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An Age Analysis of the Susceptibility of Gram-positive and Gram-negative Pathogens from Centers in the Middle East: The T.E.S.T. Program (2004-2008)

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Revised Abstract

Objectives: 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 2008. This report analyzes differences in susceptibilities in different age groups from this study. **Methods**: A total of 1,875 clinical isolates from 20 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, tigecycline %S was pediatric>young adult>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 9.1% (young adults) to 33.3% (pediatrics), while MRSA rates ranged from 64% (geriatrics) to 22% (pediatrics). **Conclusions**: 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.

Introduction

Tigecycline is the first marketed glycylcycline 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 MIC_{90} values of $\leq$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 and tested from 2004 to 2008 in 20 medical centers from Israel, Lebanon, Oman, and Turkey. 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 when MIC results for ceftriaxone 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; *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].

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Results

The results are presented in the following tables.

Table 1. Frequency distribution of age groups for 1,875 isolates from the Middle East.

Age Group	Total N	% of Total
Pediatric (NB-13)	262	14.0
Young Adult (14-29)	180	9.6
Adult (30-64)	775	41.3
Geriatric (65+)	658	35.1
Total	**1,875**	**100**

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.

		Pediatric (NB-13)		Young Adult (14-29)		Adult (30-64)		Geriatric (65+)	
Organism	Drug	%Sus	MIC_{90}	%Sus	MIC_{90}	%Sus	MIC_{90}	%Sus	MIC_{90}
***Enterobacter* spp**	Tigecycline	87.5	4	80	4	100	1	92.9	2
Ped n=40	Amikacin	100	4	100	4	90	32	100	4
Young Adult n=22	Cefepime	87	32	100	4	95	8	100	8
Adult n=96	Imipenem	100	2	100	2	100	1	100	2
Geriatric n=102	Levofloxacin	100	0.12	80	8	80	>8	85.7	4
E. coli	Tigecycline	100	0.25	100	0.25	100	1	100	0.5
Ped n=30	Amikacin	100	2	100	2	100	8	92.9	16
Young Adult n=27	Cefepime	100	≤0.5	100	≤0.5	70.5	>32	60.7	>32
Adult n=168	Imipenem	100	0.5	100	0.5	100	0.5	100	1
Geriatric n=140	Levofloxacin	100	0.03	33.3	4	45.5	>8	50	>8
***Klebsiella* spp**	Tigecycline	100	1	100	1	100	2	100	2
Ped n=46	Amikacin	95.2	16	100	8	92.9	16	88.2	32
Young Adult n=22	Cefepime	57.1	>32	83.3	32	71.4	>32	47.1	>32
Adult n=108	Imipenem	100	1	100	1	100	0.5	100	1
Geriatric n=122	Levofloxacin	95.2	0.12	100	0.06	78.6	>8	64.7	>8
ESBL producing *E.coli* and *Kleb.*	Tigecycline	100	1	100	0.5	100	2	100	2
Ped n=24	Amikacin	92.9	16	100	8	94.4	8	84.2	32
Young Adult n=4	Cefepime	42.9	>32	100	2	16.7	>32	5.3	>32
Adult n=47	Imipenem	100	0.5	100	0.5	100	2	100	1
Geriatric n=58	Levofloxacin	92.9	0.5	100	0.03	11.1	>8	31.6	>8
***Acinetobacter* spp**	Tigecycline	na	1	na	4	na	2	na	2
Ped n=18	Amikacin	24	64	42.9	>64	35.3	>64	35.7	>64
YAdult n=17	Cefepime	25	>32	14.3	>32	17.6	>32	0	>32
Adult n=66	Imipenem	25	>16	50	>16	76.9	>16	45.5	>16
Geriatric n=71	Levofloxacin	75	8	14.3	>8	23.5	>8	0	>8
H. influenzae	Tigecycline	na	1	na	2	na	1	na	2
Ped n=43	AmoxClav	100	1	100	0.5	100	2	100	2
Young Adult n=10	Ampicillin	87.5	>32	66.7	2	87.5	4	55.6	>32
Adult n=43	Ceftriaxone	100	0.12	100	≤0.06	100	≤0.06	100	≤0.06
Geriatric n=27	Imipenem	100	2	100	0.5	100	2	100	1
	Levofloxacin	100	0.03	100	0.03	100	0.03	100	0.06
***Enterococcus* spp**	Tigecycline	100	1	100	0.12	100	0.25	100	0.12
Ped n=13	Levofloxacin	66.7	>32	50	>32	35.3	>32	26.7	>32
Young Adult n=21	Linezolid	100	2	87.5	4	100	2	100	2
Adult n=80	Penicillin	33.3	>8	75	>8	70.6	>8	60	>8
Geriatric n=74	Vancomycin	100	1	100	2	94.1	2	93.3	2
S. aureus	Tigecycline	100	0.25	100	0.25	100	0.5	100	0.5
Ped n=42	Imipenem	100	1	83.3	>16	69.6	>16	54.5	>16
YAdult n=35	Levofloxacin	100	1	60	8	71.9	16	31.8	16
Adult n=147	Linezolid	100	2	100	4	100	4	100	4
Geriatric n=94	Penicillin	22.2	>8	0	>8	6.3	>8	4.5	>8
	Vancomycin	100	1	100	2	100	1	100	1
***S. aureus*, MRSA**	Tigecycline	100	0.25	100	0.25	100	0.5	100	0.5
Ped n=9	Imipenem	100	1	0	>16	0	>16	0	.16
Young Adult n=8	Levofloxacin	100	1	0	16	20	16	0	16
Adult n=35	Linezolid	100	2	100	4	100	2	100	4
Geriatric n=39	Penicillin	0	4	0	>8	0	>8	0	.8
	Vancomycin	100	1	100	1	100	2	100	1
S. agalactiae	Tigecycline	100	0.03	100	0.06	100	0.06	100	0.06
Ped n=5	Levofloxacin	100	1	100	1	27.3	1	50	4
Young Adult n=22	Linezolid	100	1	100	1	27.3	1	75	1
Adult n=45	Penicillin	100	≤0.06	100	0.12	27.3	0.12	75	0.12
Geriatric n=9	Vancomycin	100	0.5	100	0.5	27.3	0.5	75	0.5
S. pneumoniae	Tigecycline	na	0.03	na	0.03	na	0.03	na	0.03
Ped n=25	Levofloxacin	100	1	100	1	100	1	100	1
Young Adult n=3	Linezolid	100	1	100	1	100	1	100	1
Adult n=22	Penicillin	66.7	0.25	76.7	0.5	41.7	2	85.7	1
Geriatric n=19	Vancomycin	100	0.5	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 MIC_{90} 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 (33%), Adult (18%) and Geriatric (22%). The Young Adult rate was 9%.
- 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.