

# In Vitro Activity of Tigecycline Against Pathogens From France – T.E.S.T.



OT038

## Program 2004 – 2008

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### Revised Abstract

**Objectives:** Tigecycline (TIG), a new glycylycine, 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 isolates collected from 2004 to 2008. **Methods:** A total of 6,081 clinically significant isolates from France were analyzed in this survey. The isolates were identified to the species level at 61 participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to EUCAST guidelines. **Results:** Selected pathogens tested against tigecycline are shown in the table below:

Organism (n)	Tigecycline		% inhibited at MIC				%S <sup>a</sup>
	MIC <sub>50</sub>	MIC <sub>90</sub>	≤0.5	1	2	4	
<i>Acinetobacter</i> spp. (84)	0.12	0.5	94.0	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
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> (MRSA) (43)	0.12	0.25	100				100
<i>S. aureus</i> (MSSA) (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 EUCAST where applicable.  
**Conclusions:** Tigecycline's MIC<sub>90</sub> of ≤0.25µg/ml against gram-positive pathogens (including resistant phenotypes) and MIC<sub>90</sub> of ≤1µg/ml against overall *Enterobacteriaceae* and *Acinetobacter* spp. validate the potent inhibitory activity of TIG against French community and hospital pathogens.

### Introduction

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycylycines. 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 glycylycines 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]. Furthermore, resistance to tigecycline is difficult to produce even in the laboratory.

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 90<sup>th</sup> percentile inhibited at or below 2 µg/ml, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum β-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 Trial (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 2008 from 61 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 (Siemens Medical Solutions Diagnostics, Inc., West Sacramento, CA, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in µg/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); ceftazidime (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 European Committee for Antimicrobial Susceptibility Testing (EUCAST), where applicable.
- Escherichia coli*, *Klebsiella pneumoniae*, and *K. oxytoca* were screened for ESBL activity when MIC results for ceftazidime were >1 µg/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 (2008) guidelines. ESBL presence was confirmed by testing the following antibiotic disks: ceftotaxime (30-µg), ceftotaxime/clavulanic acid (30/10-µg), ceftazidime (30-µg), and ceftazidime/clavulanic acid (30/10-µg). 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.
- 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 (2008) guidelines [8].

### References

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### Results

Table 1. In vitro activity of tigecycline and comparative agents against 2,442 strains of *Enterobacteriaceae*.

Organism Name	Drug	%S <sup>a</sup>	%NT	%RES	MIC (µg/ml)	
					MIC <sub>50</sub>	MIC <sub>90</sub>
All <i>Enterobacteriaceae</i> (n=2,442)	Tigecycline	91.6	6.2	2.2	0.5	2
	Amikacin	97.4	1.6	1.0	2	4
	AmoxClav	46.6	7.5	45.9	16	>32
	Ampicillin	12.8	0.0	87.2	>32	>32
	Cefepime	85.2	4.4	5.1	>0.5	4
	Ceftazidime	0.0 <sup>b</sup>	83.9	16.1	<8	32
	Ceftioxone	76.5	2.3	21.2	0.12	64
	Imipenem	99.1	0.9	0.0	0.25	1
	Levofloxacin	82.2	2.8	15.0	0.06	8
	Meropenem	99.4	0.4	0.2	<0.06	0.12
	Minocycline	79.4	11.7	8.9	2	8
PipTazo	84.6	2.0	8.4	2	64	
Vancomycin	100.0	0.0	0.0	<0.12	0.5	
<i>E. coli</i> (n=732)	Tigecycline	99.7	0.3	0.0	0.12	0.5
	Amikacin	97.7	1.8	0.5	2	4
	AmoxClav	73.5	13.9	12.6	8	32
	Ampicillin	42.2	0.0	99.1	>32	>32
	Cefepime	90.8	4.0	5.2	>0.5	1
	Ceftazidime	0.0 <sup>b</sup>	95.4	4.6	<8	<8
	Ceftioxone	90.2	0.7	9.2	<0.06	1
	Imipenem	100.0	0.0	0.0	0.25	0.5
	Levofloxacin	81.4	0.7	17.9	0.03	>8
	Meropenem	100.0	0.0	0.0	<0.06	<0.06
	Minocycline	81.4	9.8	8.7	1	8
PipTazo	91.6	2.5	6.0	1	8	
Vancomycin	100.0	0.0	0.0	<0.12	0.5	
<i>K. pneumoniae</i> (n=453)	Tigecycline	87.6	8.8	3.5	0.5	2
	Amikacin	97.1	1.5	1.3	1	4
	AmoxClav	81.2	10.4	8.4	>2	>16
	Ampicillin	0.9	0.0	99.1	>32	>32
	Cefepime	87.9	4.4	7.7	>0.5	2
	Ceftazidime	0.0 <sup>b</sup>	89.4	10.6	<8	16
	Ceftioxone	84.3	2.4	13.2	<0.06	16
	Imipenem	99.5	0.5	0.0	0.25	0.5
	Levofloxacin	88.5	2.0	9.5	0.06	2
	Meropenem	100.0	0.0	0.0	<0.06	<0.06
	Minocycline	75.7	8.6	15.7	2	16
PipTazo	82.8	4.0	2	2	64	
Vancomycin	100.0	0.0	0.0	<0.12	0.5	
<i>K. ornithina</i> (n=255)	Tigecycline	96.1	3.1	0.8	0.25	1
	Amikacin	99.2	0.0	0.8	2	4
	AmoxClav	84.3	7.1	8.6	2	>16
	Ampicillin	0.4	0.0	99.6	>32	>32
	Cefepime	90.6	7.5	2.0	>0.5	1
	Ceftazidime	0.0 <sup>b</sup>	97.3	2.7	<8	<8
	Ceftioxone	86.3	2.0	11.8	<0.06	4
	Imipenem	100.0	0.0	0.0	0.25	0.5
	Levofloxacin	92.2	2.7	5.1	0.03	1
	Meropenem	98.7	0.7	0.7	<0.06	<0.06
	Minocycline	85.6	5.1	3.1	1	4
PipTazo	88.6	0.4	11.0	1	128	
Vancomycin	100.0	0.0	0.0	<0.12	0.5	
ESBL-producing <i>E. coli</i> , <i>Klebsiella</i> spp. (n=102)	Tigecycline	85.3	10.8	3.9	0.5	2
	Amikacin	80.4	11.8	7.8	4	16
	AmoxClav	26.5	39.2	34.3	16	32
	Ampicillin	0.0	0.0	100.0	>32	>32
	Cefepime	9.8	26.5	63.7	32	>32
	Ceftazidime	0.0 <sup>b</sup>	37.3	62.7	32	>32
	Ceftioxone	2.0	3.9	94.1	>64	>64
	Imipenem	97.4	2.6	0.0	0.25	0.5
	Levofloxacin	33.3	5.9	60.8	8	>8
	Meropenem	100.0	0.0	0.0	<0.06	0.12
	Minocycline	47.1	16.7	36.3	8	>16
PipTazo	58.2	11.8	21.6	8	>128	
Vancomycin	100.0	0.0	0.0	<0.12	0.5	
<i>E. aerogenes</i> (n=184)	Tigecycline	86.4	12.0	1.6	0.5	2
	Amikacin	92.9	5.4	1.6	2	8
	AmoxClav	27.7	2.7	94.6	>32	>32
	Ampicillin	0.0	0.0	100.0	>32	>32
	Cefepime	83.2	11.4	5.4	>0.5	4
	Ceftazidime	0.0	99.2	40.8	<8	>32
	Ceftioxone	57.7	7.1	40.2	1	32
	Imipenem	97.5	2.5	0.0	0.5	1
	Levofloxacin	72.8	0.5	26.5	0.06	>8
	Meropenem	98.1	1.9	0.0	<0.06	0.12
	Minocycline	79.9	13.0	7.1	2	8
PipTazo	77.8	21.7	5.4	8	64	
Vancomycin	100.0	0.0	0.0	<0.12	0.5	
<i>E. cloacae</i> (n=223)	Tigecycline	86.4	8.2	5.4	0.5	2
	Amikacin	97.5	1.5	1.0	2	4
	AmoxClav	0.8	1.3	97.9	>32	>32
	Ampicillin	0.4	0.0	99.6	>32	>32
	Cefepime	69.2	24.3	6.5	>0.5	8
	Ceftazidime	0.0	58.3	41.7	<8	>32
	Ceftioxone	51.4	2.1	46.5	1	>64
	Imipenem	99.1	0.9	0.0	0.5	1
	Levofloxacin	72.7	5.2	22.2	0.06	>8
	Meropenem	99.7	0.0	0.3	<0.06	0.25
	Minocycline	72.3	18.5	9.2	4	8
PipTazo	63.7	14.9	27.4	4	>128	
Vancomycin	100.0	0.0	0.0	<0.12	0.5	
<i>S. aureus</i> (n=281)	Tigecycline	86.1	12.5	1.4	1	2
	Amikacin	97.9	0.4	1.8	2	4
	AmoxClav	1.1	1.4	97.5	>32	>32
	Ampicillin	0.0	0.0	100.0	>32	>32
	Cefepime	96.4	2.8	0.7	>0.5	>0.5
	Ceftazidime	0.0	96.8	3.2	<8	<8
	Ceftioxone	81.9	3.6	14.6	0.25	8
	Imipenem	96.6	1.4	0.0	0.5	1
	Levofloxacin	88.3	6.8	5.0	0.12	2
	Meropenem	98.2	1.2	0.6	<0.06	0.12
	Minocycline	82.6	13.5	3.9	4	8
PipTazo	82.5	6.6	1.1	2	16	
Vancomycin	100.0	0.0	0.0	<0.12	0.5	

\* Interpretive criteria as defined by EUCAST, 2008-06/19 (v2.2), where applicable; if no EUCAST criteria available, CLSI shown.

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

Organism Name	Drug	%S <sup>a</sup>	%NT	%RES	MIC (µg/ml)	
					MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Acinetobacter</i> spp. (n=422)	Tigecycline	na	na	na	1	2
	Amikacin	81.8	4.5	13.7	2	32
	Cefepime	74.9	10.9	14.2	4	32
	Ceftazidime	70.4	6.2	23.5	<8	>32
	Ceftioxone	46.0	30.8	23.2	16	>64
	Imipenem	97.3	1.6	1.1	0.5	1
	Levofloxacin	99.0	4.0	37.0	0.25	8
	Meropenem	86.4	5.5	8.1	1	4
	Minocycline	91.5	6.2	2.4	>0.5	4