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Original

Associated factors with the use of antibiotic therapy in previously healthy children under 2 years of age hospitalized for bronchiolitis

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Abstract

Aim: To identify the patient's characteristics and factors leading to antibiotic prescription in all previously healthy children under 2 years of age hospitalized with a diagnosis of bronchiolitis for 12 months in a specialized pediatric hospital.

Methods: a descriptive observational study of the clinical-epidemiological characteristics of previously healthy children under two years of age hospitalized with the diagnosis of bronchiolitis, from January 01 to December 31, 2018, at the National Children's Hospital "Dr. Carlos Sáenz Herrera" of the Caja Costarricense de Seguro Social (Costa Rican Social Security), with a comparative analysis between the factors associated with the use or not of antibiotics during their hospitalization.

Results: A total of 261 previously healthy children hospitalized with bronchiolitis were included, with a mean age of 7.3 months and a predominance of male sex (n=160, 61.3%). Exposure to passive smoking was present in 24.5% of the patients. Some (66.1%) of the patients had no history of wheezing before hospitalization and 52.2% had a family history of bronchial asthma. It was recorded that 17.2% (n=45) received antibiotics during hospitalization. Factors associated with antibiotic prescription were the presence of pulmonary opacities *(p=0.001, OR: 32.2)* and broncho pneumonic infiltrates *(p=0.002, OR:2.72)* on chest radiography, 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 the physician to prescribe antibiotics to a healthy patient with bronchiolitis are the deterioration of the respiratory pattern leading to the need for intubation and ventilation and the presence of pulmonary opacities and broncho-pneumonic infiltrates.

Keywords: Bronchiolitis, Respiratory Syncytial Virus, Infants, antibiotics.

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Abbreviations:
BQL, Bronchiolitis; CAF, high flow cannula; CCSS, Caja Costarricense de Seguro Social; MAV, assisted mechanical ventilation; RSV, Respiratory Syncytial Virus; PCR, Polymerase Chain Reaction.

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Bronchiolitis (BQL) is an "acute infectious disease of the lower airway affecting children under [2] years of age, characterized by inflammation and necrosis of the bronchial epithelium involving the lung diffusely and bilaterally, causing obstructive ventilatory disability".[4] In 80% of cases the etiology of the disease

is secondary to respiratory syncytial virus (RSV)[1]. It has been described by Cody Meissner et al. that approximately 800,000 children in the United States required outpatient medical care during the first year of life due to BQL caused by RSV[1] and other publications indicate that between 2% to 5% of all children under 12 months of age are hospitalized for bronchiolitis, and in 2005, Nair et al. showed that there were between 66,000 to 199,000 deaths from RSV in children under 5 years of age globally.[2,3]

Risk factors associated with increased severity of illness include prematurity, low birth weight, congenital heart disease, bronchopulmonary dysplasia, cystic fibrosis, neuromuscular disease, exposure to tobacco smoke, and overcrowding; however, what happens in previously healthy infants is not well documented. Warning signs that indicate worsening of the disease are cyanosis crisis, grunting, irregular breathing, altered consciousness, high fever, and hypoxia.[1-3] The most commonly used diagnostic test is the chest radiography, with indications to perform this study when there is suspicion of pneumonia, atelectasis, pneumothorax, or foreign body and, in this case, the radiography may show alterations 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 the management of the disease, which suggest different interventions, and the cost of hospitalization varies depending on the type of hospitalization.[7-9]

Antibiotics in a viral illness should not be routinely used; it has been reported that bacterial coinfection can occur in up to 26% of ventilated children with severe bronchiolitis.[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 patients are started on antibiotic therapy, despite the low risk of bacteremia and the knowledge that a percentage of patients will have these manifestations due to viral infection.[10,11]

Ruvinsky et al. published in 2011 on antibiotic prescribing in a high-complexity pediatric hospital and reported that 35% of patients had an inadequate prescription of these drugs.[12,13] In 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 from 2.11 to 23).[14]

Therefore, the objectives of this study were to characterize previously healthy patients under 2 years of age hospitalized for BQL and to identify the factors that lead to the prescription of antibiotics in them, in a specialized pediatric hospital in Costa Rica.

Methods

An observational and descriptive study was conducted, based on the retrospective review of records of all previously healthy children under two years of age hospitalized with a diagnosis of BQL, during the period from January 1 to December 31, 2018, at the National Children's Hospital of the Caja Costarricense de Seguro Social (CCSS).

Inclusion criteria were hospitalization with a diagnosis of BQL in children between 28 days old and under 2 years of age. Exclusion criteria were children referred from other hospitals with a diagnosis of BQL, children with a hospital stay of fewer than 24 hours, and children diagnosed with congenital heart disease, immunodeficiency, cystic fibrosis, chronic non-progressive or oxygen-dependent encephalopathy, pulmonary or respiratory malformations, chromosomal pathologies, and prematurity.

The data were obtained from the electronic clinical record of the CCSS and the laboratory data were collected from the electronic system of the same institution.

The variables evaluated were clinical-epidemiological, such as sex, type of insurance, route of delivery, hereditary-family history, profile of the prescribing physician, complications derived from the use of the antibiotic, hospital stay, need for central venous catheter placement, visit to the operating room for venous access placement, catheter loss due to infiltration or obstruction of the catheter, and the development of bacteremia secondary to the catheter.

For this study, the prescribing physician variable was divided into two groups: first, the assistant prescriber, identified as a physician assistant specialist who graduated as a pediatrician/sub-specialist, and second the resident physician as

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the general practitioner who was in training in the specialty of pediatrics during the study period.

The data was tabulated in EpiData 3.1 and analyzed in Stata 14. To describe the clinical and epidemiological characteristics, descriptive statistics were used with measures of central tendency (mean, mode, median), measures of dispersion (standard deviation, range) for quantitative variables, and frequency distributions for qualitative variables.

For the comparison of groups, a separation was made between children who received antibiotics and children who did not receive antibiotics; for the inferential analysis, the t-*student* test was used to identify differences between averages, for qualitative variables the chi-square test was applied as a non-parametric statistical method, subsequently a multivariate analysis was performed with OR, a significance level of $p<0.05$ was used and 95% confidence intervals were estimated.

The study was approved by the Scientific Ethical Committee of the National Children's Hospital (HNN) under number CEC-HNN-02-2020.

Results

Of the patients hospitalized during 2018 at the National Children's Hospital with a diagnosis of BQL, a total of 261 patients met the selection criteria, of whom 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% were indirectly insured through their legal guardian, and the rest were insured by the state (Table 1). Among the antecedents, 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 cow's milk protein allergy (2.7%, n=7) and allergic rhinitis (1.2%, n=3) (Table 1).

Among the other characteristics, 93.9% (n= 245) were vaccinated, 8.1% attended a childcare center, 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). Concerning family history, a history of bronchial asthma predominated in the family (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, upon separation by a group of children without antibiotics vs. with antibiotics, it was found that 17.7% of the patients who received antibiotics had a history of previous hospitalization for BQL, while only 6.9% of the patients without antibiotics had such a history *(p=0.020)* (Table 1).

In the analysis between the group of patients who received antibiotic therapy and the group of patients who did not receive antibiotics, there was no difference between the demographic profile, perinatal history, associated diseases, heredofamilial antecedents, or environmental risk factors (passive smoking, daycare attendance).

In 99.6% of patients hospitalized with BQL supplemental oxygen was received, the device of choice being the nasocannula. A total of 20.7% required escalation to high-flow cannula (HFC) and a minority (3.8%) to mechanical assisted ventilation (MAV) (n=10). A statistically significant association was documented between the need for escalation to CAF (*p= <0.001, OR:4)* and MAV *(p=0.001 OR:7)* and the prescription of antibiotics in BQL, the need to advance to these ventilatory support devices increased the likelihood of antibiotic prescription in the healthy patient with BQL by 4 and 7 times.

In the total number of hospitalized patients, the most used pharmacological treatment was nebulized salbutamol (60.1%), followed by systemic steroids (18.4%), nebulizations with ipratropium bromide (6.9%) and hypertonic saline (5%).

17.2% received intravenous antibiotic treatment (n=45), ampicillin was the antibiotic of first choice in 71.1% of cases, and other antibiotics used were cefotaxime (22.2%) and combination therapy: cefotaxime and clindamycin (4.4%) and amikacin and ampicillin (2.2%). The specialist assistant physician was the main prescriber of antibiotics (48.9%).

Table 1. Distribution of characteristics of previously healthy children under two years of age hospitalized with the diagnosis of bronchiolitis according to the use of antibiotics during hospitalization, during the period between January 01 and December 31, 2018, National Children's Hospital, Caja Costarricense de Seguro Social, 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
Another	4 (1.5)	2 (0.9)	4 (1.0)
Type of Insurance			
By the Government	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 section	42 (16.1)	34 (15.7)	8 (17.8)
Unknown	25 (9.6)	24 (11.1)	1 (2.2)
Neonatal history			
Hospitalization in the neonatal period due to sepsis	8 (3.1)	8 (3.7)	0
Hospitalization during the neonatal period for jaundice	11 (4.2)	10 (4.6)	1 (2.2)
History of Intubation in the neonatal period	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			
Atopic dermatitis	011 (4.2)	11 (5.1)	0
Allergy to cow's milk protein	7 (2.7)	5 (2.3)	2 (4.4)
Allergic rhinitis	3 (1.2)	2 (0.9)	1 (2.2)

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

The most frequently performed complementary studies in all patients were: chest X-ray (99.2%), viral immunofluorescence assay (VIA; 97.3%), hemogram (55.5%), PCR (36.7%), arterial or venous gases (10.3%) and procalcitonin (PCT) (2.68%).

Chest radiography was the most frequently performed study (99.2%). The findings of pulmonary hyperinflation were the most common in patients who received antibiotics and in those who did not. A significant association was evidenced between the presence of broncho pneumonic infiltrates (*p=0.002, OR: 2.72)* and pulmonary opacities (*p=0.001, OR: 32.2)* with antibiotic prescription (Table 2).

Table 2. Distribution of radiological findings and type of ventilatory support in previously healthy children under two years of age hospitalized with the diagnosis of bronchiolitis according to the use of antibiotics during hospitalization, 2018, Hospital Nacional de Niños, Caja Costarricense del Seguro Social, Costa Rica

	Total n (%)	No antibiotic n(%)	With antibiotic n(%)	OR (Confidence Interval)	*p*
Radiological findings (n=259)					
Bronchopneumonia infiltrates	93(35.9)	68 (31.5)	25 (55.6)	2.72 (1.41 - 5.23)	0.002
Pulmonary opacities	21 (8.1)	4 (1.9)	17 (37.8)	32. 2 (10.1 -102.47)	<0.001
Pulmonary hyperinflation	120 (46.3)	98 (45.4)	22 (48.9)	1.15 (0.60 - 1.19)	0.667
Atelectasia	11 (4.2)	9 (4.2)	2 (4.4)	1.07 (0.22 - 5.12)	0.933
Ventilatory support (n=260)					
Nasocannula	260 (100)	215 (99.5)	45 (100)	0.83 (0.78 - 0.87)	0.647
High-flow cannula escalation	53 (20.4)	33 (15.3)	20 (44.4)	4.43 (2.21 - 8.89)	<0.001
Escalation to non-invasive 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

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

Table 3. Virologic outcomes in previously healthy children under two years of age hospitalized with the diagnosis of bronchiolitis according to antibiotic use during hospitalization, 2018, at the National Children's Hospital, Caja Costarricense del Seguro Social, Costa Rica

	Total sample n=261	No antibiotic 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
Parainfuenza 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

There was no statistically significant association between a positive PCR or PCT result at the time of hospital admission and the subsequent use of antibiotics; it was even documented that 60% of the patients who had a positive PCR at hospital admission did not receive antibiotic treatment. When comparing the mean value of the hemoleukogram results between the group of patients who received antibiotics and the group that did not, it was found that the absolute neutrophil count was slightly higher among the patients who received antibiotics (7,910 vs. 5,549 cells/mL) but without showing a significant statistical difference.

Concerning blood gas analysis, an average CO_2 level at admission of 39.4 mmHg was identified, significantly lower in patients who did not receive antibiotic therapy versus 51.9 mmHg in those who received antibiotic therapy ($p<0.05$). No difference was found between oxygen concentration, HCO_3 value, or lactate concentration between the two groups of patients.

Cultures were taken in 23.3% of the hospitalized patients and were more frequent in the group of patients who received antibiotics compared to those who did not. The bacterial agent was isolated in only 3.9% of all cultures performed. No blood cultures were positive (0/45), 2 of 6 of the urine cultures were positive, and in 10 patients' bronchial washings were positive.

It has been documented that 4.44% (n=2) of the patients who received antibiotics required central venous catheter placement (CVC). No patient presented complications during CVC placement or use. No toxicity or allergic reactions secondary to antibiotic use were reported.

100% of the patients in the sample were discharged alive, with an overall 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)*.

Discussion

This study reported that most cases hospitalized for BQL were male and the mean age in both study groups was the same.

The prescription of antibiotics was higher in children under 3 months of age with BQL, probably due to the perception of treating physicians of a higher risk in this age group of presenting a concomitant severe bacterial infection as a consequence of immaturity in their 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 where 459 healthy patients hospitalized with BQL between 2010-2017 in a pediatric hospital in Poland were analyzed and the use of antibiotic therapy was reported in 16%.[15] Different from what was found in 2016 by Plint et al. who observed an antibiotic therapy use of 29.1% in hospitalized healthy patients with BQL.[16] In 80% of patients the indication for antibiotic therapy was the presence of pulmonary opacities and broncho-pneumonic infiltrates on chest X-ray. However, international publications agree that the radiological findings of BQL are very nonspecific, and often in BQL there are areas of patchy consolidation on chest radiography, not implying the presence of bacterial superinfection. [19] In this regard, Patra et al. reported that 40% of patients with BQL of viral etiology show consolidations, infiltrates, and atelectasis on chest radiography.[19]

It has been reported that the routine use of chest radiography in patients with BQL increases inappropriate prescription of antibiotic therapy by 10 times, regardless of the antibiotic finding.19,20 Despite this, our BQL management guidelines recommend performing a chest radiograph in all patients who warrant hospitalization (CCSS. Technical Guideline LT.GM.DDSS.261018 Acute bronchiolitis in children. 2018) which explains that 99.2% of patients had such a study at the time of hospital admission and that the findings in the chest X-ray 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 the use of antibiotics; these findings differ from those reported by Wrotek et al. who indicate that patients receiving antibiotics have values of significantly higher PCR, higher neutrophil count, and lower lymphocyte count 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 discontinuation of antibiotics.[24]

On the other hand, of the 45 blood cultures performed in our population, none were positive, which agrees with international reports that establish 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 in 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 the patients with BQL, all those who merited MAV 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 greater 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 MAV.12,15,24,26 Similarly, the literature agrees that the greater the respiratory involvement, the greater the prescription of antibiotics; since clinical worsening produces fear in medical personnel regarding the risk of associated bacterial co-infection. [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 and concluded that specialist physicians prescribe antibiotics less frequently than general practitioners and, within the medical specialties, the pediatrician is the one who uses antibiotics the least.[14] This differs from our study, where the pediatric physician assistant was identified as the main prescriber of antibiotics, prescribing them to 48.9% of patients who receive them.

This study is based on medical records, which may generate information bias due to the existence of incomplete data, which should be considered a limitation of the design.

In conclusion, based on the results, it is recognized that the two factors that lead the physician to prescribe antibiotics in the previously healthy patient with BQL are the deterioration of the respiratory pattern leading to the need to intubate and ventilate the patient and the radiological findings. Therefore, as indicated in the literature reviewed, it is considered necessary that when preparing management guidelines for BQL, the need to routinely perform chest radiography in all patients requiring hospitalization should be carefully analyzed, even in those with minimal oxygen requirements and who present a favorable clinical evolution. It should be considered that the indication of antibiotic therapy in patients with BQL should be based on an integral approach, where the clinical evolution is evaluated, and associated with radiological and laboratory changes, as recommended in the scientific literature.

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