	>32	<8 >32	
	Ceftriaxone	67.5	2.1	30.4	0.12	>64	<0.06 >64	
	Imipenem	98.0	1.4	0.6	0.25	1	<0.06 >16	
	Levofloxacin	80.1	3.0	16.8	0.06	>8	<0.008 >8	
	Meropenem	98.0	1.3	0.7	<0.06	0.25	<0.06 >16	
	Minocycline	76.9	12.4	10.7	2	16	<0.5 >16	
	Pip-Tazo	77.8	9.1	13.1	2	128	<0.06 >128	
	<i>E. coli</i> (670)	Tigecycline	98.8	1.2	0.0	0.12	0.5	<0.008 2
		Amikacin	93.7	3.7	2.5	2	8	<0.5 >64
AmoxClav		65.2	19.7	15.1	8	32	<0.12 >32	
Ampicillin		34.1	0.0	65.9	>32	>32	<0.5 >32	
Cefepime		84.6	6.9	8.5	<0.5	8	<0.5 >32	
Ceftazidime		0.0	91.6	8.4	<8	<8	<8 >32	
Ceftriaxone		86.1	0.6	13.3	<0.06	32	<0.06 >64	
Imipenem		99.4	0.3	0.3	0.25	0.5	<0.06 >16	
Levofloxacin		74.0	1.3	24.6	0.03	>8	<0.008 >8	
Meropenem		99.7	0.3	0.0	<0.06	<0.06	<0.06 8	
Minocycline		79.9	7.9	12.2	1	16	<0.5 >16	
Pip-Tazo		88.1	4.2	7.8	1	32	<0.06 >128	
<i>Klebsiella</i> spp.(1,000)		Tigecycline	88.6	7.3	4.1	0.5	2	<0.008 16
		Amikacin	92.3	4.3	3.4	2	8	<0.5 >64
	AmoxClav	67.6	12.3	20.1	4	32	0.5 >32	
	Ampicillin	0.6	0.0	99.4	>32	>32	1 >32	
	Cefepime	75.7	10.1	14.2	<0.5	32	<0.5 >32	
	Ceftazidime	0.0	79.0	21.0	<8	>32	<8 >32	
	Ceftriaxone	70.8	2.0	27.2	<0.06	>64	<0.06 >64	
	Imipenem	98.2	0.9	0.9	0.25	0.5	<0.06 >16	
	Levofloxacin	80.1	2.8	17.1	0.06	>8	<0.008 >8	
	Meropenem	97.4	1.3	1.3	<0.06	0.12	<0.06 >16	
	Minocycline	78.1	9.7	12.2	2	16	<0.5 >16	
	PipTazo	79.3	4.8	15.9	2	>128	0.12 >128	
	ESBL+ (221) <i>E. coli</i> and <i>Klebsiella</i> spp.	Tigecycline	82.4	11.8	5.9	0.5	2	0.06 8
		Amikacin	72.4	14.0	13.6	4	32	<0.5 >64
AmoxClav		17.2	37.1	45.7	16	>32	0.5 >32	
Ampicillin		0.5	0.0	99.5	>32	>32	2 >32	
Cefepime		6.3	30.8	62.9	32	>32	<0.5 >32	
Ceftazidime		0.0	25.3	74.7	>32	>32	<8 >32	
Ceftriaxone		2.7	1.8	95.5	>64	>64	0.12 >64	
Imipenem		99.1	0.9	0.0	0.25	0.5	<0.06 4	
Levofloxacin		36.2	5.4	58.4	8	>8	<0.008 >8	
Meropenem		98.1	0.9	0.9	<0.06	2	<0.06 16	
Minocycline		54.3	17.6	28.1	4	>16	<0.5 >16	
PipTazo		57.5	10.4	32.1	16	>128	0.5 >128	
<i>Enterobacter</i> spp. (1,047)		Tigecycline	86.8	7.7	5.4	0.5	2	0.06 8
		Amikacin	95.3	2.9	1.8	2	8	<0.5 >64
	AmoxClav	1.6	1.6	96.8	>32	>32	1 >32	
	Ampicillin	0.5	0.0	99.5	>32	>32	1 >32	
	Cefepime	66.7	25.0	8.3	<0.5	8	<0.5 >32	
	Ceftazidime	0.0	55.5	44.5	<8	>32	<8 >32	
	Ceftriaxone	46.9	2.6	50.5	4	>64	<0.06 >64	
	Imipenem	97.4	2.2	0.4	0.5	1	<0.06 >16	
	Levofloxacin	79.6	3.3	17.1	0.06	>8	<0.008 >8	
	Meropenem	96.9	2.4	0.7	<0.06	0.25	<0.06 >16	
	Minocycline	73.7	15.0	11.3	4	16	<0.5 >16	
	PipTazo	63.6	17.5	18.9	8	128	<0.06 >128	
	<i>P. aeruginosa</i> (847)	Tigecycline	na	na	na	8	>16	<0.06 >16
		Amikacin	86.8	6.1	7.1	4	16	<0.5 >64
AmoxClav		na	na	na	>32	>32	4 >32	
Ampicillin		na	na	na	>32	>32	8 >32	
Cefepime		69.1	0.0	30.9	8	32	<0.5 >32	
Ceftazidime		69.2	0.0	30.8	<8	>32	<8 >32	
Ceftriaxone		12.6	24.8	62.6	64	>64	<0.06 >64	
Imipenem		72.1	12.1	15.8	1	16	<0.06 >16	
Levofloxacin		52.5	9.1	38.4	1	>8	0.015 >8	
Meropenem		63.4	16.3	20.3	1	16	<0.06 >16	
Minocycline		na	na	na	>16	>16	<0.5 >16	
PipTazo		81.3	0.0	18.7	8	>128	<0.06 >128	
<i>Acinetobacter</i> spp. (647)		Tigecycline	na	na	na	0.5	1	<0.008 16
		Amikacin	56.3	5.1	38.6	8	>64	<0.5 >64
	AmoxClav	na	na	na	>32	>32	0.25 >32	
	Ampicillin	na	na	na	>32	>32	2 >32	
	Cefepime	45.0	17.3	37.7	16	>32	<0.5 >32	
	Ceftazidime	39.6	8.7	51.8	32	>32	<8 >32	
	Ceftriaxone	21.5	20.6	58.0	>64	>64	<0.06 >64	
	Imipenem	74.6	7.2	18.2	1	>16	<0.06 >16	
	Levofloxacin	39.7	5.6	54.7	4	>8	0.03 >8	
	Meropenem	54.3	14.9	30.8	2	>16	<0.06 >16	
	Minocycline	92.3	5.4	2.3	<0.5	4	<0.5 >16	
	PipTazo	42.2	12.8	45.0	64	>128	<0.06 >128	

* Interpretive criteria as defined by EUCAST; if no EUCAST criteria exist, CLSI breakpoints are shown, where available; na = not available. Species with n's <20 were omitted from individual analysis but included as part of an aggregate total.

Table 2. In vitro activity of tigecycline and comparative agents against selected gram-positive organisms.

Organism (n)	Drug	%S*	%I	%R	MIC (mcg/ml)		
					MIC ₅₀	MIC ₉₀	Min Max
<i>S. aureus</i> (686)	Tigecycline	100.0	0.0	0.1	0.12</		