CURRENT TREATMENT STRATEGIES FOR ASTHMA IN PRESCHOOL CHILDREN.

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Rationale: *Current recommendations for preschool asthma treatment are based mostly on the one-fits-all paradigm and lack patient phenotyping. Current knowledge enables stratifying those children according to "treatable traits," which is likely to impact management.*

ABSTRACT

Purpose of review

Half of all children will experience an episode of wheezing by six years. Recurrent preschool wheezing is associated with early lung function loss and has a lifelong impact on airway health, so deciding which children should be treated to prevent exacerbations and avoid irreversible health consequences is crucial. The purpose of this review is to provide a practical approach to the pediatric patient under five years of age with asthma, in particular given the recent identification of wheeze phenotypes.

Recent findings,

Here we note the difficulty of defining "asthma" for this age group and advocate that it be determined by the set of respiratory symptoms presented, without assumptions about the underlying mechanisms of the disease. In addition, we propose a forward-looking approach, what treatment to apply to particular phenotypes, which child should be treated, and, if so, which treatment strategy to choose. No clear recommendation exists for the management of nonallergic preschool wheezing.

Summary,

We recommend an empathetic approach to parent anxiety and considering objective markers: timing, severity, and frequency of symptoms, along with an assessment of other biomarkers, including viral etiology, aeroallergen sensitization, and blood eosinophils, that contribute to successful decision-making.

Keywords

Preschool, Wheeze, Asthma, Phenotype, Virus

INTRODUCTION

Asthma is one of the most common chronic diseases in preschool children, the leading cause of childhood morbidity as measured by emergency department visits and hospitalizations and it is often diagnosed early in life [1]. In Europe alone, almost 10 million people <45 years of age have asthma [2]. The prevalence of asthma in the European Union (EU) is 8.2% in adults and 9.4% in children. Most wheezing episodes are triggered by viral respiratory tract infections, occurring in 30%-50% of preschool children [3]. In the majority of cases, episodes of wheezing are mild and transient and are managed in non-hospital settings; however, some infants develop recurrent episodes severe enough to require medical review. Preschool children with wheezing consume disproportionately large amounts of healthcare resources, are five times more likely to become hospital emergency patients, and twice as likely to attend outpatient visits [4]. The economic burden of asthma for the 25 countries of the European Union is estimated at EUR 3 billion, and EUR 5,2 billion for wheezing [5].

Altogether, these data highlight the importance of identifying effective strategies to reduce the significant morbidity associated with recurrent wheezing asthma in the preschool age group.

There is an ongoing debate to what extent 'Preschool Wheezing' coincides with putative or diagnosed asthma defined as "eosinophilic allergic airways disease" [6], for which good guidelines and treatment regimens exist [7]. The fact is that many children presenting with preschool wheezing develop eosinophilic asthma, and the major task is to detect during early childhood those who respond to steroid treatment. However, only 40% of these children will develop recurrent wheezing later in childhood [8]. Less known about non-atopic or non-

eosinophilic asthma. Fortunately, many of these children outgrow their wheezing patterns before school-age.

At the same time, in many cases and countries, the word "asthma" is used as a label to describe a combination of asthma symptoms (described as wheezing, shortness of breath, difficulty breathing, manifested by acute attacks with or without interval symptoms) or the use asthma medications in the last 12 months [9], which is in line with the recent Lancet Commissioned consensus [10]. This label and the plethora of other labels are used to classify wheezy preschoolers and which otherwise is a source of confusion for physicians, basic researchers, and finally, the patients we treat. That is why every attempt to phenotype children with preschool wheeze is essential, because understanding the pathophysiology of wheeze in particular groups of patients will allow for identifying treatable traits.

Given the clear expectations of the families of our patients who expect symptomatic relief in their preschool children who wheeze, as well as the sparse knowledge of the underlying inflammatory and pathological processes in this age group, this brief review will outline the latest trends in the phenotyping of preschool wheezing/asthma patients and the most recent treatment trends for these children and their families.

1. Clinical phenotypes in Preschool Wheeze.

Recently, two independent studies have attempted to identify and classify clusters in children with preschool wheeze based on the presence of sensitization, eosinophilia, structural abnormalities and bronchoscopic microbiology [11,12]. According to these reports, there are

at least four to five clusters differing in etiopathology and most likely response to different treatment options (Figure 1):

- Cluster 1: atopic, with high total IgE, sensitization, high blood eosinophils, high use of ICS, moderate rate of bacterial or viral detection,
- Cluster 2: infectious nonatopic, with low IgE, high BAL neutrophils, high rate of bacterial and viral infection,
- Cluster 3: nonatopic with low BAL neutrophils, low infection rate, low bacteriology and low viral detection
- Cluster 4: structural abnormalities characterized by early-onset wheeze, structural abnormalities, mostly tracheomalacia, low IgE and agranulocytic BAL
- Cluster 5: microaspiration-associated late-onset wheeze, with a high rate of gastroesophageal reflux, little atopy, and high BAL lipid-laden macrophages

This division into these clusters (phenotypes) seems promising in daily clinical practice, as clinicians are often frustrated by the lack of a good response of wheezing preschoolers to anti-inflammatory/control treatments. However, apart from peripheral eosinophilia and sensitization features, we still do not have readily available biomarkers that would allow a quick assignment of a given patient to a given phenotype, particularly the "infectious" one.

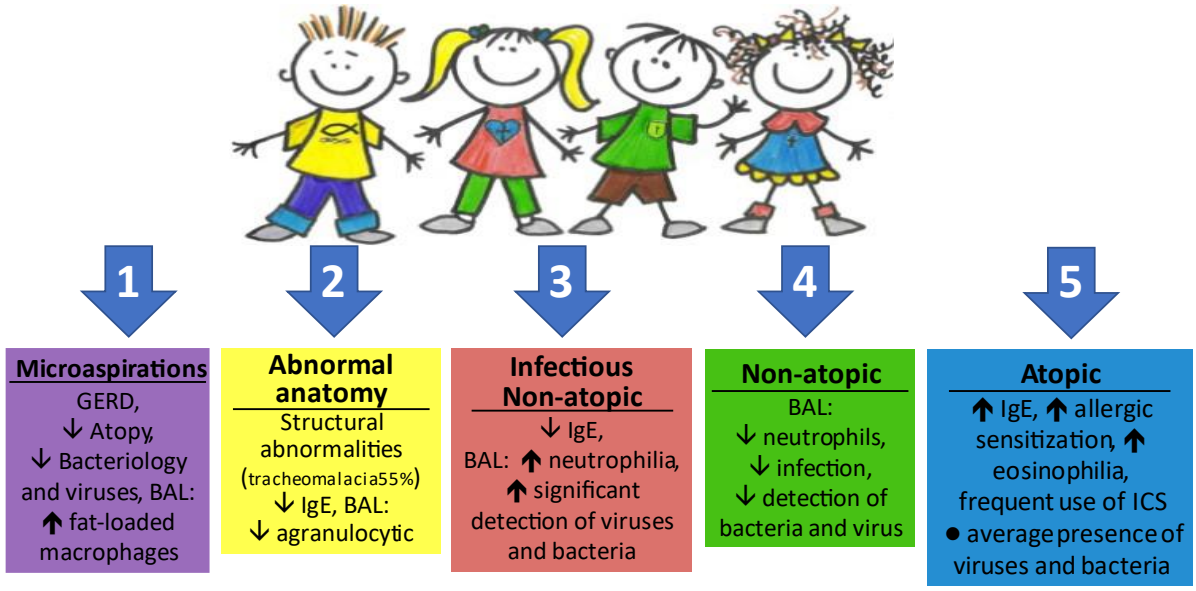

Figure 1: Five putative phenotypes identified recently in severe preschool wheeze and treatment-resistant preschool wheeze children (according to [11,12]. Phenotypes analysis was based on bronchoscopic analysis; peripheral eosinophilia, IgE, allergen sensitization, evidence of specific airway microorganisms, neutrophilic features, and any infection.

2. Rationale for identifying different phenotypes in "preschool wheeze/asthma"

Many studies have shown that patients with different characteristics respond differently to asthma control medications. This is naturally important to optimize the control of the disease and efficacy-safety ratio of a drug. Perhaps an even more important goal is the disease modification towards a permanent cure. This is the aim of, e.g., the immunotherapy for allergic rhinitis. However, asthma has been considered an incurable disease. The lack of feasible human models targeting early inflammatory events has challenged drug discovery programs, and environmental control has shown mixed results. Currently, there is no

established prevention strategy for asthma. Investigations are ongoing regarding the identification of at-risk preschool-aged children by phenotyping them according to asthma predictive indices, exposures, triggers (allergen, exercise, virus), types of inflammation (eosinophilic, neutrophilic), and microbiology [13,14]. Recent studies have submitted enough data to stratify preschool wheezers into a few distinct clinically relevant phenotypes, and phenotype-directed therapy may become possible soon [11,12].

Interestingly, recent studies have given promising results by showing that we may affect the natural course of asthma with optimal early treatment strategy, i.e., rhinovirus induced first-time wheezing children appear to be highly responsive to oral corticosteroids in terms of 30% less school-age asthma [15,16]. The finding suggests early Type 2 underlying airway inflammation increases susceptibility to rhinovirus infection, and effective downregulation of this inflammation at an early stage may have a long-term disease-modifying effect. Corticosteroid does not affect virus replication. The critical issue for achieving an optimal response appears to be the identification of these at-risk children early.

3. Current tools for identifying phenotypes (API, eosinophilia, virus detection at the first episode) and "treatable traits."

Persistent childhood asthma is mainly eosinophilic/atopic and dominated by type 2 inflammation [17]. In cytokine level, it is characterized by increased expression of cytokines such as interleukin (IL)-4, IL-5, and IL-13 produced by the adaptive immune system. In addition, the innate immune system triggers the production of IL-25 and IL-33, and thymic stromal

lymphopoietin (TSLP) by epithelial cells in response to infections. Clinically, type 2 indicators include the following atopic characteristics: (i) mainly aeroallergen sensitization, (ii) increased FeNO, and (iii) peripheral blood eosinophil count and (iv) clinical characteristics of atopic dermatitis and (v) parental atopic asthma. One of the most widely used indexes to predict school-age asthma among young recurrently wheezing children is the Asthma Predictive Index (API), which mainly consists of atopic characteristics [18]. When the index was applied to a birth cohort that was followed through 13 years of age, and it was found that 76% of school-age children with asthma had a positive index before three years of age, whereas 97% of school-age children without asthma had a negative index before three years of age [18]. The index was later refined as the modified asthma predictive index (mAPI). Its criteria include in less than 3-year-old children the following: four or more episodes of wheezing during the previous year and either one of the following main risk factors a parental history of asthma, a physician diagnosis of atopic dermatitis, or evidence of sensitization to aeroallergens, or two of the following minor risk factors evidence of sensitization to foods, ≥4% blood eosinophil count, or wheezing apart from colds [19]. More recently, rhinovirus-induced early wheezing has been recognized as an important early risk factor for school-age asthma odds ratio reaching 10 in atopic families [20]. The rhinovirus-induced early wheezing-associated risk is further potentiated by polymorphism of the 17q21 (odds ratio up to 26) and aeroallergen sensitization (odds ratio up to 45) [21,22]. Further analyses have indicated that locus 17q12-21 is the "wheezy locus," and polymorphism of rs2305480 may determine remission or persistence of wheezy symptoms [23]. Of the bacteria, Moraxella colonization has been associated with severe childhood wheezing [11,24].

4. Partnership with parents in the decision-making process

Most studies indicate that nearly one-third of children presenting to emergency departments for acute wheezing in preschoolers are discharged after only 4 hours. These data do not indicate that these stays are "unnecessary," "avoidable," or initiated by "overreactive parents." Rather, they indicate that even if these patients do not have objective indicators of exacerbation and hospital admission, the rapid deterioration of the child's condition causes parental anxiety, reduces the child's quality of life, and, in the longer perspective, leads to multiple family dysfunctions [25]. Therefore, it is believed that one of the tools to assess asthma control should be PROMs (patient-reported outcomes), which, if routinely used, will help determine the threshold at which treatment begins and the critical aspects of home care for the child [26].

If a wheezing preschool child's symptoms are severe enough that parents seek medical attention, then regardless of objective symptoms, the child must be treated for current wheezing attacks and prevent future symptoms.

It is known from birth cohort studies that a proportion of wheezing preschoolers with frequent symptoms are those in whom asthma develops during school age and the steady deterioration of lung function continues into adulthood [27,28]. These are patients who should be offered early, individualized treatment. Therefore, the decision to treat a wheezing preschooler should be made jointly with the parents and depends on whether this is the first or a single episode, whether the disease is chronic, and whether the wheezing is recurrent. Keep in mind that this decision threshold can vary from family to family and depends on the impact of asthma on the child's activities.

5. Wheezy preschoolers: Differential diagnosis

The study mentioned above by Teague et al. has shown that among children with corticosteroid-refractory recurrent preschool wheezers, a significant part was children with structural abnormalities (39%) or gastroesophageal reflux (27% percent) [12]. Therefore, alternative causes should be considered in children with recurrent wheezing before starting treatment for preschool asthma. Other causes of recurrent wheezing are, in order of frequency: recurrent viral respiratory infections, gastroesophageal reflux, foreign body aspiration, malformation of the airways, congenital malformations (vascular ring), cystic fibrosis, bronchopulmonary dysplasia, protracted bacterial bronchitis, immunodeficiency, primary ciliary dyskinesia, congenital heart disease and tuberculosis [1,29](Figure 2).

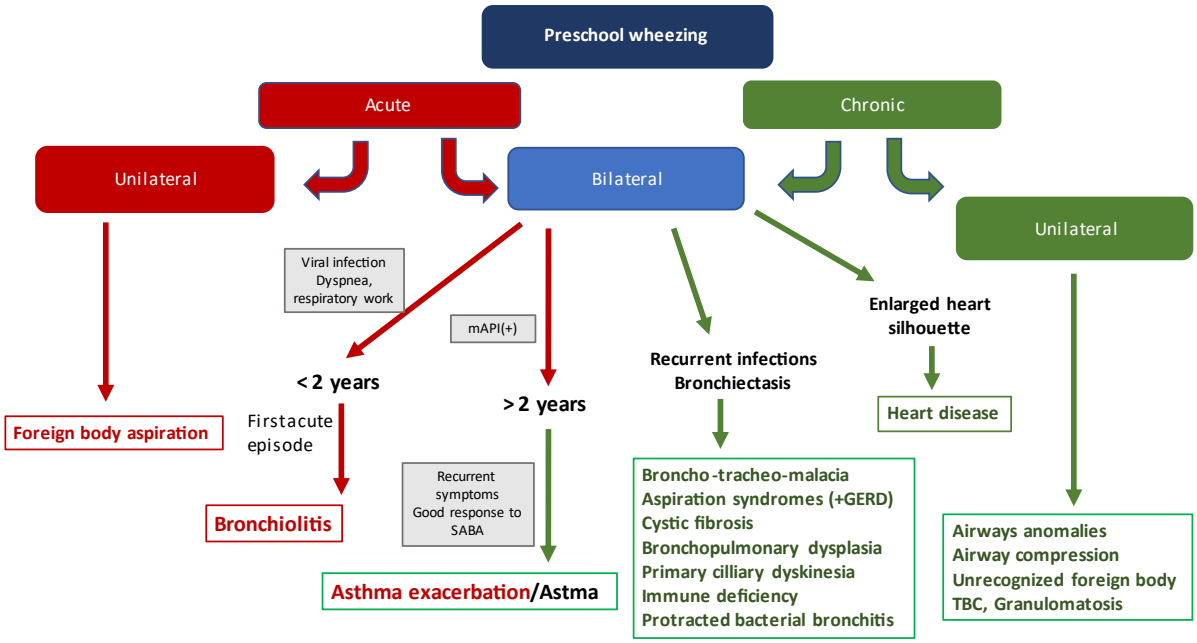

Figure 2 . Flow chart on the differential diagnosis of preschool wheeze. The leading causes of acute wheezing are highlighted in red, whereas the conditions underlying chronic wheezing are shown in green (modified according to Roversi et al. Front Ped 2020 [30]).

In older preschoolers, other considerations include sinusitis and allergic rhinitis. The list of symptoms prompting additional tests or investigations includes dyspnoea, cardiovascular symptoms, persistent hypoxemia, failure to thrive, no-response to 6-weeks inhaled asthma controller medication (ICS), finger clubbing, or X-ray abnormalities [1].

6. Phenotype-Directed Treatment of Preschool Children with Recurrent Wheezing and Asthma

Several approaches to the description and definition of patterns, or phenotypes, of recurrent wheezing in early life, now allow for the personalized treatment informed by the underlying phenotype. As described below, the presence of features of underlying type 2 inflammation, such as peripheral blood eosinophilia and aeroallergen sensitization, have been repeatedly reported to portend better response to ICS.

Stokes and Bacharier [31] recently outlined one strategy for phenotype-directed treatment based upon a classification initially defined by the nature of the wheezing episodes. Among children with intermittent wheezing, typically in the context of viral URIs and with the absence of symptoms in between episodes, an initial treatment choice would be based upon the underlying modified Asthma Predictive Index (mAPI) status (Figure 3a).

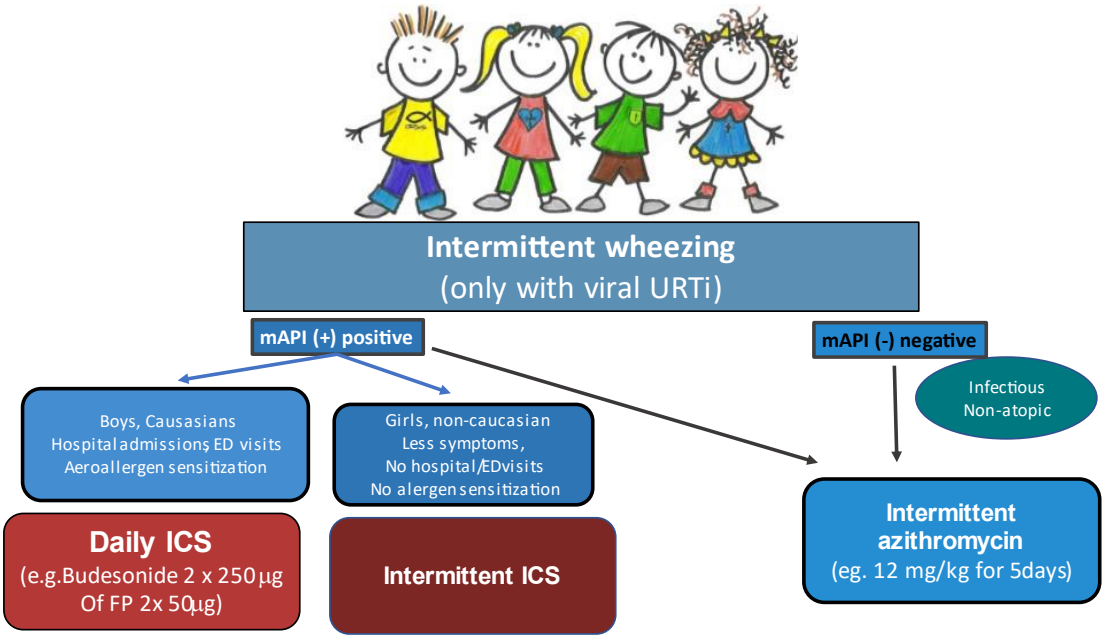

Figure 3a.

For children with positive mAPIs and with features associated with a higher wheezing burden such as male gender, white race, greater baseline symptom frequency, need for recent ED care of hospitalization, and/or evidence of sensitization to aeroallergen(s), daily low dose ICS would be the preferred approach. However, among children with positive mAPIs but with lower disease burden (i.e. females, non-white race, fewer symptoms, no recent ED or hospital care, and absence of aeroallergen sensitization), an initial trial of high dose intermittent ICS at the onset of URI symptoms is recommended. For children with negative

mAPIs, a trial of azithromycin started at the onset of respiratory tract infection symptoms is recommended based upon its potential to reduce episode progression, but with close attention to the response and the potential for antimicrobial resistance [32].

Among children with more frequent and persistent asthma symptoms or episodes, initial treatment decisions can be guided by assessing type 2 biomarkers such as peripheral blood eosinophil counts and/or aeroallergen sensitization (Figure 3b). Based upon the INFANT trial [33], children with either blood eosinophil counts ≥300 cells/uL and/or aeroallergen sensitization are most likely to benefit from daily low dose ICS therapy, whereas children without either feature may benefit from daily low dose ICS, daily LTRA or intermittent ICS taken whenever albuterol is used for rescue.

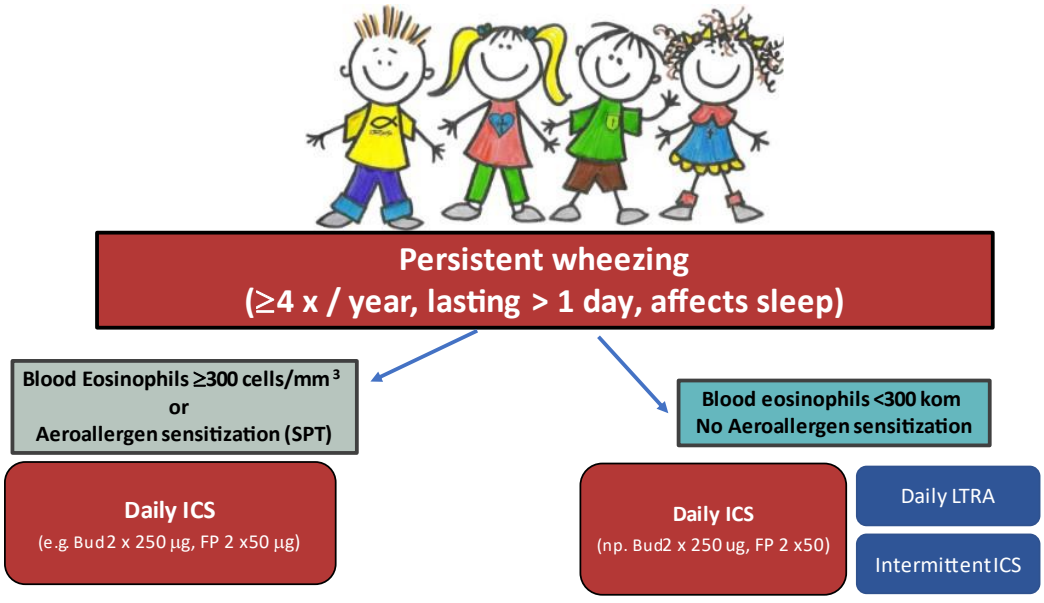

Figure 3b

An alternative approach towards patient characteristic-directed therapy involves the identification of treatable traits [34]. Two such patterns include patients with eosinophilic, allergic asthma (type 2 high), and non-atopic, bacterial infection associated with neutrophil-predominant wheezing (type 2 low). For those with the former trait, as evidenced by peripheral blood eosinophils $\geq$300 cells/μL with or without concomitant aeroallergen sensitization, ICS response has been demonstrated (as noted above), although it remains uncertain if blood eosinophils (and at what cut-point) represent the optimal biomarker to guide treatment in this age group.

Non-supervised analytic strategies, such as latent class analysis, have identified wheezing phenotypes in preschool children, and a recent study related such phenotypes to ICS response [35]. Using data from a collection of clinical trials in preschool children with recurrent wheezing, Fitzpatrick and colleagues identified four phenotypes that differed based upon patterns of sensitization, exposures, and exacerbation rates. Two phenotypes, those described by (1) sensitization along with indoor pet exposure and (2) multiple sensitization and eczema, experienced the greatest improvements in severe exacerbation rates with ICS therapy, whereas those described as "minimal sensitization" and "sensitization with tobacco smoke exposure" did not experience a reduction in exacerbations with ICS.

A recent report by Thorsen and colleagues highlights an additional strategy that may eventually be used to guide treatment among recurrently wheezing children [36,37]. Using nasopharyngeal aspirates obtained from young children during acute episodes of asthma-like symptoms, they identified specific microbiome patterns, including several specific operational taxonomic units (OTUs), that were associated with greater response to oral

azithromycin. Thus, having rapid access to such microbiome data could lead to directed therapies, such as azithromycin, in selected children early in episodes to reduce episode severity and progression.

7. Conclusions

Asthma has more than one name.

- Before deciding whether infants and preschool children with asthma and preschool wheeze should be treated, it is necessary to define the type of asthma. Early identification of children presenting with features of eosinophilic inflammation should be performed, as there are many good international recommendations for management of this type of asthma [7].
- Peripheral eosinophilia, allergen sensitization, evidence of specific airway microorganisms, neutrophilic features, and infection may provide some information.
- With the identification of several different phenotypes of preschool wheeze, we will soon have a chance to identify biomarkers in each phenotype and propose appropriate interventions for children with nonatopic preschool wheeze.
- Notably, empathetic communication with parents will help us decide whether to continue or abandon the ineffective treatment modalities.

We believe that shortly we will come significantly closer to proposing effective diagnostics to improve the care of preschool children with asthma and wheezing, which will significantly

improve health care in infants and preschool children. However, there are the following unmet needs in the research:

- understanding of environmental control both on protective and risk factors in primary prevention of asthma
- need for more feasible human models (on the tissue level) or organoids for targeting early inflammatory events.
- Need for the clinical research on infants at-risk and their appropriate management strategies to prevent asthma.
- Need for the understanding of key features of non-atopic/non-eosinophilic asthma, including appropriate and clinically feasible biomarkers

8. Key points:

- In preschool wheeze at least four to five distinct clusters have been identified recently, with different etiopathology and most likely response to different treatment options.
- Microbial biomarkers: Rhinovirus-induced early wheezing is considered an important early risk factor for school-age asthma and *Moraxella* colonization is associated with severe childhood wheezing.
- Empathetic relationship with parents of a wheezy preschooler should guide the treatment.
- Asthma Predicive Index together with blood eosinophilia and allergen sensitization are essential tools to distinguish preschool wheezers who respond to daily dose ICS, LTRA, intermittent ICS or azithromycin.

- Airway microbiome patterns in preschool wheezers may become soon an interesting approach to identify patients who respond to oral azithromycin.

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●● *First report that identifies in 136 children who underwent bronchoscopy four main clusters of severe preschool wheeze, distinguished based on sensitization, peripheral eosinophilia, lower airway neutrophilia, and bacteriology.*

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