

## REVISED ABSTRACT

**Background:** Tigecycline (TIG), a new glycolcycline, 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 gram-positive and -negative species. Isolates were collected from 213 hospital sites in 32 countries from 2004 to 2006. **Methods:** Over 38,000 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 <sub>50</sub>
Pediatric (0-13)	Enterobacteriaceae	1470	97.9	1
	Acinetobacter spp.	202	n/a	1
	S. aureus	485	99.9	0.25
	S. pneumoniae	613	n/a	0.5
Young Adult (14-29)	Enterobacteriaceae	1367	97.8	1
	Acinetobacter spp.	275	n/a	1
	S. aureus	539	99.8	0.25
	S. pneumoniae	192	n/a	1
Adult (30-64)	Enterobacteriaceae	6448	96.2	1
	Acinetobacter spp.	1205	n/a	1
	S. aureus	2213	99.1	0.25
	S. pneumoniae	1126	n/a	0.5
Geriatric (65+)	Enterobacteriaceae	6611	95.7	1
	Acinetobacter spp.	950	n/a	1
	S. aureus	1688	99.2	0.25
	S. pneumoniae	813	n/a	0.5

n/a = breakpoints not available.

**Conclusion:** Tigecycline showed excellent inhibitory activity against all groups of pathogens regardless of patient age group. Tigecycline MIC<sub>50</sub> of 0.25mcg/ml and 0.5mcg/ml against *S. aureus* and *S. pneumoniae*, respectively, and MIC<sub>90</sub> 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 glycolcycline 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, its anti-bacterial activity is significant and 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<sup>-8</sup> 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 MIC<sub>50</sub> 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 was postulated and the consistency of activity for different age groups was explored across various species and organism groups.

## MATERIALS &amp; 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 213 medical centers in 32 countries and tested between 2004 to 2006. 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.
- 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].

## REFERENCES

- Sun, P.E. and P. Petersen. *Synthesis and structure-activity relationship of novel glycolcycline 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.
- Gates, 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. 19-36.
- Herwood, 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: glycolcyclines and tetracycline efflux pump inhibitors*. Drug Resist Updat, 2002, 5(3-4): p. 119-25.
- Projan, S.J. *Preclinical pharmacology of GAR-936, a novel glycolcycline antibacterial agent*. Pharmacotherapy, 2000, 20(9 Pt 2): p. 2195-2235; discussion 2245-2285.
- Biedenbach, D.J., M.L. Beach, and R.N. Jones. *In vitro antimicrobial activity of GAR-936 tested against antibiotic-resistant gram-positive blood stream infection isolates and strains producing extended-spectrum beta-lactamases*. Diagn Microbiol Infect Dis, 2001, 40(4): p. 173-7.
- 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, 38(3): p. 177-9.
- Petersen, P.J., et al. *In vitro and in vivo antibacterial activities of a novel glycolcycline, the 9-t-butylglyclamide derivative of minocycline (GAR-936)*. Antimicrob Agents Chemother, 1999, 43(4): p. 738-44.
- Petersen, P.J., et al. *In vitro and in vivo activities of tigecycline (GAR-936), daptomycin, and comparative antimicrobial agents against glycopeptide-intermediate Staphylococcus aureus and other resistant gram-positive pathogens*. Antimicrob Agents Chemother, 2002, 46(8): p. 2595-601.
- Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing: Sixteenth Informational Supplement*. CLSI document M100-S16. Wayne, PA, 2006.

## RESULTS

Table 1. Frequency distribution of age groups for all isolates.\*

Age Group	Total N	% of Total
Pediatric (NB-13)	3,723	11.20%
Young Adult (14-29)	3,238	9.70%
Adult (30-64)	13,902	41.90%
Geriatric (65+)	12,355	37.20%
Total	33,218	100.00%

\* *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 study organisms combined.

	Quartile MIC (mcg/ml)					Mean	Std Error <sup>1</sup>	t-Test Statistical Category	One-Way ANOV
	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	

<sup>1</sup> Std error uses a pooled estimate of error variance.<sup>2</sup> 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.

	Quartile MIC (mcg/ml)					Mean	Std Error <sup>1</sup>	t-Test Statistical Category	One-Way ANOV
	10%	25%	Median	75%	90%				
<i>Enterobacteriaceae</i>									
Pediatric (NB-13)	0.12	0.25	0.5	0.5	1	0.5635	0.02593	A	
Young Adult (14-29)	0.12	0.12	0.25	0.5	1	0.5257	0.02697	A	Prob > F
Adult (30-64)	0.12	0.25	0.5	0.5	1	0.6499	0.01242	B	<0.001
Geriatric (65+)	0.12	0.25	0.5	0.5	1	0.672	0.01227	B	
<i>Enterococcus spp.</i>									
Pediatric (NB-13)	0.03	0.06	0.06	0.12	0.12	0.0935	0.00537	A B	Prob > F
Young Adult (14-29)	0.03	0.06	0.06	0.12	0.12	0.1038	0.00556	A	0.0768
Adult (30-64)	0.03	0.06	0.06	0.12	0.12	0.0905	0.00216	B	
Geriatric (65+)	0.03	0.06	0.06	0.12	0.12	0.0884	0.00219	B	
<i>Haemophilus spp.</i>									
Pediatric (NB-13)	0.06	0.12	0.12	0.25	0.25	0.1994	0.0093	A	Prob > F
Young Adult (14-29)	0.06	0.12	0.12	0.25	0.5	0.2027	0.01509	A	0.4908
Adult (30-64)	0.06	0.12	0.12	0.25	0.5	0.1951	0.0079	A	
Geriatric (65+)	0.06	0.12	0.12	0.25	0.5	0.2132	0.0089	A	
<i>Acinetobacter spp.</i>									
Pediatric (NB-13)	0.06	0.06	0.12	0.5	1	0.3498	0.05073	A	Prob > F
Young Adult (14-29)	0.06	0.12	0.25	1	1	0.5581	0.04348	B	<0.001
Adult (30-64)	0.06	0.12	0.5	1	1	0.5931	0.02077	B	
Geriatric (65+)	0.06	0.12	0.5	1	1	0.6098	0.02339	B	
<i>S. aureus</i>									
Pediatric (NB-13)	0.06	0.12	0.12	0.12	0.25	0.1271	0.00733	A B	Prob > F
Young Adult (14-29)	0.06	0.12	0.12	0.12	0.25	0.1386	0.00695	A	0.063
Adult (30-64)	0.06	0.12	0.12	0.12	0.25	0.1481	0.00343	B	
Geriatric (65+)	0.06	0.12	0.12	0.12	0.25	0.1437	0.00393	B	
<i>S. pneumoniae</i>									
Pediatric (NB-13)	0.015	0.015	0.03	0.25	0.5	0.1922	0.01111	A	Prob > F
Young Adult (14-29)	0.015	0.015	0.03	0.25	1	0.2158	0.01986	A	0.1999
Adult (30-64)	0.015	0.015	0.03	0.25	0.5	0.1746	0.0082	A	
Geriatric (65+)	0.015	0.03	0.06	0.25	0.5	0.1789	0.00965	A	
Other Streptococci									
Pediatric (NB-13)	0.015	0.015	0.03	0.25	0.5	0.1922	0.01111	A	Prob > F
Young Adult (14-29)	0.015	0.015	0.03	0.25	1	0.2158	0.01986	A	0.1999
Adult (30-64)	0.015	0.015	0.03	0.25	0.5	0.1746	0.0082	A	
Geriatric (65+)	0.015	0.03	0.06	0.25	0.5	0.1789	0.00965	A	

<sup>1</sup> Std error uses a pooled estimate of error variance.<sup>2</sup> 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 MIC<sub>50</sub> of ≤1 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 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 gram-positive species (p-values 0.063 - 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.