

REVISED ABSTRACT

Background: Tigecycline (TIG), a new glycylicycline, 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 gram positive/negative species. Isolates were collected from 2004 to 2006. **Methods:** A total of 1,252 clinically significant isolates from France were analyzed in this survey. The isolates were identified to the species level at five participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to CLSI (formerly NCCLS) guidelines. **Results:** Selected pathogens tested against tigecycline are shown in the table below:

Organism (n)	Tigecycline		% inhibited at MIC						%S
	MIC ₅₀	MIC ₉₀	≤0.5	1	2	4	8		
<i>Acinetobacter</i> spp. (84)	0.12	0.5	94	98.8	98.8	100			n/a
<i>E. faecalis/faecium</i> (79)	0.12	0.25	100						100
<i>Enterobacteriaceae</i> (493)	0.25	1	81.7	91.1	95.9	99.6	100		95.9
ESBLs (8)	0.25	4	87.5	87.5	87.5	100			87.5
<i>P. aeruginosa</i> (120)	8	>16			0.8	12.5	52.5		n/a
<i>S. aureus</i> (MR)(43)	0.12	0.25	100						100
<i>S. aureus</i> (MS)(90)	0.12	0.12	100						100
<i>S. pneumoniae</i> (69)	0.06	0.25	100						n/a
<i>H. influenzae</i> (78)	0.12	0.5	93.6	94.9	100				n/a

Breakpoints defined by FDA Tygacil[®] Package Insert where applicable.

Conclusion: Tigecycline's MIC₉₀ of 0.25mcg/ml or lower against gram-positive pathogens (including resistant phenotypes) and MIC₉₀ of 1mcg/ml or lower against overall *Enterobacteriaceae* and *Acinetobacter* spp. validate the potent inhibitory activity of TIG against French community/hospital pathogens.

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycylicyclines. This synthetic analogue of the tetracyclines exhibits significant antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as fourfold better than vancomycin and daptomycin [1, 2]. The development of tigecycline is important in that tigecycline and other glycylicyclines are active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. Certain substituents at the 9-position of the tetracycline molecule restore activity against bacteria harboring genes encoding either or both efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible gram-positive, gram-negative, aerobic, and anaerobic bacteria [3].

Previous studies have demonstrated excellent in vitro activity for tigecycline against clinical and laboratory strains of gram-positive and -negative bacteria with minimum inhibitory concentrations for the 90th percentile inhibited at or below 2 mcg/ml, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE), and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [4-6]. This study was undertaken to document the in vitro activity of tigecycline against significant numbers of clinical pathogens collected in French laboratories. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, body fluids, and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested from 2004 to 2006 from 5 study centers in France. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database, were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age, or gender. All sites identified each study isolate utilizing local laboratory criteria.
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [7]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., West Sacramento, CA, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amikacin (0.5-64); amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.5-32, gram-negative panel, and 0.06-16, gram-positive panel); cefepime (0.5-32); ceftriaxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [8] and the recent US Food and Drug Administration package insert for tigecycline [9], where applicable.
- Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftaxone were >1 mcg/ml using broth microdilution panels. ESBL activity was confirmed using the CLSI (2006) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2006) guidelines. ESBL presence was confirmed by testing the following antibiotic disks: ceftazidime (30-mcg), ceftazidime/clavulanic acid (30/10-mcg), ceftazidime (30-mcg), and ceftazidime/clavulanic acid (30/10-mcg). Antimicrobial disks were manufactured by Oxoid, Inc. (Ogdensburg, NY, USA). Mueller-Hinton agar used in testing was manufactured by Remel, Inc. (Lenexa, KS, USA). An organism was interpreted as containing an ESBL if there was an increase of >5 mm in the inhibition zone of the combination disk when compared to that of the cephalosporin alone. *K. pneumoniae* ATCC 700793 was used to QC the ESBL confirmation test. *K. pneumoniae* ATCC 700603 was used to QC the ESBL confirmation tests.
- Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *E. coli* ATCC 25922; *E. coli* ATCC 35218; *H. influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *Pseudomonas aeruginosa* ATCC 27853; *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2006) guidelines [8].

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RESULTS

The results are listed in the following tables.

Table 1. In vitro activity of tigecycline and comparative agents against 493 strains of *Enterobacteriaceae*.^a

Organism Name	Drug	%SUS	%INT	%RES	MIC (mcg/ml)	
					MIC ₅₀	MIC ₉₀
All <i>Enterobacteriaceae</i> (n=493)	Tigecycline	95.9	3.7	0.4	0.25	1
	Amikacin	98	1	2	8	8
	AmoxClav	47.7	6.1	46.2	16	>32
	Ampicillin	15.4	7.1	77.5	>32	>32
	Cefepime	91.5	1.4	7.1	<0.5	4
	Ceftazidime	84	4.1	12	<0.5	32
	Ceftriaxone	84.6	6.7	8.7	<0.06	32
	Imipenem	100	0	0	0.5	1
	Levofloxacin	86.6	2.4	11	0.06	8
	Minocycline	81.1	11.2	7.7	2	8
	PipTazo	84.6	5.9	9.5	1	64
	<i>E. coli</i> (n=148)	Tigecycline	100	0	0	0.12
Amikacin		99.3	0.7	0	2	8
AmoxClav		76.4	9.5	14.2	4	32
Ampicillin		50.7	1.4	48	4	>32
Cefepime		93.2	0.7	6.1	<0.5	<0.5
Ceftazidime		94.6	2	3.4	<0.5	<0.5
Ceftriaxone		93.2	0.7	6.1	<0.06	0.5
Imipenem		100	0	0	0.25	0.5
Levofloxacin		84.5	2.7	12.8	0.03	8
Minocycline		88.5	8.8	2.7	1	8
PipTazo		90.5	2	7.4	1	16
<i>K. pneumoniae</i> (n=94)		Tigecycline	93.6	5.3	1.1	0.5
	Amikacin	96.8	2.1	1.1	1	4
	AmoxClav	76.6	12.8	10.6	2	32
	Ampicillin	0	13.8	86.2	>32	>32
	Cefepime	92.6	1.1	6.4	<0.5	1
	Ceftazidime	92.6	1.1	6.4	<0.5	1
	Ceftriaxone	91.5	1.1	7.4	<0.06	4
	Imipenem	100	0	0	0.5	1
	Levofloxacin	94.7	2.1	3.2	0.06	1
	Minocycline	73.4	8.5	18.1	2	16
	PipTazo	94.7	1.1	4.3	1	8
	<i>K. oxytoca</i> (n=50)	Tigecycline	100	0	0	0.25
Amikacin		98	0	2	2	4
AmoxClav		90	4	6	2	8
Ampicillin		0	12	88	>32	>32
Cefepime		96	0	4	<0.5	1
Ceftazidime		96	4	0	<0.5	1
Ceftriaxone		96	2	2	<0.06	2
Imipenem		100	0	0	0.5	0.5
Levofloxacin		94	2	4	0.06	2
Minocycline		94	2	4	1	4
PipTazo		92	0	8	1	4
ESBL-producing <i>E. coli</i> , <i>Klebsiella</i> spp. (n=8)		Tigecycline	87.5	12.5	0	0.25
	Amikacin	87.5	0	12.5	4	>64
	AmoxClav	37.5	25	37.5	16	32
	Ampicillin	0	0	100	>32	>32
	Cefepime	50	25	25	4	>32
	Ceftazidime	75	12.5	12.5	<0.5	32
	Ceftriaxone	37.5	12.5	60	16	>64
	Imipenem	100	0	0	0.25	0.5
	Levofloxacin	62.5	12.5	25	2	8
	Minocycline	75	12.5	12.5	2	>16
	PipTazo	87.5	0	12.5	4	128
	<i>E. aerogenes</i> (n=39)	Tigecycline	94.9	5.1	0	0.5
Amikacin		100	0	0	2	8
AmoxClav		2.6	2.6	94.9	>32	>32
Ampicillin		0	7.7	92.3	>32	>32
Cefepime		84.6	5.1	10.3	<0.5	32
Ceftazidime		61.5	10.3	28.2	<0.5	>32
Ceftriaxone		76.9	23.1	0	0.25	32
Imipenem		100	0	0	1	2
Levofloxacin		79.5	0	20.5	0.06	>8
Minocycline		82.1	10.3	7.7	2	8
PipTazo		89.7	10.3	0	2	32
<i>E. cloacae</i> (n=105)		Tigecycline	89.5	9.5	1	0.5
	Amikacin	96.2	1	2.9	2	8
	AmoxClav	1.9	0	98.1	>32	>32
	Ampicillin	0	6.7	93.3	>32	>32
	Cefepime	84.8	1.9	13.3	<0.5	32
	Ceftazidime	55.2	9.5	35.2	<0.5	>32
	Ceftriaxone	59	17.1	23.8	2	>64
	Imipenem	100	0	0	0.5	1
	Levofloxacin	76.2	3.8	20	0.06	>8
	Minocycline	70.5	19	10.5	4	16
	PipTazo	80	14.3	25.7	4	128
	<i>S. marcescens</i> (n=51)	Tigecycline	98	2	0	1
Amikacin		98	2	0	2	8
AmoxClav		0	2	98	>32	>32
Ampicillin		0	5.9	94.1	>32	>32
Cefepime		100	0	0	<0.5	<0.5
Ceftazidime		100	0	0	<0.5	<0.5
Ceftriaxone		92.2	5.1	10.3	<0.5	32
Imipenem		100	0	0	0.5	2
Levofloxacin		96.1	2	2	0.12	1
Minocycline		86.3	11.8	2	2	8
PipTazo		88.2	9.8	2	1	32

Table 2. In vitro activity of tigecycline and comparative agents against *Acinetobacter* spp. and *P. aeruginosa*.^a

Organism Name	Drug	%SUS	%INT	%RES	MIC (mcg/ml)		
					MIC ₅₀	MIC ₉₀	
<i>Acinetobacter</i> spp. (n=84)	Tigecycline	na	na	na	0.12	0.5	
	Amikacin	85.7	7.1	7.1	4	32	
	Cefepime	73.8	14.3	11.9	4	32	
	Ceftazidime	77.4	6	16.7	<0.5	>32	
	Ceftriaxone	51.2	35.7	13.1	8	>64	
	Imipenem	97.6	1.2	1.2	0.25	1	
	Levofloxacin	72.6	9.5	17.9	0.25	8	
	Minocycline	98.8	0	1.2	<0.5	2	
	PipTazo	79.8	13.1	1	1	128	
	<i>P. aeruginosa</i> (n=120)	Tigecycline	na	na	na	>16	>16
		Amikacin	96.7	2.5	0.8	4	8
		Cefepime	78.3	12.5	9.2	4	16
Ceftazidime		86.7	4.2	9.2	<0.5	16	
Ceftriaxone		13.3	18.3	68.3	>64	>64	
Imipenem		86.7	5.8	7.5	1	8	
Levofloxacin		60.8	10	29.2	1	>8	
Minocycline		2.5	13.3	84.2	>16	>16	
PipTazo		90	0	10	4	64	

^ana=not available. ^bESBL=extended spectrum beta-lactamase. ^cESBL-producing *E. coli*, *Klebsiella* spp., *E. aerogenes*, *E. cloacae*, *S. marcescens*, *S. pneumoniae* intermediate to penicillin resistant, *S. pneumoniae* resistant to penicillin, *H. influenzae* beta-lactamase positive.

Table 3. In vitro activity of tigecycline and comparative agents against gram-positive pathogens.^a

Organism Name	Drug	%SUS	%INT	%RES	MIC (mcg/ml)	
					MIC ₅₀	MIC ₉₀
<i>S. aureus</i> (MR) (n=43)	Tigecycline	100	0	0	0.12	0.25
	AmoxClav	60.5	0	39.5	4	>8
	Ampicillin	2.3	0	97.7	>16	>16
	Ceftriaxone	11.6	67.4	20.9	16	