

Review

Assessment and Long-Term Follow-Up of Recurrent Wheezing in Non-Asthmatic Children

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Abstract

Wheezing is one of the leading respiratory causes for medical treatment and hospitalization during the first years of life, consequently leading to a decline in lung function, poor quality of life, and a huge economic burden. Recurrent wheezing refers to experiencing more than one wheezing episode in one year, and it is considered a risk factor for asthma development in childhood and adolescence. Main causes of wheezing in infants include asthma, bronchiolitis, and respiratory viral infections. Several phenotypes and patterns of wheezing have been discovered in infants and children. Long-term cohort studies reported a strong association between wheezing phenotypes and asthma development. Risk factors that contribute to asthma progression include recurrent wheezing, allergen sensitization, exposure to tobacco, and parental asthma. Proper assessment and determination of key environmental triggers will lead to efficient management of the wheezing episode and better clinical outcomes. As recurrent wheezing is strongly associated with decline in lung function, management strategies should aim to alleviate symptom severity and prevent further functional impairment of the lungs. In this narrative review, we aim to summarize current evidence regarding causes and phenotypes of wheezing in children and key predictors for asthma progression and lung impairment in long-term follow-up studies, in addition to possible prevention strategies.

Keywords: Recurrent Wheezing, Persistent Wheezing, Bronchiolitis, Asthma

Introduction

Wheezing refers to a continuous, high-pitched whistling sound that occurs during breathing due to narrowing or obstruction in some part of the respiratory airways (1). Experiencing more than one episode of wheezing in a year is considered recurrent wheezing, and it is a clinical challenge in preschool children (2). About 20% of infants have recurrent wheezing in their first year, and in most instances, recurrent wheezing progresses to severe episodes, visits to the emergency department, and hospitalization, which significantly impairs quality of life and causes high utilization of health care resources (3). Many studies reported that recurrent wheezing during infancy and early childhood is a strong risk factor for developing asthma in children and later in life (4-6).

Asthma and bronchiolitis are the two most common causes of recurrent wheezing in children (1). Other causes include recurrent viral infections in the lower respiratory tract, especially in children (7), in addition to cystic fibrosis, vocal cord abnormality, airway structural abnormalities, foreign body recurrent aspiration, gastroesophageal reflux disease, and cardiac disorders (1).

Diagnosis of recurrent wheezing is complicated and challenging because, as a symptom, it can be associated with several diseases. Consequently, misdiagnosis of the disorder, such as pneumonia or other respiratory disorders, leads to improper management and further complications (8). Proper assessment involves history taking and physical examination to confirm that the child has a wheezing disorder and determine the symptom pattern and severity and identify potential trigger factors (9). Management of recurrent wheezing involves administration of inhaled corticosteroids, oral corticosteroids, long-acting inhaled β_2 -agonists, and short-acting β_2 -agonists, in addition to environmental accommodations (7, 9, 10). In this narrative review, we aim to outline current evidence regarding the proper assessment of recurrent wheezing in non-asthmatic children and the determination of risk factors for asthma development and lung function decline in long-term

follow-up studies, in addition to possible prevention approaches. A better understanding of the etiology of wheezing and predictors for asthma progression will lead to the development of tailored management strategies and the prevention of further decline in lung function associated with persistent wheezing and asthma.

Methodology

This narrative review is based on an extensive literature search conducted on 13 October 2025 in PubMed, Cochrane, and Web of Science databases. Using medical subject headings (MeSH) and relevant keywords, the search aimed to identify studies examining the assessment and long-term follow-up of recurrent wheezing in non-asthmatic children and potential prevention strategies of wheezing and asthma development. The review focused on articles that address the prognosis of recurrent wheezing and risk factors for progression into asthma. No restrictions were applied regarding publication date, language, or type of publication to ensure a broad investigation of the available literature.

Discussion

Phenotypes and etiologies of wheezing in children

Wheezing infants and children are considered a heterogeneous group with different phenotypes and outcomes. They fall into three main phenotypes, according to the Tucson cohort study: transient early wheezers (60%), nonatopic persistent wheezers (20%), and atopic persistent wheezers (20%) (11). Transient early wheezers are children who experience wheezing during the first three years of life, have no history of atopy, and outgrow wheezing symptoms by school age. While non-atopic persistent wheezers are children with recurrent wheezing symptoms that start in late infancy or preschool age and continue after the age of six, with a possibility to disappear in pre-adolescence, and they do not have a history of atopy. On the other hand, atopic persistent wheezers are the children who experience wheezing during the first three years of life, mostly due to viral infection, and continue wheezing during school age. They have a

history of atopy and a lung capacity that significantly declines at the age of six (12, 13).

Further longitudinal studies identified additional intermediate wheezing phenotypes with less frequency. Intermediate wheezing (3%) refers to wheezing symptoms that start between 18 and 42 months and continue into later childhood. It is strongly associated with atopy and allergic sensitization. Another recognized phenotype is late-onset wheezing (1.7–6%), which manifests as infrequent wheezing from 6 to 42 months, becoming more frequent at 42 months of age, and then persisting to the age of six (14, 15).

This heterogeneity of wheezing in preschool children is the result of the unique interaction between a child's genetic makeup and environmental factors. The 17q21 locus, which contains the *ORMDL3* and *GSDMB* genes, is considered the most common genetic risk factor associated with childhood asthma (16-18). However, the gene variants only contribute a small proportion of asthma heritability it is evident that gene-environment interactions clearly have a significant role in asthma progression.

A study that investigated risk factors for occasional and recurrent wheezing in the first year of life concluded that the most important predictors are having a cold in the first three months of life and attending nursery school. Other risk factors included male gender, maternal smoking during pregnancy, and familial history of asthma and eczema. Moreover, the study reported that breastfeeding for more than three months, avoiding smoking, and improving the mother's education protected from recurrent wheezing (19). A pooled analysis of five cohort studies reported that allergic sensitization and parental asthma, either maternal or paternal, are significantly associated with persistent wheezing (20). A retrospective study revealed that low birth weight, a history of respiratory and cardiovascular diseases, severe pneumonia, and admission to the pediatric intensive care unit (PICU) are also risk factors for recurrent wheezing (2).

The role of lower respiratory viral infections during infancy and early childhood as a predictor for

recurrent wheezing has been extensively studied. Bronchiolitis, which is obstruction and inflammation of the small bronchiolar airways, is considered a risk factor for recurrent wheezing and the leading cause of infant hospitalization (21). The two most common viruses for bronchiolitis and subsequent asthma progression are the respiratory syncytial virus (RSV) and the human rhinovirus (HRV) (22). RSV is the main etiological agent for bronchiolitis, while HRV is usually detected in wheezing children afterwards and causes less damage to the airways than RSV (23). Multiple studies reported the strong association between RSV- and HRV-induced bronchiolitis and wheezing and asthma development (24-26). And although HRV is a stronger risk factor than RSV for asthma progression, RSV has been reported to cause less damage to the airways than HRV (23). Although less common, other viruses have been associated with recurrent wheezing, including influenza, parainfluenza, adenovirus, human metapneumovirus, and human bocavirus. These viruses are also associated with later asthma development (27, 28).

Another risk factor for recurrent wheezing and asthma progression is dysbiosis in the respiratory tracts in infants, especially when associated with RSV infection. Findings show that neonates with the hypopharyngeal region colonized with the pathogenic bacteria, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus* were at increased risk of recurrent wheezing and development of childhood asthma (29). Moreover, abundance of these pathogenic bacterial strains was associated with increased susceptibility to RSV-induced bronchiolitis, increased viral load in the nasopharynx of infants, and increased bronchiolitis severity (30-32), and higher risk of recurrent wheezing and asthma development at age 3 and 5 years (33, 34). These findings highlight the influence of lung microbiota on lung health and disease progression in wheezing infants, which should be further investigated for its potential in early prediction of recurrent wheezing and asthma progression.

Long-term follow-up: discovery of key predictors of asthma progression

Long-term follow-up studies revealed that viral wheezing, atopic dermatitis, allergen sensitivity, and severe recurrent wheezing in infants are among the strongest predictors for asthma progression in later childhood and adolescence. A study investigated the follow-up of 89 infants for three years after being hospitalized for wheezing. Results showed that early allergic sensitization, especially to pets, and atopic dermatitis are key predictors for asthma development (35). Another study that investigated asthma development in 227 recurrent wheezing infants revealed that allergic sensitization to multiple airborne allergens, initial atopic dermatitis, severe recurrent wheezing, and hypereosinophilia $\geq 470/\text{mm}^3$ were all risk factors for asthma progression at the age of 13 (36). Furthermore, a study that investigated the outcome of 82 infants for eleven years after hospitalization for wheezing found that 40% developed asthma, and atopic dermatitis was reported as a key factor in asthma progression. Moreover, risk for asthma progression increased 5-fold after respiratory syncytial virus (RSV)-induced wheezing and more than 10-fold after human rhinovirus (HRV)-induced wheezing (37).

Wheezing and the decline of lung function

Respiratory syncytial virus (RSV)-induced wheezing in infancy impacts lung health for years. Evidence shows that RSV-induced bronchiolitis can impair the airways, leading to their obstruction and consequently to recurrent wheezing (23). A possible explanation for the role of RSV-induced wheezing during the first year of life on asthma development and subsequent lung impairment is that infants under 4 months of age have lost most of their maternal immunoglobulin G (IgG) antibodies, and their own IgG levels are at their lowest point (38, 39). Moreover, infection with RSV during this period of infancy, when both the immune system and developing lungs are immature, impacts immune regulation and lung development, leading to airway dysfunction (21).

Moreover, a cohort study reported the association between all wheezing phenotypes in early childhood and increased risk of asthma progression and decreased lung function in mid-childhood (8–9 years), with further functional impairment in the lungs between the ages of 8–9 and 14–15 years. The strongest association was observed between persistent wheezing and asthma progression and further decline of lung function in adolescence (40). Pooled analysis of five cohort studies reported the association between all wheezing phenotypes and lung functional impairment starting even earlier, at school age (6 years), with the most impairment in persistent wheezing (20). These findings highlight the need for proper assessment and accuracy in phenotype determination and the development of tailored management strategies for better lung development and, consequently, the prevention of further impairment in childhood and adolescence.

Proper assessment: determination of risk factors for recurrent wheezing

The effect of environmental triggers on the occurrence of wheezing, its severity and recurrence, in addition to progression into asthma, is evident. Therefore, a better understanding of wheezing phenotypes and patterns will help to avoid certain risk factors related to asthma development. Proper assessment involves history taking, physical examination, allergen sensitization tests, microbiological examination, and identification of potential environmental triggers. The pattern and triggers of wheezing and a history of atopy, either personal or familial, in addition to parental smoking, should be assessed through history taking (9).

Novel approaches include microbial profiling of the nasal microbiome in infants hospitalized for bronchiolitis for the identification of high-risk patients and the prediction of recurrent wheezing and asthma progression. It was observed that the presence of a *Staphylococcus*-dominant microbiome during the first 6 months of life was associated with a higher risk of recurrent wheezing by age 3 years and asthma that persisted throughout childhood (33). Moreover, a study published recently investigated differences in nasal transcriptomes in early infants. Findings revealed

differences in gene expression between healthy infants and infants with recurrent wheezing, where recurrent wheezing was associated with upregulation of chemokine-mediated signaling and immune cell chemotaxis, decreased epithelial barrier function, and altered cilium organization and mitochondrial function (41). Further studies are needed to evaluate the use of the nasal transcriptome in the early detection of infants at risk of recurrent wheezing.

Potential prevention and management strategies

Unfortunately, traditional treatment of wheezing that involves inhaled corticosteroids does not alter the disease prognosis and does not prevent progression into asthma, in addition to their controversial adverse effects on children's growth (42, 43). Therefore, proper assessment and accurate identification of high-risk subjects will help to avoid certain risk factors that predict asthma development. Moreover, early intervention in the form of reduction of atopic and viral-mediated inflammation at early ages, specifically between 1 and 3 years, will help to prevent disease initiation and lead to better prognosis and avoidance of complications.

The anti-RSV monoclonal antibody palivizumab is considered a potential preventive treatment. A recent Cochrane review reported a reduction of hospitalization due to RSV infection by 56% and a reduction of the number of wheezing days by 61% in high-risk children upon systemic palivizumab administration (44). Therefore, a long-term investigation of the medication, including its cost-effectiveness, as well as its impact on asthma progression and lung function, should be pursued.

An interesting approach for the prevention and management of wheezing involves the use of probiotics. The beneficial effects of probiotics against respiratory diseases are mediated by three different mechanisms: antibacterial and antiviral activities, improvement of the epithelial barrier in the lungs, and modulation of the immune response (45). The Probiotics in Pediatric Asthma Management (PROPAM) study provided evidence that the probiotic mixture of *Ligilactobacillus salivarius* LS01 and *Bifidobacterium breve* B632

significantly reduced the frequency of asthma exacerbations and wheezing episodes (46).

The bacterial lysate OM-85 has been shown to have an immunomodulatory effect. OM-85 is a lyophilized extract derived from several bacterial respiratory pathogens, and it has a long history of safe use in children. Oral administration of the lysate has been reported to reduce wheezing episodes and other lower respiratory illnesses in high-risk infants (47). However, further research is needed to determine its efficacy in infants for preventing wheezing and other related illnesses. Another preventive approach involves the use of vaccination against pathogenic bacteria that colonize the pharynx of high-risk infants, which has been reported to be used for asthma control in preschool children (48). Further studies are needed to investigate the immunomodulation effect of these vaccines, in addition to their efficacy on wheezing symptoms in high-risk infants.

Conclusion

Recurrent wheezing is one of the leading causes for infant hospitalization, and although most of the children outgrow their symptoms by school age, a significant proportion develop asthma. Understanding the underlying mechanisms for recurrent wheezing, its phenotypes and patterns, and the gene-environment interactions that predispose asthma progression is important. Moreover, the exact cellular and molecular processes of recurrent wheezing are still unclear. Further research is needed to understand the effects of wheezing on lung function and the reasons behind the impairment observed in several wheezing children even after symptom recovery. It is important to prevent atopic and viral-mediated inflammation at an early age to prevent disease initiation. Besides, identification of the high-risk patients will help to avoid certain predictors for asthma development. Better understanding of wheezing phenotypes and etiologies will lead to tailored management strategies, better prognosis, and preservation of lung health, and consequently, enhanced quality of life and efficient utilization of healthcare resources.

Disclosure

Conflict of interest

There is no conflict of interest.

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Ethical consideration

Non applicable.

Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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