Current and Future Management of the Young Child with Early Onset Wheezing

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Abstract

\textbf{Purpose of Review—} In this review, we discuss current thinking in relation to available guidelines for the care of preschool-aged children with recurrent wheezing, while highlighting the gaps in our knowledge and discussing changes that could occur over the next 5 years.

\textbf{Recent Findings—} The Asthma Predictive Index (API) as well as allergen-specific IgE, peripheral eosinophil count, and exhaled nitric oxide are perhaps under-utilized sources of information that can assist in predicting progression to asthma and response to therapies. Inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA) decrease impairment and exacerbation frequency in wheezing children but are not disease modifying. Macrolides may be useful during acute wheezing episodes for preventing progression to more severe symptoms. Monoclonal antibodies targeting IgE and T\textsubscript{H2} cytokines have been successful in trials of adults and older children with asthma, but trials in younger children are needed.

\textbf{Summary—} Establishing the phenotype and endotype of young wheezing children can be useful for prognostication of future asthma risk as well as for selection of the most appropriate treatment. Primary asthma prevention strategies are needed during the critical developmental window in early life prior to the onset of irrecoverable loss of lung function.

\textbf{Keywords} wheezing; asthma; phenotype; endotype; prevention; monoclonal antibodies

Introduction

Asthma is an increasingly prevalent chronic disease among children worldwide and is associated with significant morbidity, mortality, and economic burden. Much research effort has focused on management strategies for established asthma, yet there are significant knowledge gaps in our understanding of young children with recurrent wheezing and...
progression to asthma. At the 2016 AAAAI/Life Spectrum of Asthma meeting, workshop
groups were asked to discuss a case of an 18-month-old child with recurrent wheezing. This
case presented a unique opportunity to assimilate current thinking in relation to available
guidelines with significant changes that could occur over the next 5 years.

Case presentation

An 18-month-old male child has experienced four episodes of wheezing, some severe
enough to require evaluation in an urgent care clinic and a course of oral corticosteroids. The
child has a positive asthma predictive index (API). How would you counsel the parents who
want to prevent their child from developing asthma and/or more severe symptoms?

What is this child’s risk of developing asthma?

Approximately 40% of children wheeze during the first year of life, but only one-third of
children with recurrent wheezing will have asthma in later childhood (1, 2). In this section,
we will discuss techniques to approximate risk of progression to asthma.

The Asthma Predictive Index

Originally developed from the Tucson Children’s Respiratory Study, the Asthma Predictive
Index (API) is a well validated tool that uses major and minor criteria to predict which
children with early wheezing will go on to have asthma (2–5). The presence of recurrent
wheezing in the first 3 years of life plus one major or two minor clinical criteria is considered
positive and associated with an OR of 9.8 [5.6–17.2] for asthma at age 6 years (Table 1)(5).
Modified versions of the API have been developed and validated and include allergen
sensitization as a criterion that increases risk of asthma by school-age (6–8).

The Tucson Children’s Respiratory Study found that young children with persistent
wheeze demonstrated reduced maximal expiratory flow at age 6 compared to children who
never wheezed. A follow up of this study found that this pulmonary deficit persisted at age
16, suggesting that the insults resulting in reduced lung function occur in the first few years
of life (9). The appeal of the API lies in its potential to capture high-risk children during this
critical window before development of abnormal lung function so that targeted treatment can
be initiated. The API has high specificity and negative predictive value but low sensitivity
and positive predictive value, and therefore it cannot be used to definitively rule out future
asthma development or predict asthma severity (3–5, 10). Despite its limitations, the API is a
well-validated and easily applied screening tool to evaluate asthma risk in young wheezing
children.

Allergen-specific IgE

Allergic sensitization appears to be a key player in asthma inception (11, 12), particularly
aeroallergen sensitization early in life (13, 14). This relationship appears to be more
complex than simply the presence or absence of atopy, with age at onset and type and
number of aeroallergens playing an important role in asthma risk (15). Multiple studies have
shown a significant relationship between sensitization to multiple allergens in early life and
persistent wheezing, reduced lung function, and hospital admissions for asthma (15–19). Additionally, allergen sensitization appears to enhance the risk of rhinovirus-induced wheezing, and the combination of early sensitization and viral infection increases asthma risk (20–22). The National Asthma Education and Prevention Program (NAEPP) suggests that allergy testing be considered in young children with wheezing/asthma as the results can provide information about asthma risk and can impact asthma control (23).

**Peripheral Blood Eosinophils**

Persistent eosinophilia in early childhood is associated with asthma later in life (24), and blood eosinophils ≥4% is included as a minor criterion in the API (5). The Tucson Children’s Respiratory Study found a linear relationship between blood eosinophils and presence of asthma across the ages of 9 months to 11 years, independent of atopy, with the most chronic asthma found in the group with peripheral eosinophil counts greater than 5% (24). Similarly children under 2 with bronchiolitis and peripheral eosinophil count of >0.45 ×10^9 cells/L were at increased risk of asthma at ages 7 and 12 years (25, 26). The Individualized Therapy for Asthma in Toddlers (INFANT) study showed that children 12–59 months with blood eosinophils ≥300/µL and/or sensitization to at least one aeroallergen showed the most significant improvement in asthma control days and frequency of exacerbations when treated with daily inhaled corticosteroids (ICS) (27), suggesting that these biomarkers can predict steroid-responsiveness (28). Measuring peripheral eosinophilia may represent a minimally invasive surrogate for airway eosinophilia, though the strength of this correlation varies between studies and remains controversial (29, 30). Peripheral eosinophil count may be an under-utilized source of information that could aid in predicting a young wheezing child’s risk of asthma and response to treatment.

**Exhaled nitric oxide (FeNO)**

Elevated FeNO has been associated with eosinophilic airway inflammation in children, though like peripheral blood eosinophilia, the correlation between FeNO and airway eosinophilia is moderate and varies between studies (30–32). FeNO is increasingly used in both research and clinical care of asthma patients and can be performed by children as young as 4 years (33). FeNO level at 4 years of age is higher in persistent wheezers compared to transient wheezers and those who have never wheezed (34), and higher FeNO at age 4 is associated with greater risk of asthma at age 7 (14, 35). These findings have been replicated in several similar studies (36–39). Moreover, FeNO also appears to predict responsiveness to inhaled corticosteroids (40, 41), with higher FeNO predicting greater improvement in symptoms, lung function, and inflammatory markers in children with asthma treated with ICS compared to montelukast (28, 42). Use of FeNO in clinical practice is increasing and should be considered for establishing the endotype of airway disease and predicting steroid-responsiveness.

**What interventions, if any, can impact the risk for and severity of asthma?**

Guidelines for management of young wheezing children are lacking. In this section, we will discuss evidence-based treatment options as well as potential primary preventive strategies.
**Inhaled Corticosteroids**

According to the NAEPP, ICS are the preferred long-term controller therapy in children regardless of age to improve symptom control and quality of life (23). Despite this recommendation, there is continuing debate in the field regarding the usefulness of corticosteroids in wheezing preschool-aged children. Some of this debate has arisen from studies showing a lack of efficacy of oral corticosteroids for acute wheezing episodes in this age group (43, 44). However, certain groups of wheezing children may be more responsive to corticosteroids than others, as seen in the INFANT study (27) as well as others showing greater response to ICS in children with higher FeNO and peripheral eosinophilia (28, 42). While effective for reducing impairment and exacerbations, ICS do not appear to impact loss of lung function over time. The Childhood Asthma Management Program (CAMP) study found that daily inhaled budesonide improved asthma control in 5–12 year old children but did not impact the degree of change in lung function over time when compared to placebo (45). The Prevention of Early Asthma in Kids (PEAK) trial found that daily ICS treatment in preschool-aged children with positive modified API was associated with fewer symptoms and exacerbations, but the effect was lost upon discontinuation of ICS, suggesting a lack of disease-modifying effects (6, 7) (Figure 1).

Most preschool-aged wheezing children experience little or no impairment between exacerbations, which tend to be associated with viral respiratory infections. Many clinicians have begun the practice of using ICS only during acute wheezing episodes or seasonally during fall and winter seasons when viral illnesses are most likely to occur. The Maintenance vs Intermittent Inhaled Steroids in Wheezing Toddlers (MIST) trial compared high dose ICS at the first signs of viral respiratory illness to daily ICS treatment in preschool-aged children with positive API but low degree of impairment (not meeting criteria for Step 2 asthma therapy (23, 46). The authors reported no difference between the groups in frequency of severe exacerbations.

While ICS is not effective for primary prevention of asthma, the evidence suggests some benefit in preschool-aged children with recurrent wheezing episodes. Those children who demonstrate elevated blood eosinophils and/or aeroallergen sensitization may benefit the greatest from ICS treatment. More study is needed to better characterize ICS responders and non-responders to allow for development of additional treatment options.

**Leukotriene Receptor Antagonists**

Montelukast is approved for children as young as 1 year of age and is recommended as an alternative to ICS when initiating controller therapy for asthma (23). Efficacy studies of montelukast in young children demonstrate benefit particularly in the setting of viral-induced wheezing. The PREVIA study of children 2–5 years of age treated with montelukast daily for 12 months demonstrated reduction in the frequency of viral-induced exacerbations of asthma compared to placebo (47). Another study demonstrated reduced symptoms, need for rescue medications and oral corticosteroids in 2–5 year old children with asthma who received montelukast daily for 12 weeks (48). Children with favorable response to montelukast tend to be of younger age and shorter disease duration with lower FeNO,
peripheral eosinophilia, and serum IgE levels according to one study (28). The recently published INFANT trial found that many participants responded best to daily LTRA compared to daily or as-needed ICS but was unable to identify characteristics or biomarkers that predicted this response (27). Montelukast may be an appropriate first line therapy for a select population of preschool-aged wheezing children, but further study is needed to identify those most likely to have a favorable response.

### Macrolides

Antibiotics are commonly prescribed during outpatient visits for wheezing, with macrolides being the most common (49). Macrolides are frequently prescribed for cystic fibrosis and COPD due to their anti-inflammatory properties and may have a role in treatment of recurrent wheezing and asthma as well. Bacharier et al conducted a randomized, double-blinded trial of preschool children, half of whom had a positive modified API, using early administration of azithromycin 12 mg/kg for 5 days or placebo at the onset of respiratory illness and found a reduction in episodes of severe lower airway respiratory illness in the azithromycin group compared to placebo (50). Subgroup analyses found no significant effect of API on response to azithromycin. In an unselected Danish birth cohort, COPSAC 2010, a 3-day course of 10 mg/kg azithromycin after the onset of respiratory illness resulted in significant shortening of episodes of asthma-like symptoms compared to placebo in children ages 1–3 (51). In a randomized placebo-controlled study of infants hospitalized with RSV bronchiolitis, azithromycin treatment during the episode prolonged time to the next wheezing episode and resulted in fewer symptomatic days over the subsequent year (52).

Macrolides are thought to be more effective in non-eosinophilic airway inflammation, particularly neutrophilic inflammation associated with some types of asthma (53, 54). While not part of the current asthma management guidelines, macrolides could be considered for use during respiratory illness in preschool-aged children with wheezing to prevent progression to more severe symptoms.

### Allergen-specific Immunotherapy

Allergen-specific subcutaneous immunotherapy (SCIT) has been shown to effectively reduce asthma symptoms, corticosteroid requirement, and improve quality of life, and may be one of the only available treatment options, apart from avoidance of tobacco smoke, for primary prevention of asthma in children (55–57). The European multicenter Preventive Allergy Treatment (PAT) study randomized children 6–14 years with allergic rhinoconjunctivitis but without asthma who were sensitized to birch and/or grass pollen to SCIT containing birch and/or grass pollen or to an open control group for 3 years. Subjects who received SCIT were less likely to have asthma at 2 years and 7 years after study completion than the control group (58–60). Sublingual immunotherapy (SLIT) trials have shown less consistent benefit in treatment of allergic asthma in older children, and a recent Cochrane review concluded that further research is needed to determine if SLIT is an effective treatment for asthma (61). Clinical trials in preschool aged children are needed to confirm the efficacy and safety of allergen-specific immunotherapy for asthma prevention.
Anti-IgE therapy

Omalizumab is currently approved for adults and children 6 years and older with persistent asthma not well controlled on ICS and with sensitization to perennial allergen(s). In children and adolescents with allergic asthma, omalizumab resulted in decreased ICS dosage (62, 63), frequency of asthma exacerbations (62–65), reduced rescue medication requirement (62), and decreased unscheduled healthcare visits (62) and hospitalizations (65). Recently there has been increasing interest in the use of anti-IgE therapies for primary prevention of asthma, presumably by preventing the cascade of inflammatory events early in life that lead to asthma. Studies in adults have suggested that frequent exacerbations are associated with more rapid decline in lung function over time (66), potentially due to repetitive injury leading to airway remodeling. By preventing exacerbations, omalizumab may have the potential to prevent irrecoverable loss of lung function, but to date this has not been studied. Trials of omalizumab in preschool aged children are likely on the horizon as a potential treatment for primary asthma prevention.

Other Anti-T\(_{H2}\) therapies

Additional biologics aimed at T helper cell type 2 (T\(_{H2}\)) cytokines IL-4, 5, and 13 are currently under investigation for treatment of T\(_{H2}\)-high asthma. Anti-IL-5 monoclonal antibody (mAb) therapy has been shown to reduce exacerbations in adults with eosinophilic asthma (67, 68), and clinical trials in children are ongoing. Similarly, anti-IL-4R\(\alpha\) therapy appears to reduce the frequency of asthma exacerbations and improves lung function in adults with eosinophilic asthma (69), but no studies have been published in children. Results of anti-IL-13 therapies have shown mixed results in studies of adults with asthma, with some showing a reduction in asthma exacerbations (70) and improved lung function (70, 71), while others showed no improvement in exacerbation rates and or change in asthma questionnaire scores (72). There are currently no active trials of anti-IL-13 mAb in children under 12 years. Use of anti-T\(_{H2}\) biologics in current practice is limited, especially among preschool-aged children due to a lack of evidence demonstrating efficacy and safety in this population. The potential use of biologics for asthma prevention or disease-modification is an exciting area in our field and one that is likely to dramatically change practice in the coming years as further clinical trials in this age group are performed.

Conclusions

While there have been many advances to our understanding of early life wheezing phenotypes, we are still left with many questions regarding how to best treat these young children. As not all children respond the same way to conventional asthma therapies, appropriate phenotyping and endotyping of wheezing children is essential to guide practitioners to the most effective therapies for management of symptoms. The bigger dilemma is the lack of proven treatment options for primary prevention of asthma. Allergen-specific immunotherapy and biologics such as anti-IgE therapy will likely be further explored for their potential for primary prevention of asthma in certain groups of young children with recurrent wheezing.
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Abbreviations

API  Asthma predictive index
NAEPP  National Asthma Education and Prevention Program
ICS  Inhaled corticosteroid
LTRA  Leukotriene receptor antagonist
FeNO  exhaled nitric oxide
ETS  environmental tobacco smoke
SCIT  subcutaneous immunotherapy
T$_{H2}$ cell  T helper cell type 2
mAb  monoclonal antibody

References

Papers of particular interest have been highlighted as:

* of special interest
** of outstanding interest


23. 3 EPR. Guidelines for the Diagnosis and Management of Asthma. 2007. Available from: www.nhlbi.nih.gov/guidelines/asthma/


27**. Fitzpatrick AM, Jackson DJ, Mauger DT, et al. Individualized Therapy for Persistent Asthma in Young Children. J Allergy Clin Immunol. 2016 This study demonstrated a differential response to daily ICS among wheezing toddlers with aeroallergen sensitization and elevated blood eosinophils.


52*. Beigelman A, Isaacson-Schmid M, Sajol G, et al. Randomized trial to evaluate azithromycin's effects on serum and upper airway IL-8 levels and recurrent wheezing in infants with respiratory syncytial virus bronchiolitis. J Allergy Clin Immunol. 2015; 135:1171–1178. e1171. The authors found that azithromycin is beneficial in infants with RSV bronchiolitis, prolonging time to the next wheezing episode as well as reducing objective markers of inflammation. [PubMed: 25458910]


Key Points

• Insults resulting in reduced lung function occur in the first few years of life, so primary preventive strategies should be targeted towards very young children.

• The Asthma Predictive Index (API) and biomarkers such as specific IgE, blood eosinophils, and exhaled nitric oxide (FeNO) are useful tools to estimate asthma risk in young wheezing children.

• Daily ICS use in young wheezing children does not modify progression to asthma or prevent decline in lung function but does reduce impairment and exacerbations particularly in children with elevated blood eosinophils and/or aeroallergen sensitization.

• Allergen immunotherapy and monoclonal antibodies targeting TH2 inflammation may represent strategies for primary prevention of allergic asthma, but efficacy and safety studies in young children are needed.
While fluticasone did increase the proportion of episode-free days during the treatment period compared to placebo, this effect was lost during the observation period after treatment was discontinued. The listed p-values are for comparison between the treatment groups during the treatment and observation periods. The vertical bars represent 95% confidence intervals. (From New England Journal of Medicine, Guilbert, T. et al., Long-Term Inhaled Corticosteroids in Preschool Children at High Risk for Asthma, 354:1985-199. Copyright © (2006) Massachusetts Medical Society. Reprinted with permission. http://www.nejm.org/doi/full/10.1056/NEJMoa051378.)
Table 1

Versions of the Asthma Predictive Index

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Stringent API⁵</th>
<th>Loose API⁵</th>
<th>Modified API⁵⁻⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheezing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (≤3 years) frequent wheezing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (≤3 years) wheezing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4 episodes/yr during first 3 years of life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent with asthma</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MD-diagnosed Atopic dermatitis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sensitization to ≥1 aeroallergen</td>
<td>Not included</td>
<td>Not included</td>
<td>Yes</td>
</tr>
<tr>
<td>Minor criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheezing unrelated to colds</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Blood eosinophils ≥4%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MD-diagnosed Allergic rhinitis</td>
<td>Yes</td>
<td>Yes</td>
<td>Not included</td>
</tr>
<tr>
<td>Sensitization to foods (milk, egg, peanut)</td>
<td>Not included</td>
<td>Not included</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*For a positive API in each version, children must meet the wheezing criterion as well as at least 1 major criterion or at least 2 minor criteria.*

*Score of ≥3 on scale of 1–5 for wheezing (1 = "very rarely", 5 = "most days").