Epidemiological features and risk factors for mortality in *Pseudomonas aeruginosa* bacteremia in children

María T. Rosanova, M.D.[a], María S. Mussini, M.D.[a], Ana P. Arias, M.D.[a], María I. Sormani, M.D.[a], Alejandra Mastroianni, Laboratory Technician[b], María E. García, Biochemist[b], Vanesa Reijtman, Biochemist[b] and Claudia Sarkis, M.D.[a]

ABSTRACT

The objective was to describe the epidemiological, clinical, microbiological, and evolutionary characteristics and the risk factors for mortality.

Retrospective, cohort study. A total of 100 patients were included. Of these, 42 (42 %) had septic shock upon admission and 56 (56 %) were admitted to the intensive care unit. Bacteremia was primary in 17 patients (17 %); catheter-related, in 15 (15 %); and secondary, in 68 (68 %). The most common source of infection was the skin and mucous membrane. Resistance to one or more antibiotic groups was 38 %. Thirty-one patients died (31 %).

Risk factors for mortality were septic shock ($p < 0.0005$), admission to the intensive care unit ($p < 0.0001$), primary bacteremia ($p < 0.009$) or secondary, non-catheter-related bacteremia ($p < 0.003$), presence of mucocutaneous or pulmonary source of infection ($p < 0.004$), and multidrug resistance ($p < 0.01$) or resistance to carbapenems ($p < 0.01$).

Key words: *bacteremia,* Pseudomonas aeruginosa, *mortality, pediatrics.*

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a. Department of Epidemiological Control and Infectious Diseases.
b. Department of Microbiology. Hospital de Pediatría SAMIC "Prof. Dr. Juan P. Garrahan," Autonomous City of Buenos Aires.

E-mail address:
María T. Rosanova: M.D.: margris2@yahoo.com.ar

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INTRODUCTION

Pseudomonas aeruginosa (PAE) is a Gram-negative bacillus, an opportunistic nosocomial pathogen.[1-2] It causes a wide range of infections, especially, in immunocompromised hosts with burn wounds and carriers of cystic fibrosis, among others.[2-5] Treatment is challenging because of PAE's intrinsic antibiotic resistance and its ability to acquire new resistance mechanisms. PAE bacteremia is related to a high mortality.[6]

OBJECTIVES

To describe the epidemiological, clinical, microbiological, and evolutionary characteristics of PAE bacteremia. To assess the risk factors for mortality.

MATERIALS AND METHODS

This was a retrospective, cohort study in children older than 1 month and younger than 18 years admitted between 9/1/2014 and 9/1/2017 with PAE isolation in, at least, one blood culture with or without isolation in a different sterile site.

Data were collected from medical records and included age, sex, origin of bacteremia, underlying disease, prior antibiotic therapy, presence of neutropenia, use of vascular or urinary catheters, invasive procedures in the previous 72 hours, mechanical ventilation (MV) requirement, presence of septic shock at baseline, admission to the intensive care unit (ICU), antibiotic resistance, and clinical course.

Definitions

Prior exposure to antibiotics was defined as any antibiotic therapy received in the month prior to bacteremia.

Primary bacteremia: positive blood cultures for PAE without other concomitant source of infection.

Secondary bacteremia: positive blood cultures associated with an evident clinical source of infection related to the microorganism, with or without isolation.

Catheter-related bacteremia: isolation of PAE

in a blood culture from a peripheral vein and in a quantitative or semiquantitative catheter tip culture or from an implantable or semi-implantable catheter without other source of infection other than the catheter.

Shock was defined as a patient with systolic blood pressure below the 5th percentile of the normal range for age, in spite of fluid replacement or inotrope administration.

Deaths during hospitalization of patients diagnosed with PAE bacteremia were considered infection-related.

Microbiological analysis

Two samples were collected from peripheral blood and/or catheters and the clinical source of infection for culture, as applicable.

Blood samples were inoculated in PF Plus® and FN Plus® bottles (Biomérieux) and incubated in the Bact/Alert 3D® automated system (Biomérieux) during 5 and 7 days, respectively. Microorganisms were identified using a Maldi-Tof mass spectrometer in the Vitek MS® system (Biomérieux). Sensitivity tests were done using the Kirby-Bauer disc diffusion method and the Vitek 2C® automated system (Biomérieux). These tests were interpreted in accordance with the recommendations made in the Clinical and Laboratory Standards Institute (CLSI) guidelines.[7] Carbapenemases were detected using phenotypic methods and confirmed by molecular biology.

Sensitivity tests included the following antibiotics: piperacillin, piperacillin/tazobactam, ceftazidime, cefepime, meropenem and imipenem, gentamicin amikacin, quinolones, and colistin.

Resistance was defined when PAE was resistant to at least one group of active antibiotics. Multidrug resistance was defined when PAE was resistant to three or more families of antibiotics, including antipseudomonal penicillins (piperacillin), cephalosporins (ceftazidime, cefepime), carbapenems, aminoglycosides, monobactams, quinolones and/or polymyxins. Empiric antibiotic therapy was considered adequate if the isolated PAE strain was sensitive to at least one of the antibiotics used.

Statistical analysis

Data were processed using the Epi-Info version 6.0 software. Continuous outcome measures were expressed as median and interquartile range (IQR); whereas, categorical outcome measures, as absolute quantity and percent relative frequency.

The significance of differences ($p < 0.05$) was assessed based on outcome measure characteristics, with Fisher's exact test or the χ^2 test, as applicable. Potential risk factors for mortality due to PAE bacteremia were identified using a univariate analysis.

RESULTS

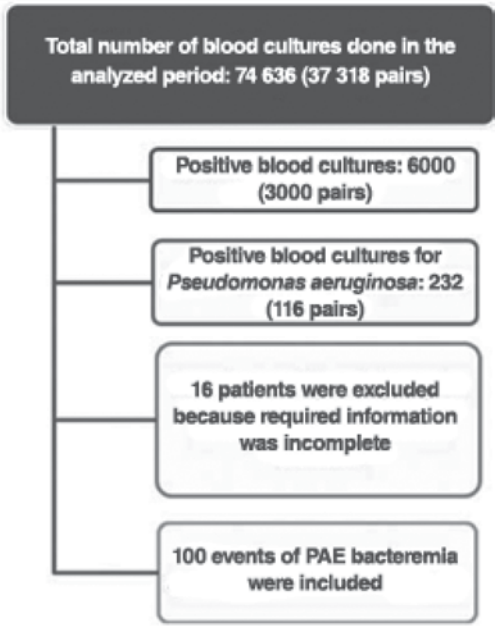
In the studied period, the incidence of PAE bacteremia was 3.1 isolations per every 1000 blood cultures (*Figure 1*).

A total of 100 events were included, which corresponded to 100 patients. All the information required was collected from the medical record review.

Patients' median age was 27 months (IQR: 6-88). Male sex predominated: 52 patients (52 %). An underlying disease was observed in 93 patients (93 %); blood disease and cancer were the most common ones. Eighty-five patients (85 %) had received antibiotics in the previous month. Invasive procedures were done in 60 (60 %), and 81 (81 %) had been previously hospitalized. Forty-two patients (42 %) had septic shock upon admission, and 56 (56 %) were admitted to the ICU. MV was required in 49 patients (49 %).

Bacteremia was primary in 17 patients (17 %); catheter-related, in 15 (15 %); and secondary, in 68

FIGURE 1. *Flow chart*



PAE: *Pseudomonas aeruginosa*.

(68 %). The most common source of infection was the skin and mucous membrane, in 21 patients; followed by the lungs, in 20; and the abdomen, in 14 (*Table 1*). Empiric treatment was adequate in 84 patients (84 %). Resistance to one or more antibiotic groups was observed in 38 strains, whereas 11 showed multidrug resistance. Fifteen strains were resistant only to carbapenems.

No carbapenemases were detected. All strains were sensitive to colistin (*Table 2*).

Thirty-one patients died (31 %). Risk factors for mortality in the univariate analysis were septic shock at baseline ($p < 0.0005$), admission to the ICU and MV requirement ($p < 0.0001$), primary bacteremia ($p < 0.009$) or secondary bacteremia ($p < 0.003$), presence of mucocutaneous or pulmonary source of infection ($p < 0.004$), and multidrug resistance ($p < 0.01$) or exclusive resistance to carbapenems ($p < 0.01$).

DISCUSSION

Bacteremia is a common manifestation of PAE infection; its incidence is approximately 1 event per every 1000 blood cultures,[1] somewhat lower than that observed in our study.

Immunocompromised patients and those with severe burn wounds, chemotherapy-induced neutropenia or underlying pulmonary disease are more likely to develop PAE infection.[6,8,9]

Although, in some series, an underlying disease in children was a factor correlated to mortality,[2,6] this was not the case in our study.

Kim et al.[10] demonstrated that, with an adequate empiric treatment, the presence of neutropenia did not increase mortality, similar to this series.

Cattaneo et al.,[11] assessed PAE bacteremia in cancer patients and reported similar mortality percentages between patients with and without neutropenia.

In our study, catheter-related bacteremia was not a risk factor for mortality, unlike primary or secondary bacteremia. This was similar to what was reported in other studies where catheter-related bacteremia was not associated with mortality.[11,12]

The secondary sources of infection in PAE bacteremia varied, with predominance of respiratory and mucocutaneous sources, like in our series.[10,11]

Kim et al.,[10] reported, in children with neutropenia, a 30 % and 20 % frequency of respiratory and mucocutaneous source of infection, respectively.

PAE bacteremia had a high rate of morbidity and mortality. High gross mortality rates were associated with patients that required admission to the ICU in some series.[11-13]

In other series, the presence of respiratory distress and MV requirement was an independent risk factor related to mortality.[1,13]

Consistent with other authors,[1,10,13] the clinical presentation of sepsis was also a predictor of mortality.

In this study, lethality was high and related to admission to the ICU, MV requirement, and the presence of sepsis.

PAE is intrinsically resistant to different antibiotic classes due to the reduction in the patency of its external membrane, the expression of efflux pumps, and the production of antibiotic-

TABLE 1. *Patient characteristics and type of bacteremia*

Outcome measure	n (%)
Mean age in months (IQR)	27 (6-88)
Underlying disease	93 (93)
Underlying blood disease and cancer	42 (42)
Heart disease	9 (9)
Immunodeficiency	9 (9)
Burn wound	7 (7)
Kidney malformation	7 (7)
Other	19 (19)
Prior antibiotic use	85 (85)
Prior hospitalization	81 (81)
Prior invasive procedure	60 (60)
Catheter	82 (82)
Admission to the intensive care unit	56 (56)
Mechanical ventilation	49 (49)
Septic shock	42 (42)
Median length of stay in days (IQR)	26 (14-61)
Secondary bacteremia	68 (68)
Primary bacteremia	17 (17)
Catheter-related bacteremia	15 (15)
Mucocutaneous source of infection	21 (21)
Pulmonary source of infection	20 (20)
Abdominal source of infection	14 (14)
Mortality	31 (31)

IQR: interquartile range.

TABLE 2. *Antibiotic sensitivity (100 strains)*

Antibiotic	Resistant (n)
Antipseudomonalpenicillins	16
Antipseudomonalcephalosporins	14
Carbapenems	30
Monobactams	7
Aminoglycosides	17
Quinolones	11
Polymyxins	0

inactivating enzymes, and is also capable of acquiring new resistance mechanisms through mutations. Prior antibiotic use favors the development of antibiotic resistance, which is consistent with the outcomes of this study.[1,4,6,9,10]

The consequences of resistance and the impact of an inadequate treatment on the course of patients with PAE bacteremia are not entirely clear. Carbapenems have been considered first-line agents for the treatment of severe PAE infections; however, resistance has increased.[10-14]

Some studies have suggested that the antibiotic resistance of PAE was not a predictor of mortality.[10] Other authors have reported that carbapenem-resistance would be associated with a higher mortality than from infections caused by sensitive strains.[11,12]

In other series, multidrug resistance was independently associated with an inadequate therapy, which was a major predictor of mortality, synergistic with the severity of the underlying disease.[10-14]

Carbapenem resistance and multidrug resistance were statistically significant predictors of mortality in our series. A high percentage of our patients received an adequate empiric therapy, which would explain the fact that the latter outcome measure did not show a statistically significant relation to mortality.

CONCLUSIONS

PAE bacteremia predominated among patients with an underlying disease. Mortality was high and risk factors included septic shock at baseline, admission to the ICU, MV requirement, presence of primary bacteremia or non-catheter-related secondary bacteremia, presence of mucocutaneousor pulmonary source of infection, and multidrug resistance or exclusive resistance to carbapenems. ■

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