

Revised Abstract

Background: Tigecycline (TIG), a new glycycline, 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 determined the *in vitro* activity of tigecycline and 10 comparators against respective gram-positive/negative species. Isolates were collected from 320 hospital sites in 24 countries from 2004 through 2008. **Methods:** 34,401 clinically significant isolates were identified to the species level at participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** *In vitro* activity on selected pathogens are shown in the table below. Data on resistant phenotypes will be presented.

Organism (n)	Tigecycline		% inhibited at MIC (mg/L)				
	MIC ₅₀	MIC ₉₀	≤0.5	1	2	4	8
<i>A. baumannii</i> (2053)	0.25	1	72.5	91.7	97.7	99.8	100
<i>E. faecalis/faecium</i> (2458)	0.12	0.12	100	-	-	-	-
<i>Enterobacteriaceae</i> (14311)	0.5	1	77.3	91.2	97.2	99.6	100
ESBLs (919)	0.5	2	71.6	87.6	95.6	99	100
<i>P. aeruginosa</i> (3394)	8	16	1.5	3.2	6.7	23.7	63.4
<i>S. aureus</i> (4063)	0.12	0.25	100	-	-	-	-
<i>S. pneumoniae</i> (1784)	0.12	0.25	99.9	100	-	-	-
<i>H. influenzae</i> (2066)	0.25	0.5	94.5	99.1	100	-	-

Conclusions: Tigecycline has been described as an expanded broad spectrum antimicrobial because of its consistent activity against *Enterobacteriaceae* including extended spectrum β-lactamase producers, *S. aureus* including methicillin-resistant strains, *S. pneumoniae* including penicillin-resistant strains, both vancomycin-sensitive and -resistant *Enterococcus* spp., and *H. influenzae* including β-lactamase producers. The agent's wide spectrum of activity promises to provide enhanced antimicrobial coverage of serious nosocomial/community pathogens.

Introduction

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycyclines. 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 infrequent and is also difficult to induce in the laboratory setting [3, 5, 6, 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 active 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 MIC₉₀ values of ≤0.5 mg/L against methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive organisms [2, 4-6]. Tigecycline has shown potent activity against animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4, 5] with diverse genotypes van-A, -B and -C [6].

This study was designed to better define the *in vitro* activity of tigecycline in selected clinical isolates collected from 320 study centers in Europe.

Materials & Methods

- Isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids and few other defined sources. Only one isolate per patient was accepted. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Clinical isolates (n=34,401) were collected tested between January 2004 – December 2008 from 320 study centers in 24 countries.
- Custom broth microdilution panels were supplied by MicroScan (Dade MicroScan, Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mg/L): amoxicillin/clavulanic acid (0.12-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftiraxone (0.06-64); cefepime (0.5-32); ampicillin (0.5-32); amikacin (0.5-64); minocycline (0.5-16); ceftazidime (8-32); tigecycline (0.008-16); and imipenem (0.06-16).
- MIC interpretive criteria for all drugs primarily followed published guidelines established by EUCAST. In the absence of EUCAST breakpoints, CLSI [12] or FDA breakpoints [13] were used.
- Quality control of broth microdilution panels followed manufacture's and CLSI guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Klebsiella pneumoniae* ATCC 700603 (positive ESBL control); *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *Pseudomonas aeruginosa* ATCC 27853.
- The collection and transportation of organisms and the confirmation of identification, as well as, 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 *Enterobacteriaceae* and selected species.*

Organism	Drug	%SUS**	%INT	%RES	MIC (mg/L)		
					MIC ₅₀	MIC ₉₀	
All <i>Enterobacteriaceae</i> (n=14,311)	Tigecycline	91.2	5.9	2.8	0.5	1	
	Amikacin	95.7	2.4	1.9	2	4	
	Amox-Clav	na	na	na	16	>32	
	Ampicillin	12.2	0	87.8	>32	>32	
	Cefepime	82.2	10.4	7.4	≤0.5	8	
	Ceftazidime	0	82.5	17.5	≤8	>32	
	Ceftriaxone	74.8	2.1	23.2	0.12	64	
	Imipenem	98.8	0.9	0.2	0.25	1	
	Levofloxacin	80.4	2.4	17.2	0.06	>8	
	Minocycline	98.7	0.8	0.5	≤0.06	0.12	
	Pip/Tazo	na	na	na	2	16	
	<i>Enterobacter aerogenes</i> (n=845)	Tigecycline	88.5	8.5	3	0.5	2
		Amikacin	93.6	4	2.4	2	8
Amox/Clav		na	na	na	>32	>32	
Ampicillin		0.1	0	99.9	>32	>32	
Cefepime		80.8	13	6.2	≤0.5	4	
Ceftazidime		0	62.4	37.6	≤8	>32	
Ceftriaxone		56.8	5	38.2	0.5	64	
Imipenem		95.7	4.3	0	0.5	2	
Levofloxacin		74	2	24	0.06	>8	
Minocycline		98	1.7	0.2	≤0.06	0.25	
Pip/Tazo		na	na	na	2	8	
<i>Enterobacter cloacae</i> (n=3,092)		Tigecycline	87.4	7.2	5.5	0.5	2
		Amikacin	96.4	1.7	1.8	2	4
	Amox/Clav	na	na	na	>32	>32	
	Ampicillin	0.6	0	99.4	>32	>32	
	Cefepime	72.2	2.1	6.8	≤0.5	8	
	Ceftazidime	0	64.3	35.7	≤8	>32	
	Ceftriaxone	57.1	2.7	40.2	0.5	>64	
	Imipenem	98.5	1.1	0.4	0.5	1	
	Levofloxacin	82.5	2.9	14.7	0.06	>8	
	Minocycline	98	1.3	0.7	≤0.06	0.25	
	Pip/Tazo	na	na	na	4	16	
	<i>Escherichia coli</i> (n=4,346)	Tigecycline	99.3	0.7	0	0.12	0.5
		Amikacin	96.4	2.3	1.3	2	8
Amox/Clav		na	na	na	8	32	
Ampicillin		38.9	0	61.1	>32	>32	
Cefepime		86.7	6	7.3	≤0.5	4	
Ceftazidime		0	93.2	6.8	≤8	>32	
Ceftriaxone		86.3	0.9	12.9	≤0.06	32	
Imipenem		99.8	0.1	0.1	0.25	0.5	
Levofloxacin		73.3	1.1	25.6	0.03	>8	
Minocycline		99.8	0.2	0	≤0.06	≤0.06	
Pip/Tazo		na	na	na	1	16	
<i>Klebsiella pneumoniae</i> (n=3,034)		Tigecycline	88.6	7	4.4	0.5	2
		Amikacin	93.5	3.4	3.1	2	8
	Amox/Clav	na	na	na	4	32	
	Ampicillin	0.4	0	99.6	>32	>32	
	Cefepime	79.1	8.3	12.6	≤0.5	16	
	Ceftazidime	0	81.3	18.6	≤8	>32	
	Ceftriaxone	76.2	1.5	22.3	≤0.06	>64	
	Imipenem	99	0.7	0.3	0.25	0.5	
	Levofloxacin	82	2.3	15.7	0.06	8	
	Minocycline	98	1	1	≤0.06	0.12	
	Pip/Tazo	na	na	na	2	25	
	<i>Klebsiella oxytoca</i> (n=1,166)	Tigecycline	93.8	4.4	1.8	0.25	1
		Amikacin	98.1	0.8	1.1	2	4
Amox/Clav		na	na	na	4	32	
Ampicillin		0.9	0	99.1	>32	>32	
Cefepime		87.7	8.9	3.4	≤0.5	2	
Ceftazidime		0	94.4	5.6	≤8	>32	
Ceftriaxone		81.8	2.1	16	≤0.06	8	
Imipenem		99.6	0.4	0	0.25	0.5	
Levofloxacin		91.2	2.2	6.6	0.06	1	
Minocycline		99.3	0.5	0.2	≤0.06	0.12	
Pip/Tazo		na	na	na	1	8	
<i>S. marcescens</i> (n=1,541)		Tigecycline	81.4	15.6	2.9	1	2
		Amikacin	95.8	2.1	2	2	8
	Amox/Clav	na	na	na	>32	>32	
	Ampicillin	0.4	0	99.6	>32	>32	
	Cefepime	91.8	5.6	2.5	≤0.5	1	
	Ceftazidime	0	92.9	7.1	≤8	>32	
	Ceftriaxone	79.3	3.5	17.2	0.25	8	
	Imipenem	97.8	1.5	0.7	0.5	1	
	Levofloxacin	87	6	7	0.12	2	
	Minocycline	98.4	0.6	1	≤0.06	0.25	
	Pip/Tazo	na	na	na	4	8	
	All ESBL producers (<i>E. coli</i> , <i>K. pneumoniae</i> , <i>K. oxytoca</i>) (n=919)	Tigecycline	87.6	8.1	4.4	0.5	2
		Amikacin	77.3	12.6	10.1	4	32
Amox/Clav		na	na	na	16	>32	
Ampicillin		0.3	0	99.7	>32	>32	
Cefepime		9.5	30.5	60.1	16	>32	
Ceftazidime		0	34.1	65.9	32	>32	
Ceftriaxone		2.2	2	95.9	>64	>64	
Imipenem		98.9	1.1	0	0.25	0.5	
Levofloxacin		33.8	3.5	62.7	8	>8	
Minocycline		na	na	na	4	>16	
Pip/Tazo		na	na	na	8	>128	

* Species with n's <20 were omitted.
 ** Susceptibility data are based on EUCAST breakpoints where available. Where no EUCAST breakpoints are available, CLSI breakpoints (defined by CLSI document M100-S16, 2008) or FDA breakpoints were used (Tygacil®, 2005).

Table 2. *In vitro* activity of tigecycline and comparative agents against *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

Organism	Drug	%SUS**	%INT	%RES	MIC (mg/L)	
					MIC ₅₀	MIC ₉₀
<i>Acinetobacter baumannii</i> (n=2,053)	Tigecycline	na	na	na	0.25	1
	Amikacin	66.2	4.4	29.4	4	>64
	Cefepime	56.1	14.1	29.8	8	>32
	Ceftazidime	51.6	8.2	40.2	≤8	>32
	Ceftriaxone	31.2	24.5	44.3	32	>64
	Imipenem	80.7	6.6	12.6	0.5	16
	Levofloxacin	48.9	5.1	46.0	2	>8
	Minocycline	93.1	4.8	2.1	≤0.5	4
	Pip/Tazo	54.8	10.2	35.0	16	>128
	Tigecycline	na	na	na	8	16
<i>Pseudomonas aeruginosa</i> (n=3,394)	Amikacin	87.5	5.3	7.2	4	16
	Cefepime	76.4	0.0	23.6	4	32
	Ceftazidime	76.2	0.0	23.8	≤8	32
	Ceftriaxone	15.3	28.7	56.0	64	>64
	Imipenem	82.6	7.6	9.7	1	8
	Levofloxacin	57.0	9.0	34.0	1	>8
	Minocycline	na	na	na	>16	>16
	Pip/Tazo	76.3	0.0	23.7	4	128

* Species with n's <20 were omitted.
 ** Susceptibility data are based on EUCAST breakpoints where available. Where no EUCAST breakpoints are available, CLSI breakpoints (defined by CLSI document M100-S18, 2008) or FDA breakpoints were used (Tygacil®, 2005).

Table 3. *In vitro* activity of tigecycline and comparative agents against non-fastidious gram-positive pathogens.

Organism	Drug	%SUS**	%INT	%RES	MIC (mg/L)	
					MIC ₅₀	MIC ₉₀
<i>S. aureus</i> (n=4,863)	Tigecycline	100.0	0.0	0.0	0.12	0.25
	Amox-Clav	76.1	0.0	23.9	1	>8
	Ampicillin	54.2	0.0	45.8	8	>16
	Ceftriaxone	75.0	0.0	25.0	4	>64
	Imipenem	75.8	0.0	24.4	0.25	8
	Levofloxacin	75.3	1.6	23.1	0.25	6
	Linezolid	100.0	0.0	0	2	