

Revised Abstract

Background: Tigecycline was approved for use in Europe in 2006 for complicated skin and soft tissue infections and has demonstrated promising activity against multiply-resistant species and phenotypes. The Tigecycline Evaluation Surveillance Trial (T.E.S.T.) program is an ongoing global surveillance with the first post-marketing prospective report of tigecycline and comparator *in vitro* activity for the years 2004 through 2008. This study evaluates trends in susceptibility of *Acinetobacter* spp. and *Pseudomonas aeruginosa* isolated in Europe during this time period. **Methods:** More than 11,578 clinical isolates were collected from 320 investigative sites in 24 countries in Europe. Clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentrations (MICs) were determined by the local laboratory using supplied broth microdilution panels and interpreted according to EUCAST guidelines. **Results:** Summary data for tigecycline and comparators by year are as follows:

	MIC ₅₀ in mg/L									
	<i>Acinetobacter</i> spp.					<i>Pseudomonas aeruginosa</i>				
n	2004	2005	2006	2007	2008	2004	2005	2006	2007	2008
Tigecycline	1	1	1	1	2	>16	>16	>16	16	16
Amikacin	>64	64	>64	>64	>64	16	16	16	16	16
Amox/Clav	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Ampicillin	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Cefepime	32	32	>32	>32	>32	32	32	32	32	32
Ceftazidime	>32	>32	>32	>32	>32	32	32	>32	32	32
Ceftriaxone	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Levofloxacin	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Meropenem	2	>16	16	16	>16	>16	>16	>16	16	16
Minocycline	8	1	2	2	>16	>16	>16	>16	>16	>16
Pip/Tazo	>128	>128	>128	>128	>128	128	64	128	128	>128

Conclusions: Tigecycline demonstrated no shift in MIC values in Europe over four years from its pre-marketing baseline values when tested against non-fermenters. Consistent MIC₉₀ values against *Acinetobacter* spp., including strains resistant to other drugs, may make it an option when treating infections caused by strains resistant to treatment with other agents.

Introduction

Tigecycline is a novel antimicrobial with an expanded broad-spectrum of activity from a new class of compounds, glycylcyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it is perceived to be bacteriostatic, it 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 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 10⁻⁹ [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]. The MIC₉₀ values for pseudomonad isolates are generally elevated, in the range of 8-16 mg/L due to synergism between outer membrane impermeability and efflux mechanisms [10]. However, tigecycline has been shown to be active against multi-drug resistant *Acinetobacter* spp. [5].

This study prospectively compared the *in vitro* activity of tigecycline with comparative antimicrobial agents against *Acinetobacter* spp. and *P. aeruginosa* from 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.
- Clinical isolates were collected tested between January 2004 and December 2008 from 320 study centers in Europe.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring, Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mg/L): piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftriaxone (0.06-64); cefepime (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 defined by EUCAST, where available (<http://www.srga.org/eucastwt/MICTAB/index.html>, 2009); CLSI breakpoints were used where EUCAST not available. [12].
- Isolates were identified to genus and species at each site by the local laboratory. Isolates were tested by the local laboratory.
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922.
- The collection and transporting 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. *In vitro* activity of tigecycline and comparative agents against *P. aeruginosa* year by year (2004-2008).

Organism (n), Year	Drug	MIC (mg/L)			
		MIC ₅₀	MIC ₉₀	Range	%Sus*
<i>P. aeruginosa</i> n= 610 2004	Tigecycline	8	>16	0.06 ->16	na
	Amikacin	4	16	<=0.5 ->64	89.2
	Cefepime	4	32	<=0.5 ->32	73.9
	Ceftazidime	<=8	32	<=8 ->32	76.4
	Ceftriaxone	>64	>64	<=0.06 ->64	14.9
	Imipenem	1	16	0.12 ->16	78.8
	Levofloxacin	1	>8	0.015 ->8	59.5
	Meropenem	8	>16	0.5 ->16	42.9
	Minocycline	>16	>16	<=0.5 ->16	na
	PipTazo	4	128	<=0.06 ->128	77.9
<i>P. aeruginosa</i> n= 364 2005	Tigecycline	8	>16	0.06 ->16	na
	Amikacin	4	16	<=0.5 ->64	88.5
	Cefepime	4	32	<=0.5 ->32	76.1
	Ceftazidime	<=8	32	<=8 ->32	78.8
	Ceftriaxone	32	>64	0.25 ->64	21.4
	Imipenem	1	8	0.25 ->16	85.7
	Levofloxacin	1	>8	<=0.008 ->8	51.6
	Meropenem	1	>16	0.5 ->16	62.5
	Minocycline	>16	>16	<=0.5 ->16	na
	PipTazo	4	64	<=0.06 ->128	79.1
<i>P. aeruginosa</i> n= 794 2006	Tigecycline	8	>16	0.12 ->16	na
	Amikacin	4	16	<=0.5 ->64	87.0
	Cefepime	4	32	<=0.5 ->32	74.8
	Ceftazidime	<=8	>32	<=8 ->32	76.8
	Ceftriaxone	32	>64	0.12 ->64	16.4
	Imipenem	1	8	<=0.06 ->16	84.8
	Levofloxacin	1	>8	<=0.008 ->8	56.3
	Meropenem	1	>16	0.12 ->16	63.4
	Minocycline	>16	>16	<=0.5 ->16	na
	PipTazo	4	128	0.12 ->128	76.8
<i>P. aeruginosa</i> n= 1,124 2007	Tigecycline	8	16	0.12 ->16	na
	Amikacin	4	16	<=0.5 ->64	86.8
	Cefepime	4	32	<=0.5 ->32	79.7
	Ceftazidime	<=8	32	<=8 ->32	77.0
	Ceftriaxone	64	>64	<=0.06 ->64	14.6
	Imipenem	1	16	<=0.06 ->16	80.4
	Levofloxacin	1	>8	<=0.008 ->8	59.1
	Meropenem	1	16	<=0.06 ->16	75.5
	Minocycline	16	>16	<=0.5 ->16	na
	PipTazo	8	128	<=0.06 ->128	75.6
<i>P. aeruginosa</i> n= 502 2008	Tigecycline	8	16	0.06 ->16	na
	Amikacin	4	16	<=0.5 ->64	86.9
	Cefepime	4	32	<=0.5 ->32	74.9
	Ceftazidime	<=8	32	<=8 ->32	71.1
	Ceftriaxone	>64	>64	0.5 ->64	11.4
	Levofloxacin	1	>8	0.03 ->8	54.4
	Meropenem	1	16	<=0.06 ->16	74.1
	Minocycline	16	>16	1 ->16	na
	PipTazo	8	>128	<=0.06 ->128	73.1

*Breakpoints as defined by EUCAST, where available, 2009; CLSI breakpoints were used where EUCAST not available.
 *na = not available; breakpoints not defined.

Table 2. *In vitro* activity of tigecycline and comparative agents against *Acinetobacter* spp year by year (2004-2008).

Organism (n), Year	Drug	MIC (mg/L)			
		MIC ₅₀	MIC ₉₀	Range	%Sus
<i>Acinetobacter</i> spp n= 455 2004	Tigecycline	0.25	1	<=0.008 - 4	na
	Amikacin	4	>64	<=0.5 ->64	69.0
	Cefepime	8	32	<=0.5 ->32	58.7
	Ceftazidime	<=8	>32	<=8 ->32	56.0
	Ceftriaxone	16	>64	<=0.06 ->64	40.9
	Imipenem	0.5	>16	<=0.06 ->16	81.4
	Levofloxacin	1	>8	0.015 ->8	53.2
	Meropenem	0.12	2	<=0.06 - 2	100.0
	Minocycline	<=0.5	8	<=0.5 ->16	89.9
	PipTazo	4	>128	<=0.06 ->128	61.3
<i>Acinetobacter</i> spp n= 233 2005	Tigecycline	0.25	1	0.015 - 4	na
	Amikacin	4	64	<=0.5 ->64	78.5
	Cefepime	4	32	<=0.5 ->32	65.2
	Ceftazidime	<=8	>32	<=8 ->32	61.8
	Ceftriaxone	16	>64	0.5 ->64	46.4
	Imipenem	0.5	4	<=0.06 ->16	87.4
	Levofloxacin	0.25	>8	0.015 ->8	58.8
	Meropenem	16	>16	0.25 ->16	9.1
	Minocycline	<=0.5	1	<=0.5 - 8	96.6
	PipTazo	1	>128	<=0.06 ->128	69.1
<i>Acinetobacter</i> spp n= 559 2006	Tigecycline	0.25	1	0.015 - 8	na
	Amikacin	2	>64	<=0.5 ->64	73.2
	Cefepime	8	>32	<=0.5 ->32	59.7
	Ceftazidime	<=8	>32	<=8 ->32	58.1
	Ceftriaxone	16	>64	<=0.06 ->64	37.6
	Imipenem	1	8	<=0.06 ->16	81.2
	Levofloxacin	0.25	>8	0.015 ->8	58.1
	Meropenem	2	16	<=0.06 ->16	57.9
	Minocycline	<=0.5	2	<=0.5 ->16	97.0
	PipTazo	8	>128	<=0.06 ->128	64.8
<i>Acinetobacter</i> spp n= 760 2007	Tigecycline	0.25	1	<=0.008 - 16	na
	Amikacin	4	>64	<=0.5 ->64	71.1
	Cefepime	8	>32	<=0.5 ->32	62.8
	Ceftazidime	<=8	>32	<=8 ->32	53.8
	Ceftriaxone	16	>64	<=0.06 ->64	35.9
	Imipenem	0.5	1	<=0.06 ->16	96.7
	Levofloxacin	0.5	>8	<=0.008 ->8	55.9
	Meropenem	1	16	<=0.06 ->16	72.2
	Minocycline	<=0.5	4	<=0.5 ->16	95.8
	PipTazo	16	>128	<=0.06 ->128	57.6
<i>Acinetobacter</i> spp n= 388 2008	Tigecycline	0.25	2	<=0.008 - 8	na
	Amikacin	4	>64	<=0.5 ->64	62.1
	Cefepime	8	>32	<=0.5 ->32	58.5
	Ceftazidime	<=8	>32	<=8 ->32	52.8
	Ceftriaxone	16	>64	<=0.06 ->64	33.5
	Levofloxacin	1	>8	0.015 ->8	50.3
	Meropenem	1	>16	<=0.06 ->16	66.8
	Minocycline	<=0.5	8	<=0.5 ->16	89.2
	PipTazo	16	>128	<=0.06 ->128	51.8

*Breakpoints as defined by EUCAST, where available, 2009; CLSI breakpoints were used where EUCAST not available.
 *na = not available; breakpoints not defined.

Conclusions

- Tigecycline inhibited 83.8 % of *Acinetobacter* spp. tested *in vitro* at a MIC₉₀ of 1 mg/L.
- Tigecycline's MIC₉₀ of 1 mg/L against *Acinetobacter* spp. was the lowest among all broad spectrum antimicrobials tested.
- Tigecycline's limited activity against *P. aeruginosa* is similar to tetracyclines and their analog derivatives.
- Meropenem a member of the carbapenem family show variable susceptibility against *Acinetobacter* spp. and *Pseudomonas aeruginosa* from *Enterobacteriaceae* family.

Figure 1. MIC₅₀ and MIC₉₀ of tigecycline and comparative agents against *P. aeruginosa* (2004-2008).

