

# Antimicrobial Susceptibility of 2,537 Bacteremia Causative Pathogens: Tigecycline Evaluation Surveillance Trial (TEST) in Europe 2004-2006

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## 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 bacterial pathogens isolated from the blood stream, collected in Europe from 2004 to 2006. **Methods:** 3,138 bacteremia pathogens were collected and identified from 2004-2006 at 77 hospitals in 21 countries in Europe. MICs for each strain were determined per EUCAST guidelines at each facility using broth microdilution. **Results:** Tigecycline MICs are recorded in the following table:

Organisms (n=3,138)	Tigecycline MICs (mcg/ml)		
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range
<i>Acinetobacter</i> spp. (n=211)	0.25	1	0.015 - 4
<i>P. aeruginosa</i> (n=249)	8	16	0.5 - >16
<i>Enterobacter</i> spp. (n=399)	0.5	1	0.06 - 8
<i>Enterococcus</i> spp. (n=287)	0.06	0.12	0.015 - 0.25
VREs (n=25)	0.06	0.12	0.015 - 0.12
<i>E. coli</i> (n=644)	0.12	0.25	0.03 - 2
<i>Klebsiella</i> spp. (n=497)	0.5	1	0.12 - 8
ESBLs (n=78)	0.5	2	0.06 - 8
<i>Serratia</i> spp. (n=140)	0.5	1	0.12 - 8
<i>H. influenzae</i> (n=22)	0.12	0.25	0.03 - 1
<i>S. aureus</i> (n=357)	0.12	0.12	0.03 - 0.5
MRSA (n=88)	0.12	0.25	0.03 - 0.5
<i>S. agalactiae</i> (n=91)	0.03	0.12	0.015 - 0.25
<i>S. pneumoniae</i> (n=241)	0.03	0.5	≤0.008 - 0.5

**Conclusion:** Tigecycline showed excellent inhibitory activity against all causative bacteremic pathogens with the exception of *P. aeruginosa*. Tigecycline demonstrated MIC<sub>90</sub> values of 0.5 mcg/ml against gram-positive pathogens (including resistant phenotypes) and MIC<sub>90</sub> values of 2 mcg/ml against the *Enterobacteriaceae* and *Acinetobacter* spp. validate the potent inhibitory activity of TIG against these invasive 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, 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 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<sup>-9</sup> [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 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<sub>90</sub> values of ≤0.5 mcg/ml against methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive organisms [2, 4-6].

The Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program determined the in vitro activity of tigecycline compared to most commonly prescribed broad spectrum antibiotics against gram-positive and gram-negative species collected from 320 hospitals globally from 2004 to 2006. This study was designed to evaluate the in vitro activity of tigecycline against bacteremia pathogens collected from European hospitals.

## MATERIALS & METHODS

- All isolates were derived from blood culture specimens. Only one isolate per patient was accepted.
- Clinical isolates (n=3,138) were collected and tested between January 2004 and January 2006 from 77 sites in 21 European countries (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Norway, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, The Netherlands, and the United Kingdom). Isolates were identified to the species level and tested using broth microdilution at each site by the participating laboratory.
- 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): 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 breakpoints established by EUCAST where applicable [15]. If no EUCAST guidelines were available for a given antibiotic, CLSI breakpoints [12] were used.
- MIC interpretive criteria for tigecycline followed published guidelines established by the FDA where applicable [13].
- 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; *Escherichia coli* ATCC 35218; *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; *Klebsiella pneumoniae* ATCC 700603 and *Pseudomonas aeruginosa* ATCC 27853.
- Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftriaxone 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: cefotaxime (30-mcg), cefotaxime/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.
- 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, USA).

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## ACKNOWLEDGEMENTS

We gratefully acknowledge contributions of the investigators, laboratory personnel and all members of the T.E.S.T. program group. This study was supported by a grant from Wyeth Pharmaceuticals.

Figure 1. The distribution of 3,138 European blood culture isolates by organism type.

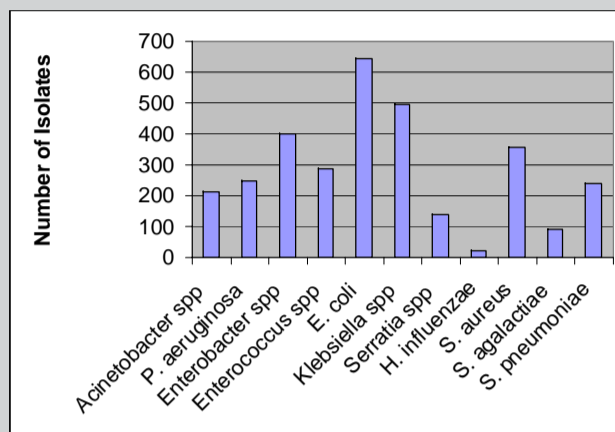


Table 1. The in vitro activity of tigecycline and comparative agents against *Enterobacteriaceae* isolated from European blood specimens.

Organism	Drug	%Sus <sup>a</sup>	MIC (mcg/ml)		
			MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>95</sub>
<i>Enterobacter</i> spp. (n=399)	Tigecycline	90.7	0.5	1	2
	Amikacin	95.7	0.5	1	2
	Amox/Clav	1.5	>32	>32	>32
	Ampicillin	0	>32	>32	>32
	Cefepime	71.7	0.5	>64	>64
	Ceftriaxone	57.1	0.5	>64	>64
	Imipenem	99	0.5	1	2
	Levofloxacin	82	0.06	8	16
	Minocycline	83.5	2	8	16
	PipTazo	69.4	2	128	256
<i>E. coli</i> (n=644)	Tigecycline	99.8	0.12	0.25	0.5
	Amikacin	99.1	2	4	8
	Amox/Clav	75.5	4	16	32
	Ampicillin	42.4	>32	>32	>32
	Cefepime	91.9	0.5	1	2
	Ceftriaxone	91.3	0.06	0.5	1
	Imipenem	100	0.03	0.5	1
	Levofloxacin	77.2	0.03	>8	>8
	Minocycline	82.5	1	8	16
	PipTazo	94.7	1	8	16
<i>Klebsiella</i> spp. (n=497)	Tigecycline	91.3	0.5	1	2
	Amikacin	95.6	1	8	16
	Amox/Clav	77.1	2	32	64
	Ampicillin	0	>32	>32	>32
	Cefepime	83.9	≤0.5	4	8
	Ceftriaxone	80.7	≤0.06	32	64
	Imipenem	99.4	0.25	0.5	1
	Levofloxacin	86.3	0.12	16	32
	Minocycline	83.1	0.25	8	16
	PipTazo	85.7	2	128	256
All ESBL producers <sup>b</sup> (n=78)	Tigecycline	87.2	0.5	2	4
	Amikacin	79.5	4	16	32
	Amox/Clav	34.6	16	>32	>32
	Ampicillin	1.3	>32	>32	>32
	Cefepime	6.4	8	>32	>32
	Ceftriaxone	1.3	>32	>32	>32
	Imipenem	100	0.5	1	2
	Levofloxacin	38.5	4	>8	>8
	Minocycline	61.5	4	>16	>16
	PipTazo	67.9	8	>128	>128
<i>Serratia</i> spp. (n=140)	Tigecycline	90.7	0.5	1	2
	Amikacin	97.9	2	4	8
	Amox/Clav	2.1	>32	>32	>32
	Ampicillin	2.1	>32	>32	>32
	Cefepime	94.3	0.5	1	2
	Ceftriaxone	76.4	0.25	1	2
	Imipenem	99.3	0.5	1	2
	Levofloxacin	92.9	0.12	1	2
	Minocycline	89.3	2	8	16

<sup>a</sup> Interpretive criteria as defined by EUCAST, where available and CLSI breakpoints, where available, if no EUCAST breakpoints exist.  
<sup>b</sup> ESBL-Extended Spectrum Beta-lactamase producing strain; includes *E. coli*, *K. pneumoniae* and *K. oxytoca*.

## RESULTS

Table 2. The in vitro activity of tigecycline and comparative agents against *Acinetobacter* spp. and *Pseudomonas aeruginosa* isolated from European blood cultures.

Organism	Drug	%Sus <sup>a</sup>	MIC (mcg/ml)			
			MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>95</sub>	
<i>Acinetobacter</i> spp. (n=211)	Tigecycline	na	0.25	1	2	
	Amikacin	70.6	2	>64	>64	
	Cefepime	65.4	4	32	64	
	Ceftriaxone	48.3	1.6	>64	>64	
	Imipenem	78.6	0.5	>16	>16	
	Levofloxacin	61.6	0.25	>8	>8	
	Minocycline	97.2	≤0.5	2	4	
	PipTazo	66.4	1	>128	>128	
	<i>P. aeruginosa</i> (n=249)	Tigecycline	na	8	16	32
		Amikacin	92.8	4	8	16
Cefepime		81.5	4	16	32	
Ceftriaxone		20.5	32	>64	>64	
Imipenem		83	1	8	16	
Levofloxacin		65.1	0.5	>8	>8	
Minocycline		6.8	>16	>16	>16	
PipTazo	92.4	4	64	128		

<sup>a</sup> Interpretive criteria as defined by EUCAST, where available and CLSI breakpoints, where available, if no EUCAST breakpoints exist; na = not available.

Table 3. The in vitro activity of tigecycline and comparative agents against non-fastidious gram-positive pathogens isolated from European blood cultures.

Organism	Drug	%Sus <sup>a</sup>	MIC (mcg/ml)			
			MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>95</sub>	
<i>Staphylococcus aureus</i> (n=88)	Tigecycline	100	0.12	0.25	0.5	
	Amox-Clav	0	>8	>8	>8	
	Ampicillin	0	>16	>16	>16	
	Ceftriaxone	0	>64	>64	>64	
	Imipenem	0	4	>16	>16	
	Levofloxacin	10.2	8	>32	>32	
	Linezolid	100	2	4	8	
	Minocycline	98.9	≤0.25	0.5	1	
	PipTazo	0	>16	>16	>16	
	Vancomycin	100	1	1	1	
<i>Streptococcus pneumoniae</i> (n=269)	Tigecycline	100	0.12	0.12	0.12	
	Amox-Clav	100	0.5	1	1	
	Ampicillin	21.6	4	>16	>16	
	Ceftriaxone	100	2	4	4	
	Imipenem	99.6	≤0.12	0.25	0.25	
	Levofloxacin	98.9	0.12	0.25	0.25	
	Linezolid	100	2	4	4	
	Minocycline	100	≤0.25	≤0.25	≤0.25	
	Pip-Tazo	100	0.5	1	1	
	Vancomycin	100	0.5	1	1	
<i>Enterococcus</i> spp. (n=287)	Tigecycline	100	0.06	0.12	0.12	
	Ampicillin	70.7	1	>16	>16	
	Levofloxacin	47.4	8	>32	>32	
	Linezolid	100	2	2	2	
	Minocycline	100	≤0.25	≤0.25	≤0.25	
	Penicillin	17.8	4	>8	>8	
	Pip-Tazo	100	0.5	1	1	
	Vancomycin	100	0.5	1	1	
	<i>S. agalactiae</i> (n=81)	Tigecycline	100	0.03	0.12	0.12
		Ampicillin	100	0.12	0.12	0.12
Levofloxacin		97.8	0.5	1	1	
Linezolid		100	1	1	1	
Minocycline		100	≤0.06	0.12	0.12	
Penicillin		100	≤0.06	0.12	0.12	
PipTazo		100	0.5	0.5	0.5	
<i>S. pneumoniae</i> (n=241)		Tigecycline	100	0.03	0.12	0.12
		Ampicillin	100	0.12	0.12	0.12
		Levofloxacin	97.8	0.5	1	1
	Linezolid	100	1	1	1	
	Minocycline	100	≤0.06	0.12	0.12	
	Penicillin	100	≤0.06	0.12	0.12	
	PipTazo	100	0.5	0.5	0.5	

<sup>a</sup> Interpretive criteria as defined by EUCAST, where available and CLSI breakpoints, where available, if no EUCAST breakpoints exist.  
<sup>b</sup> MIC<sub>90</sub> values based upon cefoxitin 30 mcg disk results; beta-lactam susceptibilities based on methicillin phenotypic.  
<sup>c</sup> Linezolid FDA breakpoints for enterococci are approved for vancomycin-susceptible *E. faecalis* only; susceptibilities for all other enterococci are entered for comparison purposes only. [14]

Table 4. The in vitro activity of tigecycline and comparative agents against fastidious gram-positive pathogens isolated from European blood specimens.

Organism	Drug	%Sus <sup>a</sup>	MIC (mcg/ml)		
			MIC <sub>50</sub>	MIC <sub>90</sub>	MIC