

# In Vitro Activity of Tigecycline Against Pathogens from Switzerland, Sweden, and The Netherlands – T.E.S.T. Program 2008



OT037

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## Revised Abstract

**Objectives:** Tigecycline (TIG), a new glycylcycline, 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 TIG and 10 comparators against respective gram positive/negative species. Isolates were collected during 2004 to 2008.

**Methods:** More than 2,200 clinically significant isolates from Switzerland, Sweden and The Netherlands were analyzed in this survey. Isolates were identified to the species level at the participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to EUCAST guidelines. **Results:** Selected pathogens tested against tigecycline are shown in the table below:

Organism	E. coli and Klebsiella spp. (n=597)		Enterobacter spp. (n=284)		Acinetobacter spp.* (n=168)		P. aeruginosa* (n=239)	
	%S	MIC <sub>90</sub>	%S	MIC <sub>90</sub>	%S	MIC <sub>90</sub>	%S	MIC <sub>90</sub>
Tigecycline	96.3	0.5	100	1	n/a	0.25	n/a	16
Amikacin	100	2	100	2	100	4	98.4	8
Cefepime	97.3	0.5	100	0.5	91.9	8	90.3	8
Ceftazidime	99.3	8	90	16	91.9	8	90.3	8
Imipenem	100	0.5	100	1	97.3	1	93.5	2
Levofloxacin	93.9	0.5	98.3	0.06	97.3	0.12	93.5	2
Minocycline	92.6	4	93.3	4	100	0.5	n/a	>16
Pip-Tazo	96.6	2	95	8	97.3	4	96.8	8

**Conclusions:** Overall, the pathogens analyzed from these three countries are still very susceptible to most broad spectrum antimicrobials. Tigecycline's MIC<sub>90</sub> of ≤0.25µg/ml against Gram-positive pathogens (including resistant phenotypes) and MIC<sub>90</sub> of ≤1.0µg/ml against overall *Enterobacteriaceae* and *Acinetobacter* spp. validate the potent inhibitory activity of TIG against community/hospital pathogens isolated from Switzerland, Sweden, and The Netherlands.

## Introduction

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycylcyclines. This synthetic analogue of the tetracyclines exhibits significant antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as four-fold better than vancomycin and daptomycin [1, 2]. The development of tigecycline is important in that it is active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. Certain substituents at the 9-position of the tetracycline molecule restore activity against bacteria harboring genes encoding either or both efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible Gram-positive, Gram-negative, aerobic, and anaerobic bacteria [3]. Furthermore, resistance to tigecycline is difficult to produce even in the laboratory.

Previous studies have demonstrated excellent in vitro activity for tigecycline against clinical and laboratory strains of gram-positive and -negative bacteria with minimum inhibitory concentrations for the 90<sup>th</sup> percentile at or below 2 µg/ml, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Staphylococcus aureus* (VRE) and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [4-6]. This study was undertaken to document the in vitro activity of tigecycline against significant numbers of clinical pathogens collected in population centers in Switzerland, Sweden, and The Netherlands. 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 2008 from 20 study centers in Switzerland, Sweden, and The Netherlands, respectively. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, as well as 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., Sacramento, CA, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in µg/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); meropenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by EUCAST where applicable [10]. If no EUCAST guidelines were available for a given antibiotic, CLSI breakpoints [8] were used. MIC interpretive criteria for tigecycline followed the recent US Food and Drug Administration package insert [9].
- Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftazidime were >1 µg/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: ceftazidime (30-µg), ceftazidime/clavulanic acid (30/10-µg), ceftazidime (30-µg), and ceftazidime/clavulanic acid (30/10-µg). 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 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 EUCAST (2007) guidelines [10].

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## 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.

## Results

Table 1. In vitro activity of tigecycline and comparative agents against *Enterobacteriaceae*.

Organism Name	Drug	%SUS*	%INT	%RES	MIC (µg/ml)	
					MIC <sub>50</sub>	MIC <sub>90</sub>
<i>E. coli</i> (n=302)	Tigecycline	100	0	0	0.12	0.25
	Amoxiclav	99.0	0	0	0.5	2
	Amoxicillin	83.1	8.2	2.7	4	16
	Ampicillin	58.9	0	41.1	4	>32
	Cefepime	95.9	1.4	2.7	<0.5	<0.5
	Ceftazidime	98.6	1.4	0	<0.5	<0.5
	Ceftazidime	94.5	0	5.5	<0.06	0.12
	Imipenem	100	0	0	<0.06	0.25
	Levofloxacin	87.7	6.8	5.5	0.03	4
	Meropenem	100	0	0	<0.06	<0.06
	Minocycline	91.8	6.8	1.4	1	8
	Pip-Tazo	96.0	2.3	1.7	1	1
<i>K. pneumoniae</i> (n=204)	Tigecycline	91.2	5.9	2.9	0.5	1
	Amikacin	100	0	0	1	2
	Amoxiclav	85.8	6.9	7.4	2	16
	Ampicillin	0	33.3	66.7	32	>32
	Cefepime	94.1	3.9	2	<0.5	<0.5
	Ceftazidime	0	97.1	2.9	<0.5	<0.5
	Ceftazidime	96.1	0	3.9	<0.06	0.25
	Imipenem	100	0	0	<0.06	0.25
	Levofloxacin	94.1	1	4.9	0.06	0.5
	Meropenem	100	0	0	<0.06	<0.06
	Minocycline	80.4	3.4	16.2	2	>16
	Pip-Tazo	89.2	2.4	7.8	2	32
<i>E. coli</i> (n=91)	Tigecycline	95.6	4.4	0	0.25	0.5
	Amikacin	100	0	0	1	2
	Amoxiclav	90.1	5.5	4.4	2	8
	Ampicillin	0	11.1	88.9	>32	>32
	Cefepime	97	3	0	<0.5	<0.5
	Ceftazidime	0	98.9	1.1	<0.5	<0.5
	Ceftazidime	89	4.4	6.6	<0.06	0.25
	Imipenem	100	0	0	0.25	0.5
	Levofloxacin	97.8	0	2.2	0.03	0.12
	Meropenem	100	0	0	<0.06	<0.06
	Minocycline	95.6	2.2	2.2	1	4
	Pip-Tazo	90.1	5.5	4.4	1	16
<i>E. aerogenes</i> (n=61)	Tigecycline	96.7	1.6	1.6	0.25	0.5
	Amikacin	100	0	0	2	2
	Amoxiclav	0	0	100	>32	>32
	Ampicillin	0	0	100	>32	>32
	Cefepime	88.4	10.6	1	<0.5	2
	Ceftazidime	85	2.5	12.5	<0.5	32
	Ceftazidime	87.5	7.5	5	0.25	16
	Imipenem	100	0	0	0.25	0.5
	Levofloxacin	95.8	0.5	3.7	0.06	0.25
	Meropenem	96.9	0	3.1	<0.06	0.12
	Minocycline	92.5	0	7.5	2	8
	Pip-Tazo	83.8	9.7	6.5	2	64
<i>S. marcescens</i> (n=107)	Tigecycline	92.5	5.6	1.9	1	1
	Amikacin	96.3	2.8	0.9	2	8
	Amoxiclav	0	0	100	>32	>32
	Ampicillin	0	0	100	>32	>32
	Cefepime	97.2	2.8	0	<0.5	<0.5
	Ceftazidime	0	100	0	<0.5	<0.5
	Ceftazidime	96.2	3.8	0	0.12	1
	Imipenem	100	0	0	0.25	1
	Levofloxacin	96.2	0	3.8	0.12	1
	Meropenem	100	0	0	<0.06	0.12
	Minocycline	100	0	0	4	8
	Pip-Tazo	99.1	0	0.9	1	4

\* Interpretive criteria as defined by EUCAST (March, 2008). Where EUCAST breakpoints were not available, CLSI breakpoints were used (M100-S18, 2008). † Tigecycline susceptibility breakpoints are according to FDA package insert (Tygacil®), 2005, where applicable [9]. ‡ Species with n < 10 are omitted.

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

Organism Name	Drug	%SUS*	%INT	%RES	MIC (µg/ml)		
					MIC <sub>50</sub>	MIC <sub>90</sub>	
<i>Acinetobacter</i> spp. (n=168)	Tigecycline	na	na	na	0.12	0.25	
	Amikacin	96.4	1.2	2.4	2	4	
	Cefepime	91.9	8.1	0	2	16	
	Ceftazidime	91.9	2.7	5.4	<0.5	8	
	Ceftazidime	78.4	18.9	2.7	8	32	
	Imipenem	97.3	0	2.7	0.5	2	
	Levofloxacin	97.3	2.7	0	0.12	0.25	
	Meropenem	96.7	0	3.3	0.5	1	
	Minocycline	98.2	0	1.8	<0.5	<0.5	
	Pip-Tazo	97.1	0	2.7	0.25	0.16	
	<i>P. aeruginosa</i> (n=239)	Tigecycline	na	na	na	16	16
		Amikacin	98.4	1.6	0	4	8
Amoxiclav		90.3	6.5	3.2	2	8	
Cefepime		90.3	1.6	8.1	<0.5	<0.5	
Ceftazidime		29	6.5	64.5	32	>64	
Imipenem		93.3	6.5	5	1.7	0.5	
Levofloxacin		93.3	5	1.7	0.5	2	
Meropenem		93.5	4.8	1.6	0.5	4	
Minocycline		96.6	0	3.2	4	16	
Pip-Tazo		97.1	0	2.7	0.25	0.16	

\* Interpretive criteria as defined by EUCAST (March, 2008). Where EUCAST breakpoints were not available, CLSI breakpoints were used (M100-S18, 2008). † Tigecycline susceptibility breakpoints are according to FDA package insert (Tygacil®), 2005, where applicable [9]. ‡ Species with n < 10 are omitted.

Table 3. In vitro activity of tigecycline and comparative agents against Gram-positive pathogens.

Organism Name	Drug	%SUS*	%INT	%RES	MIC (µg/ml)	
					MIC <sub>50</sub>	MIC <sub>90</sub>
<i>S. aureus</i> (n=275)	Tigecycline	100	0	0	0.12	0.25
	Amoxiclav	80	0	12	0.2	2
	Ampicillin	24	0	76	4	>16
	Cefepime	86.7	1.3	12	2	8
	Ceftazidime	91.3	0	0	0.12	0.5
	Levofloxacin	81.3	0	18.7	0.12	2
	Linezolid	100	0	0	2	4
	Minocycline	91.3	0	0	0.12	0.5
	Penicillin	53.5	0	46.5	4	>8
	Pip-Tazo	87.3	0	12.7	1	2
	Vancomycin	100	0	0	1	1
	<i>S. aureus</i> (MR) (n=41)	Tigecycline	100	0	0	0.12
Amoxiclav		14.6	0	85.4	4	>8
Ampicillin		0	0	100	16	>16
Cefepime		91.9	0	0	2	8
Ceftazidime		0	0	100	16	>16
Imipenem		0	0	100	0.25	>16
Levofloxacin		56.1	0	43.9	0.5	16
Linezolid		100	0	0	2	2
Minocycline		91.9	0	0	2	8
Meropenem		0	0	100	2	8
Penicillin		92.7	0	7	<0.25	>0.25
Pip-Tazo		14.6	0	85.4	8	>16
Vancomycin	100	0	0	1	1	
<i>Enterococcus</i> spp. (n=181)	Tigecycline	100	0	0	0.06	0.12
	Amoxiclav	81.3	0	18.8	0.1	>16
	Amoxicillin	49.2	0	51.8	2	>32
	Linezolid	100	0	0	2	2
	Minocycline	50	0	50	0.2	>8
	Penicillin	81.3	0	18.8	4	>8
	Vancomycin	100	0	0	1	2
	<i>E</i>					