

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:** More than 38,000 clinical isolates were collected from 213 investigative sites in 32 countries worldwide. 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	1464/1049/191	0.25	1	0.5	1	0.5	1
<i>Enterobacteriaceae</i>	8236/6737/1519	0.5	1	0.5	1	0.25	1
ESBL producers	374/288/30	0.5	2	0.5	2	0.5	2
<i>Enterococcus</i> spp	1448/1232/346	0.06	0.12	0.06	0.12	0.06	0.12
VRE	204/208/68	0.06	0.12	0.06	0.12	0.03	0.12
<i>S. aureus</i>	2504/2191/369	0.12	0.25	0.12	0.25	0.12	0.25
MRSA	1134/ 1027/196	0.12	0.25	0.12	0.25	0.12	0.25
<i>S. pneumoniae</i>	1273/1117/257	0.06	0.5	0.03	0.12	0.03	0.06
<i>P. aeruginosa</i>	2015/1625/387	8	>16	8	>16	8	>16

Conclusion: Tigecycline demonstrated no significant shift in MIC values over three years from its pre-marketing baseline values. Tigecycline activity was retained even against strains resistant to other antimicrobials, including 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 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].

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 against significant numbers of clinical pathogens collected from a large geographically diverse population 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. More than 38,000 clinical isolates were collected and tested between 2004 to 2006 from 213 investigative sites in 32 countries worldwide. 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 [7]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., West 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); ceftriaxone (0.06-64); ceftazidime (8-32); 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 guidelines established by the Clinical and Laboratory Standards Institute [8] and the recent US Food and Drug Administration package insert for tigecycline [9], where applicable.
- Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* were screened for ESBL activity using MIC results for ceftaxime of >1 mcg/ml using broth microdilution panels. ESBL activity was confirmed using the CLSI (2006) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2006) guidelines. ESBL presence was confirmed by testing the following antibiotic disks: ceftaxime (30-mcg), ceftaxime/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. *K. pneumoniae* ATCC 700793 was used to QC the ESBL confirmation test.
- 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 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 against selected pathogens by year of isolation.

Organism	n (04/05/06)	2004		2005		2006	
		MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Acinetobacter</i> spp	1464/1049/191	0.25	1	0.5	1	0.5	1
<i>A. baumannii</i>	1287/927/146	0.5	1	0.5	1	0.5	1
<i>A. lwoffii</i>	109/64/11	0.06	0.25	0.12	0.5	0.12	0.12
<i>Enterobacteriaceae</i>	8236/6737/1519	0.5	1	0.5	1	0.25	1
<i>E. coli</i>	2477/2146/520	0.12	0.25	0.12	0.25	0.12	0.25
<i>Klebsiella</i> spp.	2485/2007/450	0.5	2	0.5	2	0.5	1
<i>K. pneumoniae</i>	1996/1580/353	0.5	2	0.5	2	0.5	2
<i>K. oxytoca</i>	478/383/74	0.25	1	0.25	1	0.25	0.5
ESBL producers*	374/288/30	0.5	2	0.5	2	0.5	2
<i>E. aerogenes</i>	607/429/105	0.5	1	0.5	1	0.5	1
<i>E. cloacae</i>	1620/1277/246	0.5	2	0.5	2	0.5	2
<i>S. marcescens</i>	950/728/149	1	2	1	2	1	2
<i>Enterococcus</i> spp	1448/1232/346	0.06	0.12	0.06	0.12	0.06	0.12
<i>E. faecalis</i>	1042/866/198	0.12	0.12	0.06	0.12	0.06	0.12
<i>E. faecium</i>	369/301/95	0.06	0.12	0.03	0.12	0.03	0.06
All VRE	204/208/68	0.06	0.12	0.06	0.12	0.03	0.12
<i>S. aureus</i>	2504/2191/369	0.12	0.25	0.12	0.25	0.12	0.25
MRSA	1134/ 1027/196	0.12	0.25	0.12	0.25	0.12	0.25
<i>S. pneumoniae</i>	1273/1117/257	0.06	0.5	0.03	0.12	0.03	0.06
<i>S. pneumoniae</i> (PISP)	313/316/81	0.06	0.5	0.03	0.12	0.03	0.06
<i>S. pneumoniae</i> (PRSP)	143/124/31	0.06	0.5	0.03	0.12	0.03	0.06
<i>P. aeruginosa</i>	2015/1625/387	8	>16	8	>16	8	>16

Figure 1. In vitro activity of tigecycline against 2,704 strains of *Acinetobacter* spp. by year of isolation.

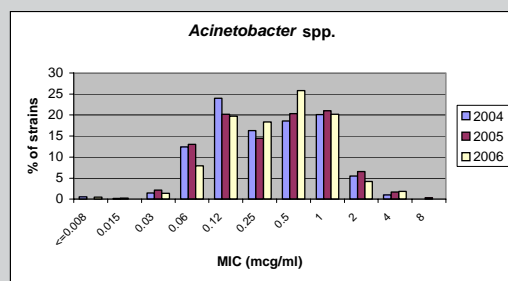


Figure 2. In vitro activity of tigecycline against 5,143 strains of *E. coli* by year of isolation.

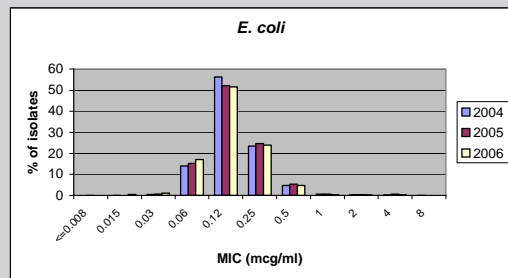


Figure 3. In vitro activity of tigecycline against 4,942 strains of *Klebsiella* spp. by year of isolation.

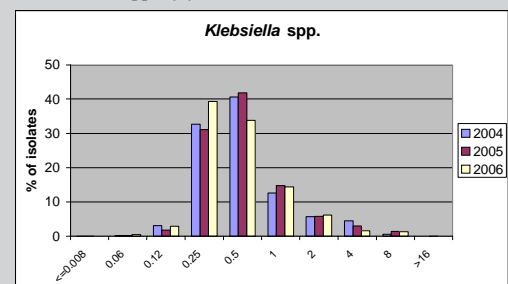


Figure 4. In vitro activity of tigecycline against 4,499 strains of *Enterobacter* spp. by year of isolation.

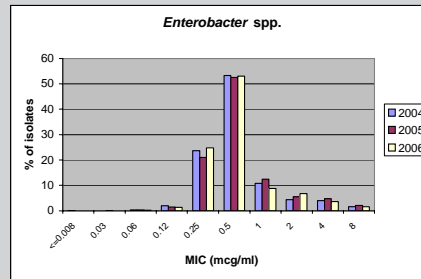


Figure 5. In vitro activity of tigecycline against 1,909 strains of *Serratia* spp. by year of isolation.

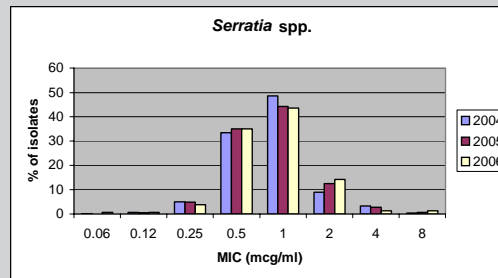


Figure 6. In vitro activity of tigecycline against 3,026 strains of *Enterococcus* spp. by year of isolation.

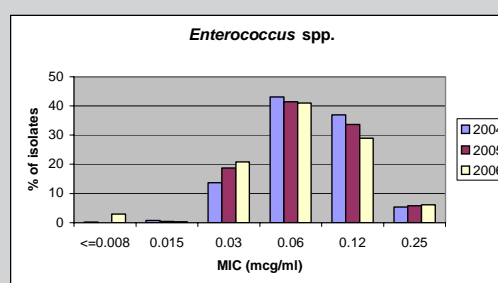


Figure 7. In vitro activity of tigecycline against 5,064 strains of *S. aureus* by year of isolation.

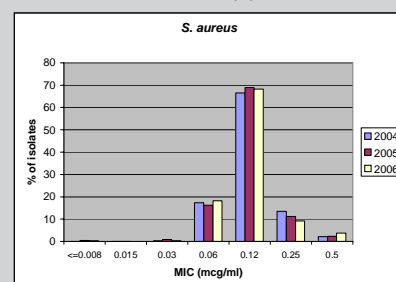
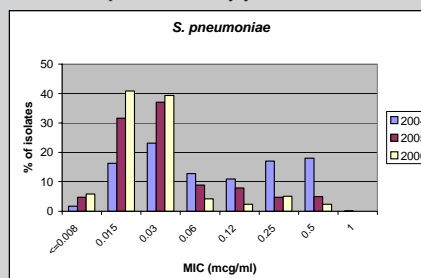


Figure 8. In vitro activity of tigecycline against 2,647 strains of *S. pneumoniae* by year of isolation.



CONCLUSIONS

- Other than the MIC₉₀s for *S. pneumoniae*, no other MIC₅₀ or MIC₉₀ value for any organism group differed by more than a single dilution when comparing 2004, 2005, and 2006 results.
- The tigecycline *S. pneumoniae* MIC₉₀ values demonstrated a decrease from 0.5 mcg/ml in 2004 to 0.12 mcg/ml in 2005, and then to 0.06 mcg/ml in 2006. Further investigation is ongoing.
- During the 3 years covered by this analysis, tigecycline has fully retained its excellent activity against a broad spectrum of bacteria, including many strains resistant to various other antimicrobials. Looking forward, as tigecycline's usage increases around the world, it will be important to continue to monitor its activity for any changes in susceptibility levels.