

In-patient and Out-patient Enterobacteriaceae Collected from Australia – T.E.S.T. Program 2008

OB016

J. Johnson¹, R. Badal¹, S. Hawser¹, M. Hackel¹, S. Bouchillon¹, B. Johnson¹, D. Hoban¹, M. Renteria¹, M. Dowzicky²

¹International Health Management Associates, Inc., Schaumburg, IL, USA
²Wyeth Pharmaceuticals, Collegeville, PA, USA



IHMA, Inc.
 2122 Palmer Dr.
 Schaumburg, IL
 60173
 Tel: 847.303.5003
 Fax: 847.303.5601

Revised Abstract

Objectives: Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have broad spectrum activity against 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 1016 sites globally from 2004 to 2008. **Methods:** A total of 910 clinical *Enterobacteriaceae* isolates from 20 sites in Australia were identified to the species level and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by each site using broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Results are in the table as follows*:

	<i>Enterobacteriaceae</i>			
	In-patients (n=726)		Out-patients (n=184)	
	%S	MIC ₉₀	%S	MIC ₉₀
Tigecycline	97.1	1	99.5	1
Amikacin	99.9	4	100	4
Cefepime	97.2	2	99.5	≤0.5
Ceftazidime	83.9	32	91.8	≤8
Imipenem	99.6	1	100	0.25
Levofloxacin	94.6	0.25	94.6	0.25
Minocycline	84.3	8	88.6	8
Pip-Tazo	83.6	64	88.6	32

*Tigecycline susceptibility defined according to FDA package insert (Tygacil® 2005). **Conclusions:** Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed broad spectrum antimicrobials without any demonstrable change between in- and out-patient bacterial study strains. Tigecycline's inhibitory activity was essentially comparable to that of most broad spectrum antimicrobials. The presented data suggest that tigecycline may be an effective and reliable therapeutic option against nosocomial or community enteric pathogens.

Introduction

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycylcyclines. 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].

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 from 20 hospitals in Australia from 2004 to 2008. This study was designed to evaluate the in vitro activity of tigecycline in in-patient and out-patient isolates from these centers.

Materials & Methods

- For the T.E.S.T. program 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.
- Clinical isolates (n=910) were collected from 2004 to 2008 from twenty testing sites in Australia.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring, West Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/ml): amoxicillin-clavulanic acid (0.12-32); piperacillin-tazobactam (0.06-128); levofloxacin (0.008-8); ceftriaxone (0.06-64); cefepime (0.5-32); ampicillin (0.5-32); amikacin (0.5-64); minocycline (0.5-16); ceftazidime (8-32); tigecycline (0.008-16); and imipenem (0.06-16).
- 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].
- Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- 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; *K. pneumoniae* ATCC 700603; *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, confirmation of identification, and 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 glycylcycline 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 antibacterial 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 glycylcycline, GAR-936 tested against 1,203 recent clinical bacterial isolates*. Diagn Microbiol Infect Dis, 2000, 36(1): p. 19-36.
- 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: glycylcyclines 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 glycylcycline antibacterial 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. 173-7.
- 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 antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamide 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. 2595-601.
- National Committee for Clinical Laboratory Standards (CLSI). Performance Standards for Antimicrobial Susceptibility Testing, Nineteenth Informational Supplement. CLSI document M100-S19. Wayne, PA, 2009.
- Tygacil®. 2005. Tigecycline FDA package insert.

Acknowledgements

This study was supported by a grant from Wyeth Pharmaceuticals. We gratefully acknowledge contributions from the participants in the T.E.S.T. program who have helped make this program a success.

Results

The results are listed in the following tables and figures.

Table 1. In vitro activity of tigecycline and comparative agents against gram-negative isolates

Organism Name	Drug	In-patients						Out-patients					
		n	%SUS*	MIC ₅₀	MIC ₉₀	Low	High	n	%SUS*	MIC ₅₀	MIC ₉₀	Low	High
<i>Enterobacteriaceae</i> ^a													
		726						184					
Tigecycline		97.1	0.5	1	0.06	8	99.5	0.25	1	0.03	4		
Amikacin		99.9	2	4	≤0.5	32	100	2	4	≤0.5	8		
AmoxClav		44.1	16	>32	≤0.12	>32	56	8	>32	1	>32		
Ampicillin		11.2	>32	>32	1	>32	18.6	>32	>32	1	>32		
Cefepime		97.2	≤0.5	2	≤0.5	>32	99.5	≤0.5	≤0.5	≤0.5	16		
Ceftazidime		83.9	≤8	32	≤8	>32	91.8	≤8	≤8	≤8	>32		
Ceftriaxone		87.5	0.12	32	≤0.06	>64	92.4	≤0.06	8	≤0.06	>64		
Imipenem		99.6	0.25	1	≤0.06	16	100	0.25	1	≤0.06	2		
Levofloxacin		94.6	0.06	0.5	≤0.008	>8	94.6	0.03	0.25	≤0.008	>8		
Minocycline		84.3	2	8	≤0.5	>16	88.6	2	8	≤0.5	>16		
PipTazo		83.6	2	64	0.25	>128	88.6	2	32	0.25	>128		
<i>E. coli</i>													
		196					87						
Tigecycline		100	0.12	0.25	0.06	2	100	0.12	0.25	0.03	0.5		
Amikacin		99.5	2	4	≤0.5	32	100	2	4	≤0.5	8		
AmoxClav		66.3	8	32	0.5	>32	72.4	8	32	1	>32		
Ampicillin		40.5	>32	>32	1	>32	37.9	>32	>32	1	>32		
Cefepime		98.5	≤0.5	≤0.5	≤0.5	>32	100	≤0.5	≤0.5	≤0.5	8		
Ceftazidime		93.9	≤8	≤8	≤8	>32	96.6	≤8	≤8	≤8	>32		
Ceftriaxone		96.4	≤0.06	2	≤0.06	>64	96.6	≤0.06	4	≤0.06	>64		
Imipenem		100	0.25	0.25	≤0.06	>64	100	0.25	0.5	≤0.06	1		
Levofloxacin		90.3	0.03	2	≤0.008	>8	92	0.03	0.5	≤0.008	>8		
Minocycline		84.2	1	8	≤0.5	>16	86.2	1	8	≤0.5	>16		
PipTazo		90.3	1	16	0.25	>128	94.3	1	8	0.25	>128		
<i>Klebsiella spp.</i>													
		216					43						
Tigecycline		95.8	0.5	1	0.12	8	97.7	0.5	1	0.25	4		
Amikacin		100	1	2	≤0.5	16	100	1	2	1	8		
AmoxClav		84.3	2	32	1	>32	90.7	2	4	1	32		
Ampicillin		0.9	>32	>32	2	>32	2.3	>32	>32	8	>32		
Cefepime		99.5	≤0.5	≤0.5	≤0.5	>32	100	≤0.5	≤0.5	≤0.5	8		
Ceftazidime		97.2	≤8	≤8	≤8	>32	100	≤8	≤8	≤8	16		
Ceftriaxone		97.7	≤0.06	2	≤0.06	>64	95.3	≤0.06	1	≤0.06	32		
Imipenem		100	0.25	0.5	≤0.06	1	100	0.25	0.5	≤0.06	1		
Levofloxacin		96.3	0.06	0.25	0.03	>8	100	0.06	0.12	0.015	0.25		
Minocycline		91.2	2	4	≤0.5	>16	93	2	4	≤0.5	16		
PipTazo		93.1	2	8	0.25	>128	93	2	8	0.5	>128		
<i>Enterobacter spp.</i>													
		217					42						
Tigecycline		95.4	0.5	1	0.12	8	100	0.5	1	0.12	2		
Amikacin		100	2	2	≤0.5	8	100	2	2	1	4		
AmoxClav		1.8	>32	>32	1	>32	2.4	>32	>32	2	>32		
Ampicillin		0.5	>32	>32	2	>32	0	>32	>32	16	>32		
Cefepime		93.5	≤0.5	8	≤0.5	>32	97.6	≤0.5	2	≤0.5	16		
Ceftazidime		58.1	≤8	>32	≤8	>32	71.4	≤8	32	≤8	>32		
Ceftriaxone		66.4	1	>64	≤0.06	>64	78.6	0.5	32	≤0.06	>64		
Imipenem		100	0.5	1	≤0.06	2	100	0.5	1	≤0.06	2		
Levofloxacin		96.8	0.06	0.5	≤0.008	>8	97.6	0.06	0.25	0.015	8		
Minocycline		81.1	4	16	1	>16	90.5	2	4	1	8		
PipTazo		62.2	8	128	0.5	>128	69	4	128	0.5	>128		
<i>Serratia spp.</i>													
		97					12						
Tigecycline		97.9	1	2	0.25	4	100	1	1	0.12	2		
Amikacin		100	2	4	≤0.5	16	100	2	4	1	8		
AmoxClav		4.1	>32	>32	≤0.12	>32	0	>32	>32	16	>32		
Ampicillin		2.1	>32	>32	8	>32	0	>32	>32	16	>32		
Cefepime		97.9	≤0.5	≤0.5	≤0.5	>32	100	≤0.5	≤0.5	≤0.5	≤0.5		
Ceftazidime		91.8	≤8	≤8	≤8	>32	100	≤8	≤8	≤8	>32		
Ceftriaxone		93.8	0.25	4	≤0.06	>64	100	0.12	1	≤0.06	2		
Imipenem		96.9	0.5	2	0.12	16	100	0.5	1	0.5	1		
Levofloxacin		94.8	0.25	0.5	0.03	>8	83.3	0.12	>8	0.015	>8		
Minocycline		76.3	4	8	1	16	83.3	2	8	≤0.5	16		
PipTazo		96.9	2	8	0.25	64	100	2	2	0.5	8		

* Interpretive criteria as defined by CLSI, M100-S19 (2009) [12], where available; tigecycline susceptibility breakpoints are according to FDA package insert (Tygacil® 2005), where available [13].

^a In-patient isolates include 11 ESBL-producing tigecycline-susceptible *E. coli* and *K. pneumoniae* strains with a tigecycline MIC of 1 mcg/ml.

Figure 1: In vitro activity of tigecycline against 726 in-patient and 184 out-patient *Enterobacteriaceae* strains.

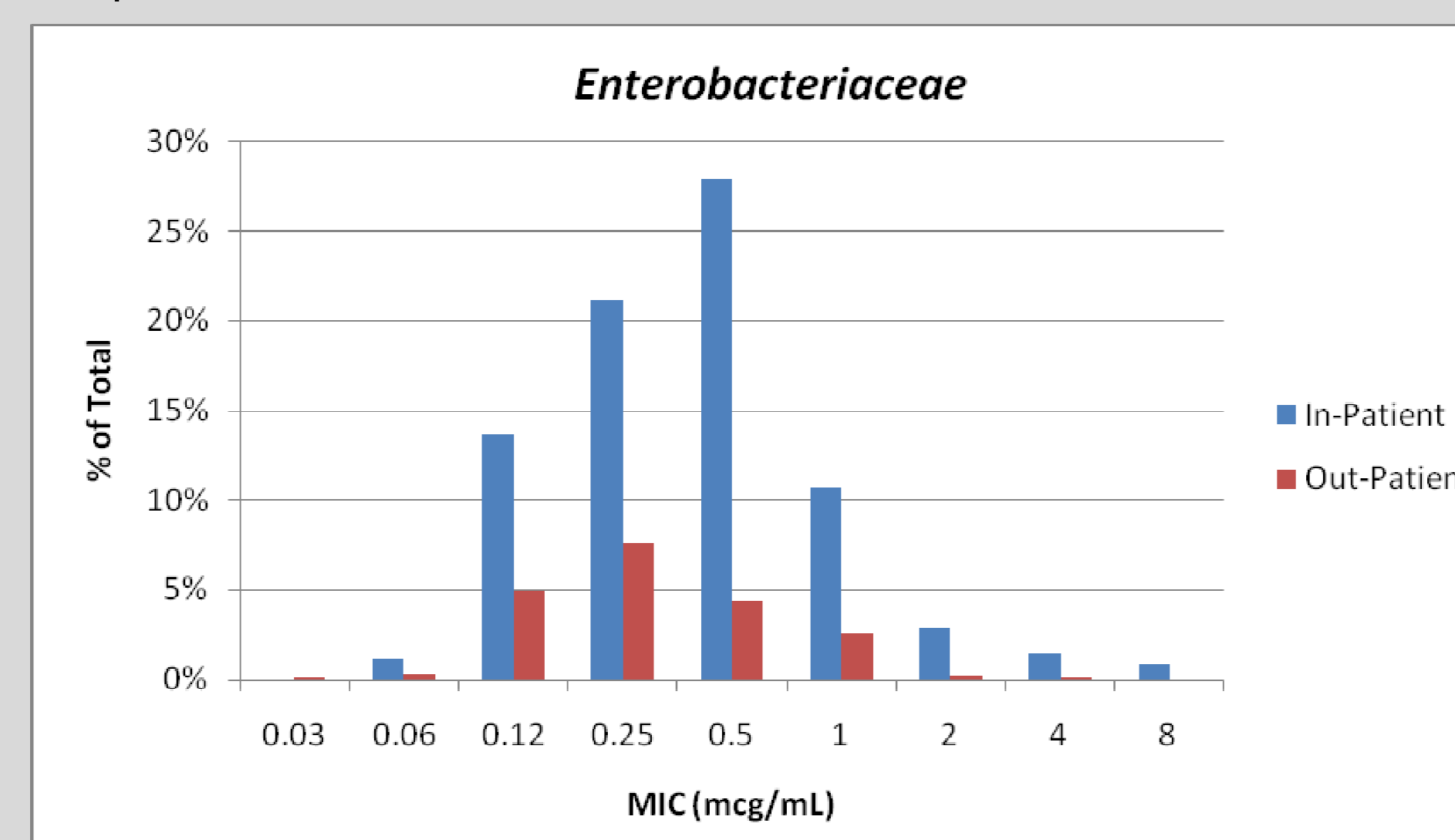


Figure 2: In vitro activity of tigecycline against 196 in-patient and 87 out-patient *E. coli* strains.

