

Clinical and microbiological profile of primary bacteremia caused by *Streptococcus pneumoniae* infection in pediatric patients hospitalized at tertiary care centers of Red Neumocolombia. 2017 – 2019

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Abstract

Objective: To describe the clinical and microbiological characteristics and outcomes of primary *S. pneumoniae* bacteremia in pediatric patients hospitalized in tertiary care centers belonging to the Red Neumocolombia (2017-2019).

Materials and methods: Observational, descriptive, longitudinal, exploratory study with an analytical scope. Information was obtained from clinical records reporting positive blood cultures for *S. pneumoniae*, without other infectious foci, performed in pediatric hospitals of the Red Neumocolombia (2017-2019).

Results: Information from 51 clinical records was analyzed. 62.7% of the patients were males with a median age of 25 months (IQR 9-49). The most common symptom was fever (78.4%). Immunization with PCV-10 was reported in 47% of the cases. The most frequent serotype was 19A (39.4%) and *S. pneumoniae* showed non-susceptibility to erythromycin (3%), penicillin (5.4%), and cefotaxime (1.7%). Factors related to admission to the pediatric intensive care unit (PICU) were: pleuritic pain (OR: 27.9; 95%CI: 3.13 - 248.16; $p = 0.03$), cough (OR:6.04; 95%CI: 1.46-24.88; $p=0.013$), abdominal pain (OR:6.5; 95%CI: 1.85-22.80; $p=0.003$), respiratory distress (OR:12; 95%CI: 2.95-48.77; $p=0.001$), intercostal retraction (OR:22.71; 95%CI: 4.65-141.90; $p=0.001$), cyanosis (OR:8.69; 95%CI: 1.95-38.65; $p=0.004$), hypothermia (OR:42.62; 95%CI: 4.77-380.74; $p=0.001$), and serotype 19A (OR:3.9; 95%CI:1.10-13.81; $p=0.035$). Mortality rate was 11.7%.

Conclusion: Epidemiology changes have been reported after the introduction of the PCV10 vaccine in Colombia in 2012, with a decrease in vaccine serotypes and an increase in serotype 19A, which is one of the risk factors for admission to the PICU due to primary bacteremia. Increased resistance to erythromycin, penicillin and cefotaxime is also reported.

Keywords: Pneumococcal disease; Bacteremia; Intensive Care Units, Pediatric; Vaccination.

Perfil clínico y microbiológico de bacteremia primaria por *Streptococcus pneumoniae* en pacientes pediátricos hospitalizados a la red de atención terciaria Neumocolombia. 2017 – 2019

Resumen

Objetivo: Describir las características clínicas, microbiológicas y los desenlaces de las bacteriemias primarias por *S. pneumoniae* ocurridas en población pediátrica hospitalizada en instituciones de alta complejidad, pertenecientes a la Red Neumocolombia (2017-2019).

Metodología: Estudio observacional, descriptivo, longitudinal, exploratorio con alcance analítico, en donde se tomó información de las historias clínicas con hemocultivos positivos para *S. pneumoniae* sin otro foco infeccioso, realizados en los hospitales pediátricos, reportados a la Red Neumocolombia (2017-2019).

Resultados: Durante el periodo de estudio se analizó información de 51 registros, 62,7% fueron hombres, la mediana de edad fue 25 meses (RIC 9-49). El síntoma predominante fue fiebre (78,4%), se reportó vacunación con Vacuna Neumocócica Conjugada decavalente (PCV-10) en 47%. El serotipo más frecuente fue 19A (39,4%). El porcentaje de resistencia antibiótica fue: eritromicina 43%, penicilina 25,4%, cefotaxima 11,7%. Los factores relacionados al ingreso a Unidades de Cuidado Intensivo Pediátrico (UCIP) fueron: dolor pleurítico (OR27,9; IC95%3,13 – 248,16 $p=0,03$), tos (OR6,04; IC95%1,46 – 24,88; $p=0,013$), dolor abdominal (OR 6,5; IC95%1,85 – 22,80; $p=0,003$), dificultad respiratoria (OR12; IC95%2,95 – 48,77 $p=0,001$), tirajes (OR22,71; IC95%4,65 – 141,90 $p=0,001$), cianosis (OR8,69; IC95%1,95 – 38,65 $p=0,004$), hipotermia (OR42,62; IC95%4,77 – 380,74 $p=0,001$), serotipo 19A (OR3,9; IC95%1,10 – 13,81 $p=0,035$). La letalidad fue del 11,7%.

Conclusión: Después de la introducción de la vacuna PCV10 en Colombia en el año 2012 se reportaron cambios en la epidemiología, con disminución de los serotipos vacunales, y aumento en el serotipo 19A, siendo uno de los factores que intervienen en el ingreso a UCIP por bacteriemia primaria. Se reporta aumento en la resistencia por eritromicina, penicilina y cefotaxima.

Palabras claves: *Streptococcus pneumoniae*, bacteriemia, Unidades de Cuidado Intensivo Pediátrico, vacunación.

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Introduction

Streptococcus pneumoniae is considered one of the most common causes of community-acquired bacterial infections in children. Pneumonia, meningitis and primary bacteremia are a major cause of morbidity and mortality worldwide^{1,2}. In high-income countries, the incidence of invasive pneumococcal infections (IPN) is 8 to 75 cases per 100 000 children under 5 years of age every year, with a case fatality rate of 6.5%, while in low-income countries, this rate increases from 100 to 500 cases per 100 000 children every year, with a case fatality rate of 8%^{3,4}.

Primary bacteremia is defined as the presence of bacteria in the bloodstream without an identifiable source of infection⁵. Studies conducted in the United Kingdom (2014) established the following as risk factors for bacteremia: functional or anatomical asplenia, immunosuppression, nephrotic syndrome, chronic respiratory, cardiac and/or kidney disease, diabetes, cochlear implants and children under 5 years of age with cerebrospinal fluid fistulas^{6,7}.

It has been reported that serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F accounted for 90% of invasive pneumococcal infections in children under the age of 5 and for 80% of antibiotic-resistant pneumococcal strains in the United States (USA) in the pre-vaccine era^{8,9}. After the introduction of the heptavalent pneumococcal conjugate vaccine (PCV7) in 2000, primary bacteremia rates decreased by 55% at ages between 3 and 36 months, but the frequency of non-vaccine serotypes increased¹⁰.

According to the National Institute of Health of Colombia, 591 isolates of *S. pneumoniae* were collected from patients with invasive disease in 2019, of which 143 were of children under 5 years of age. The most predominant serotypes were 19A⁴⁵, 35B¹⁸ and 3¹⁶, distributed in Bogotá (37.5%), Antioquia (19.3%) and Valle del Cauca (18.95%), with resistance to penicillin (40%) and ceftriaxone (37.8%)¹¹.

The objective of this research was to perform a clinical, epidemiological, and microbiological characterization of primary bacteremia caused by *S. pneumoniae* in pediatric patients reported to Red Neumocolombia, in order to contribute to the strengthening of local information.

Materials and methods

A longitudinal, exploratory, descriptive observational study with an analytical scope was conducted in pediatric patients diagnosed with primary bacteremia due to pneumococcus, confirmed with at least one positive blood culture, and reported to the Red Neumocolombia between January 1, 2017, and December 31, 2019.

Our study population ranged from 0 to 17 years of age and were enrolled in different health insurance schemes: a) the

contributory scheme, which is characterized by the payment of a mandatory monthly fee by the employee and his employer, and allows the enrollment of the entire employee's family group; b) the subsidized scheme, which provides access to health services to the country's poorest citizens who lack the financial means to pay the monthly fee; c) the special schemes, which include the sectors of the population governed by the legal norms conceived prior to the entry into force of Law 100 of 1993 (teachers, national police, military forces); and d) the joint scheme, which includes all persons who do not have the capacity to pay but require to exercise their right to health care services while they become beneficiaries of the subsidized scheme.

The Red Neumocolombia was created in 2008 by the Colombian Association of Infectious Diseases (ACIN by its acronym in Spanish) and the Colombian Society of Pediatrics (SCP by its acronym in Spanish), with the objective of monitoring the behavior of invasive pneumococcal disease in pediatric patients. At present, it comprises 17 tertiary care hospitals, of which 5 treat children exclusively and 12 are general hospitals with pediatric units; they are located in 4 Colombian cities (Cali, Medellín, Bogotá, and Cartagena) and 4 belong to the public network. The number of *Streptococcus pneumoniae* isolates reported by these hospitals represents approximately 51% of the cases reported annually to the National Surveillance System, so this sample is representative of the epidemiological situation in the country.

Serotyping was performed by means of the Quellung reaction. This method uses specific commercial antisera that bind to the polysaccharide capsule of *Streptococcus pneumoniae*, causing a change in the capsule due to the antigen-antibody reaction that is demonstrated microscopically by agglutination or capsular swelling.

Antimicrobial resistance profiling was performed using the minimum inhibitory concentration (MIC) for non-meningitis *Streptococcus pneumoniae* recommended by the CLSI (Clinical & Laboratory Standards Institute) in 2019, considering as resistance breakpoint a MIC of (≥ 8 $\mu\text{g/mL}$) and intermediate MIC of (4 $\mu\text{g/mL}$) for penicillin; a MIC of (≥ 4 $\mu\text{g/mL}$) and intermediate MIC of (2 $\mu\text{g/mL}$) for cefuroxime; a MIC of (≥ 1 $\mu\text{g/mL}$) for erythromycin; and a MIC of (≥ 1 $\mu\text{g/mL}$) for clindamycin. Identification and antibiogram were achieved using the automated methods (Vitek® 2) in 16 hospitals and (BD® Phoenix) in 1 hospital.

Statistical analysis

Descriptive statistics were applied. Quantitative variables were summarized through measures of central tendency and dispersion. Normality was contrasted with the Shapiro-Wilk test, assuming significant values of $p \leq 0.05$. Qualitative variables were summarized as proportions and are presented in frequency tables. To identify possible factors related to "admission to PICU" outcomes, bivariate analyzes were per-

formed using odds ratio (OR) and their corresponding confidence intervals (CI=95%) as measures of association. Statistically significant differences were evaluated with chi-square tests (χ^2). Analyses were performed using the Stata 15.0 statistical software (Stata Corporation, College Station, TX, USA).

Results

Between 2017 and 2019, the 17 hospitals of Red Neumocolumbia reported 284 cases of invasive pneumococcal disease (IPD), of which 51 (17.9%) were primary bacteremias. The median age of the patients was 25 months (IQR: 9–49) and 62.7% of them were males (19/51). Most patients were enrolled in the contributory scheme (66.7%; 34/51) and only one case was of foreign origin. Bogotá reported the majority of cases (31.4%; 16/51), followed by Medellín (23.5%; 12/51), Cali (17.6%; 9/51) and Cartagena (5.9%; 3/51).

Regarding clinical characteristics, 78% reported at least one comorbidity, with chronic diseases (chronic lung disease, chronic kidney failure, chronic liver disease) being the most frequent in 41.2% (21/51), followed by neoplasms in 17.6% (9/51), and primary immunodeficiencies in 13.7% (7/51). Fever was the most common symptom in 78.4% (40/51), followed by cough, abdominal pain, and dyspnea in 21.6% (11/51).

Concerning laboratory tests, 44 patients underwent a blood count (86.27%; 44/51), of whom 27 (53%; 27/44) had leukocytosis >15.0000 . C-Reactive Protein was performed on 40 patients, of which 34 were positive (66.64%; 34/40), and 24 had received at least one dose of the PCV10 vaccine (47%; 24/51) (Table 1).

On the other hand, serotyping by Quellung reaction and/or PCR was performed in 74.5% of the patients (38/51). The predominant serotype was 19A in 39.4% (15/38), followed by 6C in 10.53% (4/38), 25A and 23B in 7.89% (3/38) each, and 6A and 5A in 5.26% (2/38) each; serotypes 35B, 15B, 8X, 6B, 23A, 24F, 15C, 38 and 23F had only one report (2.6%) each (Table 2).

Antimicrobial susceptibility testing of *Streptococcus pneumoniae* was performed using the minimal inhibitory concentration (MIC) breakpoints for non-meningitis *Streptococcus pneumoniae* recommended by the CLSI (Clinical & Laboratory Standards Institute) in 2019, finding resistance to penicillin in 25.4% (n=13) with a MIC (≥ 8 $\mu\text{g/mL}$), an intermediate level of resistance in 7.8% (n=4) with a MIC (4 $\mu\text{g/mL}$), as well as resistance to cefotaxime in 11.7% (n=6) with a MIC (≥ 4 $\mu\text{g/mL}$), an intermediate level of 4% (n=2) with MIC (2 $\mu\text{g/mL}$), resistance to erythromycin in 43% (n=22) with MIC (≥ 1 $\mu\text{g/mL}$), resistance to clindamycin in 33.3% (n=17) with MIC (≥ 1 $\mu\text{g/mL}$), and susceptibility to vancomycin in 100% (≤ 1 $\mu\text{g/mL}$).

All patients were hospitalized, and the median hospital stay was 10.1 days (SD: 10.6). A total of 37.2% (19/51) required PICU, with a case fatality rate of 11.7% (6/51) (Table 3).

Table 1. Sociodemographic and clinical characteristics of pediatric patients with primary bacteremia. 2017-2019.

Sociodemographic characteristics		n=51	%
Age (months)		Median	IQR
25		(9- 49)	
Sex	Male	32	62.7
	Female	19	37.3
Insurance scheme	Contributory	34	66.7
	Subsidized	15	29.4
	Special	1	2.0
	Enrolled	1	2.0
Nationality	Colombian	50	98.0
	Venezuelan	1	2.0
Municipality	Bogotá	16	31.4
	Medellín	12	23.5
	Cali	9	17.6
	Cartagena	3	5.9
	Other	11	21.5
Clinical features			
Comorbidities	Neoplasm	9	17.6
	Primary immunodeficiency	7	13.7
	Autoimmunity	2	3.9
	Splenectomy	1	2.0
	Another clinic disease	21	41.2
	None	11	21.56
Signs and symptoms	Fever	40	78.4
	Cough	11	37.3
	Abdominal pain	11	21.6
	Respiratory distress	11	21.6
	Intercostal retractions	6	11.8
	Cyanosis	3	5.9
Diagnostic			
	leukocytes $>15 \times 10^3/\mu\text{L}$	44	86.27
	C-reactive protein	34	66.64
	Quellung reaction and/or PCR Serotype	38	74.5
Immunization			
	PCV10	24	47
Clinical outcomes			
PICU		19	37.2
Death		6	11.7
Days of hospital stay SD \pm		Mean	SD \pm
10.1		10.6	

IQR: Interquartile range

PCR: Polymerase chain reaction

SD: Standar deviation

Table 2. *Streptococcus pneumoniae*, serotypes.

Serotype	n=38	Percentage
19A	15	39.40
6C	4	10.53
25A	3	7.89
23B	3	7.89
6A	2	5.26
15A	2	5.26
35B	1	2.63
15B	1	2.63
8	1	2.63
6B	1	2.63
23A	1	2.63
24F	1	2.63
15C	1	2.63
38	1	2.63
23F	1	2.63

Factors associated with admission to PICU were: pleuritic pain (OR: 27.9; 95%CI: 3.13-248.160; $p=0.003$), cough (OR:6.04; 95%CI: 1.46-24.88; $p=0.013$), abdominal pain (OR:6.5; 95%CI: 1.85-22.80; $p=0.003$), respiratory distress (OR:12; 95%CI: 2.95-48.77 $p=0.001$), intercostal retractions (OR: 22.71; 95%CI: 4.65-141.90; $p=0.001$), cyanosis (OR:8.69; 95%CI: 1.95-38.65; $p=0.004$), hypothermia (OR:42.62; 95%CI: 4.77-380.74; $p=0.001$) and serotype 19A (OR:3.9; 95%CI: 1.10-13.81; $p=0.035$). Sex, age and immunization status were not statistically significant factors.

Discussion

This study analyzed information of pediatric patients diagnosed with primary pneumococcal bacteremia and reported by the 17 tertiary care hospitals of Red Neumocolombia between 2017 and 2019. Frequency, clinical and demographic characteristics, antimicrobial resistance profile and outcomes were determined.

With regard to age, a median age of 25 months was found, with 41% incidence in children under two years of age. These findings are consistent with studies conducted in the USA^{12,13}. For example, the study by Tazeen *et al.* found that the median age of the cohort was 2.5 years and that 30% of the cases were infants¹⁴. On the other hand, in the study by Laaksonen *et al.*, which included bacteremia with and without pneumonic infiltration, the median age was 21 months and infants <12 months were less likely to present with pneumonic infiltration¹⁵.

Fever was the most common symptom and reason for emergency department consultation in 78.4% of the cases, which is in agreement with Laaksonen, who reported fever in 72.5%^{13,16}. The present study found a leukocyte count >15,000/mm³ in 86.27% of the patients, similar to other studies such as Herz *et al.*, who reported a white blood cell count

(WBC) >15,000/mm³ in its cohort of children routinely immunized with the pneumococcal conjugate vaccine (PCV7), being a poor predictor of bacteremia with a sensitivity of 74.0% and specificity of 54.5%¹⁷. The cut-off point of leukocytes in other studies was between 17,591/mm³ and 20,910/mm³ in occult bacteremia, but it did not have any statistical significance¹⁸. Finally, Stollet *et al.* reported that a positive predictive value of a blood count with leukocyte counts greater than or equal to 15,000/mm³ was 3.2%¹⁹. Other diagnostic methods are available, such as blood culture, which remains the gold standard for the diagnosis of bacteremia²⁰.

Clinical conditions that usually determine admission to PICU, such as primary immunodeficiency, autoimmunity, asplenia, chronic diseases and corticosteroid use, were not statistically significant, which contrasts with other studies, where the presence of underlying diseases increased the risk of non-vaccine-related IPD²¹.

During the era of conjugate vaccines, the incidence of primary bacteremia has decreased, and its epidemiology has been substantially modified. A multicenter study conducted in the USA showed that IPD caused by serotypes included in PCV7 vaccine decreased by 64% (95%CI: 59-68), while IPD caused by the six additional serotypes of the PCV13 dropped by 93% (95%CI: 91-94)²². Another study conducted in Israel found a reduction in the prevalence of the serotypes included in the PCV7 vaccine from 21% in 2009 to 2.6% in 2016 in children under 5 years of age²³. In our study, PCV10 vaccine coverage was 47%, which was not statistically significant for PICU admission, contrasting with Budnik *et al.*, who reported that the vaccination coverage of

Table 3. Antimicrobial resistance and susceptibility

Antimicrobials				
<i>Streptococcus pneumoniae</i>				
Categories 2019 MIC cut-off points (µg/mL)				
	Susceptible	Intermediate	Resistant	Nd
Parenteral penicilin (not meningitis)	≤2 µg/mL	4 µg/mL	≥8 µg/mL	
	n=34	n=4	n=13	
	66.7%	7.8%	25.4%	0
Cefotaxime (not meningitis)	≤1 µg/mL	2 µg/mL	≥4 µg/mL	
	n=41	n=2	n=6	
	80.3%	4%	11.7%	2
Erythromycin	≤2 µg/mL	4 µg/mL	≥8 µg/mL	
	n=26	-	n=22	
	51%		43%	3
Vancomycin	≤2 µg/mL	4 µg/mL	≥8 µg/mL	
	n=51			
	100%	-	-	-
Clindamycin	≤2 µg/mL	4 µg/mL	≥8 µg/mL	
	n=31		n=17	
	60.7%		33.3%	3

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* Nd: No data

Table 4. Clinical characteristics associated with admission to the PICU in patients with a diagnosis of primary bacteremia.

Features		PICU n = 19	Non- PICU n = 32	Crude OR (95%CI)	p-value
Sex	Female	5	14	2.17(0.63– 7.50)	0.218
	Male	14	18		
Age	<2 years	11	12	2.29(0.71– 7.29)	0.161
	> 2 years	8	20		
PCV10 vaccine	Yes	7	16	1.71(0.53– 5.47)	0.363
	No	12	16		
Primary immunodeficiency	Yes	4	12	2.57 (0.50– 13.04)	0.25
	No	15	20		
Autoimmunity	Yes	2	1	3.64(0.30– 43.21)	0.305
	No	17	31		
Asplenia	Yes	1	2	0.83(0.07– 9.85)	0.885
	No	18	30		
Neoplasm	Yes	2	7	0.42(0.07– 2.27)	0.314
	No	17	25		
Corticosteroids	Yes	3	5	1.01(0.20– 4.69)	0.998
	No	16	27		
Another chronic disease	Yes	8	13	1.062(0.33– 3.36)	0.917
	No	11	19		
Fever	Yes	17	26	1.96(0.35– 10.87)	0.441
	No	2	6		
Pleuritic pain	Yes	9	1	27.9(3.13– 248.16)	0.003*
	No	10	31		
Cough	Yes	16	15	6.04(1.46– 24.88)	0.013*
	No	3	17		
Abdominal pain	Yes	13	8	6.5 (1.85– 22.80)	0.003*
	No	6	24		
Respiratory distress	Yes	12	4	12(2.95– 48.77)	0.001*
	No	7	28		
Intercostal retractions	Yes	12	2	22.711(4.65- 141.90)	0.001*
	No	7	30		
Cyanosis	Yes	9	3	8.69(1.95– 38.65)	0.004*
	No	10	29		
Hypothermia	Yes	11	1	42.625(4.77– 380.74)	0.001*
	No	8	31		
Serotype 19A	Yes	9	6	3.9(1.10– 13.81)	0.035
	No	10	26		

PCV10 was 64.6%, generating a 66.2% decrease between 2007 and 2014 in children under 1 years of age²⁴. Furthermore, in our study, serotype 19A was the most frequently isolated serotype and one of the factors associated with admission to the PICU, being the cause of nine cases in children vaccinated with PCV10. Muñoz *et al.*, in a study carried out in Barcelona, reported a coverage of 50% for PCV7 in his cohort, with an admission to the PICU of 22% (43/128); the vaccine serotypes corresponded to 72% of the isolates²⁵.

Finally, the present study found an increase in resistance to penicillin of 25.4% and to cefotaxime in 11.7% of the cases, which contrasts with data obtained in Europe in 2017, where resistance to penicillin was 3% and to cephalosporins was 2%²⁶. According to the 2019 Surveillance Report on *S. pneumoniae* in Colombia, an increase in resistance to penicillin (40%) and to cephalosporin (37.8%) is evident in children under 5 years of age¹⁰.

Currently, bacteremia is the second most common disease among invasive pneumococcal diseases, and it poses a significant health risk to the pediatric population due to epidemiological variations caused by the appearance of serotypes not covered by the vaccine. Therefore, it is critical to emphasize the necessity of mandatory reporting to the Surveillance System in order to increase the proportion of serotyped isolates, establish antibiotic susceptibility and guide empirical treatment, and determine the actual incidence of this disease in our country.

Limitations

Although information was collected from patients treated in the 17 hospitals of the Red Neumocolombia, the number of isolates obtained did not allow for a logistic regression. For this reason, the results presented here are exploratory and allow us to propose new hypotheses for further studies.

Ethical considerations

The authors state that no experiments on human subjects were performed for this research, which was approved by the ethics committee of each of the participating centers and the Universidad Libre - Cali Campus.

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