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Analysis of Activities of Piperacillin-Tazobactam and Comparators Against *Pseudomonas aeruginosa* from Europe: 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], B. Johnson[1], M. Hackel[1], D. Sahm[1], H. Leister-Tebbe[2] [1]International Health Management Associates, Inc., Schaumburg, USA [2]Pfizer Inc., Collegeville, PA, USA

Revised Abstract

Background:
Infections with *P. aeruginosa* present major problems in hospitals due to their frequency, high morbidity and mortality rate, prolongation of hospital stay and escalating antimicrobial resistance with attendant additional costs. Monitoring of antimicrobial resistance is necessary for effective empiric and directed 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 *P. aeruginosa* isolated from multiple infection sources in patients in nine European countries since 2013.
Methods:
Hospital sites in nine European countries collected 5927 *P. aeruginosa* isolates from multiple infection sites 2013-2016. MICs were determined locally using supplied micro-broth panels following CLSI guidelines and categorical results were interpreted using current EUCAST guidelines.
Results:
The *in vitro* activity of piperacillin-tazobactam and comparators against *P. aeruginosa* isolates are shown below.

Country	AMK	FEP	Drug CAZ	%S/MIC$_{90}$ LVX	MEM	TZP
Spain (1455)	92.0/8	75.6/16	81.7/> 16	57.3/> 8	68.3/16	79.0/64
Italy (1232)	87.0/16	70.4/32	75.3/> 16	56.1/> 8	66.6/16	72.4/128
Germany (1133)	94.7/8	83.4/16	86.9/16	65.1/> 8	71.8/16	84.3/64
France (808)	91.5/8	79.1/16	79.8/> 16	65.7/> 8	74.4/16	78.3/128
Belgium (484)	89.9/16	78.3/16	80.0/> 16	64.9/> 8	72.7/16	81.2/64
Portugal (279)	90.3/8	74.2/16	72.0/> 16	49.1/> 8	62.7/> 16	71.0/128
Switzerland (197)	96.5/4	87.3/16	89.9/16	80.7/4	85.8/4	89.3/32
U. Kingdom (188)	95.2/8	84.0/16	84.6/16	79.8/4	83.0/8	84.6/32
Ireland (151)	90.1/8	74.2/32	77.5/> 16	62.9/> 8	68.9/16	80.8/64

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

Conclusions:
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 anti-pseudomonal agent underscores the need for continuous and careful surveillance.

Introduction

Pseudomonas aeruginosa is a well-recognized gram-negative bacillus that is a common cause of both community and hospital infections. *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 *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 *P. aeruginosa* isolated in nine European countries from 2013-2016 during the Tigecycline European Surveillance Trial (TEST) program.

Materials & Methods

- Between 2013 and 2016 hospital sites in nine European countries (Spain, Italy, Germany, France, Belgium, Portugal, Switzerland, United Kingdom and Ireland) participated in the TEST program. For this report 5927 *P. aeruginosa* were identified 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) panels [1]. All antimicrobials were supplied by the panel manufacturers.
- 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 [3].
- MIC interpretive criteria followed EUCAST published guidelines [2].
- Multi-drug resistance (MDR) was defined as resistance to ≥3 drug classes.

Results

Table 1. *In vitro* activity of Piperacillin -Tazobactam and Comparators vs. *P. aeruginosa* by Country

Country	Drug	% S	% I	% R	MIC$_{50}$	MIC$_{90}$	MIC Range
Spain (n=1455)	Amikacin	92.0	3.2	4.7	4	8	≤0.5 - >64
	Cefepime	75.6	0	24.4	4	16	≤0.5 - >32
	Ceftazidime	81.7	0	18.4	2	>16	≤1 - >16
	Levofloxacin	57.3	0	42.7	1	>8	0.015 - >8
	Meropenem	68.3	14.4	17.3	1	16	≤0.06 - >16
	Pip - Tazo	79.0	0	21.0	4	64	≤0.06 - >128
Italy (n=1232)	Amikacin	87.0	4.4	8.6	4	16	≤0.5 - >64
	Cefepime	70.4	0	29.6	4	32	≤0.5 - >32
	Ceftazidime	75.3	0	24.7	2	>16	≤1 - >16
	Levofloxacin	56.1	0	43.9	1	>8	≤0.008 - >8
	Meropenem	66.6	13.4	20.1	1	16	≤0.06 - >16
	Pip - Tazo	72.4	0	27.6	8	128	≤0.06 - >128
Germany (n=1133)	Amikacin	94.7	2.0	3.3	4	8	≤0.5 - >64
	Cefepime	83.4	0	16.6	4	16	≤0.5 - >32
	Ceftazidime	86.9	0	13.2	2	16	≤1 - >16
	Levofloxacin	65.1	0	34.9	0.5	>8	0.015 - >8
	Meropenem	71.8	14.8	13.3	1	16	≤0.06 - >16
	Pip - Tazo	84.3	0	15.7	4	64	0.12 - >128
France (n=808)	Amikacin	91.5	3.5	5.1	4	8	≤0.5 - >64
	Cefepime	79.1	0	20.9	4	16	≤0.5 - >32
	Ceftazidime	79.8	0	20.2	2	>16	≤1 - >16
	Levofloxacin	65.7	0	34.3	1	>8	0.015 - >8
	Meropenem	74.4	15.4	10.3	1	16	≤0.06 - >16
	Pip - Tazo	78.3	0	21.7	4	128	≤0.06 - >128
Belgium (n=484)	Amikacin	89.9	3.7	6.4	4	16	≤0.5 - >64
	Cefepime	78.3	0	21.7	4	16	≤0.5 - >32
	Ceftazidime	80.0	0	20.0	2	>16	≤1 - >16
	Levofloxacin	64.9	0	35.1	1	>8	≤0.008 - >8
	Meropenem	72.7	11.0	16.3	1	16	≤0.06 - >16
	Pip - Tazo	81.2	0	18.8	4	64	0.12 - >128
Portugal (n=279)	Amikacin	90.3	4.7	5.0	4	8	≤0.5 - >64
	Cefepime	74.2	0	25.8	4	16	≤0.5 - >32
	Ceftazidime	72.0	0	28.0	2	>16	≤1 - >16
	Levofloxacin	49.1	0	50.9	2	>8	≤0.008 - >8
	Meropenem	62.7	14.0	23.3	1	>16	≤0.06 - >16
	Pip - Tazo	71.0	0	29.0	8	128	0.25 - >128
Switzerland (n=197)	Amikacin	96.5	2.0	1.5	4	4	≤0.5 - >64
	Cefepime	87.3	0	12.7	2	16	≤0.5 - >32
	Ceftazidime	89.9	0	10.2	2	16	≤1 - >16
	Levofloxacin	80.7	0	19.3	0.5	4	0.03 - >8
	Meropenem	85.8	10.2	4.1	0.5	4	≤0.06 - >16
	Pip - Tazo	89.3	0	10.7	4	32	≤0.06 - >128
U. Kingdom (n=188)	Amikacin	95.2	3.2	1.6	4	8	≤0.5 - >64
	Cefepime	84.0	0	16.0	2	16	≤0.5 - >32
	Ceftazidime	84.6	0	15.4	2	16	≤1 - >16
	Levofloxacin	79.8	0	20.2	0.5	4	0.06 - >8
	Meropenem	83.0	8.5	8.5	0.5	8	≤0.06 - >16
	Pip - Tazo	84.6	0	15.4	4	32	0.25 - >128
Ireland (n=151)	Amikacin	90.1	4.0	6.0	4	8	≤0.5 - >64
	Cefepime	74.2	0	25.8	4	32	≤0.5 - >32
	Ceftazidime	77.5	0	22.5	2	>16	≤1 - >16
	Levofloxacin	62.9	0	37.1	0.5	>8	0.06 - >8
	Meropenem	68.9	11.9	19.2	1	16	≤0.06 - >16
	Pip - Tazo	80.8	0	19.2	4	64	0.12 - >128

Figure 1. MIC Distribution of Cefepime, Ceftazidime, Meropenem and Piperacillin Tazobactam Against *P. aeruginosa*

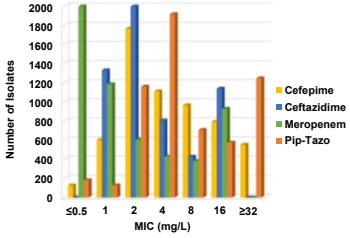

Figure 2. MIC Distribution of Amikacin and Levofloxacin Against *P. aeruginosa*

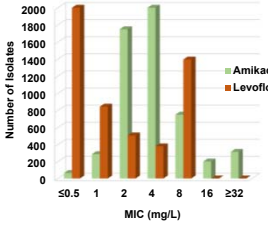

Table 2. *In vitro* activity of Piperacillin -Tazobactam and Comparators vs. Non-MDR and MDR≥3 *P. aeruginosa* by Country

Country	Drug	NON-MDR *P. aeruginosa* % S	NON-MDR *P. aeruginosa* MIC$_{90}$	*MDR≥3 *P. aeruginosa* % S	*MDR≥3 *P. aeruginosa* MIC$_{90}$
Spain	Amikacin	96.4	8	57.3	64
Non-MDR = 1291	Cefepime	85	16	3.1	>32
MDR≥3 = 164	Ceftazidime	90	8	12.2	>16
	Levofloxacin	64	>8	6.7	>8
	Meropenem	76.3	8	4.9	>16
	Pip - Tazo	88	32	7.9	>128
Italy	Amikacin	93.2	8	51.1	64
Non-MDR = 1052	Cefepime	82	16	4.4	>32
MDR≥3 = 180	Ceftazidime	87	16	10.0	>16
	Levofloxacin	65	>8	6.7	>8
	Meropenem	76.9	16	6.1	>16
	Pip - Tazo	82	64	14.4	>128
Germany	Amikacin	98.1	8	55.6	64
Non-MDR = 1043	Cefepime	90	8	3.3	>32
MDR≥3 = 90	Ceftazidime	93	8	11.1	>16
	Levofloxacin	70	8	10.0	>8
	Meropenem	77.8	8	3.3	>16
	Pip - Tazo	91	16	7.8	>128
France	Amikacin	96.7	8	44.4	>64
Non-MDR = 727	Cefepime	87	16	7.4	>32
MDR≥3 = 81	Ceftazidime	87	16	13.6	>16
	Levofloxacin	72	8	9.9	>8
	Meropenem	81.7	8	8.6	>16
	Pip - Tazo	86	32	7.4	>128
Belgium	Amikacin	95.6	8	42.3	>64
Non-MDR = 432	Cefepime	88	16	1.9	>32
MDR≥3 = 52	Ceftazidime	88	16	9.6	>16
	Levofloxacin	71	8	11.5	>8
	Meropenem	81.0	8	3.9	>16
	Pip - Tazo	89	32	13.5	>128

Country	Drug	Non-MDR *P. aeruginosa* % S	Non-MDR *P. aeruginosa* MIC$_{90}$	*MDR≥3 *P. aeruginosa* % S	*MDR≥3 *P. aeruginosa* MIC$_{90}$
Portugal	Amikacin	97.8	8	54.2	32
Non-MDR = 231	Cefepime	87	16	10.4	32
MDR≥3 = 48	Ceftazidime	87	16	2.1	>16
	Levofloxacin	59	>8	0.0	>8
	Meropenem	74.5	16	6.3	>16
	Pip - Tazo	84	64	6.3	>128
Switzerland	Amikacin	98.4	4	33.3	>64
Non-MDR = 191	Cefepime	90	8	0.0	>32
MDR≥3 = 6	Ceftazidime	93	8	0.0	>16
	Levofloxacin	83	2	16.7	>8
	Meropenem	88.0	4	16.7	>16
	Pip - Tazo	92	16	0.0	128
U. Kingdom	Amikacin	97.2	8	60.0	64
Non-MDR = 178	Cefepime	89	16	0.0	>32
MDR≥3 = 10	Ceftazidime	89	16	0.0	>16
	Levofloxacin	81	2	50.0	8
	Meropenem	87.6	4	0.0	>16
	Pip - Tazo	89	32	0.0	>128
Ireland	Amikacin	94	8	61.1	>64
Non-MDR = 133	Cefepime	83	16	5.6	>32
MDR≥3 = 18	Ceftazidime	87	16	5.6	>16
	Levofloxacin	70	>8	11.1	>8
	Meropenem	77.4	16	5.6	>16
	Pip - Tazo	90	16	11.1	>128

MDR≥3 Multi-drug resistance (MDR) was defined as resistance to ≥3 drug classes

Conclusions

- **Infections caused by *P. aeruginosa* present significant treatment challenges due to multiple resistance mechanisms that affect many drug classes.**
- **Decreased activities among several agents were observed among *P. aeruginosa* isolates collected in nine European countries in 2013-2016.**
- **Amikacin was the most active agent tested 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

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