

REVISED ABSTRACT

Background: The TEST project is an ongoing surveillance study designed to monitor the activity of tigecycline (tig), a new broad-spectrum antimicrobial, compared to other widely-used drugs. This report evaluates differences in susceptibility of strains from patients of different age groups, collected in the USA from 2004-2006. **Methods:** 22,264 strains were collected and identified from patients categorized into 4 age groups from 2004-2006 at 137 hospitals in the USA. MICs for each strain were determined per CLSI guidelines at each facility using broth microdilution. MIC₅₀/90 and % S were analyzed to identify differences in susceptibility patterns. **Results:** Generally, %S was pediatric<young adult>adult=geriatric. *Acinetobacter* spp. in particular showed significantly higher rates of susceptibility with pediatric patients. Levofloxacin showed greater activity vs. pediatric strains of *E. coli*, *Klebsiella*, *P. aeruginosa*, non-VR enterococci, and MRSA. *S. pneumoniae* penicillin susceptibility was <65% for each age group, with pediatric isolates 13-16% lower than others. Tigecycline activity was essentially the same for all age groups. **Conclusion:** Although many drugs showed little difference in activity among patient age groups, overall susceptibility levels were higher in the pediatric and young adult groups than in adults and geriatrics. Some of the problematic therapy issues seen in older patients (VRE, ESBL, reduced fluoroquinolone efficacy) are not as prevalent in younger patients. Tig's spectrum covers most of these resistant strains, and offers an effective alternative to clinicians faced with diminished potency of older agents.

INTRODUCTION

Tigecycline is the first marketed glycylicycline 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 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 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 137 medical centers in the United States and tested from 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); 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.
- 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].

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RESULTS

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

Age Group	Total N	% of Total
Pediatric (NB-13)	2,570	11.5
Young Adult (14-29)	2,228	10
Adult (30-64)	9,383	42.1
Geriatric (65+)	8,083	36.3
Total	22,264	100

*All isolates having no age given are excluded.

Table 2. Statistical analysis of tigecycline MIC values by age groups for all study organisms 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	0.5	0.31358	0.01634	C	
Young Adult (14-29)	0.03	0.06	0.12	0.5	0.5	0.326285	0.01728	C	Prob >F
Adult (30-64)	0.03	0.12	0.12	0.5	1	0.418611	0.00848	A	<0.0001
Geriatric (65+)	0.06	0.12	0.25	0.5	1	0.47551	0.00917	B	

¹Std error uses a pooled estimate of error variance.

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

Table 3. Comparative activity of tigecycline against clinical pathogens categorized by age groups.*

Organism	Drug	Pediatric (NB-13)			Young Adult (14-29)			Adult (30-64)			Geriatric (65+)			
		%Sus	MIC ₅₀	MIC ₉₀	%Sus	MIC ₅₀	MIC ₉₀	%Sus	MIC ₅₀	MIC ₉₀	%Sus	MIC ₅₀	MIC ₉₀	
Enterobacter spp.	Tigecycline	97.8	0.5	0.5	95.2	0.5	1	93	0.5	2	90.6	0.5	2	
	Ped = 274	Amikacin	99.3	2	2	100	2	4	99.2	2	4	99.6	2	4
	Y.Adult = 248	Cefepime	98.2	<0.5	4	97.2	<0.5	1	95.6	<0.5	4	96.7	<0.5	4
	Adult = 1100	Imipenem	100	0.5	1	100	0.5	1	100	0.5	1	100	0.5	1
	Geriatric = 927	Levofloxacin	99.3	0.03	0.12	96.4	0.03	0.25	90	0.06	2	88.6	0.06	4
Enterococcus spp.	Tigecycline	100	0.06	0.12	97	0.06	0.12	99.6	0.06	0.12	99.7	0.06	0.12	
	Ped = 125	Levofloxacin	75.2	1	>32	55.6	1	>32	40.1	32	>32	37.3	32	>32
	Y.Adult = 99	Linezolid	99.2	2	2	97	2	2	97.3	2	2	99	2	2
	Adult = 783	Penicillin	86.4	2	>8	75.8	2	>8	72.4	2	>8	73.8	2	>8
	Geriatric = 798	Vancomycin	88.8	1	8	80.8	1	>32	75.5	1	>32	75.9	1	>32
VRE, Enterococcus	Tigecycline	100	0.03	0.06	100	0.03	0.06	100	0.06	0.12	100	0.06	0.06	
	Ped = 11	Levofloxacin	0	>32	>32	0	>32	>32	1.7	>32	>32	0.6	>32	>32
	Y.Adult = 18	Linezolid	100	2	2	83.3	2	4	96.6	2	2	98.9	2	2
	Adult = 177	Penicillin	0	>8	>8	5.6	>8	>8	14.1	>8	>8	15.6	>8	>8
	Geriatric = 180	Vancomycin	0	>32	>32	0	>32	>32	0	>32	>32	0	>32	>32
E. coli	Tigecycline	99.6	0.12	0.25	99.7	0.12	0.25	99.7	0.12	0.25	99.2	0.12	0.25	
	Ped = 282	Amikacin	99.3	2	4	100	2	4	99.5	2	4	99.7	2	4
	Y.Adult = 332	Cefepime	98.9	<0.5	<0.5	99.4	<0.5	<0.5	98.1	<0.5	<0.5	97.6	<0.5	<0.5
	Adult = 1140	Imipenem	100	0.25	0.5	100	0.25	0.5	100	0.25	0.5	99.9	0.25	0.5
	Geriatric = 1185	Levofloxacin	93.3	0.03	0.25	89.8	0.03	4	75.8	0.03	>8	71.6	0.03	>8
Klebsiella spp.	Tigecycline	95.9	0.5	1	96.7	0.5	1	94.9	0.5	2	95	0.5	2	
	Ped = 245	Amikacin	99.6	2	2	99.5	2	2	98.3	2	2	98.4	2	4
	Y.Adult = 184	Cefepime	99.6	<0.5	<0.5	98.4	<0.5	1	95.2	<0.5	2	94.5	<0.5	4
	Adult = 1117	Imipenem	100	0.5	0.5	100	0.5	0.5	98.6	0.5	0.5	98.5	0.5	0.5
	Geriatric = 1272	Levofloxacin	98	0.06	0.25	92.9	0.06	1	89.9	0.06	4	87.3	0.06	8
ESBL producing E.coli and Kleb.	Tigecycline	85.7	0.25	4	86.7	0.5	4	93.4	1	2	90.8	1	2	
	Ped = 7	Amikacin	100	2	16	100	4	16	83.5	8	32	90.8	8	16
	Y.Adult = 15	Cefepime	57.1	8	>32	66.7	4	>32	45.1	16	>32	50.3	8	>32
	Adult = 91	Imipenem	100	0.5	0.5	100	0.5	0.5	82.4	0.5	8	87.6	0.5	8
	Geriatric = 153	Levofloxacin	71.4	0.25	>8	26.7	>8	>8	19.8	>8	>8	17	>8	>8
Acinetobacter spp.	Tigecycline	97.8	0.12	1	98.3	0.25	1	97.9	0.5	1	97.9	0.5	2	
	Ped = 137	Amikacin	91.2	2	16	85.1	4	32	83	4	32	81.1	4	64
	Y.Adult = 174	Cefepime	78.8	4	32	57.5	8	>32	47.1	16	>32	43.4	16	>32
	Adult = 717	Imipenem	97.8	0.5	4	92	0.5	4	85.4	0.5	8	84.8	0.5	8
	Geriatric = 512	Levofloxacin	85.4	0.12	8	64.4	0.25	>8	49.2	4	>8	42.6	8	>8
H. influenzae	Tigecycline	100	0.12	0.5	100	0.12	0.25	100	0.12	0.25	100	0.12	0.5	
	Ped = 377	AmoxClav	99.7	0.5	2	100	0.5	1	100	0.5	1	100	0.5	1
	Y.Adult = 136	Ampicillin	66	<0.5	>32	72.1	<0.5	>32	74.4	<0.5	>32	72.4	<0.5	>32
	Adult = 481	Ceftazidime	99.7	<0.06	<0.06	99.3	<0.06	<0.06	100	<0.06	<0.06	100	<0.06	<0.06
	Geriatric = 326	Imipenem	100	0.5	1	100	0.5	1	100	0.5	1	100	0.5	1
H.influenzae (BL Pos)	Tigecycline	100	0.12	0.25	100	0.12	0.25	100	0.12	0.25	100	0.12	0.5	
	Ped = 124	AmoxClav	99.2	1	2	100	1	2	100	1	2	100	1	2
	Y.Adult = 37	Ampicillin	0	32	>32	0	32	>32	0	32	>32	0	32	>32
	Adult = 117	Ceftazidime	100	<0.06	<0.06	97.3	<0.06	<0.06	100	<0.06	<0.06	100	<0.06	<0.06
	Geriatric = 90	Imipenem	100	0.5	1	100	0.5	1	100	0.5	1	100	0.5	1
S. aureus	Tigecycline	100	0.12	0.25	99.7	0.12	0.25	99	0.12	0.25	99	0.12	0.25	
	Ped = 307	Imipenem	97.4	0.25	0.5	95.6	0.25	1	92.3	0.25	2	87.4	0.25	8
	Y.Adult = 343	Levofloxacin	78.5	0.12	8	68.5	0.12	16	53.3	0.5	>32	32.6	8	>32
	Adult = 1408	Linezolid	100	2	2	100	2	2	100	2	2	100	2	2
	Geriatric = 639	Penicillin	5.5	>8	>8	5.8	>8	>8	7	>8	>8	7.9	>8	>8
S. aureus, MRSA	Tigecycline	100	0.12	0.25	99.4	0.12	0.25	99.2	0.12	0.25	98.9	0.12	0.25	
	Ped = 103	Imipenem	92.2	0.5	2	91.6	0.25	4	86	0.5	16	80.3	0.5	16
	Y.Adult = 167	Levofloxacin	45.6	4	32	43.7	4	32	23.9	8	>32	5.6	32	>32
	Adult = 750	Linezolid	100	2	2	100	2	2	100	2	2	100	2	2
	Geriatric = 639	Penicillin	0	>8	>8	0	>8	>8	0	>8	>8	0	>8	>8
S. agalactiae	Tigecycline	100	0.03	0.25	100	0.03	0.12	100	0.03	0.12	100	0.03</		