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Antimicrobial Susceptibility Profile of *Pseudomonas aeruginosa* Causing Bloodstream Infections in Brazilian Medical Centers: Results of the SENTRY Antimicrobial Surveillance Program (2001-2006)

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AMENDED ABSTRACT

Background:
The SENTRY Antimicrobial Surveillance Program is a global resistance monitoring system designed to assess antimicrobial resistance trends worldwide. Nosocomial bloodstream infections (BSI) are a leading cause of death in critically ill patients. PSA was the fifth most frequently isolated pathogen from bloodstream infections in Latin America overall and in Brazil. The main purpose of this study was to determine the geographic and year-to-year variation in susceptibility rates of PSA collected from hospitalized patients with BSI in participant Brazilian medical centers, for a consecutive 6-year period (2001-2006).

Methods:
The first 20 unique bacterial isolates of each month from clinically significant BSI during the period of January 2001 to December 2006 were included in the study. Four Brazilian medical centers participated in this study. They were located throughout three regions: South, Southeast and Midwest. Species identifications were confirmed by the central monitoring laboratory (JMI Laboratories) and all isolates were tested using CLSI methods and interpretative criteria (M100-S17) against antimicrobial agents commonly utilized as empiric or directed therapy.

Results:
A total of 503 PSA isolates were analyzed in this study. The most active compound against this pathogen in Brazil was polymyxin B (99.8% susceptibility), followed by piperacillin/tazobactam (75.6% susceptibility) and amikacin (68.8% susceptibility). Susceptibility rates to carbapenems, imipenem and meropenem, was 67.6% and 68.2%, respectively. No resistance to polymyxinB was detected in this period.

Conclusions:
PSA showed relatively low rates of susceptibility to the majority of the antimicrobial agents tested. Decreased susceptibility rates to carbapenems and increase in aztreonam susceptibility could indicate dissemination of metallo-ß-lactamase-producing strains. The therapeutic choices available are limited for BSI caused by PSA due a rapid increase in resistance to most clinically available agents.

INTRODUCTION

Pseudomonas aeruginosa is a frequent nosocomial pathogen that particularly causes severe diseases in immunocompromised patients, including those with cancer, burns, cystic fibrosis and hospitalized in intensive care units. Infections caused by this microorganism are often difficult to treat because of intrinsic and acquired resistance mechanisms that affect several antimicrobial agents, such as decreased permeability of the outer membrane, drug efflux and metallo-ß-lactamase (MBL) production.

Carbapenems (imipenem and meropenem) are the main therapeutic options for treatment of multidrug-resistant *P. aeruginosa* infections. The prevalence of carbapenem-resistant *P. aeruginosa* has increased worldwide, and particularly in Latin America, jeopardizing the clinical use of these compounds.

The purpose of this study was to determine the geographic and year-to-year variation in the antimicrobial susceptibility profile of *P. aeruginosa* isolates collected from hospitalized patients with bloodstream infections (BSI) in the Brazilian medical centers participating in the SENTRY Antimicrobial Surveillance Program (2001-2006).

MATERIAL AND METHODS

Bacterial strains: Each participating center contributed results (organism identification, date of isolation, antimicrobial susceptibility profile, etc) for the first 20 consecutive episodes of BSI per month from January 2001 to December 2006. Only one isolate per patient was included in this study.

SENTRY participating medical centers: Four Brazilian medical centers participated in this study. They were located in four cities from four distinct states and represented three different Brazilian geographic regions: Porto Alegre and Florianópolis (South region), São Paulo (Southeastern region) and Brasília (Midwest region).

Susceptibility testing: Antimicrobial susceptibility testing was performed and interpreted using the reference broth microdilution method as described by Clinical and Laboratory Standards Institute (CLSI). Dry-form microdilution panels and broth for inoculation were produced by TREK Diagnostics (Cleveland, OH). Quality control strains *Escherichia coli* ATCC 25922 and 35218 and *P. aeruginosa* ATCC 27853 were concurrently tested.

Statistical analysis: Annual antimicrobial resistance trends were determined by the chi-square test and values of $p < 0.05$ were considered statistically significant.

RESULTS

- Among 1,215 *P. aeruginosa* collected from all types of infections, 503 (41.4%) strains were isolated from BSI. *P. aeruginosa* ranked as the 5th most frequently isolated pathogen causing BSI (Table 1).
- The prevalence of *P. aeruginosa* isolates as a cause of BSI increased from 6.8% in 2001 to 8.7% in 2006, but this increase was not statistically significant (p = 0.12).

Table 1. Top 10 pathogens causing bloodstream infections in Brazilian medical centers (SENTRY Program, 2001-2006).

	Organism	Number of Isolates	%
1	*S. aureus*	1511	23.7
2	Coagulase-negative staphylococci	994	15.6
3	*E. coli*	761	11.9
4	*K. pneumoniae*	634	9.9
5	*P. aeruginosa*	503	7.9
6	*A. baumannii*	307	4.8
7	*E. faecalis*	288	4.5
8	*E. cloacae*	196	3.1
9	*S. marcescens*	163	1.6
10	*S. maltophilia*	112	1.8

Table 2. Susceptibility rates of selected antimicrobial agents tested against *P. aeruginosa* isolated from BSI (SENTRY Program, 2001-2006).

	MIC (µg/ml)			
Antimicrobial agent	MIC_{50}	MIC_{90}	% Susceptible	% Resistant
Cefepime	8	>16	60.0	26.4
Ceftazidime	4	>16	59.8	32.4
Piperacillin/tazobactam	16	>64	75.6	24.4
Imipenem	1	>8	67.6	22.7
Meropenem	1	>8	68.2	25.7
Aztreonam	8	>16	55.5	27.2
Ciprofloxacin	0.5	>4	55.9	42.6
Levofloxacin	1	>4	55.5	42.7
Amikacin	4	>32	68.8	29.6
Gentamicin	2	>8	56.9	41.7
Polymyxin B	≤1	2	99.8	0.0

Table 3. Resistance and susceptibility rates of *P. aeruginosa* isolates from bloodstream infection (BSI) of patients hospitalized in Brazilian medical centers (SENTRY Program, 2001-2006).

	2001		2002		2003		2004		2005		2006	
Antimicrobial agent	%S	%R	%S	%R	%S	%R	%S	%R	%S	%R	%S	%R
Cefepime	67.2	15.5	60.6	29.6	59.8	27.6	53.7	26.3	58.1	29.0	63.6	27.3
Ceftazidime	70.7	25.9	62.0	33.8	60.9	34.5	54.7	34.7	57.0	36.6	58.6	27.3
Piperacillin/tazobactam	75.9	24.1	66.7	33.3	67.8	32.2	72.6	27.4	82.8	17.2	84.8	15.2
Imipenem	77.6	19.0	69.0	26.8	69.0	23.0	67.4	18.9	61.3	21.5	65.7	26.3
Meropenem	79.3	19.0	73.2	22.5	70.1	25.3	68.4	24.2	62.4	28.0	61.6	31.3
Aztreonam	53.4	29.3	53.5	32.4	51.7	35.6	51.6	27.4	61.3	21.5	59.6	20.2
Ciprofloxacin	72.4	27.6	57.7	42.2	57.5	42.5	51.6	46.3	51.6	48.4	51.5	42.4
Amikacin	72.4	25.9	70.4	29.6	73.6	24.1	68.4	30.5	62.4	34.4	67.7	31.3
Gentamicin	70.7	29.3	59.2	36.6	52.9	46.0	54.7	44.2	51.6	46.2	57.6	42.4
Polymyxin B	98.3	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0

- Overall, the most active compound against BSI *P. aeruginosa* was (MIC_{50} [µg/ml]/% susceptible): polymyxin B (≤ 1/99.8%), followed by piperacillin/tazobactam (16/75.6%), amikacin (4/68.8%), meropenem (1/68.2%) and imipenem (1/67.6%).
- Comparison of 1997 and 2006 susceptibility rates showed important decreases in the susceptibility rates for imipenem (67.6% *vs.* 55.7% susceptible; p=0.11), meropenem (79.3% *vs.* 61.6% susceptible; p=0.02), and ciprofloxacin (72.4% *vs* 51.5% susceptible; p=0.01). In contrast, an increase in the susceptibility rates to aztreonam (53.4 *vs.* 59.4%) was documented.
- No resistance to polymyxin B was detected.
- The antimicrobial susceptibility patterns varied significantly among the medical centers evaluated (Table 4).

Table 4. Susceptibility patterns by medical center (SENTRY Program, 2001-2006).

	% Susceptible by Medical Center			
Antimicrobial agent	Florianópolis	São Paulo	Porto Alegre	Brasília
Cefepime	79.1	43.1	65.0	60.6
Ceftazidime	77.4	43.8	86.7	53.1
Piperacillin/tazobactam	83.5	72.2	80.0	72.0
Imipenem	86.1	51.0	81.7	65.1
Meropenem	87.8	52.3	80.0	65.1
Aztreonam	67.0	56.9	50.0	48.6
Ciprofloxacin	73.0	42.5	53.3	57.1
Levofloxacin	73.9	41.8	53.3	56.0
Amikacin	80.9	45.8	61.7	83.4
Gentamicin	74.8	44.4	55.0	56.6
Polymyxin B	100.0	100.0	100.0	99.4

CONCLUSIONS

- *P. aeruginosa* isolated from patients with BSI hospitalized in Brazilian medical centers showed relatively low susceptibility rates to most antimicrobial agents tested.
- The decreased susceptibility to carbapenems coupled with the increased susceptibility to aztreonam could indicate a rise in the frequency of MBL-producing *P. aeruginosa* and/or dissemination of epidemic clones since isolates of the SPM-1-producing clones are usually more susceptible to aztreonam.
- The therapeutic choices available for treatment of BSI caused by multidrug-resistant *P. aeruginosa* are very limited and restricted mainly to polymyxins (99.8% susceptible).

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