

Revised Abstract

Objective: *Pseudomonas aeruginosa* infections continue to pose a treatment challenge worldwide. The ongoing Tigecycline European Surveillance Trial (TEST), a comprehensive surveillance study, makes possible the evaluation of regional differences in antibiotic susceptibility. In this report, the antimicrobial activity of piperacillin-tazobactam (pip-tazo) and several comparators was evaluated in Eastern European countries. **Methods:** Between 2006 and 2010, 1,351 *P. aeruginosa* isolates from several specimen sources were collected in 11 countries in Eastern Europe. The number of contributing sites per country ranged from 1 (Latvia) to 7 (Bulgaria). MICs were determined by each participating laboratory using commercially-prepared microbroth panels. Results were interpreted according to EUCAST breakpoints. The Fisher exact test was used to determine the statistical significance of differences in % susceptible between the Eastern European average and each individual country. **Results:** Comparing 2006 to 2010, the *in vitro* activity of all five reported antimicrobials was relatively stable with the MIC₅₀ remaining the same or changing by only one dilution; therefore, all *P. aeruginosa* isolates collected during the five-year period were combined. The following table shows the % susceptible (%S) and MIC₅₀ for pip-tazo and four comparators by country and all Eastern European data combined:

	n	Pip-Tazo		Amikacin		Ceftazidime		Levofloxacin		Meropenem	
		%S	MIC ₅₀	%S	MIC ₅₀	%S	MIC ₅₀	%S	MIC ₅₀	%S	MIC ₅₀
Eastern Europe	1351	58.1	16	72.8	4	61.8	≤8	44.4	2	60.1	1
Bulgaria	135	60.7	8	60.0*	4	64.4	≤8	45.9	2	65.9	1
Croatia	191	51.3	16	65.5*	8	55.0	≤8	37.7	2	48.2*	4
Czech Republic	164	70.1*	16	83.5*	4	67.1	≤8	45.7	2	64.2	1
Hungary	155	60.0	16	91.6*	4	63.2	≤8	56.8*	1	66.5	0.5
Latvia	57	64.9	8	84.2	4	63.2	≤8	50.9	1	68.4	1
Lithuania	59	52.5	16	74.6	8	64.4	≤8	37.3	8	61.5	1
Poland	129	54.3	16	57.4*	8	58.9	≤8	44.2	2	54.3	2
Romania	101	35.6*	64	57.4*	8	40.6*	32	31.7*	8	33.7*	16
Slovak Republic	79	60.8	16	76.0	4	65.8	≤8	41.8	4	79.8*	1
Slovenia	140	72.1*	8	83.6*	4	77.1*	≤8	50.7	1	75.7*	1
Turkey	141	52.5	16	69.5	8	59.6	≤8	41.8	2	52.5	2

* %S significantly different from Eastern European average (p<0.05).

Conclusions: Piperacillin-tazobactam exhibited activity similar to that of meropenem and ceftazidime against *P. aeruginosa* in Eastern Europe. Only amikacin demonstrated statistically significantly better *in vitro* susceptibility results than pip-tazo (72.8% vs. 58.1%). Variations in activity for all five antimicrobials existed across countries. Romania (with 3 participating sites) showed the highest MIC₅₀ and lowest % susceptible for all reported drugs. Overall, Slovenia (3 sites) exhibited the highest susceptibility levels. The Czech Republic (3 sites), Hungary (4 sites), and the Slovak Republic (2 sites) also reported susceptibility levels significantly higher than the Eastern European average for at least one of the reported drugs (p<0.05).

Introduction

Pseudomonas aeruginosa is a nosocomial pathogen implicated in serious infections affecting mainly hospitalized patients, individuals with an underlying medical condition, and severely immunocompromised patients. Antimicrobial resistance in *P. aeruginosa* may complicate the treatment of infections and can adversely affect clinical outcomes and patient treatment costs. Increasing resistance rates have greatly limited the number of therapeutic choices. The limited number of efficacious anti-infective drugs for the treatment of multi-drug resistant gram-negative pathogens, especially *P. aeruginosa*, currently represents a serious clinical concern [1]. This report examined regional variations in the activity of piperacillin-tazobactam (pip-tazo) and comparator agents against *P. aeruginosa* in countries of Eastern Europe. The study is part of the Tigecycline European Surveillance Trial (TEST), a comprehensive, ongoing surveillance study.

Materials & Methods

Between 2006 and 2010, 1,351 *P. aeruginosa* isolates were collected in 11 countries in Eastern Europe. The number of contributing sites per country ranged from 1 (Latvia) to 7 (Bulgaria). Isolates were derived from respiratory tract (29%), blood (18%), wounds (15%), bodily fluids (12%), genito-urinary tract (10%), and various other infection sources. Only one isolate per patient was accepted into the study. 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.

Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [2]. Antimicrobial agents were supplied by the panel manufacturers MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) and TREK (TREK Diagnostic Systems, Cleveland, OH).

Quality control (QC) of broth microdilution panels followed manufacturers' and CLSI guidelines using *E. coli* ATCC 25922 and ATCC 35218 as well as *P. aeruginosa* ATCC 27853.

MIC interpretive criteria followed EUCAST guidelines [3].

Linear trends in percent susceptible over time were assessed with the Cochran-Armitage test. The Fisher exact test was used to determine the statistical significance of differences in percent susceptible between the Eastern European average and each individual country as well as between different antimicrobial agents. 95% confidence intervals for percent susceptible were calculated using the adjusted Wald method.

References

- Vidailiac C, Leonard S, Sader H, Jones R, Rybak M. 2009. *In vitro* activity of Ceftazidime alone and in combination against clinical isolates of Enterobacteriaceae and Pseudomonas aeruginosa. *Antimicrob. Agents and Chemother.* 53:2360-2366.
- Clinical Laboratory Standards Institute. 2009. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Eighth Edition. CLSI document M07-A8. Wayne, PA.
- European Committee on Antimicrobial Susceptibility Testing (EUCAST). 2011. *Breakpoint tables for interpretation of MICs and zone diameters, version 1.3*, <http://www.euca.st.org>.

Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline European Surveillance Trial program group. This study was sponsored by Pfizer Inc.

Results

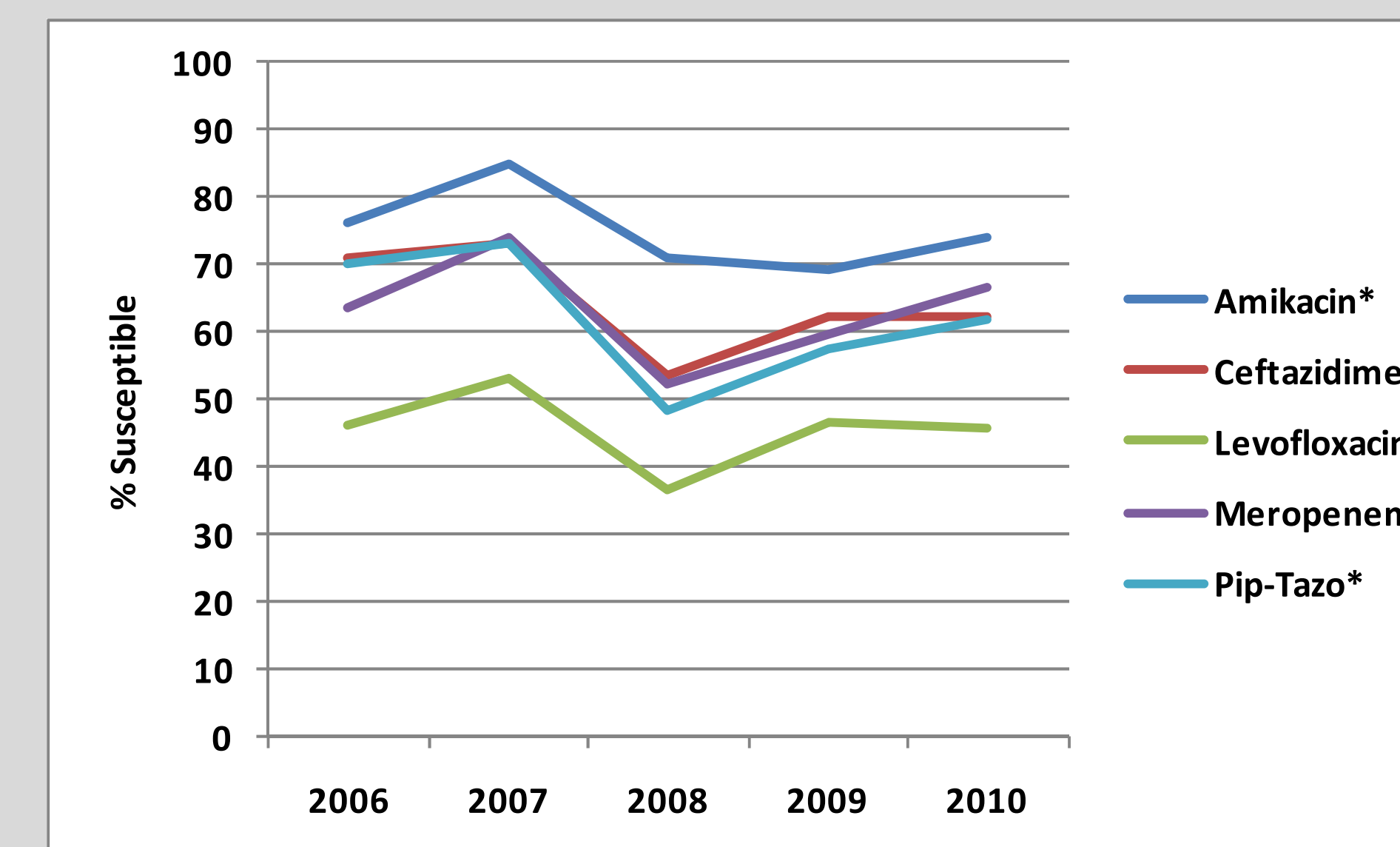
Table 1. MIC₅₀ (mg/L) for *P. aeruginosa* from Eastern Europe, 2006-2010.

	MIC ₅₀				
	2006	2007	2008	2009	2010
Amikacin	8	4	4	4	4
Ceftazidime	≤8	≤8	≤8	≤8	≤8
Levofloxacin	2	1	4	2	2
Meropenem	1	1	2	1	1
Pip-Tazo	8	4	32	16	16
n	100	185	414	537	115

Table 2. MIC_{50/90} (mg/L) of piperacillin-tazobactam and comparators against *P. aeruginosa* in countries of Eastern Europe, 2006-2010.

	n	MIC _{50/90}				
		Pip-Tazo	Amikacin	Ceftazidime	Levofloxacin	Meropenem
Eastern Europe	1351	16/>128	4/64	≤8/>32	2/>8	1/>16
Bulgaria	135	8/128	4/>64	≤8/>32	2/>8	1/16
Croatia	191	16/>128	8/>64	≤8/>32	2/>8	4/>16
Czech Republic	164	16/>128	4/32	≤8/32	2/>8	1/8
Hungary	155	16/>128	4/8	≤8/32	1/>8	0.5/16
Latvia	57	8/128	4/32	≤8/>32	1/>8	1/16
Lithuania	59	16/128	8/16	≤8/32	8/>8	1/16
Poland	129	16/>128	8/>64	≤8/>32	2/>8	2/>16
Romania	101	64/>128	8/>64	32/>32	8/>8	16/>16
Slovak Republic	79	16/>128	4/64	≤8/>32	4/>8	1/8
Slovenia	140	8/128	4/16	≤8/32	1/>8	1/8
Turkey	141	16/>128	8/32	≤8/>32	2/>8	2/>16

Figure 1. Percent susceptible for *P. aeruginosa* from Eastern Europe, 2006-2010.



* p-value for linear trend < 0.05.

Table 3. Percent susceptible of *P. aeruginosa* to piperacillin-tazobactam and comparators in countries of Eastern Europe, 2006-2010.*

	n	%S (95% confidence interval)				
		Pip-Tazo	Amikacin	Ceftazidime	Levofloxacin	Meropenem
Eastern Europe	1351	58.1 (55.5-60.7)	72.8 (70.4-75.1)	61.8 (59.2-64.4)	44.4 (41.8-47.1)	60.1 (57.5-62.7)
Bulgaria	135	60.7 (52.3-68.6)	60.0 (51.6-67.9)	64.4 (56.1-72.0)	45.9 (37.7-54.3)	65.9 (57.6-73.4)
Croatia	191	51.3 (44.3-58.3)	65.4 (58.4-71.8)	55.0 (47.9-61.9)	37.7 (31.1-44.8)	48.2 (41.2-55.2)
Czech Republic	164	70.1 (62.7-76.6)	83.5 (77.1-88.5)	67.1 (59.6-73.8)	45.7 (38.3-53.4)	64.0 (56.4-71.0)
Hungary	155	60.0 (52.1-67.4)	91.6 (86.1-95.1)	63.2 (55.4-70.4)	56.8 (48.9-64.3)	66.5 (58.7-73.4)
Latvia	57	64.9 (51.9-76.0)	84.2 (72.4-91.7)	63.2 (50.2-74.5)	50.9 (38.3-63.4)	68.4 (55.5-79.0)
Lithuania	59	52.5 (40.0-64.7)	74.6 (62.1-84.0)	64.4 (51.6-75.4)	37.3 (26.1-50.1)	61.0 (48.2-72.4)
Poland	129	54.3 (45.7-62.6)	57.4 (48.7-65.6)	58.9 (50.3-67.0)	44.2 (35.9-52.8)	54.3 (45.7-62.6)
Romania	101	35.6 (27.0-45.4)	57.4 (47.7-66.6)	40.6 (31.5-50.4)	31.7 (23.4-41.3)	33.7 (25.2-43.3)
Slovak Republic	79	60.8 (49.7-70.8)	75.9 (65.4-84.1)	65.8 (54.8-75.4)	41.8 (31.5-52.8)	79.7 (69.5-87.2)
Slovenia	140	72.1 (64.2-78.9)	83.6 (76.5-88.9)	77.1 (69.5-83.4)	50.7 (42.5-58.9)	75.7 (68.0-82.1)
Turkey	141	52.5 (44.3-60.5)	69.5 (61.5-76.5)	59.6 (51.3-67.3)	41.8 (34.0-50.1)	52.5 (44.3-60.5)

* Green highlighted results are significantly higher than the European average; red highlighted values are significantly lower (p<0.05).

Conclusions

- Comparing 2006 to 2010, the *in vitro* activity of all five reported antimicrobials was relatively stable with the MIC₅₀ remaining the same or changing by only one dilution. Also, only two of the reported agents (amikacin and piperacillin-tazobactam) showed a slight, statistically significant, decreasing trend in % susceptible between 2006 and 2010 (p<0.05). Therefore, all *P. aeruginosa* isolates collected during the five-year period were combined for the country-to-country comparison.
- Piperacillin-tazobactam exhibited activity similar to that of meropenem and ceftazidime against *P. aeruginosa* in Eastern Europe. Only amikacin demonstrated statistically significantly better *in vitro* susceptibility results than pip-tazo (72.8% vs. 58.1%, p<0.0001).
- Variations in activity for all five antimicrobials existed across countries. Romania (with 3 participating sites) demonstrated the highest MIC₅₀ and lowest % susceptible for all reported drugs. Overall, Slovenia (3 sites) exhibited the highest susceptibility levels for most antimicrobials. The Czech Republic (3 sites), Hungary (4 sites), and the Slovak Republic (2 sites) also reported susceptibility levels significantly higher than the Eastern European average for at least one of the reported drugs (p<0.05).