

The 2008 Australian Tigecycline Evaluation Surveillance Trial (T.E.S.T)



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Revised Abstract

Objectives: Tigecycline, the first of a new antimicrobial class of glycolycyclines in clinical trials, has been shown to have potent activity against most species of Gram-positive and -negative bacteria. The T.E.S.T. program determined the in vitro activity of tigecycline compared to amikacin, ampicillin, amoxicillin/clavulanic acid, imipenem, cefepime, ceftazidime, ceftioxone, levofloxacin, minocycline, piperacillin/tazobactam, linezolid, penicillin and vancomycin against selected clinical isolates collected from three investigative sites in Australia. **Methods:** Minimum Inhibitory Concentration (MICs) of 2235 clinical bacterial isolates collected during 2005 through 2008 were determined by broth microdilution and evaluated according to CLSI guidelines. **Results:** The broad-spectrum antimicrobials levofloxacin, cefepime, amikacin, and imipenem were highly active against Gram-negative strains (excluding *Pseudomonas* and *Serratia marcescens*) in this study and demonstrated susceptible percentages rates of 97%, 96%, 93%, 98%, respectively. Tigecycline's activity was comparable to imipenem presenting an MIC₉₀ value of 1 mcg/mL against all Gram-negative strains (excluding *Pseudomonas*). Tigecycline MIC₉₀ was 0.25 mcg/mL against all Gram-positive study pathogens. Tigecycline MICs were 8- to 16-fold lower than vancomycin and linezolid against *S. pneumoniae* and 4- and 16-fold lower than those for linezolid and vancomycin against staphylococci and enterococci. Tigecycline was also successful in inhibiting 100% of *S. aureus* at a MIC of ≤ 0.5 mcg/mL regardless of methicillin phenotypes. Tigecycline inhibited all *H. influenzae* at ≤ 1 mcg/mL without regard to beta-lactamase production. **Conclusions:** Tigecycline's activity was comparable to the activities of broad spectrum antimicrobials and highly effective most strains of Gram-negative and Gram-positive bacteria. Tigecycline's activity was comparable to imipenem, linezolid and vancomycin which are often considered as last therapeutic option for the treatment of serious nosocomial infections caused by this class of organisms. Tigecycline, as other tetracyclines, had limited activity against *P. aeruginosa*. These data present strong in vitro antibiogram activity for tigecycline in twenty medical centers in Australia.

Introduction

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycolycyclines. 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 Gram-positive pathogens and has demonstrated significant broad-spectrum 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 observed at less than 10⁻⁹ [3, 5, 7]. With the exception of *P. aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-4, 7-11]. Tigecycline has shown to be active against multi-resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections. Similar activity has been observed against *Enterobacteriaceae*, even extended-spectrum β -lactamase (ESBL) and AmpC producing strains [10]. 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 against 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].

This study was designed to communicate clinical laboratory in vitro experience with activity of tigecycline in a limited number of clinical isolates collected from twenty medical centers in Australia.

Materials & Methods

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids and few other defined sources. Only one isolate per patient was accepted. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- 2235 Clinical isolates were collected and tested between January 2005 – December 2008 from twenty study centers from Australia.
- Custom broth microdilution panels were supplied by MicroScan (Dade MicroScan, Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/mL): amoxicillin/clavulanic acid (0.03-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-32); ceftioxone (0.03-64); cefepime (0.5-32); ampicillin (0.06-32); amikacin (0.5-64); minocycline (0.25-16); ceftazidime (8-32); tigecycline (0.008-16); imipenem (0.06-16); linezolid (0.5-8); penicillin (0.06-8); and vancomycin (0.12-32).
- MIC interpretive criteria followed published guidelines established by the CLSI where applicable [12]. MIC interpretive criteria for Tigecycline followed published guidelines established by the FDA where applicable [13].
- Quality control of broth microdilution panels followed manufacture's and CLSI guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Klebsiella pneumoniae* ATCC 700603 (positive ESBL control); *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *Pseudomonas aeruginosa* ATCC 27853.
- The collection and transportation of organisms and the confirmation of identification, as well as, construction and management of a centralized database were conducted and coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA).

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Results

The results of this study are presented in the following tables:

Table 1. Gram-negative Antibiogram for Tigecycline and 10 Comparators with MIC₉₀ (mcg/mL) and Percent Susceptible (%) against 1531 selected Pathogens.

Gram-Negative Organisms	N=	MIC ₉₀ in mcg/mL (% Susceptible)*										
		Tigecycline	Amikacin	AmoxClav	Ampicillin	Cefepime	Ceftazidime	Ceftioxone	Imipenem	Levofloxacin	Minocycline	Pip/Tazo
<i>A. baumannii</i>	135	1(na)	8(96.3)	>32(na)	>32(na)	>32(76.3)	>32(71.9)	>64(34.8)	>16(71.1)	8(60)	4(90.4)	>128(70.4)
<i>A. Iwoffii</i>	23	1(na)	16(91.3)	16(na)	>32(na)	8(100)	16(69.6)	32(60.9)	0.25(100)	1(100)	2(95.7)	16(91.3)
<i>Acinetobacter</i> spp	161	1(na)	8(95)	>32(na)	>32(na)	32(79.5)	>32(71.4)	>64(39.1)	>16(76.6)	8(83.2)	4(91.3)	>128(73.3)
All ESBLs	15	1(93.3)	4(100)	32(20)	>32(na)	>32(73.3)	>32(73.3)	>64(33.3)	0.25(100)	>8(46.7)	8(73.3)	>128(66.7)
<i>EcoKoxKpn</i>	570	1(98.1)	4(98.8)	32(76.7)	>32(22.3)	<0.5(99.3)	<0.5(96.1)	2(97)	0.5(100)	0.5(93.7)	8(97.4)	8(92.8)
<i>E. aerogenes</i>	88	1(95.5)	2(100)	>32(2.3)	>32(1.1)	1(96.6)	>32(68.2)	16(88.6)	1(100)	0.25(95.5)	4(92)	64(73.9)
<i>E. cloacae</i>	182	1(96.7)	2(100)	>32(1.6)	>32(na)	8(92.9)	>32(58.2)	>64(59.9)	1(100)	0.5(97.3)	16(78)	128(59.9)
<i>Enterobacter</i> spp	276	1(96.4)	2(100)	>32(1.8)	>32(0.4)	4(94.2)	>32(60.9)	>64(68.8)	1(100)	0.5(96.4)	8(82.2)	128(63.8)
<i>E. coli</i>	297	0.25(100)	4(99.7)	32(69)	>32(39.5)	<0.5(99)	<0.5(99)	<0.5(99)	2(96.6)	0.25(100)	2(90.9)	16(91.9)
<i>H. influenzae</i>	156	0.5(na)	8(na)	2(100)	>32(74.4)	<0.5(100)	<0.5(na)	<0.06(100)	1(100)	0.03(100)	1(22.4)	<0.06(100)
<i>H. influenzae</i> (BL Neg)	122	0.5(na)	8(na)	2(100)	1(95.1)	<0.5(100)	<0.5(na)	<0.06(100)	1(100)	0.015(100)	1(22.1)	<0.06(100)
<i>H. influenzae</i> (BL Pos)	34	1(na)	8(na)	4(100)	>32(na)	<0.5(100)	<0.5(na)	<0.06(100)	1(100)	0.03(100)	2(23.5)	<0.06(100)
<i>K. oxytoca</i>	75	1(97.3)	2(100)	32(77.3)	>32(1.3)	<0.5(100)	<0.5(98.7)	2(97.3)	0.5(100)	0.12(97.3)	4(94.7)	>128(86.7)
<i>K. pneumoniae</i>	198	1(95.5)	2(100)	16(87.9)	>32(1)	<0.5(99.5)	<0.5(97)	2(97.5)	0.5(100)	0.25(96.5)	8(84)	8(95)
<i>Klebsiella</i> spp	274	1(96)	2(100)	32(85)	>32(1.1)	<0.5(99.6)	<0.5(97.4)	2(97.4)	0.5(100)	0.25(96.7)	4(90.1)	8(93.4)
<i>P. aeruginosa</i>	255	16(na)	16(94.5)	>32(na)	>32(na)	16(81.6)	32(84.7)	>64(7.8)	8(88.2)	8(75.3)	>16(na)	64(81.8)
<i>S. marcescens</i>	112	2(99.1)	4(100)	>32(0.9)	>32(na)	<0.5(98.2)	<0.5(92)	2(94.6)	2(97.2)	0.5(95.5)	8(78.6)	8(97.3)

* na = not applicable; breakpoint is undefined or agent is not applicable for this species/drug combination.

Table 2. Gram-positive Antibiogram for Tigecycline and 10 Comparators with MIC₉₀ (mcg/mL) and Percent Susceptible (%) against 704 selected Pathogens.

Gram-Positive Organisms	N=	MIC ₉₀ in mcg/mL (% Susceptible)*										
		Tigecycline	AmoxClav	Ampicillin	Ceftioxone	Imipenem	Levofloxacin	Linezolid	Minocycline	Penicillin	Pip/Tazo	Vancomycin
All VREs	8	0.25(100)	>8(25)	>16(25)	>16(na)	>16(na)	>32(na)	4(100)	>8(62.5)	>8(25)	>16(na)	>32(na)
<i>E. faecalis</i>	126	0.25(100)	1(99.2)	2(100)	>64(na)	8(na)	>32(51.6)	2(100)	>8(27)	4(100)	8(na)	2(96.8)
<i>E. faecium</i>	48	0.12(100)	>8(12.5)	>16(12.5)	>64(na)	>16(na)	>32(37.3)	4(100)	>8(62.5)	>8(14.6)	>16(na)	32(87.5)
<i>Enterococcus</i> sp.	177	0.25(100)	>8(75.7)	>16(76.3)	>64(na)	>16(76.2)	>32(37.3)	2(100)	>8(37.3)	>8(76.8)	>16(na)	4(94.4)
<i>S. aureus</i>	285	0.25(100)	>8(78.9)	>16(16.1)	32(77.9)	16(76.1)	1(91.2)	2(100)	1(95.6)	>8(61.1)	>16(80)	1(100)
MSSA	224	0.25(100)	2(100)	>16(77.7)	4(95.1)	4(95.1)	0.25(99.1)	2(100)	0.5(98.2)	>8(77.7)	2(100)	1(100)
MRSA	61	0.25(100)	>8(1.6)	>16(na)	>64(na)	>16(na)	16(82.3)	2(100)	8(86.5)	>8(na)	>16(6.6)	1(100)
<i>S. agalactiae</i>	113	0.25(95.6)	0.12(0.9)	0.25(99.1)	0.12(100)	0.25(na)	1(100)	2(100)	<0.09(0)	0.12(99.1)	0.5(na)	0.5(100)
<i>S. pneumoniae</i>	129	0.06(na)	0.5(97.7)	0.5(na)	0.25(97.7)	0.25(87.9)	1(100)	1(100)	4(na)	1(74.4)	1(na)	0.5(100)
Penicillin-Sus	99	0.06(na)	<0.03(100)	<0.06(na)	<0.03(100)	<0.12(100)	1(100)	1(100)	<0.25(na)	<0.06(100)	<0.25(na)	0.5(100)
Penicillin-Inter	29	0.06(na)	1(100)	2(na)	0.5(96.6)	0.5(95.6)	1(100)	1(100)	1(na)	2(na)	0.5(100)	
Penicillin-Res	4	0.015(na)	4(25)	4(na)	1(50)	<0.12(100)	1(100)	1(100)	4(na)	4(na)	4(na)	0.5(100)

* na = not applicable; breakpoint is undefined or agent is not applicable for this species/drug combination.

Table 3. Frequency Distribution (n) and Cumulative Percents Inhibited (%) of Tigecycline against 2235 isolates of selected Gram-negative and Gram-positive Pathogens.

Organism	N / Cum%	MIC (mcg/mL)											
		0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16
<i>Acinetobacter baumannii</i>	135	2	12	59	22	14	20	2	4				
<i>Acinetobacter Iwoffii</i>	23	1	3	7	6	3	1	2					
<i>Acinetobacter</i> spp	161	4	17.4	47.8	73.9	87.0	91.3	100					
All ESBLs	15	2	3	6	4	2	4						
<i>Enterobacter aerogenes</i>	88			13.3	33.3	73.3	80	93.3	100				
<i>Enterobacter cloacae</i>	182			2.2	19.8	82.4	94.5	96.7	97.3	100			
<i>Enterobacter</i> spp	276			4	66	162	27	7	3	7			
<i>EcoKoxKpn</i>	570	1	13	171	208	115	41	10	1				
<i>E. aerogenes</i>	88	0.2	2.5	32.5	69	89.1	96.3	98.1	99.8	100			
<i>Enterococcus faecalis</i>	126	1	20	54	51								
<i>Enterococcus faecium</i>	48	0.8	16.7	100	100								
All VREs	8			2	4	2							
<i>Enterococcus</i> spp	177	7	37	78	55								
<i>Escherichia coli</i>	297	1	13	169	97	15	1	1					
<i>Haemophilus influenzae</i>	156	1	4	22	30	83	15						
<i>Klebsiella oxytoca</i>	75	1	3	17.9	37.2	90.4	100						
<i>Klebsiella pneumoniae</i>	198			2.7	73.3	86.7	94.7	97.3	100				
<i>Klebsiella</i> spp	274			2	112	100	40						
<i>Pseudomonas aeruginosa</i>	255			0.7	41.6	78.1	92.7	96	96.6	100			
<i>Serratia marcescens</i>	112					2	30	65	14	1			
<i>Staphylococcus aureus</i>	285				33	159	80	13	86.6	99.1	100		
<i>Streptococcus agalactiae</i>	113	1	49	30	19	9	5						
<i>Streptococcus pneumoniae</i>	129	0.9	44.2	70.8	87.6	95.6	100						

Conclusions

- Tigecycline inhibited 96.3% of all *E. coli*, *K. pneumoniae* and *K. oxytoca* tested in vitro