

REVIEW

Can early intervention in pediatric asthma improve long-term outcomes? A question that needs an answer

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Abstract

Objective: Although many children with asthma do not experience persistence into adulthood, recent studies have suggested that poorly controlled asthma in childhood may be associated with significant airflow obstruction in adulthood. However, data regarding disease progression are lacking, and clinicians are not yet able to predict the course of a child's asthma. The goal of this article was to assess the current understanding of childhood asthma treatment and progression and to highlight gaps in information that remain.

Data Sources: Nonsystematic PubMed literature search and authors' expertise.

Study Selection: Articles were selected at the authors' discretion based on areas of interest in childhood asthma treatment and progression into adulthood.

Results: Uncontrolled asthma in early childhood can potentially have lasting effects on lung development, but it is unclear whether traditional interventions in very young children preserve lung function. Although not all children respond to standard interventions, certain asthma phenotypes have been identified that can help to understand which children may respond to a particular treatment.

Conclusion: Clinicians should monitor children's asthma control and pulmonary function over time to assess the long-term impact of an intervention and to minimize the effect of uncontrolled asthma, especially exacerbations, on lung development. New biologic therapies have shown promise in treating adults with severe, uncontrolled asthma, and some of these therapies are approved in the United States for children as young as age 6. However, knowledge gaps regarding the efficacy and safety of these treatments in younger children hamper our understanding of their effect on long-term outcomes.

KEYWORDS

biologic, biomarkers, childhood, progression

1 | INTRODUCTION

Pediatric asthma is a chronic lung disease characterized by airflow obstruction and airway hyperresponsiveness.^{1,2} The 2018 Global Initiative for Asthma (GINA) report defines two major long-term goals

of asthma management: (i) to maintain good control of symptoms with no restrictions on activity level and (ii) to limit future exacerbation risk, adverse effects, and fixed airflow limitation.² Additional goals of therapy include minimizing the necessity for short-acting β_2 -agonist (SABA) use and preventing progressive loss of lung function. This

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concept of managing future risk is gaining momentum, yet only a small number of studies have investigated the long-term effects of asthma treatment from childhood into adulthood. Furthermore, evidence-based guidelines appear to have had little impact on improving outcomes, suggesting that a new approach is warranted.³ The paradigm of childhood asthma management is shifting toward more personalized therapies and earlier intervention.^{4,5} In this narrative review, we discuss the current understanding of childhood asthma treatment, what is known about the long-term effects of these treatments, and highlight open questions that remain.

2 | THE NATURAL HISTORY OF PEDIATRIC ASTHMA

Similar to adult asthma, the underlying etiology of pediatric asthma symptoms is chronic airway inflammation. Pediatric patients may present with a number of respiratory symptoms, including wheezing, shortness of breath, cough, and reductions in forced expiratory volume in 1 s (FEV₁).² Symptom presentation can vary significantly over time. Furthermore, serial measurements of lung function over time are usually limited to patients with the most severe asthma and seldom evaluated over time in less severe patients. Unfortunately, measurement of lung function and other physiologic tests are not feasible for the younger population aged <6 years. Overall, there is a paucity of data investigating diagnosis and treatment of asthma in very young children (aged ≤5 years). Figure 1 outlines criteria for asthma diagnosis by age group, which are adapted from the GINA report.² Furthermore, the British Thoracic Society/Scottish Intercollegiate Guidelines Network asthma guidelines suggest obtaining fractional concentration of exhaled nitric oxide (FeNO), airway responsiveness, and spirometry measurements (depending on the child's age) to assess asthma in children, but do not make recommendations about regular follow-up for these tools.⁶ It is noteworthy that although children aged ≤5 years have similar asthma symptoms as older patients with asthma, the presentation is complicated by the recurrent wheezing from frequent respiratory infections that occurs in this age group. In fact, in children aged <3 years, wheezing alone is a poor predictor of asthma development later in life.⁷ A number of factors have been linked to asthma development in children, including allergic sensitization to aeroallergens and family history of asthma.⁸

The 2007 National Asthma Education and Prevention Program (NAEPP) Guidelines for the Diagnosis and Management of Asthma initiated a stepwise model based on an ongoing assessment of asthma severity and control.⁹ An increasing step number corresponds to augmenting levels of intervention, and a decreasing step number corresponds to tapering down levels of intervention. Asthma severity refers to the intensity of the disease process, which is intrinsic to an individual's disease; severity is determined upon initiation of treatment. In contrast, asthma control is the degree to which symptoms impact a patient's life (eg, activity limitations); control must be continually assessed in order to adjust therapy accordingly. The NAEPP guidelines further focus on two domains of severity and

control: impairment and risk. Impairment refers to the extent to which the frequency and intensity of asthma symptoms result in functional limitations for the patient, and risk refers to the likelihood of future asthma exacerbations, decline in lung function/lung growth, or adverse effects from medication. Severity also takes into account the amount of medication necessary to achieve control. Achieving and maintaining control is a major goal of asthma therapy; poorly controlled asthma is associated with increased risk of exacerbations.¹⁰ Reducing impairment (eg, by preventing chronic symptoms) as well as minimizing future risk (eg, by preventing exacerbations) are therefore critical to the long-term management of asthma.⁹ The 2018 GINA report, which is updated and revised more frequently, also recommends a stepwise approach for asthma therapy.²

Because asthma is heterogeneous in presentation and variable in course over time, its clinical consequences can be unpredictable if not assessed by objective determinants, such as lung function or airway hyperresponsiveness. Limiting the evaluation to the periodic use of subjective determinants of asthma, such as past interval history or asthma control scores, does not accurately reflect the natural history of an individual into adulthood. Persistent asthma refers to a continuation of symptoms, whereas asthma progression can be considered a worsening of asthma symptoms, potentially accompanied by a decline in lung function.¹¹ Although some children experience persistent or even progressive asthma as they enter adulthood, others experience a remission of symptoms as they age.¹²⁻¹⁴

3 | EVALUATING THE PROGRESSION OF CHILDHOOD ASTHMA

In one study of the progression into adulthood for individuals with moderate to severe childhood asthma, 15% experienced remission and 22% had intermittent asthma.¹² The remaining subjects had persistent asthma, including 14% with mild, 29% with moderate, and 19% with severe asthma.¹² Objective factors predicting remission included lower childhood total serum immunoglobulin E (IgE), fewer positive allergy skin tests, and milder childhood asthma.¹² Remission during adolescence occurs more commonly in males than in females and may account for the greater incidence of asthma in females starting at this age.^{15,16} In addition, fluctuations in estrogen during women's menstrual cycles have been linked to worsening asthma symptoms (perimenstrual asthma).¹⁷ In one study, female patients with asthma who used an oral contraceptive (which stabilizes hormone levels throughout a cycle) had reduced asthma symptoms, improved pulmonary function, and improved asthma control compared with those not taking an oral contraceptive.¹⁷

The Asthma Predictive Index (API) was developed from the Tucson Children's Respiratory Study to help predict which pediatric patients will experience asthma into adulthood and which patients will not develop asthma based on a combination of major and minor criteria for children with frequent wheezing episodes.¹⁸ For a positive API score, major criteria include any one of the following: the presence of physician-diagnosed parental asthma or child eczema; minor criteria

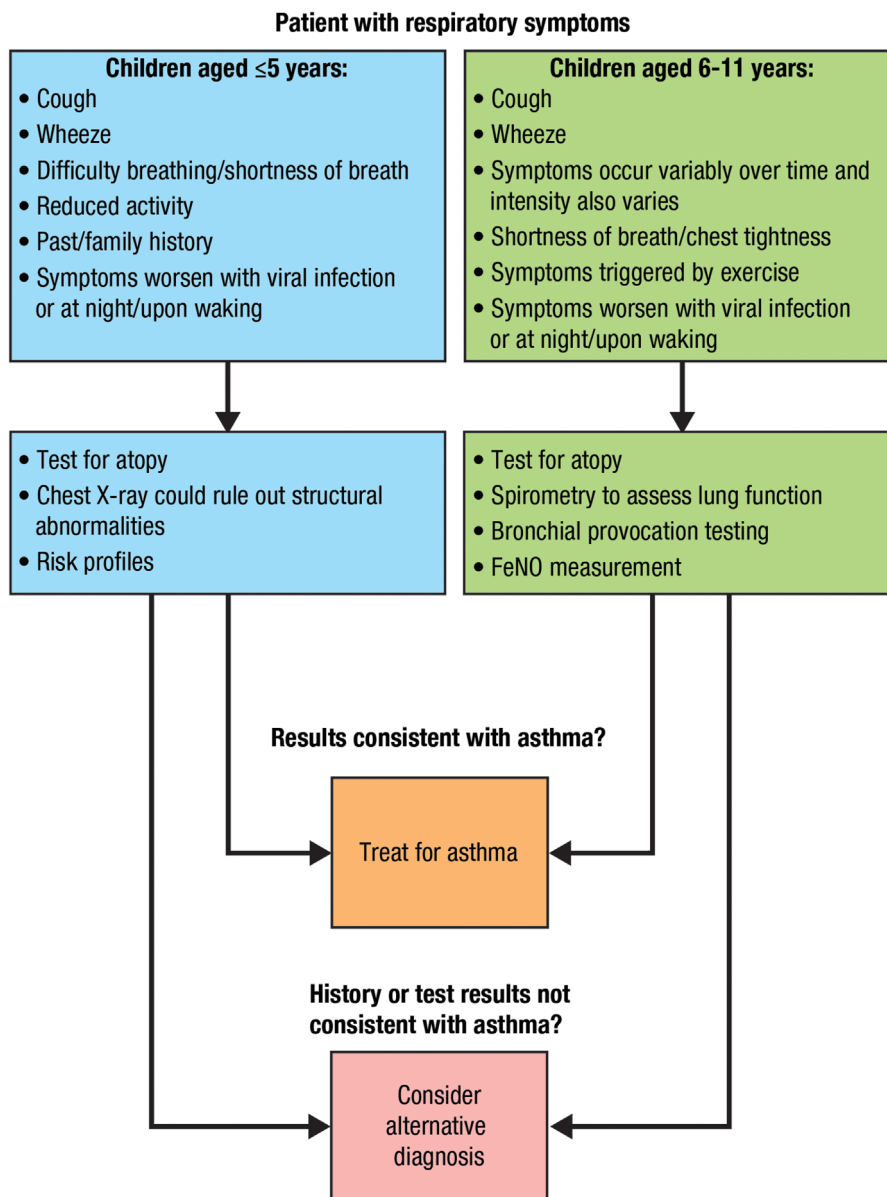


FIGURE 1 Diagnostic flow chart for childhood asthma adapted from the 2018 GINA report.² Flow chart for asthma diagnosis in children ≤ 5 years and 6-11 years of age. FeNO, fractional concentration of exhaled nitric oxide; GINA, Global Initiative for Asthma. [Color figure can be viewed at wileyonlinelibrary.com]

include any two of the following: the presence of physician-diagnosed allergic rhinitis, wheezing apart from colds, or elevated blood eosinophils $\geq 4\%$. Table 1 shows the criteria for assessing a patient's asthma risk using the API based on the onset of wheezing episodes and the number of criteria and which criteria are met.¹⁸ Additional studies have validated the accuracy of the API and offered further guidelines on the number of each type of criterion necessary to predict asthma development in later childhood, including additional criteria such as the presence of allergen sensitivities (the modified API).¹⁵

A number of factors in early childhood can contribute to asthma progression, leading to impaired lung growth and an incomplete response to bronchodilators or anti-inflammatory therapy, which may result in fixed obstructive disease. These so-called "childhood disadvantage factors" have been associated with

reduced lung function in adulthood and include low birth weight, parental asthma, maternal smoking, and childhood respiratory infections.^{19,20} In a prospective observational study of 3099 adults, those with asthma were 12.5 times more likely to develop fixed airflow obstruction than those without asthma, even adjusting for smoking history and other confounders.²¹ Furthermore, recent studies of lifetime lung function trajectories (measured as FEV_1) have shown that fixed airflow obstruction may develop not only from rapid decline in FEV_1 , but also from lower maximal FEV_1 attained in early adulthood due to abnormal lung growth and/or development.^{22,23} Therefore, effective management of childhood asthma could potentially slow the trajectory of FEV_1 decline in adulthood and ultimately lessen the risk of fixed airflow obstruction.

TABLE 1 Major and minor criteria for predicting asthma in young children.^{18,a}

Major criteria	Minor criteria
1. Parental MD asthma ^b	1. MD allergic rhinitis ^d
2. MD eczema ^c	2. Wheezing apart from colds
	3. Eosinophilia ($\geq 4\%$)

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^aLoose index for the prediction of asthma: early wheezer plus at least 1 of the 2 major criteria or 2 of 3 minor criteria. Stringent index for the prediction of asthma: early frequent wheezer plus at least 1 of 2 major criteria or 2 of 3 minor criteria.

^bHistory of a physician diagnosis of asthma.

^cPhysician diagnosis of atopic dermatitis as reported in questionnaires at ages 2 or 3.

^dPhysician diagnosis of allergic rhinitis as reported in questionnaires at ages 2 or 3.

4 | THE EFFECTS OF ASTHMA ON LUNG DEVELOPMENT

Severe asthma in childhood can cause inflammation and airway remodeling, potentially leading to persistent airflow obstruction and marked decline in FEV₁ into adulthood.²⁴ The Melbourne Asthma Study showed that, for children with severe asthma at 7 years of age, only 14% achieved remission by age 50, suggesting that the changes in lung function associated with severe asthma occur early and may not be reversible.²⁵ An update to this study showed that 75% of patients with chronic obstructive pulmonary disease (COPD) at age 53 had one of three types of lung function trajectories.²⁶ Childhood asthma was one factor that was associated with the risk of these three trajectories, and of interest, these were the only trajectories that were then associated with moderate to severe COPD later in life.

A study in 285 younger children (aged 2-3 years) with positive API concluded that, although 2 years of inhaled corticosteroids (ICS) could alleviate asthma symptoms during the treatment period, the natural course of the disease was unchanged. These results suggest that ICS therapy can help to control existing asthma symptoms, but it is not effective at preventing asthma in young children at high risk of persistent asthma in childhood.²⁷ Overall, the connection between airway remodeling in children and the development of chronic airflow obstruction in adulthood requires further investigation. An open question remains regarding how clinicians can better monitor the course of childhood asthma and minimize further damage to the lung.

To determine how childhood asthma may affect lung development, 684 children in the Childhood Asthma Management Program (CAMP) cohort have been classified according to four patterns of lung function trajectory: normal pattern (25%), reduced growth and early decline (26%), reduced growth only (23%), and normal growth and early decline (26%; Figure 2).²⁸ The two most significant predictors of abnormal lung function growth and decline were reduced FEV₁ in

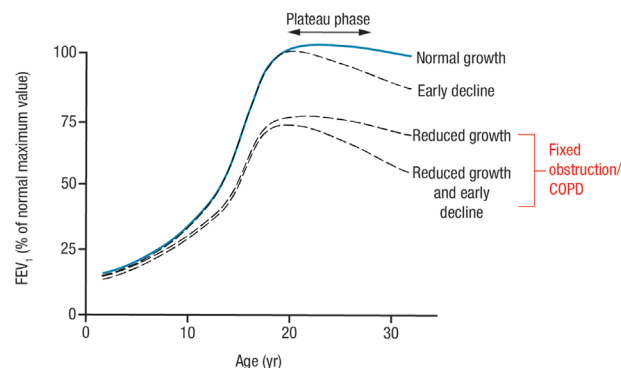


FIGURE 2 Longitudinal lung function trajectories.²⁸ Four possible lung-function trajectories over time are shown. The lung function plotted at each age is the percentage of normal FEV₁ (FEV₁ for a person with no lung disease) for that age. Abnormal trajectories resulting in fixed airflow obstruction are reduced growth and reduced growth with early decline, according to the GOLD criteria. COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s GOLD, Global Initiative for Chronic Obstructive Lung Disease. From *New England Journal of Medicine*, McGeachie et al, "Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma," Vol. 374, Page No. 1842-1852. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. [Color figure can be viewed at wileyonlinelibrary.com]

childhood and male sex.²⁸ Lung development plateaus at approximately 22 years of age and impaired growth can result in lower baseline lung function, putting an individual at risk for more rapid reduction in function either as a result of progressive airway inflammation or exposure to lung irritants, such as tobacco.²⁸ Early and continued monitoring of FEV₁ over time, especially in those with persistent asthma, may help to identify individuals at risk for abnormal lung development that could lead to fixed airflow obstruction, including decreased lung function consistent with COPD in adulthood, so it is important to perform periodic pulmonary function tests on children with asthma. These measures can be graphically displayed over time to begin to identify a lung development trajectory for an individual patient. These graphs should become part of spirometry interpretation over time similar to the way we monitor linear growth over time in children.

5 | ASSESSMENT OF ASTHMA OUTCOMES

Yearly in-office spirometry evaluations to determine FEV₁ are recommended, as per the 2012 European Respiratory Society (ERS) Task Force, for patients with asthma aged 3-95 years.^{24,29} For children with symptoms of poorly controlled asthma, such as exercise limitations or suspected nonresponse to treatment, high-level assessments, such as evaluation of bronchial hyperresponsiveness, are recommended in a specialist's office.²⁴ In addition, short-term monitoring of peak expiratory flow can be used to evaluate response to treatment because variation in peak expiratory flow is associated with poor asthma control.² Ideally, a patient's asthma control should be

assessed 1-3 months after starting treatment and every 3-12 months thereafter, as well as within 1 week of an exacerbation.² As a child gets older, additional measures can be taken to protect lung growth, including age-appropriate counseling on smoking avoidance/cessation, assessment of symptom reversibility with conventional therapy, occupational counseling, and environmental assessment.

A number of questionnaires have been validated for the assessment of asthma control in children.³⁰ The Asthma Control Test (ACT) is a five-item questionnaire answered monthly by children aged ≥ 12 years.³¹ The Asthma Control Questionnaire (ACQ) and the ACQ for children (cACQ) are seven-question tests that have been validated in children aged ≥ 6 -16 years (cACQ) and in adults (ACQ).^{32,33} The Pediatric Asthma Therapy Assessment Questionnaire for Children and Adolescents (pATAQ) is designed for patients aged 6-17 years.³⁴ The Childhood ACT (cACT)³⁵ is used for younger children (aged 4-11 years) and does not assess rescue therapy use. The ACT, cACT, pATAQ, ACQ, and cACQ do not take exacerbations into account in scoring asthma control. The Test for Respiratory and Asthma Control in Kids (TRACK)³⁶ is used for preschool-aged children (aged ≤ 5 years) to assess both the impairment and risk domains of asthma control. Because asthma can be difficult to diagnose in this young population, the TRACK score can be used to identify children with respiratory control problems (TRACK < 80), allowing clinicians and caregivers to monitor these children for symptoms consistent with asthma. For older children, the Composite Asthma Severity Index (CASI) is a recently developed assessment tool that has been validated in children aged 5-17 years.³⁷ CASI is free to use (available at www.asthmaseverity.org), measures overall asthma burden in terms of both impairment and risk, and correlates well with levels of severity.^{4,38}

6 | BIOMARKERS OF ASTHMA PHENOTYPES

The use of biomarkers to identify patients with a particular molecular basis for disease and who are therefore most likely to respond to a corresponding treatment is becoming increasingly available to personalize asthma management.³⁹ For patients with eosinophilic asthma classified as the phenotype type 2-high, a number of biomarkers for inflammation are readily available to the clinician. An easily quantified biomarker is the amount of eosinophils in the blood. Elevated blood eosinophil counts (> 300 cells/ μ L) have been strongly correlated to more frequent asthma exacerbations.⁴⁰

Another potential biomarker, FeNO, is released from bronchial epithelium in response to type 2 cytokines,⁴¹ and it has been shown to be correlated with increased asthma morbidity when simultaneously elevated with blood eosinophils, rather than either indicator alone.⁴² In fact, one study of children aged 6-17 years showed that elevated FeNO and eosinophil counts at baseline were associated with favorable responses to inhaled fluticasone propionate over oral montelukast,⁴³ indicating that FeNO measurement could potentially be used to predict treatment response to ICS.^{43,44} FeNO measurement is straightforward, provides immediate results, and can be performed

in both infants and young children. The American Thoracic Society (ATS) recommends that FeNO > 35 ppb be used to indicate eosinophilic inflammation in children.⁴⁵ FeNO values between 20 and 35 ppb are also considered elevated in children, but should be evaluated carefully in clinical context.⁴⁵

With better understanding of the mechanisms driving asthma, opportunities to integrate precision medicine into asthma management are numerous. Using a phenotype-based approach to therapy, in which a specific patient's observable characteristics are considered in making treatment decisions, has the potential to improve outcomes for both children and adults with asthma by addressing their endotype, the mechanism of a patient's disease.⁴⁶ For example, biomarkers could be used to identify which pathway should be targeted in a specific patient (eg, anti-IgE or anti-interleukin [IL]-5/anti-eosinophil, IL-4, or IL-13). The INFANT trial conducted by National Heart, Lung, and Blood Institute (NHLBI) AsthmaNet showed that biomarkers of type 2 inflammation, such as blood eosinophil counts, can be used to identify children who may benefit from daily ICS treatment.⁴⁷ Evaluation of a child's atopic status could also help to distinguish between patients at risk for persistent asthma, those who are likely to respond to daily ICS therapy, and those likely to develop severe, uncontrolled asthma.⁴⁸ Figure 3 illustrates how asthma treatment could be personalized based on phenotype observed for children with uncontrolled asthma. Precision treatment of asthma will be especially important in young children, as early identification and individualized therapy for asthma may prevent disease progression.⁴⁸ However, prospective studies with or without various interventions other than long-term ICS have not

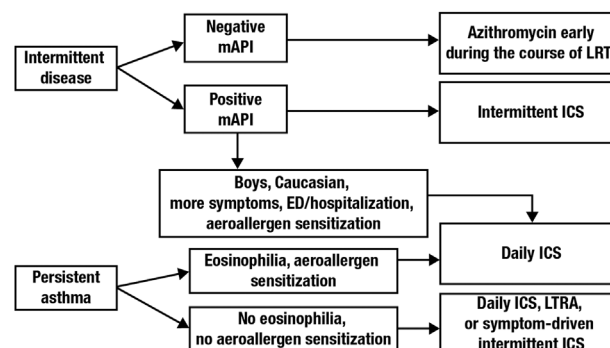


FIGURE 3 Personalized asthma treatment algorithm for uncontrolled asthma.⁸⁷ Personalized courses of therapy for uncontrolled asthma from phenotype to targeted treatment. The phenotypes observed in a patient can point to the asthma endotype, which is confirmed by specific biomarkers. The presence of biomarkers then guides treatment decisions and allows the clinician to choose a therapy that will address the underlying pathophysiology of a patient's asthma. ED, emergency department; ICS, inhaled corticosteroids; LRTI, lower respiratory tract illness; LTRA, leukotriene receptor antagonist; mAPI, modified asthma predictive index. From Beigelman and Bacharier, "Management of preschool recurrent wheezing and asthma: a phenotype-based approach," *Current Opinion in Allergy and Clinical Immunology*, 17(2) 131-138 (2017). Reprinted with permission from Wolters Kluwer Health, Inc. https://journals.lww.com/co-allergy/Abstract/2017/04000/Management_of_preschool_recurrent_wheezing_and.14.aspx

been done to assess the specific relationship of uncontrolled asthma to long-term fixed airway obstruction. This is another information gap that should be addressed in future studies.

7 | ICS THERAPY AND LINEAR GROWTH

ICS therapy is part of the recommended long-term treatment to control asthma, but there is concern that initiating this treatment in prepubertal children may cause reductions in final adult height.⁹ A study implementing a primate model of childhood asthma reported that ICS therapy also altered alveolarization in rhesus monkeys.⁴⁹ A 2012 study investigating the effects of glucocorticoid therapy on prepubertal children in the CAMP population (aged 5-13 years) did show that height deficits observed 1-2 years after initiation of therapy persisted into adulthood.⁵⁰ A 2014 review of the literature comparing studies of different ICS preparations concluded that despite the risk of growth suppression seen in some studies, ICS continue to have a more favorable safety profile than oral glucocorticoids.⁵¹ Furthermore, a recent systematic review and meta-analysis of 23 studies concluded that there was limited impact of ICS on growth velocity in children; compared with non-ICS users, there was an average of 0.7% reduction in adult height for children who used ICS for >12 months.⁵² The authors suggested that this effect may be considered clinically insignificant when compared to the known benefits of ICS therapy in controlling childhood asthma, but noted that clinicians should aim to prescribe the lowest effective dose.⁵² In addition, current ICS formulations were designed for adults and could potentially lead to greater growth suppression in young children due to a higher dose per weight.⁵³

8 | BIOLOGIC THERAPIES

Biologic agents that target inhibition of IgE and IL-5 are already approved in adults and adolescents, and more agents are currently under investigation in clinical trials including older children.^{30,54-56} However, specific data in children younger than 12 years and even adolescents are limited. Furthermore, the long-term effects of these therapies remain to be seen; more investigation is still necessary to determine if biologic therapy can prevent disease progression or even reverse airway damage.⁵⁷ One agent targeting IgE, which plays a role in allergen sensitization and airway inflammation, is omalizumab, an anti-IgE monoclonal antibody approved by the US Food and Drug Administration (FDA) for asthma with atopy in patients aged ≥ 6 years.⁵⁸ One study in children aged 6-12 years showed that omalizumab treatment resulted in a larger median reduction in maintenance ICS dosage (100%) compared with placebo (66.7%, $P = 0.001$), and also significantly reduced the percentage of patients with severe exacerbations (18.2%) compared with placebo (38.5%, $P < 0.001$) during the 12-week ICS dose-reduction phase of the study.⁵⁹ In a subsequent study for the same age group, omalizumab treatment resulted in a 50% reduction in severe

exacerbations over 52 weeks compared with placebo ($P = 0.004$).⁶⁰ A study is underway with anti-IgE to determine its long-term effect on disease modification in children (ClinicalTrials.gov Identifier: NCT02570984).

IL-5 is a cytokine involved in the growth, differentiation, and migration of eosinophils to the airway. Mepolizumab^{61,62} (FDA-approved as add-on maintenance treatment in patients aged ≥ 12 years with severe eosinophilic asthma) and reslizumab^{63,64} (approved in adults) are anti-IL-5 monoclonal antibodies that block its effects. Studies have shown that both mepolizumab and reslizumab significantly reduced the frequency of exacerbations compared with placebo in patients with asthma and high blood eosinophil counts.^{62,63} Unlike mepolizumab and reslizumab, benralizumab is a humanized, afucosylated monoclonal antibody against the IL-5 receptor α . It is FDA-approved for the add-on maintenance treatment of patients with severe asthma aged ≥ 12 years, and with an eosinophilic phenotype.⁶⁵ In contrast to mepolizumab and reslizumab, which bind IL-5 itself, benralizumab binds the α subunit of the IL-5 receptor on the surface of eosinophils and basophils. Afucosylation of the antibody enhances its binding to the Fc γ RIIIA receptor on natural killer cells, which induces rapid and near-complete depletion of eosinophils by enhanced antibody-dependent cell-mediated cytotoxicity.⁶⁶ Studies have demonstrated that benralizumab add-on therapy significantly reduced the frequency of exacerbations, improved lung function, and reduced the need for oral corticosteroid use in patients with elevated blood eosinophils.⁶⁷⁻⁶⁹ However, there is limited information on the use of anti-IL-5 or anti-IL-5 receptor α agents in pediatric asthma, and further studies are warranted for these therapies in pediatric patients, especially those aged 6-<12 years.

The cytokine IL-4 contributes to the type 2 inflammation associated with allergic response by inducing differentiation of T cells into Th2 lymphocytes and stimulating B cells to produce IgE.⁷⁰ IL-4 and IL-13 both activate the same receptor subunit IL-4 receptor α , so there is a significant overlap in the function of these two cytokines. Dupilumab is an anti-IL-4 receptor α monoclonal antibody under investigation in asthma that inhibits both IL-4 and IL-13 signaling by binding the receptor. Studies have shown that dupilumab reduces exacerbations in adult patients with moderate to severe asthma and elevated eosinophil counts (≥ 300 cells/ μ L).⁷¹ In a larger subsequent study, dupilumab improved lung function in addition to reducing severe exacerbations in adult patients with persistent uncontrolled asthma regardless of eosinophil count.⁷² The LIBERTY ASTHMA QUEST study investigated the efficacy of dupilumab in patients aged ≥ 12 years with uncontrolled asthma for 1 year of treatment.⁷³ These results were similar to the adult studies; dupilumab significantly reduced asthma exacerbation rates, improved lung function, and improved asthma control compared with placebo. Greater benefits were observed for patients with elevated baseline blood eosinophil counts (≥ 300 cells/ μ L) and FeNO (≥ 25 ppb). Dupilumab is also currently being evaluated in younger children aged 6-<12 years with uncontrolled asthma in the VOYAGE study (ClinicalTrials.gov Identifier: NCT02948959).

9 | HETEROGENEITY IN TREATMENT RESPONSE

Children that present with asthma exacerbations generally have more severe disease and signs of eosinophilic inflammation.⁷⁴ According to recent estimates, approximately 38% of children with asthma have uncontrolled disease, and 52% of children with uncontrolled asthma were already taking long-term controller medications.⁷⁵ In addition, some children whose asthma is still not controlled despite ICS therapy respond to other standard therapies differently.⁷⁶ Another issue to consider is difficult-to-treat asthma, defined by the need for multiple medications, frequent and/or severe exacerbations, inability to avoid triggers, and complicated treatment regimens.⁷⁷ Although this type of asthma is not a phenotype as defined by treatment guidelines, it can describe asthma of any severity level and is likely to contribute to the population of children with uncontrolled asthma. Overall, efficacy can be difficult to demonstrate in young children due to the confounding influences of socioeconomic status, race/ethnicity, and comorbidities, as well as the heterogeneity of asthma itself.

Cultural and economic factors can contribute to suboptimal asthma management. For example, there is a greater prevalence and worse management of asthma in children from families with lower socioeconomic status and certain racial minorities than other children with asthma. Lower household income has been identified as a significant predictor of missed school days as well as activities limited by asthma symptoms.⁷⁸ A study investigating Medicaid claims across multiple states revealed a greater prevalence of asthma, as well as a greater number of emergency department visits, for black children compared with non-Hispanic white children.⁷⁹ The results of the BARD study investigating the best medication response in black patients will provide further information on ICS and ICS/long-acting β_2 -agonist (LABA) response in children and adults (ClinicalTrials.gov Identifier: NCT01967173).

The BADGER study investigated the response to different step-up therapies in patients aged 6–17 years with uncontrolled asthma despite the use of low-dose ICS.⁷⁶ Children were randomized to receive ICS, LABA, or leukotriene receptor antagonist (LTRA) as add-on therapy for each of the three 16-week periods of the 48-week study. It showed a differential response to asthma therapy based on their racial or ethnic group.⁷⁶ Black patients did not respond as well to an LTRA addition as they did to an ICS or LABA, and non-Hispanic white patients did best with the addition of a LABA.⁷⁶ Figure 4 illustrates the response to step-up therapy by race, age, and eczema status from the BADGER study. Although the reasons for this differential response are not clear, it has been suggested that they may be due to genetic variations or gene-by-environment interactions affecting responsiveness to treatment.⁸⁰ A post hoc analysis of the BADGER data further showed that children without a history of eczema responded better to LABA step-up therapy regardless of race.⁸¹

In the CHASE 3 study, budesonide/formoterol combination therapy (80/4.5 μ g two inhalations twice daily) resulted in significant, clinically meaningful improvements in lung function compared with budesonide alone in children aged 6–<12 years with symptomatic

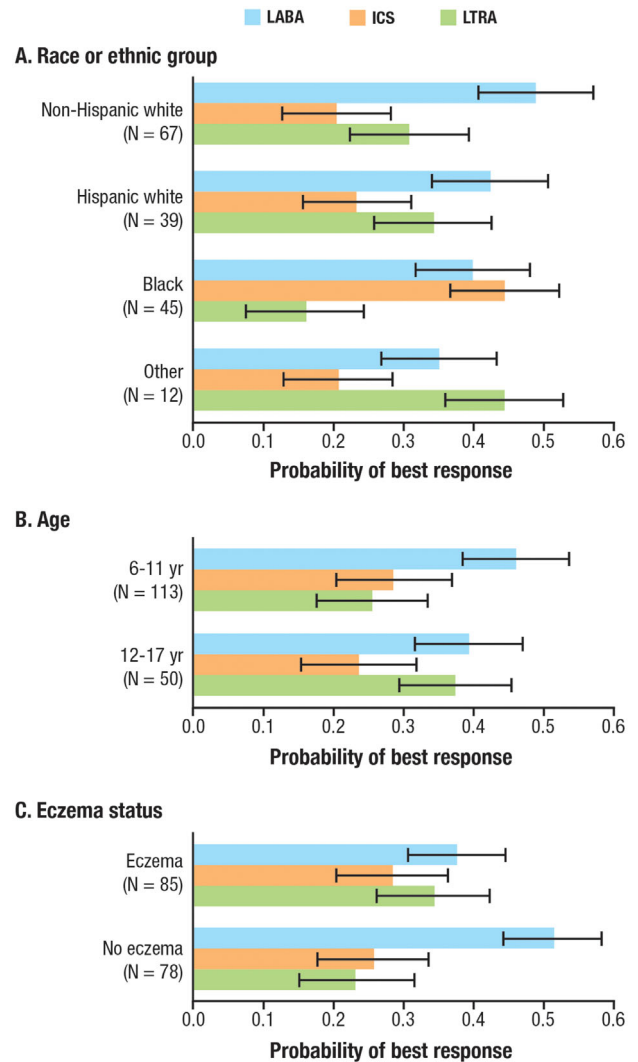


FIGURE 4 Differential probability of best response to step-up therapy in children with asthma.⁷⁶ Potential secondary predictors of response to therapy in a post hoc analysis included (A) race or ethnic group, (B) age, and (C) the presence or absence of eczema. ICS, inhaled corticosteroids; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist. From *New England Journal of Medicine*, Lemanske et al, "Step-up Therapy for Children with Uncontrolled Asthma While Receiving Inhaled Corticosteroids," Vol. 362, Page No. 975-985. Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. [Color figure can be viewed at wileyonlinelibrary.com]

asthma despite low-dose ICS therapy, and there was no difference in the safety profile.⁸² Although CHASE 3 did not stratify treatment by ethnic group or other status, the results supported the use of combined ICS/LABA therapy in children with asthma that was uncontrolled by low-dose ICS therapy alone.

Poor asthma control is strongly associated with exacerbation risk,¹⁰ and having a history of exacerbations is the strongest predictor for future exacerbations.⁷⁷ Although these asthma exacerbations are acute events, the accompanying inflammation may trigger sustained pathologic airway remodeling, which negatively affects lung function.⁸³ Prevention of exacerbations

in childhood may therefore preserve lung function in adulthood, so it is vital to tightly control childhood asthma early on. By monitoring risk as well as impairment, clinicians may therefore help reduce further damage to the lungs.⁸⁴ Future studies are needed to determine if alternative therapeutic strategies to relieve symptoms beyond SABA and directed toward the underlying inflammation in asthma would ultimately decrease exacerbations and enhance lung function in younger children. The SYGMA 1⁸⁵ and SYGMA 2⁸⁶ studies in patients with mild asthma aged ≥ 12 years showed that the combination of budesonide/formoterol, taken only as needed rather than as a daily maintenance therapy, reduced the risk of asthma exacerbations with a substantially lower total exposure to inhaled glucocorticoids. However, this strategy has not yet been evaluated in younger children, and these patients would need to be closely monitored for any effects on height.

10 | CONCLUSIONS

Frequent asthma exacerbations in childhood can negatively impact lung function and development. Moreover, unchecked airway inflammation in childhood may result in reduced FEV₁ and fixed obstruction in adulthood. The resultant airway remodeling leads to accelerated loss of lung function with clinical consequences in some individuals and has been shown to be the strongest predictor of fixed airflow obstruction in adults. Key open questions are: (i) what other factors may be contributing to this lung function decline and (ii) why do some children experience remission of asthma and not others. More effective management of asthma in childhood could potentially preserve lung function and halt (or at least significantly slow) disease progression. Identification of phenotypes specific to children may help predict the future risk and rate of disease progression. With this information in hand, clinicians will be able to take steps to minimize future damage of the lower airways.

Further investigation is required to determine how clinicians can diagnose and treat asthma earlier in life to prevent additional lung damage and to predict which patients will respond to which interventions; childhood asthma patient registries may aid future analyses. In addition, newer, more personalized therapies that target the molecular mechanisms of an individual's own asthma are showing promise in adults, but more investigation must be done in pediatric patients. In the near future, novel biomarkers that correspond to a specific disease mechanism could soon guide clinicians to choose more effective therapies for each patient.


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CONFLICTS OF INTEREST

MJL has consulted or is a speaker for AstraZeneca, Novartis, and Optinose; and has received research support from Genentech and Stallergens. SJS has consulted for Aerocrine, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Genentech, Merck, Novartis, Propeller Health, Roche, and Teva; and has received research support from the National Institutes of Health; the National Heart, Lung, and Blood Institute; the Colorado Department of Public Health and Environment; Colorado Cancer, Cardiovascular, and Pulmonary Disease Program; and GlaxoSmithKline. KRM has consulted for and is a speaker for AstraZeneca, Boehringer Ingelheim, Genentech, Greer, Merck, Mylan, Novartis, and Teva. IG is an employee of AstraZeneca.

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