

# Multi-year Analysis of Changes in Susceptibility Patterns for Tigecycline and Comparators in Western Europe from 2004-2008

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## Revised Abstract

**Objectives:** Tigecycline, the first member of the glycylycylines, was marketed in mid 2005 and has demonstrated success against multiply-resistant species and phenotypes. Due to its chemical structure, resistance to tigecycline is reportedly difficult to produce even in the laboratory. The T.E.S.T. program is an ongoing global surveillance with the first post-marketing prospective report of tigecycline and comparator in vitro activity for the years 2004 through 2008. **Methods:** 30,340 clinical isolates were collected from 279 investigative sites in 16 countries in Western Europe. MICs were determined by broth microdilution according to CLSI guidelines using identical panels. **Results:** Results are given by year for all pathogens and antimicrobials. Summary data for tigecycline and key species are as follows:

Antimicrobial	2004	2005	2006	2007	2008
Amikacin	0.12	0.12	0.12	0.12	0.12
Amoxiclav	0.12	0.12	0.12	0.12	0.12
Ampicillin	0.12	0.12	0.12	0.12	0.12
Cefazidime	0.12	0.12	0.12	0.12	0.12
Ceftriaxone	0.12	0.12	0.12	0.12	0.12
Linezolid	0.12	0.12	0.12	0.12	0.12
Meropenem	0.12	0.12	0.12	0.12	0.12
Minocycline	0.12	0.12	0.12	0.12	0.12
Pip/Tazo	0.12	0.12	0.12	0.12	0.12
Vancomycin	0.12	0.12	0.12	0.12	0.12

**Conclusions:** Tigecycline demonstrated no shift in MIC values over five years from its pre-marketing baseline values. Tigecycline activity was retained even against strains resistant to other antimicrobials, such as ESBL-producers, multi-resistant *Acinetobacter* spp., methicillin-resistant *S. aureus*, vancomycin-resistant enterococci, and penicillin-resistant *S. pneumoniae*.

## Introduction

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycylycylines. 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 fourfold better than vancomycin and daptomycin [1, 2]. The development of tigecycline is important in that tigecycline and other glycylycylines are 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].

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 inhibited at or below 2 mcg/ml, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum  $\beta$ -lactamase (ESBL) producing *Enterobacteriaceae* [4-6]. This study was undertaken to document the in vitro activity of tigecycline and comparators against significant numbers of clinical pathogens collected from Western Europe over five years time. This study is part of the 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. 30,340 clinical isolates were collected and tested between 2004 and 2008 from 279 investigative sites in 16 countries in Western Europe. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and 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 at the local laboratory using broth microdilution panels from either MicroScan<sup>®</sup> panels (Dade Behring Inc., Sacramento, CA, USA) or Sensititre<sup>®</sup> plates (TREK Diagnostic Systems, West Sussex, England). Due to performance issues with lower concentrations of imipenem on MicroScan panels, meropenem was substituted for imipenem in June 2006. Furthermore, in order to augment the supply of panels was changed from MicroScan to Trek Diagnostic Systems, Inc. in May 2006. Two custom configurations were made one each for gram-positive and gram-negative organisms. Antimicrobial agents tested with concentrations (expressed in mcg/mL) were: amikacin (0.5-64); amoxicillin/clavulanic acid (0.12/0.06-32/16, tested using 2:1 ratio amoxicillin/clavulanic acid; reported concentrations refer to amoxicillin); ampicillin (0.5-32, gram-negative) and (0.5-16, gram-positive); ceftazidime (0.5-32); ceftaxone (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); 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 [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 using MIC results for ceftazidime were  $\geq 1$  mcg/ml when both microdilution panels. ESBL activity was confirmed using the CLSI (2005) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2005) guidelines. ESBL presence was confirmed by testing the following antibiotic disks: ceftazidime (30-mcg), ceftazidime/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 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; *K. pneumoniae* ATCC 700603 (positive ESBL control); *Haemophilus influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *Pseudomonas aeruginosa* ATCC 27853; *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2008) guidelines [8].

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## Results

Table 1. In vitro activity of tigecycline and comparators against *Acinetobacter* spp. by year of isolation.

Antimicrobial	2004		2005		2006		2007		2008	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Amikacin	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Amox/Clav	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Ampicillin	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Cefazidime	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Ceftriaxone	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Linezolid	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Meropenem	na	na	na	na	na	na	na	na	na	na
Minocycline	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Pip/Tazo	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Vancomycin	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32

Table 2. In vitro activity of tigecycline and comparators against *Enterobacteriaceae* by year of isolation.

Antimicrobial	2004		2005		2006		2007		2008	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Amikacin	2	4	2	4	2	4	2	4	2	4
Amox/Clav	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Ampicillin	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Cefazidime	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Ceftriaxone	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Linezolid	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Meropenem	na	na	na	na	na	na	na	na	na	na
Minocycline	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Pip/Tazo	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Vancomycin	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32

Table 3. In vitro activity of tigecycline and comparators against ESBL<sup>a</sup> producers by year of isolation.

Antimicrobial	2004		2005		2006		2007		2008	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Amikacin	4	16	4	16	4	16	4	16	4	16
Amox/Clav	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Ampicillin	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Cefazidime	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Ceftriaxone	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Linezolid	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Meropenem	na	na	na	na	na	na	na	na	na	na
Minocycline	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Pip/Tazo	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Vancomycin	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32

<sup>a</sup>ESBL producers include *K. pneumoniae*, *K. oxytoca* and *E. coli*.

Table 4. In vitro activity of tigecycline and comparators against *P. aeruginosa* by year of isolation.

Antimicrobial	2004		2005		2006		2007		2008	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	8	>16	8	>16	8	>16	8	>16	8	>16
Amikacin	4	8	4	8	4	8	4	8	4	8
Amox/Clav	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Ampicillin	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Cefazidime	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Ceftriaxone	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Linezolid	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Meropenem	na	na	na	na	na	na	na	na	na	na
Minocycline	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Pip/Tazo	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Vancomycin	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32

Table 5. In vitro activity of tigecycline and comparators against *Enterococcus* spp. by year of isolation.

Antimicrobial	2004		2005		2006		2007		2008	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
Amox/Clav	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Ampicillin	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Cefazidime	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Ceftriaxone	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Linezolid	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Meropenem	na	na	na	na	na	na	na	na	na	na
Minocycline	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Pip/Tazo	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Vancomycin	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8

Table 6. In vitro activity of tigecycline and comparators against vancomycin-resistant enterococci (VRE) by year of isolation.