Invasive pneumococcal disease in a third level pediatric hospital in Mexico City: epidemiology and mortality risk factors

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Abstract

Objective. To assess the epidemiologic characteristics of invasive pneumococcal diseases (IPD) among a population in a pediatric hospital in Mexico City and analyze mortality-related risk factors, serotype distribution and antibiotic susceptibility related to *S.pneumoniae*. **Material and Methods**. We performed a retrospective review of IPD cases at a third level pediatric hospital between 1997-2004. **Results**. A total of 156 patients were included. The mortality rate was 27.5% and was associated with six pneumococcal serotypes: 14, 6B, 23F, 6A, 19F and 19A. There was no relationship between mortality and antimicrobial susceptibility pattern. A total of 28.2% of isolates were resistant to penicillin and 24.6% were resistant to cefotaxime. A statistically significant relationship was observed between mortality and previous underlying disease (CI 95%; 2.5-18.3; $p< 0.05$) using a multivariate logistic regression model. **Conclusions**. Our outcomes show that IPD mortality in our population is closely related to underlying disease and to six serotypes, five of which are included in the 7-valent pneumococcal conjugate vaccine.

Key words: pneumococcal infections; epidemiology; microbial sensitivity tests; Mexico

Gómez-Barreto D, Espinosa-Monteros LE, López-Enríquez C, Jiménez-Rojas V, Rodríguez-Suárez R. Enfermedad neumocócica invasora en un hospital pediátrico de tercer nivel en la Ciudad de México: características epidemiológicas y factores de riesgo asociados con mortalidad. Salud Publica Mex 2010;52:391-397.

Resumen

Objetivo. Conocer la epidemiología de la enfermedad neumocócica invasora (ENI) en un hospital pediátrico y analizar los factores de riesgo relacionados con la mortalidad, la distribución de serotipos y el patrón de susceptibilidad de *S. pneumoniae*. **Material y métodos.** Revisión retrospectiva de los casos de ENI en un hospital pediátrico de tercer nivel, entre 1997 y 2004. **Resultados**. En 156 pacientes la mortalidad fue de 27.5%. Los serotipos de neumococo más frecuentemente relacionados con la mortalidad fueron: 14, 6B, 23F, 6A, 19F y 19A; no hubo relación de mortalidad con la resistencia a antibióticos. El 28.2% mostró resistencia a penicilina y 24.6% a cefotaxima. A través del modelo multivariado, se encontró una relación estadísticamente significativa entre la mortalidad y enfermedad previa (IC 95%; 2.5-18.3; $p<0.05$). **Conclusiones**. La mortalidad asociada a la ENI tuvo relación significativa con antecedente de una enfermedad previa y con seis serotipos, cinco incluidos en la vacuna neumocócica conjugada 7-valente.

Palabras clave: infecciones neumocócicas; epidemiología; pruebas de sensibilidad microbiana; México

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Pneumococcal-related infections are a significant cause of morbidity and mortality worldwide.[1,2] Invasive pneumococcal disease (IPD) has a fatality rate between 2.6% and 6% in industrialized countries,[3] and some studies have described the relationship between mortality risk and host factors (age, depleted immune response, chronic disease and infection site).[4-6] There is also evidence of an association between pneumococcal serotype and risk of serious and fatal disease.[7]

The annual incidence of the disease in industrialized countries where the 7-valent pneumococcal conjugate vaccine (PCV7) is not universally administered is 160 cases per 100 000 inhabitants.[1] Attack rates are 1-2 per 1 000 children for the invasive form of pneumococcal disease, with *Streptococcus pneumoniae* isolated in children less than 2 years of age.[1] Nevertheless, the current *Streptococcus pneumoniae* disease attack rate, both invasive and non-invasive, is underestimated because the real load is determined by pneumonia and otitis media, conditions that are not regularly reported.[8,9] In addition, many invasive infections caused by pneumococcus are bacteremias with no apparent infectious focus.

A study of 728 children (2000-2005) describes the pneumococcal serotypes in IPD in 10 Latin American countries (SIREVA study), including Mexico. This study does not, however, make any references to risk factors associated with death or with IPD in children.[10]

The current IPD load is considered a worldwide public health problem since every year 1.2 million children die from this disease, surpassing the number of deaths caused by any other infectious diseases that are preventable through vaccination. Thus, this is a very significant problem for developing countries. In addition, in industrialized countries such as the United States, pneumococcus caused 40 000 deaths each year (mainly adults) before universal vaccination was implemented.[1,9,11]

Another relevant global aspect of epidemiological pneumococcus is that in the past 20 years there has been a decrease in susceptibility to penicillin and other antibiotics[10] resulting in strategic changes in IPD therapeutics leading to increased morbidity and treatment costs.[12-14] At present, the best way to control IPD –especially for the pediatric population under 2 years of age and for patients with IPD factors– is the application of the PCV7. This is the only vaccine approved by the Food and Drug Administration (FDA) and has shown to be especially effective for IPD (97%).[15] Furthermore, additional beneficial effects have been reported, such as herd immunity and a decreased resistance to penicillin and other antibiotics for serotypes included in the vaccine, as well as for the new serotypes (post-vaccine) associated with IPD.[16-19]

This study was performed in a third-level pediatric hospital in Mexico City to determine the conditions associated with IPD, pneumococcal serotypes, antibiotics susceptibility and host risk factors and their association with morbidity and mortality rates. In addition, we aimed to identify the potential impact of conjugate vaccines in order to achieve, as reported in other countries, decreased IPD-related mortality and increased susceptibility of pneumococcus to different antibiotics.[19]

Materials and Methods

We performed a retrospective review of patients who had *S.pneumoniae* isolated in a sterile site [cerebrospinal fluid (CSF), blood, pleural fluid, peritoneal fluid, synovial secretion] from January 1997 to August 2004 and who had no history of vaccination with PCV7, since this vaccine has only been applied since 2007 as part of nationwide vaccinations in Mexico. The protocol was submitted to the Institutional Research Committee and approval of this clinical study was obtained. The following variables were reviewed: age in months, gender, attendance in daycare centers, nutritional status, previous health status, use of beta-lactam antimicrobials within 30 days of condition onset, and isolation. We analyzed the relationship between age (younger than 24 months), previous health status, *S. pneumoniae* serotype, antimicrobial susceptibility and beta-lactam antimicrobials mortality rate. The mortality risk was the most important variable in the study.

Identification and susceptibility test

Pneumococcus was identified by standardized microbiological methods. Penicillin and cefotaxime susceptibility tests were conducted with the microdilution method as established by the Clinical and Laboratory Standards Institute (CLSI before NCCLS).[20] The serotyping was conducted using *Quellung* reaction with serum produced by the Statens Institute (Copenhagen, Denmark); the serogroup and serotype were identified according to Danish nomenclature.[21] All these procedures were conducted in a specialized reference laboratory for streptococcal disease in the Hospital Infantil de México Federico Gomez, in Mexico City.

Clinical definitions

The clinical syndromes found in patients from whom *S. pneumoniae* was isolated from a sterile site (specified as inclusion criteria) were defined as invasive pneumococcal disease according to international standards.[22]

Pneumococcal meningitis: any patient with neurologic findings compatible with meningitis and pneumococcal growth in the CSF culture associated with cytochemical abnormalities (low glucose, elevated proteins and increased cellularity with polymorphonuclear predominance). *Pneumococcal bacteremia:* a positive blood culture in a patient with fever and no localized infectious source. *Pneumonia with effusion*: a patient with clinical and/or radiological data compatible with pneumonia and/or effusion and positive blood and/or pleural fluid cultures. *Pneumococcal peritonitis:* isolation of *S. pneumoniae* in the peritoneal fluid or in blood from a patient with acute peritonitis and/or compatible cytochemical abnormalities of the peritoneal fluid. *Pneumococcal septic arthritis:* a patient with arthritis and pneumococcus isolated from synovial fluid.

Statistical method

A retrospective review was conducted to assess risk factors associated with mortality. All values are expressed as mean and percentage. Differences between groups were estimated using the X^2 test. Progression to death was estimated with a multivariate logistic regression model, considering $p<0.05$ a statistically significant difference. The logistic regression analysis was performed with the SPSS 12 program.

Results

Demographic characteristics

From January 1997 to August 2004, 156 IPD cases were identified in 156 patients with the following ages: 41% were under 2 years of age and 59% were over 2 years of age, 1.8% were under two months of age, and median age was 24 months with a mean of 45.7 months (range: 1 -170 months).

Daycare center attendance

Ten percent had a history of daycare attendance and 29.4% of those were previously healthy patients.

Health status

A total of 30.7% of the patients were previously healthy and 69.3% had an underlying disease. IPD distribution among these can be observed in Figure 1.

The more frequent IPD syndromes in healthy subjects (30.1%) were meningitis (16/156; 10.3%) and complicated pneumonia (15/156; 9.6%), followed by bacteremia without apparent infectious source (13/156; 8.3%). Two patients experienced peritonitis (1.3%) and one patient had arthritis (0.6%). Among patients who had underlying disease (69.9%), the most frequent IPD syndrome was bacteremia without apparent infectious source (37.8%), followed by meningitis (15.4%), pneumonia (7.7%), peritonitis (5.8%) and arthritis (3.2%).

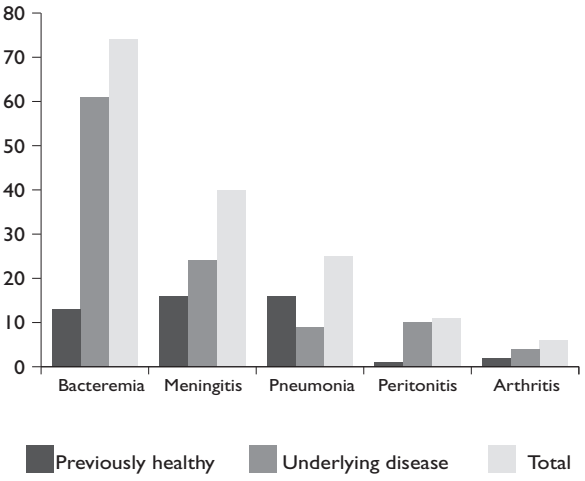

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FIGURE 1. PREVIOUS HEALTH STATUS IN PATIENTS WITH INVASIVE PNEUMOCOCCAL DISEASE

We observed that meningitis and peritonitis were more significant for the group with underlying disease than for the healthy patients ($p>0.05$) (Table 1).

In our total sample of patients, no statistically significant relationship was found between previous attendance in nurseries or daycare centers and IPD risk; this was also true for previous nutritional status.

Nutritional status at the moment of IPD diagnosis was 45% eutrophic and 55% malnutrition, 13.7% of which had third degree malnutrition according to the Gómez rating scale.[23] Of the previously healthy patients, 84.6% had no type of malnutrition, 13.5% of patients experienced first degree malnutrition and 1.9% second degree malnutrition.

Previous antibiotic therapy

A total of 53.6% of the children included in the study had received beta-lactam antibiotics (cephalothin, cephalexin, cefuroxime, ceftriaxone, amoxicillin and/or amoxicillin/clavulanate). A statistically significant relationship was found between the history of previous use of beta-lactam antibiotics and penicillin and third

Table I
Isolation of *Streptococcus pneumoniae* site and its relation with previous health status

Isolation site	Previously healthy (PH)	Underlying disease (UD)	Mortality		Total	
			PH	UD	Cases	Deaths
Bacteremia	13	61	1	22	74	23
Meningitis	16	24	6	9	40	15
Pneumonia	16	9	1	3	25	4
Peritonitis	1	10	1	0	11	1
Arthritis	2	4	0	0	6	0
Total	48	108	9	34	156	43

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generation cephalosporin resistance (OR 5.4; 95% CI 2.4-16.1; $p < 0.05$).

Isolation site and relation to age

The distribution was: occult bacteremia 74/156 (47.5%), mean age 41.1 months; meningitis 40/156 (25.6%), mean age 34.1 months; pneumonia 25/156 (16%), mean age 43.7 months; peritonitis 11/156 (7.1%), mean age 92 months; arthritis 6/156 (3.8%), mean age 42.6 months (Table 1).

A statistically significant relationship was found between meningitis and underlying disease ($p>0.05$), and we therefore believe that this is why we found so many meningitis cases among children who were over 2 years of age.

Isolated serotypes

The distribution for the nine most frequent serotypes, in decreasing order, was: 23F, 19.5%; 6B, 10.4%; 19F, 9.5%; 6A and 14, 8.5% each; 19A and 9V, 5.5% each; and finally 5 and 11D, 4.9% each.

The five most frequently isolated serotypes in previously healthy children were: 6B, 5.8%; 14, 5.1%; 5, 3.2%; 19F, 3.2% and 4, 2.6%. In children with previous underlying conditions they were: 23F, 18.3%; 6A, 8.5%; 19F, 6.5%; 6B, 4.9%; and 14, 3.7%. We found a statistically significant relationship ($p<0.05$) between the IPD serotype 23F and underlying disease and previously healthy patients. No statistically significant relationship was found with health status for the remaining serotypes.

Dispersion variables showed a statistically significant relationship ($p<0.05$) among different serotypes and the type of disease caused.

Susceptibility

Out of 40 *S. pneumoniae* isolated in CSF (meningitis), 61% were penicillin-susceptible and 39% were penicillin resistant. In the case of cefotaxime, 65.4% susceptible isolates were found and 34.6% were resistant (3.8% with intermediate susceptibility and 30.8% resistant). The most frequent serotypes that were penicillin resistant, in decreasing order, were: 14 (28%) 19F, 6B and 23F (16% each), 15C (8%) and 6B (14.2%). Cefotaxime non-susceptible serotypes were: 23F (33.3%), 19F, 14 and 6B (22.2%, each).

Out of 116 non-meningitis isolates of *S. pneumoniae*, 83.5% were penicillin-susceptible and 16.5% were penicillin resistant (12.2% with intermediate susceptibility and 4.3% were highly resistant). The most frequent serotypes that were penicillin resistant, in decreasing order, were: 6B (31.6%), 14, 23F and 19F (15.8% each), 9V (10.4%), 3 and 5 (5.3% each).

In the case of cefotaxime, 90 susceptible isolates were found (77.6%) and 26 (22.4%) were resistant (71.8% with intermediate susceptibility and 28.2% resistant). Cefotaxime non-susceptible serotypes were: 23F (33.4%), 19F (23.1%), 14 (15.3%) 6B (10.3%), 9V (7.7%), 19A (7.7%) and 18A (2.6%).

A total of 61 isolates of *S. pneumoniae* in patients with a history of beta-lactam therapy were resistant as follows: 51 (31.1%) to penicillin, 17 (10.4%) to cefotaxime and 11 (6.7%) to other beta-lactam.

A statistically significant relationship was found between serotypes 23F, 19F, 14 and 6B and non-susceptibility to penicillin and cefotaxime (Figure 2). No statistically significant relationship was found in the remaining serotypes with regard to non-susceptibility to these antimicrobial agents.

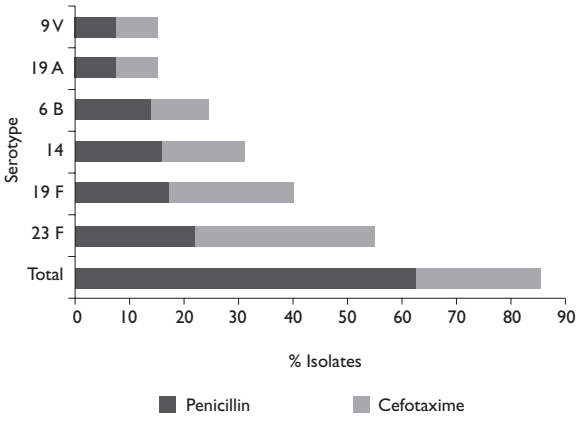

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FIGURE 2. PERCENT OF PENICILLIN AND CEFOTAXIME RESISTANCE RELATED TO *STREPTOCCUS PNEUMONIAE* SEROTYPES

Mortality

Overall mortality was 27.5% (43/156); 81.4% had an underlying disease and 18.6% was previously healthy. A statistically significant relationship was found between mortality and underlying disease (OR 5.4; 95% CI 2.5-18.3; $p < 0.05$) (Table II). Patients with IPD who correlated with a greater mortality risk had bacteremia and meningitis (OR 2.3; 95% CI 0.9 -6) (Table III). Of the isolates from patients who died, 40.8% were non-penicillin-susceptible and 18.6% were non-cefotaxime-susceptible. No statistically significant relationship was found between antimicrobial susceptibility and mortality.

Serotypes more highly related to mortality were: 14(16.7%), 6B(16.7%), 23F(14.6%), 6A (12.5%), 19F(6.3%), 19A(6.3%), 9V (4.1%), 18C (4.1%) and 10A (4.1%) ($p<$ 0.005).

Table II
RISK FACTORS ASSOCIATED WITH MORTALITY IN PATIENTS WITH IPD

Factor	*OR (95% CI)*	*p*
Age (under 24 months)	0.8 (0.2-6.8)	0.073 (NS)
Gender (male)	0.5 (0.1-2,0)	0.16 (NS)
Meningitis and/or bacteremia diagnosis	2.3 (0.9 -6.1)	0.0003
Previous beta-lactam	5.9 (2.2-15.0)	0.004
Previous underlying disease	5.4 (2.5 (18.3)	0.0001
Decreased penicillin susceptibility	0.9 (0.2-4.8)	0.19 (NS)

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Discussion

The age distribution in our study was different than that reported by other authors,[24-26] and primarily corresponded to ages over 24 months. This is related to particular characteristics of the population involved, since 68.9% had an underlying disease in contrast with other series for which this figure was lower (23% and 29%).[27] Importantly, most previously healthy children in our study who had IPD were under 2 years of age, as was found in other studies.[24,25,27] We also found that meningitis and bacteremia were related with a high mortality rate, a fact that has been reported in other studies.[7,25]

In the present study, we analyzed 156 *S. pneumoniae* isolates in 6 years, we found 27 serotypes, 59% are including in PCV7, 68.6% in PCV10, and 81.4% in PCV13.

The most frequent serotypes isolated in this group were: 23F (20.5%), 6A (10.9%), 19F (10.3%), 6B (9%), 14 (9%), 9V (5.6%), 19A (5.6%), 5 (5.1%), and 11D (5.1%). These results are different than those of the SIREVA study, in which they included 8 993 *S. pneumoniae* sero-

Table III
AGE AND MORTALITY RISK FOR PATIENTS WITH IPD

Variable	*Total patients (n= 156)*	*Living patients n (%) (n= 113)*	*Dead patients n(%) (n=43)*	*p value (CI)*
Age (months)				
0-23 /12	64	48	16	
24-59 /12	45	34	11	0.073 (NS)
≥60 /12	47	31	16	

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type isolates from 10 Latin American countries (including Mexico).

Compared to the Mexican SIREVA study during a similar period (2000-2005),[10] we found that only 41% of our children was younger than 2 years of age, as opposed to 77.8%. Said difference may be related to the kind of patients in the study (our patients were from only one Mexico City reference hospital and 68.9% had underlying disease). Nevertheless, we must be cautious when trying to make a comparison with our results, since geographical contrasts can result in some variations among the different serotypes. Whereas we present data from 156 cases of *S. pneumoniae* isolated from invasive pneumococcal disease in a single concentration hospital in Mexico City, the SIREVA data is based on 728 cases from different cities in Mexico.

An interesting fact is that in the SIREVA study, serotype 14 was the most frequent, unlike our data in which it ranked fifth (9%). On the other hand, we identified serotype 23F as one of the most frequent (19.5%), and serotype 19F was more frequent than in the SIREVA study (9.5% vs. 5-6.8%). Finally, serotypes 6A and 6B were similar in both studies. Our results are similar with world reports in which serotypes 23F, 19F, 14 and 6B are most prevalent in children with IPD.[28]

In African and Latin American countries, serotypes 1 and 5 are most frequently found in children younger than 5 years of age.[25,29] In this study, the mortality was very high (28%) as compared with the series from industrialized countries such as Canada, where mortality is 2%, the United States (2.16%) and Europe (1%).[3,30] Nevertheless, patients with IPD in said series[23,27,28,31] were previously healthy, in contrast with ours where 68.9% had a debilitating underlying disease, which is a mortality risk factor also shown in a study conducted in the US, where mortality was higher in children with previous debilitating disease.[32] In industrialized countries where PCV7 is regularly applied, mortality figures for IPD in children with infection secondary to the human immunodeficiency virus (HIV) and cancer were lower than in our population.[23,32,33]

In our study, underlying disease was a significant risk factor associated with mortality, where previous debilitating disease has an OR of 5.4 as compared to previously healthy cases (95% CI; $p<0.05$). Our mortality data are comparable to those reported for Latin America.[26,28,34]

Regarding gender, in this study, similar to other studies,[8,9,28,33] we found more male cases (1:1-5), but we didn't find statistic association between genders from both age groups and the mortality risk.

Since most (62.5%) mortality-related serotypes are included in the serotypes contained in the PCV7, they could be prevented by the vaccination.

Of the isolated serotypes in patients who died due to IPD, 62.5% are included in PCV7, 66.7% are included in the 10-valent pneumococcal conjugate vaccine (PCV10), and 85.4% in the 13-valent pneumococcal conjugate vaccine (PCV13).

When analyzed separately in terms of the potential protection provided by PCV7 in different clinical settings, the study showed that bacteremia would be 65.7%, meningitis 73.2% and complicated pneumonia 40%. Since 25% of the isolated serotypes in this clinical entity were 1 and 5, we did not compare these results with SIREVA results because they analyzed only pneumonia and meningitis, and did not analyze other IPD.[10]

With the new pneumococcal conjugate vaccines (PCV10 and PCV13), and particularly in the case of complicated pneumonia, potential protection increases from 40% with the application of PCV7 to 88% with PCV13; these results are similar to those reported by the SIREVA study.[10]

Out of 156 *S. pneumoniae* serotypes isolated from IPD in our population, 59% are included in the PCV7, more than that stated in other regional reports.[10]

Regarding antibiotic susceptibility, 74.2% of the penicillin resistant serotypes are included in PCV7, 77.1% would be covered by PCV10 and 93.4% by PCV13. Of the cefotaxime resistant serotypes, 71.8% are covered by PCV7, 78.9% by the experimental PCV10 and 91.7% by the experimental PCV13.

Conclusions

The results we are reporting are based on experience in a third level pediatric hospital, thus they may not reflect IPD epidemiological behavior throughout the country or its relationship with prevalent serotypes. It is therefore critical to create surveillance programs to generate nationwide data before the universal application of conjugate vaccines, which are already in process in Mexico.

Invasive pneumococcal disease in Mexican children in a third level hospital is a significant cause of morbidity and mortality since it is a sizeable disease among children with previous underlying disease. The key to the control of this disease is the introduction of conjugate vaccines that are effective in children under 2 years of age, those with the greatest IPD incidence. In Mexico, the recent universal introduction of PCV7 addresses this problem.

Declaration of conflicts of interest

We declare that we have no conflicts of interest.

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