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Trends in Susceptibility of *P. aeruginosa* to Piperacillin-Tazobactam and Comparators 2004-2009 – Global TEST Analysis

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Revised Abstract

Introduction: Piperacillin-tazobactam (PT) has been a mainstay of therapy for *P. aeruginosa* infections for many years. The Tigecycline Evaluation and Surveillance Trial (TEST) has monitored the *in vitro* activity of PT and several comparators globally vs. *P. aeruginosa* since 2004. This report is a longitudinal analysis of regional susceptibility of *P. aeruginosa* to PT through 2009, and compares that activity to other drugs commonly used to treat infections caused by this species.

Methods: 19,527 isolates of *P. aeruginosa* were collected from a variety of infection sources in Latin America, Europe, Asia/Pacific, and Africa/Middle East from 2004-2009 in 1560 sites. Susceptibility testing was done at each site using broth microdilution panels, and results interpreted using CLSI guidelines. Data were analyzed by global region and year, comparing susceptibility to PT and 5 other drugs (meropenem, amikacin, cefepime, ceftazidime, and levofloxacin).

Results: Global % susceptible for all drugs declined from 2004 to 2009, with the decreases ranging from 1.8% for levofloxacin to 13.4% for ceftazidime; PT activity declined 8.6%, from 88.0 to 79.4%. All declines were significant (p<0.05). Regionally, the biggest decline in PT activity was seen in Asia/Pacific, going from 90.3 to 72.9%.

Conclusions: All drugs declined significantly over the 6 years of this analysis, and none inhibited 90% of isolates in 2009. Although PT activity vs *P. aeruginosa* declined since 2004, it maintained its position as the second-most active drug tested, after amikacin. *P. aeruginosa* continues to pose therapeutic challenges as its susceptibility to most commonly-used antimicrobials diminishes.

Introduction

P. aeruginosa continually represents a therapeutic challenge because of the intrinsic and acquired resistance to many antimicrobial agents, as well as its ability to integrate several mechanisms associated with the suppression of the immune system with the subsequent development of multi-drug resistance. It is one of the most common pathogens of all in patient healthcare-associated infections (HAIs), both localized and systemic. In fact, *P. aeruginosa* is the leading cause of nosocomial infections [1], ranking as the second most common cause of hospital acquired pneumonia, the third most common cause of urinary tract infection, the fourth most common cause of surgical site infection, the seventh most frequently isolated pathogen from the bloodstream, and the fifth most common isolate overall from all sites [2]. It accounts for 8% of the HAIs [3]. The guidelines for the treatment of community-acquired pneumonia, published in 2007 by the Infectious Diseases Society of America and the American Thoracic Society recommended the anti-pseudomonal beta-lactam piperacillin-tazobactam as the first option to treat this severe type of infection with the addition of a quinolone or an aminoglycoside. [4].

Materials & Methods

- A total of 19,527 clinical isolates were collected and tested between January 2004 and December 2009 from1560 cumulative sites around the world. Isolates were identified to the species level and MICs determined at each site by the participating laboratory using supplied broth microdilution panels.
- 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 [5]. MIC interpretive criteria followed published guidelines established by the CLSI [6], where available, and the FDA (tigecycline) [7]. Linear trends over time in percent susceptible were assessed with the Cochran-Armitage Trend Test (two-tailed).
- Quality controls (QC) were performed by each testing site on each day of testing using appropriate ATCC control strains [6]. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2009) guidelines.

References

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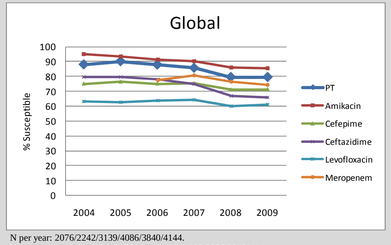
Results

Table 1. Overall percent susceptible and MIC_{90} for PT and comparators against *P. aeruginosa* in all regions 2004-2009.

	%Susceptible/MIC_{90}					
	2004	2005	2006	2007	2008	2009
PT	88.0/128	90.2/64	87.9/128	85.7/128	79.5/>128	79.4*/>128
Amikacin	94.9/8	93.4/16	91.5/16	90.4/16	85.8/32	85.4*/64
Cefepime	75.0/32	76.3/32	75.0/32	75.3/32	71.0/32	71.3*/32
Ceftazidime	79.4/32	79.8/32	78.2/32	75.1/>32	66.7/>32	66.0*/>32
Levofloxacin	63.1/>8	62.8/>8	63.7/>8	64.1/>8	59.8/>8	61.3*/>8
Meropenem	na	na	77.8/16	80.6/16	76.3/16	74.2*/16
n	2076	2242	3139[b]	4086	3840	4144

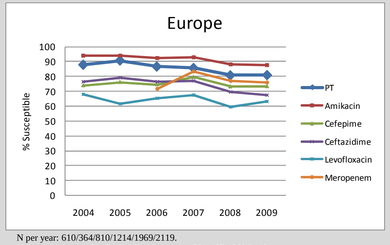
[a]Meropenem was not being tested during this year. No data is available.
[b]Meropenem n=1,205 in 2006, 3,986 in 2007.
*Statistically significant trend in % susceptible (p<0.05, Cochran-Armitage Trend Test, two-tailed)

Figure 1. Susceptibility trends for PT and comparators against *P. aeruginosa* in all global regions 2004-2009.



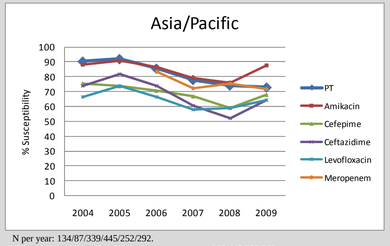
N per year: 2076/2242/3139/4086/3840/4144.
*Meropenem was added in 2006; n per year: 1205/3986/3840/4144.

Figure 2. Susceptibility trends for PT and comparators against *P. aeruginosa* in Europe, 2004-2009.



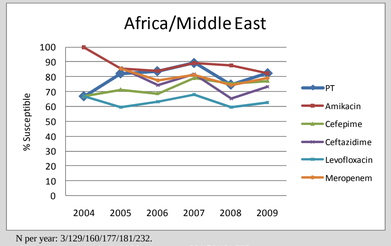
N per year: 610/364/810/1214/1969/2119.
*Meropenem was added in 2006; n per year: 178/1167/1969/2119.

Figure 3. Susceptibility trends for PT and comparators against *P. aeruginosa* in Asia/Pacific, 2004-2009 .



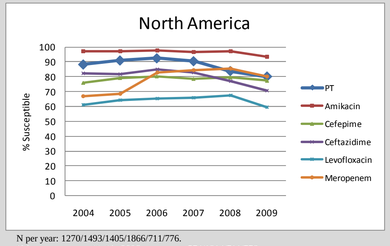
N per year: 134/87/339/445/252/292.
*Meropenem was added in 2006; n for meropenem: 168/445/252/292.

Figure 4. Susceptibility trends for PT and comparators against *P. aeruginosa* in Africa/Middle East, 2004-2009.



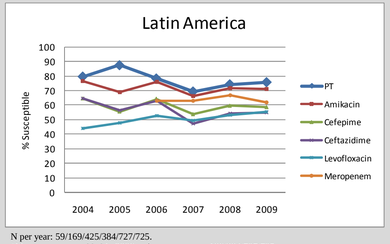
N per year: 3/129/160/177/181/232.
*Meropenem was added in 2006; n per year: 99/176/181/232.

Figure 5. Susceptibility trends for PT and comparators against *P. aeruginosa* in North America 2004-2009.



N per year: 1270/1493/1405/1866/711/776.
*Meropenem was added in 2006; n per year: 574/1814/711/776.

Figure 6. Susceptibility trends for PT and comparators against *P. aeruginosa* in Latin America 2004-2009.



N per year: 59/169/425/384/727/725.
*Meropenem was added in 2006; n for meropenem: 186/384/727/725.

Conclusions

- All drugs in this study had significant decreases in their in vitro susceptibility against *P. aeruginosa* over the 6 years of this analysis (p<0.05). Amikacin and piperacillin-tazobactam were the most active antimicrobial agents in vitro, inhibiting 85.4% and 79.4%, respectively, of this species in 2009 at their CLSI breakpoints.
- From year to year and region to region piperacillin-tazobactam had consistently better *in vitro* results than meropenem, ceftazidime, cefepime and levofloxacin. Piperacillin-tazobactam continues to exhibit potent *in vitro* activity against *P. aeruginosa* after a decade and a half of clinical use since its approval in 1993.
- Amikacin and piperacillin-tazobactam continue to be first line treatment choices against *P. aeruginosa* as recommended by the Infectious Diseases Society of America and the American Thoracic Society [4], nevertheless, this difficult-to-treat pathogen poses therapeutic challenges as its susceptibility to most commonly-used antimicrobials diminishes.