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Characteristics of infants hospitalized with bronchiolitis at University Hospital of Split between 2011 and 2015

Petra Milić[1], Maja Sikirica[1], Vjekoslav Krželj[1,2], Joško Markić[1,2]

The aim was to determine and analyze clinical and epidemiological characteristics of infants treated at University Hospital of Split from 2011 to 2015 with the diagnosis of bronchiolitis. Bronchiolitis is an acute lower respiratory tract infection common in early childhood. The most frequent etiologic agent is respiratory syncytial virus (RSV) found in 60% to 80% of cases. Coughing, wheezing and impaired nutrition are the major symptoms. Medical records of children under the age of one year who were hospitalized at University Hospital of Split due to bronchiolitis between January 1, 2011 and December 31, 2015 were retrospectively analyzed. A total of 560 infants were hospitalized during the 5-year period, out of them 340 were males. The most frequent symptoms were nasal congestion, followed by wheezing, fever >38 °C, and crackles. Rapid antigen test for RSV was conducted in 193 infants and was positive in 134 (69.4%) cases. Bronchodilators were administered in a vast majority of infants (74.5%), whereas inhaled corticosteroids were used in 24.6% and racemic adrenaline in 14.1% of infants. Additional oxygen therapy was required only in 5% of cases. Study results confirmed the greater incidence of bronchiolitis in boys and the mean duration of hospital stay was 7.6±3.3 days. Antibiotic therapy was administered in 85.2% of infants, which is considerably higher than in other published studies. Therefore, additional effort should be invested to lower antibiotic administration.

Key words: infant; bronchiolitis; therapeutics; population characteristics

INTRODUCTION

Bronchiolitis is an acute lower respiratory tract infection usually presenting in early childhood with coughing, wheezing, and feeding problems (1). Approximately 20% of children develop acute bronchiolitis in the first year of life and 2%-3% of them, most frequently infants between 30 and 60 days of age, will be hospitalized (2, 3). Bronchiolitis is generally seasonal, appearing most frequently in epidemics during the winter months. Respiratory syncytial virus (RSV) causes 60%-80% of cases (4). For RSV, the same seasonal pattern is observed throughout the northern hemisphere, with most cases occurring from October until May. Adults with chronic obstructive pulmonary disease and other immunocompromised patients may have RSV infection throughout the year and represent a reservoir of the virus (5). Diagnosis of bronchiolitis is based on the combination of clinical characteristics, infant age, period of the year, and physical examination. Bronchiolitis usually starts with rhinorrhea and fever, and within few days spreads to lower airways resulting in symptoms of obstructive dyspnea (6). Depending on the severity of the disease, cyanosis can be present, whereas in most severe cases apnea can occur (2, 7, 8). Inflammation in the bronchioles is characterized by peribronchial infiltration of white blood cells, mostly mononuclear cells, as well as edema of the submucosa and adventitia (9). Edema, mucus secretion, and damage to the airway epithelium with necrosis may cause partial or total airflow obstruction, distal air trapping, atelectasis, and ventilation perfusion mismatch leading to hypoxemia (9). As the disease progresses, drowsiness and lethargy may occur, and

[1] University of Split, School of Medicine
[2] University Hospital of Split, Split, Croatia

Correspondence to:
Joško Markić, MD, PhD, University Hospital of Split, Spinčićeva 1, HR-21000 Split, Croatia, E-mail: josko.markic@gmail.com

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TABLE 1. Demographic characteristics of infants hospitalized for bronchiolitis

Characteristic / number of patients	Mean ± Standard deviation	Males	Females
Age at admission (N=560) (months)	4.7 ± 3.27	4.84 ± 3.25	4.47 ± 3.3
Body weight at admission (N=560) (g)	6536,72 ± 2040,49	6830,15±2130,87	6083,23±1085,19
Body length at admission (N=503) (cm)	63,93 ± 7,85	65,07±8,05	62,16±4,31
Birth weight (N=557) (g)	3326,88 ± 772,36	3414,01±735,53	3191,37±809,63
Birth length (N=556) (cm)	49,36 ± 3,82	50,12±3,51	49,00±4,19
Gestational age (N=557) (weeks)	38,61 ± 3,05	38,62±2,87	38,58±3,33

TABLE 2. Clinical symptoms/signs found in infants hospitalized for bronchiolitis (N=560)

Symptom / sign	Number (percentage)
Copious nasal secretion	383 (68.4%)
Wheezing	184 (32.9%)
Fever >38°	168 (30%)
Crackles	144 (25.7%)
Cyanosis	16 (2.9%)
Episodes of apnea	2 (0.4%)

shortness of breath, dyspnea, nasal secretion and feeding problems will be more pronounced (10). In 2006, the Scottish Intercollegiate Guidelines Network (SIGN) issued a clinical scoring system classifying bronchiolitis into mild, moderate and severe forms (11). Chest radiography is not usually recommended as a routine test, but it can be useful in children with severe bronchiolitis (12). Etiologic diagnosis is most often made by using rapid viral antigen test. This test has a high predictive value and meets the criteria of both price and speed (13, 14).

A conservative approach to treatment seems appropriate in the majority of children, especially the youngest ones. The treatment is generally supportive, as no other treatment has been shown to improve important clinical outcomes (1, 3). In 2006, guidelines were issued in New Zealand to help doctors decide whether or not there is a need of hospitalization (9).

The aim of this research was to determine and analyze clinical and epidemiological characteristics of infants treated at University Hospital of Split between 2011 and 2015 with the diagnosis of bronchiolitis.

MATERIAL AND METHODS

We conducted a retrospective analysis of all children younger than one year, diagnosed with bronchiolitis and hospitalized for more than 24 hours at University Hospital of Split between January 1, 2011 and December 31, 2015. The diagnosis was made clinically, as described elsewhere (3). The infants were hospitalized if bronchiolitis was classified as moderate or severe (11). Patient data were obtained from medical records. Children with hemodynamically significant heart disease, chromosomal anomalies, immunodeficiency (e.g., Di George syndrome), cystic fibrosis, bronchopulmonary dysplasia and epileptic encephalopathy were not included in the study. The Ethics Committee of the University Hospital of Split approved the study and the parents or guardians of the included infants signed the informed consent. Data analysis was performed using the Microsoft Excel 2010 software (Microsoft, Redmond, USA).

RESULTS

During the study period, 560 infants were admitted to Department of Pediatrics, University Hospital of Split with bronchiolitis. There were 340 (60.7%) male and 220 (39.3%) female infants. Demographic characteristics are shown in Table 1. Regarding the method of delivery, 433 (77.7%) infants were born *via* vaginal delivery and 124 (22.3%) infants *via* cesarean delivery. For three infants, the method of delivery was not noted in medical charts.

At the time of admission, oxygen saturation was assessed by pulse oximetry in 342 (61.1%) infants (mean ± standard deviation (SD), 95±4.3%). All values were obtained at room air, without administration of supplemental oxygen. Other clinical symptoms/signs are shown in Table 2.

Respiratory syncytial virus testing was ordered in all consequently admitted infants regardless of symptom severity, and was performed when available. Rapid RSV antigen testing was done in 193 (34.5%) infants and was positive in 134 (69.4%) infants. The mean duration of hospitalization was 7.6±3.3 days. The majority of infants were treated with antibiotic therapy (n=477, 85.2%) and inhalational bronchodilators (n=417, 74.5%), followed by inhaled corticosteroids (n=138, 24.6%) and with racemic epinephrine (n=79, 14.1%). Ceftriaxone was the most frequently administered antibiotic (n=223, 46.7%), followed by a combination of ceftriaxone and azithromycin (n=148, 31%) and azithromycin alone (n=68, 14.3%). Additional oxygen *via* facemask or nasal prongs was administered in 28 (5%) infants.

DISCUSSION

In this research, clinical and epidemiological characteristics of infants hospitalized for bronchiolitis at University Hospital of Split are presented. The majority of our patients were males (60.7%). Although there are other studies reporting that boys are generally more likely to be diagnosed with bronchiolitis and different mechanisms have been proposed to explain this issue, it is still not fully understood. The mean age of the hospitalized infants was 4.7 months. This is higher than in four major hospitals in the northeastern United States of America, where the average age at admission was 68 (67-88) days (15). However, similar results were found in a European study conducted in University Hospital of Geneva where the mean age was 4.57±3.4 (range 0.3-11.8) months (16). Due to financial restrictions, in our study, rapid RSV antigen testing was done when available in 193 (34.5%) infants and was positive in 134 (69.4%) infants tested. Better understanding of bronchiolitis etiology and the emergence of more advanced techniques for viral detection have raised the question of the relevance of the etiologic agent in the course of the disease. As concluded in the previously mentioned study, RSV-positive patients have a heavier economic impact; and it was shown that these patients have generally longer duration of hospitalization, oxygen therapy and nasogastric tube requirements (16). However, different from other studies, their study indicates that at the individual level, as a performance test, virology testing alone seems insufficient to precisely predict the outcomes (16). Therefore, virology testing should not be routinely done in all patients presenting to emergency department because it may increase costs without adding significant further information. These findings warrant additional validation and analysis in prospective studies.

Wheezing was the most frequent sign of bronchiolitis in our study, recorded in 32.6% of infants. In a study conducted in New York, the same symptom was found in 16% to 49% of participants. The authors observed no significant correlation between the presence of wheezing on physical examination and the severity of illness or level of saturation (17).

The main goal of bronchiolitis treatment is to regularly assess the patient and to ensure that he/she is clinically stable, well oxygenated and well hydrated. Placing an infant in a drainage position to ease breathing and gentle nasal suction to keep the airway patent is beneficial in infants with copious secretion and can lead to improvement in infants with a less severe form of bronchiolitis (1). Inhalation of hypertonic saline has been shown to increase mucociliary clearance, possibly through induction of the osmotic flow of water to the mucus layer and by breaking ionic bonds within the mucus gel. A meta-analyses including infants with mild to moderate bronchiolitis concludes that the use of hypertonic saline (3%-5%) may reduce the length of hospital stay and the rate of hospitalization (18). However, conflicting results have been reported from a study where Respiratory Distress Assessment Instrument scores showed no improvement after nebulization with hypertonic saline. It was also shown that hypertonic saline nebulization had no short-term effect on wheezing, breathing frequency, or inspiration/expiration ratios in children admitted for RSV bronchiolitis (19). Considering heterogeneity of the effect sizes and combined treatment modalities in all studies, the effect of monotherapy with nebulized hypertonic saline remains unclear. Oxygen should be administered in hypoxic infants with bronchiolitis, and administered *via* nasal cannula or facemask (1). However, there is no consensus on the level of oxygen saturation (SpO_2) we should be aiming at, and no randomized controlled trials have compared alternative oxygen supplementation regimens (1). In the United Kingdom, oxygen is commonly given to achieve SpO_2 of 92%-95% (1), whereas in accordance with the American Academy of Pediatrics (AAP) guidelines, supplemental oxygen should be administered if SpO2 levels are persistently below 90% at ambient air (3, 20). It is important to measure SpO2 correctly by pulse oximetry using pediatric probes, with nasal aspiration prior to measurement, and when the child is not moving limbs or is hypothermic. In our study, it was necessary to administer oxygen therapy in 5% of the infants, similar to the research conducted in Connecticut in which 8% of the participants were placed on oxygen therapy (21). However, there are much higher reported values, as in the study where oxygen therapy was administered in 22.5% to up to 36.8% of the infants with bronchiolitis (17). High flow oxygen therapy with humidified and heated oxygen (High Flow Nasal Cannula, HFNC) is a new noninvasive ventilation support modality that generates positive pressure in the pharynx and decreases workload of respiratory muscles. Studies suggest that the use of HFNC may rapidly improve oxygen saturation in infants suffering from bronchiolitis (22).

The most commonly used inhalation treatments are beta-2-agonists and racemic adrenaline. In our study, 74.5% of infants were given inhalation of salbutamol as part of the management of bronchiolitis, similar to another research where 72% of patients were given bronchodilators (21). Two recent systematic reviews (23, 24) have confirmed that inhaled beta agonists are not effective for bronchiolitis, as they do not improve oxygen saturation, do not decrease the need for and length of hospital stay, nor reduce overall duration of symptoms. Inhalation with adrenaline should reduce mucosal swelling and it has led to its frequent use in infants with bronchiolitis. However, no clinically important

effect has been documented for either adrenaline or beta-2-agonists (24, 25). Studies from two hospitals in New York showed the frequency of antibiotic therapy administration of 23.4% and 36.4% patients with bronchiolitis, respectively (17). Often, clinicians are concerned that, if they do not use antibiotics in an infant presenting with fever and clinical symptoms and signs of severe form of bronchiolitis, they may be putting a child at a risk of serious complications such as pneumonia, septicemia and death. There also are analyses suggesting a relationship between RSV and pneumococcal pneumonia hospitalizations since RSV is associated with increases in the incidence of pneumococcal pneumonia, particularly in young infants (26). That was the reason why antibiotic therapy was administered in the vast majority of patients (85.2%) in this study. There are insufficient data to support the use of antibiotics in bronchiolitis in children although they are used at rates of 34% to 99% in uncomplicated cases, but they can be justified in the case of concomitant bacterial infections in infants with severe disease and respiratory failure (27). Macrolides are thought to have anti-inflammatory activities, as well as antibiotic activity (28), and so were thought to have a potential in treating bronchiolitis caused by viruses. In our study, azithromycin was administered in 14.3% of patients. However, a study examining azithromycin, a macrolide antibiotic, confirmed the hypothesis that macrolide antibiotics would make no difference in bronchiolitis (29). Another two studies also demonstrated no statistically significant benefit of azithromycin compared to placebo for their primary outcomes (30, 31). The latest Cochrane review article indicates that administration of antibiotic therapy does not result in shortening of the length of hospitalization (32). We can conclude that the habitual use of antibiotics for bronchiolitis must be avoided because of the risk of side effects, significant costs, and possible development of antibiotic resistance.

The data obtained in our study showed that corticosteroid therapy was used in the management of 24.6% of the participants. The use of corticosteroids in bronchiolitis is controversial. On the one hand, a combined use of oral corticosteroids and racemic epinephrine was shown to lead to shortening of hospital stay (33). Van Woensel *et al*. demonstrated that dexamethasone (0.15 mg/kg every 6 hours for 48 hours) could be useful in mechanically ventilated children or critically ill children in general (34). On the other hand, the Pediatric Emergency Care Applied Research Network multicenter study found that a single oral dose of dexamethasone was not much more effective than placebo during treatment of the first episode of bronchiolitis in previously healthy children (35). Furthermore, a Cochrane meta-analysis including 17 randomized controlled trials concluded that there was no beneficial effect of inhaled corticosteroids in children with bronchiolitis, either on the rate of hospitalization for outpatients or on the length of stay for inpatients (36).

In our population of infants with bronchiolitis, the frequency of treatments with antibiotics and bronchodilators was high. This prevalence suggests that these therapies continue to be used routinely, perhaps due to the perceived benefit. Nonetheless, the small number of treatments effective for bronchiolitis emphasizes the importance of prevention in decreasing the impact of this disease. It has been estimated that up to 13% of childhood asthma cases could be prevented by primary prevention of RSV bronchiolitis (37). This concept is supported by two trials demonstrating reductions in early life wheezing among late-preterm children who received the anti-RSV monoclonal antibody palivizumab (38, 39). Palivizumab immunoprophylaxis consists of a monoclonal antibody to glycoprotein F of RSV. It significantly reduces the number of hospitalizations of infants with risk factors such as bronchopulmonary dysplasia, prematurity, and hemodynamically significant congenital heart disease. Therefore, in our hospital, infants born at a gestational age ≤32 weeks and younger than six months at the beginning of the RSV epidemic season receive palivizumab once a month for five months during the season. Although palivizumab is an effective modality for the prevention of RSV infection and subsequent wheezing, its use has limitations: it is expensive, requires monthly injections during the RSV season, has not been studied in full term infants, and is unlikely to be feasible for routine use in large populations. There is a need to identify other pharmacological interventions that could be used in children hospitalized for RSV bronchiolitis, which may prevent subsequent recurrent wheezing. Zhivaki *et al*. found a neonatal-specific regulatory B cell that is recruited in the respiratory tract, gets infected by the virus, and correlates with high viral load and disease severity (40). nBreg cells represent a newly described target cell for RSV and a biomarker for the severity of acute bronchiolitis. Their activity may constitute an early-life host response that favors microbial pathogenesis and may represent a target for the treatment of low respiratory tract viral infections and their pathologic consequences later in life (40).

The length of hospital stay in this study was 7.6±3.3 days. These data can be compared with those obtained in a survey conducted in Norway, where the average length of hospital stay was 80±67 hours (41). In another research, the length of hospitalization of infants in the intensive care was 5.3±8.5 days, while the length of hospitalization on the ward was 2.9±1.6 days (15). Although our hospitalization time was longer, it is comparable with the results from a

study where the mean length of hospital stay was 5.7±8.2 days (42).

There were limitations in this study. Due to the retrospective nature of our study, we were limited to the data that were available in medical records for clinical purposes only. Also, viral and bacterial tests were not performed in all children of this cohort.

In conclusion, the recent clinical practice guidelines do not recommend administration of albuterol (or salbutamol) and nebulized epinephrine to infants and children diagnosed with bronchiolitis. However, our study revealed that the frequency of bronchodilators, corticosteroids and racemic epinephrine administration was high in our institution, perhaps due to the perceived benefit. Also, antibiotics were administered in 85.2% of the subjects. Therefore, it is advisable to adjust our practice to the existing guidelines and additional effort should be invested to lower antibiotic administration. Antibiotics should be administered when there is a concomitant bacterial infection, or if it is strongly suspected.

Abbreviations:

RSV - respiratory syncytial virus
AAP - American Academy of Pediatrics
HFNC - high flow nasal cannula

NOVČANA POTPORA/*FUNDING*
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ETIČKO ODOBRENJE/*ETHICAL APPROVAL*
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SAŽETAK

Značajke dojenčadi hospitalizirane zbog bronhiolitisa u KBC Split od 2011. do 2015. godine

Petra Milić, Maja Sikirica, Vjekoslav Krželj, Joško Markić

Cilj istraživanja bio je utvrditi i analizirati kliničke i epidemiološke značajke dojenčadi s dijagnozom bronhiolitisa i liječene u Kliničkom bolničkom centru Split od 2011. do 2015. godine. Bronhiolitis je akutna infekcija donjega dišnog sustava koja je česta u ranom djetinjstvu. Najčešći etiološki uzročnik je respiracijski sincicijski virus (RSV) koji se nalazi u 60% do 80% slučajeva. Glavni simptomi su kašalj, sipnja i poteškoće pri hranjenju. Retrospektivno su analizirani medicinski zapisi djece mlađe od jedne godine hospitalizirane u KBC Split zbog bronhiolitisa od 1. siječnja 2011. do 31. prosinca 2015. godine. Tijekom 5-godišnjeg razdoblja hospitalizirano je ukupno 560 dojenčadi, 340 od njih muškog spola. Najčešći simptomi bili su nosna kongestija, potom sipnja, vrućica >38 °C i hropci. Brzi test antigena na RSV učinjen je u 193 dojenčadi i pokazao se pozitivnim u 134 (69,4%) slučaja. U velike većine dojenčadi (74,5%) primijenjeni su bronhodilatatori, dok su inhalirajući kortikosteroidi davani u 24,6%, a racemični adrenalin u 14,1% dojenčadi. Dodatna terapija kisikom bila je potrebna u samo 5% slučajeva. Rezultati ovoga istraživanja potvrđuju veću incidenciju bronhiolitisa u dječaka, a srednje trajanje bolničkog liječenja bilo je 7,6±3,3 dana. Antibiotska terapija primijenjena je u 85,2% dojenčadi, što je znatno više od podataka iz drugih objavljenih istraživanja. Stoga treba uložiti dodatne napore kako bi se smanjila primjena antibiotika.

Ključne riječi: dojenče; bronhiolitis; lijekovi; značajke populacije