

REVISED ABSTRACT

**Background:** Bacterial resistance patterns vary over both time and geography. One of the goals of surveillance studies is to identify those patterns 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 Western Europe 2004-2006. **Methods:** 6,936 strains isolated from 10 specimen types were collected and identified from 2004-2006 at 37 hospitals in 12 countries in Western Europe. MICs for each strain were determined per CLSI guidelines at each facility using broth microdilution. MIC<sub>50/90</sub> were analyzed to identify any significant differences in antibiograms from different sources. **Results:** Tigecycline (TIG) MIC<sub>50</sub> values for almost all organism/specimen pairings were +/ - 2 log<sub>2</sub> dilutions of each other, with no single source giving a higher MIC<sub>50</sub> than the others. The same was seen for TIG MIC<sub>90</sub> values, which were also almost always within 1-2 log<sub>2</sub> dilutions of the MIC<sub>50</sub>, except for *S. pneumoniae*, whose TIG MIC<sub>50</sub> were 3-4 fold higher than the MIC<sub>90</sub> for all specimen sources. Although comparator drugs also generally showed little variability in MIC<sub>50</sub> between body sites, much more variability was seen with MIC<sub>90</sub>s. **Conclusion:** Bacteria isolated from more than 10 different body sites had generally similar antibiograms, with no isolates from any single source showing significantly different sensitivity patterns. TIG's broad spectrum of activity and consistently low MIC<sub>90</sub>/MIC<sub>50</sub> ratios, including strains resistant to other drugs, may make it an excellent therapeutic option when treating infections often caused by strains refractory to treatment with other agents.

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 considered a bacteriostatic agent, it has shown some bactericidal activity against key 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, 7]. Tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are usually sensitive to tigecycline [2-4, 7-11], except for *Pseudomonas aeruginosa*. Tigecycline has been shown to be 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*, including most extended-spectrum beta-lactamase (ESBL) producing strains [10]. Tigecycline has demonstrated MIC<sub>50</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].

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 Western Europe 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 37 study centers in Western Europe.
- 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* ATCC 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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RESULTS

Table 1. Tigecycline MIC<sub>50</sub> and MIC<sub>90</sub> (mcg/ml) for gram-negative isolates with n>=10 from various body sites<sup>a</sup>. (GI = Gastrointestinal; GU = Genitourinary; HEENT = Head, Ears, Eyes, Nose, Throat; Resp = Respiratory; SSS = Skin/Soft Tissue)

Organism	n	Blood	Cath/Drain	GI	GU	HEENT	Resp	SSS
<i>E. coli</i>	n	244	15	63	148	13	78	124
	MIC <sub>50</sub>	0.12	0.12	0.12	0.12	0.12	0.12	0.12
	MIC <sub>90</sub>	0.25	0.25	0.5	0.25	0.25	0.5	0.25
<i>Klebsiella</i> spp.	n	221	32	43	158		120	105
	MIC <sub>50</sub>	0.5	0.25	0.25	0.25		0.5	0.25
	MIC <sub>90</sub>	1	2	0.5	1		2	2
ESBL-producers	n	31		10	18		12	19
	MIC <sub>50</sub>	0.5		0.25	0.25		0.25	0.5
	MIC <sub>90</sub>	2		0.5	4		2	2
<i>Enterobacter</i> spp.	n	183	30	37	117		152	139
	MIC <sub>50</sub>	0.5	0.5	0.5	0.5		0.5	0.5
	MIC <sub>90</sub>	1	2	1	2		2	1
<i>Serratia</i> spp.	n	65	10		34		91	55
	MIC <sub>50</sub>	0.5	0.5		1		0.5	1
	MIC <sub>90</sub>	1	1		2		2	1
<i>P. aeruginosa</i>	n	126	38	16	54	23	140	152
	MIC <sub>50</sub>	8	16	4	16	8	8	8
	MIC <sub>90</sub>	>16	>16	16	>16	16	>16	>16
<i>Acinetobacter</i> spp.	n	90	26	11	50		103	99
	MIC <sub>50</sub>	0.25	0.5	0.25	0.12		0.25	0.12
	MIC <sub>90</sub>	0.5	1	1	0.5		1	1
<i>H. influenzae</i>	n	15				35	309	13
	MIC <sub>50</sub>	0.12				0.12	0.12	0.12
	MIC <sub>90</sub>	0.25				0.12	0.25	0.12
<i>H. influenzae</i> (B-lac positive)	n						47	
	MIC <sub>50</sub>						0.12	
	MIC <sub>90</sub>						0.25	

<sup>a</sup>MIC<sub>50</sub> not calculated if n<10.

Table 2. Tigecycline MIC<sub>50</sub> and MIC<sub>90</sub> (mcg/ml) for gram-positive isolates with n>=10 from various body sites.<sup>a</sup>

Organism	n	Blood	Bone	Cath/Drain	CNS	GI	GU	HEENT	Resp	SSS
<i>S. aureus</i>	n	173	10	27			34	22	154	263
	MIC <sub>50</sub>	0.12	0.12	0.12			0.12	0.12	0.12	0.12
	MIC <sub>90</sub>	0.25	0.25	0.25			0.12	0.25	0.25	0.25
<i>S. aureus</i> MRSA	n	59					12		415	41
	MIC <sub>50</sub>	0.12					0.12		0.12	0.12
	MIC <sub>90</sub>	0.25					0.25		0.25	0.25
<i>E. faecalis</i>	n	62		20		29	83		17	88
	MIC <sub>50</sub>	0.12		0.12		0.12	0.06		0.12	0.12
	MIC <sub>90</sub>	0.12		0.25		0.25	0.25		0.25	0.25
<i>E. faecium</i>	n	27				21	11			20
	MIC <sub>50</sub>	0.06				0.06	0.03			0.06
	MIC <sub>90</sub>	0.12				0.12	0.06			0.12
All VRE <sup>b</sup>	n									
	MIC <sub>50</sub>									
	MIC <sub>90</sub>									
<i>S. pneumoniae</i>	n	112			12			34	237	11
	MIC <sub>50</sub>	0.06			0.03			0.06	0.06	0.12
	MIC <sub>90</sub>	1			0.5			1	0.5	1
<i>S. pneumoniae</i> (pen-intermed.)	n	20							59	
	MIC <sub>50</sub>	0.03							0.12	
	MIC <sub>90</sub>	0.5						1		
<i>S. pneumoniae</i> (pen-resistant)	n	13							19	
	MIC <sub>50</sub>	0.06							0.06	
	MIC <sub>90</sub>	1						1		
<i>S. agalactiae</i>	n	44				105			16	75
	MIC <sub>50</sub>	0.03				0.03			0.03	0.03
	MIC <sub>90</sub>	0.12				0.25		0.25	0.25	0.06

<sup>a</sup>MIC<sub>50</sub> not calculated if n<10.  
<sup>b</sup>All n's were <10; however, MIC<sub>50</sub>/max for all 17 VRE from all body sites were 0.03-0.25.

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

Table 3a. *E. coli* MIC<sub>50/90</sub>

Source (n)	Cpe	Cax	Min	P/T
Blood (244)	<=0.5/>0.5	<=0.06/0.25	1/8	1/8
Cath/Drain (15)	<=0.5/2	<=0.06/1	1/>16	1/4
GI (63)	<=0.5/2	<=0.06/8	1/8	1/8
GU (148)	<=0.5/4	<=0.06/8	1/8	1/8
HEENT (13)	<=0.5/1	<=0.06/0.25	1/>16	1/128
Resp (78)	<=0.5/1	<=0.06/0.25	1/16	1/16
SSS (124)	<=0.5/1	<=0.06/2	1/4	1/4

Table 3b. *Klebsiella* spp. MIC<sub>50/90</sub>

Source (n)	Cpe	Caz	Cax	P/T
Blood (221)	<=0.5/2	<=8/16	<=0.06/8	1/32
Cath/Drain (32)	<=0.5/16	<=8/>32	<=0.06/>64	2/>128
GI (43)	<=0.5/8	<=8/>32	<=0.06/8	2/128
GU (158)	<=0.5/1	<=8/>8	<=0.06/8	1/8
Resp (120)	<=0.5/4	<=8/>8	<=0.06/16	2/32
SSS (105)	<=0.5/8	<=8/>32	<=0.06/32	2/>128

Table 3c. *Enterobacter* spp. MIC<sub>50/90</sub>

Source (n)	Cpe	Cax	Lvx	P/T
Blood (183)	<=0.5/4	0.5/64	0.06/>8	1/32
Cath/Drain (30)	<=0.5/>32	0.5/64	0.06/>8	2/>128
GI (37)	<=0.5/>32	4/>64	0.06/1	2/128
GU (117)	<=0.5/4	0.5/64	0.06/2	1/8
Resp (152)	<=0.5/4	0.25/>64	0.06/>8	2/32
SSS (139)	<=0.5/4	0.25/32	0.03/2	2/>128

Table 3d. *Serratia* spp. MIC<sub>50/90</sub>

Source (n)	Caz	Cpe	Lvx
Blood (65)	<=8/>8	<=0.5/>0.5	0.12/0.5
Cath/Drain (10)	<=8/>32	<=0.5/4	0.12/0.25
GU (34)	<=8/>8	<=0.5/1	0.12/8
Resp (91)	<=8/>8	<=0.5/>0.5	0.12/1
SSS (55)	<=8/>8	<=0.5/2	0.12/1

Table 3e. *Acinetobacter* spp. MIC<sub>50/90</sub>

Source (n)	Ak	Imp	Lvx	Min	P/T
Blood (90)	4/>64	0.5/>16	0.5/>8	<=0.5/1	2/>128
Cath/Drain (26)	4/>64	0.5/16	0.25/>8	<=0.5/8	16/>128
GI (11)	4/32	0.5/16	4/8	<=0.5/16	16/>128
GU (50)	2/16	0.5/0.5	0.12/8	<=0.5/4	2/128
Resp (103)	4/64	0.5/16	0.25/>8	<=0.5/8	4/>128
SSS (99)	2/32	0.5/2	0.12/8	<=0.5/8	0.12/>128

Table 3f. *Pseudomonas aeruginosa* MIC<sub>50/90</sub>

Source (n)	Caz	Imp	Lvx	P/T
Blood (126)	<=8/16	1/8	1/8	4/64
Cath/Drain (38)	<=8/32	1/>16	0.5/>8	4/128
GI (16)	<=8/32	1/16	0.5/1	4/64
GU (54)	<=8/16	1/8	1/8	4/64