



IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL
60173
Tel: 847.303.5003
Fax: 847.303.5601

Tigecycline Activity in Current (2008) Global Population – An Age Analysis: T.E.S.T. Program

OB018

S. Hawser¹, M. Hackel¹, S. Bouchillon¹, B. Johnson¹, D. Hoban¹, M. Renteria¹, J. Johnson¹, R. Badal¹, M. Dowzicky²

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

Revised Abstract

Objectives: Tigecycline (TIG), a new glycolcyclocline, 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 from 1,016 hospital sites in 53 countries from 2004 to 2008. **Methods:** Over 120,000 clinically significant isolates collected worldwide were analyzed in this survey. The 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 CLSI guidelines. **Results:** Selected pathogens tested against tigecycline are shown in the table below:

		Tigecycline		
		n	%S	MIC ₉₀
Pediatric (0-13)	Enterobacteriaceae	4,940	97.9	1
	<i>Acinetobacter</i> spp.	689	n/a	1
	<i>S. aureus</i>	1,651	100	0.25
	<i>S. pneumoniae</i>	1,704	n/a	0.06
Young Adult (14-29)	Enterobacteriaceae	4,216	97.8	1
	<i>Acinetobacter</i> spp.	809	n/a	1
	<i>S. aureus</i>	1,793	99.9	0.25
	<i>S. pneumoniae</i>	485	n/a	0.12
Adult (30-64)	Enterobacteriaceae	20,576	96.2	1
	<i>Acinetobacter</i> spp.	3,763	n/a	2
	<i>S. aureus</i>	6,715	100	0.25
	<i>S. pneumoniae</i>	2,685	n/a	0.06
Geriatric (65+)	Enterobacteriaceae	21,660	95.7	1
	<i>Acinetobacter</i> spp.	3,109	n/a	2
	<i>S. aureus</i>	5,102	99.9	0.25
	<i>S. pneumoniae</i>	2,000	n/a	0.12

n/a = breakpoints not available.

Conclusions: Tigecycline showed excellent inhibitory activity against all groups of pathogens regardless of age group. Tigecycline MIC₉₀ of 0.25mcg/ml and 0.5mcg/ml against *S. aureus* and *S. pneumoniae*, respectively, and MIC₉₀ of ≤1mcg/ml against *Enterobacteriaceae* and *Acinetobacter* spp. validate the potent inhibitory activity of TIG against community/hospital pathogens in all age populations.

Introduction

Tigecycline is the first marketed glycolcyclocline with expanded broad-spectrum activity against both aerobic and anaerobic pathogens. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it is perceived to be bacteriostatic, it has shown some bactericidal activity against key targeted pathogens [1, 2]. Tigecycline was developed to provide activity against tetracycline- and multi-drug-resistant pathogens and has demonstrated significant activity against aerobic and anaerobic Gram-positive and Gram-negative microorganisms [2-4].

Tigecycline resistance is very infrequent and is also difficult to induce in the laboratory [5, 6] with a selection frequency of less than 10⁻⁹ observed [3, 5]. With the exception of *Pseudomonas aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-4]. Tigecycline has demonstrated MIC₉₀ values of ≤0.5 mcg/ml against methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive organisms [2, 4-6]. Tigecycline has shown potent activity in animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4, 5] with diverse genotypes van-A, -B and -C [6].

Tigecycline has now been tested on large numbers of diverse demographic and geographic populations. This study documents the in vitro activity of tigecycline against these diverse populations segregated by age. Since tigecycline has shown no age related pharmacokinetic parameters and few, if any, inconsistencies within species, mostly without regard to resistant phenotypes, consistency in activity across various age groups is postulated and the consistency of activity for different age groups is explored across various species and organism groups.

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 from 1,016 medical centers in 53 countries and tested between 2004 to 2008. 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., 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); ceftazidime (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 when MIC results for ceftazidime were >1 µg/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-µg), cefotaxime/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 CLSI (2005) guidelines [8].

References

- Sum, P.E. and P. Petersen, Synthesis and structure-activity relationship of novel glycolcyclocline derivatives leading to the discovery of GAR-936. *Bioorg Med Chem Lett* 1999, 9(10): p. 1459-62.
- Abbanat, D., M. Macielag, and K. Bush, Novel antibacterial agents for the treatment of serious Gram-positive infections. *Expert Opin Investig Drugs*, 2003, 12(3): p. 379-99.
- Betriu, C., et al., In vitro activities of tigecycline (GAR-936) against recently isolated clinical bacteria in Spain. *Antimicrob Agents Chemother*, 2002, 46(3): p. 892-5.
- Gales, A.C. and R.N. Jones, Antimicrobial activity and spectrum of the new glycolcyclocline, GAR-936 tested against 1,203 recent clinical bacterial isolates. *Diagn Microbiol Infect Dis*, 2000, 36(1): p. 19-36.
- Henwood, C.J., et al., Antibiotic resistance among clinical isolates of *Acinetobacter* in the UK, and in vitro evaluation of tigecycline (GAR-936). *J Antimicrob Chemother*, 2002, 49(3): p. 479-87.
- Chopra, I., New developments in tetracycline antibiotics: glycolcyclocline and tetracycline efflux pump inhibitors. *Drug Resist Updat*, 2002, 5(4-6): p. 119-25.
- CLSI, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, Approved Standard—Sixth Edition, in Document M7-A6, 2005. Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- CLSI, Performance Standards for Antimicrobial Susceptibility Testing, in Document M100-S15, 2005. Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- Tygacil, Product insert, 2005. Wyeth Pharmaceuticals, Inc., Philadelphia, PA, USA.

Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation Study Trials (TEST) program group. This study was sponsored by a grant from Wyeth Pharmaceuticals.

Results

Results are shown in the following tables.

Table 1. Frequency Distribution of Age Groups for All Isolates.*

Age Group	Total N	% of Total
Pediatrics (NB-13)	13,879	11.6
Young Adult (14-29)	11,066	9.2
Adult (30-64)	48,304	40.2
Geriatric (65+)	44,982	37.4
No Age Given	1,890	1.6
Total	120,121	100

* *Pseudomonas aeruginosa* is excluded from all analyses as well as all isolates having no age given.

Table 2. Statistical Analysis of Tigecycline MIC values by Age Groups for all 120,121 Study Isolates Combined.

	Quartile MIC (mcg/mL)					Mean	Std Error ¹	t-Test Statistical Category ²	One-Way ANOVA
	10%	25%	Median	75%	90%				
Pediatric (NB-13)	0.03	0.06	0.12	0.5	1	0.330904	0.01261	A	
Young Adult (14-29)	0.03	0.06	0.12	0.5	1	0.333379	0.01352	A	Prob > F
Adult (30-64)	0.03	0.12	0.12	0.5	1	0.414097	0.00653	B	<0.001
Geriatric (65+)	0.06	0.12	0.25	0.5	1	0.459822	0.00692	C	

¹ Std Error uses a pooled estimate of error variance

² Different letters represent statistically different groups. Same letters represent groups that are statistically similar.

Table 3. Statistical Analysis of Tigecycline MIC values by Age Groups Categorized by Individual Species or Family Groups.

Age Group (n)	Quartile MIC (mcg/mL)					Mean	Std Error ¹	t-Test Statistical Category ²	One-Way ANOVA
	10%	25%	50%	75%	90%				
Enterobacteriaceae									
Pediatric (4940)	0.12	0.25	0.5	0.5	1	0.5635	0.02593	A	
Young Adult (4216)	0.12	0.12	0.25	0.5	1	0.5257	0.02697	A	Prob > F
Adult (20576)	0.12	0.25	0.5	0.5	1	0.6499	0.01242	B	<0.001
Geriatric (21660)	0.12	0.25	0.5	0.5	1	0.6720	0.01227	B	
Enterococcus spp									
Pediatric (710)	0.03	0.06	0.06	0.12	0.12	0.0935	0.00537	A B	
Young Adult (638)	0.03	0.06	0.06	0.12	0.12	0.1038	0.00556	A	Prob > F
Adult (3963)	0.03	0.06	0.06	0.12	0.12	0.0905	0.00216	B	0.0768
Geriatric (4086)	0.03	0.06	0.06	0.12	0.12	0.0884	0.00219	B	
Haemophilus spp									
Pediatric (1812)	0.06	0.12	0.12	0.25	0.25	0.1994	0.0093	A	
Young Adult (670)	0.06	0.12	0.12	0.25	0.5	0.2027	0.01509	A	Prob > F
Adult (2413)	0.06	0.12	0.12	0.25	0.5	0.1951	0.0079	A	0.4908
Geriatric (2007)	0.06	0.12	0.12	0.25	0.5	0.2132	0.0089	A	
Acinetobacter spp									
Pediatric (689)	0.06	0.06	0.12	0.5	1	0.3498	0.05073	A	
Young Adult (809)	0.06	0.12	0.25	1	1	0.5581	0.04348	B	Prob > F
Adult (3763)	0.06	0.12	0.5	1	1	0.5931	0.02077	B	<.0001
Geriatric (3109)	0.06	0.12	0.5	1	1	0.6098	0.02339	B	
S. aureus									
Pediatric (1615)	0.06	0.12	0.12	0.12	0.25	0.1271	0.00733	A B	
Young Adult (1793)	0.06	0.12	0.12	0.12	0.25	0.1386	0.00695	A	Prob > F
Adult (6715)	0.06	0.12	0.12	0.12	0.25	0.1481	0.00343	B	0.063
Geriatric (5102)	0.06	0.12	0.12	0.12	0.25	0.1437	0.00393	B	
S. pneumoniae									
Pediatric (1704)	0.015	0.015	0.03	0.03	0.06	0.1922	0.01111	A	
Young Adult (485)	0.015	0.015	0.03	0.03	0.12	0.2158	0.01986	A	Prob > F
Adult (2685)	0.015	0.015	0.03	0.03	0.06	0.1746	0.0082	A	0.065
Geriatric (2000)	0.015	0.03	0.03	0.03	0.12	0.1789	0.00965	A	
S. agalactiae									
Pediatric (NB-13)	0.015	0.015	0.03	0.06	0.12	0.1922	0.01111	A	
Young Adult (14-29)	0.015	0.015	0.03	0.06	0.12	0.2158	0.01986	A	Prob > F
Adult (30-64)	0.015	0.015	0.03	0.06	0.12	0.1746	0.0082	A	0.1999
Geriatric (65+)	0.015	0.03	0.06	0.06	0.12	0.1789	0.00965	A	

¹ Std Error uses a pooled estimate of error variance

² Different letters represent statistically different groups within the same species or organism group. Same letters represent groups that are statistically alike.

Conclusions

- Tigecycline demonstrated an MIC₉₀ of ≤2 mcg/ml for all organisms and age groups.
- Tigecycline demonstrated statistically different in vitro activity among the various age groups for all study organism combined (p<0.001). Although within this same combined organism group no statistical difference in activity was noted between the pediatric and young adult age groups (p=0.8935, not shown in tables).
- An Analysis of Variance (ANOVA) demonstrated varying activity of tigecycline among the four age groups for the *Enterobacteriaceae* and *Acinetobacter* spp (p<0.001) while showing more consistent activity across age groups for *Haemophilus* and the streptococci (p-values range 0.065 – 0.4908).
- A paired t-Test demonstrated varied degrees of similar activity of tigecycline among age groups within species and organism groups. Tigecycline activity was more consistent in Pediatric/Young Adult age groups in most species while the Adult/Geriatric populations were often paired with similar activity.
- While the activity of tigecycline varied slightly among age groups within different organism groups and species, the overall activity of tigecycline was consistently within the FDA susceptible ranges for >90% of all organism groups and species (where breakpoints exist) and in all age groups.