Preschool Wheezing: Trajectories and Long-Term Treatment

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Wheezing is very common in infancy affecting one in three children during the first 3 years of life. Several wheeze phenotypes have been identified and most rely on temporal pattern of symptoms. Assessing the risk of asthma development is difficult. Factors predisposing to onset and persistence of wheezing such as breastfeeding, atopy, indoor allergen exposure, environmental tobacco smoke and viral infections are analyzed. Inhaled corticosteroids are recommended as first choice of controller treatment in all preschool children irrespective of phenotype, but they are particularly beneficial in terms of fewer exacerbations in atopic children. Other therapeutic options include the addition of montelukast or the intermittent use of inhaled corticosteroids. Overuse of inhaled steroids must be avoided. Therefore, adherence to treatment and correct administration of the medications need to be checked at every visit.

Keywords: preschool wheezing, phenotype, asthma, therapy, inhaled corticosteroids, skin prick test, allergy, infection

INTRODUCTION

In preschool children, wheezing is very heterogeneous and evidence on pathophysiology and treatment is scant (1). Preschool wheezing should be considered an umbrella term for distinctive diseases with different observable and measurable features (phenotypes). Each phenotype may be the result of different endotypes, described by a mechanism that links clinical features with a molecular pathway. Different approaches have been used in the search of wheezing phenotypes. The selection of observable variables can be driven by the investigator or by data. The design can be cross-sectional or longitudinal. In this review, we discuss knowledge on expression of preschool wheezing phenotypes and their value regarding outcomes, prognosis and long-term treatment.

WHEEZE TRAJECTORIES

About one in three children experiences wheezing during the first 3 years of life (2, 3) but not all will develop asthma in later age (4). Several phenotypes of preschool wheeze that mostly rely on temporal pattern of symptoms have been proposed to identify individuals at risk for asthma onset at school age (1). Other variables including symptoms, bronchial inflammation, allergic sensitization, medication use, and lung function have been also used for classifying subgroups in relation to timing of occurrence and resolution of wheezing.

Birth longitudinal cohort studies have reported numbers of preschool wheeze phenotypes varying from 2 to 6. Three phenotypes are more common (3): (a) *transient early wheeze* occurs before the age of 3 years and resolves by age of 6 years without lung function impairment; (b) *late-onset wheeze* develops after 3 years of age and persists in childhood, it is linked to atopy, and, in some studies, it is associated to reduced lung function and high bronchial hyperresponsiveness;

(c) *persistent wheeze* starts in early life before 3 years of age and it is associated with atopy, high IgE levels, early allergen sensitization and diminished lung function by school age (3, 5–13). In Project Viva, a prebirth cohort study in Massachusetts (14), transient-early wheeze and persistent wheeze were found. Children with persistent wheezing or late-onset wheezing more frequently have asthma in adolescence (15).

In the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, two more phenotypes were identified at 9 years of age (9, 16): (a) *prolonged early wheeze* group (onset between 6 and 54 months of age), not associated with airborne allergen sensitization and weakly associated with higher airway responsiveness and impaired lung function; (b) *intermediate-onset wheeze* group (onset between 18 and 42 months) with persisting symptoms, atopy, poor lung function and at more risk of developing asthma in childhood. At 15 years of age, symptoms continued in school age-onset persisting phenotype and in late childhood onset persisting phenotype and in continuous wheeze group and they were associated with bronchodilator reversibility, fractioned exhaled nitric oxide (FeNO) levels ≥35 ppb and impaired pulmonary function (16, 17). Finally, preschool wheeze persisting after 18 months of age is a risk factor for asthma, reduced pulmonary function and higher FeNO value in adolescence (16). Wheezing phenotypes identified in the ALSPAC study have been confirmed by the PIAMA study with the exception of the *prolonged early wheeze* phenotype (13).

In the Manchester Asthma and Allergy Study (MAAS) a new phenotype named *persistent troublesome wheeze*, has been characterized. Children in this category had more frequent exacerbations, hospitalizations, and unscheduled visits, reduced lung function, higher bronchial hyperreactive airways, higher IgE levels to inhalant allergens in comparison with other phenotypes. A sum of medium wheal diameter of skin prick tests (SPT) ≥ 10 mm and a history of exacerbations by age 3 years predicted persistent troublesome wheeze (8). In the MAAS cohort (18), new phenotypes of children with severe wheeze exacerbations were found when trajectories were examined at 8 years of age and at adolescence. Early-onset frequent exacerbations compared to infrequent exacerbations or no exacerbation had shorter breastfeeding, lower lung function, higher FeNO.

Despite the limitations in categorizing preschool wheeze (1), wheeze trajectories have been used to determine several models for predicting the onset of asthma at school age in high-risk population or in general population (4, 19–31). Unfortunately, the clinical value of predictive indexes for ruling out the development of asthma at school age has been shown to be too low to be adopted in clinical practice (32–34). However, original API is a very promising predictive tool, since it has an appreciable likelihood ratio (∼7.4) and it consists only of four clinical parameters and blood eosinophil count (34). Over the last years, many groups attempted to update these definitions and

identify more detailed phenotypes using for example latent class analysis (LCA) technique (17, 35, 36) but results from a clinical point of view were rather disappointing.

Several factors that can be potentially modified by simple interventions may change wheeze trajectories. In the Canadian Asthma Primary Prevention Study, pre-school wheezers were classified as *early-transient* (10%) who did not develop asthma, *low-progressive* (69%) who gradually developed asthma over time, and *early-persistent* (21%) with higher risk of asthma occurrence (37). Only in the early-persistent group wheezing prevalence was significantly reduced by intervention including breastfeeding, delayed weaning, avoidance of house dust mite, pets and environmental tobacco smoke.

In the Urban Environment and Childhood Asthma birth cohort, five phenotypes were described (38). Asthma developed in the 60–70% of children with high wheeze/low atopy and high wheeze/high atopy while it was infrequent in low wheeze/high atopy (14%) and in low wheeze/low atopy (1%) and absent in transient wheeze/low atopy. Environmental exposures in early life differed among phenotypes. Maternal stress and depression, prenatal smoke exposure were associated with the high wheeze/low atopy group. Indoor allergen exposure was high in the low wheeze/low atopy group and low in the two high wheeze phenotypes. Household microbial richness and diversity were low in high wheeze/high atopy and highest in transient wheeze/low atopy.

In the French Longitudinal Study of Children, wheezing infants at 2 months of age with 1 or 2 siblings, nocturnal cough, respiratory distress, extreme bronchial secretion, reflux, maternal asthma and maternal smoking during pregnancy were found to be at risk for persistent wheezing at 1 year of age (39).

VIRUS AND ALLERGY

In the past, an ERS task force (40) proposed a simple clinical classification of wheezing as "*episodic viral wheezing*" (EVW) or "*multiple trigger wheezing*" (MTW) based on triggers and symptoms. A wheezing typically exacerbated by a viral upper respiratory tract infection with few or no symptoms in the interval between the episodes was described as EVW, the commonest phenotype between 1 and 5 years of age. Children who have symptoms that resemble asthma with wheezing also between respiratory infections and during activity, crying or laughing show the phenotype traditionally called MTW. Children with MTW are usually atopic and may have a family history for asthma. The usefulness of such classification of wheezing in clinical practice is hampered by several factors. It does not consider that is based on patient characteristics at the time of examination (symptom pattern, trigger factors, allergic features…) that change over time (41). Another limitation is that does not take into account the severity of the episodes and cannot identify children responding to specific treatments (42). Furthermore, the two phenotypes can have similarities and cover different endotypes.

In young children, the endotype is difficult to assess because airway samples like bronchoalveolar lavage and bronchial

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Abbreviations: FeNO, fractioned exhaled nitric oxide; LCA, latent class analysis; EVW, episodic viral wheezing; MTW, multiple trigger wheezing; ICS, inhaled corticosteroids; RCTs, randomized controlled trials; LTRA, leukotriene receptor antagonist; LABA, long acting beta-agonists; SABA, short acting beta-agonists; OCS, oral corticosteroids.

biopsies are not easy to obtain (43). A research performed on a small sample of preschool children with severe wheezing suggested that EVW might be associated to airway neutrophilia and to airway microbiota dominated by Moraxella although the statistical significance was not reached (44). To date, in young children no study has linked lower airway inflammation or infection to a particular wheeze phenotype (1).

Regarding the Th2 high endotype, Fitzpatrick AM et al. (43) distinguished by LCA four latent classes of recurrent preschool wheeze on the basis of type-2 inflammatory features including blood eosinophils, atopic eczema, aeroallergen and food sensitization and/or pet exposures. The probability of exacerbation was greater in children with sensitization and indoor pet exposure (latent class 2) and children with multiple sensitization and eczema (latent class 4). Overall in children sensitized to aeroallergens this risk was higher than in children with minimal sensitization (latent class 1- sporadic eczema, low blood eosinophils, low serum IgE levels, >90% with no sensitization to aeroallergen and food) or with sensitization plus tobacco smoke exposure (latent class 3) with no exposure to pets. It is not surprising that children with atopic eczema are at risk for exacerbation because airway inflammation has been found in children with atopic eczema without asthma symptoms (45).

Sensitization to foods is more frequent than airborne allergy under 5 years of age (46). It has been shown that asthma that remains over time and severe asthma attacks are more common in children with food allergy and depends on number of offending foods (47). These findings suggest that it may be worthwhile to perform skin prick tests to foods in patients with wheezing and/or atopic eczema (48).

Since atopy is a risk factor for asthma, it has been proposed that probiotics may potentially stimulate Th1 and decrease allergic asthma. Accordingly, there are some data that probiotics supplementation may be of benefit in the prevention of wheeze or asthma (49). Another potential approach is to investigate strategies that prevent viral respiratory tract infections to reduce the development of asthma. However, the impact of probiotics or immunostimulant agents on recurrence of such infections seems to be small (50, 51).

LONG-TERM THERAPEUTIC APPROACH AND PHENOTYPES

To date, the optimal therapy for preventing recurrent episodes of wheezing in preschool children is not well-defined and remains a matter of study and debate (52–54). In preschool children, inhaled corticosteroids (ICS) are recommended as first choice of controller treatment in all subjects with frequent exacerbations irrespective of phenotype or endotype (55, 56).

A systematic review of 29 randomized controlled trials (RCTs) in preschool children (no 3,592) showed that ICS reduced the frequency of wheeze episodes independently from phenotype and atopy (57). Similarly, a more recent meta-analysis including 15 studies for a total number of 3,278 children aged ≤6 years demonstrated that daily medium dose ICS reduced the risk of exacerbations by 30% compared to placebo. Moreover, when

the analysis was performed in the subgroup of children with persistent asthma the risk of exacerbation was reduced by 44% (53).

The question arises on which preschool children with wheeze may benefit from ICS. The finding of peripheral blood eosinophilia, that in this age group reflects higher airway eosinophilia (58), can suggest the possible response to a continuous therapy with ICS (57). Accordingly, the Individualized Therapy for Asthma in Toddlers (INFANT) trial showed that daily therapy with ICS is beneficial in terms of fewer exacerbations and better symptom control in children aged 12–59 months with aeroallergen sensitization and high blood eosinophils ($\geq 300/\mu$L) (54). Along this line, daily ICS were found to significantly reduce future exacerbations in children with sensitization and indoor pet exposure (latent class 2) and children with multiple sensitization and eczema (latent class 4), but not in children with minimal sensitization (latent class 1) or children with sensitization and second hand tobacco smoke exposure (latent class 3) (43). Therefore, children with MTW experiencing symptoms most days of the week and children with frequent episodes of wheezing (every 6–8 weeks) and/or severe exacerbations requiring systemic corticosteroids irrespective of wheezing phenotype are good candidates to start a trial (at least 6–8 weeks) with daily very low or low dose ICS (**Table 1**) (55, 57, 59, 60). Other guidelines suggest beginning with moderate dose ICS (56). After a therapeutic trial with ICS for 8–12 weeks, the child should be reassessed to see if symptoms have resolved and treatment can be tapered down or interrupted. Subsequently, ICS treatment should be given again when needed to control symptoms.

In children with mild symptoms aged 6–11 years, the updated GINA recommendations (59) showed a change in the management of wheezing recommending the use of ICS with short acting beta-agonists (SABA) as needed or regular ICS with as needed SABA. However, trials on this issue are lacking in preschool children. The INFANT study showed that some children benefited from as-needed ICS/albuterol as daily ICS or daily montelukast plus as-needed albuterol. Further studies are warranted to clarify endotypes that are associated with response to treatment. If the initial treatment with low dose ICS is not enough to reach good control, various alternatives are available

TABLE 1 | Inhaled corticosteroid by recommended dose.

Inhaled corticosteroid	Very low dose	Low dose	Medium dose
Fluticasone propionate HFA	50 mcg one puff twice a day	50 mcg two puffs twice a day	125 mcg two puffs twice a day
Beclomethasone dipropionate HFA	50 mcg two puffs twice a day	100 mcg two puffs twice a day	200 mcg two puffs twice a day
Budesonide nebulized	250 mcg/day	500 mcg/day	>500–1,000 mcg/day

Fluticasone and beclomethasone are considered as pressurized metered dose inhalers (pMDI) with spacer. Adapted from BTS guidelines and GINA recommendations (55, 59). HFA, Hydrofluoroalkane propellant.

(59). The preferred option is doubling the dose (see "medium dose" in **Table 1**). The beneficial effects of daily ICS have been shown up to 400 mcg/day of beclomethasone equivalent (or 200 mcg/day fluticasone) via pressurized metered-dose inhaler with spacer without any further improvement for higher doses (61).

Before increasing or changing the therapy, checking that the medication is regularly administered and that inhalers are correctly used is mandatory. Adherence to ICS is crucial in achieving and maintaining control of symptoms in young children with wheeze. In an observational study in asthmatic children aged 2–6 years adherence to ICS was measured daily for 12 months showing that adherence was the only determinant significantly associated with asthma control (62). Moreover, if the child is not too sick to use inhalers, an MDI/spacer combination is the gold standard strategy to deliver corticosteroids and bronchodilators and inhalation technique should regularly checked (63). In those children where regular intake of low dose ICS plus as-needed SABA fails to control symptoms or exacerbations, the preferred option is increasing the dose of ICS (56, 59), after having excluded other diagnosis, allergen exposure and check adherence to treatment. Latest recommendations suggest that in children with EVW and no signs of atopy adding a leukotriene receptor antagonist (LTRA), rather than doubling the dose of ICS may be an option (59, 60). However, RCTs comparing the association of LTRA plus ICS vs. ICS alone need to be performed before physicians can recommend this combination in preschoolers. Moreover, montelukast may cause several adverse effects and the US Food and Drug Administration has required to add a boxed warning about mental health side effects. So, the risk-benefit balance of montelukast may not be favorable in some patients, particularly when the symptoms may be mild and controlled with other drugs (64). When medium dose ICS does not control symptoms other add-on therapies [LTRA, long acting beta-agonists (LABA)] in children >4 years of age) may be considered. Further options include the addition of theophylline or oral corticosteroids (OCS). Allergen-specific immunotherapy can be a therapeutic opportunity (65, 66). It is recommended that all children, including asthmatics, timely perform vaccinations for infectious diseases and this is feasible even if they have had allergic reactions to vaccines (67). It is important that children suffering from asthma receive influenza and pneumococcal vaccinations. The risk for invasive pneumococcal disease is declined in asthmatics after the introduction of pneumococcal vaccination. However, Castro-Rodriguez JA et al. (68) documented that even among children who received pneumococcal conjugate vaccine, asthmatic children were at higher risk for invasive pneumococcal disease and pneumonia in comparison with non-asthmatic children (68). Therefore, trials are warranted to assess whether asthmatics >2 years of age should receive a supplemental 23-valent pneumococcal polysaccharide vaccination after pneumococcal conjugate vaccine regardless the intake of high-dose OCS as reported in the current guidelines in US. Recently the US Food and Drug Administration and the European Medicines Agency extended the use of tiotropium as add-on maintenance treatment in children > 6 years of age. Vrijlandt et al. (69) has found that tiotropium add-on therapy reduced exacerbations in preschool asthma symptoms not controlled by ICS and LABA or montelukast. Unfortunately, in this study an association of efficacy of tiotropium with Th2 high endotype was not determined.

OTHER BASELINE TREATMENTS

The use of intermittent high dose of ICS is an alternative option in preschool wheeze. In preschool children with EVW who are asymptomatic between the episodes the intermittent use of high doses of steroids (for example beclomethasone dipropionate 400 mcg twice daily, fluticasone propionate 250 mcg twice daily or budesonide 1 mg twice daily) at the first sign of respiratory tract infection and continued for up to 7–10 days may be the preferred choice (53). Interestingly, this approach is not inferior to daily steroids also in children at risk of developing asthma (70). A Cochrane review comparing high ICS doses demonstrated a reduction in requirement for OCS compared to placebo (71). Ducharme et al. (52) in a meta-analysis of 4 RCTs (no. 1,024) reported that compared to placebo, high doses of ICS reduced the risk of exacerbations requiring OCS in preschoolers with moderate or severe episodic viral wheeze. A further Cochrane meta-analysis comparing intermittent ICS with placebo in 490 preschool children with persistent asthma found a reduction in the need of rescue OCS of almost 50% (72). A more recent meta-analysis of RCTs showed that, compared to placebo, the use of intermittent ICS for at least 7–10 days in children with episodic viral wheeze reduced the risk of exacerbation by 36%. Interestingly, no significant differences in severe exacerbation rate were found when this strategy was compared to daily ICS (53). However, the comparison between intermittent and continuous therapy yielded controversial results. In the study by Papi et al. (73) intermittent therapy with nebulized beclomethasone 800 mcg/day was not inferior to daily low dose ICS in symptom control but exacerbation rate was lower with continuous therapy. In contrast, the study by Zeiger et al. (70) showed no difference between the two treatments in exacerbation frequency but a significant lower exposure to steroids with intermittent modality. A 2013 Cochrane meta-analysis including two trials in preschool children with persistent asthma found inconclusive evidence about the efficacy of intermittent vs. daily ICS (74). Though, the meta-analysis by Castro-Rodriguez evaluating daily and intermittent ICS in preschoolers, school-aged children and adults with persistent wheezing and mild to moderate persistent asthma showed no statistically significant difference in the rate of asthma exacerbations but more free asthma days in those on daily preventing therapy (75).

When the use of inhaled steroids is intermittent the prescribed dose should be enough high to be successful because low-moderate doses seem to be ineffective (76, 77). Indeed, in an Italian RCT the intermittent use of 400 mcg of nebulized beclomethasone twice a day for 10 days did not affect neither the evolution nor the symptoms of the exacerbation in preschool

children with viral wheeze (78). However, high doses of steroids imply the use of the highest licensed dose and this is particularly important to avoid an overload of these medications since in this age range children can experience a significant high number of viral exacerbations along the year (76).

Another option for the baseline treatment can be the regular therapy with montelukast, a leukotriene antagonist that modestly reduces symptoms and need for rescue bronchodilator or OCS compared with placebo (79). However, the strength of evidence to support the use of montelukast is limited by the difficulty of the studies in distinguishing EVW from an asthma-like phenotype like MTW. A systematic review and meta-analysis including two RCTs on the use of intermittent or continuous montelukast in children with episodic viral wheeze and no interval symptoms showed that there is no statistically significant difference between the treatment with montelukast and placebo in the number of exacerbations requiring OCS (80). Krawiec et al. (81) reported a similar result in 70 children aged 36 months to 6 years where daily therapy with montelukast did not have any influence in preventing wheeze episodes over 1 year. Furthermore, in comparative studies montelukast is less efficacious than daily steroids in reducing wheeze exacerbations requiring OCS (82). The use of intermittent montelukast in preschool children with wheeze is likely effective only in a specific genotype-dependent subgroup carrying the promoter 5/5 ALOX5 (83).

LIMITATION OF ICS

The effectiveness of ICS for preventing attacks of wheezing in preschool children is always questioned. Very recently, a UK cohort study of children aged 1–5 years reported that initiation of the controller therapy with ICS did not result in fewer exacerbations compared to bronchodilators over 1 year. That said, the electronic data of this study might have represented a very general population of children with mild forms of wheezing since children on ICS before the age of 1 and those prescribed ICS or montelukast during the baseline year were excluded (84). On the other hand, a cohort study including children under 5 years recorded in the same country an increase in ICS prescriptions and treatment of exacerbations over the last 10 years (85). In interpreting these findings it should be considered that prescription of ICS is frequent in children with low tract respiratory infections who do not wheeze. Therefore, choosing the appropriate pharmacological treatment in children with airways disorders is still challenging, a correct diagnostic work up is crucial to avoid inadequate prescriptions (86, 87).

The treatment with continuous or intermittent ICS and the treatment with montelukast do not prevent the progression of any phenotype of preschool wheeze to asthma in later ages but aim to improve symptom control and reduce exacerbations (88–90). The main side effect of a long-term therapy with steroids is growth suppression (91), a topic that should be always discussed with parents. The effects of ICS on growth velocity are seen in pre-pubertal children in the first 1–2 years of treatment

resulting in a decrease of 0.5–1 cm in height growth (88). This is not progressive or cumulative and one study on long-term outcomes of continuous ICS showed a difference of 0.7% in adult height (92). It is likely that intermittent treatment has less effect on linear growth because of the lower cumulative dose (53, 70, 74). However, asthma itself as the other chronic diseases, has transient negative impact on growth in children, but the final height is not affected. So, there is a need of trials that investigate whether adult height is reduced by ICS in asthmatics (93). The long-term use of ICS at high doses may have effects on hypothalamic-pituitary-adrenal axis, resulting in reduced adrenal cortisol production (94). However, many studies show a wide variability on the partial suppression of adrenal cortisol, depending on the individual susceptibility, the severity of asthma, the type of inhaled corticosteroid and the inhalation device used. In most cases the suppression is asymptomatic and life-threatening condition are extremely rare. Severe hypoglycaemia due to adrenal insufficiency is reported only in two cases of preschool children treated with inhaled fluticasone propionate at a dosage of 780 μg/m2/day (95).

In the first year of life, symptoms are triggered by viral or bacterial infections. Both atopic and non-atopic wheezers have no eosinophilic airway inflammation (96). Treatment options for controlling symptoms include trials with montelukast or beta2-agonists. Beta2-agonists should be stopped after 4–8 weeks and, when effective, they can be given if necessary. Regarding montelukast, a course of 2–3 months, should be regarded as useful for assessing the efficacy.

CONCLUSIONS

Studies on preschool wheezing phenotypes are of little clinical help for identifying children who are more likely to develop asthma at school age. Drawbacks of such studies include heterogeneous results, with only partial consistency, overlapping features and instability of phenotypes over time. Disagreements between the results may be explained by different study populations, variations in approaches for selecting observational features, lack of uniformity in choosing type and number of variables. Regarding long-term treatment, ICS are the first-line therapy in preschool children with asthma or recurrent wheezing. With the limitations related to a classification based on temporal phenotype, daily ICS are the preferred choice in children with MTW and frequent symptoms, especially those with blood eosinophilia and aeroallergen sensitivity, while intermittent high dose ICS can be considered in children with EVW and no symptoms between the episodes. To date, there is no evidence to recommend the use of intermittent or daily montelukast.

AUTHOR CONTRIBUTIONS

VF, AS, and CC co-wrote the manuscript and approved the final version.

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