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Healthcare-associated Infections by *Pseudomonas aeruginosa* and Antimicrobial Resistance in a Public Hospital from Alagoas (Brazil)

Infecções Associadas à Assistência à Saúde por Pseudomonas aeruginosa e Resistência Antimicrobiana em Hospital Público de Alagoas (Brasil)

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ABSTRACT

Introduction: *Pseudomonas aeruginosa* infections are common worldwide, affecting mainly hospitalized patients and causing healthcare-associated infections (HAIs), with a high frequency of antibiotic resistance and complicated outcomes.

Objective: To investigate the *P. aeruginosa* frequency in HAIs in a medium/high-complexity hospital in Alagoas (Brazil) and the antibiotic susceptibility profiles of the strains.

Methods: A retrospective cross-sectional study was conducted from January 2013 to December 2014, when *P. aeruginosa* related-HAIs were evaluated after automated identification (Vitek®2) and documental analysis.

Results: Seventy-eight samples were positive for P. aeruginosa, with 37 (47.4%) isolates from patients of the general Intensive Care Unit (ICU) and 13 (16.7%) from the surgical unit. Tracheal secretion (25.6%), wound secretions (20.5%) and sputum (18.0%) were the main positive biological samples. Among 68 strains tested, 73.53% showed resistance to aztreonam, while cefepime, ceftriaxone and cefotaxime were not effective for any isolates (all resistant). High resistance to carbapenems imipenem (61.76%) and meropenem (55.88%) was observed, as well as 46 isolates resistant to piperacillin/tazobactam (67.64%); 47 (60.2%) from the general ICU and neonatal ICU were resistant to all antibiotics tested (MDR profile), except for colistin.

Conclusion: Our results indicated antibiotic-resistant *P. aeruginosa* highly present in ICU and the therapy with aminoglycosides and colistin as important choices in cases with failure against *P. aeruginosa* isolates. A constant screening of multidrug-resistant *P. aeruginosa* is necessary for the control in the hospital environment, evaluating the antibiotic susceptibility to guide the therapeutic choice.

Key words: *Pseudomonas aeruginosa*; antimicrobial resistance; healthcare-associated infections; ICU.

INTRODUCTION

Pseudomonas aeruginosa is a Gram-negative bacillus (GNB) able to survive in a number of environments, with a predilection for humid environments, colonizing sites such as the perineum, armpit and ear of healthy individuals in low prevalence. Besides, it persists in typical reservoirs such as showerheads, dialysis tubing, infusion pumps and respiratory equipment, while hospitalized patients have a higher colonization rate[1-3].

Worldwide, HAIs are considered as a serious public health problem, which has been growing in both incidence and complexity, causing several social and economic implications[4]. As an opportunistic human pathogen, P. aeruginosa is known as the major cause of healthcare-associated infections (HAIs) and the second

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most common cause of sepsis in Intensive Care Units (ICU)[5,6].

The reduction of susceptibility to antimicrobials in P. aeruginosa has been observed in Brazil and in other countries for years[7-9,1,6], highlighting the decrease in sensitivity to antibiotics of choice such as carbapenems and anti-Pseudomonas cephalosporins[10,11]. Several resistance mechanisms have already been identified in P. aeruginosa (classified into intrinsic, acquired and adaptive resistance), including limited permeability of the outer membrane, efflux pumps and the production of antibiotic-inactivating enzymes (e.g., β-lactamases) and resistance mediated by transferred plasmids and/or mutations[12,13,7].

Factors in the hospital environment contribute to the increase in infections by drug-resistant P. aeruginosa, such as the selective pressure of antimicrobials, facility to survive for prolonged periods in humid environments and hospital equipment/utensils and host factors: basic diseases such as diabetes, kidney failure or neoplasms, long periods of hospitalization, surgical procedures, use of catheters, mechanical ventilation and previous antibiotic therapy, in addition to failures in the biosafety for HAI control[14,15].

Multidrug resistance (MDR) profile has been frequently observed in Gram-negative bacilli (GNB), such as Escherichia coli, Klebsiella pneumoniae and P. aeruginosa[2]. Basak and collaborators (2016)[16] received samples from ICU and from wards of different clinical specialities, isolating P. aeruginosa as the second most frequent GNB (28.4%) and the major GNB extensively drug-resistant (XDR), a type of MDR organism that is resistant to basically all approved antimicrobial agents.

Hospital infection rate assessments, prevalence of the most common infections and which pathogens are involved, as well as their antibiotic sensitivity profiles, are extremely relevant indicators that should be monitored periodically, aiming at improving the prevention and control policies and practices of these infections. Thus, this study aimed to explore the clinical isolates of P. aeruginosa identified in an important hospital in northeastern Brazil for 2 years, investigating the frequency of infections of this pathogen and each susceptibility profile to antibiotics.

METHODS

Study design, period and local

This retrospective and cross-sectional study was developed from January 2013 to December 2014 in the Professor Alberto Antunes University Hospital (HUPAA; Maceió, Alagoas, Brazil), a public teaching hospital classified as medium- and high-complexity and in agreement with the Unified Health System (SUS) that provides health services to the population of Alagoas. No consent term was required, since no patient samples or their demographic data were manipulated, but only bacterial strain data on a register book.

Strain identification and susceptibility profile

Data from positive cultures for P. aeruginosa previously identified were obtained from the reports of the microbiology laboratory of HUPAA and included in this study. The clinical samples came from all types of inpatient units of the hospital; we considered only patients diagnosed as having P. aeruginosa -related HAI after 48 h of admission, according to medical report analysis and the criteria and HAI definition from CDC[17].

The phenotypic characteristics and antibiotic susceptibility profile of the P. aeruginosa strains were identified using the automated Vitek®2 system (BioMérieux, France), according to the manufacturer's instructions. For sensitivity and resistance evaluation, the following classes of antibiotics were used in the antibiotic sensitivity tests (AST): β-lactam (aztreonam [ATM; 30 µg]), aminoglycosides (gentamycin [GEN; 10 µg] and amikacin [AMK; 30 µg]), fluoroquinolones (ciprofloxacin [CIP; 10 µg]), 3rd- and 4th-generation cephalosporins (cefotaxime [CTX; 30 µg], ceftriaxone [CFT; 30 µg] and cefepime [CFP; 30 µg]), polymyxin E/colistin (CST; 10 µg), carbapenems (meropenem [MEM; 10 µg] and imipenem [IMP; 10 µg]) and a β-lactam/β-lactamase inhibitor combination (piperacillin/tazobactam [TZP; 100/10 µg]). The results were interpreted using the guideline of the Clinical and Laboratory Standards Institute (CLSI) and the minimum inhibitory concentration (MIC) determinations for colistin were made (data not informed)[18].

Ciprofloxacin was evaluated only in P. aeruginosa isolated from urine samples, and P. aeruginosa isolates were classified with multidrug-resistant (MDR) pattern when nonsusceptibility to at least one agent in three or more antimicrobial classes was observed[16]. Given the reality of a public hospital in Brazil, which occasionally goes through periods of low resources, it was not possible to test all isolates with all antimicrobials described due to limited materials at some times, as indicated in the results.

Statistical analysis

For the data organization and analysis was used Microsoft® Office Excel for Windows® (Microsoft) and statistical data analyses were carried out with GraphPad Prism 8® usingchi-square test ($p > 0.05$).

RESULTS

During the period analyzed, 78 samples with positive isolation

for P. aeruginosa were obtained, of which 42 (53.8%) were collected from January to December 2013 and 36 (46.2%) from January to December 2014. P. aeruginosa accounted for 47.4% (37), 16.7% (13) and 12.8% (10) of HAIs in general ICU, surgical clinic and neonatal ICU, respectively, followed by medical clinic (9; 11.5%), pediatric (7; 9.0%) and ophthalmic units (2; 2.6%).

The strains analyzed were isolated from different clinical specimens, mainly tracheal secretion (20; 25.6%), wound secretion (16; 20.5%) and sputum (14; 18.0%). In Table 1, one can see the frequency of P. aeruginosa strains in all variety of clinical samples analyzed.

TABLE 1 - Clinical specimens positive for Pseudomonas aeruginosa obtained from patients with healthcare-associated infections (2013-2014).

Clinical specimens	Cases		Total (%)
	2013	2014	
Tracheal secretion	10	10	20 (25.6%)
Wound secretion	10	6	16 (20.5%)
Sputum	8	6	14 (18.0%)
Urine	5	5	10 (12.8%)
Catheter	3	5	8 (10.2%)
Blood culture	4	3	7 (9.0%)
Ascitic fluid	1	-	1 (1.3%)
Pleural fluid	-	1	1 (1.3%)
Cornea	1	-	1 (1.3%)
Total	42 (53.8%)	36 (46.2%)	78 (100.0%)

The aminoglycosides were among the antibiotics tested in all P. aeruginosa strains that showed better action against them, with a higher sensitivity rate compared to the number of resistant strains: 53.8% sensitive to amikacin and 51.3% sensitive to gentamycin (Table 2). However, among the 68 strains tested, 73.53% of the isolates (50) did not respond to the attack with aztreonam, with a high level of resistance to this b-lactam (Table 2).

Amongst the cephalosporins evaluated, it was observed that all tested isolates were resistant to cefepime, being the only from the 4th generation evaluated in AST, as well as to ceftriaxone and cefotaxime (3rd-generation cephalosporins) due to intrinsic resistance (Table 2).

In addition, it was possible to confirm a high resistance to carbapenems imipenem and meropenem, important drugs in the treatment against P. aeruginosa, with a prevalence of resistance of 61.76% and 55.88%, respectively. Forty-six isolates also showed resistance to the piperacillin/tazobactam combination.

Forty-seven isolates (60.2%) from the general ICU and neonatal ICU were resistant to all antibiotics tested, except for colistin (MIC not informed), the only drug with an effective response against them. Thus, all P. aeruginosa strains circulated in the general ICU had an MDR profile, since they showed resistance to the 5 classes tested and to β-lactam/β-lactamase inhibitor combination.

TABLE 2 - Distribution of Etiology of cirrhosis and laboratory data on patients undergoing liver transplantation at HC-UFMG between 2003 and 2015

Etiology of cirrhosis and laboratory data	Distribution
Etiology	n (%)
Ethanol	16 (44.4)
HCV	14 (38.9)
Cryptogenic	6 (16.7)
Laboratory data:	Median (min-max)
ALT (U / L)	48.0 (11.0 - 275.0)
AST (U / L)	53.0 (20.6 - 177.0)
BT (mg / dL)	2.15 (0.6 - 8.7)
RNI	1.49 (0.99 - 2.51)
Creatinine (mg / dL)	0.89 (0.4 - 3.0)
AFP (ng / ml) *	n (%)
<10	17 (73.9)
> 10	6 (26.1)
MELD **	n (%)
<20	22 (78.6)
> 20	6 (21.4)

Source: Authors. * n=23 cases. ** n=28 cases.
HCV: Hepatitis C virus; ALT: Alanine transaminase; AST: Aspartate transaminase; BT: Total bilirubin; RNI: International normalized ratio; AFP: alpha-fetoprotein; MELD: Model of end-stage liver disease.

DISCUSSION

This research showed the antimicrobial susceptibility profile of P. aeruginosa isolated from a variety of infections from patients admitted to an important public hospital in northeastern Brazil, with MDR strains in different sectors. The bacterium focused here is an ESKAPE member, a group that encompasses six pathogens with increasing resistance to multiple drugs and virulence, responsible for most HAIs[19,20].

P. aeruginosa remains as a frequent cause of pneumonia and bloodstream infections in hospitalized individuals of many countries since 1997, according to the SENTRY Antimicrobial Surveillance Program[21]. A systematic revision evaluated P. aeruginosa infections in Latin American, and eligible studies perfomed in Brazil and Colombia (2005 to 2012) reinforced the bloodstream and respiratory tract as the main infection sites for this GBN[14], pointing out to risk factors for MDR P. aeruginosa acquisition such as co-occurring disease, surgical procedure, hospital stay, inappropriate therapy, enteral/parenteral feeding, mechanical ventilation, use of nasogastric tubes under endotracheal suctioning daily, in addition to the continuous sedation that decreases the ciliary movements of the respiratory tree[22].

Different screenings in Brazil indicated P. aeruginosa as the 1st and 2nd most isolated bacterium in infection processes (Recife/PE and São Paulo/SP), with a high prevalence of respiratory infections isolated from tracheal secretions and nasal site (10; 23).

In the current study, we found P. aeruginosa more frequently in tracheal secretions and wounds in Maceió/AL, as observed in a previous study (24), when among 85 P. aeruginosa isolates it was found in 28.2% and 25.9% from tracheal aspirates and wounds, respectively. These are common infected sites in patients undergoing long hospitalization and invasive procedures.

An ESKAPE-type bacterium canescape the action of antibiotics and become resistant to one or more agents, combined or not, due to the natural selection of resistant strains and horizontal gene transfer (HGT) for sensitive strains (20). In our results, the overall data showed an important frequency of P. aeruginosa resistant to a variety of antibiotics, mainly in inpatient units with more critical patients (general and neonatal ICUs).

A better sensitivity rate of aminoglycosides gentamicin and amikacin was confirmed here, which are antibiotics commonly used against P. aeruginosa; however, there has been an increase in the frequency of P. aeruginosa isolates resistant to aminoglycosides, as Teixeira et al[25] and Holbrook et al[26] observed in Venezuela and USA, respectively. Aminoglycoside monotherapy appears to be an effective treatment option only for lower urinary tract infection (UTI) in nonseptic patients, since aminoglycosides accumulate in kidneys in high concentrations[27,28]. Basseti et al[29] suggested a combination therapy with beta-lactams and aminoglycosides for high-risk severe patients (i.e., severe immunocompromised neutropenic patients or with septic shock) in an empirical administration, until the etiologic agent and its susceptibility profile are identified.

An important rate of resistance to beta lactam antibiotics aztreonam, 3rd- and 4th-generation cephalosporins, carbapenems and TZP combination tested was observed in ourP. aeruginosaisolates. Therefore, we can infer that there was a high production of the β-lactamase enzymes by the strains of this public hospital. β-lactamases hydrolyze β -lactam rings, a common and important mechanism of resistance in GBN, and are divided in class A, B (metallo-β-lactamases/MβLs), C and D serine b-lactamases[30].

P. aeruginosa resistant to meropenem and aztreonam was found in different hospitals in Alagoas years before, with the MDR phenotype in 50.6% and nine of these strains with $_{bla}$SPM gene and one $_{bla}$IMP-positive, MBL producers in ICU and other hospital units[24]. Noting that resistance to cephalosporins has been increasing in Recife (Brazil), Figueiredo et al[10] suggest that the use of 3rd-generation cephalosporins on a large scale as a dominant therapeutic option for years has resulted in decreased sensitivity to this drug.

Worldwide, the rate of meropenem non-susceptible P. aeruginosa was the highest in 2009-2012 (27.3%) and decreased to 22.7% in 2013-2016[21], but in a screening for important GNB in HAIs from different countries of Latin America, Labarca et al[31] found rates of carbapenem resistance up to 66% for P. aeruginosa strains. Mladenovic-Antic and colleagues[32]observed a significant increase in rates of antimicrobial resistance of P. aeruginosa to carbapenems and beta-lactams and attested a correlation between the consumption and resistance. In the same way, Baditoiu et al[33] found during 1 year of research in the ICU that the incidence of carbapenem-resistant P. aeruginosa and combinations increased significantly, in parallel with the increase in the consumption of β-lactams with β-lactamase inhibitors (TZP) and meropenem.

The general ICU from HUPAA/Alagoas was the area with the highest record of HAI by P. aeruginosa, a hospital sector with critical patients under prolonged hospitalization, invasive interventions and antibiotic-resistant bacteria. According to Braga et al[34], the prevalence of ICU-acquired HAIs in Brazilian hospitals was higher than that reported in most European countries and the USA, an extremely worrying situation.

P. aeruginosa strains sensible to colistin, were recurrent in studies from different countries, e.g., all 245 isolates from Latin American countries were susceptible to colistin [14], as well as 212P. aeruginosa MDR isolates from India[16] and outbreak strains from German, where even those resistant to penicillins, aminoglycosides, cephalosporins, carbapenems and quinolones remained susceptible only to colistin[35].

Thus, these studies explain why colistin is considered as a last resource agent in the case of infections by multidrug-resistant GNB, e.g., Acinetobacter baumannii and P. aeruginosa, with efficacy for systemic therapy in the treatment of HAIs comproved, despite the nefrotoxicity[36,37,9]. Labarca et al[31] confirmed that clinicians have considered the use of alternative agents as this polymyxin against carbapenem-resistant P. aeruginosa, and to our knowledge there was no confirmation of P. aeruginosa isolates resistant to this drug in Alagoas.

P. aeruginosa has developed several mechanisms that interfere in the antimicrobials activities, which can coexist and generate cross resistance, decreasing the sensitivity to antibiotics in GNB[38], making many common therapies increasingly ineffective. Care in prevention and therapy continues to be encouraged to prevent the emergence of more resistant species, as well as basic and epidemiological researches that help in the understanding of

the acquisition and prevalence of resistance mechanisms, in the expectation that new drugs are capable of combating multi-resistant strains and/or new drug target candidates are discovered.

CONCLUSION

This study concluded that antibiotic-resistant P. aeruginosa were highly present in this important public hospital from Maceió/Alagoas, mainly in the ICUs when compared to the other hospital areas. Aminoglycosides can be a better option in many cases, but the multiple resistance to the drugs observed complicate therapeutic management of infections by P. aeruginosa. We confirmed the colistin as an alternative for the treatment of cases with failure to the drugs of first choice or in front of MDR isolates, when applicable.

Healthcare professionals are constantly fighting against different pathogens from HAIs, and the necessary subsidies for adequate hospital biosafety and epidemiological surveillance must always be guaranteed, and periodic drug-resistance evaluations of the microorganisms most frequently isolated in addition to the providing of continuing education to these professionals, strengthening infection control strategies.

Conflict of Interest: All authors disclaim any conflict of interest.

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