Antimicrobial Susceptibility of Isolates Collected from Different Body Sites in Asia and the Pacific Rim: Tigecycline Evaluation Surveillance Trial (TEST)

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REVISED ABSTRACT

Background: One of the goals of surveillance studies is to identify changing patterns of bacterial resistance to help guide current therapy. The Tigecycline Evaluation Surveillance Trial (TEST) is an ongoing global study that can serve to help recognize current trends in resistance on many levels. This report evaluates differences in susceptibility of strains from different body sites, collected in Asia/Pacific 2004-2006. **Methods:** 1,509 strains isolated from 10 specimen types were collected and identified from 2004-2006 at 9 hospitals in 7 countries in Asia/Pacific. MICs for each strain were determined per CLSI guidelines at each facility using broth microdilution. $MIC_{50/90}$ values were analyzed to identify any significant differences in antibiograms from different sources. **Results:** Tigecycline (TIG) MIC_{50} values for almost all organism/specimen pairings were +/- 2 dilutions of each other, with no single source giving a higher MIC_{50} than others. The same was seen for TIG MIC_{90} values, which were almost always within 1-2 dilutions of the MIC_{50}. Comparator drugs generally showed similar absence of variability in activity vs. isolates from various body sites; however, their MIC90/MIC50 ratios were usually much higher than those of TIG. Even imipenem had such high ratios with Acinetobacter and staphylococci. **Conclusions:** Bacteria isolated from more than 10 different body sites had generally similar antibiograms, with no single source showing significantly different sensitivity patterns. TIG demonstrated a broad spectrum of activity and consistently low $MIC_{90/50}$ ratios, including strains resistant to other drugs (MRSA, ESBL-producers, imipenem-resistant *Acinetobacter*, etc.), clearly reinforcing its position as a viable alternative for therapy of difficult-to-treat infections.

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, 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 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 has been observed against *Enterobacteriaceae*, even extended-spectrum beta-lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC_{90} 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].

With such a broad spectrum of activity, tigecycline has the potential to be useful in a variety of infections. This report describes the in vitro activity of tigecycline against a large, diverse population of clinical isolates collected from various specimen types in hospitals in Asia/Pacific Rim from 2004 through 2006.

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.
- 6,936 clinical isolates were collected and tested between January 2004 and June 2006 from 9 centers in 7 countries in Asia and the Pacific Rim.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring Inc., 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]. Tigecycline breakpoints (in units of mcg/ml), as approved by the US Food and Drug Administration (FDA), are defined as follows: *Enterobacteriaceae*: susceptible ≤2, intermediate = 4, and resistant ≥8; *Staphylococcus aureus* (including MRSA): susceptible ≤0.5, no intermediate or resistant breakpoints; *Enterococcus faecalis* (vancomycin-susceptible): susceptible ≤0.25, no intermediate or resistant breakpoints; non-pneumococcal streptococci: susceptible ≤0.25, no intermediate or resistant breakpoints.
- 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: *E. faecalis* ATTC 29212; *Escherichia coli* ATCC 25922; *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *S. aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *P. 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).

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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

Table 1. Tigecycline MIC_{50} and MIC_{90} (mcg/ml) for gram-negative isolates with n 10 from various body sites[a].

Organism		Blood	GI	GU	Resp	SSS
E. coli (192)	MIC_{50}	0.12	0.12	0.12	0.12	0.12
	MIC_{90}	0.25	0.25	0.5	0.5	0.25
Klebsiella spp. (190)	MIC_{50}	0.5	-	0.5	0.5	0.25
	MIC_{90}	2	-	1	1	0.5
ESBL-producers[b]	MIC_{50}	0.5	-	0.5	0.5	-
(68)	MIC_{90}	2	-	0.5	1	-
Enterobacter spp. (106)	MIC_{50}	0.5	-	0.5	0.5	0.5
	MIC_{90}	2	-	2	1	1
Serratia spp. (67)	MIC_{50}	1	-	1	1	1
	MIC_{90}	2	-	1	1	2
P. aeruginosa (105)	MIC_{50}	8	-	-	8	8
	MIC_{90}	>16	-	-	16	>16
Acinetobacter spp. (104)	MIC_{50}	0.12	-	0.12	0.12	0.25
	MIC_{90}	0.5	-	0.5	1	1
H. influenzae (89)	MIC_{50}	-	-	-	0.12	-
	MIC_{90}	-	-	-	0.25	-
H. influenzae (19)	MIC_{50}	-	-	-	0.12	-
(B-lac positive)	MIC_{90}	-	-	-	0.25	-

[a] $MIC_{50/90}$ not calculated if n<10.
[b] ESBL producers: *E. coli, K. pneumoniae, K. oxytoca*

Table 2. Tigecycline MIC_{50} and MIC_{90} (mcg/ml) for gram-positive isolates with n 10 from various body sites[a].

Organism		Blood	GI	GU	Resp	SSS
S. aureus (173)	MIC_{50}	0.25	-	-	0.12	0.12
	MIC_{90}	0.5	-	-	0.5	0.25
MRSA (72)	MIC_{50}	-	-	-	0.25	0.12
	MIC_{90}	-	-	-	0.5	0.25
E. faecalis (79)	MIC_{50}	0.12	-	0.12	-	0.12
	MIC_{90}	0.12	-	0.12	-	0.25
S. pneumoniae (92)	MIC_{50}	0.03	-	-	0.12	-
	MIC_{90}	0.5	-	-	0.5	-
S. pneumoniae PRSP (10)	MIC_{50}	-	-	-	0.015	-
	MIC_{90}	-	-	-	1	-
S. agalactiae (52)	MIC_{50}	-	-	0.03	-	0.06
	MIC_{90}	-	-	0.06	-	0.06

[a] $MIC_{50/90}$ not calculated if n<10.

Tables 3a - 3k. Drugs with MIC_{50} or MIC_{90} varying by >2 log_2 dilutions among specimen sources (n 10). Cpe=cefepime, Cax=ceftriaxone, Min=minocycline, P/T=piperacillin/tazobactam, Caz=ceftazidime, Lvx=levofloxacin, Ak=amikacin, Imp=imipenem, Min=minocycline, Va=vancomycin, AUG=amoxicillin/clavulanic acid, Am=ampicillin, P=penicillin.

Table 3a. *E. coli* $MIC_{50/90}$

Source (n)	Cpe	Cax	Min	P/T	Lvx	Ak
Blood (81)	0.5/4	0.06/32	1/8		0.03/>8	
GI (13)	2/>32	4/>64	2/>16	1/16	0.5/>8	
GU (61)	0.5/32	0.06/>64	-	1/16		
Resp (15)	0.5/32	2/>64				2/16
SSS (22)	0.5/8	0.06/64			0.12/>8	

Table 3b. *Klebsiella* spp. $MIC_{50/90}$

Source (n)	Cpe	Caz	Cax	P/T	AUG	Lvx	Min
Blood (56)	0.5/>32	8/>32	0.25/>64	2/64	4/>32	0.06/8	2/>16
GU (61)	0.5/8		0.06/64	2/128	2/32		0.03/2
Resp (62)	0.5/4	8/>32	0.12/64		4/>32		0.06/8

Table 3c. *Enterobacter* spp. $MIC_{50/90}$

Source (n)	Cpe	Cax	Lvx	P/T	Caz	AUG
Blood (28)	0.5/32	0.25/>64	0.06/8	1/64	8/>32	
GU (39)	0.5/8	0.06/64	0.03/2	2/128		2/32
Resp (53)	0.5/4	0.12/64	0.06/8		8/>32	4/32
SSS (38)	0.5/16	0.06/>64	0.06/0.5			2/16

Table 3d. *Serratia* spp. $MIC_{50/90}$

Source (n)	Caz	Cpe	Lvx	Ak	Cax	P/T
Blood (13)	8/>32	0.5/>32		4/>64	0.5/>64	
GU (13)					0.25/2	
Resp (31)					0.5/8	2/16

Table3e. Acinetobacter spp. $MIC_{50/90}$

Source (n)	Ak	Imp	Lvx	Min	P/T	Cpe	Caz	Cax
Blood (35)	2/>64	0.25/>16	0.12/4		1/>128	4/>32	8/>32	16/>64
GU (10)	4/>64		0.06/8	0.5/4		4/>32	8/>32	16/>64
Resp (40)	4/>64		0.25/8	0.5/4	2/>128	4/>32	8/>32	16/>64
SSS (19)	4/>64	0.5/>16		0.5/4	2/>!28		8/>32	

Table 3f. *Pseudomonas aeruginosa* $MIC_{50/90}$

Source (n)	Caz	Imp	Lvx	P/T	Ak	Caz	Cpe	Min
Blood (12)			0.5/>8	4/64				
GU (14)		1/8	1/>8		4/64	8/>32		
Resp (65)		1/8	1/>8	4/128		8/>32	4/32	
SSS (44)		1/16	1/>8		4/64	8/>32	4/>32	4/64

Table 3g. *Enterococcus faecalis* $MIC_{50/90}$

Source (n)	Lvx
Blood (17)	1/>32
GU (30)	1/32
SSS (32)	1/32

Table 3h. *Streptococcus pneumoniae* $MIC_{50/90}$

Source (n)	Aug	Am	Cax	Min	P	P/T
Blood (30)	0.03/0.25	0.06/0.5	0.03/0.25	0.25/8		
Resp (62)	0.03/1	0.06/2	0.03/1	1/8	0.06/2	0.25/2

Table 3i. *Staphylococcus aureus* $MIC_{50/90}$

Source (n)	Aug	Am	Cax	Imp	Lvx	Min	P/T
Blood (14)	1/>8		4/>64	0.25/>16	0.25/8	0.25/8	1/>16
Resp (47)							
SSS (112)	1/>8		4/>64		0.25/4	0.25/4	1/>16

Table 3j. *Haemophilus influenzae* $MIC_{50/90}$

Source (n)	Am
Resp (89)	0.5/32

CONCLUSIONS

- Tigecycline MIC_{50} values for each species/group were within 2 log_2 dilutions, demonstrating remarkable consistency regardless of specimen source.
- Tigecycline MIC_{90} values for strains of each species/group isolated from various sources were likewise within 2 log_2 dilutions including ESBL-producers from all sources.
- Tigecycline MIC_{90} values were within 1-2 log_2 dilutions of the MIC_{50} in almost all cases, with a notable exception being PRSP *S. pneumoniae*, where up to 6 doubling dilutions separated them.
- Most MIC_{50} values for comparator drugs were within 2 doubling dilutions across specimen sources; however, there were numerous observations of MIC_{90}s varying by more than 2 log_2 dilutions across specimen sources. In most of these cases the higher MIC_{90} values from one or more sources were due to a higher frequency of resistant strains isolated from those sources (i.e., MRSA, ESBL+ *E. coli/Klebsiella* spp., VRE, penicillin-non-susceptible *S. pneumoniae*).
- Tigecycline's consistent activity against most strains in this study, including those resistant to one or more other antimicrobics, indicates that it should have an important role in treatment of serious infections.