

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) - In Vitro Antibacterial Activity against 3,686 Gram-positive and Gram-negative Pathogens in Europe

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REVISED ABSTRACT

Background: Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent expanded 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 tigecycline compared to amikacin, ampicillin, imipenem, cefepime, ceftazidime, ceftriaxone, levofloxacin, minocycline and piperacillin/tazobactam against Gram-negative strains in addition to linezolid, penicillin and vancomycin for the Gram-positive species. Isolates were collected from 15 hospitals located in Germany, France, Italy, Spain, Hungary, Latvia, Poland, Switzerland, Netherlands and United Kingdom throughout 2004. **Methods:** A total of 3,686 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by the local laboratory using supplied broth microdilution panels from Dade Behring MicroScan and interpreted according to CLSI guidelines. **Results:** Tigecycline's activity was similar to imipenem against most *Enterobacteriaceae*. Tigecycline inhibited ESBL producers with MICs equal or lesser than 4 mcg/mL. Although similar to other classes of broad spectrum antimicrobial agents against glucose non-fermenters, tigecycline was especially active against *Acinetobacter* spp. presenting the lowest MIC₉₀ at 1 mcg/mL. Tigecycline inhibited *S. aureus* with a MIC₉₀ of 0.25 mcg/ml regardless of methicillin susceptibility. Similar results were noticed against enterococci with a tigecycline MIC₉₀ of 0.25 mcg/mL without regard to vancomycin susceptibility. **Conclusion:** Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed antimicrobials against a broad spectrum of aerobic clinical pathogens from a diverse populations. The presented data suggest that tigecycline may be an effective therapeutic option against many aerobic Gram-positive and Gram-negative bacteria, including problematic strains with ESBL, VRE and MRSA resistance phenotypes.

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 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 β -lactamase (ESBL) and AmpC producing strains. [10]. Tigecycline has demonstrated MIC₉₀ values of \leq 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].

This study was designed to better define the in vitro activity of tigecycline in a large diverse population of clinical isolates collected from hospitals across Europe.

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.
- Approximately, 3,686 clinical isolates were collected and tested between January 2004 - December 2004 from 15 study centers in 10 European countries.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring MicroScan, 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 NCCLS where applicable [12]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined as susceptible \leq 2; intermediate = 4; and resistant \geq 8.
- Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution panels.
- Quality control of broth microdilution panels followed manufacture's and NCCLS guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619 and *Pseudomonas 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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Table 1. List of countries and number of investigative sites that contributed to T.E.S.T. program.

Country	Investigative Sites
France	2
Germany	4
Hungary	1
Italy	2
Latvia	1
Poland	1
Spain	1
Switzerland	1
The Netherlands	1
United Kingdom	1
Total	15

Table 2. In vitro activity of tigecycline and comparative agents against 2,015 strains of *Enterobacteriaceae*.

Organism Name*	Drug [†]	MICs (mg/mL)				
		%SUS	%INT	%RES	MIC ₅₀	MIC ₉₀
<i>E. coli</i> (n=215)	Tigecycline	99.5	0.5	0	0.25	1
	Amikacin	74.5	8.1	19.4	2	64
	Amox-Clav	na	na	na	32	>32
	Ampicillin	na	na	na	32	>32
	Cefepime	68.4	14.8	17	8	32
	Ceftazidime	63	9	28	>8	>32
	Ceftriaxone	42.9	20.8	36.3	16	>64
<i>S. aureus</i> (n=20)	Tigecycline	100	0	0	0.12	0.25
	Amikacin	100	0	0	0.12	0.25
	Amox-Clav	na	na	na	16	32
	Ampicillin	na	na	na	16	32
	Cefepime	95	5	0	4	8
	Ceftazidime	95	5	0	4	8
	Ceftriaxone	55	40	5	8	16
<i>A. baumannii</i> (n=150)	Tigecycline	100	0	0	0.12	0.25
	Amikacin	99.6	0.6	2.8	>0.5	4
	Amox-Clav	na	na	na	>0.5	70.5
	Ampicillin	100	0	0	>0.5	70.5
	Cefepime	100	0	0	>0.5	70.5
	Ceftazidime	100	0	0	>0.5	70.5
	Ceftriaxone	100	0	0	>0.5	70.5
<i>P. aeruginosa</i> (n=30)	Tigecycline	100	0	0	0.06	0.25
	Amikacin	100	0	0	0.06	0.25
	Amox-Clav	na	na	na	1	8
	Ampicillin	na	na	na	>2	>32
	Cefepime	59	17.9	23.1	8	32
	Ceftazidime	52.3	11.6	36.1	>8	>32
	Ceftriaxone	23.1	8.8	48.2	32	>64
<i>S. pneumoniae</i> (n=150)	Tigecycline	100	0	0	0.25	0.5
	Amikacin	98.1	0.5	1.4	>0.03	1
	Ampicillin	100	0	0	0.5	1
	Ceftriaxone	98.6	0.8	0.5	>0.03	1
	Imipenem	69	30	1	>0.12	0.25
	Levofloxacin	100	0	0	0.5	1
	Linezolid	100	0	0	>0.5	1
<i>K. pneumoniae</i> (n=25)	Tigecycline	100	0	0	0.12	0.25
	Amikacin	98.8	0.8	0.8	0.5	2
	Amox-Clav	73.2	10.8	14.2	32	>32
	Ampicillin	47	9.1	88.2	>32	>32
	Cefepime	88.8	3.8	8.5	>32	>32
	Ceftazidime	44.3	11	14.6	>8	>32
	Ceftriaxone	61.1	4.3	14.8	>0.06	>64
<i>K. oxytoca</i> (n=16)	Tigecycline	100	0	0	0.12	0.25
	Amikacin	97.4	0.9	1.2	2	4
	Amox-Clav	86.4	6.8	7.8	2	16
	Ampicillin	7.8	19.3	>32	>32	>32
	Cefepime	81.4	2.4	4	>8	4
	Ceftazidime	62.2	1.7	6.1	>8	>8
	Ceftriaxone	61.4	5.1	>0.06	8	8
<i>S. pneumoniae</i> (n=150)	Tigecycline	100	0	0	0.12	0.25
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