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PEDIATRIC ASTHMA: NATURAL HISTORY, ASSESSMENT AND TREATMENT

Ronit Herzog, MD[1] and **Susanna Cunningham-Rundles, PhD**[2]
Weill Medical College of Cornell University, New York, NY

Abstract

Wheezing and childhood asthma are not synonymous but rather comprise a heterogeneous group of conditions that have different outcomes over the course of childhood. Most infants who wheeze have a transient condition associated with diminished airway function at birth and have no increased risk of asthma later in life. However, children with persistent wheezing throughout childhood and frequent exacerbations represent the main challenge today. Studying the natural history of asthma is important for the understanding and accurate prediction of the clinical course of different phenotypes. To date, a great improvement has been achieved in reducing the frequency of asthma symptoms. However, neither decreased environmental exposure nor controller treatment, as recommended by the recent national asthma education and prevention program, can halt the progression of asthma in childhood or the development of persistent wheezing phenotype. This review focuses on the recent studies that led to the current understanding of asthma phenotypes in childhood and the recommended treatments.

Keywords

asthma; pediatric; phenotypes; exacerbation; treatment; inhaled corticosteroid (ICS); short acting beta agonist (SABA); long acting beta agonist (LABA)

Asthma is a heterogeneous disorder in children that is characterized by recurrent airway obstruction, bronchial hyper-responsiveness, and airway inflammation. Asthma presents with different phenotypes depending on age, gender, genetic background, and reflects antecedent events that have modified host response including environmental exposures(1) and epigenetic factors. Asthma is the most common chronic illness in children, affecting approximately 8.5% of children in the United States(2), and is a leading cause of childhood hospitalization and school absenteeism. Asthma is more prevalent in boys in the first years of life, but in adolescents it predominates among female subjects. Asthma affects minority and low-income groups disproportionately, with African American and Latino children who live in low-socioeconomic status urban environments experiencing higher asthma morbidity and mortality than white children(3, 4).

Increased prevalence of asthma among black compared with white children (unadjusted prevalence for asthma was 3.0% among white children and 7.2% among blacks) was associated with younger maternal age (2 standard deviation [SD] drop in age, relative odds (RO = 1.4),

Corresponding author: Ronit Herzog MD; roh9033@med.cornell.edu; tel, 917-669-1863; fax, 646-962-0246.
Postmail addresses, Ronit Herzog MD, Department of Pediatrics, Division of Allergy, Immunology and Pulmonology, Weill Medical College of Cornell University, 505 East 70th Street, New York, NY 10021
Susanna Cunningham-Rundles PhD, Department of Pediatrics, Division of Hematology and Oncology, Weill Medical College of Cornell University, 1300 York Avenue, New York, NY 10021

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residence in the city center (RO = 1.6), family income (RO for the lowest versus highest tertile, RO = 1.7), low birth weight (2 SD deficit in birth weight, RO = 1.4), and overweight or obesity (increase in odds of asthma for 2 SD increase in skinfold, RO = 1.6)(5). However, even after controlling for environmental exposures, parental history, and demographic factors, black children still had 1.6 times the odds of asthma diagnosis compared with white children(6) and are 2.5 times more likely to experience asthma-related emergency department visits and hospitalizations(7). Moreover, blacks were 5 times more likely to die from asthma than whites (8), which was more than the difference expected from the disparity in prevalence, and might be related to other issues such as access to care, exposure to smoking, and adherence to treatment among inner-city children.

This review describes the landmark studies that have led to the current understanding of the natural history of childhood asthma, and treatment options for prevention of asthma exacerbations. While the advent of new treatments has enhanced the quality of life for the asthmatic child and has undoubtedly ameliorated many associated or contributory conditions, loss of lung function and exacerbations remain the central problem. As discussed here, examination of the natural history of asthma in childhood and integrated assessment of phenotypes offer a valuable approach to clinical management and can prevent delay in recognition of clinical subtypes or treatment and promote improved outcome.

EARLY CHILDHOOD WHEEZING PHENOTYPES AND RISK FOR LATE CHILDHOOD ASTHMA

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Numerous excellent studies have contributed to our knowledge of wheezing phenotypes in children. One of the landmark childhood wheezing studies is the Tucson Children's Respiratory prospective birth cohort study which has provided detailed information regarding the natural history of asthma over the first 6 years of life(9–11).

In this study, approximately 51 percent of the children never wheezed, 20 percent were transient wheezers with at least one lower respiratory infection (LRTI) with wheezing during the first 3 years of life but no wheezing thereafter. 15 percent were late-onset wheezers with no LRTI associated wheezing during the first 3 years of life and wheezing at 6 years of age. 14 percent were persistent wheezers with at least one LRTI with wheezing during the first 3 years of life and still wheezing at 6 years of age(9). Overall, one third of children three years of age or younger had LRTI associated with wheezing, and almost 60 percent of these children stopped wheezing by the age of six years. This analysis was limited by the dichotomized outcome at 2 age points however, risk factors seemed to differ between the groups. Transient wheezers, who had diminished airway function shortly after birth(10) before any LRTI had occurred and at the age of six years(9), were more likely to have mothers who smoked, but not mothers with asthma (Table 1). Morgan et al reported that their lung function remains stable but lower than normal during the school years and at age 11 and 16(11).

Persistent wheezers showed no significant difference in pulmonary function testing at birth and before 1 year of age in comparison to non-wheezers. However, at age 6 persistent wheezers had significantly lower forced expiratory flows compared with non-wheezers or late wheezers, which persisted at 11 and 16 years of age(11).

In the British Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, data on wheezing was obtained at 7 time points from birth to 7 years of age and confirmed the temporal wheezing patterns from the Tucson Children's Respiratory Study, as well as the contribution of associated risk factors(12). This analysis also suggested additional phenotypes including an intermediate-onset wheeze phenotype (onset of symptoms after 18 months of age) and another phenotype with early prolonged wheeze (onset in the first year of life but remission at 69 months of age). Similarly, Sears el at(13) found that patients with persistent wheezing in early adulthood had consistently lower lung function that was measured in this study from age 9 to 26 years of age, as assessed by the ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC), when compared to non-wheezers. These patients had no further losses of lung function when compared to age 9, regardless of the severity of their symptoms. The study showed that lung function was persistently impaired throughout the transition from childhood into adulthood in patients with persistent asthma. Therefore the investigators concluded that impairment of lung function had occurred in early childhood before the first study measurement was made at 9 years of age.

Thus, significant loss of pulmonary function in children with persistent wheezing, seems to be acquired after birth during the first years of life before age 6. Lung function does not appear to change significantly by adolescence or early adulthood for patients who wheeze during their preschool years.

> [Callout] Significant loss of pulmonary function in children with persistent wheezing seems to be acquired after birth during the first years of life.

Persistent wheezers are more likely to have mothers with a history of asthma ($p<0.001$), and to have been exposed to maternal smoking. They show elevated serum IgE levels at 9 month of age ($P<0.01$) but not in cord blood, and often have eczema, and rhinitis which is not associated with respiratory infection. Maternal smoking is likely to cause decreased airway growth in utero, enhanced bronchial responsiveness(14); and diminished lung function at birth (9, 15). Therefore, maternal smoking is the only risk factor common to both transient and persistent wheezers.

> [Callout] Persistent wheezers are more likely to have mothers with a history of asthma and to have been exposed to maternal smoking. The children show elevated serum IgE with eczema and rhinitis that is not associated with respiratory infection.

Lower pulmonary function at age 6, but not at birth in persistent wheezers, suggests that elevated serum IgE levels, airway inflammation and bronchial hyper-responsiveness(16, 17) may be associated with abnormal airway function. Late wheezers did not experience deficits in lung function.

Stein et al characterized three main childhood asthmatic phenotypes based on serum IgE and skin test reactivity at age 6 and 11, methacholine responsiveness and peak flow variability at age 11(1). The transient early wheezing phenotype in the first three years of life was not associated with airway hyper-responsiveness or peak flow variability. Non-atopic wheezing at ages 3 and 6 was associated with peak flow variability, but not with methacholine responsiveness. The persistent atopic wheezing phenotype was associated with elevated serum IgE, positive skin testing, methacholine hyper responsiveness, and peak flow variability (Table 1). Another birth cohort study by Illi et al reported that a chronic course of asthma characterized by airway hyper-responsiveness and impairment of lung function at school age is determined by continuing allergic airway inflammation beginning in the first 3 years of life. In this study, children with a non-atopic wheezing phenotype lost their symptoms during school years and retained normal lung function at puberty(18). In addition, the Childhood Asthma Management Program (CAMP) study, which looked at predictors of remitting, periodic, and persistent asthma, observed that remission was associated with lack of sensitization and allergen

exposure, milder symptoms, older age, higher FEV1, and less bronchial hyper-responsiveness (19).

Considering the multiple causes of wheezing among preschool children and the heterogeneity of childhood asthma, a useful Asthma Predictive Index for the development of persistent asthma in children younger than 3 years of age, who had more than 3 episodes of wheezing during the prior year, was developed by Castro-Rodriguez(20, 21). A positive API requires documentation of recurrent episodes of wheezing during the first 3 years of life and one of two other major criteria (physician-diagnosed eczema or parental asthma) or 2 of 3 minor criteria (physician-diagnosed allergic rhinitis, wheezing without colds, or peripheral eosinophilia ≥4%). A positive stringent API (≥3 episodes of wheeze per year and 1 of the major or 2 of the minor criteria by age 2 years) was associated with a 77% chance of active asthma from ages 6 to 13 years. A negative API at 3 years of age had less than a 3% chance of having active asthma during the school years (Table 2). The stringent API has the best combination of sensitivity (although low at 22%, at 6–8 years of age, and 16% at 6–13 years of age), excellent specificity (97%, at 6–13 year of age), and good predictive value of indices when compared to other scores to predict which preschoolers with recurrent wheezing would have asthma at school age(21). Furthermore, the API has been tested in different populations and in randomized clinical trials. The stringent API is a simple, inexpensive tool which can be used worldwide to identify children at risk for asthma. The most important practical aspect of the API is its ability to rule out the likelihood of asthma by school age in young children with wheezing. Future scores may need to include more variables such as genetic polymorphisms, environmental and socioeconomic factors, sex, and ethnicity.

EVALUATION OF ASTHMA IN CHILDREN

The diagnosis of asthma includes determination of recurrent episodes of airflow obstruction that are at least partially reversible or airway hyper-responsiveness while excluding alternative diagnoses(22). However, not all children are able to perform spirometry or impulse oscillometry. Thus, the diagnosis of asthma in young children is based on individual history, physical examination and their response to treatment.

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The history in children should include information about maternal smoking during pregnancy, presence of night or early morning cough, and breathlessness or chest tightness that is relieved by short acting beta2 agonists (SABA). The history should also include information about oral corticosteroids use for exacerbation, emergency department visits or hospitalizations and the triggers for exacerbation (such as upper respiratory infections, an exposure to environmental allergens, tobacco, irritants, change in temperature), and whether symptoms are perennial or seasonal. Family history of asthma is also helpful in assessing the risk and API.

Physical examination should include observation for distress or increased work of breathing, vital signs, height, weight, oxygen saturation in room air, evaluation of the upper respiratory tract (including examination of the nasal turbinates to assess for allergic rhinitis, post nasal drip and presence of nasal polyps), presence of tonsils, and auscultation of the larynx to assess for vocal cord dysfunction. Examination of the chest is important for assessment of malformation, hyperexpansion thorax, use of accessory muscles, and sign and symptoms of airways obstruction. Examination of the skin and the nails is important for the assessment of presence of atopic dermatitis or clubbing.

Spirometry is recommended to assess the forced flow volumes in children older than 4 years of age. Testing before and after inhalation of SABA bronchodilator can indicate bronchial

hyper-reactivity, large or small airways obstruction and reversibility (defined as an increase in FEV1 of >12 percent from baseline, or an increase >10 percent of predicted FEV1 after inhalation of SABA). Observational and non-randomized studies suggest that low FEV1/ FVC is a more sensitive measure of severity in the impairment domain of asthma assessment, while FEV1 is a useful measure of risk for exacerbations. The recent National Asthma Education and Prevention Program, (NAEPP) expert panel repport-3 (EPR-3)(23) includes the FEV1/ FVC as part of the severity classification for children. When airway obstruction is present testing of lung volume is warranted.

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The degree of airway reversibility correlates with airway inflammation, which can be measured by sputum eosinophils and fractional exhaled nitric oxide (FeNO)(24). In addition, patients who have a high degree of reversibility in response to SABA may be at the greatest risk of developing fixed airflow obstruction and loss of lung function. The post bronchodilator FEV1 measure can then be used to follow lung growth patterns over time.

While assessment of surrogate markers of inflammation, including sputum eosinophil count, exhaled nitric oxide, breath condensate and peripheral eosinophilia, is not routinely recommended by the NAEPP guidelines for diagnosis and management of asthma, it can be helpful in further characterizing asthma phenotype and individualizing treatment. Total IgE is important when considering omalizumab treatment (recombinant humanized monoclonal anti-IgE antibody), and the differential diagnosis of allergic bronchopulmonary aspergillosis (ABPA).

Bronchoprovocation with methacholine, cold air or exercise challenge are useful when spirometry is normal with minimal bronchial hyper-reactivity. A positive methacholine bronchoprovocation test is diagnostic for airway hyper-responsiveness, a characteristic feature of asthma but can be present in other conditions such as allergic rhinitis. Therefore, a positive test is consistent with asthma, while a negative test may be more helpful to rule out asthma.

Chest x-ray is helpful for assessment of peribronchial cuffing, hyperinflation and atelectasis. Further imaging may be needed if other diagnosis is suspected. Immune evaluation is needed in non-classical presentations, such as recurrent productive cough, recurrent otitis, sinusitis or pneumonia.

INDOOR AND OUTDOOR ENVIRONMENTAL FACTORS

Indoor and outdoor allergens and pollutants cause asthma symptoms, lead to exacerbations and influence the risk of developing asthma in children (Table 5).

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Allergens lead to increased airway inflammation through an IgE mediated mechanism. Pollutants however, may elicit inflammation by generation of free radicals on exposed airway epithelium(25) . Allergic sensitization is an important risk factor for childhood asthma, leading to 4–20 fold increase in the risk for asthma(26–28). As discussed before, children who were sensitized to a perennial allergen during the first 3 years of life were more likely to have decreased lung function at age 13 years; and those with concomitant exposure to the allergen have the worse lung function(18). Sensitivity to indoor allergens is more prevalent than sensitivity to outdoor allergens in inner-city children with asthma(29). This evidence underscores the importance of indoor allergens in childhood asthma.

Studies also suggest that pollutants can lead to epigenetic changes that may increase the risk of asthma.

Nadeau et al(30) found that children with asthma who were exposed to high levels of air pollution had increased methylation of forkhead box P3 (FOXP3) and decreased chemotaxis of T regulatory cells compared to healthy children and asthmatic children who were not exposed. Similarly, in utero exposure to tobacco has been associated with DNA hypermethylation in infants(31). Studies(32–34) have also identified genetic susceptibility factors that increase an individual's risk for developing asthma. Factors such as polymorphisms of glutathione transferase gene when combined with exposure to pollutants may determine an individual's risk for developing asthma. Wu et al(35) found that children with high mold exposure who were homozygous for a single nucleotide polymorphism (SNP) for the CHIT1 gene (encodes an enzyme that cleaves chitin) were at an increased risk for hospitalization from asthma exacerbation. This study suggests that there are underlying individual genetic susceptibility factors for environmental exposures.

Multifaceted environmental interventions to decrease indoor air pollutants and allergen exposure were found to be effective in decreasing childhood asthma morbidity. Therefore, it is important to evaluate for allergic sensitization and counsel the patient regarding the impact of their indoor environment on their respiratory health. Causal relation between exposure to pollutants and allergens and the subsequent development of asthma have been demonstrated most strongly for dust mite allergen and second hand smoking.

ASTHMA EXACERBATION IN CHILDREN

Most clinical manifestations of asthma in childhood involve intermittent episodes of cough and wheezing, called exacerbations. Wheezing is likely a result of turbulent air flow through narrowed large, central airways that causes oscillation of bronchial walls. A flow of air in narrowed peripheral small airways is slow and therefore does not generate audible oscillation, unless it causes a dynamic compression of the central airways.

Thirty percent of children with persistent asthma who are taking inhaled corticosteroids (ICS) as a controller medication, which decreases airway inflammation and reduces the risk for exacerbations, have one or more episodes of asthma exacerbation requiring oral corticosteroid treatment in a year(36). Similarly, in the Pediatric Asthma Controller Trial (PACT), 39% of children who were treated with 100 mcg fluticasone twice daily, had at least one exacerbation requiring oral steroid during the 48 week treatment period(37). Asthma exacerbation is the most important cause of loss of school days for children with asthma(38) and involves three times higher health care costs than for patients who do not experience an exacerbation(39). Most episodes of asthma exacerbation in preschool aged children involve signs of airway obstruction, cough and wheezing associated with a cold(40) that is caused by viral infection, primarily rhinovirus (41).

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Asthma exacerbation also occurs when viral infections and increased exposure to allergens occurs in a sensitized subject(42). Allergic inflammation and viral respiratory infections can injure airway epithelium and may act synergistically to promote exacerbations(43). Furthermore, rhinovirus replication is increased in damaged epithelium, and it is possible that the underlying allergic inflammation serves to enhance viral growth, driving more severe respiratory infections and promotes exacerbation(44, 45). Respiratory syncytial virus (RSV) LRTI in early childhood is an independent risk factor for wheezing and subsequent

development of wheezing up to age 11 years. This association is not caused by an increased risk of allergic sensitization and appears to be independent of other known risk factors for asthma such as family history of asthma or atopy. RSV associated LRTI was not associated with an increased risk for allergic sensitization(46).

Factors such as aberrations in the innate immune response to viruses in the asthmatic patient can determine the risk for exacerbation. Wark et al(47) found that bronchial epithelial cells from asthmatic patients that were infected with rhinovirus[16], had a 50 fold increase in viral RNA expression and a 7 fold increase in late virus release into the supernatant when compared with healthy control subjects. There was an impaired virally induced apoptotic response of bronchial epithelial cells from subjects with asthma when studied in vitro. In addition the interferon-beta messenger RNA response was lower less in the early phase after viral infection compared to healthy individuals. Adding interferon-beta to the cell cultures partially restored the immune response in cells of asthmatic patients. Contoli et al(48), showed that bronchial epithelial cells and alveolar macrophages from asthmatic subjects demonstrated deficient induction of interferon-lambda when infected with rhinovirus.

Sputum induced during asthma exacerbation demonstrates the heterogeneous nature of asthma exacerbations in children. Features range considerably and can include either increased neutrophils with few eosinophils, increased eosinophils and also neutrophils, and an increase in neither eosinophils nor neutrophils (49, 50). The fact that neutrophils are the predominant cells in a significant proportion of asthmatic exacerbations(49) has suggested that these asthma patients may be less sensitive to ICS controllers(51) and this may play a role in the pathogenesis of asthma exacerbation. However there is insufficient evidence to support treatment based on sputum eosinophilia.

Analysis of the CAMP(36, 52) has shed light on the predictors for asthma exacerbation in children. Children with persistent asthma symptoms were at greater risk for emergency department visits, hospitalizations or requirement for systemic corticosteroids. Predictors of having severe asthma exacerbation were younger age, history of hospitalization or emergency department visit in the prior year, oral corticosteroids in the prior three months, lower FEV1/FVC ratio, lower provocative concentration of methacholine causing 20% fall in FEV1 (PC20) and higher log 10 eosinophil count. Additional predictors for severe exacerbations in children include persistent airflow obstruction on spirometry, a history of intubation or admission to the intensive care unit(53–56). The strongest predictor for risk of exacerbations is a history of previous exacerbation(53, 57). Predictors of persistent asthma are different from predictors of severe asthma exacerbations. Children who are at risk for exacerbations from asthma may not experience greater asthma symptoms prior to the event(58). Persistent symptoms were associated with severe exacerbation, however, since 14% of subjects in the CAMP study(52) never had persistent symptoms during the four years of the trial, yet experienced one or more severe exacerbations. This study supports the 2007 NAEPP guideline recommendations for definition of intermittent asthma, which is no longer categorized as mild intermittent asthma since even patients with intermittent asthma can have exacerbations.

TREATMENT

The recent NAEPP EPR-3 asthma guidelines require assessment of asthma severity to initiate therapy and assessment of asthma control to adjust therapy in a stepwise approach (Tables 3–4). The guidelines recommend assessment of control in children with asthma at 2–6 week intervals for patients who are just starting therapy or who require step up in therapy, at 1–6 month intervals after asthma control is achieved and at 3 month intervals if a step down in therapy is anticipated. The assessment of severity and control includes two domains:

1. *Impairment*. Assessment includes an evaluation of the frequency and intensity of symptoms, nocturnal awakenings, use of quick-relief medications, and level of lung function.
2. *Risk*. Evaluation includes an assessment of the likelihood of asthma exacerbations (22).

The goals of asthma therapy in children include reducing impairment by preventing symptoms and reducing risk by preventing exacerbations.

There is evidence that use of controller medication is effective in preventing asthma exacerbations in children who are two years of age or older. In the CAMP study, children age 5–12 who received 200 mcg budesonide twice daily required significantly less oral prednisone for exacerbation when compared to placebo(36). However, despite daily ICS for a period of 4–6 years there was no effect on airway function, growth and FEV1 after bronchodilator use, when compared with children who were treated with nedocromil or placebo(36). In addition, there was a 1.1 cm lower mean increase in height in the budesonide group compared to the placebo group (22.7 vs. 23.8 cm, P=0.005), which was evident primarily within the first year of treatment, with normal growth velocity by the end of the treatment period. Parallel changes in bone density were observed as well. At the end of treatment, the bone age, projected final height, and Tanner stage were similar to the placebo group. ICS treatment in asthma was also not associated with increased risk for pneumonia(59).

Another study that involved ICS use, the inhaled Steroid Treatment as Regular Therapy in early asthma (START), was designed as a randomized, double-blind, 3 year trial that evaluated whether early intervention using low dose ICS would prevent severe asthma exacerbations and accelerated decline in lung function in over 7,000 patients with less than 2 years of mild, persistent asthma(60). While the study revealed that patients on ICS compared with placebo had significantly less risk for a severe asthma exacerbation, had fewer courses of systemic corticosteroids, required less additional medications, and had more symptom free days, both budesonide and placebo treated groups showed a reduction in post bronchodilator FEV1 percent predicted over 3 year period. Although the ICS group incurred less decline in lung function compared with the placebo group (mean difference of 0.88, P<0.0005), the differences in the 3 year change in post bronchodilator FEV1 between the budesonide and placebo treated groups were narrower in the 5 to 10 year age group and even reversed in favor of placebo in the 11–17 year old age group.

These data strongly suggest that low dose ICS therapy has limited benefit compared with placebo in preventing reduction of post bronchodilator FEV1 percent predicted in children with mild persistent asthma even at an early onset. The limitations were possibly due to corticosteroid independent mechanisms such as neurogenic inflammation(61) or subepithelial fibrosis and increased deposition of elastin(62).

A trial of ICS controller treatment for preschool children age 2–5 years, who had a high risk for asthma, was carried out in the Prevention of Early Asthma in Kids (PEAK) study. Children received 2 years of 88 mcg fluticasone twice daily. The investigators demonstrated significant less frequent exacerbations, more symptom free days, and decreased use of controller medications, when compared to placebo(63). However, the two years of therapy did not change the development of asthma symptoms or prevent decline in lung function during a third, treatment-free year.

ICS is now recommended as the first line treatment for children with persistent asthma (Table 4), but has not been shown to have a disease-modifying effect in young children after the

treatment is discontinued as noted in the investigation described above and in other studies as well(64, 65).

> [Callout] ICS is now recommended as the first line treatment for children with persistent asthma (Table 4), but has not been shown to have a disease-modifying effect in young children.

An alternative controller to ICS for children with persistent asthma is montelukast. The use of daily montelukast among children with persistent asthma has decreased the likelihood of mild, but not severe, asthma exacerbations compared with placebo(66). In addition, low dose fluticasone for children with mild to moderate persistent asthma, has the advantage of lower cost and higher effectiveness compared with montelukast, especially for those children with more airway inflammation, as indicated by increased levels of eNO(67).

However, despite the significant decrease in exacerbations, approximately 30% of children receiving ICS alone or in combination with long acting beta2 agonist (LABA) do experience exacerbation(36, 37). To address this problem, Ducharmeet al(68) followed preschool children age 1–6 years (83% were 1–3 years of age) with history of three or more episodes of virally-induced wheezing and no suspected environmental allergies. They provided preemptive treatment with high-dose fluticasone (750 mcg twice daily) at the first sign of upper respiratory tract infection (URI) such as rhinorrhea or nasal congestion, and compared this treatment to the placebo group. Albuterol was given for cough, wheezing or dyspnea. The use of fluticasone reduced the need for rescue oral corticosteroids from 18 percent in the placebo group to eight percent in the fluticasone group. Although the proportion of symptoms of dyspnea, wheezing or cough, acute care visits, and hospital admissions did not differ significantly between the groups, children in the fluticasone group had shorter duration of symptoms and required fewer days of albuterol use. In this study, treatment with fluticasone was associated with a smaller gain in height and weight compared to placebo(68). The post hoc analyses showed a significant correlation between the cumulative dose of fluticasone and the change in height ($r = -0.21$, $p = 0.02$) but not in weight ($r = -0.11$, $p = 0.21$), which was the same magnitude of the effect observed with 1 year treatment with daily low dose fluticasone (200 mcg) in preschool children (63). There were no significant group differences in the change in lumbar bone mineral density, bone mineral content, or bone age.

In the Best Add-on Therapy Giving Effective Responses (BADGER) trial, the best step-up therapy for children age 6–17 years of age with uncontrolled asthma while receiving ICS was studied(69). In this study, Lemanske at al concluded that LABA step-up was significantly more likely to provide the best response as measured by asthma exacerbation, asthma-control days and FEV1 than either ICS or LTRA step up alone. A better asthma control at baseline was associated with a higher probability that LABA would be the best add-on therapy.

Black children were equally likely to have a best response to LABA or ICS step-up therapy but were least likely to have a best response to LTRA step-up alone. In contrast, in white subjects, LABA step-up was most likely to provide the best response. However the potential increased risk of asthma related exacerbation and death associated with LABA should not be underestimated as summarized by the Food and Drug Administration's approved labeling (70). It is not known whether there are similar risks when LABAs are added to inhaled corticosteroids. Therefore, the FDA issued a requirement to conduct controlled clinical trial to assess the safety of a regimen of LABAs plus inhaled corticosteroids as compared with inhaled corticosteroids alone for children 4 to 11 years, adolescent and adults.

In contrast, Price et al(71) recently conducted two multicenter real-life community open label studies that evaluated the effectiveness of LTRA as compared with ICS for first-line asthma controlled therapy, and as compared with LABA for an add-on therapy for patients already

receiving ICS. At 2 months, the LTRA was essentially equivalent in efficacy to either the ICS as first-line controller therapy or to the LABA as add-on controller therapy. This study was limited by a lack of crossover between treatment groups and the lack of a placebo group, but may reflect the real world when taking a pill once a day is easier than using an inhaler twice a day. The rate of adherence to the oral LTRA was 65% and 74% in the first-line controlled and add-on therapy trial respectively, as compared to 41% and 46% for ICS.

Patients with allergic asthma that are not controlled with implementation of higher treatment step up were considered in the recent NAEPP guidelines. The recommendation was to use omalizumab,(22, 72, 73). Omalizumab forms a complex with free IgE thus blocking its interaction with mast and basophil cells. In the recent Inner City Anti-IgE Therapy for Asthma (ICATA) Study patients with persistent asthma ages 6–20 with at least one positive skin test for a perennial allergen and IgE between 30–1300 IU per milliliter, were randomized in a double-bind, placebo controlled trial to parallel groups receiving omalizumab or placebo. Omalizumab reduced exacerbations, symptoms and the dose of ICS needed to control disease (72, 74). The benefit of omalizumab was greatest in participants who were both sensitized and exposed to cockroach or dust mite allergens and revealed an especially marked reduction in spring and fall seasonal exacerbations(75). Other medications such as theophylline and nedocromil are also included as an alternative therapy in the NAEPP guidelines, but are not frequently used, and therefore were not discussed in detail.

CONCLUSION

Despite many significant accomplishments in managing asthma in children, the goal of current medical practices to alter the natural history of the disease has not been achieved. Studies support the value of the recent NAEPP step wise approach to treatment, but preventing exacerbations remains the most important and challenging goal for asthma management in childhood. Indoor and outdoor allergens and pollutants cause asthma symptoms, lead to exacerbations and influence the risk of developing asthma in children. The association of genetic susceptibility factors and host modifier genes in asthma is currently a major area of investigation. Continued research efforts to understand the natural history of asthma may facilitate the development of early and personalized intervention for asthma in childhood.

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Table 1

Presentation and Risk Factors for Different Wheezing Phenotypes in Childhood

Type: Early Transient Wheezing **Presentation:** Lung function diminished at birth and remains reduced at age 6 and 11	**Risk Factors:** • Maternal smoking during pregnancy • Post-natal exposure to tobacco smoke • Prematurity • No family history of asthma or atopy • No peak flow variability or methacholine responsiveness • No elevated serum IgE or skin test reactivit
Type: Atopic Persistent Wheezing **Presentation:** Normal lung function at birth with diminished (lowest) lung function at age 6 and 11	**Risk Factors:** • Maternal asthma, maternal smoking • Genetic pre-disposition for sensitization to aero-allergens • Allergic sensitization and chronic airway inflammation<1 year • Atopy, elevated serum IgE at 9 months of age and at age 6, but not in cord blood • Eczema, rhinitis apart from cold • Early onset wheezing and severe disease • Peak flow variability and methacholine responsiveness
Type: Non-atopic Persistent Wheezing **Presentation:** Normal lung function at birth with diminished lung function at age 6	**Risk Factors:** • Maternal smoking • Lower respiratory illnesses in the first 3 years • RSV before 3 years of age associated with wheeze at age 10 • Peak flow variability but no methacholine responsiveness
Type: Late Onset Wheezing **Presentation:** Normal lung function at birth and at age 6	**Risk Factor:** • Maternal asthma • No elevated IgE at 9 month of age

Table 2

Asthma Predictive Index (API)

Early frequent wheezing in the first 2 years of life plus at least 1 major criteria:
1 Parental asthma
2 Eczema at age 2–3
or at least 2 minor Criteria:
1 Allergic rhinitis at age 2–3
2 Wheezing apart from colds
3 Eosinophilia (≥ 4%

Table 3

Asthma Control in Children

	Well Controlled			Not Well Controlled			Very Poorly Controlled		
Age (years)	**0–4**	**5–11**	**>12**	**0–4**	**5–11**	**>12**	**0–4**	**5–11**	**≥12**
Impairment									
Symptoms days/week	≤ 2	≤ 2	≤ 2	> 2	> 2	> 2	throughout the day		
Night awakening/month	1	≤ 1	≤ 2	> 1	≥ 2	1 to 3	> 1/wk	≥ 2	≥ 4
SABA/week	≤ 2	≤ 2	≤ 2	> 2	> 2	> 2	several times/day		
Activity interference	none	none	none	some limitations			extremely limited		
Lung function									
FEV1 %	-	> 80	> 80	-	60 to 80	60 to 80	-	< 60	< 60
FEV1/FVC %	-	> 80		-	75 to 80		-	< 75	
Questionnaire									
ATAQ			0			1 to 2			3 to 4
ACQ			≤ 0.75			≥ 1.5			N/A
ACT			≥ 20			16 to19			≤ 15
Risk									
Exacerbations/year	0 to 1	0 to 1	0 to 1	2 to 3	2 to 3	0 to 1	> 3	≥ 2	> 3

Modified from the 2007 NAEPP EPR-3. *SABA*- short acting beta2 agonist, *FEV1*-forced expiratory volume in 1 second, *FVC*- forced vital capacity.

Table 4

Asthma Severity in Children

	Intermittent			Mild Persistent			Moderate Persistent			Severe Persistent		
Age (years)	0–4	5–11	≥ 12	0–4	5–11	≥12	0–4	5–11	≥12	0–4	5–11	≥ 12
Impairment												
symptoms days/week	≤ 2	≤ 2	≤ 2	> 2	> 2	> 2	daily	daily	daily	throughout the day		
Night awakening /month	0	≤ 2	≤ 2	1 to 2	3 to 4	3 to 4	3 to 4	> 1/w	> 1/w	>1/w	7/w	> 7/w
SABA days/week	≤ 2	≤ 2	≤ 2	> 2	> 2	> 2	daily	daily	daily	several times/day		
Activity interference	none	none	none	minor	minor	minor	some	some	some	extremely limited		
Lung function												
FEV1 %	-	> 80	> 80		≥ 80	> 80		60 to 80	>60 <80		< 60	< 60
FEV1/FVC %	-	> 85	85		> 80	> 80		75 to 80	red 5%		< 75	red>5 %
Risk												
Exacerbations/year	0–1	0–2	0–1	≥2/6mo	> 2	≥ 2	> 2/6mo	> 2		> 2/6mo	≥ 2	≥ 2
Treatment	Step 1: SABA PRN			Step 2: low dose ICS			Step 3 or 4: ICS + LABA			Step 5 or 6: high dose ICS + LABA		
Alternative				LTRA			ICS +LTRA			Omalizumab		
Immunotherapy				+			+					

Modified from the 2007 NAEPP EPR-3. *SABA*- short acting beta2 agonist, *LABA*-long acting beta2 agonist, *ICS*- inhaled corticosteroid, *LTRA*- leukotriene receptor antagonist, *FEV1*-forced expiratory volume in 1 second, *FVC*- forced vital capacity.

Table 5

Indoor Environment Effect on Childhood Asthma

Indoor air pollutants	Source, Effect and Recommended Intervention
Ambient air pollutants Particulate matter (PM) PM10 (diameter < 10 um, entering respiratory tract) Fine PM2.5 (diameter < 2.5um, entering alveoli)	• Indoor sources: cooking exhaust, wood burning stoves/fireplaces, re-suspended particles from cleaning • Increased airway reactivity, asthma exacerbations, respiratory symptoms, altered host defense(76–79) • Decreased lung function and increased respiratory symptoms in children(80–82), provoke lung inflammation • Exposure to high levels PM2.5 in children with asthma-associated with elevated FeNO(83) • Causal link between exposure to PM and the development of asthma has not been established, but such a relationship may exist: children exposed to outdoor PM in utero or in the first year of life were at increased risk of having asthma at age 3–4 years(84) • Intervention: high-efficiency particulate air (HEPA) filters- lowers the concentration of indoor PM; modest effect on reducing asthma symptoms(85–87)
Nitrogen dioxide (NO2)	• Indoor sources: gas stoves, space heaters, furnaces, fireplaces • Children exposed to ambient NO2 in utero or in the first year of life had an increased prevalence of asthma in early childhood(84) • Exposure to indoor NO2 was linked to asthma exacerbation(88–91) and increased respiratory symptoms in children with asthma • The association between NO2 and increased respiratory symptoms was stronger for non-atopic asthmatics than for atopic asthmatics(89) • Pathophysiology: NO2 may cause respiratory symptoms by producing extracellular reactive oxygen species that interact with antioxidants in the lung epithelial layer(92, 93): increased respiratory symptoms in patients with allergic asthma • Intervention(94): mean indoor NO2 was decreased by over 60% through the replacement of unflued heaters with flued heaters, with a concordant decrease in asthma symptoms in children
Second hand smoke (SHS)	• There is a causal relationship between second hand smoking exposure and asthma incidence and morbidity in children(25, 95–99) • SHS exposure in utero through maternal smoking was linked to decreased lung function, recurrent wheeze, and increased incidence of asthma in infants(100–103) • In-utero smoke exposure was associated with an increased risk of corticosteroid resistance among adolescents with asthma(104) • Intervention to reduce SHS exposure for children had limited success(105, 106). However, a recent study in Scotland (107) demonstrated a reduction in the rate of asthma related hospitalizations for children by 18.2% per year, following a smoking ban in public places in Scotland(107)
Indoor allergens	**Effect and Recommended Intervention**
Mouse allergen	• Source: urinary allergens excreted and carried on airborne particles(108) • Most inner-city and suburban homes have detectable mouse allergen levels(109–113) • 18–50% of inner-city youth are sensitized to mouse allergen(113, 114), less common in rural/suburban (112, 115) • Mouse sensitization and exposure in children with asthma is associated with increased hospitalizations, increased respiratory symptoms, decreased lung function, and increased airways inflammation(114, 116) • Sensitization to mouse allergen has been causally related to early wheeze in on study(117): mouse allergy could increase the risk of developing asthma • Intervention: integrated pest management (IPM) (extermination, cleaning, food disposal, sealing of cracks) • A reduction in mouse allergen levels by at least 50% has been associated with reductions in missed school and days with decreased activity among mouse-sensitized inner-city children(116)
Cockroach	• Source: at least half of inner-city homes have clinically relevant levels of cockroach allergen, 30% of suburban, middle class homes have detectable levels of cockroach allergen(118) • In inner-city, 60–80% of children with asthma are sensitized to cockroach(119, 120)

Indoor air pollutants	Source, Effect and Recommended Intervention
	• Sensitization to cockroach allergen has been linked to the development of wheeze in young children(117), poorer asthma outcomes in inner-city children with asthma and increased asthma related healthcare utilization(120, 121) • Intervention: IPM reduced cockroach allergen levels by 80–90%(122) • The effect of this reduction on asthma morbidity is unknown; but the strong link between cockroach allergen exposure and asthma morbidity supports recommending an IPM approach to reduce exposure
Cat or dog	• Source: the allergen was found in all homes; concentrations were 10–1000 fold lower in homes without pets (123, 124). Allergic sensitization to cat and dog is common • Pet allergen exposure has been linked to poorer asthma outcomes in sensitized patients with asthma(125, 126) • Some studies suggested that pet exposure may be protective against allergy(127–129) • Indoor pet exposure for children was associated with lower total IgE levels at age 18 years among atopic patients only(130), indicating that the protective effect of early life pet exposure that was observed at 6–7 years(129) was mostly lost by 18 years • In contrast to these studies, a recent study in Norway(131) found that cat allergen exposure during early life led to an increased risk of asthma at age 10 years, but not to an increased risk of animal sensitization • Intervention: further studies are needed to determine the role that early life pet allergen exposure may play in the development of asthma: until that time, there is not sufficient evidence to recommend early exposure to or removal of pets from the homes of children at risk for the development of asthma
Dust mites	• Source: allergic sensitization depends on the humidity of the climate • Dust mite allergen exposure has been causally linked with the development of asthma in susceptible children (26) and with asthma exacerbations in sensitized individuals • Intervention: the 2007 NAEPP guidelines recommend installation of allergen-proof mattress and pillow encasements, washing of all bedding every 1–2 weeks in hot water, removal of stuffed toys, reduction of indoor humidity, and regular vacuuming and dusting. These strategies reduce asthma symptoms, medication requirements, and improve lung function(132, 133) • 2008 meta-analysis(134): dust mite control measures do not improve clinical outcomes in patients with dust mite allergy. Platts-Mills(135) suggested that due to variability in methods among studies the current practices of dust mite control should not be changed
Molds	• Allergic responses to inhaled mold allergens are associated with increased asthma symptoms • Alternaria, found indoors and outdoors is associated with increases in asthma symptoms, bronchial hyper-responsiveness, and severe asthma in sensitized individuals(136–138) • Exposure to high levels of indoor Penicillium was associated with increases in symptoms in children with asthma(139) • Sensitization to mold was associated with increased frequency of asthma symptoms • Poor asthma control in children has been linked to the presence of visible mold at home(140) • Intervention: reduction of mold levels may be beneficial in controlling asthma symptoms • Removing molds and eliminating leaks and moisture sources at homes to help reduce asthma symptoms (141)