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In vitro Activity of Piperacillin-Tazobactam and Comparators Against *Enterobacteriaceae* from Multiple Infection Sources Encountered in Selected European Countries: TEST Data 2013-2016

IHMA, Inc.
2122 Palmer Drive
Schaumburg, IL 60173 USA
Phone: +1.847.303.5003
Fax: +1.847.303.5601
www.ihmainc.com

D. Hoban[1], M. Renteria[1], D. Sahm[1], M. Hackel[1], H. Leister-Tebbe[2] [1]International Health Management Associates, Inc., Schaumburg, USA [2]Pfizer Inc., Collegeville, PA, USA

Revised Abstract

Background: Infections with species in the family *Enterobacteriaceae* play a significant role in infections in both the community and in hospitals due to their prevalence, diversity and ability to cause a variety of infections. Monitoring of antimicrobial resistance is necessary for effective therapy. Susceptibility data from The Tigecycline European Surveillance Trial (TEST) program was evaluated to monitor the activity of piperacillin-tazobactam and comparative antimicrobial agents against pathogens isolated from multiple infection sources in both in patients and outpatients in ten European countries since 2013.
Methods: Hospital sites in selected European countries collected 29061 *Enterobacteriaceae* isolates from multiple infection sources 2013-2016. MICs were determined locally using supplied micro-broth panels following CLSI guidelines for broth microdilution, and categorical results were interpreted using current EUCAST guidelines.
Results: The *in vitro* activity of piperacillin-tazobactam and comparators against *Enterobacteriaceae* are shown below.

			Drug	%S/MIC$_{90}$			
Enterobacteriaceae	AMK	FEP	CRO	LVX	MEM	TZP	TGC
Spain (6924)	98.6/4	81/16	74.5/>32	74.5/>8	98.4/0.25	82.4/64	92.6/1
Germany (5684)	98.8/4	83.8/8	76.9/>32	83.3/4	99.2/0.12	85.2/32	93.5/1
Italy (5557)	90.4/8	66.9/>32	61.9/>32	63.1/>8	90.1/2	73.5/>128	89.5/2
France (4258)	98.3/4	76.4/32	68.9/>32	80.3/8	99.7/0.12	81.8/32	92.6/1
Belgium (2278)	97.9/4	82.1/8	72.4/>32	77.3/8	98.8/0.12	79.8/64	92.6/1
Portugal (1308)	97.3/8	75.2/32	66.7/>32	70.3/>8	98.7/0.25	73.7/128	90.1/1
Switzerland (999)	99.5/4	89.1/2	80.1/32	88.8/1	100/0.12	89.5/16	96.7/1
United Kingdom (828)	98.6/4	87.8/2	81.6/32	91.3/0.5	99.3/0.12	87/32	94.4/1
Ireland (665)	98.4/4	69.2/32	60.6/>32	75/8	99.3/0.25	75/64	91.4/1
Croatia (560)	95.2/8	62.1/>32	58.4/>32	70.5/>8	97.1/0.25	76.3/128	87/2

AMK=Amikacin, FEP=Cefepime, CRO=Ceftriaxone, LVX=Levofloxacin, MEM=Meropenem, TZP=Piperacillin-Tazobactam, TGC=Tigecycline

Regardless of country, MEM, TGC and AMK were the most active beta-lactams antimicrobials tested against *Enterobacteriaceae*, with an activity > 89%. Italy overall showed the lowest % susceptible for all drugs tested except for CRO that was slightly lower in Ireland. The evolving nature of resistance to both beta-lactams and other classes of drugs underscores the need for continuous and careful surveillance.

Introduction

Enterobacteriaceae species are well-recognized gram-negative bacilli that are common causes of both community and hospital infections. *Escherichia coli* and *Klebsiella pneumoniae* are perhaps the most common *Enterobacteriaceae* species isolated in multiple infection sources but multiple other species are increasingly isolated. Over the past decade there has been a global increase in strains with multiple antibiotic resistance mechanisms in *Enterobacteriaceae* including AmpC beta-lactamase, extended-spectrum beta-lactamase, outer membrane porin alterations, carbapenemase production and efflux pumps. Antimicrobial resistance in *Enterobacteriaceae* species has been shown to vary dramatically depending upon region and country.

This report documents the *in vitro* activity of piperacillin-tazobactam and comparative antibiotics used to treat a variety of infectious processes against *Enterobacteriaceae* isolated in 10 European countries from 2013-2016 during the Tigecycline European Surveillance Trial (TEST) program.

Materials & Methods

- Between 2013 and 2016 multiple hospital sites in France, Germany, Spain, Italy, Belgium, Portugal, Switzerland, United Kingdom, Ireland and Croatia participated in the TEST program. For this report 29061 isolates of *Enterobacteriaceae* were identified to the species level and MICs determined at each participating laboratory using supplied broth microdilution panels. All isolates were derived from multiple infection sources including blood, respiratory tract, genital- urinary tract, intra-abdominal and skin and skin structure infections. Only one isolate per patient was accepted into the study.
- Organism collection, transport, confirmation of organism identification, susceptibility testing, and development and management of a centralized database were coordinated by International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method using MicroScan (Beckman Coulter, West Sacramento, CA) panels [1]. All antimicrobials were supplied by the panel manufacturers.
- MIC interpretive criteria followed EUCAST published guidelines [3]
- Quality control (QC) was performed on each day of testing using appropriate ATCC control strains, following CLSI and manufacturer guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges [2].

Results

Fig 1. Species Distribution of Enterobacteriaceae Isolates collected from selected countries in Europe

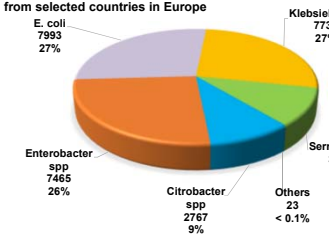
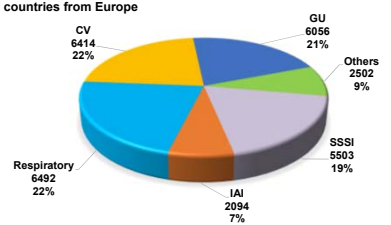


Fig 2. Source Distribution of *Enterobacteriaceae* from selected countries from Europe



* CV: Cardiovascular; IAI: Intra-abdominal Infections; GU: Genitourinary; SSSI: Skin and Skin Structure Infections

Table 1. *In vitro* Activity of Piperacillin -Tazobactam and Comparators vs. *Enterobacteriaceae* by Country

Country	Drug	% S	% I	% R	MIC$_{50}$	MIC$_{90}$	MIC Range
Spain (n=6924)	Tigecycline	92.6	5.0	2.4	0.25	1	0.015 - 8
	Amikacin	98.6	0.9	0.6	2	4	≤0.5 - >64
	Cefepime	81.0	5.7	13.3	≤0.5	16	≤0.5 - >32
	Ceftriaxone	74.5	2.1	23.5	0.12	>32	≤0.06 - >32
	Levofloxacin	74.5	2.5	23.0	0.06	>8	≤0.008 - >8
	Meropenem	98.4	1.0	0.6	≤0.06	0.25	≤0.06 - >16
	Pip-Tazo	82.4	3.4	14.2	2	64	≤0.06 - >128
Germany (n=5684)	Tigecycline	93.5	4.4	2.1	0.25	1	≤0.008 - >8
	Amikacin	98.8	0.7	0.5	2	4	≤0.5 - >64
	Cefepime	83.8	5.8	10.4	≤0.5	8	≤0.5 - >32
	Ceftriaxone	76.9	1.5	21.6	0.12	>32	≤0.06 - >32
	Levofloxacin	83.3	2.5	14.2	0.06	4	≤0.008 - >8
	Meropenem	99.2	0.5	0.4	≤0.06	0.12	≤0.06 - >16
	Pip-Tazo	85.2	3.3	11.5	2	32	≤0.06 - >128
Italy (n=5557)	Tigecycline	89.5	7.2	3.4	0.5	2	≤0.008 - 16
	Amikacin	90.4	5.9	3.7	2	8	≤0.5 - >64
	Cefepime	66.9	6.2	26.9	≤0.5	>32	≤0.5 - >32
	Ceftriaxone	61.9	1.6	36.5	0.25	>32	≤0.06 - >32
	Levofloxacin	63.1	1.8	35.1	0.12	>8	≤0.008 - >8
	Meropenem	90.1	1.4	8.5	≤0.06	2	≤0.06 - >16
	Pip-Tazo	73.5	4.4	22.2	2	>128	≤0.06 - >128
France (n=4258)	Tigecycline	92.6	5.0	2.4	0.25	1	0.03 - >8
	Amikacin	98.3	1.0	0.7	2	4	≤0.5 - >64
	Cefepime	76.4	6.9	16.7	≤0.5	32	≤0.5 - >32
	Ceftriaxone	68.9	1.8	29.4	0.12	>32	≤0.06 - >32
	Levofloxacin	80.3	2.9	16.8	0.06	8	≤0.008 - >8
	Meropenem	99.7	0.1	0.2	≤0.06	0.12	≤0.06 - >16
	Pip-Tazo	81.8	4.8	13.4	2	32	≤0.06 - >128
Belgium (n=2278)	Tigecycline	92.6	5.1	2.3	0.25	1	0.015 - 8
	Amikacin	97.9	1.5	0.6	2	4	≤0.5 - >64
	Cefepime	82.1	6.2	11.7	≤0.5	8	≤0.5 - >32
	Ceftriaxone	72.4	2.9	24.7	0.12	>32	≤0.06 - >32
	Levofloxacin	77.3	2.5	20.2	0.06	8	≤0.008 - >8
	Meropenem	98.8	0.7	0.5	≤0.06	0.12	≤0.06 - >16
	Pip-Tazo	79.8	5.0	15.2	2	64	≤0.06 - >128
Portugal (n=1308)	Tigecycline	90.1	6.1	3.8	0.5	1	≤0.008 - 8
	Amikacin	97.3	2.1	0.7	2	8	≤0.5 - >64
	Cefepime	75.2	6.4	18.5	≤0.5	32	≤0.5 - >32
	Ceftriaxone	66.7	2.1	31.1	0.25	>32	≤0.06 - >32
	Levofloxacin	70.3	4.0	25.7	0.12	>8	≤0.008 - >8
	Meropenem	98.7	0.5	0.8	≤0.06	0.25	≤0.06 - >16
	Pip-Tazo	73.7	7.5	18.8	2	128	≤0.06 - >128
Switzerland (n=999)	Tigecycline	96.7	1.9	1.4	0.25	1	0.03 - 8
	Amikacin	99.5	0.4	0.1	2	4	≤0.5 - 64
	Cefepime	89.1	4.3	6.6	≤0.5	2	≤0.5 - >32
	Ceftriaxone	80.1	1.5	18.4	0.12	32	≤0.06 - >32
	Levofloxacin	88.8	1.4	9.8	0.03	1	≤0.008 - >8
	Meropenem	100	0	0	≤0.06	0.12	≤0.06 - 2
	Pip-Tazo	89.5	2.8	7.7	1	16	0.12 - >128
U. Kingdom (n=828)	Tigecycline	94.4	2.4	3.1	0.25	1	0.03 - >8
	Amikacin	98.6	0.5	1.0	2	4	≤0.5 - >64
	Cefepime	87.8	5.7	6.5	≤0.5	2	≤0.5 - >32
	Ceftriaxone	81.6	2.3	16.1	0.12	32	≤0.06 - >32
	Levofloxacin	91.3	2.3	6.4	0.06	0.5	≤0.008 - >8
	Meropenem	99.3	0.6	0.1	≤0.06	0.12	≤0.06 - >16
	Pip-Tazo	87.0	1.7	11.4	2	32	0.25 - >128
Ireland (n=665)	Tigecycline	91.4	5.0	3.6	0.25	1	0.015 - 8
	Amikacin	98.4	1.1	0.6	2	4	≤0.5 - >64
	Cefepime	69.2	8.7	22.1	≤0.5	32	≤0.5 - >32
	Ceftriaxone	60.6	3.2	36.2	0.25	>32	≤0.06 - >32
	Levofloxacin	75.0	5.1	19.9	0.12	8	≤0.008 - >8
	Meropenem	99.3	0.6	0.2	≤0.06	0.25	≤0.06 - >16
	Pip-Tazo	75.0	7.4	17.6	2	64	≤0.06 - >128
Croatia (n=560)	Tigecycline	87.0	10.7	2.3	0.5	2	0.06 - 8
	Amikacin	95.2	3.9	0.9	2	8	≤0.5 - >64
	Cefepime	62.1	5.7	32.1	≤0.5	>32	≤0.5 - >32
	Ceftriaxone	58.4	1.1	40.5	0.25	>32	≤0.06 - >32
	Levofloxacin	70.5	4.8	24.6	0.12	>8	0.015 - >8
	Meropenem	97.1	2.3	0.5	≤0.06	0.25	≤0.06 - >16
	Pip-Tazo	76.3	5.5	18.2	2	128	0.25 - >128

Conclusions

Infections caused by species of the family *Enterobacteriaceae* present significant treatment challenges due to multiple resistance mechanisms that affect many drug classes. Decreased activities among several agents were observed among *Enterobacteriaceae* isolates collected in 10 European countries in 2013-2016.

Overall tigecycline, meropenem, and amikcacin were the most active agents tested. The *in vitro* activity of studied antimicrobials varied from one European country to another and continued monitoring a country by country basis is warranted.

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