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Invited review

Wheezing in children: Approaches to diagnosis and management

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1. Introduction

Wheezing in early life is a common disorder, with approximately 50% of children having an episode of wheezing in the first year of life [1]. A recurrent wheeze is estimated to occur in one-third of children of preschool age and can cause significant morbidity, decrease quality of life, and increase the frequency of the use of health care services and economic costs [2]. Data have confirmed that wheezing is clinically heterogeneous in early life in terms of its temporal pattern (i.e., age of onset and duration until symptoms disappear) and its risk factors, which include atopy and genetic or environmental factors, and the outcomes are different for such phenotypes [3,4]. Different wheezing phenotypes have been reported in the literature, with the first such report being the Tucson childhood respiratory study of Martinez et al. [5], in which children were classified into four main subtypes, including never wheezing, early transient wheezing, persistent wheezing, and late-onset wheezing; later reports further categorized patients with persistent wheeze as having nonatopic persistent wheezing or atopic/IgE-associated wheezing [6,7]. This became a popular area of research, with a further six subtypes identified through longitudinal studies [8,9] and a further five subtypes reported by similar longitudinal studies [4,10–13]. Regardless of whether five or six different types are included in an assay, it remains difficult to differentiate these phenotypes clinically because the expression of symptoms and risk factors can change over time. Additionally, different factors, including genetic, environmental, and host factors (and interactions among these factors), can impact a child's condition and contribute to the development of wheezing and the progression of a patient's symptoms [14]. Our proposed operational criteria are aimed at simplifying the types of wheezing used to categorize children of preschool age and identifying risk factors for the persistent wheezing subtypes that can impact lung function [15] or lead to the subsequent development of asthma as these conditions should be treated by appropriate medical interventions [16].

Wheeze can be divided according to its pattern and duration:

1. Wheeze subtypes according to pattern (symptomatic classification):
   a. Episodic wheeze: Wheezing within a discrete period that is often associated with clinical evidence of a viral cold. There is wheezing between episodes [17].
   b. Multitrigger wheeze: Wheezing presenting with and apart from an acute viral episode [17,18].
2. Wheeze according to duration:
   a. Never or infrequent: Children who never wheeze or have presented with wheezing once in their life. In addition, 51% of patients in the Tucson study [5], 59.9% of the patients in the Avon Longitudinal Study of Parents and Children (ALSPAC) study [8], 75% of the patients in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study [10], and 83% of the patients in the Italian Studies of Respiratory Disorders in Childhood and the Environment (SIDRIA) [13] had a higher forced expiratory volume in the first second and a lower airway responsiveness than unaffected patients who were nonatopic.
   b. Transient early wheeze: This is a type of wheeze that starts early in the first year of life and then continues through the second year before beginning to subside after the third year. Most of these patients are not atopic and exhibit no evidence of eosinophilia or other markers of inflammation, which are observed in approximately 16% of affected patients [8]. The main risk factors in this group are maternal exposure to smoke, prematurity, low maternal age, low socioeconomic

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status, low birth weight, attending day-care center at an early age, and more than two siblings at home. Additionally, in these patients, pulmonary function test (PFT) scores are low even before the onset of the wheeze, suggesting that affected individuals may have had smaller airways than were observed in the control group, and remain slightly lower than those reported in their peers in adolescence [5].

c. Intermediate wheeze: This is very rare in the first 18 months (2.7%) according to the ALSPAC study and the PIAMA study (3.1%). This condition presents as wheezing with onset between 18 and 42 months that subsequently persists into later childhood and is strongly associated with atopy, allergic sensitization, hyperresponsiveness, and lower PFT scores [9].
d. Late-onset wheeze: This presents as infrequent wheezing from 6 to 42 months od age that becomes more frequent at 42 months of age and then persists to an age of 6 years (approximately 1.7–6%) [8,10]. A skin allergy test usually produces strong results in this group, and this is known to be a major prognostic factor. Allergies in the nose are also commonly associated with late-onset wheezing, similar to smoke exposure is known to be a risk factor in males [5,8].
e. Persistent wheeze: This is wheeze with onset at 6 months of age or later that occurred in approximately 3.1% of patients in the PIAMA study, 4.1% of patients in SIDRIA, and 8.9% of patients in the ALSPAC study. This subgroup presents with symptoms similar to asthma, and affected patients are further divided into two main subgroups:
   - Nonatopic persistent wheezing phenotype: This accounts for approximately 40% of patients with persistent wheeze and usually presents as episodic wheezing triggered mainly by viral illness; it is therefore often referred to in the literature as a *viral-induced wheeze* [5]. Many viruses implicated in this subgroup can also cause new-onset wheeze, and include respiratory syncytial virus (RSV), rhinovirus, parainfluenza virus, and human metapneumovirus. Exacerbations involve RSV, parainfluenza virus, influenza virus, or corona viruses or persistent wheeze, which can be caused by adenovirus, chlamydia, or mycoplasma.

     RSV causes persistent wheezing in children younger than 2 years, while rhinovirus is the most common cause of recurrent or persistent wheezing in children older than 2 years [6].
   - IgE-associated atopic and/or persistent wheezing phenotype: Accounting for 60% of persistent wheezing cases, this type of wheezing usually begins in the second year of life and persists into late childhood [3,6]. The risk factors in this subgroup include male sex, house dust mites, a family history of asthma atopic dermatitis, eosinophilia in the first year of life, and early sensitization to food and aeroallergens [3–5,19,20].

2. Pathophysiology

Although wheezing is very common in children, its pathophysiology is complex and not well understood. Multiple factors play a role in wheezy conditions and include anatomical, genetic, environmental, and immunological factors that can interact with each other and affect airway patency [3,9,21–25]. Airflow obstruction is affected by the caliber of the airway and compliance of the child's lung. Resistance to airflow through the airway is inversely related to the radius of the tube to the power of 4. A small amount of additional narrowing of the airway can cause further flow limitation and a subsequent wheeze, especially in infancy [26]. During infancy, the very compliant chest wall and inward pressure produced during expiration lead to the collapse of the intrathoracic airway and a consequentially wheezy chest, and this is why most children outgrow this type of wheeze as they get older and their airway becomes larger [26]. There is no doubt that children experience more episodes of upper respiratory tract infection, which can induce the expression of different inflammatory mediators that could be implicated in wheeze development [27–29]. It is also true that environmental factors certainly play important roles in the development of wheezing, especially when exposure occurs early in life, such as prenatal or early postnatal exposure to smoke [23] (Table 1).

3. Common causes of wheeze in children

3.1. Atopy and wheeze

Numerous studies have supported an association between atopy and wheezing, with atopy presentations including asthma in the family, allergic eye with redness and tearing, an allergic nose (e.g., sneezing, nasal itching, a clear nasal discharge or nasal blockage, snoring and difficulty in breathing), and eczema, which often affects the face or extensor surfaces of patients; additionally, in rare cases, children may wheeze because of an allergy to milk or other types of foods [13,22,30–36]. The Asthma Predictive Index was developed to help physicians who suspect asthma and has since been modified to account for the number of wheezes per year and certain minor and major factors when a suspected patient is at high risk of having asthma (Table 2) [33–35,37–39].

3.2. Investigations

Wheeze is often clinically diagnosed as requiring no further tests, but patients who continue to have recurrent or persistent wheeze should be investigated by, for example, chest X-rays, which are mainly used to identify structural anomalies or other underlying conditions, such as foreign body aspirations (Table 3) [40,41]. A chest CT scan can be used to determine whether persistent abnormal chest X-ray results or symptoms persist despite therapies [42]. In atopic patients, a full blood count could be helpful for

Table 1
Causes of wheezing in children.

Anatomical	Tracheoesophageal fistula or malacia*
	Airway compression (e.g., caused by a vascular ring, bronchogenic cyst, cystic lung over inflation, and diaphragmatic hernia)
Host defense defects	Cystic fibrosis*, primary ciliary dyskinesia, and defects in immunity
Postviral syndromes	Bronchiolitis*, protracted bacterial bronchitis*
Recurrent aspiration	Gastroesophageal reflux disease*
	Disorders of swallowing*: neuromuscular disease or mechanical disorders
Perinatal disorders	Chronic lung disease/bronchopulmonary dysplasia*
Other causes	Foreign body aspiration*, mediastinal mass, or metabolic diseases

*Common.

Table 2
Four or more wheezing episodes per year and modified Asthma Predictive Index [34,35].

At least one major criterion	Or at least two minor criteria
Physician diagnosis of atopic dermatitis at 2–3 years old	Physician diagnosis of allergic rhinitis
History of a physician-obtained diagnosis of asthma in a parent	Wheeze apart from cold
Inhaled allergen sensitization	Eosinophilia

diagnosing eosinophilia, and in some cases, the physician may perform a radioallergosorbent test, skin test, or immunoglobulin assay, especially to check IgE levels [43,44]. When a patient is not doing well, referral needs to be made to a subspecialist for further tests, which can include barium meal tests to identify structural gastrointestinal problems, such as hiatus hernia or malrotation; additionally, a pH test is often recommended if the patient shows symptoms of gastroesophageal reflux disease, and a swallowing assessment can be very helpful when there is suspicion that aspiration is the cause of the wheeze, especially in certain conditions, such as neuromuscular diseases [45,46]. Malacia is also an important cause of wheezing, especially in cardiac cases or patients with gastrointestinal anomalies, such as tracheoesophageal reflux. Such cases can be confirmed with bronchoscopy, and their management will be different [47–50]. If a facility is available to perform a PFT, as Martinez et al. confirmed, infant PFTs can reveal reduced lung volume in recurrent wheeze in infancy [5,51]. Standard spirometry could be beneficial for assessing the response to a bronchodilator. If spirometry is not available; it is worth performing a challenge with a bronchodilator or inhaled corticosteroid [52–54]. There is often no benefit to performing a viral culture, nasopharyngeal aspirate culture, or PCR for common viral illness as the results will not affect the management plan [5]. Recently, exhaled nitric oxide was found to be a simple but helpful tool in children of preschool age with wheezing, in whom it had high diagnostic accuracy (92%) [55,56].

4. Treatment

4.1. Bronchodilator

Short-acting and rapidly acting β_2-agonists are the most popular and most commonly used first-line bronchodilators used to treat acute symptoms including wheeze, cough, and shortness of breath. Furthermore, these drugs have been shown to be more effective than placebos in controlling acute wheezing in children younger than 2 years but may not achieve clinically significant improvements [57]. However, the presence of wheeze alone with no other condition may be best treated with observation alone or investigation of the potential underlying cause. Therapies can be initiated if wheeze is associated with increased difficulty in breathing [58,59]. If the patient is young (less than 6 months old), the best option is referral to a tertiary center for a detailed evaluation [57,58]. If the baby is more than 6 months old, two main factors should be considered: whether the patient is atopic and the severity of the wheeze episode.

If the severity is mild, bronchodilator therapy with a metered-dose inhaler is the preferred approach; a nebulizer is an alternative way to deliver medication, but children with atopy are more likely to respond to a bronchodilator.

If the baby has a moderate or severe type of wheezing, then the patient should be referred to a hospital for further management. Physicians should be aware that wheezy children do not display optimal responses to a bronchodilator, and the currently available evidence is too weak to suggest the use of bronchodilators as a routine treatment in the way they are used in asthmatic patients [60–63].

4.2. Inhaled steroids

Inhaled steroids can be used in recurrent wheeze in the presence of positive indicators with careful monitoring of efficacy. This treatment is effective in persistent and late-onset wheezing, but it is not as effective in transient wheezing, in which its effects are similar to those observed in viral-induced wheeze [64–68].

4.3. Systemic steroids

Systemic steroids can be used to treat wheezy patients, in whom a short course of therapy (3–5 days) has been documented to be effective in reducing recurrent wheeze after a rhinovirus infection in patients with eczema [69–71].

4.4. Antileukotriene

Montelukast (4 mg) granules are effective in treating postviral wheezing; however, a systemic review of antileukotrienes showed that they remain a weak treatment option and are therefore recommended as a routine measure that provides a modest benefit, with therapeutic trials of montelukast ranging from 1 to 3 months [72–76].

4.5. Summary of treatment

Table 4 summarizes the step approach to treatment of wheezy chest.

4.6. Other medications

4.6.1. Antibiotics

There is no justification for the routine use of antibiotics because viruses are the main causes of infections of the respiratory tract.

Table 3
Clinical clues indicating other diagnoses.

Persistent moist cough	Cystic fibrosis, aspiration, immune disorder, ciliary dyskinesia, protracted bacterial bronchitis
Paroxysmal cough	Pertussis or malacia
Cough while feeding	Gastroesophageal reflux disease with or without swallowing problems
Purulent nasal discharge	Sinus infection
Clear nasal discharge	Allergic nose
Abnormal voice or cry	Anatomical cause
Focal sign in chest	Foreign body aspiration
Episodic, seasonal	Asthma
Finger clubbing	Cystic fibrosis, ciliary dyskinesia, immune disorder
Failure to thrive	Immune disorder, cystic fibrosis
Prematurity, low birth weight	Bronchopulmonary dysplasia/chronic lung disease

Table 4
Step approach in wheezy chest.

Atopic background	Nonatopic background
First attack: step 2	First attack: step 1
Second attack: step 3	Second attack: step 2
Third attack: step 4	Third attack: step 3

Step 1: Ventolin PRN.
Step 2: Ventolin PRN and oral steroid.
Step 3: Ventolin PRN, oral steroid and a mild dose of inhaled steroid/singulair.
Step 4: Ventolin PRN, oral steroid, and a moderate dose of inhaled steroid/singulair.

Antibiotic use in infancy may increase the risk of asthma by changing the flora, although azithromycin may be justified in children of preschool age with severe types of wheeze who are at risk of admission [77–79]. Protracted bacterial bronchitis is a common cause of wet and chronic coughs. Recently, clinicians have become more aware of this condition, as there is strong evidence indicating that these patients have rates of wheeze as high as 90% and may respond to prolonged antibiotic use or other modalities [80,81, 86].

4.6.2. Palivizumab

Monoclonal antibodies can be used to prevent RSV in high-risk groups, such as premature babies or patients with congenital heart disease and chronic lung disease; for example, Simoes and his group [82] found that palivizumab significantly reduced the recurrence of wheezing in premature babies.

4.6.3. Ipratropium bromide

Inhaled ipratropium was found to be potentially beneficial in older children [83], but there is no good evidence that it is beneficial in children of preschool age [84,85].

4.6.4. Antihistamine

Antihistamines have been studied in children of preschool age with wheeze. Bassler et al. [85] concluded that children treated with ketotifen were 2.4 times more likely than those treated with placebo to reduce or stop their bronchodilator treatment.

4.7. Parental level of education

The level of education of a patient's parents is a very important factor in the management of children with wheeze because it affects the parents' knowledge and understanding of wheezing disorders in children of preschool age, and children with parents who cannot understand their child's condition often receive inadequate treatment. Furthermore, few studies have focused on this issue, and multiple teaching sessions are recommended to increase family satisfaction [87].

5. A new era in wheezy chest

5.1. Vitamin D status and recurrent wheeze in children

Data have confirmed that low maternal late-pregnancy serum 25-hydroxyvitamin D levels are associated with the development of wheeze and atopy during childhood [88,89].

5.2. Maternal obesity and recurrent wheeze

In the nonurban, white population, maternal prepregnancy obesity was associated with a 22% increase in bronchodilator dispensing in offspring in early life. Maternal prepregnancy obesity is also a prevalent risk factor for respiratory morbidity in urban, nonwhite populations [90,91].

5.3. Maternal iron and wheeze

It has been suggested that reduced maternal iron status during pregnancy is adversely associated with childhood wheeze, lung function, and atopic sensitization, and these findings suggest that further studies should be performed to explore this matter [92].

5.4. Folic acid during pregnancy

A recent study performed in Australia reported that folic acid supplementation during late pregnancy was associated with an increased risk of asthma at 3.5 years old and with persistent asthma until 5 years old [93–96].

5.5. Prenatal administration of acetaminophen

Acetaminophen is a widely used analgesic drug that is not known to have any teratogenic effects. Thus, it is the most commonly used analgesic in pregnant women (34–69%), in whom it is preferred over other nonsteroidal anti-inflammatory drugs, such as ibuprofen and naproxen, which have been associated with complications during pregnancy. Several studies have reported an increased risk of asthma in childhood is associated with the use of acetaminophen during pregnancy; however, this relationship is not clear and requires further investigation [97–102].

6. Conclusion

Wheezes are very common in children, in whom they appear as heterogeneous groups; hence, physicians should be aware of wheezing phenotypes, most of which abate with age. Few groups continue to wheeze during childhood, although exposure to environmental triggers is a poor prognostic factor. Determining the appropriate level of investigation and treatment remains a challenge to physicians at the level of investigations and treatments. The modified Asthma Predictive Index could be beneficial for predicting which groups should be treated as asthmatic patients, in whom interventions are conditional but regular follow-up and monitoring are strongly recommended. Wheezes are known to be a burden to any patient's health care, and interventions should therefore be based on evidence. This is an especially important area of research in Saudi Arabia.

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