P0329

In vitro Activity of Piperacillin-Tazobactam and Comparators against Enterobacteriaceae and *Pseudomonas aeruginosa* from Multiple Infection Sources Encountered in Selected European Countries: TEST Data 2012-2015

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Revised Abstract

Objectives: Infections with Enterobacteriaceae and *P. aeruginosa* are a major problem in hospitals due to their frequency, high morbidity rate, prolongation of hospital stay and escalating antimicrobial resistance with attendant additional costs. 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 patients in four European countries since 2012. **Methods:** Hospital sites in four European countries collected 22789 *Enterobacteriaceae* isolates and 4825 *P. aeruginosa* isolates from multiple infection sites 2012-2015. MICs were determined locally using 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* and *P. aeruginosa* isolates are shown below.

Enterobacteriaceae	AMK	FEP	CRO	LVX	MEM	TZP	TGC
France (4725)	4/98.1	16/77.6	>32/69.7	8/83.0	0.12/99.7	32/81.5	1/92.5
Germany (5664)	4/98.8	8/84.2	>32/77.1	4/86.0	0.12/99.4	32/85.0	1/93.6
Spain (6744)	4/98.3	16/81.1	>32/75.2	>8/77.0	0.25/98.5	64/83.3	1/93.4
Italy (5656)	16/88.9	>32/65.8	>32/60.4	>8/63.2	4/89.7	>128/72.7	1/90.2
P. aeruginosa	AMK	FEP	CAZ	LVX	MEM	TZP	
France (961)	16/89.9	32/77.8	>16/80.0	>8/63.7	8/74.5	128/77.1	
Germany (1147)	8/95.4	16/85.4	16/88.8	>8/66.1	16/72.8	32/86.0	
Spain (1436)	8/91.6	16/75.5	>16/81.4	>8/56.4	16/68.4	64/79.7	
Italy (1281)	32/84.1	32/69.0	>16/74.2	>8/54.0	>16/64.4	128/71.1	

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

Conclusions: Regardless of country, MEM and TZP were the most active beta-lactams tested against *Enterobacteriaceae*. Against *P. aeruginosa* TZP was more active than MEM and had comparable activity to CAZ and FEP but lower activity than AMK. The propensity of these organisms to develop resistance to any agent underscores the need for continuous and careful surveillance.

Introduction

Enterobacteriaceae species and *Pseudomonas aeruginosa* 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. *P. aeruginosa* are ubiquitous in the environment contaminating water supplies, hot tubs and various solutions and *P. aeruginosa* is found in hospitals where reservoirs for infection can be found in intensive care units and often associated with respiratory equipment. This pathogen commonly infects immunocompromised hosts and burn patients. Over the past decade there has been a global increase in strains with multiple antibiotic resistance mechanisms in both Enterobacteriaceae and *P. aeruginosa* including AmpC beta-lactamase, extended-spectrum beta-lactamase, outer membrane porin alterations, carbapenemase production and efflux pumps. Antimicrobial resistance can vary dramatically depending upon region and country.

This report documents the *in vitro* activity of piperacillin-tazobactam and comparative antibiotics against Enterobacteriaceae and *P. aeruginosa* isolated in four European countries from 2012-2015 during the Tigecycline European Surveillance Trial (TEST) program.

Materials & Methods

- Between 2012 and 2015, 191,179, 237 and 182 cumulative sites France, Germany, Spain and Italy respectively participated in the TEST program. For this report 22789 isolates of Enterobacteriaceae and 4825 isolates of *P. aeruginosa* 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, 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) or TREK (Thermo Fisher Scientific, Oakwood, OH) panels [1,2]. 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

The *in vitro* activity of Piperacillin-Tazobactam and comparators is shown in the following tables (1-8) for both Enterobacteriaceae and *P. aeruginosa* by country.

Table 1. *In vitro* activity of TZP and comparators vs. Enterobacteriaceae in France 2012-2015 (N=4725)

Drug	%S	%I	%R	MIC_{50}	MIC_{90}	Range
AMK	98.1	1.2	0.7	2	4	≤0.5->64
FEP	77.6	7.2	15.2	≤0.5	16	≤0.5->32
CRO	69.7	2.0	28.4	0.12	>32	≤0.06->64
LVX	83.0	2.3	14.7	0.06	8	≤0.008->8
MEM	99.7	0.2	0.1	≤0.06	0.12	≤0.06->16
TZP	81.5	5.1	13.4	2	32	≤0.06->128
TGC	92.5	5.1	2.5	0.25	1	0.03->8

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

Table 2. *In vitro* activity of TZP and comparators vs. Enterobacteriaceae in Germany 2012-2015 (N=5664)

Drug	%S	%I	%R	MIC_{50}	MIC_{90}	Range
AMK	98.8	0.6	0.5	2	4	≤0.5->64
FEP	84.2	5.9	10.0	≤0.5	4	≤0.5->32
CRO	77.1	1.9	21.1	0.12	>32	≤0.06->64
LVX	86.0	1.8	12.2	0.06	4	≤0.008->8
MEM	99.4	0.3	0.3	≤0.06	0.12	≤0.06->16
TZP	85.0	3.6	11.4	2	32	≤0.06->128
TGC	93.6	4.4	2.0	0.25	1	≤0.008-8

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

Table 3. In vitro activity of TZP and comparators vs. Enterobacteriaceae in Spain 2012-2015 (N=6744)

Drug	%S	%I	%R	MIC_{50}	MIC_{90}	Range
AMK	98.3	1.1	0.7	2	4	≤0.5->64
FEP	81.1	6.0	12.8	≤0.5	16	≤0.5->32
CRO	75.2	2.0	22.9	0.12	>32	≤0.06->64
LVX	77.0	2.3	20.7	0.06	0.25	≤0.008->8
MEM	98.5	1.0	0.6	≤0.06	0.25	≤0.06->16
TZP	83.3	3.1	13.6	2	64	≤0.06->128
TGC	93.4	4.4	2.2	0.25	1	≤0.008-8

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

Table 4. *In vitro* activity of TZP and comparators vs. Enterobacteriaceae in Italy 2012-2015 (N=5656)

Drug	%S	%I	%R	MIC_{50}	MIC_{90}	Range
AMK	88.9	6.2	4.8	2	16	≤0.5->64
FEP	65.8	6.6	27.6	≤0.05	>32	≤0.5->32
CRO	60.4	1.6	38.0	0.25	>32	≤0.06->64
LVX	63.2	1.4	35.5	0.12	>8	≤0.008->8
MEM	89.7	1.3	9.0	≤0.06	4	≤0.06->16
TZP	72.7	4.3	23.0	2	>128	≤0.06->128
TGC	90.2	7.0	2.8	0.5	1	≤0.008-16

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

Table 5. *In vitro* activity of TZP and comparators vs. *P. aeruginosa* in France 2012-2015 (N=961)

Drug	%S	%I	%R	MIC_{50}	MIC_{90}	Range
AMK	89.9	4.5	5.6	4	16	≤0.5->64
FEP	77.8	-	22.2	4	32	≤0.5->32
CAZ	80.0	-	20.0	2	>16	≤1->32
LVX	63.7	8.5	27.8	1	>8	0.015->8
MEM	74.5	16.0	9.6	1	8	≤0.06->16
TZP	77.1	-	22.9	4	128	≤0.06->128

AMK=Amikacin, FEP=Cefepime, CAZ=Ceftazidime, LVX=Levofloxacin, MEM=Meropenem, TZP=Piperacillin-Tazobactam

Table 6. *In vitro* activity of TZP and comparators vs. *P. aeruginosa* in Germany 2012-2015 (N=1147)

Drug	%S	%I	%R	MIC_{50}	MIC_{90}	Range
AMK	95.4	2.0	2.6	4	8	≤0.5->64
FEP	85.4	-	14.7	2	16	≤0.5->32
CAZ	88.8	-	11.2	0.5	>8	≤1->16
LVX	66.1	8.7	25.2	0.5	>8	≤0.008->8
MEM	72.8	15.1	12.1	1	16	≤0.06->16
TZP	86.0	-	14.0	4	32	≤0.06->128

AMK=Amikacin, FEP=Cefepime, CAZ=Ceftazidime, LVX=Levofloxacin, MEM=Meropenem, TZP=Piperacillin-Tazobactam

Table 7. *In vitro* activity of TZP and comparators vs. *P. aeruginosa* in Spain 2012-2015 (N=1436)

Drug	%S	%I	%R	MIC_{50}	MIC_{90}	Range
AMK	91.6	3.8	4.5	4	8	≤0.5->64
FEP	75.5	-	24.5	4	16	≤0.5->32
CAZ	81.4	-	18.6	2	>16	≤1->16
LVX	56.4	8.2	35.4	1	>8	0.015->8
MEM	68.4	15.1	16.5	1	16	≤0.06->16
TZP	79.7	-	20.3	4	64	≤0.06->128

AMK=Amikacin, FEP=Cefepime, CAZ=Ceftazidime, LVX=Levofloxacin, MEM=Meropenem, TZP=Piperacillin-Tazobactam

Table 8. *In vitro* activity of TZP and comparators vs. *P. aeruginosa* in Italy 2012-2015 (N=1281)

Drug	%S	%I	%R	MIC_{50}	MIC_{90}	Range
AMK	84.1	5.3	10.6	4	32	≤0.5->64
FEP	68.9	-	31.1	4	32	≤0.5->32
CAZ	74.2	-	25.8	4	>16	≤1->32
LVX	54.0	9.1	36.9	1	>8	≤0.008->8
MEM	64.4	14.8	20.8	1	>16	≤0.06->16
TZP	71.1	-	28.9	8	128	≤0.06->128

AMK=Amikacin, FEP=Cefepime, CAZ=Ceftazidime, LVX=Levofloxacin, MEM=Meropenem, TZP=Piperacillin-Tazobactam

Conclusions

Infections caused by species of the family Enterobacteriaceae and *P. aeruginosa* present significant treatment challenges due to multiple resistance mechanisms that affect many drug classes. Decreased activities among several agents were observed among Enterobacteriaceae isolates and very pronounced in *P. aeruginosa* isolates collected in four European countries in 2012-2015. Meropenem and Piperacillin-Tazobactam were the most active beta-lactam agents against Enterobacteriaceae while Piperacillin-Tazobactam , Meropenem, Ceftazidime and Cefepime demonstrated similar activity against *P. aeruginosa.* The *in vitro* activity of studied antimicrobials varied to varying degrees from one European country to another.

References and Acknowledgments:

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