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## Wheezing in preschool children<sup>☆</sup>



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### A B S T R A C T

Wheezing is a common condition in pediatric practice, it can be defined as a musical sound, high-pitched and continuous, emitting from the chest during breath exhalation.

Although almost 50% of children experiences wheeze in the first 6 years of life, only 40% of them will report continued wheezing symptoms after childhood. The classification of wheeze in preschool children is more difficult compared to school aged children. It is based on the onset and duration of symptoms and divided children in three categories: transient early wheezing, non-atopic wheezing and atopic wheezing/asthma.

History and physical examination, skin prick test, exhaled nitric oxide, lung function test are the parameter to evaluate children with wheezing.

The aim of management of wheezing is to finalize the control of symptoms, reduce exacerbations and improve the quality of life. All guidelines underline the complexity in making a diagnosis of asthma under five years and the need to identify phenotypes that may help paediatricians in the therapeutic choices.

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### 1. Introduction

Recurrent wheezing is a common condition in paediatric practice and some studies have shown that one in three children has at least one episode of wheezing prior to their third birthday, with a prevalence of 50% at the age of 6 years [1,2].

Wheezing may be an isolated symptom or be accompanied by cough, shortness of breath (either with or without exertion), chest tightness, and/or air hunger [3].

Wheezing and childhood asthma are not equivalent but rather include different conditions that have distinctive outcomes over the childhood.

Asthma is considered the most common condition presenting with wheezing, nevertheless not all the children with wheezing are affected by asthma: though many young children wheeze during viral respiratory infections, only a minority of them experience childhood asthma.

In fact, most children who experience wheeze have a diminished airway function at birth with no increased risk of asthma later (transient wheezer), while, other children with persistent wheezing during childhood and recurrent exacerbations have an increased risk to develop asthma [4]. From a practical viewpoint, the core question in the differential diagnosis is to distinguish among the different phenotypes of wheezing in toddlers. The quite variable history that is not fully understood, and the heterogeneity of underlying conditions with many phenotypic and variable expressions during childhood make the approach to children with wheezing challenging both from diagnostic and therapeutic implications [5].

Furthermore, the assessment of asthma in very young children is hampered by the lack of objective lung function measurements and definitive biomarkers.

Moreover, the high prevalence of wheezing requires attention on a broad and age-dependent number of differential diagnosis such as gastro-oesophageal reflux, inhaled foreign body, immune deficiency, cystic fibrosis, primary ciliary dyskinesia, bronchomalacia, cardiac abnormality, post infectious obliterative bronchiolitis [6].

### 2. Definition

Wheeze can be defined as a musical sound, high-pitched and continuous, emitting from the chest during breath exhalation resulting, irrespective of the underlying mechanism, from narrowing of intrathoracic airway and expiratory flow limitation [7]. Although this definition is well known, it may be poorly understood and defined by parents and, therefore, if based only on parental report children may be considered as experiencing wheeze when they, actually, do not. It is important that a health professional values the wheeze to confirm or reject the diagnosis, always considering that even not all physicians are equally precise in valuing the severity of wheeze [7].

### 3. Wheezing phenotypes in early childhood

Although almost 50% of children experiences wheeze in the first 6 years of life, only 40% of them will report continued wheezing symptoms in later childhood [8]. The characterization of wheeze in preschool children is more difficult compared to school aged children. In fact, the latter may be better characterized through the clinical features such as

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wheeze, reversible bronchial obstruction, bronchial hyperreactivity and spirometry, which all can be valuable tools for diagnosis.

Nevertheless, the identification of phenotypes of paediatric wheezing and the recognition of risk factors associated with each phenotype is highly warranted since these might help in predicting long-term outcomes and identify high-risk children who might benefit from secondary prevention interventions [8].

In the mid-1990s, the group led by Martinez, in Tucson, introduced a classification of children based on retrospective symptom, among 1246 new-borns followed for lower respiratory tract infections based on the presence of wheezing symptoms during the first 3 years of life and again at age 6 years [9]. This classification is based on the onset and duration of symptoms and groups the children in three categories.

- *Transient early wheezing*. This is the most prevalent phenotype of early wheezing (60%) [9]. This condition generally starts in the first month of life, peaks before 3 years and resolves during the school age. Early wheezers tend to wheeze with lower respiratory tract infections, triggered by a virus, and generally have no family history of asthma or allergic sensitization. The primary risk factor seems to be a reduced lung function that remains low at age 6 years although wheezing has finished [9].

Other conditions that cause transient wheezing include prematurity and the exposure to environmental factors such as cigarette smoking both during pregnancy as well as during the post-natal period.

- *Non-atopic wheezing*. This condition represents 20% of wheezing toddlers <3 years of age [9]. Symptoms are more frequent in the 1st year of life and children may continue wheeze over childhood, typically with less frequent episodes by early adolescence. In most cases wheeze begins after an acute respiratory syncytial virus (RSV) infection. These children present slightly lower pulmonary function compared to control from birth to 11 years of age. Typically they have not bronchial hyperreactivity. These findings are thought to be secondary to alterations in regulation of airway motor tone.
- *Atopic wheezing/asthma*. This phenotype accounts for the last 20% of wheezing children <3 years of age [9]. More than half of all cases of persistent asthma start before age 3, and 80% begin before age 6 and are associated with early food or aeroallergen sensitization. Patients with early-onset asthma have significant deficits in pulmonary function growth.

Although these groups have served as useful models of wheezing phenotypes in early childhood, phenotypes have been demonstrated to diverge earlier than 3 years [10] and a report described different immune responses within apparently homogeneous phenotypes of IgE-mediated asthma [11]. Hence, recently, in addition to the Tucson's groups further additional phenotypes have been proposed [12]. In particular, a group of children with *intermediate onset wheeze* has been defined with symptoms presenting between 12 and 42 months [12]. In this group it has been observed a strong association with atopy (in particular skin prick sensitivity to D. pteronyssinus and cat allergen), low lung function and higher levels of airway responsiveness. Such associations may reveal different aetiological or environmental influences on the inception of asthma in young children.

In the same report, another novel group was proposed, defined as *prolonged early wheeze*, which is characterized by wheezing from age 6 to 54 months with low prevalence from age 69 months, representing an intermediate condition between transient early wheeze and intermediate onset wheeze. This phenotype shows no relationship with aeroallergen sensitization but is associated with bronchial hyperreactivity and lower lung function at ages 8–9 years, which could reflect persistence of developmental airway abnormalities. The other groups included:

- *Never/infrequent wheeze* referring to those children with a 10% probability of wheezing at 6 months and with a declining prevalence of

sporadic wheeze later and included children who never reported wheeze.

- *Transient early wheeze* group included those children who experienced wheeze from 18 to 42 months of age. It is possible that this group and *prolonged wheezing* represents different severities of the same wide phenotype, with the more severe phenotype being associated with longer duration of symptoms and poorer outcome [12].
- *Late onset wheeze* included children who start wheezing from 42 months of age and with a rising prevalence thereafter; this group showed a strong prevalence of atopy and asthma.
- *Persistent wheeze* included children who start wheezing at 6 months with an increasing prevalence thereafter. This phenotype was less strongly associated with atopy compared to intermediate or late onset wheeze, but was related with similar lung function deficits to intermediate onset wheeze. This is suggestive for a possible mixture of structural airway abnormalities associated with early onset wheezing and atopic wheeze that develops during early childhood [12].

Though of relevant interest in the characterization of wheezing phenotypes, this grouping is not of immediate practical usefulness for the clinicians facing the single patient since they can only be applied retrospectively.

Although the phenotype of transient wheeze is often assumed to be equivalent to episodic wheeze, this assumption can be questioned and a European Respiratory Society Task Force [13] has proposed an alternative classification with the individuation of two categories including *episodic (viral) wheeze* and *Multiple-trigger wheeze*. *Episodic (viral) wheeze* is the most common phenotype in preschool children and it is characterized by distinct wheezing episodes with child being asymptomatic between episodes. Usually, it is associated with seasonal viral infection such as RSV, coronavirus, human metapneumovirus, parainfluenza virus and adenovirus. The frequency and severity of episodes are related to the severity of the first episode, atopy, prematurity and exposure to environmental factors such as tobacco smoke. Episodic wheeze declines over time disappearing within the age of 6 years, can continue as episodic wheeze in school age, change into multiple trigger wheeze or disappear later. *Multiple-trigger wheeze* is the second phenotype caused by the exposition to viruses or other important triggers such as cigarette smoking and allergen exposure, some children may also wheeze in response to spray, crying, laughter and exercise [12].

A different approach came from the PRACTALL study group [14] proposing a practical flow chart mostly upon age criteria in association with clinical patterns of presentation to define the wheezing phenotype in preschool aged children. It is recommended that the identification of asthma phenotype should be always attempted, including evaluation of atopic status.

#### 4. Assessment of preschool wheezing

##### 4.1. History and physical examination

A careful history-taking is a pivotal diagnostic instrument in the assessment of preschool wheeze, particularly in those who are not wheezing during the consultation [13]. It is of primary importance to determine the frequency and severity of respiratory symptoms, their association with trigger factors such as physical exercise, viral infections, smoke and environmental allergens as well as the presence of a history of eczema or a parental history of asthma, eosinophilia, allergic rhinitis, and wheezing without colds [15]. Although no evidence is available regarding the usefulness of physical examination in wheeze assessment, it is important to recognize unusual or atypical features that would suggest another underlying condition [13]. A clinical index has been also proposed to define the risk of asthma development in the single patient according to the criteria of the Asthma Predictive Index (API) [16]. This index is based on the identification of risk factors during the first 3 years of life for development of asthma at school age. A positive API at age of

3 years is associated with 76% of chance of asthma development, compared with a less than 5% chance of active asthma at school age in children with a negative API index [16].

#### 4.2. Skin prick test

Allergy testing may represent a valuable pre-requisite for early identification of wheezing infants at increased risk for later development of asthma [16,17]. A study comparing children aged 2–5 years with doctor-confirmed wheeze who were responding favourably to a bronchodilator to healthy non-wheezing children found that 32% of wheezy children presented positive skin prick test results to one or more aeroallergens, compared to 11% of healthy children [18]. In another study sensitisation to inhalant allergens in 1–4 years old children from general practice increased the likelihood of the presence of asthma at the age of 6 years by a factor of two to three [19].

#### 4.3. Exhaled nitric oxide

Fractional exhaled NO (FeNO) is commonly considered an indirect marker of eosinophilic airways inflammation, playing an important role in the physiopathology of childhood asthma [20]. Advances in technology and standardization have allowed a wider use of FeNO in clinical practice in preschool children [20]. In a study performed in 391 infants aged between 3 and 47 months, those with a frequent recurrent wheeze and a stringent index for the prediction of asthma (API) showed higher FeNO values than those with a loose index or those with recurrent or chronic cough but no history of wheeze [21]. This study is in agreement with the idea that objective measurement of exhaled NO in addition to the clinical characterization using an algorithm may improve the possibility of defining disease presentation and of predicting disease progression in preschool children [21].

#### 4.4. Lung function tests

Lung function tests enable clinicians to evaluate pulmonary function and to monitor the effect of treatment. Though spirometry is commonly performed after the age of 5–6 years, a significant percentage of preschoolers can be able to correctly perform a spirometric procedure [22]. In partly collaborative preschool children the measurement of respiratory resistances by interruption technique (Rint) or by the forced oscillations can be proposed [23,24]. However there are no studies supporting the usefulness of pulmonary function tests in preschool children in distinguishing between episodic and multiple-trigger wheeze [13]. In a longitudinal, prospective study conducted in preschool children with symptoms suggestive of asthma both FeNO and specific IgE measured at age four, but not lung functional tests (Rint), improved the prediction of asthma symptoms until the age of eight years, and independent of clinical history [25]. In the individual patient, however, determination of lung function in preschool children can help in the discrimination of common wheezing disorders from other conditions [13].

### 5. Monitoring of childhood asthma

The recent update of international GINA guidelines suggests tailoring asthma treatment to the level of disease control rather than severity. As clearly indicated in the GINA guidelines, good levels of control consider only minimal symptoms as acceptable [26]. To achieve and maintain this target, patients should be reviewed three months after the initial assessment and then every three months. In the case of an exacerbation, a follow-up visit should be scheduled within two–four weeks [27]. In a study conducted in younger children, it was observed that clinicians are likely to obtain important and complementary information from children and their parents about symptoms reports and quality of life measures [28]. For these reasons, the childhood asthma control test (C-ACT) was recently validated and proposed as an accurate and a

reliable tool, complementary to lung function testing, to assess the level of disease control in asthmatic children [29]. However C-ACT should be used as a complement to, and not as an alternative to, other tools such as spirometry and exhaled nitric oxide (FeNO) measurement in the evaluation of asthma control in children [30]. This is in keeping with the concept that, though a number of tools have been considered in the monitoring of childhood asthma, a combination of different ones is still recommended for the purpose of a comprehensive evaluation of the level of control [26]. Since asthma is primarily an inflammatory disease, the addition of a measure of inflammation, like FeNO determination, to standard spirometry and asthma control surveys may add novel information to assess asthma burden during the routine clinical follow-up of asthmatic children [20].

### 6. Treatment

The aim of management of wheezing is to finalize the control of symptoms, reduce exacerbations and improve the quality of life [31,14,7].

Given the multifactorial nature of wheezing, heterogeneity of the clinical manifestations and the lack of good levels of evidence about the pathophysiological mechanisms and treatment options, it is difficult to standardize the therapeutic approach to wheezing and the ERS document clearly states that the evidence on drug treatment are low level [13].

The treatment of exacerbations, regardless phenotype, is based mainly on the use of beta2-agonists with short duration of action. The bronchodilator action of these drugs and their protective effect against broncho-obstructive stimuli have been widely demonstrated from randomized controlled trials in preschooler.

Ipratropium bromide can be considered as adjunctive therapy to beta-2 agonist in the acute phase; tolerability of the drug is good and appears to be particularly useful in moderate–severe forms [26].

The efficacy of systemic steroids in acute episodic viral wheeze in preschooler has recently been called into question. Some studies demonstrate the lack efficacy of a short course of systemic steroid therapy in post-viral episodic wheezing [32]. Panickar et al [33] have shown that the treatment with prednisone in children with mild to moderate virus-induced wheezing did not improve the symptoms of wheezing. Moreover, Ducharme et al [34] demonstrated that in preschool-age children with moderate-to-severe virus-induced wheezing, preventive treatment with high-dose fluticasone reduced the use of rescue oral corticosteroids. Nevertheless, since 10% of children have more than 10 viral colds per years and symptoms may last 2 weeks or more, some children would receive a large cumulative dose of oral corticosteroids with potential adverse effects, this therapeutic strategy should not be recommended in clinical practice. On the basis of these two studies [35] the administration of prednisolone to preschoolers without atopy who have episodic wheezing is not recommended, unless wheezing is severe enough to require admission to an intensive care unit.

In children with uncontrolled respiratory symptoms between the episodes, recurrent episodes by infective trigger and children who have had severe episodes with need for access to the emergency room and hospitalization a maintenance therapy are indicated [7,26].

The ERS Task Force recommend different therapeutic approaches depending on wheezing phenotype. The common goal is to reduce the risk of relapse and control symptoms in intercritical periods.

Bisgaard et al show that in episodic viral wheezing, the use of montelukast [36] reduces the frequency of exacerbations by approximately 32% compared with placebo. Another study demonstrated, as the second level step, the association between montelukast and inhaled steroids in children with frequent episodes [14].

In the multi-trigger wheezing the use of inhaled corticosteroids (ICS) has been proposed.

Because asthma origins in the preschool group, early intervention in children at risk might be useful in preventing subsequent asthma development.



Unfortunately, studies of the role of ICS to modify the natural history of asthma allow negative findings [37–39]. However, some studies demonstrated that when ICS therapy was used daily, there were significant reductions in asthma-related morbidity, exacerbations, or both [40,41].

Several studies [42–44] have demonstrated the effectiveness of ICS in reducing the severity of symptoms, bronchial hyperresponsiveness and the frequency of exacerbations, as well as in improving lung function [45–47], in multi-trigger phenotype.

Bacharier and colleagues [48], demonstrated that male gender, Caucasian, severe episodes and sensitization to inhalant are better predictors of response to ICS; however characteristics predictive of persistence of asthma symptoms, such as family history of asthma, eczema, sensitization to aeroallergens, cannot be considered as predictive markers of responsiveness to steroids.

Current guidelines recommend a trial of three months ICS to assess its effectiveness in multi-trigger wheezing. If symptoms persist despite therapy with ICS can be considered the association with montelukast [26,14,49]. Nevertheless, in recurrently wheezy very young infants [50] (6–24 months of age), it has been shown that 8 weeks of montelukast therapy has no significant effect on the number of symptom-free days, use of rescue medication, lung function or on airway responsiveness.

A significant percentage of children with wheezing undergoes spontaneous resolution at school-age. In accord to that, after a treatment period, regardless of the phenotype, the clinician must evaluate the opportunity to withhold the maintenance therapy and monitor the evolution of symptoms in the absence of therapy [50]. However, the ERS Task Force recommendations suggest that if a significant response to the therapy cannot be obtained the patient has to be referred to a specialist centre for further investigation in order to exclude any other pathology for wheezing.

## 7. Conclusions

All guidelines emphasize the difficulty in making a diagnosis of asthma under five years and the need to identify phenotypes that may help paediatricians in the therapeutic choices. The ERS document emphasizes the importance of define the child with wheezing in a clinical phenotypes (episodic viral wheeze and multi-trigger wheeze).

On the basis of the available evidence, a trial of montelukast or inhaled steroids should be considered. The search for biomarkers which can help paediatrician to make a decisional program in the pharmacological treatment in children with wheezing is positively warranted.

## Conflict of interest

The authors have no conflict of interest to report.

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