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Anti-Pseudomonal Activity of Piperacillin/tazobactam: More than a Decade of Experience from the SENTRY Antimicrobial Surveillance Program (1997-2007)

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ABSTRACT

Objectives: To summarize the susceptibility rate (% susceptible [S]) experience for piperacillin/tazobactam [P/T] tested against *Pseudomonas aeruginosa* isolates from the Asia-Pacific (APAC), Europe (EU), Latin America (LA) and North America (NA) for 1997-2007. All testing was by reference CLSI (2006) methods and interpreted by contemporary CLSI and USA-FDA breakpoint criteria (2008).

Methods: A total of 25,460 *P. aeruginosa* were tested originating from APAC (4,441), EU (7,695), LA (4,277) and NA (9,047); >110 medical centers/year and samples averaging >30 nations/year. CLSI M07-A8 (2009) and M100-S19 (2009) methods and categorical criteria were applied and all quality control results were within published limits. For this analysis results from 1997-2007, 1997-1999, 2005-2007, APAC, EU, LA and NA were assessed against several broad-spectrum beta-lactams (cefepime [CPM]), ceftazidime [CAZ], imipenem [IMP], meropenem [MER], and piperacillin alone [PIP]; total of 12 agents overall.

Results: Using CLSI *P. aeruginosa* breakpoints (≤64 mg/L), P/T had the broadest coverage (% S) in two regions (EU, LA) and overall at 83.6% followed by MER (83.0%)>IMP (79.7%)>PIP (79.5%)>CPM (77.5%)>CAZ (75.8%). Other non-beta-lactam activity results (% S) were ciprofloxacin at only 71.5%, but tobramycin and polymyxin B had higher S rates (81.0 and 99.5%, respectively). Trends toward P/T resistance (R) were noted between 1997-1999 and 2000-2007 in APAC (-11.6% S), NA (-4.0%) and EU (-2.3%). LA S rates were lowest but actually increased over time by +2.9%; current rate 79.4% S. For beta-lactamase inhibitor combinations, S rates were higher for P/T when compared to PIP alone in all regions (+2.6 to 7.1%), greatest for LA isolates. In contrast, ticarcillin/clavulanate S rates were lower than ticarcillin tested alone in NA (-1.5%; antagonism) and this agent only inhibited 70.3% of isolates worldwide.

Beta-lactam	% susceptible by region (no. tested): APAC (4,441)	EU (7,695)	LA (4,277)	NA (9,047)	All (25,460)
P/T	82.9	83.0	74.8	88.7	83.6
MER	83.5	81.5	71.6	89.4	83.0
IMP	80.4	78.0	68.7	85.9	79.7
PIP	79.3	78.4	67.7	86.1	79.5
CPM	77.0	77.1	64.6	84.0	77.5
CAZ	74.7	75.9	62.8	82.4	75.8

Conclusions: P/T remained the most active beta-lactam tested in vitro against clinical isolates of *P. aeruginosa* found in the SENTRY Program (1997-2007). Trends toward slightly decreased S were noted in all regions over the decade, except LA; only polymyxins had S rates at >90%. R surveillance programs should be sustained to document emerging patterns of old and newer agents for difficult to treat pathogens such as *P. aeruginosa*.

INTRODUCTION

Piperacillin combined with the ß-lactamase inhibitor tazobactam, was developed and approved by the United States Food and Drug Administration (USA-FDA) in 1993. The introduction of piperacillin/tazobactam into the market was for the following indications: 1) to treat nosocomial pneumonia, 2) community-acquired pneumonia (moderate severity only caused by ß-lactamase producing *Haemophilus influenzae*), 3) appendicitis (complicated by rupture or abscess) or peritonitis, 4) uncomplicated and complicated skin and skin structure infections, and 5) postpartum endometritis or pelvic inflammatory disease cause by ß-lactamase producing *E. coli*.

Piperacillin/tazobactam became a very widely used intravenous penicillin/ß-lactamase inhibitor combination delivered as an 8:1 ratio (4 grams of piperacillin and 0.5 grams of tazobactam every six hours) as directed by the product package insert. Two alternative dosing vials may contain 2 or 3 grams of piperacillin and 0.25 or 0.375 grams of tazobactam, respectively, were also available. The original worldwide sponsor/developer of this product (Zosyn® or Tazocin®) was Wyeth Pharmaceuticals (Philadelphia, Pennsylvania, USA) and the patent rights to produce this combination varies geographically. Generic formulations containing piperacillin/tazobactam have various global markets, but have been questioned as to their potencies when compared to the branded product.

As branded and generic piperacillin/tazobactam continues to be applied clinically to serious infections caused by *Pseudomonas aeruginosa,* we measure the contemporary activity of this valuable ß-lactam/ß-lactamase inhibitor combination using the global SENTRY Antimicrobial Surveillance Program results for 1997-2007. All tests were reference-quality and *P. aeruginosa* cultures were received from five continents.

MATERIALS AND METHODS

Broth microdilution methods were performed according to the Clinical and Laboratory Standards Institute (CLSI) documents to determine the antimicrobial susceptibility of each organism. Validated MIC panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA) were utilized. *P. aeruginosa* was tested in cation-adjusted Mueller-Hinton (MH) broth (M07-A8, 2009), and concurrent testing of quality control (QC) strains assured that proper test conditions and procedures were used. These QC strains included American Type Culture Collection (ATCC) organisms: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. Susceptibility percentages and validation of QC results were based upon the CLSI guidelines (M100-S19, 2009) and the CLSI and EUCAST breakpoints were utilized to determine susceptibility over the 11-year interval.

All testing was performed in central laboratories (JMI Laboratories, North Liberty, Iowa, USA; and Women's and Children's Hospital, North Adelaide, Australia) under GLP and CLIA certified conditions. A total of 25,460 *P. aeruginosa* strains were tested, each obtained from a consecutively cultured patient case (non-duplicates) in more than 110 medical centers (>30 nations per year). The distribution of cultures was: Asia-Pacific (APAC) region (4,441 isolates), Europe (EU; 7,695 isolates), Latin America (LA; 4,277 isolates) and North America (dominantly United States [USA]; 9,047 isolates). Although 20-30 antimicrobials were tested annually, only 10 agents are presented here as the principal comparison compounds that includes cephalosporins (2), penicillins (4), carbapenems (2), aminoglycosides (1) and fluoroquinolones (1). Polymyxin B was also tested and 99.5% of isolates had MIC results at ≤2 mg/L (susceptible), with only <0.1% at >4 mg/L (data not shown). Similar data was obtained for colistin.

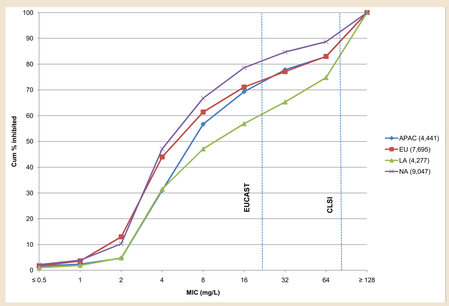
RESULTS

- Piperacillin/tazobactam remained quite active against *P. aeruginosa* over the 11 years with a MIC_{50} and MIC_{90} of 8 and >64(128) mg/L, respectively; 83.6% susceptible at ≤64 mg/L.
- Variations in antimicrobial potency were noted among the four regions with piperacillin/tazobactam exhibiting the widest coverage of *P. aeruginosa* in EU (83.0% susceptible) and Latin America (74.8%), but being less active than tobramycin (92.0% susceptible) and meropenem (83.5% susceptible) in North America and APAC, respectively (**Table 1**).
- **Figure 1** and **Table 1** illustrate that highest piperacillin/tazobactam resistance was observed in Latin America and highest susceptibility in North America followed by APAC and EU (CLSI breakpoints).

Table 1. Susceptibility rates of piperacillin/tazobactam and 7 other ß-lactam agents tested against 25,460 *P. aeruginosa* isolates collected in the SENTRY Program (1997-2007).

Antimicrobial Agent	% susceptible by region (no. tested): Europe (7,695)	North America (9,047)	Latin America (4,277)	Asia-Pacific (4,441)
Piperacillin/tazobactam	83.0	88.7	74.8	82.9
Piperacillin	78.4	86.1	67.7	79.3
Ticarcillin/clavulanate	71.6	77.2	56.4	67.6
Ticarcillin	70.0	78.7	55.4	73.6
Cefepime	77.1	84.8	64.6	77.0
Ceftazidime	75.9	82.4	62.8	74.7
Imipenem	78.0	85.9	68.7	80.4
Meropenem	81.5	89.4	71.6	83.5
Ciprofloxacin	70.7	76.1	58.6	75.8
Tobramycin	77.0	92.0	63.8	82.2

Figure 1. MIC distribution (Cumulative % inhibited) for *P. aeruginosa* isolates from four regions (1997-2007).



- EUCAST breakpoints for piperacillin ± tazobactam, ticarcillin ± clavulanate, meropenem and ciprofloxacin differ from those of the CLSI. **Table 2** shows the impact on the perception of the anti-*P. aeruginosa* spectrum that markedly changes the rank order for these broad-spectrum agents. The EUCAST breakpoints (two- or four-fold lower than CLSI) decrease the susceptibility rate for piperacillin/tazobactam by 12.6%.

Table 2. Impact of applied breakpoints (CLSI versus EUCAST) on the perceived rank order of ß-lactam spectrums against *P. aeruginosa* (25,460 isolates).

Antimicrobial Agent	% susceptible using (rank): CLSI	EUCAST	Variation
Piperacillin/tazobactam	83.6 (1)	71.0 (6)	-12.6%
Piperacillin	79.5 (5)	66.9 (7)	-12.6%
Ticarcillin/clavulanate	70.3 (10)	21.3 (10)	-49.0%
Ticarcillin	71.5 (8)	28.8 (9)	-42.7%
Cefepime	77.5 (6)	77.5 (3)	NC
Ceftazidime	75.8 (7)	75.8 (5)	NC
Imipenem	79.7 (4)	79.7 (2)	NC
Meropenem	83.0 (2)	76.6 (4)	-6.4%
Ciprofloxacin	71.5 (8)	66.4 (8)	-5.1%
Tobramycin	81.0 (3)	81.0 (1)	NC

- **Table 3** illustrates the changing patterns of resistance for piperacillin/tazobactam over time (1997-1999 versus 2005-2007) by geographic region. Susceptibility declined 2.3-11.6% (greatest for APAC) in all regions except Latin America, where the rate increased by 2.9%.

Table 3. Trends in piperacillN/tazobactam susceptibility (1997-1999 versus 2005-2007) for *P. aeruginosa* in four geographic regions.

Time interval (no. tested)	% susceptible by region (change): Europe	North America	Latin America	Asia-Pacific
1997-1999 (7,007)	86.0	89.7	76.5	88.7
2005-2007 (6,831)	83.7 (-2.3)	85.7 (-4.0)	79.4 (+2.9)	77.1 (-11.6)
All years (25,460)	83.0	88.7	74.8	82.9

- The rank order of *P. aeruginosa* activity for the top six agents was as follows (% susceptible): piperacillin/tazobactam (83.6%; CLSI) > meropenem (83.0%; CLSI) > tobramycin (81.0%) > imipenem (79.7%) > cefepime (77.5%) > meropenem (76.6%; EUCAST) > ceftazidime (75.8%) > piperacillin/tazobactam (71.0%; EUCAST). Coverage by ciprofloxacin (66.4-71.5%) and ticarcillin/clavulanate (21.3-70.3%) was compromised.

CONCLUSIONS

- Piperacillin/tazobactam remains highly active against *P. aeruginosa* isolates worldwide as demonstrated by reference testing of 25,460 clinical isolates from five continents (four regions).
- Inter-regional differences in susceptibility rates were noted with greatest levels of resistance in Latin America.
- Trends toward greater resistance rates were noted at 2.3 to 11.6% over 11 years; however, Latin America has shown improved piperacillin/tazobactam susceptibility.
- Susceptible interpretive breakpoints (CLSI, EUCAST, USA-FDA) can alter the perceptions of anti-pseudomonal agent activity (**Table 2**). Harmonization between these organizations is encouraged using a multidisciplinary approach (microbiology, PK/PD, clinical trial outcomes, etc.).

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