

# Pneumococcal meningitis: A 12 year experience in a children's hospital prior to the universal immunization with a conjugate vaccine

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## ABSTRACT

**Introduction.** Pneumococcal meningitis is caused by *Streptococcus pneumoniae* and has high morbidity and mortality rates. The objective of this study was to identify the epidemiological and clinical characteristics, antibiotic sensitivity and evolution of pneumococcal meningitis in children prior to the introduction of the vaccine in Argentina.

**Methods.** Patients younger than 18 years old hospitalized at Hospital J.P. Garrahan between 1999 and 2010 were included. Children's microbiology lab records and case records were reviewed.

**Results.** One hundred and eleven children with *S. pneumoniae* meningitis were identified. Forty cases were found in the 1999-2002 period, 35 in the 2003-2006 period, and 36 in the 2007-2010 period. The mean age was 7 months old (range: 1-191). One hundred and four patients were immunocompetent (94%). Only 20 patients (18%) had an underlying disease. The most commonly observed clinical presentation was neurological involvement in 80 patients (75%), and sepsis in 59 (53%). Forty-nine patients (44%) had to be admitted to the ICU. A second clinical source of infection was identified in 24 patients (22%); half of these cases corresponded to pneumonia. Positive findings were observed in the cerebrospinal fluid culture of 103 patients (93%) and in the blood culture of 88 (79%).

Resistance to penicillin was identified in 15% of cases, while 5% showed resistance to cefotaxime. Antibiotic resistance was reduced over the years. Complications occurred in 56 patients (50%), and 11 (10%) died because of the infection.

**Conclusion.** Antimicrobial resistance by *S. pneumoniae* was reduced over time. It is important to maintain epidemiological surveillance to assess the impact of immunization in Argentina.

**Key words:** *Streptococcus pneumoniae*, meningitis, pediatrics, antibiotic resistance.

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## INTRODUCTION

Bacterial meningitis is an important cause of morbidity and mortality in pediatrics. In developed countries, it is estimated that between 10% and 20% of children with bacterial meningitis die because of this condition.<sup>1</sup> This rate increases up to 50% in developing

countries, with a large number of survivors with sequelae.<sup>2</sup>

The primary etiologic agents of bacterial meningitis in children include *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* type b.<sup>3</sup> Its frequency varies depending on the epidemiological and demographic characteristics, and the immunization schedule implemented in each region.

In Argentina, based on data published by the National Ministry of Health of Argentina in 2012, *S. pneumoniae* was still the main causative etiologic agent of bacterial meningitis.<sup>4</sup> Recent population studies have assessed the impact of pneumococcal meningitis in Argentina and found that *S. pneumoniae* was the cause of meningitis in 27% of patients with hearing loss, in 15% of patients with profound deafness, and in 17% of patients with mental retardation.<sup>5</sup>

The sensitivity of *S. pneumoniae* to antimicrobials has changed over the past years. Up-to-date knowledge regarding antibiotic sensitivity in the population is necessary in order to be able to indicate an adequate empiric antibiotic therapy when pneumococcal meningitis is suspected.

The objective of this study was to evaluate the epidemiological, clinical and evolutionary characteristics of children with pneumococcal meningitis and to establish the evolution of antimicrobial sensitivity prior to the introduction of the conjugate vaccine in the Argentine immunization schedule in 2011.

## MATERIAL AND METHODS

This was a retrospective, observational study. All patients younger than 18 years old admitted to the hospital

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with a diagnosis of *S. pneumoniae* meningitis between January 1<sup>st</sup>, 1999 and December 31<sup>st</sup>, 2010 were included. Inclusion criteria were that children had to be younger than 18 years old, had to be hospitalized with the diagnosis of acute meningitis or meningoencephalitis, and *S. pneumoniae* had to be identified in cerebrospinal fluid (CSF) and/or blood culture samples. Patients diagnosed with secondary meningitis, ventriculo peritoneal shunt or postoperative meningitis and those who were pneumococcus positive in the latex agglutination test with no microbiological isolation were excluded.

Data were obtained by reviewing clinical records and microbiological tests. Demographic, clinical and evolutionary characteristics were recorded, together with antimicrobial sensitivity in each case. Thirty day post-discharge mortality and neurological sequelae at the time of discharge were assessed. The study was conducted in accordance with health research ethical principles.

**Microbiological aspects:** *S. pneumoniae* was characterized because it displayed the typical morphology by Gram staining and because it presented alpha hemolysis in Columbia Agar plates with 5% sheep blood. Final identification was conducted by growth inhibition in optochin discs (Britania Lab, Argentina), solubility in bile salts and agglutination with latex particles (Directigen, Becton Dickinson, Cockeysville, Maryland, USA). All strains showed penicillin sensitivity in 1- $\mu$ g oxacillin discs, according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI), USA. The minimum inhibitory concentration (MIC) to penicillin and third-generation cephalosporins was determined by the Etest method (Biomérieux, Argentina).

Sensitivity to penicillin and third-generation cephalosporins was determined as per the cut-off points suggested by the CLSI for meningitis:<sup>6</sup> MIC for sensitivity  $\leq 0.06 \mu\text{g/mL}$  and MIC for resistance  $\geq 0.12 \mu\text{g/mL}$ . For third-generation cephalosporins, Pneumococci were considered sensitive if the MIC was  $\leq 0.5 \mu\text{g/mL}$  and resistant if the MIC was  $\geq 2 \mu\text{g/mL}$ . Pneumococci showing MIC =  $1 \mu\text{g/mL}$  were considered as having intermediate sensitivity.

## RESULTS

One hundred and eleven children with a clinical presentation compatible with *S. pneumoniae* meningitis and who tested positive for this condition in CSF and/or blood cultures between January 1<sup>st</sup>, 1999 and December 31<sup>st</sup>, 2010

were included. Their mean age was 7 months old (range: 1-191 months); 58 patients (54%) were girls. One hundred and four patients were immune competent (94%). Only 7 patients (6%) had some sort of immune compromise: nephrotic syndrome in 4 patients, HIV in 1 patient, and AML in 1 patient.

Twenty-three patients (18%) had an underlying disease, and the most common were congenital heart disease in 7 patients (6%), central nervous system conditions in 3 patients (3%), and congenital anomalies with no heart disease in 3 patients (3%).

Only 2 patients (2%) had received a pneumococcal vaccine. The mean evolution prior to diagnosis was 2 days (range: 1-7).

Forty-nine patients (44%) had to be admitted to the ICU, with a mean length of stay of 5 days; 33 patients (30%) required mechanical ventilation.

At the time of admission to the hospital, all children had fever, and 80 patients (72%) had at least one neurological symptom. In this series, an altered state of consciousness was the most commonly observed sign. Meningitis was associated with a second clinical source of infection in 24 patients (22%): pneumonia in 12 patients (50%), otitis media in 7 patients (29%), periorbital cellulitis in 2 patients (8%), sinusitis in 2 patients (8%), diarrhea in 2 patients (8%). Sepsis developed in 59 patients (53%). The mean duration of fever was 3.5 days (range: 2-15).

Lab tests upon admission showed a mean white blood cell count of  $15\ 900/\text{mm}^3$  (range: 5-45 000) and a erythrocyte sedimentation rate in the first hour of 80 mm (range: 40-120).

CSF cytochemistry showed the following mean values:  $1335 \text{ cells}/\text{mm}^3$  (range: 0-10 000), glucose 28 mg/dL (range: 0-51) and proteins 250 mg/dL (range: 11-967). Predominance of polymorphonuclear leukocytes was observed in 82% (n= 91 patients). At the time of admission, a computed tomography scan of the brain was indicated in 84 patients (77%), which was pathological in 56 patients (66%).

The initial empiric treatment was adequate in 107 patients (96%). In all cases, third-generation cephalosporins were used as first-line treatment. In addition, vancomycin was added to the treatment in 22 patients (20%). The mean duration of antibiotic therapy was 13 days (range: 1-45). Corticosteroids were administered before antimicrobials in 100 patients (90%).

At least one complication related to meningitis was observed in 58 children (52%).

The most common complications were subdural fluid collection in 24 patients (46%), non-communicating hydrocephalus in 7 patients (13%), vasculitis in 3 patients (6%), subdural empyema in 1 patient (2%), and brain abscess in 1 patient (2%).

The mean length of stay in the hospital was 18 days (range: 1-150). Thirty day post-event mortality was 10% (11 patients).

Thirty-six patients (33%) had permanent neurological sequelae: developmental delay in 10 patients (9%), epilepsy in 6 patients (5%), hemiparesis in 6 patients (5%), and cranial nerve involvement in 4 patients (4%). During follow-up, hearing was assessed only in 54 patients, and 10 (19%) showed certain degree of hearing involvement.

*S. pneumoniae* was isolated in all patients: in the CSF of 103 patients (93%) and in the blood culture of 88 patients (79%). Upon identification, 94 (85%) strains were sensitive to penicillin and 105 (95%) were sensitive to third-generation cephalosporins.

By dividing the study into three subsequent periods of 4 years each (period I: 1999-2002; period II: 2003-2006; period III: 2007-2010), it was observed that penicillin resistance was reducing throughout all periods: 10/40 (25%) over period I, 5/35 (14%) over period II, and 2/36 (5%) over period III. However, resistance to third-generation cephalosporins was only observed in the first period (6/40 cases). As seen all over the world, no vancomycin-resistant *S. pneumoniae* was identified.

## DISCUSSION

Invasive pneumococcal disease is one of the main causes of morbidity and mortality in the pediatric age group. At present, in Argentina, *S. pneumoniae* is the main causative agent of bacteremia and bacterial meningitis in children.<sup>3</sup>

Meningitis, together with sepsis, are the most severe clinical forms of invasive *S. pneumoniae* disease given its high mortality and associated sequelae rates.<sup>4</sup> Prior to the introduction of the pneumococcal conjugate vaccine, invasive *S. pneumoniae* meningitis was the prevalent etiology in children younger than 2 years old.<sup>7</sup> Pneumococcal meningitis has been reported in even younger children.<sup>8,9</sup> In agreement with the literature, in our series the mean age of patients was 7 months old.

Even though immune system disturbances, a history of basilar skull fracture and CSF

fistulae are considered predisposing factors to *S. pneumoniae* meningitis,<sup>10</sup> most cases are observed in previously healthy children. The frequency of comorbidities identified in the literature ranges from 13%<sup>11</sup> to 32%.<sup>12</sup> In this study, 18% of children had an underlying disease.

The most common neurological sign of *S. pneumoniae* meningitis described in the literature and in this study was an altered state of consciousness.<sup>11</sup>

An increase in the number of cells observed in CSF, above 500 cells/mm,<sup>3</sup> hypoglycorrhachia and hyperproteinorrhachia have been consistently described in the different series of patients with *S. pneumoniae* meningitis.<sup>9-13</sup> Geiseler, et al.<sup>13</sup> studied 1064 patients with bacterial meningitis and only 1.5% had normal cellularity. In this study, all patients who had meningitis without pleocytosis corresponded to *Neisseria meningitidis* meningitis.

Complications and secondary morbidity are the most serious problems associated with meningitis. Some studies have found a higher rate of neurological complications in patients whose etiologic agent was *S. pneumoniae*.<sup>14,15</sup> A study conducted on 81 meningitis patients at Hospital de Niños Pedro de Elizalde, in the City of Buenos Aires, reported that 60% of patients with *S. pneumoniae* meningitis had complications, compared to 22% of patients with other etiologies.<sup>15</sup> Abate, et al.<sup>16</sup> found that 42% of 221 patients with *S. pneumoniae* meningitis experienced complications. In this study, half of patients had at least one meningitis-associated complication, while a third of them developed neurological sequelae.

According to the bibliography, mortality associated with pneumococcal meningitis ranges between 2.6%<sup>6</sup> and 11.4%.<sup>17</sup> In our study, the mortality rate was 10%, similar to other pediatric studies.

Antibiotic resistance by *S. pneumoniae* varies depending on the local epidemiological characteristics, circulating serotypes, administration of pneumococcal vaccines, and local guidelines on the use of antimicrobials.<sup>18</sup>

The evolution of antibiotic resistance by *S. pneumoniae* in Latin America has been described in the reports issued by the Surveillance System for the Bacterial Agents Responsible for Pneumonia and Meningitis (SIREVA), which has been established to monitor antibiotic sensitivity and predominant serotypes at a regional level. In 2006 in Argentina, 23.3% of strains of *S. pneumoniae* meningitis were identified as penicillin-resistant,

and 5.4% of pneumococci, as resistant to third-generation cephalosporins.<sup>19</sup> In 2012, penicillin-resistance was observed in 20.8% of strains, with no strain being resistant to third-generation cephalosporins.<sup>20</sup> This is consistent with the reduction of antibiotic resistance in terms of MIC over the study observation period.

In those countries where universal immunization with a pneumococcal vaccine has been implemented, a significant reduction in the number of hospitalizations due to meningitis<sup>21</sup> and increased non vaccine serotypes have been described.<sup>22</sup>

Based on circulating serotypes, studies conducted in Argentina reported a potential vaccine coverage against invasive infections of 73%<sup>23</sup> and 2.2%<sup>24</sup> with the 10 and 13 valent conjugate vaccines, respectively. The recent inclusion of this vaccine in the national immunization schedule of Argentina points to the need of continuous surveillance to find out the impact of this action on pneumococcal meningitis epidemiology across the country.<sup>25</sup>

The selection of an empiric antibiotic treatment for *S. pneumoniae* meningitis depends on penicillin and third-generation cephalosporin resistance patterns observed in each region. According to the results reported in this and other regional studies,<sup>19</sup> third-generation cephalosporins continue being the recommended antibiotic for primary meningitis in the community for immunocompetent hosts.

The retrospective nature of this study, the difficulty to perform a long-term follow-up to assess sequelae, and the fact that *S. pneumoniae* serotypes of cases included in the study were not identified account for the main limitations of this study.

## CONCLUSIONS

The number of pneumococcal meningitis cases was similar along the 12 year study period, but resistance decreased during the period of study.

The latest finding of *S. pneumoniae* resistant to third-generation cephalosporins corresponded to 2001. It is necessary to continue with epidemiological surveillance of the number, resistance patterns and circulating serotypes of *S. pneumoniae* as of the inclusion of the pneumococcal vaccine in the national immunization schedule to evaluate possible modifications in this setting. ■

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