Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 11 (60) No. 1 - 2018

PSEUDOMONAS AERUGINOSA IN THE ETIOLOGY OF PAEDIATRIC HEALTHCARE-ASSOCIATED INFECTIONS

P.C. CHIRIAC[1] V. POROCH[2*] A.M. PASCU[3*]
M. HOGEA[3] V. CÂRLIG[1]

***Abstract**: Antimicrobial resistance is a global burden and crisis but also a significant threat to public health. **The study aim** was to evaluate descriptively a group of paediatric patients with healthcare-associated infections with Pseudomonas aeruginosa, highlighting the strains antibiotic resistance. **Material and methods**: the study was conducted on a group of 28 patients admitted to „Sf. Maria" Clinical Emergency Hospital for Children, Iasi. **Result**: most of infections were diagnosed in infants (0-12 months) (42.85%), males (M/F ratio = 1.54), admitted in acute therapy unit and intensive care unit, with predominance of ventilator-associated pneumonia (31.74 %). The antibiotic resistance of P. aeruginosa strains was noted for Imipenem (50.00%) and Meropenem (46.42%), as well as Cefepime (42.85%) and Ceftazidime (28.57%). Only 12 isolates were tested for Piperacillin-Tazobactam (17.85% of them being resistant). **Conclusions**: antibiotic resistance of isolated strains had important levels of antibiotic resistance to Imipenem and Meropenem.*

***Key words:** healthcare-associated infections, Pseudomonas aeruginosa, antibiotic resistance, paediatrics.*

1. Introduction

Antimicrobial resistance represents a global burden and crisis but also a significant threat to public health nowadays. Healthcare-associated infections (HAIs) with multi-drug resistant (MDR) bacteria lead to increased morbidity and mortality rates, with a continuous increasing incidence in paediatric and neonatal patients, both at national and global levels. The selective

[1]University of Medicine and Pharmacy, Department of Pharmacology, Craiova, România
[2]"Grigore T. Popa" University of Medicine and Pharmacy, Department of Surgery; Regional Institute of Oncology, Iași, România
[3]Transilvania" University, Faculty of Medicine, Brașov, România
*Corresponding authors: Vladimir Poroch, e-mail: <vlader2000@yahoo.com>;
Alina Pascu, e-mail: <alina.pascu@unitbv.ro>

pressure created by the widespread use of antibiotics might be the main explanation of this burden [8]. *Pseudomonas aeruginosa* is an aerobic and Gram-negative microorganism, being isolated frequently from water, soil and environment. It is known that *P. aeruginosa* is inoffensive for immunocompetent people. Infections with *P. aeruginosa* can appear in patients suffering from malignancies or other conditions associated with a decrease in the immunity, as well as in preterm infants [18].

From a historical point of view, MDR strains have affected patients in wards where exposure to antibiotics, frequent and/or long-term hospitalization, and host factors posed a risk for the acquisition of such characteristics [5]. In 2006, Colombia was the first country to report *P. aeruginosa* strains producing carbapenemases. The highest prevalence of these isolates was reported by Brazil, and then spread throughout the American continent [5], [7], [15].

In recent years, several studies have been reported on *P. aeruginosa* infections in paediatric patients. For example, bacteraemia in children is reported rarely but the diagnosis could be life-threatening [8]. Risk factors are not well known especially in previous healthy children [19].

It is known that *P. aeruginosa* is one of the most frequent bacteria involved in the aetiology of ventilator-associated pneumonia, with a relative high prevalence in patients admitted to intensive care units and a high mortality rate. Studies showed that the presence of MDR strains could be an important predictor of hospital death [9].

The study aim was to evaluate descriptively the group of paediatric patients with healthcare-associated infections with *P. aeruginosa* strains, highlighting antibiotic resistance.

2. Material and Methods

The retrospective study was performed on a group of 28 patients admitted to the "Sf. Maria" Clinical Emergency Hospital for Children, Iasi, between January-December 2016. Various pathological products were collected, in order to detect *P. aeruginosa* as a determinant of HAIs. The study group was part of the 214 cases reported as HAIs in 2016 (13.08%). The inclusion criteria were paediatric age (0-18 years) and HAIs with *P. aeruginosa* strains. The exclusion criteria did not take into account the residence area, gender, admission units or the type of pathological prelevate.

The data were collected from the patients' medical reports. The antimicrobial sensitivity of each strain was determined by the diffusion method, and the interpretation criteria were considered as those of the laboratory standards. The data were statistically processed using MS Excel 2010 and SPSS v.20.0 software.

3. Results

Distribution by paediatric age groups of patients with HAIs with *P. aeruginosa* strains showed that most cases were infants 0-12 months (12 cases - 42.85%), then children aged 12-18 years (5 cases - 17.85%) (*Figure 1*).

Quarterly distribution of the cases evidenced that most cases were reported in the first trimester of the year (11 patients - 39.28%) and the fewest during the second trimester (2 cases - 7.14%)

(*Figure 2*).

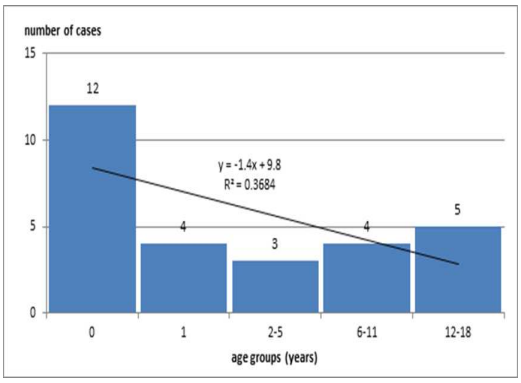

Fig. 1. *Age histogram of the study group*

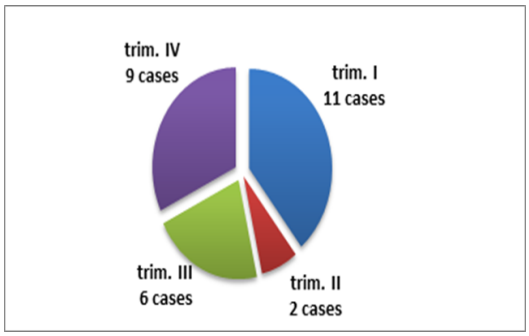

Fig. 2. *Quarterly distribution of the cases*

Gender distribution showed that most cases were reported in males with a M/F ratio of 1.54. There were three times more male infants than females infected, but the 2-5 years age group was represented exclusively by girls (*Table 1*).

Table 1

Distribution by age groups

Age group	Male	Female	Total
0 – 12 months	9	3	**12**
1 year	3	1	**4**
2-5 years	0	3	**3**
6-11 years	2	2	**4**
12-18 years	3	2	**5**
Total	**17**	**11**	**28**

Regarding the distribution by the admission units, most cases were reported in the acute therapy and paediatric intensive care units (PICU) (9 cases, each), then from neonatal ICU and paediatric surgery (3 cases each), and only 1 case each in burns unit, paediatric oncology and paediatric urology (*Figure 3*).

The most frequently reported types of infections were ventilator-associated infection (10 cases, 35.71%), followed by surgical wound infection (5 cases, 17.85%), urinary tract infection (4 cases, 14.28%), and sepsis (2 cases, 7.14%) (*Figure 4*).

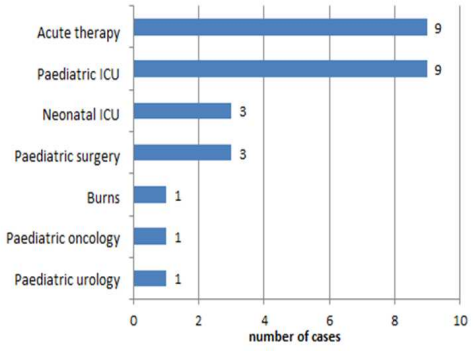

Fig. 3. *Distribution by admission units*

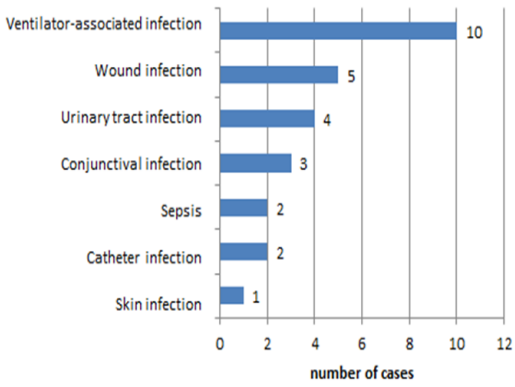

Fig. 4. *Type of infections with P. aeruginosa*

Antimicrobial resistance of *P. aeuginosa* strains revealed that half of the isolated were resistant to Imipenem (50.00%) and Meropenem (46.42%). Among cephalosporins, increased resistance to Cefepime (42.85%) and Ceftazidime (28.57%) was noted. For Piperacillin-Tazobactam, only 12 isolates were tested, with a 17.85% resistance (*Figure 5*).

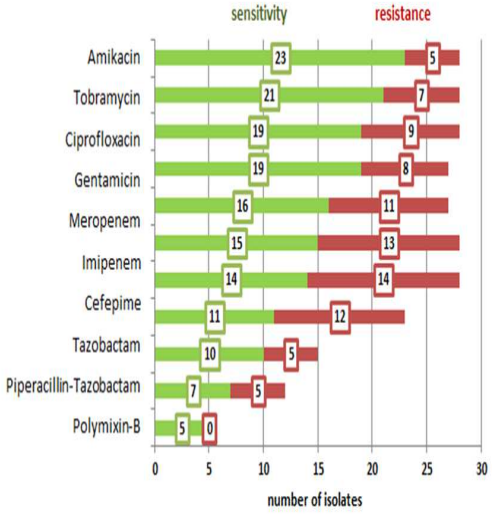

Fig. 5. *Antibiotic sensitivity and resistance of P. aeruginosa strains*

The study recorded 11 cases sensitive to all tested antibiotics. Five cases were resistant to all tested antibiotics, except for Polymixin-B (3 cases) and Polymyxin/Aztreonam (2 cases).

The time interval from admission to the onset of HAI was of 34.57 days in average, varying between a minimum of 5 days in a female patient aged 3 years admitted with the diagnosis of "Uretero-hydronephrosis. Recurrent pyelonephritis" (urinary HAI), and a maximum of 137 days in a male patient diagnosed with "Tracheostomy. Giant ruptured omphalocele" (wound HAI) (*Figure 6*).

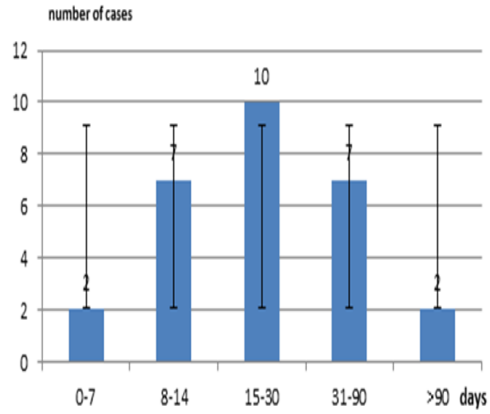

Fig. 6. *The time interval between admission and the onset of HAI (error bars and standard deviation)*

4. Discussions

Our study reported that ventilator-associated infections accounted for over one-third of HAIs with *P. aeruginosa*. A prospective observational cohort study published in 2017 was conducted in 47 centres in the United States, Canada and Australia on a group of 229 paediatric patients with assisted ventilation for more than 48 hours. Subsequently samples from tracheal secretion were performed, cultivated and recorded as ventilator-associated infection. Subjects with positive cultures associated chronic respiratory conditions, tracheostomy and shorter hospitalization in PICU. There were no differences between positive and negative patients in terms of assisted ventilation days or mortality rate [17]. Immunocompromised status and low scores of organ dysfunction scales have been associated with increased mortality rates, reported by recent studies [9], [12]. Positive tracheal aspiration cultures were the main determinant of continuous

antibiotic therapy in children with ventilator-associated infection. Regardless of the antibiotic therapy, positive cultures were not associated with a higher mortality, but this was significantly lower in patients with endotracheal tubes [17].

In a study performed in a PICU, in Greece, in 2011, the authors reported 13 patients with VAP and 8 of them having positive for *P. aeruginosa* (55%). The antibiotic resistance was found for Piperacillin-Tazobactam in 13% of strains, and to Ciprofloxacin – 47%, to Imipenem – 42%, to Meropenem – 66% [2].

In our study, only two cases of sepsis have been reported, one of which in an oncological patient. Sepsis with *P. aeruginosa* in paediatric patients is uncommon and occurs in those with immunosuppression because of malignancy, burns, congenital immune deficiency or premature children. Many of these infections are identified and reported as HAIs. Literature data regarding sepsis with *P. aeruginosa* in previously healthy children are few and the published studies showed that this pathogen caused serious conditions with a high mortality rate in children without any comorbidity. *P. aeruginosa* is therefore a rare cause of bacteraemia in previously healthy infants and in children with community acquired fever and presumed sepsis in which the initial antibiotic recommendations did not include antibiotics with standard susceptibility for *P. aeruginosa*. Sepsis with *P. aeruginosa* strains in the community rarely occurs in previously healthy children, as it usually appears linked to an important comorbidity. Protocols for antibiotic therapy in children with malignancies and febrile neutropenia recommend the use of broad spectrum antimicrobials including *P. aeruginosa* coverage as first choice, even if most of the children do not have bacteraemia with this pathogen in order to optimize the initial management of paediatric patients with deep sepsis with *P. aeruginosa.* The results of a five-year cohort study performed in China confirmed that *P. aeruginosa* bacteraemia is still uncommon among hospitalized children, accounting for only 2.6% of all positive blood cultures. Bacteraemia occurred in children with and without risk conditions and one third of the cases were children without co-morbidities. The mortality rate was high (52%), much higher than that reported by authors of a 10-year Korean study (14.5%). A major difference was that in the Korean study predominated children with comorbidities and important immunosuppression. The multiresistance of *P. aeruginosa* strains was not significantly as reported in the Chinese study compared to Korean one. Mortality rates in the Chinese study did not significantly differ between previously healthy children and patients with co-morbidities. A previous administration of an appropriate treatment was essential in the evolution of the cases [18], [19].

A study conducted on more than 87,000 *P. aeruginosa* isolates in paediatric patients without cystic fibrosis and aged 1 - 17 years revealed a significant increase in the number of MDR isolates from 15.4% to 26% between 1999 and 2012. Carbapeneme resistance has increased from 9.4% to 20% in the same interval. The study showed that MDR strains were more common in paediatric intensive care units (PICU) among children with respiratory infections aged between 13 and 17. Resistance to other classes of antibiotics (aminoglycosides, fluoroquinolones, cephalosporins and

piperacillin-tazobactam) has also increased during the study period [6].

In our study, we reported 5 cases of wound infections and 4 patients with urinary tract reported as HAIs. *P. aeruginosa* may colonize chronic wounds and also gastrointestinal and urinary tracts, especially in hospitalized patients or patients with localized catheters, causing HAIs [11].

Infections caused by *P. aeruginosa* have always been troublesome for healthcare providers because of the intrinsic resistance of isolates to a wide variety of antimicrobials. *P. aeruginosa* is one of the major causes of HAIs due to minimal nutrition requirements and may be found almost anywhere in the hospital, including on objects. Numerous studies have shown that the risk factors associated with the acquisition of carbapenem-resistant strains are the presence of multiple co-morbidities, length of hospital stay, invasive procedures and previous use of antibiotics [1], [3].

Several studies have shown a positive correlation between the length of hospital stay prior to confirmation of carbapenem-resistant strains and the rate of contracting such a strain, and the risk of infection increased by 1% for each additional day of hospitalization. The antimicrobial sensitivity of *Ps. aeruginosa* isolates was still reported as valuable for Amikacin, Piperacillin - Tazobactam, Gentamicin, Ciprofloxacin, and Levofloxacin. A previous study indicated that monotherapy might play a role in the development of antibiotic resistance, and other studies have rather taken into account patient outcomes and safety, comparing carbapenem monotherapy and combination therapy. According to pharmacokinetic and pharmacodynamic studies, continuous carbapenem perfusion as monotherapy increased the therapeutic effects, while reducing side effects. Thus, the question of the association between antibiotic resistance and the use of carbapenems alone or in combination therapy have been raised in some recent studies [4], [13], [14], [16].

The limitation of our study consisted of the small group of patients and one-year statistical coverage. We intend to expand our research to a 5-year longitudinal descriptive study with more statistical variables including diagnoses and data regarding specific patients' therapies.

5. Conclusions

Our study provided several indications regarding the prevalence of healthcare-associated infections with *P. aeruginosa* in paediatric patients, possible useful for guiding antibiotic therapy. The sensitivity of circulating strains of *P. aeruginosa* was increased for Amikacin and Tobramycin. Antibiotic resistance of *P. aeruginosa* strains was important for Imipenem and Meropenem. These results are very useful for paediatric specialists to prescribe the appropriate treatment for their patients.

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