

An Age Analysis of Gram-positive and Gram-negative Isolates from Centers in the Middle East: The T.E.S.T. Program

M. Hackel¹, B. Johnson¹, R. Badal¹, S. Bouchillon¹, 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

#E-295

REVISED ABSTRACT

Background: Tigecycline 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 tigecycline compared to most commonly prescribed broad spectrum antimicrobials against gram negative and gram positive species collected in the Middle East during 2004 to 2007. This report analyzes differences in susceptibilities in different age groups from this study. **Methods:** A total of 601 clinical isolates from Middle Eastern testing sites were identified to the species level. Minimum Inhibitory Concentrations (MICs) were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** In general, %S was pediatric>young adult>geriatric. Levofloxacin showed reduced activity against adult vs. pediatric isolates of *Acinetobacter* spp., *Enterobacteriaceae*, ESBLs, *Enterococcus* spp. and MRSA. *S. pneumoniae* penicillin susceptibility ranged from 85.7% for geriatric isolates to 41.7% for adults. ESBL rates were high, ranging from 12.5% (young adults) to 61% (pediatrics), while MRSA rates ranged from 64% (geriatrics) to 22% (pediatrics). **Conclusion:** Although many drugs showed little difference in activity among patient age groups, overall susceptibility levels were generally higher in the pediatric and young adult groups than in adults and geriatrics. Some of the problematic therapy issues seen in older patients (VRE, reduced fluoroquinolone efficacy) are not as prevalent in younger patients, while others (ESBLs, MRSA) can be found across all age groups. Tigecycline's broad spectrum covers most of these resistant strains, and offers an effective alternative to clinicians faced with the diminished potency of older agents. Tygacil has not been approved for use in the pediatric age population.

INTRODUCTION

Tigecycline is the first marketed glycylycylone 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 10⁻⁹ 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 isolates from the Middle East. 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 & 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 medial centers in the Middle East and tested from 2004 to 2007. 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.
- 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; *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 (2007) guidelines [8].

REFERENCES

- Sum, P.E. and P. Petersen, *Synthesis and structure-activity relationship of novel glycylycylone 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 glycylycylone, 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: glycylycylones and tetracycline efflux pump inhibitors*. Drug Resist Updat, 2002. 5(3-4): p. 119-25.
- CLSI, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Sixth Edition, in Document M7-A7*. 2006: 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-S17*. 2007: 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 program group. This study was sponsored by a grant from Wyeth Pharmaceuticals.

RESULTS

The results are presented in the following tables. Table 1. Frequency distribution of age groups for all isolates from the Middle East.

Age Group	Total N	% of total
Pediatric (NB-13)	80	15.4 (80/519)
Young Adult (14-29)	51	9.8 (51/519)
Adult (30-64)	225	43.4 (225/519)
Geriatric (65+)	163	31.4 (163/519)

Table 2. In vitro activity (% susceptible, MIC mcg/mL) of tigecycline and comparative agents against selected organisms from the Middle East with analysis by age groups.

Organism	Drug	Pediatric (NB-13)		Young Adult (14-29)		Adult (30-64)		Geriatric (65+)	
		%Sus	MIC ₉₀	%Sus	MIC ₉₀	%Sus	MIC ₉₀	%Sus	MIC ₉₀
<i>Enterobacter</i> spp	Tigecycline	87.5	4	80	4	100	1	92.9	2
	Amikacin	100	4	100	4	90	32	100	4
	Cefepime	87	32	100	4	95	8	100	8
	Imipenem	100	2	100	2	100	1	100	2
Geriatric n=14	Levofloxacin	100	0.12	80	8	80	>8	85.7	4
<i>E. coli</i>	Tigecycline	100	0.25	100	0.25	100	1	100	0.5
	Amikacin	100	2	100	2	100	8	92.9	16
	Cefepime	100	<0.5	100	<0.5	70.5	>32	60.7	>32
	Imipenem	100	0.5	100	0.5	100	0.5	100	1
Geriatric n=28	Levofloxacin	100	0.03	33.3	4	45.5	>8	50	>8
<i>Klebsiella</i> spp	Tigecycline	100	1	100	1	100	2	100	2
	Amikacin	95.2	16	100	8	92.9	16	88.2	32
	Cefepime	57.1	>32	83.3	32	71.4	>32	47.1	>32
	Imipenem	100	1	100	1	100	0.5	100	1
Geriatric n=17	Levofloxacin	95.2	0.12	100	0.06	78.6	>8	64.7	>8
ESBL producing									
<i>E. coli</i> and <i>Kleb.</i>	Tigecycline	100	1	100	0.5	100	2	100	2
	Amikacin	92.9	16	100	8	94.4	8	84.2	32
	Cefepime	42.9	>32	100	2	16.7	>32	5.3	>32
	Imipenem	100	0.5	100	0.5	100	2	100	1
Geriatric n=19	Levofloxacin	92.9	0.5	100	0.03	11.1	>8	31.6	>8
<i>Acinetobacter</i> spp	Tigecycline	na	1	na	4	na	2	na	2
	Amikacin	24	64	42.9	>64	35.3	>64	35.7	>64
	Cefepime	25	>32	14.3	>32	17.6	>32	0	>32
	Imipenem	25	>16	50	>16	76.9	>16	45.5	>16
Geriatric n=14	Levofloxacin	75	8	14.3	>8	23.5	>8	0	>8
<i>H. influenzae</i>	Tigecycline	na	1	na	2	na	1	na	2
	AmoxClav	100	1	100	0.5	100	2	100	2
	Ceftriaxone	87.5	>32	66.7	2	87.5	4	55.6	>32
	Imipenem	100	0.12	100	<0.06	100	<0.06	100	<0.06
Geriatric n=9	Imipenem	100	2	100	0.5	100	2	100	1
Levofloxacin	100	0.03	100	0.03	100	0.03	100	0.06	
<i>Enterococcus</i> spp	Tigecycline	100	1	100	0.12	100	0.25	100	0.12
	Levofloxacin	66.7	>32	50	>32	35.3	>32	26.7	>32
	Linezolid	100	2	87.5	4	100	2	100	2
	Penicillin	33.3	>8	75	>8	70.6	>8	60	>8
Geriatric n=15	Vancocmycin	100	1	100	2	94.1	2	93.3	2
<i>S. aureus</i>	Tigecycline	100	0.25	100	0.25	100	0.5	100	0.5
	Imipenem	100	1	83.3	>16	69.6	>16	54.5	>16
	Levofloxacin	100	1	60	8	71.9	16	31.8	16
	Linezolid	100	2	100	4	100	4	100	4
Geriatric n=22	Penicillin	22.2	>8	0	>8	6.3	>8	4.5	>8
Vancocmycin	100	1	100	2	100	1	100	1	
<i>S. aureus</i> , MRSA	Tigecycline	100	0.25	100	0.25	100	0.5	100	0.5
	Imipenem	100	1	0	>16	0	>16	0	0.16
	Levofloxacin	100	1	0	16	20	16	0	16
	Linezolid	100	2	100	4	100	2	100	4
Geriatric n=14	Penicillin	0	4	0	>8	0	>8	0	0.8
Vancocmycin	100	1	100	1	100	2	100	1	
<i>S. agalactiae</i>	Tigecycline	100	0.03	100	0.06	100	0.06	100	0.06
	Levofloxacin	100	1	100	1	27.3	1	50	4
	Linezolid	100	1	100	1	27.3	1	75	1
	Penicillin	100	<0.06	100	0.12	27.3	0.12	75	0.12
Geriatric n=4	Vancocmycin	100	0.5	100	0.5	27.3	0.5	75	0.5
<i>S. pneumoniae</i>	Tigecycline	na	0.03	-	-	na	0.03	na	0.03
	Levofloxacin	100	1	-	-	100	1	100	1
	Linezolid	100	1	-	-	100	1	100	1
	Penicillin	66.7	0.25	-	-	41.7	2	85.7	1
Geriatric n=7	Vancocmycin	100	0.5	-	-	100	0.25	100	0.5

CONCLUSIONS

- Tigecycline demonstrated excellent activity against organisms from the Middle East across all age groups. While the activity of tigecycline varied slightly among age groups within different organism groups and species, the overall activity was consistently within the FDA susceptible range (where breakpoints exist).
- Although many drugs showed little difference in activity among patient age groups, overall susceptibility levels were higher and MIC₉₀ values tended to be lower in the pediatric and young adult groups than in adult and geriatric age groups for all study drugs as well as tigecycline.
- ESBL rates were high for all age groups, particularly Pediatric (61%), Adult (25%) and Geriatric (42%). The Young Adult rate was 11%.
- Some of the problematic therapy issues seen in older patients (VRE, ESBL, reduced fluoroquinolone efficacy) are not as prevalent in younger patients. Tigecycline's antibiotic spectrum covers most of these resistant strains, and offers an effective alternative to clinicians faced with diminished potency of older agents.
- Tygacil has not been approved for use in the pediatric age population.