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# Acute Bronchiolitis and Other Predictors for Early Diagnosis of Childhood Asthma

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## Abstract

**BACKGROUND:** Early onset of acute bronchiolitis is associated with early onset of childhood asthma. Unfortunately, childhood asthma tends to be frequently overlooked and not optimally managed. Family pediatricians, however, possess an exceptional opportunity to recognize the connection of these conditions and promptly identify, address, and oversee children with asthma. It is important to note that childhood asthma typically begins in the early years of life, often triggered by viral infections.

**AIM:** We aimed to analyze the early predictors linked to childhood asthma, such as previous episodes of acute bronchiolitis and the presence of atopy, to facilitate the early identification of children with childhood asthma within primary care settings.

**MATERIALS AND METHODS:** Retrospectively analyzed data from 1652 children from health records at the Primary Health Care Polyclinic - Pediatric Primary Health Care Practice -"Vitalino" in Veles, North Macedonia. Within this cohort, 108 children had experienced acute bronchiolitis in 2016, at an age range of 0–2 years. In 2020 and 2023, the data were analyzed to determine the existence of a connection between acute bronchiolitis and other predictors with the early onset of childhood asthma.

**RESULTS:** This retrospective research showed that from the total number of children, 108 children aged up to 2 years suffered from acute bronchiolitis, of which the analysis in 2020 showed that 50 children had atopy, 19 allergic rhinitis, 33 children had recurrent laryngitis, 24 children recurrent otitis, 68 children with recurrent bronchial obstructions (≤3), and 39 children developed early onset of bronchial asthma. The analysis in 2023 showed that 51 children have asthma. Based on the obtained results, the prevalence of acute bronchiolitis in the Republic of North Macedonia is 6.54%. If acute bronchiolitis is considered an early manifestation of childhood asthma, then the prevalence of childhood asthma in the Republic of North Macedonia is about 6.54%.

**CONCLUSION:** Based on the obtained results, we can conclude that early onset of acute bronchiolitis is an early manifestation of childhood asthma. Additional predictors are early signs of atopy, frequent viral infections with broncho-obstruction, allergic rhinitis, and recurrent laryngitis.

## Introduction

Childhood asthma, a chronic inflammatory disease of the airways, is characterized by various symptoms of cough, wheezing, difficulty breathing, and/or chest tightness [1]. Recognizing childhood asthma, especially in early childhood, is very difficult due to the various asthma phenotypes described in children, while at the same time, there are limited diagnostic possibilities for early diagnosis of the disease. For this reason, early recognition of certain predictors for the occurrence of childhood asthma is crucial, which include: Occurrence of acute bronchiolitis before the age of 2 years, signs of atopy in early infancy, a family background of allergic diseases, history of recurrent viral infections ending in broncho-obstruction and hospitalization (with a minimum frequency of 3 in a period of 6 months to a year), and the excessive use of antibiotics, particularly within the initial 6 months–2 years of life [2]. Frequently the disease is underdiagnosed or diagnosed with different names (*Bronchitis obstruens recidivans, Bronchopneumonia,* and *Bronchitis chronica*), that leads to the utilization of numerous unnecessary diagnostic tests and prolonged courses of antibiotic treatment [3].

Asthma's etiology is multifactorial, influenced by both genetic and environmental factors in a complex interplay. While a positive family history increases the risk of childhood asthma, it alone is insufficient to trigger asthma development [4]. Recurrent lower respiratory viral infections, including respiratory syncytial virus (RSV) infection and the use of antibiotics, are linked to coughing and wheezing; however, they have not been definitively established as the primary etiological factors in childhood asthma [5]. Viral respiratory infections are the most common cause of asthma exacerbations in children [6]. Roughly, 40% of infants experience wheezing during their 1$^{st}$ year of life, whereas about 30% of pre-school children encounter recurrent wheezing that persists as asthma until the age of 6 years [7].

Acute bronchiolitis is the greatest risk factor for the development of childhood asthma, but research shows different heterogeneity regarding bronchiolitis. A prospective study was conducted in the United States and Finland, encompassing three cohorts of infants diagnosed with bronchiolitis, which were subsequently categorized into four distinct groups. Among these, Group A comprised infants with bronchiolitis, a history of atopy, and the presence of asthma in at least 1 parent. Infants falling into this particular group face the highest risk of developing childhood asthma later on [8].

Atopy, allergic rhinitis, eczema, and urticaria are important risk factors for early childhood asthma [9]. Research shows that atopy and early sensitization to allergens intensify with increasing age and have a significant impact on the prevalence of childhood asthma. Retrospective research shows that the prevalence of childhood asthma is up to 11.2% in younger children and up to 7% in older children, and the prevalence of allergic rhino-conjunctivitis increases by 20% with increasing age of children [10], [11].

Accumulated data strongly indicate that bronchiolitis occurring early in life constitutes a significant risk factor for subsequent episodes of wheezing and the development of asthma [12], [13].

Current studies support an association between life-threatening RSV bronchiolitis and the diagnosis of asthma in early childhood and school age. Furthermore, human rhinovirus infection in early childhood can be a precursor to future asthma. Whether viral bronchiolitis is the cause or an early manifestation of future asthma is still uncertain. Notably, vitamin D status is recognized as a potential modifying factor in virus-induced wheezing, potentially impacting the likelihood of childhood asthma development [14].

A family history of asthma and other allergic diseases is associated with risk for childhood asthma. However, our understanding of when asthma emerges and whether it continues into early adulthood remains limited. Studies indicate that a family history of asthma and allergic disorders greatly influences asthma development, but its impact within the hereditary context varies across subtypes. In certain cases, the genetic component takes precedence, while in other subtypes, environmental exposure assumes a more dominant role [15]. There is a significant correlation between asthma and increased antibiotic consumption among children and adolescents. This association is the strongest in younger children and females [16]. The use of antibiotics in early childhood is associated with the development of atopic diseases, but the etiology is still unclear. A retrospective study focused on twins aged 3–10 years, encompassing participants from the Netherlands and Sweden, evaluated antibiotic usage during the 0–2 years age span, while asthma and eczema diagnoses were established between the ages of 3 and 12. The findings suggested a potentially elevated likelihood of asthma development in children who had used antibiotics for respiratory infections during their early years [17]. The early use of antibiotics can change the intestinal microflora and cause an intestinal imbalance disorder in the development of the immune system [18]. The microbiome plays a key role in the development of CD4 T cells that differentiate into helper T cells, namely Th1 and Th2 cells. Early exposure to antibiotics delays the postnatal maturation of Th1, subsequently leading to a diminished Th2 response, which is closely associated with allergic reactions. This disruption is believed to compromise immune functionality and elevate the potential for atopy in later life, attributed to insufficient production of key immune factors [19]. A notable correlation between the presence of airway house dust mites allergies in young children and their intestinal microbiome is apparent. Identifying the existence of house dust mite's allergies in both the airways and gut microbiome is imperative, necessitating the measurement of specific immunoglobulin E antibodies targeting these house dust mites [20]. In addition, a strong association between childhood asthma and allergic rhinitis was found [21].

We aimed to analyze the early predictors linked to childhood asthma, such as previous episodes of acute bronchiolitis and the presence of atopy, to facilitate the early identification of children with childhood asthma within primary care settings.

## Materials and Methods

The current study comprises a retrospective analysis of records gathered within primary health-care settings, presented in the form of a comprehensive report. We analyzed medical records of 1652 children, ranging from 0 to 14 years of age, who regularly seek medical attention at the Primary Health Care Polyclinic - Pediatric Primary Health Care Practice - "Vitalino" in Veles, North Macedonia. This study's dataset specifically focused on a subgroup of 108 children aged 0–2 years, all of whom had acute bronchiolitis during the year 2016. In 2020, an analysis was conducted on the medical records of these 108 children to determine the presence of indicators related to childhood asthma. This investigation involved the examination of various parameters. For this particular cohort, extensive data were collected regarding factors such as gender, age, atopy (early onset of eczema), prematurity, breastfeeding, supportive care, treatment within primary care settings, instances of hospitalization due to acute bronchiolitis, occurrences of recurrent bronchitis, recurrent otitis, allergic rhinitis, laryngitis, nationality, antibiotic therapy, preventive measures, and the outcome observed 4 years after the initial bronchiolitis episode. Subsequently, in 2023 (7 years following the initial bronchiolitis occurrence), a

reevaluation of the medical records pertaining to the same 108 children was carried out, focusing exclusively on the presence of childhood asthma.

## Results

Out of the total cohort of 1652 children, a specific subset comprising 108 children aged 0–2 years, all of whom exhibited symptoms of acute bronchiolitis in the year 2016, was chosen for inclusion in the study.

The analysis of 108 children in 2020 focusing on the identification of early predictors associated with childhood asthma as well as the determination of the presence of childhood asthma itself showed that 39 children developed childhood asthma (36.1%). Gender representation did not exhibit a significant difference, with 52 male children and 56 female children included in the study. The majority of these children (79) were placed on artificial nutrition during their 1$^{st}$ year of life. In addition, 77 children received antibiotics categorized under semi-synthetic penicillin and cephalosporins. The analysis aiming to identify the early predictors linked to childhood asthma-revealed several significant findings. Among the participants, 24 children (22.2%) exhibited recurrent acute otitis, whereas atopy was observed in 50 individuals (46.3%). Acute bronchiolitis coupled with recurrent broncho-obstructions (occurring in up to 3 episodes) was identified in 68 children (63.0%). Allergic rhinitis affected 19 participants (17.6%), and acute recurrent laryngitis was noted in 33 children (30.6%). Detailed information is provided in Table 1.

**Table 1: Analyses of the early predictors associated with childhood asthma and determination of the presence of childhood asthma in 2020 (n = 1652)**

| Early predictors of childhood asthma | 2020 year n (%) | 2020 year prevalence % |
|---|---|---|
| Recurrent acute otitis | 24 (22.2) | 1.45 |
| Atopy | 50 (46.3) | 3.03 |
| Recurrent bronchitis (up to 3 attacks) | 68 (63.0) | 44.7 |
| Allergic rhinitis | 19 (17.6) | 1.15 |
| Acute recurrent laryngitis | 33 (30.6) | 1.99 |
| Childhood asthma | 39 (36.1) | 2.36 |

The prevalence is a frequently used epidemiological measure of how commonly a disease or condition occurs in a population. The prevalence measures how much of some disease or condition there is in a population at a particular point in time. The prevalence is calculated by dividing the number of persons with the disease or condition at a particular time point by the number of individuals examined. For example, in our study, 1652 individuals completed the questionnaire (were examined). Of these 1652 people, 108 currently suffered acute bronchiolitis and so had the condition at the particular time point of the study. Thus, the prevalence of acute bronchiolitis was 108/1652 = 0.0654. The prevalence is often expressed as a percentage, calculated by multiplying the ratio by 100. The above study expresses the prevalence as a percentage; thus the prevalence of acute bronchiolitis is 6.54%. Based on the obtained results, the prevalence of acute bronchiolitis in the Republic of North Macedonia is 6.54%. If acute bronchiolitis is considered an early manifestation of childhood asthma, then the prevalence of childhood asthma in the Republic of North Macedonia is about 6.54%. The prevalence as a percentage of early predictors of childhood asthma in the Republic of North Macedonia varies from 1.5% for allergic rhinitis to 44.7% for recurrent bronchitis (up to 3 attacks) (Table 1).

In 2023, a reanalysis of the same cohort of 108 children was conducted to ascertain the prevalence of childhood asthma. The results indicated that the number of children with childhood asthma had risen to 51 (47.2%). Among these, 31 children exhibited mild intermittent asthma (28.7%), whereas 20 children were classified as having moderate asthma (18.5%).

## Discussion

Asthma is a multifactorial disease, the occurrence of which includes genetic factors and environmental factors [4]. It is a chronic disease with the highest prevalence in children and is difficult to diagnose in infants and pre-school children [2]. The disease is frequently triggered by viral respiratory infections [1], [3]. In the case of youngsters, especially infants and young children, conventional diagnostic measures, including pulmonary function tests, do not align with established norms, leading to a lack of consensus regarding asthma diagnosis in this age group [2].

Diagnosing childhood asthma in its early stages can be predicated on the following criteria: Intermittent symptoms with links to common cold occurrences; verification by a medical professional of at least 3 episodes of expiratory wheezing, each persisting for more than 24 h, within the preceding year in a child with the risk factors for asthma; and a minimum of 4 instances of expiratory wheezing during a year, irrespective of the presence of risk factors [22], [23], [24].

The influence of several predictors such as atopy, recurrent viral infections, allergic rhinitis, recurrent laryngitis, recurrent wheezing, and excessive use of antibiotics has already been determined [1], [8], [9], [10], [17], [21]. Our research outcomes showed a clear correlation between acute bronchiolitis and childhood asthma. Significantly, our findings confirm the suggestion that acute bronchiolitis serves as an early exacerbation precursor to childhood asthma [13].

Considering that all participants in the study group exhibited certain predictors of early childhood

asthma onset, it becomes reasonable to consider acute bronchiolitis as an early manifestation of childhood asthma. This assumption is further supported by the fact that the cumulative count of children experiencing recurrent wheezing (up to 3 episodes within a year) and those with bronchial asthma amounts to 108 children. Our research revealed that in the Republic of North Macedonia, the prevalence of acute bronchiolitis stands at 6.5%, whereas the prevalence of children with asthma and recurrent wheezing reaches 6.48% within the analyzed sample. This observation can be explained to a common tendency among doctors to withhold the diagnosis of childhood asthma from parents, often due to parental pressure and apprehension, consequently leading to an underdiagnosis and insufficient treatment scenario for these children. Considering the comparable percentages of children with childhood asthma (6.48%) and children with recurrent wheezing, as well as the percentage of children with acute bronchiolitis (6.5%), a possible conclusion can be drawn that acute bronchiolitis might be an early presentation or even an initial exacerbation of childhood asthma.

According to the World Health Organization, the global prevalence of childhood asthma is reported at 9.4%. Among the 33 selected studies, the prevalence of childhood asthma and wheezing stands at 7.9%. Across these studies, asthma prevalence exhibits considerable variability, ranging from 1.7% in Germany to 13.48% in England, 9.82% in Greece, and a notably higher 55.37% in Spain. Notably, the worldwide estimate for wheeze prevalence is approximately 11.6% [25]. Following these figures, it becomes apparent that North Macedonia holds a place among countries with a comparatively lower percentage of children diagnosed with asthma. This could potentially be indicative of underdiagnosing practices within the region, contributing to the observed lower prevalence rate.

## Conclusion

The prevalence of acute bronchiolitis in the Republic of North Macedonia is 6.54%. If acute bronchiolitis is considered an early manifestation of childhood asthma, then the prevalence of childhood asthma in the Republic of North Macedonia is about 6.54%.

Based on this research, we can conclude that there are several predictors of the early onset of childhood asthma such as early onset of atopy, recurrent laryngitis, allergic rhinitis accompanied by otitis, frequent use of antibiotics, recurrent wheezing (more than 3 for a period of 6 months to 1 year) and the occurrence of acute bronchiolitis in early childhood from 0 to 2 years. Children with atopic diseases are susceptible to frequent viral infections that lead to increased bronchial hyperreactivity, and one viral infection is sufficient to provoke an early manifestation or exacerbation of asthma symptoms.

The early appearance of acute bronchiolitis and the presence of additional predictors such as signs of atopy, frequent viral infections with recurrent wheezing, allergic rhinitis, and recurrent laryngitis have important role in the development of childhood asthma. This insight holds significant value for medical practitioners in primary care settings, facilitating early identification and suitable management of children with childhood asthma. This approach will enhance the health of children with asthma by ensuring appropriate treatment and reducing the unnecessary use of antibiotics. Consequently, this also brings potential benefits for the community at large, spanning from reduced work and school absences to the overall well-being of families.

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