



Moving towards precision care for childhood asthma

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Purpose of review

Asthma guidelines recognize the presence of different asthma endotypes and phenotypes but treatment recommendations are limited to age groups rather than phenotypes, as the phenotype literature is regarded as emerging evidence. This review will examine the current evidence regarding the management of asthma in school age children (5–18 years old) by endotype and phenotype.

Recent findings

A number of studies have examined the effect of endotypes and phenotypes on response to conventional asthma therapy, omalizumab and specific allergen immunotherapy, and response in children with severe asthma. Emerging therapies, namely biologics and immunomodulators, have attracted considerable attention and appear to have favorable effects in adults with asthma, but additional pediatric studies are needed.

Summary

The optimal treatment strategy for children with asthma is not yet defined and likely dependent on many patient and disease characteristics. Much of the phenotypic response literature presented in this review was constrained by a limited number of pediatric and adult studies available and as such should be regarded as preliminary. Better definition of asthma phenotypes and better targeting of therapy based on individual patient phenotypes are likely to improve asthma treatment in the future.

Keywords

asthma endotypes, asthma phenotypes, childhood asthma, treatment response, wheezing

INTRODUCTION

Both the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR-3) 2007 and the Global Initiative for Asthma (GINA) 2014 guidelines recognize the existence of various asthma endotypes and phenotypes [1,2^{***}]. However, both guidelines agree that more research is needed to understand the clinical utility of phenotypic classification in asthma and continue to recommend treatment by age rather than phenotype [1,2^{***}] given the paucity of response by phenotype data. This review will examine the evidence that exists to date regarding the management of asthma in school age children (5–18 years old) by endotype and phenotype.

Asthma phenotypes and endotypes

Asthma is a heterogeneous disorder categorized by various clinical and pathophysiologic features. These features define which children are at risk of having persistent wheezing symptoms as they

age [3] and may predict their responses to therapy. Clinical features which define phenotypes include: age of onset, triggers (allergens, viruses, exercise, cigarette smoke), atopic vs. nonatopic disease, natural history (epidemiologic phenotypes), symptom-based phenotypes (episodic vs. multitrigger), severity, exacerbation-prone, and response to therapy [4]. Asthma endotypes, which are defined by distinct pathophysiological mechanisms [5], are characterized by the following features: pattern of inflammation (eosinophilic, neutrophilic, pauci-granulocytic), biomarkers (exhaled nitric oxide, eosinophilia, urinary leukotriene E₄), bronchial

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KEY POINTS

- Atopic asthmatic patients with higher exhaled nitric oxide, total eosinophil counts, and serum IgE tend to respond better to ICS vs. LTRA.
- Phenotypic LTRA response is unclear with some studies associating it with younger age and shorter disease duration whereas other studies found the response was independent of baseline characteristics.
- Emerging therapies, namely biologics or immunomodulators that target Th2-driven airway inflammation, have attracted considerable attention and appear to have favorable effects in adults with asthma, but additional studies to investigate a benefit in adolescent and pediatric outcomes and the use of therapy-guiding biomarkers are needed.
- Much of the phenotypic response literature is constrained by a limited number of pediatric and adult studies available and, as such, should be regarded as preliminary.

hyper-responsiveness (BHR), and lung function. The majority of the studies that defined these endotypes and phenotypes have been conducted in Caucasian populations, thus their application in diverse populations is not well established [6].

Endotypes and phenotypes related to conventional asthma therapy response

Multiple pediatric studies [1,2^{***}] have found a central role for airway inflammation in asthma of any severity with inhaled corticosteroids (ICSs) remaining as the first-line, guideline-recommended therapy in all age groups [1,2^{***}]. Leukotriene receptor antagonists (LTRAs) are recommended to be used as an alternative treatment option for milder asthma, and as an alternative adjunctive treatment with ICS in moderate or severe asthma [1,2^{***}]. Long-acting beta-agonists (LABAs) have been recommended as adjunctive therapy in children of more than 5 years of age who have asthma that is not controlled on step 2 therapy per EPR-3 guidelines [1] and should not be used as monotherapy [1]. Equal consideration can be given to increasing the dose of ICS, the addition of a LABA to ICS, or the addition of LTRA to ICS [1]. As per GINA guidelines, the preferred option for step 3 maintenance therapy for adults and adolescents is low dose combination ICS/LABA [2^{***}]. However, in children 6–11 years old, GINA guidelines recommend increasing ICS to medium dose as the preferred step 3 treatment option over adding a LABA as the effect may be

similar to or more effective than adding LABA in this age group [2^{***}].

A study by Sorkness *et al.* [7] compared the effectiveness of three regimens in achieving asthma control in 285 children 6–14 years of age with uncontrolled mild–moderate persistent asthma. The three regimens were fluticasone monotherapy (fluticasone propionate 100 µg morning and 100 µg evening along with placebo oral drug in the evening), Pediatric Asthma Controller Trial (PACT) combination (fluticasone propionate 100 µg/salmeterol 50 µg in the morning and salmeterol 50 µg in the evening along with placebo oral drug in the evening), and montelukast 5 mg in the evening (placebo Diskus in the morning and placebo Diskus in the evening along with montelukast 5 mg in the evening). Both fluticasone monotherapy and combination therapy achieved greater improvements in asthma control days than montelukast. However, fluticasone monotherapy was superior to combination therapy in achieving other dimensions of asthma control such as forced expiratory volume in one second/ forced vital capacity (FEV₁/FVC), maximum bronchodilator response, exhaled nitric oxide, and BHR by methacholine challenge [7]. In a post-hoc analysis, this was particularly true for children treated with fluticasone monotherapy with exhaled nitric oxide levels ≥25 ppb achieving 99 more asthma control days than children with similar levels treated with montelukast [8] (Table 1). Moreover, allergic children with peripheral eosinophilia or ≥5% or immunoglobulin E levels greater than 150 kU/l treated with fluticasone monotherapy also had significantly more asthma control days than allergic children treated with montelukast [8] (Table 1).

Szeffler *et al.* [9] conducted a crossover study comparing the response to fluticasone twice daily and montelukast by baseline asthma phenotype-associated biomarkers in children 6–17 years of age with mild–moderate persistent asthma. Percent-age change in FEV₁ was used as the primary outcome. Children with a favorable response to fluticasone alone were more likely to have higher exhaled nitric oxide, total eosinophil counts, serum IgE, serum eosinophil cationic protein, BHR by methacholine challenge, and lower pulmonary function (Table 1). Favorable response to montelukast alone was associated with younger age and shorter disease duration [9] (Table 1). Greater differential response to fluticasone over montelukast was associated with higher bronchodilator use, bronchodilator response, exhaled nitric oxide levels, eosinophil cationic protein levels, BHR by methacholine challenge, and lower pulmonary function values [9] (Table 1). In contrast, a review by Meyer *et al.* [23] of two clinical trials in children 2–14 years old found that treatment

Table 1. Emerging pediatric phenotypes/endotypes associated with response to asthma therapies

ICS	LTRAs	ICS/LABA combination therapy	Omalizumab and AIT	Biologics	Antimicrobials (macrolides)
eNO ≥ 25 [8]	Younger age [9]	Lower lung function [10]	Requiring high doses of ICS [12 [■]]	Mepolizumab (studied in adults and adolescents only): high exacerbation frequency at baseline [18]; serum eosinophilia (baseline peripheral eosinophil counts of 300/ml or greater) [18,19 [■]]	Preschool-aged children with histories of recurrent, severe lower respiratory tract illnesses [21 [■]]
Peripheral eosinophilia ($\geq 5\%$) [8]	Shorter disease duration [9]	No eczema [11 [■]]	Experiencing frequent exacerbations [12 [■]]	Reslizumab (studied in adults and adolescents only): poorly controlled asthma treated with ICS [20 [■]]; peripheral eosinophil count $\geq 400/\text{ml}$ [20 [■]]	Childhood asthma associated with persistent neutrophilic inflammation [22]
IgE $> 150 \text{ kU/l}$ [8]			Allergic sensitization [12 [■]]		
BHR by methacholine challenge [9]			Higher levels of peripheral eosinophils [13,14,15 [■] ,16,17]		
Higher bronchodilator response [9]			Higher levels of periostin [13,14,15 [■] ,16,17]		
Lower lung function [9]			Higher body mass index [13,14,15 [■] ,16,17]		

AIT, allergen immunotherapy; BHR, bronchial hyper-responsiveness; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; LABA, long-acting beta-agonist.

with montelukast was not modified by baseline characteristics or markers of atopic disease. In a randomized double-blind placebo-controlled trial in adults with moderate or severe asthma, the use of a LTRA as additional therapy to ICS did not provide additional benefit in terms of symptoms or lung function, including those with aspirin-sensitive asthma [24]. On the other hand, adults requiring high doses of ICSs demonstrated significant improvement in symptoms and lung function when high-dose zafirlukast was added, but this has not been studied in children [25]. A study by Lemanske *et al.* [10] examined whether a differential response was found among three step-up therapies in children 6–17 years of age with uncontrolled asthma despite treatment with low dose ICS. The three treatments (medium-dose ICS, low-dose ICS/LABA, or low-dose ICS/LTRA) were compared using a composite outcome that evaluated three components in defining asthma control: asthma control days, FEV₁, and steroid-requiring asthma exacerbations. A differential response occurred in 161/165 participants (98%) ($P < 0.0001$). LABA step-up was more than 1.5 times

as likely to produce the best response compared with the other treatments. Improved response to ICS/LABA step-up therapy was observed in children with lower lung function (Table 1). A post-hoc analysis showed that children without eczema responded best to ICS/LABA step-up therapy irrespective of race, whereas those with eczema demonstrated variable response by race and ethnicity [11[■]] (Table 1). They concluded that the demonstrated beneficial effects of LABA must be weighed against the potential increased risk for rare, severe asthma related events [26]. Results from five large Food and Drug Administration (FDA) mandated pharmaceutical trials of LABA safety in children and adolescents expected in 2017 should further address these concerns [27[■]].

Endotypes and phenotypes related to response to omalizumab and to specific allergen immunotherapy

Omalizumab is an injectable recombinant humanized IgG1 monoclonal anti-IgE antibody given to children with chronic allergic asthma who are not

controlled on ICS alone [12[■]] (Table 1). Two randomized, placebo-controlled studies in children aged 6–12 years with moderate-to-severe asthma reduced the ICS doses required and the number of exacerbations [28,29]. In teenagers and in adults with poorly controlled severe persistent asthma, omalizumab also significantly reduced the rate of clinically significant asthma exacerbations [13,30,31], emergency visits and hospitalizations [30,31], unscheduled doctor's office visits [31], rescue therapy use [13], and ICS dose [32]. In 419 asthmatic inner-city children and young adults of which more than half were receiving step 4–6 therapy per EPR-3 guidelines, adding omalizumab to a regimen of guidelines-based therapy further improved asthma control and decreased seasonal exacerbations, supplementary medication use, ICS dose, and LABAs use [33]. Omalizumab may be most effective in children and adolescents with allergic sensitization and asthma who require high doses of ICS and experience frequent exacerbations [12[■]] (Table 1) and those that have higher levels of peripheral eosinophils, and periostin or higher body mass index compared with those with lower levels [13,14,15[■],16,17] (Table 1). Although currently not FDA approved for children less than 12 years old, omalizumab has been shown to decrease asthma symptom burden and reduce medication use in younger children [28,33,34,35], but long-term side-effects have not been evaluated in children [12[■]].

Specific allergen immunotherapy (AIT) has been demonstrated to have beneficial effects in the management of childhood asthma, including effects on symptom control, medication use, and BHR [36,37]. The generalizability of these findings in children with severe asthma [12[■]] or polysensitization remains uncertain [38,39]. Furthermore, AIT should not be initiated in children with poorly controlled asthma symptoms [36]. In adult studies, the preadministration or concomitant treatment of omalizumab and AIT could be useful in reducing the adverse events as a result of AIT [40] enabling more adults with severe asthma to achieve the target immunotherapy maintenance dose [41] suggesting that this may also be a useful combination in children.

Phenotypes related to response in severe asthma

Severe asthma in children is a highly heterogeneous disorder associated with a number of clinical and inflammatory phenotypes [12[■],42[■]]. Higher exhaled nitric oxide, higher IgE and eosinophils, and varying airway inflammation differentiate children with severe asthma as well as differential

patterns of sensitization to aeroallergens, especially molds [38,43–45]. Guideline based management of severe childhood asthma is based primarily on extrapolated adult data [3,4,12[■]] with higher-dose ICS or oral corticosteroids (OCSs) combined with LABAs and other add on therapies such as antileukotrienes and methylxanthines.

Three phenotypes of airway inflammation have been described based on detailed analysis of induced sputum, bronchoalveolar lavage, or endobronchial biopsy: eosinophilic inflammation [43,44], paucigranulocytic inflammation [43,44], and neutrophilic inflammation [43–45]. In adults, the eosinophilic phenotype is thought to be more corticosteroid-responsive [46] with studies demonstrating fewer exacerbations with sputum eosinophilia-guided therapy [47]. However, Fleming *et al.* [48] found that incorporation of sputum eosinophils into the management of school-age children with severe asthma did not significantly reduce exacerbations or improve asthma control. Moreover, the sputum inflammatory cell levels varied significantly over time and were unrelated to changes in asthma pharmacotherapy or asthma control [48] suggesting that a subset of these children may be steroid resistant [49]. The neutrophilic phenotype may be present in children with asthma at all ages [50] and may be associated with poor response to corticosteroids [49]. A higher proportion of sputum neutrophils is associated with smoking in adults [51] and with viral infection in children [52,53]. These different airway inflammatory patterns may ultimately permit identification of specific phenotypes of severe asthma to aid in directed, pharmacologic treatment, but, to date, additional studies are still needed [12[■]].

Pediatric asthma clusters

Fitzpatrick *et al.* [54] identified four phenotypes of childhood asthma using an unsupervised cluster analysis and 12 clinical variables from children enrolled in the Severe Asthma Research Program (SARP). Three variables, the degree of airway obstruction, the duration of asthma, and the number of controller medications, explained the majority of the variance between groups. Children in cluster 1 were late-onset symptomatic asthmatic patients with normal lung function differentiated by low to medium-dose ICS use. Children in cluster 2 had early-onset atopic asthma with normal lung function, longer disease duration, and were treated with slightly higher ICS doses. Children in cluster 3 had early-onset disease and the highest prevalence of comorbid conditions such as sinusitis, pneumonia, and reflux, and had a high degree of symptoms and healthcare utilization, as well as airflow

limitation and the longest duration of asthma. Children in cluster 4 had early-onset of disease, had the most significant airflow limitation, and were treated with the highest number of controller medications, including high-dose ICS [54]. Spectral clustering of children from the Childhood Asthma Management Program (CAMP) study identified five clusters distinguished based on atopic disease, exacerbation frequency, lung function, and airflow limitation [55[■]]. Chang *et al.* [56[■]] performed an analysis of 611 participants 6–18 years from the Childhood Asthma Research and Education (CARE) trials to replicate and determine whether the SARP childhood asthma clusters were associated with treatment responses. Treatment response was generally similar across phenotype clusters. However, with the caveat of a smaller sample size, children in the early-onset/severe-lung function cluster had the best response with fluticasone/salmeterol, and children in the early-onset/comorbidity cluster had the least clinical efficacy to ICS and LTRA treatments [57]. In these cluster analyses, children with severe asthma are characterized by a younger age of disease onset, lower lung function, and increased symptom burden and exacerbation frequency.

Emerging therapies

Long-acting anticholinergics

Tiotropium is an inhaled long-acting anticholinergic agent approved by the US FDA for the treatment of chronic obstructive pulmonary disease in adults [12[■]]. Although tiotropium is not currently approved for use in asthma or for use in children, studies suggest that younger adults with higher cholinergic tone (i.e., lower resting heart rate), lower lung function, and a higher degree of bronchodilator reversibility may benefit the most from tiotropium when added on to ICS [57,58]. Tiotropium studies have not shown a response association with atopic disease markers. Recent studies demonstrated improvements in lung function with the use of tiotropium in symptomatic 6–11-year olds [59[■]] and 12–17-year olds [60[■],61[■]] but no improvement in asthma control. It is not clear if tiotropium will reduce exacerbation frequency or how comparable it will be to combination therapy with or when added to ICS/LABA combination therapy in children.

Immunomodulator/biologics

Several immunomodulatory monoclonal antibodies are currently undergoing clinical trials in adults [12[■]]. Mepolizumab is a humanized monoclonal antibody against interleukin-5 (IL-5). Initial

mepolizumab studies have demonstrated a reduction in asthma exacerbations in adults [62,63], with only recent studies enrolling adolescents as young as 12 years old [18,19[■],64[■]] although small numbers of adolescents were enrolled. Adults maintained on high-dose ICSs with at least two exacerbations in the previous year and evidence of eosinophilic inflammation demonstrated that mepolizumab reduced the number of clinically significant exacerbations, delayed the time to first exacerbation, and decreased the number of exacerbations requiring healthcare utilization [18]. In a recent trial of adolescents and adults requiring maintenance OCS for at least 6 months and with serum eosinophilia, mepolizumab decreased daily OCS by 50% from baseline even though improving FEV₁ and symptom scores compared with placebo [19[■]]. A decreased rate of clinically significant exacerbations with mepolizumab was associated with baseline peripheral eosinophil counts of 300/ml or greater and exacerbation frequency at baseline but not atopic disease, IgE levels, FEV₁, or bronchodilator response [18] (Table 1). Reslizumab is an IgG4k humanized monoclonal antibody (mAb) that binds human IL-5 and similar to mepolizumab, reslizumab reduces eosinophilia in adults with asthma [20[■],65]. A study of reslizumab in adults with poorly controlled asthma and sputum eosinophilia of 3% or greater receiving ICSs and another asthma controller medication demonstrated an increase in FEV₁ and FVC but not asthma exacerbations [65]. Most recently, a study of adolescents and adults with poorly controlled asthma treated with ICS with a peripheral eosinophil count of 400/ml or greater demonstrated reduced asthma exacerbation rates with reslizumab similar to mepolizumab studies [20[■]] (Table 1). Reslizumab also increased the time to first exacerbation, FEV₁, symptom scores, and quality-of-life scores [20[■]]. The recombinant IL-4 variant pitra-kinra, which interferes with the action of both IL-4 and IL-13, has been shown to reduce exacerbations among adults with eosinophilia [66]. Dupilumab, a fully humanized antibody to the alpha-subunit of the IL-4 receptor shared by both the IL-4 and IL-13 receptors, reduced asthma exacerbations, improved lung function, and reduced markers of Th2 inflammation in adults with persistent moderate–severe asthma and elevated eosinophils being treated with ICS plus LABA [67]. Exhaled nitric oxide values were inversely correlated with the change in FEV₁ [15[■]]. Lebrikizumab, a monoclonal antibody against IL-13, resulted in improved lung function among adults with asthma inadequately controlled by ICS [68] especially those with high pretreatment levels of serum periostin, higher baseline exhaled nitric

oxide, IgE levels, and peripheral eosinophil counts. Although periostin levels are two-fold to three-fold higher in children than in adults, children with asthma by 6 years of age [69] and 6–15-year olds [70] had significantly higher periostin levels than children who did not have asthma by that age and with the periostin level correlating with BHR in the older children, suggesting that periostin may be an important biomarker in pediatric asthma. Overall, while these biologic immunomodulators appear to have favorable effects in adults with asthma, additional adolescent and pediatric studies to investigate a benefit in asthma outcomes and the use of therapy-guiding biomarkers are needed.

Antimicrobials

Chronic infections may contribute to severe asthma [12]. In adults, infection with *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* has been associated with lower lung function and increased BHR, which has improved with macrolide therapy [71,72]. A trial in children with moderate-to-severe persistent asthma found that the addition of azithromycin to an ICS was not corticosteroid sparing, but this trial was terminated early due to randomization failure secondary to inadequate adherence to study medication and improved asthma control under close medical supervision [73]. A recent study of 607 preschool-aged children with histories of recurrent, severe lower respiratory tract illnesses demonstrated that the use of azithromycin early during an upper respiratory tract infection reduced the likelihood of severe lower respiratory tract infections compared with placebo [21] (Table 1). Macrolide antibiotics have also been suggested for the treatment of childhood asthma associated with persistent neutrophilic inflammation [22] (Table 1) although the European Respiratory Society (ERS)/American Thoracic Society (ATS) 2014 guidelines on severe asthma recommend against its routine use in children [42]. Children may develop severe asthma in the presence of fungal infections [74], but the ERS/ATS 2014 guidelines recommend that antifungal agents only be used in children if there is evidence of allergic bronchopulmonary aspergillosis [12].

CONCLUSION

The optimal treatment strategy for children with asthma is not yet defined and likely dependent on many patient and disease characteristics. Much of the phenotypic response literature presented in this review was constrained by the limited number of pediatric and adult studies available and, as such,

should be regarded as preliminary. Better definition of asthma phenotypes and better targeting of therapy based on individual patient phenotypes is likely to improve asthma treatment in the future, so we look forward to more pediatric data to truly personalize therapies in pediatric asthma.

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