

Comparative Analysis of Tigecycline in South America from 2004-2007

M. Hackel¹, R. Badal¹, S. Bouchillon¹, B. Johnson¹, J. Johnson¹, D. Hoban¹, M. Dowzicky²

¹International Health Management Associates, Schaumburg, IL, USA
²Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL
60173
Tel: (847) 303-5003
Fax: (847) 303-5601
www.ihmainc.com

REVISED ABSTRACT

Objective: Tigecycline, the first member of the glycolcyclines, was first marketed in 2005 and has demonstrated success against multiple-resistant species and phenotypes. 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 2007. **Methods:** 4,230 clinical isolates were collected from 16 investigative sites in 5 countries in South America. MICs were determined by broth microdilution according to CLSI guidelines using identical panels. **Results:** Results are given by year for pathogens and antimicrobials. Summary data for tigecycline and key species are as follows:

Organism	N (04/05/06/07)	2004		2005		2006		2007	
		MIC ₅₀ ^a	MIC ₉₀ ^a	MIC ₅₀ ^a	MIC ₉₀ ^a	MIC ₅₀ ^a	MIC ₉₀ ^a	MIC ₅₀ ^a	MIC ₉₀ ^a
Enterobacteriaceae	236/674/820/95	0.5	1	0.5	2	0.5	2	0.5	2
ESBL producers ^b	25/123/136/2	0.5	2	0.5	2	0.5	2	na	na
Acinetobacter spp	53/129/122/15	0.5	1	0.5	1	0.5	2	1	4
<i>P. aeruginosa</i>	59/159/199/29	8	>16	8	>16	16	>16	8	>16
<i>S. aureus</i>	64/250/213/24	0.06	0.12	0.12	0.25	0.12	0.25	0.25	0.5
MRSA ^c	28/120/109/16	0.12	0.25	0.12	0.25	0.12	0.25	0.25	0.25
Enterococcus spp	38/117/141/15	0.06	0.12	0.12	0.25	0.06	0.12	0.12	0.25
<i>S. pneumoniae</i>	34/98/87/8	0.03	0.12	0.03	0.12	0.015	0.06	na	na
<i>H. influenzae</i>	29/119/28/28	0.5	0.5	0.25	0.5	0.12	0.25	0.25	0.5

^a MIC_{50/90} values in mcg/mL
^b ESBL=Extended spectrum beta-Lactamase, and includes *E. coli*, *K. pneumoniae* and *K. oxytoca*
^c MRSA = methicillin resistant *Staphylococcus aureus*
na = MIC_{50/90} not calculated on n<10

Conclusion: Other than a 1-doubling dilution increase in the MIC₉₀ of *S. aureus*, and a 1-doubling dilution increase in the MIC₉₀ of *Acinetobacter* spp., tigecycline demonstrated no increase in MIC_{50/90} values over four years from its pre-marketing baseline values. Tigecycline's activity was retained even against strains resistant to other antimicrobials, including ESBL-producers, methicillin-resistant *S. aureus*, vancomycin-resistant enterococci, and penicillin-resistant *S. pneumoniae*.

INTRODUCTION

Tigecycline 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 gram-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 16 sites in five South American countries over four years time. This study is part of the ongoing global Tigecycline Evaluation and Surveillance Trial (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 4156 clinical isolates were collected and tested between 2004 and 2007 from 16 investigative sites in Argentina, Brazil, Chile, Colombia and Venezuela. 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 manufacturers, MicroScan (Dade Behring Inc., West Sacramento, CA, USA) and Trek (TREK Diagnostic Systems, Cleveland, OH). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amikacin (0.5-64, gram-negative only); amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.06-16); cefepime (0.5-32, gram-negative only); ceftazidime (8-32, gram-negative); ceftriaxone (0.06-64); imipenem (0.06-16, MicroScan only); linezolid (0.5-8, gram-positive only); meropenem (0.12-16, TREK only); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8, gram-positive only); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32, gram-positive only). 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 when MIC results for ceftriaxone were >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: 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 control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains where applicable: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Escherichia coli* ATCC 35218; *Klebsiella pneumoniae* ATCC 700603 (as positive ESBL control); *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *Pseudomonas aeruginosa* ATCC 27853. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2007) guidelines [8].

REFERENCES

- Hackel M, et al. Antipneumococcal activities of GAR-936 (a new glycolcycline) compared to those of nine other agents against penicillin-susceptible and -resistant pneumococci. *Antimicrob Agents Chemother*. 2004; 44(4): p. 1182-8.
- Laboritoulou P, P. J. Pateras, and P. A. Bradford. In vitro activity of tigecycline against *Staphylococcus epidermidis* growing in an adherent-cell biofilm model. *Antimicrob Agents Chemother*. 2003; 47(12): p. 3967-9.
- Projan, S.J. Preclinical pharmacology of GAR-936, a novel glycolcycline antibacterial agent. *Pharmacotherapy*, 2000, 20(9 Pt 2): p. 2195-2235; discussion 2245-2250.
- Cates, A.C. and R.N. Jones. Antimicrobial activity and spectrum of the new glycolcycline, GAR-936 tested against 1,203 recent clinical bacterial isolates. *Diagn Microbiol Infect Dis*. 2000; 36(1): p. 10-36.
- Patel, R. et al. In vitro activity of GAR-936 against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis*. 2000; 39(3): p. 177-9.
- Rupp, M.E. and P.D. Ten. Extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*: considerations for diagnosis, prevention and drug treatment. *Drugs*. 2003; 63(4): p. 553-65.
- CLSI. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. Approved Standards-Sixth Edition. In Document M7-A6. 2006; Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1888 USA.
- Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing: Seventeenth Informational Supplement. CLSI document M100-S17. Wayne, PA, 2007.
- Typical Product Insert. 2005; Wyeth Pharmaceuticals, Inc., Philadelphia, PA, USA.

ACKNOWLEDGEMENTS

This study was supported by a grant from Wyeth Pharmaceuticals. We gratefully acknowledge contributions from the participants in the T.E.S.T. program who have helped make this program a success.

The results are listed in the following table and figures.

Table 1. In vitro activity of tigecycline against selected pathogens from South America by year of isolation.

Organism	N (04/05/06/07)	2004		2005		2006		2007	
		MIC ₅₀ ^a	MIC ₉₀ ^a	MIC ₅₀ ^a	MIC ₉₀ ^a	MIC ₅₀ ^a	MIC ₉₀ ^a	MIC ₅₀ ^a	MIC ₉₀ ^a
<i>Acinetobacter</i> spp	53/129/122/15	0.5	1	0.5	1	0.5	2	1	4
Enterobacteriaceae	236/674/820/95	0.5	1	0.5	2	0.5	2	0.5	2
<i>E. coli</i>	72/193/262/32	0.12	0.25	0.12	0.25	0.12	0.5	0.25	0.5
<i>K. pneumoniae</i>	66/186/193/23	0.5	1	0.5	2	0.5	2	1	1
<i>K. oxytoca</i>	16/18/36/1	0.25	0.5	0.5	2	0.25	1	na	na
ESBL producers ^b	25/123/136/2	0.5	2	0.5	2	0.5	2	na	na
<i>Enterobacter</i> spp.	56/182/230/26	0.5	1	0.5	2	0.5	2	0.5	2
<i>Serratia</i> spp.	25/95/99/13	1	1	1	2	1	2	1	2
Enterococcus spp	38/117/141/15	0.06	0.12	0.06	0.12	0.06	0.12	0.06	0.12
<i>E. faecalis</i>	25/103/108/6	0.06	0.12	0.12	0.25	0.12	0.25	na	na
<i>E. faecium</i>	13/12/28/9	0.03	0.12	0.06	0.25	0.06	0.25	na	na
All VRE ^c	8/16/13/7	0.03	0.12	0.06	0.25	0.06	0.06	na	na
<i>S. aureus</i>	64/250/213/24	0.06	0.12	0.12	0.25	0.12	0.25	0.25	0.5
MRSA ^d	28/120/109/16	0.12	0.25	0.12	0.25	0.12	0.25	0.25	0.25
<i>S. pneumoniae</i>	34/98/87/8	0.03	0.12	0.03	0.12	0.015	0.06	na	na
<i>P. aeruginosa</i>	59/159/199/29	8	>16	8	>16	16	>16	8	>16
<i>H. influenzae</i>	29/119/28/28	0.5	0.5	0.25	0.5	0.12	0.25	0.25	0.5

^a MIC_{50/90} values in mcg/mL
^b ESBL=Extended spectrum beta-Lactamase, and includes *E. coli*, *K. pneumoniae* and *K. oxytoca*
^c VRE = vancomycin resistant enterococci
^d MRSA = methicillin resistant *Staphylococcus aureus*
na = MIC_{50/90} not calculated on n<10

Figure 1. In vitro activity (MIC₉₀) of tigecycline against 319 strains of *Acinetobacter* spp. by year of isolation.

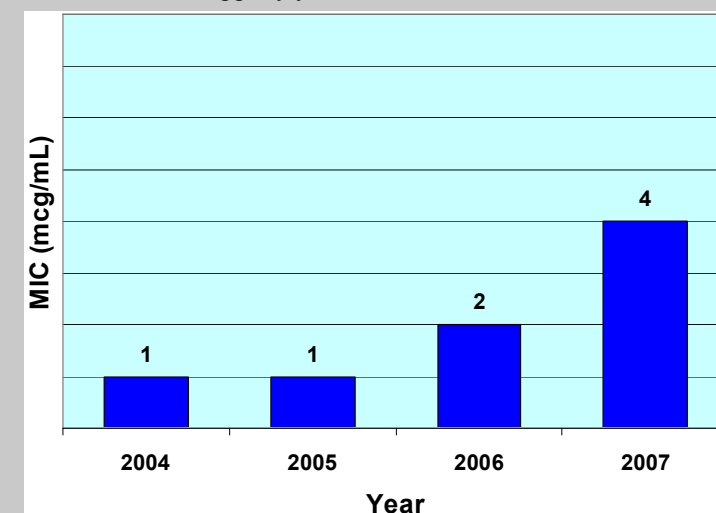
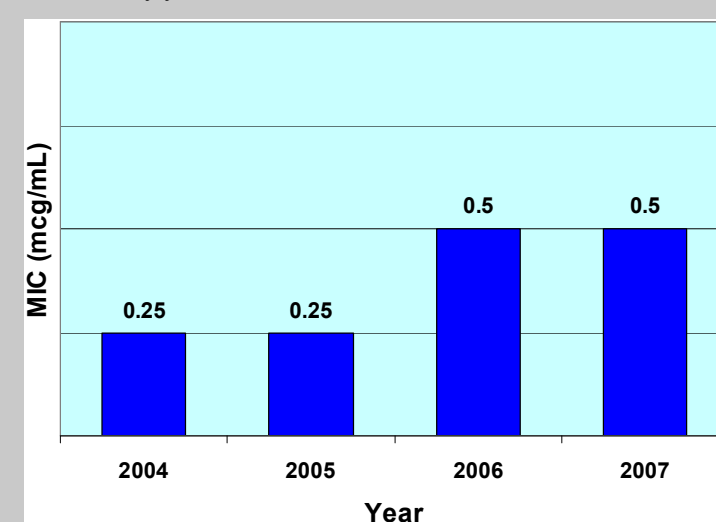


Figure 2. In vitro activity (MIC₉₀) of tigecycline against 559 strains of *E. coli* by year of isolation.



RESULTS

Figure 3. In vitro activity (MIC₉₀) of tigecycline against 539 strains of *Klebsiella* spp by year of isolation.

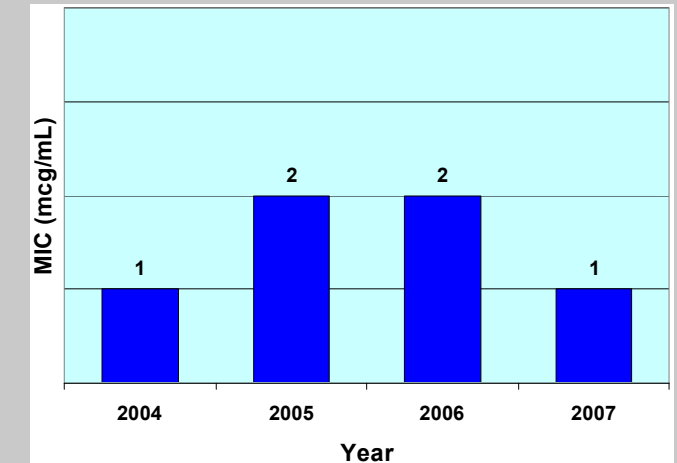


Figure 4. In vitro activity (MIC₉₀) of tigecycline against 494 strains of *Enterobacter* spp by year of isolation.

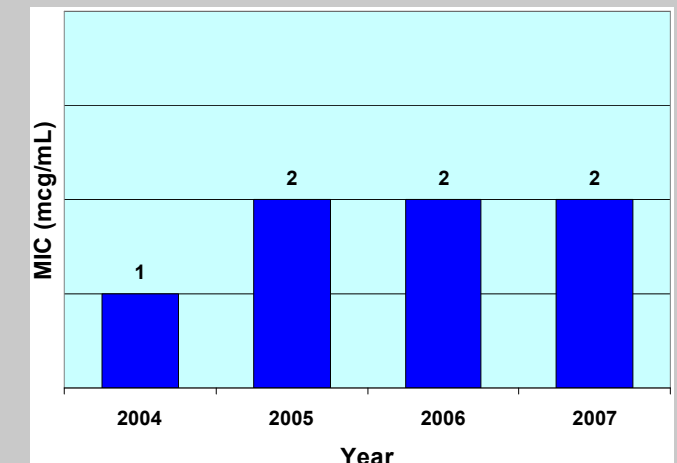


Figure 5. In vitro activity (MIC₉₀) of tigecycline against 232 strains of *Serratia* spp by year of isolation.

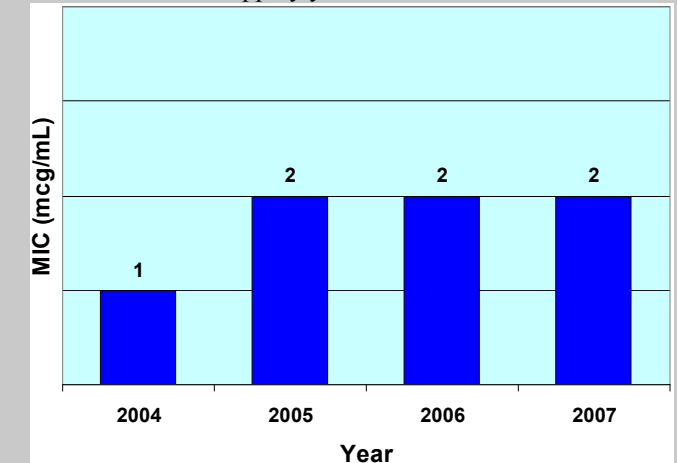


Figure 6. In vitro activity (MIC₉₀) of tigecycline against 311 strains of *Enterococcus* spp by year of isolation.

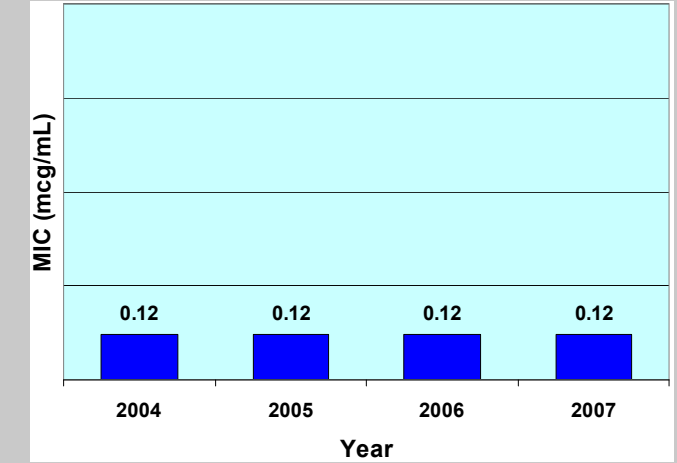


Figure 7. In vitro activity (MIC₉₀) of tigecycline against 551 strains of *S. aureus* by year of isolation.

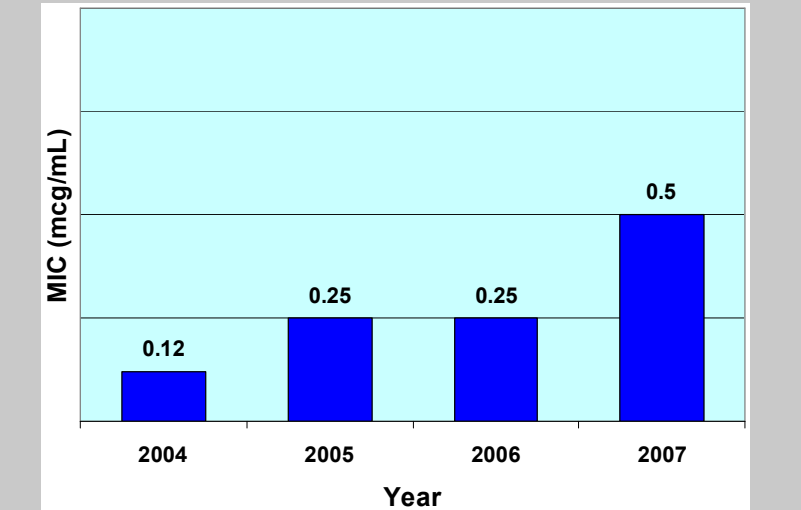
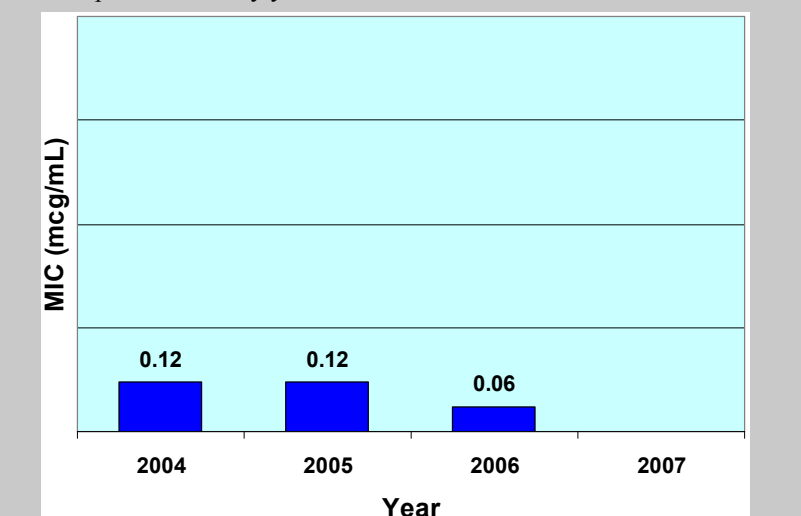


Figure 8. In vitro activity (MIC₉₀) of tigecycline against 227 strains of *S. pneumoniae* by year of isolation.



CONCLUSIONS

- Other than a 1-doubling dilution increase in the MIC₉₀ of *S. aureus*, and a 1-doubling dilution increase in the MIC₉₀ of *Acinetobacter* spp., tigecycline demonstrated no increase in MIC_{50/90} values over four years from its pre-marketing baseline values.
- The change observed with *Acinetobacter* was a 2-dilution increase in the MIC₉₀ from 2004 to 2007. Small numbers of this isolate in 2007 (n=15) may explain this. Additional data from the ongoing T.E.S.T. study will prove helpful in clarifying the possible upward shift.
- The 2-dilution increase in the MIC₉₀ between 2004 and 2007 for *S. aureus* was not seen in MIC₉₀ data for MRSA from the same period. Again, additional data from the ongoing T.E.S.T. study will be useful.
- 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.