Ten-Year Review of Invasive Pneumococcal Diseases in Children and Adults from Uruguay: Clinical Spectrum, Serotypes, and Antimicrobial Resistance

Maria Hortal, MD; Teresa Camou, MBS; Rosario Palacio, MD; Hugo Dibarboure, MD; and Alberto Garcia, MD

ABSTRACT

Objectives: Since 1987, the Reference Laboratory of the Ministry of Health of Uruguay has been monitoring infections due to Streptococcus pneumoniae in patients under 5 years of age, in those between 5 to 14 years of age, and in adults. The purpose of the present study was to retrospectively analyze a 10-year collection of invasive S. pneumoniae isolates from children 5 to 14 years of age and adults.

Methods: The Reference Children's Hospital, Pasteur Hospital, and two private hospitals in Montevideo as well as four hospitals located in other representative areas of the country participated in the pneumococcal surveillance program. Based on the information available at the Microbiology Department of the Central Public Health Laboratory (demographic data, date and site of isolate, and clinical diagnosis), all patients with an invasive pneumococcal disease were recorded. Pneumonia was clinically and radiologically diagnosed and etiology was assessed by isolation of S. pneumoniae from blood or pleural fluid. All specimens were collected at the Emergency Service. Capsular serotyping and antimicrobial susceptibilities were determined for each isolate.

Results: During the 10-year period, 228 invasive S. pneumoniae were identified and included in the study (blood, n = 129; cerebrospinal fluid [CSF], n = 73; pleural fluid, n = 20; peritoneal fluid, n = 3; synovial fluid, n = 1; pericardic fluid, n = 1; abscess, n = 1). The most frequent clinical presentations were pneumonia (n = 71) and meningitis (n = 69). Thirty-five adults had an underlying condition including, four with malignancies, four with lupus, two with human immunodeficiency virus (HIV)-infected, and two patients in hemodialysis among others. Eighteen of the 228 patients died (7.9% fatality rate), but only four of these had an underlying condition. Eleven fatal cases were attributable to meningitis (2 children, 9 and 11 years old; 9 adults, mean age, 59 y). Four patients with pneumonia and three with sepsis died, including a splenectomized woman. Nine different capsular serotypes (1, 5, 7, 9, 12, 15, 19A, 20, and 23A) were identified among the 18 fatal cases. Resistance to penicillin, generally combined with trimethoprim-sulfamethoxazole, fluctuated annually, not surpassing 10%.

Conclusions: The study results indicated that 96% of the serotypes involved in severe pneumococcal diseases were included in the 23-valent vaccine and that S. pneumoniae resistance to penicillin was moderate.

Key Words: antimicrobial resistance, pneumococcal disease, serotype distribution


The expanded Program on Immunization (EPI) and supplementary vaccines used regularly and consistently by the health authorities initiative in Uruguay have reduced and almost eliminated several infectious diseases including polio, mumps, measles, rubella, and Haemophilus influenzae type B invasive infections. However, there still are infections caused by microorganisms capable of producing high morbidity and mortality, hospitalizations, and social costs. This is the situation with infections caused by Streptococcus pneumoniae, which has some peculiar characteristics. Although it affects people at any age, the severity and frequency are greater in extreme ages of life. The prevention of these infections in adults is one of the concerns faced by Public Health. The increasing resistance to β-lactam antibiotics and the phenomenon of multiresistance, observed among pneumococci worldwide, are additional causes of concern. This resistance is difficult to overcome; it increases costs of medical care and interferes with the outcome of the disease. These factors emphasize the need for resources for the specific prevention of invasive pneumococcal infections in Uruguay, as in the rest of the world.
Since 1983, a 23-valent pneumococcal polysaccharide vaccine has been available, containing the serotypes most frequently isolated in cerebrospinal fluid (CSF), blood, and pleural and synovial fluids from patients from various countries. This vaccine gives immunocompetent individuals a reasonable degree of protection. Although the immunity conferred averages 80%, many factors lead to its underutilization. Revaccination after 3 to 5 years is recommended for some at risk groups, such as the elderly. The capsular polysaccharide vaccine, which comprises T-cell-independent antigens, is poorly immunogenic in infants whose immune systems are immature. Therefore this vaccine is not recommended for use in children younger than 2 years of age.

The present goal is to prepare a 7- to 11 valent protein-conjugated vaccine containing the most frequently occurring pediatric pneumococcal types that will prevent the majority of invasive infections. These vaccines induce immunologic responses during the first months of life and, at the same time, provide an effective immunologic memory. This type of vaccine also could be useful for protection in immunocompromised people or in elderly people with a diminished immunologic response. Frequency and serotype distribution vary according to the age of the patient, and because there is geographic variability of pneumococcal serotypes that cause invasive infections, the potential benefit of such vaccines should be determined for each region. Consequently, for an adequate formulation of these vaccines and for their rational use, it is necessary to know which capsular types are locally predominant in systemic infections of children and adults.

Since 1987, the Reference Laboratory of the Ministry of Health has been monitoring these infections, to characterize the S. pneumoniae isolated from patients under 5 years of age, those between 5 and 14 years of age, and from adult patients. The purpose of the present study was to retrospectively analyze a 10-year collection of invasive S. pneumoniae isolates from children, aged 5 to 14 years, and adults.

MATERIALS AND METHODS

Study Population

The population of Uruguay is 3,146,200 million inhabitants (National Census, 1996) of whom approximately 50% reside in the metropolitan region of Montevideo. In 1996, infant mortality was 17.5 per 1000 live births. In Uruguay, 35% of the total population receives health care from the government health system. The EPI is coordinated and defined at the national level by the Ministry of Health. The Reference Children's Hospital, Pasteur Hospital, and two private hospitals in Montevideo as well as four hospitals located in other representative areas of the country participated in the pneumococcal surveillance program.

To assess the occurrence of invasive pneumococcal disease among children older than 5 years and adults, 10 years of laboratory data were reviewed (January 1987 to December 1997). Based on the information available at the Microbiology Department of the Central Public Health Laboratory (demographic data, date and site of isolate, and clinical diagnosis), all patients with an invasive pneumococcal disease were recorded. Some children and adults were outpatients, but most of them were hospitalized with community-acquired infections. Pneumonia was clinically and radiologically diagnosed and etiology was assessed by isolation of S. pneumoniae from blood or pleural fluid. All specimens were collected at the Emergency Service. Only one isolate per patient was considered.

Microbiologic Methods

Conventional bacterial methods were used for S. pneumoniae identification (colonial morphology, optochin test, bile solubility). According to the National Committee for Clinical Laboratory Standards (NCCLS) criteria, susceptibility to seven antimicrobial agents was assayed by disk diffusion technique (oxacillin, erythromycin, chloramphenicol, trimethoprim-sulfamethoxazole [TMP-SMZ], tetracycline, rifampin, and vancomycin).

In strains resistant to oxacillin (≤19 mm), the minimal inhibitory concentration (MIC) was determined by broth microdilution or E-test (AB Biodisk, Solna, Sweden) for penicillin, cefotaxime, and ceftriaxone. Isolates with MIC values to penicillin of less than 0.1 mg/L were considered susceptible; MICs 0.1 to 1.0 mg/L, intermediate resistant, and those with MIC values above 1.0 mg/L were defined as resistant, according to the guidelines of the NCCLS. The same guidelines applied when other antibiotics were considered. Multiresistance was defined as being resistant to three or more antimicrobial classes.

Capsular serotyping was performed in Uruguay, based on the Quellung technique, according to a chessboard scheme using 12 pools of antisera and additional factors produced by the Statens Seruminstitut (SSI) of Copenhagen, Denmark. Periodically, isolates were sent to the SSI, for quality control and factoring of the least frequent types.

RESULTS

During the 10-year period, 228 invasive S. pneumoniae were identified and included in the study (blood, n = 129; CSF, n = 73; pleural fluid, n = 20; peritoneal fluid, n = 3; synovial fluid, n = 1; pericardial fluid, n = 1; abscess, n = 1). Table 1 lists the different pathologies according to age groups in those patients whose age was recorded. The most frequent clinical presentations were pneumonia.
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Table 1. Age Distribution of Invasive Pneumococcal Infections According to Clinical Diagnosis

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>5-14</th>
<th>15-24</th>
<th>25-44</th>
<th>45-64</th>
<th>&gt;65</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 171 (100%)</td>
<td>n = 28 (%)</td>
<td>n = 7 (%)</td>
<td>n = 31 (%)</td>
<td>n = 41 (%)</td>
<td>n = 64 (%)</td>
</tr>
<tr>
<td>Meningitis n = 69 (40%)</td>
<td>8 (29)</td>
<td>3 (43)</td>
<td>18 (58)</td>
<td>21 (51)</td>
<td>19 (30)</td>
</tr>
<tr>
<td>Pneumonia n = 71 (42%)</td>
<td>20 (71)</td>
<td>3 (43)</td>
<td>6 (19)</td>
<td>13 (32)</td>
<td>29 (45)</td>
</tr>
<tr>
<td>Other n = 31 (18%)</td>
<td>1 (14)</td>
<td>7 (23)</td>
<td>7 (17)</td>
<td>16 (25)</td>
<td></td>
</tr>
</tbody>
</table>

*Age not recorded for 57 patients; †bacteremia or sepsis, peritonitis, cellulitis, etc.

(n = 71) and meningitis (n = 69). Clinical presentations varied depending on age. In elderly people pneumonia predominated, whereas meningitis was most frequently observed in patients between 25 and 65 years of age. Other pathologies, including sepsis or bacteremia (n = 22), peritonitis (n = 2), abscess (n = 2), and others (n = 5), were not recorded among children.

Thirty-five adults had an underlying condition, including four with malignancies, four with lupus, two with human immunodeficiency virus (HIV) infection, and two patients in hemodialysis, among others. Eighteen of the 228 patients died (7.9% fatality rate), but only four of these had an underlying condition. Eleven fatal cases were due to meningitis (2 children, 9 and 11 years old; 9 adults, mean age, 59 y). Four patients with pneumonia and three with sepsis died, including a splenectomized woman. Nine different capsular serotypes (1, 5, 7, 9, 12, 15, 19A, 20, and 23A) were identified among the 18 fatal cases.

Table 2 shows the serotype distribution of the predominant pathologies and, in order of frequency, the 12 most frequently noted serotypes, which represented 81.1% of the S. pneumoniae associated with systemic infections. Seven of the predominant capsular serotypes persisted over the observation period and were responsible for 71% of pneumonia cases and 50.6% of meningitis. Serotype 5 and 14 were more frequently associated with pneumonia, whereas group-type 12-12F predominated in meningitis. Only 3.9% of serotypes identified were not included in the 23-valent vaccine, and serotypes 2 and 53F included in this vaccine, were not diagnosed during the surveillance period. Group types 11, 18-18F, and 19 only became associated with systemic infections after 1994.

Table 3 presents the occurrence of antimicrobial resistance by years. Resistance to penicillin, generally combined with TMP-SMZ, fluctuated annually, not surpassing 10%.

The 20 isolates resistant to oxacillin showed MICs between 0.1 and 4.0 mg/L (10 intermediate and 10 resistant). Of those isolates, eight had MIC values of 1.0 mg/L for cefotaxime and ceftriaxone. The majority of the resistant isolates belonged to serotype 14 (17/20), but none of the isolates from the fatal cases were resistant to penicillin.

Of 28 strains resistant only to TMP-SMZ, 10 were already present in the earlier years of the study (1987–1993). Two of them belonged to serotype 14 and 16 (61%) belonged to the following serotypes: 11 (n = 6), 1 (n = 5), and 5 (n = 5). Only two multiresistant strains were recognized (serotypes 11 and 23F). All the isolates were susceptible to vancomycin and rifampin.
### Table 3. Susceptibility to Antibiotics of Invasive Pneumococcal Isolates by Years

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Isolates</th>
<th>Susceptible Isolates n = 228</th>
<th>Number of Isolates</th>
<th>TMP-SMZ n = 28</th>
<th>Oxacillin-TMP-SMZ n = 19 (86%)</th>
<th>Tetracycline n = 6</th>
<th>Oxacillin-Erythromycin n = 1</th>
<th>TMP-SMZ-Erythromycin n = 1</th>
<th>Multiresistant n = 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987-90</td>
<td>14</td>
<td>9 (64)</td>
<td>4 (29)</td>
<td>1 (7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1991-93</td>
<td>22</td>
<td>18 (72)</td>
<td>6 (24)</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1994</td>
<td>55</td>
<td>35 (64)</td>
<td>9 (16)</td>
<td>5 (9)</td>
<td>4 (7)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1995</td>
<td>54</td>
<td>45 (83)</td>
<td>3 (6)</td>
<td>5 (9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>1996</td>
<td>43</td>
<td>35 (81)</td>
<td>3 (7)</td>
<td>4 (9)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1997</td>
<td>37</td>
<td>30 (81)</td>
<td>3 (8)</td>
<td>3 (8)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

\*TMP-SMZ = trimethoprim-sulfamethoxazole.

### DISCUSSION

The 23-valent vaccine available since 1983 is recommended for persons aged 65 years of age or older and for persons between 2 and 64 years of age who have chronic illness with an increased risk for severe pneumococcal disease, for example, asplenic patients and those with sickle cell disease, cardiac or pulmonary chronic diseases, diabetes mellitus, malignancies, organ or bone marrow transplantation, HIV or acquired immunodeficiency syndrome (AIDS).16

The U.S. Advisory Committee on Immunization Practices (ACIP) and committees from other countries,17,18 including Uruguay, recommend vaccination of persons at increased risk for severe morbidity and mortality associated with pneumococcal disease. However, immunization programs in adults have not been as successful as expected.7

The present study suggests that the additional risk of certain underlying conditions should be considered. In this series 27% of cases occurred in patients between 25 and 65 years of age. It is advisable to evaluate individual risks before offering vaccination to patients.19 Likewise, when elective splenectomy is being planned, pneumococcal vaccine should be administered at least 2 weeks before surgery with revaccination 3 years after the first dose.20

The immunogenicity of pneumococcal vaccines can be evaluated by serologic studies of antibody response, indicated by a twofold or greater rise in serotype-specific antibodies, developed within 2 to 3 weeks after vaccination.21,22 Efficacy can be estimated by the decrease of pneumococcal invasive diseases and by closely monitoring the types of isolates involved in disease occurring either in vaccinated people or in unprotected individuals. It is important to survey the susceptibility to first line antibiotics, to support the empirical management of patients, and to verify if all resistant types are included in the vaccine formulas. To date, it is noteworthy that all β-lactam-resistant isolates detected in our study belonged to serotypes represented in the 23-valent vaccine. During the 1993-97 period, a progressive increase in the percentages of resistance to penicillin among isolates from children under 5 years of age was described.15 The 1987-1992 studies23 demonstrated a low frequency of resistance (6%), but in 1994 penicillin resistance increased to 29%, reaching 40% in 1996,15 whereas resistance to penicillin among invasive isolates from older children and adults remained lower (10%).

These notable differences were probably attributable to the introduction and dissemination among the youngest group of a clone serotype 14 resistant to penicillin and to TMP-SMZ.24 Serotype 14 isolates resistant to penicillin, although predominant in the study population younger than 5 years, was also identified in some adults. Molecular techniques were used to demonstrate that these belonged to the same clone (Camou T. Personal communication).

Results indicate that because of the baseline provided by this study it is possible to certify that 97% of the serotypes involved in severe pneumococcal diseases were included in the 23-valent vaccine. If these epidemiologic data are taken into account for the application of the new protein polysaccharide conjugate vaccines, it is noteworthy that the most frequently isolated serotypes in the surveillance population, serotypes 1 and 5, are included in only two of those vaccines, and type 7F is represented in only one of those vaccines.25,26 Therefore additional epidemiologic studies are mandatory to predict the potential success of the vaccines and, after the vaccine application, to detect changes in S. pneumoniae serotype prevalence or in susceptibility patterns.

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### REFERENCES


