

# Variability of Antimicrobial Susceptibility in Isolates from Patients in Different Age Groups in the USA: 2004-2006

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## 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:** 22,540 isolates 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. MIC<sub>50/90</sub> 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 (20-40%) with pediatric patients. Levofloxacin showed greater activity vs. pediatric strains of *E. coli*, *Klebsiella*, non-VR enterococci, and MRSA. *S. pneumoniae* penicillin susceptibility was <65% for each age group, with pediatric isolates 13-16% lower than others. VRE rates ranged from 8.9% (pediatrics) to 22.6% (adults and geriatrics). ESBL production rates ranged from 1.3% (pediatrics) to 6.2% (geriatrics). Tig's activity was statistically greater in pediatric and young adults as compared to adults and geriatric populations. **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 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>-9</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>90</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 & 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, as well as development and management of a centralized database was 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 site 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); 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 recent US Food and Drug Administration packaging 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; *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 (2006) guidelines [8].

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## RESULTS

The results are listed in the following tables.

Table 1. In vitro activity (% susceptible, MIC mcg/mL) of tigecycline and comparative agents against selected organisms with analysis by age groups.

Organism	Drug	Quartile MIC (mcg/mL)					Std Error <sup>1</sup>	t-Test Statistical Category <sup>2</sup>	One-Way ANOVA
		10%	25%	Median	75%	90%			
<b>Enterobacter spp</b>									
Ped n=274	Tigecycline	97.8	0.5	95.2	1	93	2	90.6	2
YAdult n=248	Amikacin	99.3	2	100	4	99.2	4	99.6	4
Adult n=1100	Cefepime	98.2	4	97.2	1	95.6	4	96.7	4
Geriatric n=927	Imipenem	100	1	100	1	100	1	100	1
<b>E. coli</b>									
Ped n=282	Levofloxacin	99.3	0.12	96.4	0.25	90	2	88.6	4
YAdult n=332	Tigecycline	99.6	0.25	99.7	0.25	99.7	0.25	99.2	0.25
Adult n=1140	Amikacin	99.3	4	100	4	99.5	4	99.7	4
Geriatric n=1185	Cefepime	98.9	≤0.5	99.4	≤0.5	98.1	≤0.5	97.6	≤0.5
<b>Klebsiella spp</b>									
Ped n=245	Imipenem	100	0.5	100	0.5	100	0.5	99.9	0.5
YAdult n=184	Levofloxacin	98.3	0.25	89.8	4	75.8	>8	71.6	>8
Adult n=1140	Tigecycline	95.9	1	96.7	1	94.9	2	95	2
Geriatric n=1272	Amikacin	99.6	2	99.5	2	98.3	2	98.4	4
<b>ESBL producing E.coli and Kleb.</b>									
Ped n=7	Cefepime	99.6	≤0.5	98.4	1	95.2	2	94.5	4
YAdult n=15	Imipenem	100	0.5	100	0.5	98.6	0.5	98.5	0.5
Adult n=91	Levofloxacin	98	0.25	92.9	1	89.9	4	87.3	8
Geriatric n=153	Tigecycline	85.7	4	86.7	4	83.4	2	80.8	2
<b>Acinetobacter spp</b>									
Ped n=137	Amikacin	100	16	100	16	83.5	32	90.8	16
YAdult n=174	Cefepime	57.1	>32	66.7	>32	47.1	>32	50.3	>32
Adult n=717	Imipenem	97.8	4	92	4	85.4	8	84.8	8
Geriatric n=512	Levofloxacin	85.4	8	64.4	>8	49.2	>8	42.6	>8
<b>H. influenzae</b>									
Ped n=377	Tigecycline	100	0.5	100	0.25	100	0.25	100	0.5
YAdult n=136	AmoxClav	99.7	2	100	1	100	1	100	1
Adult n=481	Ampicillin	66	>32	72	>32	74.4	>32	72.4	>32
Geriatric n=326	Ceftriaxone	99.7	≤0.06	99.3	≤0.06	100	≤0.06	100	≤0.06
<b>H.influenzae (BL Pos)</b>									
Ped n=124	Imipenem	100	1	100	1	100	1	100	1
YAdult n=37	Levofloxacin	100	0.03	100	0.03	100	0.03	100	0.03
Adult n=117	Tigecycline	100	0.25	100	0.25	100	0.25	100	0.5
Geriatric n=90	AmoxClav	99.2	2	100	2	100	2	100	2
<b>Enterococcus spp</b>									
Ped n=125	Ampicillin	0	>32	0	>32	0	>32	0	>32
YAdult n=99	Ceftriaxone	100	≤0.06	97.3	≤0.06	100	≤0.06	100	≤0.06
Adult n=783	Imipenem	100	1	100	1	100	1	100	1
Geriatric n=798	Levofloxacin	100	0.03	100	0.03	100	0.03	100	0.03
<b>VRE, Enterococci</b>									
Ped n=11	Tigecycline	100	0.12	97	0.12	99.6	0.12	99.7	0.12
YAdult n=18	Levofloxacin	75.2	>32	55.6	>32	40.1	>32	37.3	>32
Adult n=177	Linezolid	99.2	2	97	2	97.3	2	99	2
Geriatric n=180	Penicillin	86.4	>8	75.8	>8	72.4	>8	73.8	>8
<b>S. aureus</b>									
Ped n=307	Vancomycin	88.8	8	80.8	>32	75.5	>32	75.9	>32
YAdult n=343	Tigecycline	100	0.06	100	0.06	100	0.12	100	0.06
Adult n=1408	Levofloxacin	0	>32	0	>32	1.7	>32	0.6	>32
Geriatric n=639	Linezolid	100	2	83.3	4	96.6	2	98.9	2
<b>S. aureus, MRSA</b>									
Ped n=103	Penicillin	0	>8	5.6	>8	14.1	>8	15.6	>8
YAdult n=167	Vancomycin	100	>32	0	>32	0	>32	0	>32
Adult n=750	Tigecycline	100	0.12	99.7	0.25	99	0.25	99	0.25
Geriatric n=639	Imipenem	97.4	0.5	95.6	1	92.3	2	87.4	8
<b>S. agalactiae</b>									
Ped n=86	Levofloxacin	78.5	8	68.5	16	53.3	>32	32.6	>32
YAdult n=314	Linezolid	100	2	100	2	100	2	100	2
Adult n=487	Penicillin	0	>8	0	>8	0	>8	0	>8
Geriatric n=231	Vancomycin	100	1	100	1	100	1	100	1
<b>S. pneumoniae</b>									
Ped n=384	Tigecycline	100	0.25	100	0.12	100	0.12	100	0.12
YAdult n=121	Levofloxacin	100	1	99.7	1	99.2	1	93.9	1
Adult n=724	Linezolid	100	1	100	1	100	1	100	1
Geriatric n=441	Penicillin	100	0.12	100	0.12	100	0.12	100	0.12
	Vancomycin	100	0.5	100	0.5	100	0.5	100	0.5

Table 2. Statistical analysis of tigecycline MIC values by age groups for all 22,540 study organisms combined.

Organism / Age Group	Quartile MIC (mcg/mL)					Std Error <sup>1</sup>	t-Test Statistical Category <sup>2</sup>	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
Adult (30-64)	0.03	0.12	0.12	0.5	1	0.418611	0.00848	B
Geriatric (65+)	0.06	0.12	0.25	0.5	1	0.47551	0.00917	A

<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 against selected organisms by age groups.

Organism / Age Group	Quartile MIC (mcg/mL)					Std Error <sup>1</sup>	t-Test Statistical Category <sup>2</sup>	One-Way ANOVA
	10%	25%	Median	75%	90%			
<b>Enterobacteriaceae</b>								
Pediatric (NB-13)	0.12	0.25	0.5	0.5	1	0.5355	0.0338	B
Young Adult (14-29)	0.12	0.12	0.25	0.5	1	0.5182	0.0343	B
Adult (30-64)	0.12	0.25	0.5	0.5	1	0.6682	0.0163	A
Geriatric (65+)	0.12	0.25	0.5	0.5	1	0.6978	0.0162	A
<b>Acinetobacter spp</b>								
Pediatric (NB-13)	0.06	0.12	0.12	0.5	1	0.3701	0.0662	C
Young Adult (14-29)	0.06	0.12	0.25	1	1	0.5559	0.0587	B
Adult (30-64)	0.06	0.12	0.5	1	2	0.6545	0.0285	A B
Geriatric (65+)	0.06	0.12	0.5	1	2	0.6975	0.0333	A
<b>H. influenzae</b>								
Pediatric (NB-13)	0.06	0.12	0.12	0.25	0.5	0.2197	0.0122	A B
Young Adult (14-29)	0.06	0.12	0.12	0.25	0.5	0.2064	0.0205	A B
Adult (30-64)	0.06	0.12	0.12	0.25	0.5	0.196	0.0109	B
Geriatric (65+)	0.06	0.12	0.12	0.25	0.5	0.2382	0.0129	A
<b>Enterococcus spp</b>								
Pediatric (NB-13)	0.03	0.06	0.06	0.12	0.12	0.0825	0.0052	B
Young Adult (14-29)	0.03	0.06	0.06	0.12</				