

It's Time to Start Phenotyping Our Patients with Asthma



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KEYWORDS

• Asthma • Biologic • Biomarker • Controller • Endotype • Management • Pediatric • Phenotype

KEY POINTS

- Phenotyping pediatric patients with asthma could aid medical providers in assessing response to treatment and difficulty in gaining asthma control, predicting asthma development, and initiating or stepping-up controller therapy.
- Phenotyping can be done in the clinic using demographics and readily attainable biomarkers including IgE, skin prick testing, ImmunoCAP testing, fractional exhaled nitric oxide, and spirometry.
- The development of biologic therapies for asthma emphasize the importance of phenotyping, especially when deciding which biologic to select and predicting response to therapy.

INTRODUCTION

The advent of new therapies, ranging from inhaled corticosteroids (ICS) to biologics, has led to advances in the management of pediatric patients with asthma. These therapies offer practitioners the ability to provide tailored, precision treatments to individual patients, thereby targeting therapies based on likelihood of response, reducing unnecessary or potentially harmful interventions, and minimizing side effects. Despite these advances, asthma treatment guidelines are lagging behind these advancements, leaving providers with limited guidance of which new therapeutic is best for their patients, especially for pediatric patients.

Precision medicine has been defined as targeted therapies based on genetic, biomarker, phenotypic, or psychosocial features differentiating an individual patient from another.¹ Precision medicine distinguishes a specific patient from others with

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a similar or even the same presentation. Although arguably precision medicine has existed for a long time, the rapid rate of diagnostic and therapeutic advances is allowing caregivers to provide even more individualized therapy plans than were previously available. Precision medicine is being used routinely in many fields of medicine. The discovery of estrogen receptor expression in certain forms of breast cancer led to the development of selective estrogen receptor modulators for those with estrogen receptor–positive breast cancer.² The understanding of genetic abnormalities leading to different defects in the protein structure of cystic fibrosis transmembrane conductance regulator led to the advent of ivacaftor and lumacaftor to treat patients with cystic fibrosis who have specific genetic mutations.³

Current asthma management is based on avoidance of known triggers and the use of a variety of controller medications including ICS, long-acting beta agonists (LABAs), leukotriene receptor antagonists (LTRAs), and now most recently multiple biologics, targeting the mechanisms of T_H2 inflammation. Using precision medicine to select the correct therapy for individual patients could both improve day-to-day asthma control and reduce exacerbations while decreasing health care costs and decreasing the side effects from unnecessary medications. Attempting to identify biomarkers to better understand a patient's underlying disease process is critical to selecting new treatments. Only recently, the Global Initiative for Asthma has embarked on this endeavor of precision medicine by providing guidance on biologic choice for severe asthma based on specific biomarkers identified from clinical trials.⁴ This review is intended to highlight the importance of phenotyping pediatric patients with asthma to provide an individualized approach to care.

BIOMARKERS, PHENOTYPES, AND ENDOTYPES

Asthma is a heterogeneous condition involving an array of underlying mechanisms that ultimately result in inflammation of the airways and present as reversible airway obstruction. Phenotypes and endotypes have been used to try to better categorize patients and understand their underlying mechanisms for disease. Phenotypes are observable characteristics or outward manifestations of underlying genetics and pathophysiology.⁵ Endotypes further subtype phenotypes based on pathophysiologic mechanisms underlying the disease process.⁵ A phenotype–endotype association in asthma is exemplified in aspirin-exacerbated respiratory disease. Aspirin-exacerbated respiratory disease has an underlying pathophysiologic mechanism involving an upregulation in leukotriene production, leading to a clinical presentation including asthma, sinusitis with nasal polyposis, and sensitivity to nonsteroidal anti-inflammatory drugs.

The distinctions of phenotypes have frequently been made through the use of biomarkers. The ideal biomarker is readily available, easily interpretable, minimally invasive, and reproducible over time.⁶ Various phenotypic markers used in classifying patients with asthma have included demographics such as race, blood eosinophil levels, periostin, fractional exhaled nitric oxide (F_{ENO}), aeroallergen skin prick testing or ImmunoCAP, and serum IgE (Box 1). In the pediatric asthma population, most biomarkers to date have been associated with T_H2 inflammation, in particular F_{ENO} , sensitization to aeroallergens by skin prick testing, IgE levels, and serum eosinophils. Biomarkers have been examined in the context of predicting development of asthma in children,⁷ exacerbation rates,⁸ difficulty in gaining control,⁹ and response to therapy.^{10–12}

The following sections highlight examples of how the practicing clinician can use asthma phenotypes and biomarkers to provide tailored therapy for their patients.

Box 1**Clinical variables and biomarkers used to phenotype pediatric asthma**

- Aeroallergen skin prick testing/ImmunoCAP
- Total IgE
- Blood eosinophil count
- F_ENO
- Spirometry with bronchodilator response
- Rhinitis symptoms
- Demographic features including race and body mass index

PHENOTYPING PATIENTS TO DETERMINE ASTHMA SEVERITY

Multiple studies have sought to better define asthmatic phenotypes with the goal of identifying patient characteristics that may predict response to various therapies. An initial cluster analysis in adults with obstructive airway diseases identified specific phenotypes suggesting an alternate management strategy based on patient characteristics, which deviated from current guidelines.^{13,14} This finding led to several studies that examined children with asthma and attempted to better define underlying phenotypes (**Table 1**). Similar to the adult studies, children were grouped into clusters with phenotypic characteristics focused primarily on atopy, airway physiology, symptom onset, and asthma symptom days and exacerbations.^{15–18}

In a study by Fitzpatrick and colleagues,¹⁵ cluster analysis similar to that used in the adult Severe Asthma Research Program identified four clusters of patients. Cluster 1 children had relatively normal lung function and less atopy.¹⁵ Cluster 2 children had slightly lower lung function and increased atopy, symptoms, and medication use.¹⁵ Cluster 3 children had more comorbidities such as gastroesophageal reflux disease and chronic sinusitis, lower lung function, and increased bronchial hyperresponsiveness.¹⁵ Cluster 4 consisted of children with the lowest lung function and greatest symptoms and medication use.¹⁵ Chang and colleagues¹⁸ performed a cluster analysis in the population of children who participated in the Childhood Asthma Research and Education network clinical trials. Four clusters of pediatric patients were identified that were similar to the Severe Asthma Research Program children. Howrylak and colleagues¹⁶ used patients from the Childhood Asthma Management Program, which represented patients with more mild to moderate asthma, and defined 5 different clusters of patients based on atopy, airway physiology, and exacerbations, with differences in the more severe clusters based on their responses to ICS and nedocromil.

Most recently, Zoratti and colleagues¹⁷ examined a population participating in the Inner City Asthma Consortium to define 5 different clusters (clusters A–E) of children based on blood eosinophilia, total IgE, allergic sensitization, F_ENO, pulmonary physiology, and degree of asthma and rhinitis symptoms. The majority of the most symptomatic patients had the most allergic phenotype; however, a smaller subset of children with relatively little allergic inflammation also were identified who were symptomatic.¹⁷ Cluster E was identified as the most symptomatic, unresponsive to therapy, and also had the highest levels of markers of T_H2 inflammation, suggesting that this group may be the subset who would benefit most from newer biologic medications.¹⁷ Similarly, Pongracic and colleagues⁹ used the Inner City Asthma Consortium population to identify those patients who would have difficult-to-control asthma, as defined by higher doses of ICS with or without LABA. The baseline forced expiratory volume in

Table 1
Summary of pediatric asthma phenotype cluster analyses

Reference	Population	Age (y)	Number of Patients	Phenotypic Variables	Description of Clusters
Fitzpatrick et al, ¹⁵ 2011	Persistent asthma recruited from 4 academic centers in the United States	6–17	161	Pulmonary physiology Markers of allergic sensitization and inflammation (F _e NO, SPT, total serum IgE, and serum eosinophils) Asthma history and control	Cluster 1: Late-onset (~2–10 y old) symptomatic asthma with normal lung function Cluster 2: Early-onset (1 mo–5 y old) atopic asthma with normal lung function Cluster 3: Early-onset (2 mo–2.5 y old) atopic asthma with mild airflow limitation Cluster 4: Early-onset (2 mo–3 y old) atopic asthma with advanced airflow limitation
Zoratti et al, ¹⁷ 2016	Persistent asthma recruited from low-income areas in 9 US cities	6–17	717	Pulmonary physiology Markers of allergic sensitization and inflammation (F _e NO, SPT, total serum IgE and eosinophils) Asthma history and control Rhinitis severity	Cluster A: minimally symptomatic asthma and rhinitis, lower allergy and inflammation, and normal pulmonary physiology Cluster B: highly symptomatic asthma despite high step-level treatment, intermediate rhinitis, lower allergy and inflammation, and mildly altered pulmonary physiology Cluster C: minimally symptomatic asthma and rhinitis, intermediate allergy and inflammation, and mildly impaired pulmonary physiology Clusters D: minimally symptomatic asthma, intermediate rhinitis, higher levels of allergy and allergic inflammation, and an intermediate degree of pulmonary physiology Cluster E: most symptomatic asthma and rhinitis while receiving high step-level treatment and had the highest total serum IgE level, blood eosinophil count, and allergen sensitizations

Howrylak et al, ¹⁶ 2014	Mild to moderate persistent asthma recruited from the Childhood Asthma Management Program	5–12	1041	Pulmonary physiology Atopic history Markers of allergic sensitization and inflammation (SPT, total serum IgE and eosinophils) Asthma history (specifically exacerbation risk)	Cluster 1: Mild asthma with low atopy, obstruction and exacerbation rate Cluster 2: Atopic asthma with low levels of obstruction and medium rates of exacerbation Cluster 3: Atopic asthma with high levels of obstruction and medium rates of exacerbation Cluster 4: Moderately atopic asthma with high levels of obstruction and high exacerbation rates Cluster 5: Highly atopic asthma with high levels of obstruction and high exacerbation rates
Chang et al, ¹⁸ 2014	Mild to moderate persistent asthma recruited from Childhood Asthma Research and Education network clinical trials	6–18	611	Pulmonary physiology Markers of allergic sensitization and inflammation (F _{ENO} , SPT, total serum IgE and eosinophils) Asthma history and control Comorbidities	Cluster 1: Late onset (~3–8 y old), normal lung function, lowest F _{ENO} and IgE Cluster 2: Early onset (~2 mo–2 y old), normal lung function Cluster 3: Early onset (~4 mo–2 y old), higher comorbid conditions Cluster 4: Early onset (~2 mo–3 y old), impaired lung function

Abbreviation: SPT, skin prick testing.

1 second (FEV₁) bronchodilator responsiveness was the most important distinguishing characteristic, followed by markers of rhinitis severity and atopy.⁹

These studies illustrate that, by obtaining baseline biomarkers in patients with persistent asthma, clinicians may more readily identify those patients who are at increased risk for difficult-to-control and severe asthma, despite good adherence to standard guideline therapy. These patients may benefit from more frequent symptom monitoring, increased identification of triggers, patient education, and potentially targeted use of biologic therapies.

PREDICTING ASTHMA DEVELOPMENT IN YOUNG CHILDREN

The diagnosis of asthma in young children and the differentiation of which children may go on to develop asthma is an important question for both parents and clinicians. Typical testing such as spirometry could be attempted if you have a cooperative child nearing school age, but this modality does not help in a younger population. Anderson and colleagues⁷ demonstrated that biomarkers can aid physicians in determining which children will go on to develop asthma. They followed 244 children from birth and collected blood samples at 2, 4, 6, and 11 years of age to assess the relationships among aeroallergen sensitization, blood eosinophils, and periostin levels with the development of asthma.⁷ Aeroallergen sensitization, and eosinophilia were found to be predictors of asthma development in young children.⁷ Periostin was not found to be helpful given bone turnover in children, which can result in elevated periostin.⁷ Aeroallergen sensitization and eosinophil levels meet the aforementioned qualities of a good biomarker and importantly are easily obtainable in young children. Such testing would be beneficial to obtain in toddlers and preschool-aged children with recurrent wheezing to help guide future management and help families to anticipate their children's future care.

SELECTING CONTROLLER AND STEP-UP THERAPIES

The management of asthma for the past decade has been guided by the National, Heart, Lung and Blood Institute (NHLBI) Expert Panel 3 from 2007.¹⁹ In this report, biomarkers were discussed with respect to management; however, patient phenotypes were not taken into account in the creation of the stepwise approach to management. The traditional stepwise approach for asthma management is helpful, but with the advances in available therapies, we need an updated approach, incorporating patient phenotypes and endotypes into diagnostic and management decisions.

The initiation of asthma therapy in the very young population can be challenging for providers and parents, particularly given concerns for medication side effects in these patients, including a decrease in linear growth associated with ICSs.²⁰ The Individualized Therapy for Asthma in Toddlers study examined response to daily ICS, as needed ICS, and LTRA based on phenotyping in children 12 to 59 month old.²¹ Children with peripheral blood eosinophil counts of 300 cells/ μ L or greater and aeroallergen sensitization had better responses to daily ICS therapy with fewer exacerbations and more asthma control days than other therapies.²¹ Overall, children requiring the initiation of asthma therapy responded the best to daily ICS therapy, but the subset with the presence of these biomarkers derived the greatest benefit.²¹ In the patient group that had no aeroallergen sensitization and with peripheral blood eosinophil counts of less than 300 cells/ μ L, there was no difference in their response to daily ICS, as-needed ICS, or LTRA.²¹

In a study by Szeffler and colleagues,¹⁰ the responses to ICS and LTRA in 6- to 17-year-old patients with mild to moderate persistent asthma were compared. ICS

were superior to LTRA in patients with evidence of allergic inflammation, including elevated $F_{E}NO$, eosinophilia, and elevated IgE levels.¹⁰ Those with lower lung function and a lower methacholine PC_{20} also responded better to ICS.¹⁰ Meanwhile, the authors suggested that patients with normal lung function and no evidence of allergic inflammation could be trialed on either ICS or LTRA.¹⁰ The use of $F_{E}NO$ as a biomarker for medication selection has been validated in additional pediatric studies. Pediatric patients with asthma and elevated $F_{E}NO$ have been shown to have more asthma control days when treated with ICS.²² $F_{E}NO$ can be used by practitioners to determine the likelihood of response to ICS and for the monitoring of compliance with ICS therapy.¹¹

Biomarkers can be useful in guiding the appropriate step-up treatment for pediatric patients with uncontrolled asthma. The Best Add-on Therapy Giving Effective Response (BADGER) study found overall that LABAs were the most effective step up therapy compared with increased ICS dosing or addition of LTRA for 6- to 17-year-old children with uncontrolled asthma on low-dose ICSs.²³ A post hoc analysis of the BADGER study demonstrated differences in response to add-on therapy based on a history of eczema and patient race.²⁴ In patients without eczema regardless of ethnicity, the addition of LABA was superior to the other therapies.²⁴ In those with eczema, the best response to step-up therapy was dependent on ethnicity, with black children responding best to increased ICS, white Hispanic children responding best to LTRA addition, and white non-Hispanic children responding best to either LABA or LTRA addition.²⁴

SELECTING A BIOLOGIC

The advent of multiple biologics for the management of severe asthma in pediatric and adolescent patients highlight the imperative to phenotype our patients to provide targeted care. These therapies are ideal in the field of precision medicine given their degree of specificity to target a specific cytokine, antibody, or receptor. Given the financial and time costs to patients for these biologics, as well as their relatively more invasive administration compared with other controller therapies, identifying which patients are best suited for each therapy before initiation would be ideal. Biologic medications currently possessing an approval from the US Food and Drug Administration for pediatric and adolescent patients include omalizumab, mepolizumab, benralizumab, and dupilumab, all of which focus on T_H2 -mediated inflammation (Table 2). At the time of publication, reslizumab was only approved for adults. With the exception of omalizumab, most studies to date have only included patients as young as 12 years old, and even then that adolescent population was not robustly represented in the trials, emphasizing the need for pediatric specific trials.

Omalizumab

The benefits of omalizumab in asthma have been well-established, including reduced exacerbations, symptoms, health care use, missed school days, and oral corticosteroid use.²⁵ In inner-city patients with asthma aged 6 to 20 years with persistent or uncontrolled asthma, the addition of omalizumab to NHLBI guideline-based therapy reduced symptom days, exacerbations, and ICS dose.²⁶ Notably, the additional of omalizumab reduced seasonal exacerbations in this treatment group compared with placebo.²⁶ A post hoc analysis examining the efficacy of omalizumab found participants with $F_{E}NO$ of 20 ppb or greater, blood eosinophils of 2% or greater, and a body mass index of 25 or greater were more likely to benefit with respect to reduced exacerbations.²⁷ Beyond these biomarkers, prior exacerbations and NHLBI controller step therapy has been identified as phenotypic predictors of omalizumab response in

Table 2
Summary of biologics approved for pediatric asthma

Biologic	Mechanism of Action	FDA Approval Age for Asthma	Indications	Dose, Route and Dosing Interval	Predictors of Response
Omalizumab	Humanized, monoclonal anti-IgE binding free IgE	≥ 6 y old	Moderate-to-severe persistent asthma, symptoms inadequately controlled with ICS, perennial aeroallergen sensitization	Based on age, weight, and IgE levels; SQ	Elevated F _e NO Elevated serum eosinophils Body mass index of ≥ 25 Exacerbations on NHLBI Step 5 therapy
Mepolizumab	Humanized, monoclonal antibody binding to IL-5	≥ 12 y old	Severe persistent asthma, eosinophilic phenotype	100 mg SQ every 4 wk	Elevated serum eosinophils Frequent exacerbations
Benralizumab	Humanized, monoclonal antibody against the IL-5 α receptor leading to antibody-dependent cell-mediated cytotoxicity	≥ 12 y old	Severe persistent asthma, eosinophilic phenotype	30 mg SQ every 4 wk for the first 3 doses then spaced to every 8 wk thereafter	Elevated serum eosinophils Frequent exacerbations
Dupilumab	Fully humanized, monoclonal antibody against the IL-4 α receptor blocking both the IL-4 and IL-13 pathways	≥ 12 y old	Moderate-to-severe persistent asthma, eosinophilic phenotype, or with oral corticosteroid dependent asthma	Initial dose: 400 mg or 600 mg SQ Maintenance dose: 200 mg or 300 mg SQ every 2 wk	Elevated serum eosinophils Frequent exacerbations Elevated F _e NO

Abbreviation: SQ, subcutaneous.

pediatric patients. In the Preventative Omalizumab or Step-Up Therapy for Fall Exacerbations, Teach and colleagues²⁸ found those pediatric patients on NHLBI treatment step 5 and who had an exacerbation in the run-in period had the greatest reduction in fall exacerbations with the addition of omalizumab.

Mepolizumab

Mepolizumab has been found to reduce exacerbations, hospitalizations, and emergency room visits, while increasing the time to first exacerbations and improving pre-bronchodilator and post-bronchodilator FEV₁.^{29,30} Of note, these findings were only found when the patient population was selected for signs of eosinophilic inflammation including peripheral blood eosinophilia, sputum eosinophilia, and elevated F_ENO.^{29,30} Adolescents 12 years and older were included in both of these studies, but their numbers were relatively small compared with adult patients and no specific studies looking at a pediatric population have been published at this time. Pediatric specific studies must be performed as currently we can only extrapolate data from these adolescent and adult studies. Among adult patients, an elevated blood eosinophil count and increased exacerbation in the prior year were the greatest predictors for a decrease in exacerbations with mepolizumab.²⁹

Benralizumab

Benralizumab has been demonstrated to reduce exacerbations, improve symptoms, and increase pre-bronchodilator FEV₁ in adolescent and adult patients who were not well-controlled despite medium- to high-dose ICS/LABA therapy compared with placebo.^{31,32} Of note in both of these studies the adolescent population accounted for only a small proportion of the total study population in the final analysis at approximately 5.2% and 2.4%.^{31,32} In a study combining 2 phase III trials, the researchers concluded that the extent to which exacerbation rates were decreased with benralizumab increased with increasing blood eosinophil counts and in patients with higher rates of exacerbation.³³ The studies examined patients with peripheral blood eosinophils 300 cells/ μ L or greater and those with less than 300 cells/ μ L.³³

Dupilumab

In a study assessing efficacy and safety, dupilumab decreased exacerbation rates in patients 12 years of age or older with uncontrolled asthma and improved FEV₁ by 0.32 L compared with 0.14 L with placebo.³⁴ The annual rate of exacerbation was decreased even further in patients with an absolute eosinophil counts 300 cells/mm³ or greater, whereas those with an eosinophil count of less than 150/mm³ had no significant difference in exacerbation rates between the dupilumab and placebo groups.³⁴ Additionally, patients with elevated F_ENO showed greater benefit with respect to reduction in exacerbations.³⁴ In this study again only approximately 5.6% of participants were adolescents.³⁴ In another study examining the impact of dupilumab in reducing oral glucocorticoid doses in patients with glucocorticoid-dependent asthma, the researchers found a reduction in glucocorticoid dose regardless of eosinophil count, but found a greater impact on those with peripheral blood eosinophil counts of 300/mm³ or greater.³⁵

SUMMARY

The evidence for asthma management has advanced such that the use of basic screening biomarkers, including IgE, eosinophil counts, and aeroallergen sensitization, for pediatric patients with asthma can provide tailored, personalized

management. By phenotyping pediatric patients with asthma, health care providers can recognize which may be more difficult to treat, which may be more symptomatic or prone to exacerbations, and which may benefit from one controller therapy over another. As approval for biologics continue to move to younger populations, researchers should explore key phenotypic features that would identify which patients would best respond to one biologic over another. Future asthma management guidelines should incorporate this evidence to provide direction on which biologic or controller therapy should be chosen. Phenotyping pediatric patients with asthma will allow providers to elevate existing treatment strategies to provide precision care for their patients and hopefully improve outcomes.

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