

Wheezing in infants and preschoolers: phenotypes and treatment options

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Key message

- Knowing who will develop into asthma or who will not is important to impose proper treatment and early intervention in a child with the first episode of wheezing.
- Phenotypes of severe bronchiolitis in less than 2-year-old children with first episode of wheezing were suggested for different treatment options
- RV-induced and/or atopy-associated severe wheezing in preschool children may benefit from early intervention of asthma treatment.

Wheezing, a high-pitched whistling sound that occurs during expiration when airflow rapidly passes through small airways, is a relatively common respiratory symptom in infants and preschoolers. Up to 30% of children experience wheezing during the first 3 years of life, whereas approximately 50% of preschoolers experience at least one episode of wheezing before 6 years of age.¹⁾ However, only 40% develop recurrent wheezing or asthma in later childhood.

Asthma is a chronic airway disease characterized by airflow limitation, inflammation, and hyperresponsiveness. Diagnosing asthma is challenging among infants or toddlers who experience the first episode of wheezing. However, identifying individuals in this demographic who will eventually develop asthma is critical for implementing appropriate treatment and early intervention.

As previously described,²⁾ birth cohort studies have proposed wheezing phenotypes according to the age of onset (early, intermediate, or late), wheezing persistence (transient or persistent), or atopic predisposition (atopic or nonatopic), suggesting which school-aged children will subsequently develop asthma.

The Asthma Predictive Index (API), developed in 2000, predicts asthma in infants with wheezing, classifying patients into loose (any early wheezing) and stringent (early, frequent wheezing ≥ 3 times/yr) indices according to wheezing episode frequency.³⁾ The API includes parental asthma history, patient atopic dermatitis, wheezing unrelated to illness, high blood eosinophil count (≥ 4 %), and allergic rhinitis as asthma risk factors. A modified API included atopic sensitization to aeroallergens or food as a risk factor.⁴⁾ These models suggest that genetic factors and atopic predisposition contribute to asthma development.

Respiratory viral infections are the most common trigger for wheezing in preschoolers. The first wheezing episode during infancy is often diagnosed as bronchiolitis. Respiratory syncytial virus (RSV), detected in 50%–80% of hospitalized cases, is the most common causative virus of bronchiolitis, followed by rhinovirus (RV) which is predominantly detected after 12 months of age. Small airways in young children can easily become obstructed by airway edema, airway inflammation, mucus, bronchospasm, and necrosis due to viral infection. However, specific treatments for bronchiolitis are lacking; rather, supportive care is recom-

Table 1. Two main clusters of severe bronchiolitis in less than 2-year-old children

Virus	Gene	Risk factors	Clinical picture	Immunologic feature	Treatment options	Asthma at school age
RSV	Common asthma risk genes	Prematurity SGA Chronic lung disease Exposure to smoking	Crackles/ wheezing Noisy breathing Secretion Younger age Hospitalization during peak epidemic months	Weaker IFN-I and IFN-III responses Increased IL-17 production Mucus hyperproduction	Palivizumab (prophylaxis) Supportive care	10%–30%
RV	17q21 CDHR3	History of recurrent wheezing, eczema High eosinophils Allergic sensitization Family history of asthma	Acute wheezing Older age Hospitalization during nonpeak months	Higher CD4 T Cells producing IL-4 Lower CD8 T cells producing IFN Higher Th2 polarization	ICS (prevention of re-current wheezing) Bronchodilator OCS (for severe wheezing)	30%–80%

RSV, respiratory syncytial virus; SGA, small for gestational age; IFN, interferon; IL, interleukin; RV, rhinovirus; CDHR3, cadherin-related family member 3; ICS, inhaled corticosteroid; OCS, oral corticosteroid.

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mended.

Different treatment options for severe bronchiolitis phenotypes in less than 2-year-old children with the first wheezing episode have been recently suggested (Table 1).⁵⁾ They may differ clinically, pathophysiologically, and genetically: (1) classic bronchiolitis with RSV infection and (2) RV and/or atopy-associated wheezing episodes.^{6,7)} Classic RSV-induced bronchiolitis is usually non-atopic (low type 2 inflammation), and bronchial epithelial shedding, cell debris, or mucus plugs obstruct the airway. Approximately 10%–30% of school-aged children with RSV-induced bronchiolitis will develop asthma.⁵⁾ In contrast, RV-induced severe wheezing episodes are associated with atopic predisposition (high type 2 inflammation), and 30%–80% of affected school-aged children develop asthma.⁵⁾ RV is less cytopathic than RSV and elicits a type 2 polarized immune response only in infants with a genetic predisposition to asthma. Several asthma loci have been identified through genetic studies; in particular, 17q21 was strongly associated with early wheezing infants who are at risk of later asthma.⁸⁾ Another asthma gene is cadherin-related family member 3, which is associated with early life wheezing episodes triggered by RV type C.⁹⁾ Inhaled or systemic corticosteroids and early asthma interventions may effectively reduce recurrent wheezing and time to asthma medication among infants with RV-induced severe wheezing and an atopic predisposition.

The goal of therapeutic interventions among wheezing preschoolers is to control symptoms and reduce severity, and the ultimate goal is to modify the disease or prevent asthma. The use of oral corticosteroids (OCS) reportedly increases the time to relapse within 1 year by 20%–30% and time to asthma controller medication within 5 years by 30%–40% among young children with an RV-induced first wheezing episode.⁵⁾ This suggests that the early strong suppression of airway inflammation using OCS could affect the natural course of asthma.

Daily inhaled corticosteroids (ICS) or leukotriene receptor antagonists (LTRA) are controller medications for asthma management. They reduce airway inflammation, and hence, can prevent recurrent wheezing. The U.S. Food and Drug Administration recently issued a boxed warning for montelukast owing to increasing evidence of neuropsychiatric side effects and advised restricting its use to allergic rhinitis.¹⁰⁾ ICS is the first-choice controller therapy for persistent asthma or multiple triggered wheezing, and LTRA is an alternative for mild persistent asthma or episodic viral wheezing among preschoolers.¹¹⁾ Regular follow-up for monitoring treatment response and any possible adverse effects is required during controller treatment. Maximum respiratory flow from 6 years of age is the lowest among children with persistent wheezing than among those with late-onset, transient early, or no wheezing.¹²⁾ Therefore, minimizing wheezing relapse is important for ensuring normal lung function in childhood.

Preschool wheezing is an umbrella term with different phenotypes. Phenotype-directed treatment may prevent asthma in high-risk infants and reduce unnecessary early interventions for transient early wheezing. Although wheezing phenotypes cannot

be clearly differentiated, preschoolers with RV-induced and/or atopy-associated severe wheezing may benefit from early asthma treatment.

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Footnotes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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References

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332:133-8.
2. Chung HL. Diagnosis and management of asthma in infants and preschoolers. *Clin Exp Pediatr* 2022;65:574-84.
3. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.
4. Chang TS, Lemanske RF Jr, Guilbert TW, Gern JE, Coen MH, Evans MD, et al. Evaluation of the modified asthma predictive index in high-risk preschool children. *J Allergy Clin Immunol Pract* 2013;1:152-6.
5. Jartti T, Smits HH, Bonnelykke K, Bircan O, Elenius V, Konradsen JR, et al. Bronchiolitis needs a revisit: distinguishing between virus entities and their treatments. *Allergy* 2019;74:40-52.
6. Bush A, Saglani S. Medical algorithm: diagnosis and treatment of preschool asthma. *Allergy* 2020;75:2711-2.
7. Rodriguez-Martinez CE, Castro-Rodriguez JA, Nino G, Midulla F. The impact of viral bronchiolitis phenotyping: is it time to consider phenotype-specific responses to individualize pharmacological management? *Paediatr Respir Rev* 2020;34:53-8.
8. Caliskan M, Bochkov YA, Kreiner-Moller E, Bonnelykke K, Stein MM, Du G, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. *N Engl J Med* 2013;368:1398-407.
9. Bonnelykke K, Coleman AT, Evans MD, Thorsen J, Waage J, Vissing NH, et al. Cadherin-related family member 3 genetics and rhinovirus C respiratory illnesses. *Am J Respir Crit Care Med* 2018;197:589-94.
10. U.S. Food and Drug Administration. FDA requires Boxed Warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis. Silver Spring (MD): U.S. Food and Drug Administration, 2020.
11. Brand PL, Caudri D, Eber E, Gaillard EA, Garcia-Marcos L, Hedlin G, et al. Classification and pharmacological treatment of preschool wheezing: changes since 2008. *Eur Respir J* 2014;43:1172-7.
12. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172:1253-8.

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