

Changes of Susceptibility Patterns for Tigecycline and Comparators in Western Europe from 2004-2006

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REVISED ABSTRACT

Background: Tigecycline, the first member of the glycolcyclines, 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 2006. **Methods:** 12,454 clinical isolates were collected from 66 investigative sites in 15 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:

Organism	N (04/05/06)	2004		2005		2006	
		MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Acinetobacter</i> spp	389/165/304	0.25	1	0.12	1	0.12	1
<i>Enterobacteriaceae</i>	2233/1300/2018	0.5	1	0.25	1	0.5	1
ESBL producers*	118/60/71	0.5	2	0.5	2	0.25	1
<i>Enterococcus</i> spp	395/236/335	0.12	0.12	0.06	0.12	0.06	0.25
VRE	18/9/21	0.06	0.12	0.06	0.12	0.06	0.12
<i>S. aureus</i>	624/356/503	0.12	0.25	0.12	0.25	0.12	0.12
MRSA	170/88/91	0.12	0.25	0.12	0.25	0.12	0.25
<i>S. pneumoniae</i>	336/179/312	0.03	0.12	0.03	0.06	0.03	0.06
<i>P. aeruginosa</i>	529/314/474	8	>16	8	>16	8	16

Conclusion: Tigecycline demonstrated no shift in MIC values over three years from its pre-marketing baseline values. Tigecycline activity was retained even against strains resistant to other antimicrobials, as in 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 glycolcyclines. 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 glycolcyclines 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]. 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 90th 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 three 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. 12,454 clinical isolates were collected and tested between 2004 to 2006 from 66 investigative sites in 15 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 by the CLSI recommended broth microdilution testing method [6]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers, MicroScan (Dade Behring Inc., West Sacramento, CA, USA) and Trek (TREK Diagnostic Systems, Cleveland, OH). The following antimicrobial agents and dilution ranges (expressed in mcg/mL) were included on the panels: tigecycline (0.008-16), imipenem (0.06-16), levofloxacin (0.008-8), minocycline (0.5-16), piperacillin/tazobactam (0.06/4-128/4), amikacin (0.5-32), ceftazidime (8-32), ceftriaxone (0.06-64) and cefepime (0.5-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [7], where applicable. There are currently no breakpoints defined for tigecycline against *Acinetobacter* species.
- Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftriaxone were >1 mcg/ml using broth 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: 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 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 (2006) guidelines [8].

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RESULTS

The results are listed in the following table and figures.

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

Antimicrobial	2004 n=389		2005 n=165		2006 n=304	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.25	1	0.12	1	0.12	1
Amikacin	2	64	2	64	2	>64
Amoxicillin/Clavulanate	16	>32	16	>32	16	>32
Ampicillin	32	>32	16	>32	32	>32
Cefepime	8	>32	4	>32	4	>32
Ceftazidime	<8	>32	<8	>32	<8	>32
Ceftriaxone	16	>64	8	>64	16	>64
Imipenem	0.5	>16	0.5	4	0.5	4
Levofloxacin	0.25	>8	0.25	8	0.12	>8
Minocycline	<0.5	8	<0.5	2	<0.5	2
Piperacillin/Tazobactam	2	>128	0.5	>128	2	>128

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

Antimicrobial	2004 n=2,233		2005 n=1,300		2006 n=2,018	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.5	1	0.25	1	0.5	1
Amikacin	2	4	2	4	2	4
Amoxicillin/Clavulanate	16	>32	16	>32	16	>32
Ampicillin	>32	>32	>32	>32	>32	>32
Cefepime	<0.5	4	<0.5	4	<0.5	8
Ceftazidime	<8	>32	<8	>32	<8	>32
Ceftriaxone	0.12	32	<0.06	64	0.12	64
Imipenem	0.5	0.5	0.5	0.12	0.5	0.5
Levofloxacin	0.06	8	0.06	8	0.06	8
Minocycline	2	8	2	8	2	8
Piperacillin/Tazobactam	1	32	1	64	2	64

Table 3. In vitro activity of tigecycline and comparators against ESBL producers by year of isolation.

Antimicrobial	2004 n=118		2005 n=60		2006 n=71	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.5	2	0.5	2	0.25	1
Amikacin	4	16	4	16	4	16
Amoxicillin/Clavulanate	16	>32	16	>32	16	>32
Ampicillin	>32	>32	>32	>32	>32	>32
Cefepime	8	>32	16	>32	>32	>32
Ceftazidime	32	>32	32	>32	16	>32
Ceftriaxone	64	>64	64	>64	>64	>64
Imipenem	0.25	0.5	0.5	0.12	0.5	0.5
Levofloxacin	4	>8	8	>8	8	>8
Minocycline	4	>16	4	>16	2	>16
Piperacillin/Tazobactam	8	>128	8	128	8	>128

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

Antimicrobial	2004 n=529		2005 n=314		2006 n=474	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	8	>16	8	>16	8	16
Amikacin	4	8	4	16	4	8
Amoxicillin/Clavulanate	>32	>32	>32	>32	>32	>32
Ampicillin	>32	>32	>32	>32	>32	>32
Cefepime	4	32	4	16	4	32
Ceftazidime	<8	32	<8	32	<8	32
Ceftriaxone	>64	>64	32	>64	32	>64
Imipenem	1	8	1	8	1	8
Levofloxacin	0.5	>8	1	>8	1	>8
Minocycline	>16	>16	>16	>16	>16	>16
Piperacillin/Tazobactam	4	128	4	64	4	64

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

Antimicrobial	2004 n=395		2005 n=236		2006 n=335	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.12	0.12	0.06	0.12	0.06	0.25
Amoxicillin/Clavulanate	0.5	>8	0.5	>8	0.5	>8
Ampicillin	1	>16	1	>16	1	>16
Ceftriaxone	>64	>64	>64	>64	>64	>64
Imipenem	1	>16	1	>16	4	>16
Levofloxacin	1	>32	1	>32	2	>32
Linezolid	2	2	2	2	2	2
Minocycline	8	>8	4	>8	8	>8
Penicillin	2	>8	2	>8	2	>8
Piperacillin/Tazobactam	2	>16	2	>16	2	>16
Vancomycin	1	2	1	2	1	2

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

Antimicrobial	2004 n=18		2005 n=9		2006 n=21	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.06	0.12	na	na	0.06	0.12
Amoxicillin/Clavulanate	>8	>8	na	na	>8	>8
Ampicillin	>16	>16	na	na	>16	>16
Ceftriaxone	>64	>64	na	na	>64	>64
Imipenem	>16	>16	na	na	>16	>16
Levofloxacin	32	>32	na	na	>32	>32
Linezolid	2	2	na	na	2	4
Minocycline	<0.25	>8	na	na	<0.25	>8
Penicillin	>8	>8	na	na	>8	>8
Piperacillin/Tazobactam	>16	>16	na	na	>16	>16
Vancomycin	>32	>32	na	na	>32	>32

na = not applicable; MIC₉₀ values not calculated if n<10.

Table 7. In vitro activity of tigecycline and comparators against *Staphylococcus aureus* by year of isolation.

Antimicrobial	2004 n=624		2005 n=356		2006 n=503	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.12	0.25	0.12	0.25	0.12	0.12
Amoxicillin/Clavulanate	1	>8	1	>8	1	8
Ampicillin	8	>16	4	>16	4	>16
Ceftriaxone	4	>64	2	>64	2	16
Imipenem	0.25	8	0.25	4	<0.12	0.5
Levofloxacin	0.12	8	0.12	16	0.12	8
Linezolid	2	4	2	4	2	4
Minocycline	<0.25	0.5	<0.25	<0.25	<0.25	<0.25
Imipenem	0.25	0.5	0.5	0.12	0.5	0.5
Levofloxacin	4	>8	8	>8	8	>8
Penicillin	<8	>8	8	>8	8	>8
Piperacillin/Tazobactam	1	>16	1	>16	0.5	8
Vancomycin	1	1	0.5	1	0.5	1

Table 8. In vitro activity of tigecycline and comparators against methicillin-resistant *Staphylococcus aureus* by year of isolation.

Antimicrobial	2004 n=170		2005 n=88		2006 n=91	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	