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Factors Associated with the Use of Antibiotic Therapy in Previously Healthy Children Under 2 Years Old Hospitalized for Bronchiolitis

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Abstract: Objective: To profile patient characteristics and factors leading to antibiotic prescription in all previously healthy children under 2 years of age hospitalized with a diagnosis of bronchiolitis over a 12-month period at a specialized pediatric hospital. Methods: This was a descriptive observational study of the clinical and epidemiological characteristics of previously healthy children under 2 years of age hospitalized with a diagnosis of bronchiolitis from January 1 to December 31, 2018, at the "Dr. Carlos Sáenz Herrera" National Children's Hospital of the Costa Rican Social Security Fund. This study included a comparative analysis of factors associated with the use or non-use of antibiotics during their hospitalization. Results: A total of 261 previously healthy children hospitalized with bronchiolitis were included. The mean age was 7.3 months and the male gender predominated (n = 160, 61.3%). Exposure to passive smoking was reported in 24.5% of patients. 66.1% of patients had no history of wheezing prior to admission, and 52.2% had a family history of bronchial asthma. It was reported that 17.2% (n = 45) received antibiotics during their hospitalization. Factors associated with antibiotic prescription were the presence of pulmonary opacities (p = 0.001, OR: 32.2) and bronchopneumonic infiltrates (p = 0.002, OR: 2.72) on chest X-ray, escalation to high-flow cannula therapy (p < 0.001, OR: 4.43), and assisted mechanical ventilation (p = 0.001, OR: 7.17). Conclusion: The two factors that lead physicians to prescribe antibiotics to healthy patients with BQL are a deteriorating respiratory pattern that requires intubation and ventilation, and the presence of pulmonary opacities and bronchopneumonic infiltrates.

Key words: bronchiolitis; respiratory syncytial virus; infants; antibiotics

1. Introduction

Bronchiolitis (BQL) is an "acute infectious disease of the lower airway that affects children under 2 years of age, characterized by inflammation and necrosis of the bronchial epithelium that affects the lung in a diffuse and bilateral manner, causing obstructive ventilatory disability." [4] In 80% of cases, the etiology of the disease is secondary to the respiratory syncytial virus (RSV) [1]. It has been reported by Cody Meissner and colleagues that approximately 800,000 children in the United States required outpatient care during the first year of life due to BQL caused by RSV1, and other publications indicate that 2% to 5% of all infants younger than 12 months of age are hospitalized for bronchiolitis, and in 2005, Nair and colleagues showed that there were 66,000 to 199,000 RSV deaths in children younger than 5 years globally.

[2, 3] Risk factors associated with increased disease severity include prematurity, low birth weight, congenital heart disease, bronchopulmonary dysplasia, cystic fibrosis, neuromuscular disease, tobacco smoke exposure, and overcrowding; however, the impact on previously healthy children is not well documented. Warning signs that indicate worsening of the disease include cyanosis, grunting, irregular breathing, altered consciousness, high fever, and hypoxia. [1-3] The most commonly used routine examinations are chest x-rays, which are indicated when pneumonia, atelectasis, pneumothorax, or a foreign body is suspected. In this case, the x-ray may show changes such as bronchopneumonic infiltrates of viral origin, air trapping, and atelectasis. Radiological findings may be inconsistent with the patient's clinical presentation. [3-6] There are different guidelines for managing the disease, which suggest different interventions; hospital costs vary depending on the guidelines. [7-9] Antibiotics should not be used routinely for viral illnesses; It has been described that bacterial coinfection can occur in up to 26% of children with severe bronchiolitis who are ventilated. [10] However, the findings of Vogel et al. showed that 34% of non-ventilated patients received antibiotic coverage. [11] Fever, clinical deterioration, and radiological changes are some of the indications for which antibiotic therapy is started in patients, despite the low risk of bacteremia and the knowledge that a percentage of patients will have these manifestations due to the viral infection. [10, 11] Ruvinsky et al. published in 2011 on the prescription of antibiotics in a high-complexity pediatric hospital and reported that 35% of patients had an inappropriate prescription of these medications. [12, 13] During 2016, Rachel Ma et al. conducted a review of the factors that influenced physicians to prescribe antibiotics in viral respiratory conditions, finding that the perception of the patient's desire has an influence on the prescription (OR of 2.11 to 23). [14] Due to this, the objectives of this study were to characterize previously healthy patients under 2 years of age hospitalized with BQL and to identify the factors that lead to the prescription of antibiotics in them, in the specialized pediatric hospital in Costa Rica.

2. Methods

An observational and descriptive study was conducted based on a retrospective review of the medical records of all previously healthy children under two years of age hospitalized with a diagnosis of BQL between January 1 and December 31, 2018, at the National Children's Hospital of the Costa Rican Social Security Fund (CCSS). Inclusion criteria were hospitalization with a diagnosis of BQL in children aged older than 28 days to younger than 2 years; exclusion criteria included children referred from other hospitals with a diagnosis of BQL, children with a hospital stay of less than 24 hours, and children diagnosed with congenital heart disease, immunodeficiency, cystic fibrosis, chronic non-progressive encephalopathy or oxygen dependence, pulmonary or craniofacial malformations, chromosomal disorders, and prematurity. Data were obtained from the electronic medical record of the CCSS (Spanish National Health Service), and laboratory data were collected from the same institution's electronic system. The variables evaluated were clinical and epidemiological, such as sex, insurance type, delivery route, family history, prescribing physician profile, complications arising from antibiotic use, hospital stay, need for central venous catheter placement, operating room visit for venous access placement, catheter loss due to infiltration or obstruction, and the development of catheter-related bacteremia. For the purposes of this study, the prescribing physician variable was divided into two groups: first, the prescribing assistant, identified as the specialist assistant physician who graduated as a pediatrician/subspecialist; and second, the resident physician, identified as the general practitioner who was in training in the specialty of pediatrics during the study period. Data were tabulated in EpiData 3.1 and analyzed in Stata 14. Descriptive statistics were used to summarise the clinical and epidemiological characteristics, using measures of central tendency (mean, mode and median) for quantitative variables, and measures of dispersion (standard deviation and range) and frequency distributions for qualitative variables. Group comparisons were performed by separating children who received antibiotics from those who did not; for inferential analysis, the Student t test was used to identify differences between means; for qualitative variables, the chi-square test was applied as a

nonparametric statistical method. Subsequently, a multivariate analysis with OR was performed, a significance level of $p < 0.05$ was used, and 95% confidence intervals were estimated. The study was approved by the Scientific Ethics Committee of the National Children's Hospital (HNN) under number CEC-HNN-02-2020.

3. Results

Of the patients admitted to the National Children's Hospital with a diagnosis of BQL in 2018, a total of 261 met the selection criteria, of which 17.2% (n = 45) received intravenous antibiotic treatment during their hospitalization. The average age at hospital admission, both in the antibiotic-treated and untreated groups, was 7.3 months, with an age range of 1 - 24 months, with a predominance of males (n = 160, 61.3%). Of these previously healthy hospitalized children, 69.7% had indirect insurance through their legal guardian, and the remainder were insured by the state (Table 1). Among the medical history, vaginal delivery predominated (74.3%), with an average gestational age at delivery of 39 ± 2 weeks. As neonatal history and associated diseases, atopic dermatitis predominated in all patients (4.2%, n = 11) followed by allergy to cow's milk protein (2.7%, n = 7) and allergic rhinitis (1.2%, n = 3) (Table 1).

Table 1. Distribution of characteristics of previously healthy children under two years of age hospitalized with a diagnosis of bronchiolitis according to antibiotic use during their stay, from January 1 to December 31, 2018, National Children's Hospital, Costa Rican Social Security Fund, Costa Rica

	Total (n = 261)	Patients without antibiotics (n = 216)	Patients with antibiotics (n = 45)
	n (%)	n (%)	n (%)
Sex			
Male	160 (61.3)	131 (60.7)	29 (64.4)
Female	101 (38.7)	85 (39.3)	16 (35.6)
Nationality			
Costa Rican	248 (95)	204 (94.4)	44 (97.8)
Nicaraguan	9 (3.5)	9 (4.2)	0
Other	4 (1.5)	2 (0.9)	4 (1.0)
Type of Insurance			
By the state	79 (30.3)	63 (29.2)	16 (35.6)
Indirectly insured	182 (69.7)	153 (70.8)	29 (64.4)
Type of delivery			
Vaginal	194 (74.3)	158 (73.1)	36 (80.0)
Cesarean	42 (16.1)	34 (15.7)	8 (17.8)
Unknown	25 (9.6)	24 (11.1)	1 (2.2)
Neonatal history			
Neonatal hospitalization for sepsis	8 (3.1)	8 (3.7)	0
Neonatal hospitalization for jaundice	11 (4.2)	10 (4.6)	1 (2.2)
History of neonatal intubation	6 (2.3)	6 (2.8)	0
History of bronchiolitis episodes			
First episode	174 (66.7)	150 (69.4)	24 (53.3)
Two or more previous episodes	87 (33,3)	66 (30.5)	21 (46,6)
Previous hospitalization for bronchiolitis*	23 (8.8)	15 (3)	8 (17.8)
Associated diseases			

	Total (n = 261)	Patients without antibiotics (n = 216)	Patients with antibiotics (n = 45)
	n (%)	n (%)	n (%)
Atopic dermatitis	11 (4.2)	11 (5.1)	0
Cow's milk protein allergy	7 (2.7)	5 (2.3)	2 (4.4)
Allergic rhinitis	3 (1.2)	2 (0.9)	1 (2.2)

BQL: bronchiolitis. *Statistically significant difference chi-square test p = 0.02

Among other characteristics, vaccination was achieved in 93.9% of the patients (n = 245), 8.1% attended daycare, 68.2% had older siblings, 42.2% had the protective factor of exclusive breastfeeding, and 24.5% were passive smokers, with the father being the most frequent smoker (43.6% of cases). Regarding family history, the most common history of bronchial asthma was (52.5%), followed by allergic rhinitis (14.4%), and finally atopic dermatitis (0.8%). In most patients (66.7%), this event corresponded to their first episode of wheezing. However, when separating the groups of children without antibiotics versus those with antibiotics, it was found that 17.7% of patients who received antibiotics had a history of prior hospitalization for BQL, while only 6.9% of patients without antibiotics had this history (p = 0.020) (Table 1). When analyzing the group of patients who received antibiotic therapy and the group of patients who did not receive antibiotics, no differences were found between the demographic profile, perinatal history, associated diseases, family history, or environmental risk factors (passive smoking, daycare attendance). Ninety-nine point six percent of patients hospitalized with BQL received supplemental oxygen, with the nasocannula being the device of choice. Twenty-seven percent required escalation to a high-flow cannula (HFC), and a minority (3.8%) required assisted mechanical ventilation (AMV) (n = 10). A statistically significant association was documented between the need to escalate to HFC therapy (p = <0.001, OR:4) and AMV (p = 0.001 OR:7) and the prescription of antibiotics in BQL, with the need to escalate to these ventilatory support devices increasing the likelihood of antibiotic prescription in the healthy patient with BQL by 4 and 7 times, respectively. In the total of hospitalized patients, the most commonly used pharmacological treatment was nebulized salbutamol (60.1%), followed by the use of systemic steroids (18.4%), nebulizations with ipratropium bromide (6.9%) and hypertonic saline solution (5%). A 17.2% received intravenous antibiotic treatment (n = 45), ampicillin was the first-choice antibiotic in 71.1% of cases, other antibiotics used were cefotaxime (22.2%) and combination therapy: cefotaxime and clindamycin (4.4%) and amikacin and ampicillin (2.2%). The attending specialist was the main prescriber of antibiotics (48.9%). The most frequently performed complementary studies in all patients were: chest x-ray (99.2%), viral immunofluorescence VIF (97.3%), complete blood count (55.5%), CRP (36.7%), arterial or venous blood gases (10.3%) and procalcitonin (PCT) (2.68%). Chest x-ray was the most performed study (99.2%). The finding of pulmonary hyperinflation was the most common in both patients who received antibiotics and those who did not. A significant association was evident between the presence of bronchopneumonic infiltrates (p = 0.002, OR: 2.72) and pulmonary opacities (p = 0.001, OR: 32.2) with the prescription of antibiotics (Table 2).

Table 2. Distribution of radiological findings and type of ventilatory support in previously healthy children under two years of age hospitalized with a diagnosis of bronchiolitis according to antibiotic use during their stay, 2018, National Children's Hospital, Costa Rican Social Security Fund, Costa Rica

	Total n (%)	Without antibiotics n (%)	With antibiotic n (%)	OR (confidence interval)	*p*
Radiological findings (n = 259)					
Bronchopneumonic infiltrates	93 (35.9)	68 (31.5)	25 (55.6)	2.72 (1.41-5.23)	0.002

	Total n (%)	Without antibiotics n (%)	With antibiotic n (%)	OR (confidence interval)	*p*
Lung opacities	21 (8.1)	4 (1.9)	17 (37.8)	32.2 (10.1-102.47)	< 0.001
Lung hyperinflation	120 (46.3)	98 (45.4)	22 (48.9)	1.15 (0.60-1.19)	0.667
Atelectasis	11 (4.2)	9 (4.2)	2 (4.4)	1.07 (0.22-5.12)	0.933
Ventilatory support (n = 260)					
Nasal cannula	260 (100)	215 (99.5)	45 (100)	0.83 (0.78-0.87)	0.647
Escalation to high-flow cannula	53 (20.4)	33 (15.3)	20 (44.4)	4.43 (2.21-8.89)	< 0.001
Escalation to noninvasive ventilation	3 (1.1)	1 (0.5)	2 (4.4)	10.0 (0.88-112.76)	0.023
Escalation to assisted mechanical ventilation	10 (3.8)	0	10 (22.2)	7.17 (5.27-9.75)	< 0.001
Escalation to high-frequency ventilation	1 (0.3)	0	1 (2.2)	5.9 (4.51-7.73)	0.028

The VIF was negative in 55% of patients who did not receive antibiotics and in 33.3% of those who did; therefore, the identification of a viral agent in the VIF was not associated with lower antibiotic use in BQL. Regarding the viral agent isolated in the VIF, RSV was the most common (52%), with a significant difference in antibiotic use in children testing positive for parainfluenza virus type 3 and rhinovirus, respectively, compared with children who did not receive antibiotic therapy (Table 3).

Table 3. Virological outcome in previously healthy children under two years of age admitted with a diagnosis of bronchiolitis according to antibiotic use during their stay, 2018, at the National Children's Hospital, Costa Rican Social Security Fund, Costa Rica

	Total sample n = 261	Without antibiotics n = 216	With antibiotic n = 45	*p*-value Chi²
	n (%)	n (%)	n (%)	
Negative	130 (51)	115 (55)	15 (33.3)	0.400
Respiratory syncytial virus	52 (20.5)	38 (17.5)	14 (31.1)	0.051
Metapneumovirus	42 (16.5)	34 (15.7)	8 (17.7)	0.805
Influenza A	1 (0.4)	1 (0.47)	0	0.642
Parainfluenza 1	1 (0.4)	1 (0.47)	0	0.642
Parainfluenza 3	20 (7.9)	13 (6.0)	7 (15.5)	0.035
Rhinovirus	7 (2.8)	3 (1.4)	4 (8.8)	0.006
Human coronavirus	3 (1.2)	3 (1.4)	0	0.350
Adenovirus	4 (1.6)	4 (1.9)	0	0.350

No statistically significant association was found between a positive PCR or PCT result at hospital admission and subsequent antibiotic use. It was even documented that 60% of patients with a positive PCR upon hospital admission did not receive antibiotic treatment. A comparison of the mean complete blood count results between the group of patients who received antibiotics and the group that did not revealed a slightly higher absolute neutrophil count among those who received antibiotics (7,910 vs. 5,549 cells/mL), but without a statistically significant difference. Blood gas analysis revealed a mean CO_2 level of 39.4 mmHg upon admission, significantly lower in patients who did not receive antibiotic therapy versus 51.9 mmHg in those who did ($p < 0.05$). No differences were found between oxygen concentrations, HCO_3

levels, or lactate concentrations between the two groups of patients. Cultures were obtained from 23.3% of hospitalized patients; these were obtained more frequently in the group of patients who received antibiotics compared to those who did not. Bacterial agents were isolated in only 3.9% of all cultures performed. No blood cultures were positive (0/45), 2 of 6 urine cultures were positive, and 10 patients had positive bronchial washings. Central venous catheter (CVC) placement was documented in 4.44% (n = 2) of patients who received antibiotics. No patients experienced complications during CVC placement or use. No toxicity or allergic reactions secondary to antibiotic use were reported. All patients in the sample were discharged alive, with an average hospital stay of 4.7 ± 3.0 days. In patients who received antibiotic therapy, an average of 7.3 ± 3.7 days of hospitalization was documented, this difference was statistically significant ($p < 0.001$).

4. Discussion

This study reported that the majority of hospitalized cases with BQL were male, and the average age in both study groups was the same. Antibiotic prescription was higher in children younger than 3 months of age with BQL, likely due to the treating physicians' perception of a higher risk of presenting with a concomitant severe bacterial infection in this age group as a result of their immature immune system. [6, 14] It was found that 17.2% of hospitalized patients with BQL received antibiotic treatment, a finding similar to that published by Wroket et al. in 2019. They analyzed 459 healthy patients hospitalized with BQL between 2010 and 2017 in a pediatric hospital in Poland and reported the use of antibiotic therapy in 16% of cases. [15] This is different from the 2016 finding by Plint et al. who observed a 29.1% use of antibiotic therapy in healthy patients hospitalized with BQL. [16] In 80% of patients, the indication for antibiotic therapy was the presence of pulmonary opacities and bronchopneumonic infiltrates on chest x-ray. However, international publications agree that the radiological findings of BQL are very nonspecific and BQL frequently produce areas of patchy consolidation on the chest x-ray, not implying the presence of bacterial superinfection [19]. In this sense, Patra et al reported that 40% of patients with BQL of viral etiology show consolidations, infiltrates and atelectasis on chest x-ray. [19] It has been reported that the routine use of chest x-ray in patients with BQL increases the inappropriate prescription of antibiotic therapy by 10 times, regardless of the finding. [19, 20] Despite this, our BQL management guidelines recommend performing a chest x-ray in all patients who require hospitalization (CCSS. Technical Guideline LT.GM.DDSS.261018 Acute bronchiolitis in children. 2018), which explains why 99.2% of patients had this study at the time of hospital admission and why chest X-ray findings influenced the prescription of antibiotics in 80% of cases. Regarding inflammatory markers, our study did not document any association between a positive PCR result and antibiotic use; these findings differ from those reported by Wrotek et al., who indicated that patients receiving antibiotics have significantly higher PCR values, higher neutrophil counts, and lower lymphocyte counts compared to those not receiving antibiotics, [15, 22, 23] and viral isolation, as described by Esposito et al., is a factor highly associated with early antibiotic discontinuation. [24] On the other hand, of the 45 blood cultures performed on our population, none were positive, which is consistent with international reports establishing a low risk of bacteremia in BQL, reported by Patra and Levine as less than 1.2%. [19, 25] This reinforces the concern regarding the need to perform blood cultures on all children with bronchiolitis. It was identified that the deterioration of the respiratory pattern that leads to the need to intubate and ventilate a healthy patient with BQL is significantly associated with the prescription of antibiotics. 90% of patients with BQL, all who required AMV received empirical antibiotic therapy, which is similar to that reported in international studies, given that the groups that provide care to these patients agree that there is a higher risk of bacterial superinfection in severe BQL. [12, 15, 24, 27, 28] In our study, since bacterial coinfection was identified through bronchoalveolar lavage in 60% of patients with AMV. [12, 15, 24, 26] Similarly, the literature agrees that the greater the respiratory compromise, the greater the prescription of antibiotics; since clinical worsening produces fear in the medical staff regarding the risk of an associated bacterial coinfection. [26, 27]

McKay et al. conducted a systematic review in emergency departments in Vancouver, Canada, to identify the profile of the physician who most frequently prescribes antibiotics. They concluded that specialist physicians prescribe antibiotics less frequently than general practitioners, and within medical specialties, pediatricians are the least likely to use antibiotic treatment. [14] This differs from our study, where the pediatric specialist assistant physician was identified as the primary prescriber of antibiotics, prescribing them in 48.9% of patients who received them. This study was based on medical records, which may lead to information bias due to incomplete data; this should be considered a limitation of the design. In conclusion, based on the results, it is recognized that the two factors that lead physicians to prescribe antibiotics in previously healthy patients with BQL are the deterioration of the respiratory pattern that leads to the need to intubate and ventilate the patient, and radiological findings. Therefore, as indicated in the reviewed literature, it is considered necessary that when preparing guidelines for the management of BQL, the need for routine chest radiography in all patients requiring hospitalization be carefully analyzed, even in those with minimal oxygen requirements and who present a favorable clinical course. It should be noted that the indication for antibiotic therapy in patients with BQL should be based on a comprehensive approach, which assesses clinical course in conjunction with radiological and laboratory changes, as recommended in the scientific literature.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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