

Changes in Susceptibility of Select Non-Fermenters in Europe: 2004-2008

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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 multiple-resistant species and phenotypes. The Tigecycline European Surveillance Trial is an ongoing 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:** 7968 clinical isolates were collected from 426 cumulative investigative sites in 26 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 ₉₀ in mcg/ml									
	<i>Acinetobacter</i> spp.					<i>Pseudomonas aeruginosa</i>				
	2004	2005	2006	2007	2008	2004	2005	2006	2007	2008
n	457	265	580	800	1161	613	414	821	1191	1666
Tigecycline	1	1	1	1	2	>16	>16	>16	16	16
Amikacin	>64	64	>64	>64	>64	16	16	16	16	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	*	*	16	>16	>16	*	*	>16	16	16
Minocycline	8	2	2	4	8	>16	>16	>16	>16	>16
PipTazo	>128	>128	>128	>128	>128	128	128	128	128	>128

*Less than 20 isolates.

Conclusions: Tigecycline demonstrated a one dilution higher shift in MIC₉₀ values against *Acinetobacter* from Europe over five years compared to its pre-marketing baseline. The activity of tigecycline against this important pathogen, including strains resistant to other drugs, may make it an option when treating infections caused by strains resistant to treatment with other agents. Tigecycline has no appreciable activity against *P. aeruginosa*.

Introduction

Tigecycline, an extended-spectrum glycolcyclycline, has been in clinical use in Europe since 2006. The Tigecycline Evaluation Surveillance Trial (TEST), a global surveillance study, and the Tigecycline European Surveillance Trial have monitored the *in vitro* activity of tigecycline and comparator agents since 2004. Tigecycline's spectrum of *in vitro* activity includes aerobic and anaerobic gram-negative and gram-positive bacteria, including antibiotic resistant strains, such as vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, extended-spectrum beta-lactamase producing members of the *Enterobacteriaceae*, and multidrug-resistant *Acinetobacter* spp. [1-5]. While tigecycline was designed to avert resistance due to tetracycline efflux pumps and ribosomal protective features [6-8], the MIC₉₀ values for *Pseudomonas aeruginosa* isolates are generally in the range of 8-16 mcg/ml, seemingly due to chromosomally encoded multidrug efflux pumps [9,10]. However, tigecycline has been shown to be highly active *in vitro* against multi-drug resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections [11-13].

This study evaluates the *in vitro* activity of tigecycline and 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, body fluids, and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested between 2004 and 2008 from 426 cumulative study centers in 26 European countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, The Netherlands, Turkey, and United Kingdom).
- 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.
- MIC interpretive criteria followed published breakpoints established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST) where applicable [14]; if no EUCAST guidelines were available for a given antimicrobial, Clinical and Laboratory Standards Institute (CLSI) breakpoints [15] were used.
- Minimum inhibitory concentrations were determined by the CLSI recommended broth microdilution testing method. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers, MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) or Trek (TREK Diagnostic Systems, Cleveland, OH, 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); cefepime (0.5-32); ceftriaxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16); levofloxacin (0.008-8); meropenem (0.06-16); minocycline (0.5-16); tigecycline (0.008-16); piperacillin/tazobactam (0.06/4-128/4).
- Quality controls (QC) were performed by each testing site on each day of testing using the following ATCC control strains: *E. coli* ATCC 25922, *E. coli* ATCC 35218, and *Pseudomonas aeruginosa* ATCC 27853. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2009) guidelines [15].

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Results

Figure 1. Geographic distribution of *Acinetobacter* spp. and *P. aeruginosa* from Europe 2004 to 2008

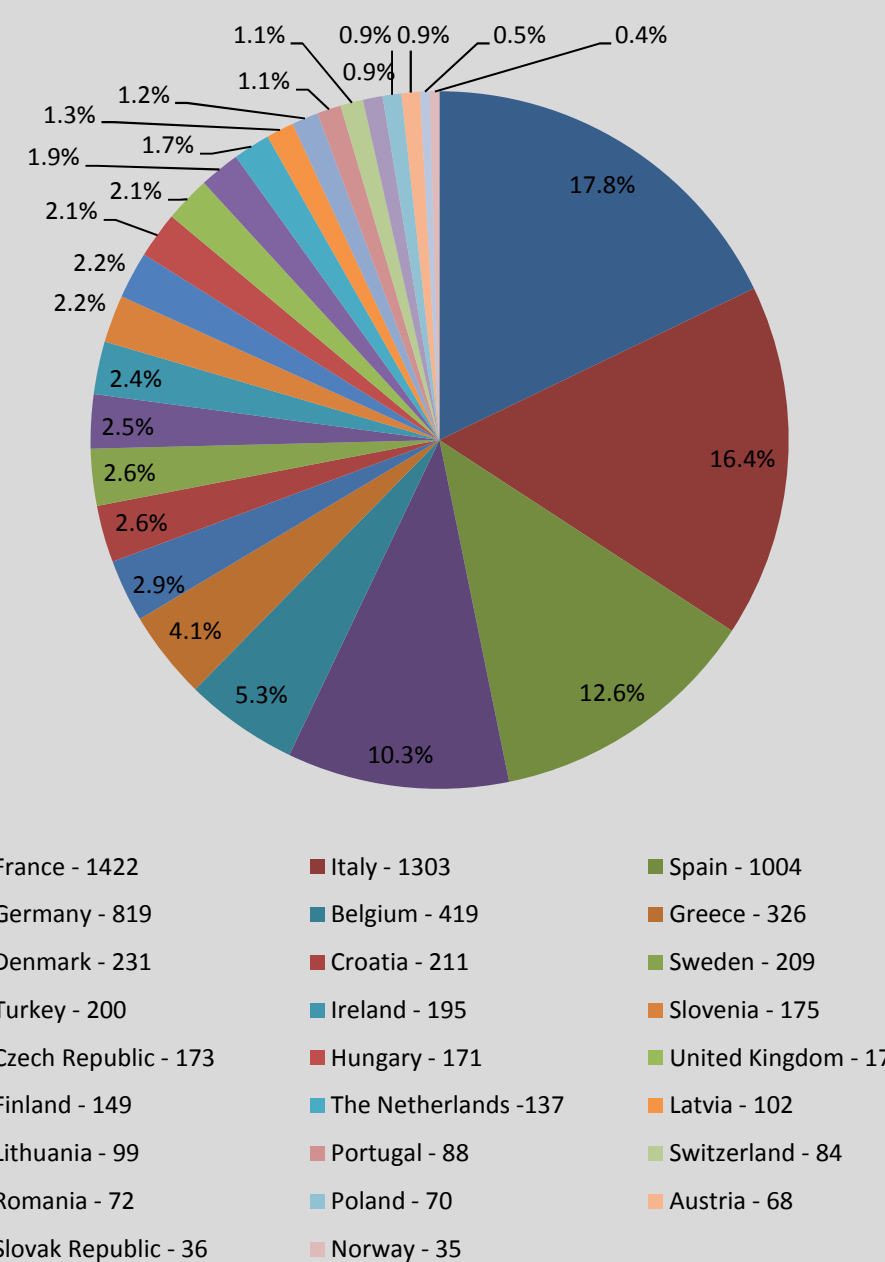


Table 1. Species distribution of 3,263 *Acinetobacter* spp. isolates from Europe (2004 – 2008).

Organism	N
<i>Acinetobacter anitratus</i>	20
<i>Acinetobacter baumannii</i>	2811
<i>Acinetobacter calcoaceticus</i>	11
<i>Acinetobacter haemolyticus</i>	14
<i>Acinetobacter johnsonii</i>	11
<i>Acinetobacter junii</i>	38
<i>Acinetobacter lwoffii</i>	288
<i>Acinetobacter</i> , non-specified	70

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

n, Year	Drug	MIC (mcg/ml)			%Sus*
		MIC ₅₀	MIC ₉₀	Range	
n= 457 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
	Levofloxacin	1	>8	0.015 - >8	53.2
	Meropenem	*	*	≤0.06 - 2	100
	Minocycline	≤0.5	8	≤0.5 - >16	89.9
	PipTazo	4	>128	≤0.06 - >128	61.3
n= 265 2005	Tigecycline	0.25	1	0.015 - 4	na
	Amikacin	4	64	≤0.5 - >64	78.5
	Cefepime	8	32	≤0.5 - >32	57.4
	Ceftazidime	≤8	>32	≤8 - >32	54.3
	Ceftriaxone	16	>64	0.5 - >64	40.8
	Levofloxacin	0.25	>8	0.015 - >8	58.8
	Meropenem	*	*	0.25 - >16	14.3
	Minocycline	≤0.5	2	≤0.5 - 16	95.8
	PipTazo	8	>128	≤0.06 - >128	60.8
n= 580 2006	Tigecycline	0.25	1	0.015 - 8	na
	Amikacin	2	>64	≤0.5 - >64	71.4
	Cefepime	8	>32	≤0.5 - >32	57.8
	Ceftazidime	≤8	>32	≤8 - >32	56.0
	Ceftriaxone	16	>64	≤0.06 - >64	36.4
	Levofloxacin	0.25	>8	0.015 - >8	56.2
	Meropenem	2	16	≤0.06 - >16	57.4
	Minocycline	≤0.5	2	≤0.5 - >16	97.0
	PipTazo	8	>128	≤0.06 - >128	62.8
n= 800 2007	Tigecycline	0.25	1	≤0.008 - 16	na
	Amikacin	4	>64	≤0.5 - >64	70.5
	Cefepime	8	>32	≤0.5 - >32	62.3
	Ceftazidime	≤8	>32	≤8 - >32	53.4
	Ceftriaxone	16	>64	≤0.06 - >64	35.8
	Levofloxacin	0.5	>8	≤0.008 - >8	55.8
	Meropenem	1	>16	≤0.06 - >16	71.6
	Minocycline	≤0.5	4	≤0.5 - >16	95.8
	PipTazo	16	>128	≤0.06 - >128	57.5
n= 1161 2008	Tigecycline	0.5	2	≤0.008 - 8	na
	Amikacin	8	>64	≤0.5 - >64	58.1
	Cefepime	8	>32	≤0.5 - >32	51.3
	Ceftazidime	16	>32	≤8 - >32	45.7
	Ceftriaxone	64	>64	≤0.06 - >64	27.4
	Levofloxacin	4	>8	≤0.008 - >8	45.4
	Meropenem	1	>16	≤0.06 - >16	59.8
	Minocycline	≤0.5	8	≤0.5 - >16	87.2
	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). * = less than 20 isolates

Table 3. *In vitro* activity of tigecycline and comparative agents against *P. aeruginosa* from Europe by year (2004-2008).

n, Year	Drug	MIC (mcg/ml)			%Sus*
		MIC ₅₀	MIC ₉₀	Range	
n= 613 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
	Levofloxacin	1	>8	0.015 - >8	59.5
	Meropenem	*	*	0.5 - >16	42.9
	PipTazo	4	128	≤0.06 - >128	77.9
	n= 414 2005	Tigecycline	8	>16	0.06 - >16
Amikacin		4	16	≤0.5 - >64	86.5
Cefepime		4	32	≤0.5 - >32	73.9
Ceftazidime		≤8	32	≤8 - >32	79.0
Ceftriaxone		64	>64	0.25 - >64	19.6
Levofloxacin		1	>8	≤0.008 - >8	51.5
Meropenem		*	*	0.5 - >16	63.6
PipTazo		4	128	≤0.06 - >128	77.8
n= 821 2006		Tigecycline	8	>16	≤0.008 - >16
	Amikacin	4	16	≤0.5 - >64	86.2
	Cefepime	4	32	≤0.5 - >32	74.4
	Ceftazidime	≤8	>32	≤8 - >32	76.5
	Ceftriaxone	32	>64	0.12 - >64	16.1
	Levofloxacin	1	>8	≤0.008 - >8	55.8
	Meropenem	1	>16	0.12 - >16	62.2
	PipTazo	4	128	0.12 - >128	76.6
	n= 1,191 2007	Tigecycline	16	16	0.12 - >16
Amikacin		4	16	≤0.5 - >64	87.0
Cefepime		4	32	≤0.5 - >32	79.8
Ceftazidime		≤8	32	≤8 - >32	77.3
Ceftriaxone		64	>64	≤0.06 - >64	15.2
Levofloxacin		1	>8	≤0.008 - >8	59.1
Meropenem		1	16	≤0.06 - >16	76.1
PipTazo		8	128	≤0.06 - >128	75.9
n= 1666 2008		Tigecycline	8	16	0.06 - >16
	Amikacin	4	32	≤0.5 - >64	82.7
	Cefepime	4	32	≤0.5 - >32	71.6
	Ceftazidime	≤8	>32	≤8 - >32	68.6
	Ceftriaxone	>64	>64	≤0.06 - >64	10.3
	Levofloxacin	2	>8	0.03 - >8	49.8
	Meropenem	1	16	≤0.06 - >16	66.3
	PipTazo	8	>128	≤0.06 - >128	65.7

* Breakpoints as defined by EUCAST, where available, 2009; CLSI breakpoints were used where EUCAST not available. na = not available (breakpoints not defined). * = less than 20 isolates

Conclusions

- Tigecycline demonstrated a one dilution higher shift in MIC₉₀ values against *Acinetobacter* spp. from Europe over five years compared to its pre-marketing baseline.
- Tigecycline's MIC₉₀ of ≤2 mcg/ml against *Acinetobacter* spp. for the years 2004 to 2008 was the lowest among all broad spectrum antimicrobials tested.
- Tigecycline's limited activity against *P. aeruginosa* is similar to that of minocycline.
- The *in vitro* activity of tigecycline against *Acinetobacter* spp. in this study suggests that it may be an option for treatment of this serious nosocomial pathogen.