

Evaluation of 11 Antimicrobial Agents Against Australian Bacteremia Isolates: The T.E.S.T. Program

66 027

S. Bouchillon¹, R. Badal¹, M. Hackel¹, J. Johnson¹, D. Hoban¹, B. Johnson¹, M. Renteria¹, 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

REVISED ABSTRACT

Objectives: Tigecycline (TIG), a new glycolcycline, 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 TIG and 10 comparators against bacteremia pathogens. Isolates were collected from 10 hospital sites in Australia throughout 2004-2008. **Methods:** 649 bacteremia isolates were identified to the species level at participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Susceptibility of selected pathogens to tigecycline is summarized below:

Organism (#)	Tigecycline		%S
	MIC ₅₀	MIC ₉₀	
<i>Acinetobacter</i> spp. (25)	0.12	0.25	-*
<i>Enterococcus</i> spp. (58)	0.12	0.25	100
<i>E. coli</i> (162)	0.12	0.25	100
<i>Klebsiella</i> spp. (101)	0.5	1	95
<i>Enterobacter</i> spp. (61)	0.5	1	95.1
<i>P. aeruginosa</i> (44)	8	16	-*
<i>S. aureus</i> MRSA (17)	0.12	0.25	100
<i>S. aureus</i> MSSA (61)	0.12	0.25	100
<i>S. pneumoniae</i> (57)	0.015	0.06	-*

*TIG breakpoint not defined.

Conclusions: TIG demonstrated a broad spectrum of antimicrobial activity, including *Acinetobacter* spp., *Enterobacteriaceae*, *S. aureus* (incl. MRSA), *S. pneumoniae* (all phenotypes), and *Enterococcus* spp. The wide spectrum of activity of tigecycline provides enhanced antimicrobial coverage of pathogens causing bacteremia.

BACKGROUND

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycolcyclines. 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 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 a highly effective against multi-resistant *Acinetobacter* spp., particularly *A. baumannii*, that are commonly associated with serious nosocomial infections. Similar activity was observed against *Enterobacteriaceae*, including extended-spectrum beta-lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC₅₀ values of ≤0.5 mcg/ml against methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive organisms [2, 4-6].

The Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program determined the in vitro activity of tigecycline compared to most commonly prescribed broad spectrum antibiotics against gram-positive and gram-negative species. This study was designed to evaluate the in vitro activity of tigecycline against bacteremic pathogens collected from Australian hospitals.

METHODS

■ Clinical isolates from hematologic sources (n=649) were collected and tested between January 2004 and April 2008 from 10 sites in Australia. Isolates were identified to the species level and tested using broth microdilution at each site by the participating laboratory. All isolates were derived from blood culture specimens. Only one isolate per patient was accepted.

■ Custom broth microdilution panels were supplied by MicroScan (Dade Behring Inc., Sacramento, CA, USA) and TREK Diagnostic Systems, West Sussex, England). Antimicrobial agents and concentrations tested (expressed in mcg/mL) were as follows: gram-positive panel: amoxicillin-clavulanic acid (0.03/0.015-8/4, tested using a 2:1 ratio of amoxicillin-clavulanic acid; reported concentrations refer to amoxicillin); ampicillin (0.06-16); ceftazidime (0.03-64); imipenem (0.06-16, MicroScan panels only); meropenem (0.12-16, MicroScan and TREK panels); linezolid (0.5-8); levofloxacin (0.06-32); minocycline (0.025-8); tigecycline (0.008-16); penicillin (0.06-8); piperacillin-tazobactam (0.25/4-16/4) and vancomycin (0.12-32); gram-negative panel: amikacin (0.5-64); amoxicillin-clavulanic acid (0.12/0.06-32/16, tested using a 2:1 ratio of amoxicillin-clavulanic acid; reported concentrations refer to amoxicillin); ampicillin (0.5-32); ceftazidime (0.06-64); ceftazidime (8-32); imipenem (0.06-16, MicroScan panels only); meropenem (0.06-16, MicroScan and TREK panels); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16) and piperacillin-tazobactam (0.06/4-128/4).

■ Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Escherichia coli* ATCC 35218; *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; *Klebsiella pneumoniae* ATCC 700603 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).

REFERENCES

- Sum, P.E. and P. Petersen. Synthesis and structure-activity relationship of novel glycolcycline 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 antibiogram 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 glycolcycline, GAR-936 tested against 1,203 recent clinical bacterial isolates. *Diagn Microbiol Infect Dis*, 2000, 36(1): p. 19-26.
- 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: glycolcyclines and tetracycline efflux pump inhibitors. *Drug Resist Updat*, 2002, 5(3-4): p. 119-25.
- Projan, S.J. Preclinical pharmacology of GAR-936, a novel glycolcycline antibiogram agent. *Pharmacotherapy*, 2000, 20(9 Pt 2): p. 219S-223S; discussion 224S-228S.
- Biedenbach, D.J., M.L. Beach, and R.N. Jones. In vitro antimicrobial activity of GAR-936 tested against antibiotic-resistant gram-positive blood stream infection isolates and strains producing extended-spectrum beta-lactamases. *Diagn Microbiol Infect Dis*, 2001, 40(4): p. 173-9.
- Patel, R., et al. In vitro activity of GAR-936 against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis*, 2000, 38(3): p. 177-9.
- Petersen, P.J., et al. In vitro and in vivo antibiogram activities of a novel glycolcycline, the 9-t-butylglycolamido derivative of minocycline (GAR-936). *Antimicrob Agents Chemother*, 1999, 43(4): p. 738-44.
- Petersen, P.J., et al. In vitro and in vivo activities of tigecycline (GAR-936), daptomycin, and comparative antimicrobial agents against glycopeptide-intermediate *Staphylococcus aureus* and other resistant gram-positive pathogens. *Antimicrob Agents Chemother*, 2002, 46(8): p. 2598-601.
- Clinical and Laboratory Standards Institute (CLSI). 2007. *Performance Standards for Antimicrobial Susceptibility Testing*; Fourteenth Informational Supplement. CLSI, document M100-S17. Wayne, PA, USA.
- Yagallu, 2005. Tigecycline FDA package insert.
- Clinical and Laboratory Standards Institute (CLSI). 2007. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*; Approved Standard-Sixth Edition, in Document M7-A7. CLSI, 940 Wayne, PA, USA.

ACKNOWLEDGEMENTS

We gratefully acknowledge contributions of the investigators, laboratory personnel and all members of the T.E.S.T. program group. This study was supported by a grant from Wyeth Pharmaceuticals.

RESULTS

Figure 1. The distribution of 649 Australian blood culture isolates by species.

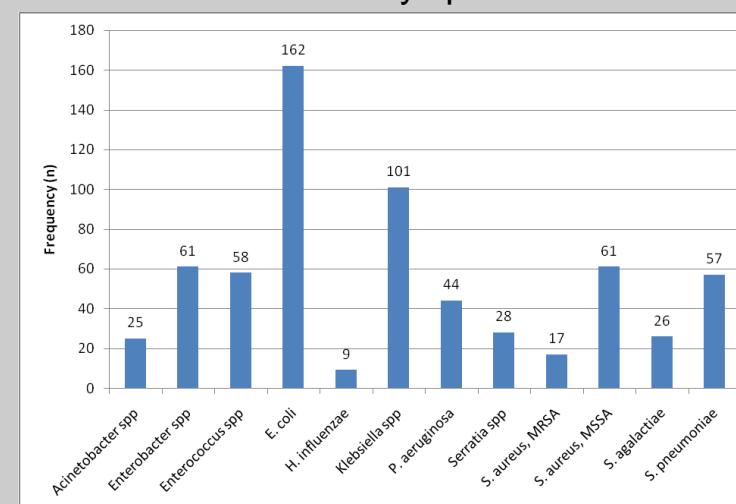


Table 1. The in vitro activity of tigecycline and comparative agents against *Enterobacteriaceae* isolated from blood specimens.

Organism	Drug	MIC (mcg/mL)			Sus ^a
		MIC ₅₀	MIC ₉₀	Range	
<i>Enterobacter</i> spp (n=61)	Tigecycline	0.5	1	0.25 - 8	95.1
	Amikacin	2	4	1 - 8	100
	AmoxClav	>32	>32	1 - >32	6.6
	Ampicillin	>32	>32	2 - >32	1.6
	Cefepime	<0.5	4	<0.5 - >32	91.8
	Ceftazidime	≤8	>32	≤8 - >32	57.4
	Ceftriaxone	0.5	>64	≤0.06 - >64	63.9
	Imipenem	0.5	1	<0.06 - 1	100
	Levofloxacin	0.06	0.5	<0.008 - 8	93.4
	Meropenem	0.12	0.25	<0.06 - 0.5	100
	Minocycline	4	8	1 - >16	80.3
	PipTazo	4	128	0.5 - >128	62.3
<i>E. coli</i> (n=162)	Tigecycline	0.12	0.25	0.06 - 2	100
	Amikacin	2	4	<0.5 - 8	100
	AmoxClav	8	32	0.5 - >32	71.6
	Ampicillin	>32	>32	1 - >32	38.3
	Cefepime	<0.5	<0.5	<0.5 - >32	98.8
	Ceftazidime	≤8	≤8	≤8 - 32	98.8
	Ceftriaxone	≤0.06	0.25	≤0.06 - >64	96.9
	Imipenem	0.25	0.25	≤0.06 - 1	100
	Levofloxacin	0.03	2	<0.008 - >8	90.1
	Meropenem	≤0.06	≤0.06	<0.06 - 0.5	100
	Minocycline	1	8	≤0.5 - >16	87.7
	PipTazo	1	8	0.25 - >128	93.2
<i>Klebsiella</i> spp (n=101)	Tigecycline	0.5	1	0.25 - 4	95
	Amikacin	1	2	≤0.5 - 4	100
	AmoxClav	2	16	1 - >32	88.1
	Ampicillin	>32	>32	1 - >32	1
	Cefepime	<0.5	<0.5	≤0.5 - 8	100
	Ceftazidime	<8	<8	<8 - 16	99
	Ceftriaxone	≤0.06	1	≤0.06 - 8	100
	Imipenem	0.25	0.5	≤0.06 - 0.5	100
	Levofloxacin	0.06	0.25	0.03 - 8	98
	Meropenem	≤0.06	0.12	<0.06 - 0.5	100
	Minocycline	2	4	≤0.5 - >16	90.1
	PipTazo	2	8	0.5 - >128	97
<i>Serratia</i> spp (n=28)	Tigecycline	1	2	0.5 - 2	100
	Amikacin	4	8	≤0.5 - 8	100
	AmoxClav	>32	>32	<0.12 - >32	7.1
	Ampicillin	>32	>32	8 - >32	3.6
	Cefepime	<0.5	<0.5	≤0.5 - 2	100
	Ceftazidime	≤8	≤8	≤8 - 16	100
	Ceftriaxone	0.25	4	<0.06 - 32	96.4
	Imipenem	1	2	0.12 - 2	100
	Levofloxacin	0.25	0.5	0.03 - 4	96.4
	Meropenem	0.12	0.12	<0.06 - 0.12	100
	Minocycline	4	8	2 - 8	82.1
	PipTazo	2	4	1 - 64	96.4

^aInterpretive criteria as defined by CLSI document M100-S17, 2007, where available. na=breakpoints not available. Tigecycline breakpoints defined by FDA (Tygacil[®], 2005).

Table 2. The in vitro activity of tigecycline and comparative agents against *Acinetobacter* spp. and *Pseudomonas aeruginosa* isolated from blood cultures.

Organism	Drug	MIC (mcg/mL)			Sus
		MIC ₅₀	MIC ₉₀	Range	
<i>Acinetobacter</i> spp (n=25)	Tigecycline	0.12	0.25	0.06 - 1	na
	Amikacin	2	8	≤0.5 - 8	100
	Cefepime	4	16	≤0.5 - >32	88
	Ceftazidime	<8	>32	<8 - >32	72
	Ceftriaxone	8	>64	0.25 - >64	52
	Imipenem	0.25	1	0.12 - >16	93.3
	Levofloxacin	0.12	0.5	0.015 - 8	96.6
	Meropenem	1	1	0.12 - 16	90
	Minocycline	≤0.5	≤0.5	≤0.5 - 8	92
	PipTazo	2	128	<0.06 - >128	72
	<i>P. aeruginosa</i> (n=44)	Tigecycline	8	16	2 - >16
Amikacin		4	4	2 - 8	100
Cefepime		2	8	1 - 32	90.9
Ceftazidime		≤8	≤8	≤8 - >32	90.9
Ceftriaxone		64	>64	8 - >64	6.8
Imipenem		1	16	0.25 - 16	83.3
Levofloxacin		0.5	4	0.25 - >8	86.4
<i>S. pneumoniae</i> (n=57)	Tigecycline	0.015	0.06	<0.008 - 0.12	na
	AmoxClav	≤0.03	0.25	≤0.03 - 1	100
	Ceftriaxone	≤0.03	0.12	≤0.03 - 1	100
	Imipenem	<0.12	<0.12	<0.12 - 0.5	94.1
	Levofloxacin	0.5	1	0.12 - 2	100
	Linezolid	≤0.5	1	≤0.5 - 1	100
	Meropenem	<0.12	<0.12	<0.12 - 0.25	95
<i>S. aureus</i> (n=17)	Tigecycline	0.12	0.25	0.06 - 0.5	100
	AmoxClav	8	>8	>8 - >16	0
	Ampicillin	>16	>16	16 - >16	0
	Ceftriaxone	32	>64	2 - >64	0
	Levofloxacin	0.25	16	<0.06 - 16	76.5
	Linezolid	2	2	1 - 4	100
	Meropenem	2	>16	<0.12 - >16	0
<i>S. aureus</i> (n=61)	Tigecycline	0.12	0.25	0.06 - 0.5	100
	AmoxClav	1	2	0.12 - 2	100
	Ampicillin	4	>16	<0.06 - >16	96.7
	Ceftriaxone	2	4	1 - 8	100
	Imipenem	≤0.12	0.25	≤0.12 - 0.25	100
	Levofloxacin	0.12	0.25	0.12 - 4	98.4
	Linezolid	2	4	1 - 4	100
<i>S. aureus</i> (n=26)	Tigecycline	0.03	0.25	0.03 - 0.5	96.2
	Ampicillin	0.12	0.25	<0.06 - 0.25	100
	Ceftriaxone	0.06	0.12	<0.03 - 0.12	100
	Levofloxacin	0.5	1	0.5 - 1	100
	Linezolid	1	2	1 - 2	100
	Meropenem	≤0.12	≤0.12	≤0.12 - <0.12	100
	Penicillin	0.12	0.12	<0.06 - 0.25	96.2
<i>S. pneumoniae</i> (n=57)	Tigecycline	0.015	0.06	<0.008 - 0.12	na
	AmoxClav	≤0.03	0.25	≤0.03 - 1	100
	Ceftriaxone	≤0.03	0.12	≤0.03 - 1	100
	Imipenem	<0.12	<0.12	<0.12 - 0.5	94.1
	Levofloxacin	0.5	1	0.12 - 2	100
	Linezolid	≤0.5	1	≤0.5 - 1	100
	Meropenem	<0.12	<0.12	<0.12 - 0.25	95
<i>S. pneumoniae</i> (n=57)	Tigecycline	0.015	0.06	<0.008 - 0.12	na
	AmoxClav	≤0.03	0.25	≤0.03 - 1	100
	Ceftriaxone	≤0.03	0.12	≤0.03 - 1	100
	Imipenem	<0.12	<0.12	<0.12 - 0.5	94.1
	Levofloxacin	0.5	1	0.12 - 2	100
	Linezolid	≤0.5	1	≤0.5 - 1	100
	Meropenem	<0.12	<0.12	<0.12 - 0.25	95
<i>S. pneumoniae</i> (n=57)	Tigecycline	0.015	0.06	<0.008 - 0.12	na
	AmoxClav	≤0.03	0.25	≤0.03 - 1	100
	Ceftriaxone	≤0.03	0.12	≤0.03 - 1	100
	Imipenem	<0.12	<0.12	<0.12 - 0.5	94.1
	Levofloxacin	0.5	1	0.12 - 2	100
	Linezolid	≤0.5	1	≤0.5 - 1	100
	Meropenem	<0.12	<0.12	<0.12 - 0.25	95
<i>S. pneumoniae</i> (n=57)	Tig				