

# Risk factors assessment and treatment methods in infants with severe bronchiolitis

Amila Hadžimuratović<sup>1</sup>, Hajrija Maksić<sup>2</sup>

<sup>1</sup>Public Institution Health Centre of Sarajevo Canton, Sarajevo, Bosnia and Herzegovina

<sup>2</sup>Clinical Center University of Sarajevo, Sarajevo; Bosnia and Herzegovina

## ABSTRACT

**Introduction:** Bronchiolitis, a viral infection of the lower respiratory tract, is one of the most substantial health burdens for infants and young children worldwide. Despite the respiratory syncytial virus (RSV) being the most common causative agent of bronchiolitis, there is a number of established risk factors associated with development of severe bronchiolitis. The aim of this study was to investigate the prevalence of established risk factors for severe bronchiolitis among hospitalized infants during the first year of life, as well as to compare the diagnostic and treatment methods between pulmonology and neonatology department.

**Material and methods:** This epidemiological, case-controlled, retrospective-prospective study included all children aged one year or younger who were diagnosed with severe bronchiolitis and hospitalized in Pediatric Clinic of Clinical Center University of Sarajevo from 1 May 2017 to 30 April 2018 (12 months). Patient data was collected from the patients' histories and through interviews with parents and filled in the previously designed questionnaire.

**Results:** The research included 95 hospitalized infants diagnosed with bronchiolitis who were less than 12 months old. Sample size was homogenized by gender ( $p>0.05$ ). Patients were predominantly term children younger than 6 months at the time of the hospitalization. Admission rate was highest during the first four months of the year (71.6%) with peak in March (23.3%). The findings show that significant risk factors are presence of viral disease in the family, smoking during pregnancy and smoking in the household. Most of the patients (87.3%) received antibiotic or corticosteroid treatment during hospitalization, with a significant difference in antibiotic and corticosteroid use between pulmonology and neonatology department ( $p<0.05$ ).

**Conclusion:** Infants with comorbidities and negative gestational and socioeconomic factors more often develop severe form of bronchiolitis during the first year of life.

**Keywords:** bronchiolitis, risk factors, infants, hospitalization

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## \*Corresponding author

Amila Hadžimuratović  
Public Institution Health Centre of Sarajevo Canton  
Vrazova 11, 71000 Sarajevo,  
Bosnia and Herzegovina  
E-mail: amilahadzimuratovic@gmail.com  
ORCID ID: <https://orcid.org/0000-0001-7607-5429>

## INTRODUCTION

Bronchiolitis, a viral infection of the lower respiratory tract, is one of the most substantial health burdens for infants and young children worldwide. It is characterized by extensive inflammation and edema of the airways, increased mucus production and necrosis of airway epithelial cells (1).

The disease is usually associated with substantial direct and indirect costs, not only for healthcare systems, but also for families and society as a whole. Severe bronchiolitis poses a significant health problem in high-income countries, but it is an even greater problem in low- and middle-income countries (LMICs), due to higher mortality rates (2). Up to 3% of all children are hospitalized with bronchiolitis in their first year of life in the United States, which accounts for between 57,000 and 172,000 hospitalizations annually. Estimated cost of these hospital charges was \$1.4 billion in 2002 and \$1.73 billion in 2009 (3–5). Although admissions to hospital have declined from 2000 to 2010, emergency department visits have increased, in addition to increased use of mechanical ventilation and hospital charges (1).

Bronchiolitis is a clinical diagnosis that is based on history (rhinorrhea, difficulty breathing, cough) and physical examination (tachypnea, crackles, retractions, wheeze). Neither diagnostic imaging nor laboratory tests are needed to recognize this common syndrome (6). The most common etiology of bronchiolitis is respiratory syncytial virus (RSV), with detection rates reaching 70 – 85% in hospitalized infants during seasonal winter epidemics. Ninety percent of children are infected with RSV in the first 2 years of life and up to 40% will experience lower respiratory tract infection during the initial infection. Infection with RSV does not grant permanent or long-term immunity, with reinfections common throughout life (3,7). Other viruses that can cause bronchiolitis include human rhinovirus, human metapneumovirus (hMPV), influenza viruses (IVs) and parainfluenza viruses (PIVs) (3,7)

Independent risk factors typically associated with a high risk of hospitalization are male gender, low birth weight, premature birth without or, especially with chronic lung disease, congenital heart disease or immunodeficiency disorders, age <6 months, birth during the first half of influenza season, crowding/siblings, cigarette smoke, mechanical ventilation as a neonate, lack of breastfeeding, delivery by elective caesarian section, maternal age, inadequate prenatal care, family history of asthma and multiple gestation (1,7–10).

There is no effective drug treatment for bronchiolitis, so the mainstay of management for infants with viral bronchiolitis is supportive care with a small proportion of more severely affected infants being treated in intensive care (10).

The aim of this study was to investigate the prevalence of established risk factors for severe bronchiolitis among infants younger than one year and hospitalized with the diagnosis of bronchiolitis at the Pediatric clinic of Clinical Center University of Sarajevo as well as to compare the diagnostic and treatment methods between pulmonology and neonatology department.

## MATERIALS AND METHODS

This epidemiological, case-controlled, retrospective-prospective study included all children aged one year or younger who were diagnosed with severe bronchiolitis and hospitalized in Pediatric Clinic of Clinical Center University of Sarajevo from 1 May 2017 to 30 April 2018 (12 months). Severe bronchiolitis was defined as rhinorrhea, cough, tachypnea, wheezing, rales, and increased respiratory effort (e.g., grunting, nasal flaring, and intercostal and/or subcostal retraction), with symptoms of severity (e.g., increased respiratory rate, retractions, and oxygen saturation at 90% or lower) (3,9).

Criteria for inclusion was the diagnosis of severe bronchiolitis, chronological age of one year or younger, date of birth during the study period and hospitalization in the pulmonology or neonatology departments of the Pediatric Clinic. Exclusion criteria was previous hospitalization for bronchiolitis or any other respiratory infection. Patients with insufficient data in the medical records were further excluded from the study.

Informed consent was obtained from the children's parents at the time of clinical evaluation.

Center for science, research and clinical studies of Clinical Center University of Sarajevo approved the study on 9<sup>th</sup> of April 2018, in accordance with the principals of the Declaration of Helsinki.

Patient data was collected from patient's medical records and through parent's interviews. All children's

parents were contacted by telephone to determine their children's exposure to potential or known risk factors for severe bronchiolitis (5,11). All data was filled in the previously designed questionnaire.

The questionnaire included demographic data: sex, chronological age, gestational age, birth weight, duration of the hospitalization, palivizumab vaccination and history of previous hospitalizations due to respiratory disease; comorbidities such as bronchopulmonary dysplasia (BPD), congenital heart anomaly (CHA), immunodeficiency, neuromuscular disease, cystic fibrosis and respiratory airway anomalies; neonatal complications after birth that included: perinatal asphyxia, meconium aspiration syndrome (MAS), assisted ventilation (mechanical ventilation or continuous positive airway pressure), respiratory distress syndrome and the use of surfactant and the stay in the neonatal intensive care unit (NICU); gestational data including: mothers age at time of child's birth, delivery by caesarean section, In vitro fertilization (IVF), twin pregnancy and smoking during pregnancy; and socioeconomic data including: child's breastfeeding history, passive exposure to house smoking, family health history (asthma, allergies, atopy, respiratory infection during child's hospitalization), coexistence of pets and overcrowding. The questionnaire also included data about diagnostic and treatment methods in pulmonology and neonatology department.

Statistical analysis was performed using the statistical package for biomedical research Med Calc version 12.3 (MedCalc Software, Antwerp, Belgium). The continuous variable data are reported as the mean and standard deviation (SD). Statistical associations were determined by Chi-square test, Student t test and ANOVA test, when appropriate. Results were considered statistically significant with p value <0.05 and the confidence interval (CI) set at 95%.

## RESULTS

During the study period, 96 children aged one year or younger were hospitalized for the first time with the diagnosis of severe bronchiolitis at the departments of pulmonology and neonatology of Pediatric Clinic.

Out of the total number, 56.8% were female. Patients were predominantly term children aged 0-3 months (66.3%) at the time of the hospitalization. Admission rate was highest during the first four months of the year (71.6%) with peak in March (23.3%) (Figure 1). The length of stay in the hospital was significantly longer for preterm children (p=0.001).

Epidemiological characteristics and assessed risk factors of the patients are shown in Table 1 and 2.

Diagnostic and treatment comparison between pul-

mology and neonatology department are given in Table 3. Significantly more causative agent analysis were performed in the pulmonology department ( $p=0.001$ ), with RSV being the predominant causative agent.

Most of the patients (87.3%) received antibiotic or corticosteroid treatment during hospitalization. Almost 90% of patients were given antibiotics as a treatment, with a significant difference in antibiotic use between pulmonology and neonatology department ( $p=0.002$ ). More than half of patients were given corticosteroids (mainly methylprednisolone) also with a significant difference between pulmonology and neonatology department ( $p=0.0001$ ). We also compared the use of antibiotics in patients with normal values of CRP and the results showed there was no significant difference between the two departments ( $p=0.10$ ).

## DISCUSSION

Acute viral bronchiolitis is a major public health problem and one of the most common reasons for hospitalization during infancy (12). Considering that bronchiolitis can lead to severe aftermath and it is often related to increased risk of asthma in later years (5), we found it important to investigate the potential risk factors that might contribute to developing of severe bronchiolitis.

Generally, it is considered that male infants have an increased risk for severe bronchiolitis and some studies report risk ratio of males to females to be 1.425:1 (13,14,15). Also, most studies suggest that prematurity and low birth weight represent an increased risk for more severe disease and hospital admission with bronchiolitis (13,15,16). The results of our study

Table 1. Epidemiological data of children hospitalized with severe bronchiolitis (n=95)

	Number of patients (N/%)
Sex	41(43.2%)/54 (56.8)
Chronological age (months)	
0-3	63 (66.3%)
4-6	23 (24.2 %)
7-9	7 (7.4%)
10-12	2 (2.1%)
Normal birth weight (2500-4200 grams)	84 (88.4%)
Term children (37 <sup>0/7</sup> to 42 <sup>6/7</sup> weeks gestation)	79 (83.2%)
Total hospital stay (days±SD)	6.5±4.4
Preterm children	12.3±8.9
Term children	6.0±3.7

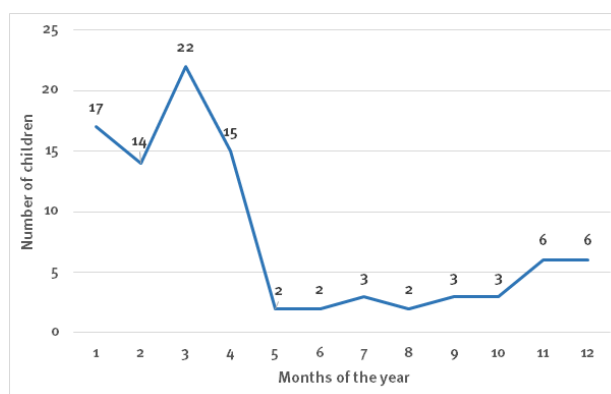


Figure 1. Admission rate due to severe bronchiolitis during the year (from January to December)

Table 2. Risk factors in children hospitalized with severe bronchiolitis (n=95)

Variable	Number of patients (N/%)
Mothers age at child's birth (older than 35 years)	13 (13.7%)
Delivery by C-section	35 (36.8%)
IVF	3 (3.2%)
Twin pregnancy	7 (7.4%)
Smoking during pregnancy	21 (22.1%)
Comorbidities (20%)	
Congenital heart anomaly	12 (12.6%)
Bronchopulmonary dysplasia	5 (5.3%)
Immunodeficiency	1 (1.0%)
Neuromuscular disease	1 (1.0%)
Neonatal complications following birth	37 (38.9%)
NICU stay	11 (11.6%)
Need for assisted ventilation	9 (9.5%)
Perinatal asphyxia	7 (7.4%)
Meconium aspiration syndrome	5 (5.3%)
Respiratory distress syndrome	5 (5.3%)
Breastfeeding	56 (58.9%)
House smoking	47 (49.5%)
Overcrowding	15 (15.8%)
Pets	7 (7.4%)
Family history of atopy	14 (14.7%)
Respiratory infection in the household prior to the hospitalization	73 (76.8%)
Palivizumab prophylaxis	3 (3.2%)

**Table 3. Diagnostic and treatment comparison between pulmonology and neonatology department**

	Pulmology (N=78)	Neonatology (N=17)
Causative agent isolation	29 (37.2)	3 (17.6)
Positive RSV infection	23 (79.3%)	1 (33.3%)
Elevated CRP values	29 (38.2%)	5 (29.4%)
Antibiotics	72 (92.3%)	11 (64.7%)
Corticosteroids	55 (70.5%)	2 (11.8%)
The use of antibiotics with normal values of CRP	43 (56.6%)	6 (35.3%)

showed that most of the children hospitalized with severe bronchiolitis were term infants with normal birth weight. There was no significant difference in gender distribution ( $p=0.182$ ). Our finding might be related to cultural and environmental factors observed in Bosnia and Herzegovina, where there is a costume of visiting healthy term newborns immediately after leaving the hospital. In contrast, preterm and late preterm infants are put under surveillance and parents and family members are instructed to avoid close contact and visits, wear masks while feeding the newborn, wash hands before contact and other measures of precautions that highly protect these infants from respiratory infection transmission. The highest number of hospitalized children were younger than three months (66.3%) and more than 90% of children were younger than six months, which was a significant difference compared to other age groups ( $p=0.0001$ ) (Table 1). The results are consistent with other studies suggesting that the chronological age younger than six months represents a risk factor for developing severe bronchiolitis (13,15,17). In these young infants, the absence of maternal antibodies, narrower airways, an immature immune system and perhaps a bias toward a TH2-type response to RSV infection may be responsible either singly or in conjunction for much more severe disease that is seen in very young infants (15). The highest number of hospitalization due to severe bronchiolitis was during the winter, i.e. during the first four months of the year. Peak months for admission to the hospital were March (23.2%) and January (17.9%). With the end of the rainy season in May there was a significant decrease in hospital admissions due to severe bronchiolitis ( $p=0.0001$ ). These results are supported by the fact that RSV has a seasonal pattern of circulation, with peaks during late winter and early spring in temperate and subtropical regions. Low temperatures and relative air humidity are considered to be a significant contributor to spreading of RSV infections in temperate climates (18, 19, 20).

Our study showed that the most significant risk fac-

tor was exposure to respiratory infection in the family before hospitalization (76.8%). These alarming results demonstrate the need for better prevention and parent's education about the transmission of respiratory infections and the protection of infants. It is important to mention that a significant percentage of mothers (22.1%) smoked during pregnancy which is considered a major risk factor for severe bronchiolitis since it is well known that pregnancy smoking decreases lung function in newborns (13,16). In a big Danish study on risk factors for RSV infant hospitalization, it was found that pregnancy smoking was one of the most important risk factors for developing severe bronchiolitis (OR:1,56; CI: 1,32-1,98) (21). Also, relatively large number of patients (49.5%) was exposed to passive smoking in the household. The result is consistent with those from previous studies that report that exposure to cigarette smoking is a major cause of increased hospitalization due to bronchiolitis among infants and young children (9,15,17,22). Although many studies suggest that overcrowding is an important risk factor (15,23), most of the patients in our study (84.2%) sleep in the same room as their parents due to night feeding habits of infants younger than 1 year. Previous studies have given differing results about predisposing role of atopy for bronchiolitis. Carslen et al. suggest that the atopic background and atopic illness manifest at 2 years of age, having started at 1 year of age, and do not predispose to acute bronchiolitis (23). This is supported by the results of our study. Some studies could not identify the absence of breastfeeding as an independent predictor for RSV- infection. However, some studies indicate that the absence of breast-feeding in combination with other risk factors like crowding, passive smoke exposure or low socioeconomic status significantly increases the risk for development of RSV lower respiratory tract infections (LRTI) (24). Mothers milk contains RSV antibodies, including IgG and IgA, that can significantly neutralize RSV activity. In addition, immunoregulators and immunomodulators in mothers milk enhance the growth of infant's immune system, which is why breastfeeding is generally considered to be a protective factor associated with severe bronchiolitis (14,15,23). In our study we considered children who were fed three or more times a day with mothers' milk to be breastfeeding. This means that 41.1% of our patients were not continually breastfed. Holberg et al. also suggest that the risk of having a RSV-LRI increases with combinations of two or more socioeconomic risk factors (25).

We compared the diagnostic and treatment methods used in two departments. Isolation of the agent that might cause bronchiolitis is not routinely performed at these two departments. The main reason is the validity of such respiratory profile in detecting IgG and

IgM antibodies, considering the low rate in forming of the IgM antibodies in young infants, which gives the analysis low diagnostic sensitivity. We compared the clinical practice of administering antibiotics and corticosteroids in treatment of severe bronchiolitis between two departments, which showed a significantly higher administration of both in the pulmonology department. A systematic review analyzing 12 studies in the use of corticosteroids for treatment of severe bronchiolitis showed that there was no significant difference in the length of hospitalization, improvement of the clinical outcome or the rate of rehospitalization which is why systemic corticosteroids are not recommended as treatment for severe bronchiolitis (15). The use of antibiotics is also not recommended unless there is confirmed bacterial infection or the need for use of the mechanical ventilation. Unration use of antibiotics puts children at a greater risk for adverse effects as well as for development of antimicrobial resistance (15).

Our study has several potential limitations. Retrieving data retrospectively from medical records was sometimes difficult to do. Also, while conducting interviews, parents could have been too subjective or given false information about socioeconomic or gestational factors for numerous reasons. Furthermore, virus isolation is not a routine practice in our Pediatric Clinic, which is why there is a possibility that some of these cases were not RSV respiratory infections. There is a possibility that some cases of bronchiolitis were misdiagnosed as pneumonia, asthma or febrile syndrome, which could affect the prevalence of severe bronchiolitis in our study. Finally, we did not have a control group of patients for comparing results, which is why we can only talk about risk factor prevalence among hospitalized children.

## CONCLUSION

Bronchiolitis is an important cause of hospitalization among infants in Bosnia and Herzegovina. The majority of children were term infants, with normal birth weight and younger than six months. Infants with comorbidities and negative gestational and socioeconomic factors more often develop severe form of bronchiolitis during the first year of life. Physicians should advise parents and family members on precautions measures they can take to limit respiratory infections and their severity. Also, physicians should take extra precaution when considering the administration of antibiotics and corticosteroids in the treatment of severe bronchiolitis. Our findings could be helpful in public health prevention campaigns and guideline writing in our country that would help reduce acute bronchiolitis in children. Further studies should assess the effect of combined nonmedical risk factors on bronchiolitis severity.

## DECLARATION OF INTEREST

The authors declare no conflict of interest for this study.

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