

Personalized Medicine and Pediatric Asthma



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KEYWORDS

• Personalized medicine • Pediatric asthma • Biologics • Preschool • School-age
• Adolescent

KEY POINTS

- In preschool-aged children, daily inhaled corticosteroids (ICSs) are most effective in those with allergic phenotypes and more persistent symptoms, whereas intermittent therapies are effective in children with intermittent asthma, such as ICS in those with a positive modified asthma predictive index (mAPI) or azithromycin in those with either a positive or negative mAPI.
- In school-aged children and adolescents, those with allergic phenotypes benefit most from ICSs alone or in combination with other therapies.
- Biologic therapies provide benefit to those with severe, poorly controlled, school-age children and adolescents with asthma who have eosinophilic phenotypes.
- Emerging therapies, such as macrolides and bronchial thermoplasty, and additional phenotypic markers, such as sputum inflammatory patterns, will allow for an improved, personalized approach to pediatric asthma in the future.

INTRODUCTION

Asthma is a heterogeneous disorder described by a large number of clinical features, including age of onset, triggers, atopy, frequency and severity of symptoms, and response to therapies.^{1,2} Biomarkers describing the pattern of inflammation, lung function, and degree of bronchial hyperresponsiveness also help to characterize specific phenotypes.^{1,2}

The existing asthma guidelines, as described previously in this journal in articles on management by Drs Kwong and Shipp, are age-based and symptom-based with the

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goal of achieving adequate control through stepwise escalation of therapies.^{3,4} A growing body of literature on more specific asthma phenotypes and mechanism-based endotypes provides evidence for a phenotype-based approach to management in which specific therapies are recommended based on patient and disease characteristics. This review summarizes this evidence for children ranging from pre-school age to adolescence with a focus on markers of response to therapies.

PRESCHOOL

Inhaled Corticosteroids

Inhaled corticosteroids (ICSs) are first-line treatment for asthma in the preschool age group.^{3,4} A recent meta-analysis emphasized their important role.⁵ Looking at 3278 subjects over 15 studies, the investigators found a 30% reduction in exacerbation risk when comparing daily, medium-dose ICSs with placebo. This effect was greater in children with persistent asthma in whom a 44% risk reduction was demonstrated compared with placebo. The same meta-analysis showed a 36% reduction in exacerbations on intermittent ICS compared with placebo in intermittent asthma and when directly comparing daily and intermittent ICS showed no significant difference in the rates of exacerbation. As described in a recent review by Beigelman and Bacharier,⁶ there are persistent questions about which specific phenotypes may respond more favorably to daily or intermittent ICSs. Prior analyses of children with recurrent episodic wheezing have shown that those children with Caucasian race, male sex, recent emergency department visits or hospitalizations, and aeroallergen sensitization through skin prick testing or specific immunoglobulin (Ig)E testing responded more favorably to daily ICS.⁷ The INFANT (Individualized Therapy for Asthma in Toddlers) trial⁸ looked at markers of treatment response through a randomized trial in which preschool-age children with mild persistent asthma received daily ICS, daily leukotriene receptor antagonist (LTRA) and intermittent, as-needed ICS. They found that greater probability of best response to daily ICS was predicted by aeroallergen sensitization and blood eosinophil counts greater than 300/ μ L with the greatest response observed in those participants with both features. Exacerbation history, sex, modified asthma predictive index (mAPI), serum IgE, and urinary leukotriene E4 levels did not predict a differential response.

Oral Corticosteroids

Although oral corticosteroid treatment for acute asthma exacerbation in older children and adolescents is a mainstay of therapy, extrapolation of this treatment to the preschool age group has not demonstrated the same efficacy. A meta-analysis looking at outpatients in the clinic or emergency department setting with moderate asthma or recurrent wheezing episodes showed that oral corticosteroids did not prevent hospitalizations or urgent visits and was associated with higher hospital admission rates than placebo.⁹ This meta-analysis and recent Global Initiative for Asthma (GINA) guidelines³ suggest that oral corticosteroid use should be limited in the preschool age group. However, certain subgroups of preschool children may be more likely to respond to oral corticosteroids, such as those with rhinovirus-induced wheezing or early atopic sensitization.¹⁰

Leukotriene Receptor Antagonists (Montelukast)

The previously described INFANT trial⁸ showed that although daily ICS was most likely to be effective in children with aeroallergen sensitization and/or elevated blood eosinophil counts, alternate therapies including daily LTRA were reasonable alternatives in

children without those allergic markers and showed similar effects on exacerbations. According to a recent meta-analysis, for preschoolers with episodic wheezing not stratified by allergic markers, neither daily nor intermittent LTRA led to a reduction in systemic corticosteroid courses.¹¹ A multicenter trial in which children age 10 months to 5 years were randomized to either montelukast or placebo did not show any clear benefit in the treatment arm but did see an increased response in those with variability in the ALOX5 gene promoter, a finding previously identified in adults.¹²

Episodic Macrolides (Azithromycin)

For children with episodic wheezing and more severe exacerbations requiring high health care utilization but minimal symptoms between episodes, azithromycin may provide significant benefit through multiple proposed mechanisms, including an anti-inflammatory effect and effects on the respiratory microbiome.^{13–15} A multicenter trial¹⁶ showed that azithromycin administration 12 mg/kg per day for 5 days started early after onset of upper respiratory tract symptoms helped to prevent progression to lower respiratory tract symptoms. The risk of progression was reduced by 36% compared with placebo, similar to the previously described improvement with ICSs. There was no difference in effect between groups with a positive or negative mAPI. Seventeen percent of those treated with azithromycin developed resistant organisms, *Staphylococcus aureus* most commonly, similar to 11% of those receiving placebo. Another trial¹⁷ in preschool-age children randomized 72 children to receive either azithromycin (10 mg/kg per day for 3 days) or placebo during apparent asthma episodes and found a significant reduction of duration of symptoms (3.4 days vs 7.7 days) with a greater effect related to earlier initiation of therapy.

Summary of Preschool Age Group

As proposed in the review by Beigelman and Bacharier⁶ and summarized in [Fig. 1](#), a phenotypic approach to asthma management in the preschool age group would first classify children based on pattern of exacerbations and degree of impairment. Those with intermittent episodes but minimal persistent symptomatology are likely to benefit from an intermittent therapy such as ICSs or azithromycin. Oral corticosteroids have not been shown to provide clear benefit in this age group. For those with a negative mAPI, intermittent azithromycin has proven benefit in this group that has previously not been well-represented in asthma trials. Those with positive mAPI are likely to benefit from intermittent ICSs. Although there is evidence to support use of azithromycin in the positive mAPI group, there is an alternative therapy in the form of ICSs that avoids the potential risk of acquisition for azithromycin-resistant organisms. Certain clinical features (males, Caucasians, those with increased symptoms burden or health care utilization, and aeroallergen sensitization) may show increased benefit from daily ICSs. Finally, in those children with more persistent symptoms and allergic phenotypes represented by elevated eosinophils and/or aeroallergen sensitization, daily ICSs are the most effective therapy. Additional evidence and development of emerging therapies are required to better treat those children with persistent symptoms and a nonallergic phenotype.

SCHOOL-AGE CHILDREN AND ADOLESCENTS

Inhaled Corticosteroids

As in the preschool-age group, ICSs are the first-line treatment for all school-age and adolescent children with persistent asthma.^{3,4} In a study of children aged 6 to 14 years with poorly controlled, mild-moderate persistent asthma, ICSs alone showed

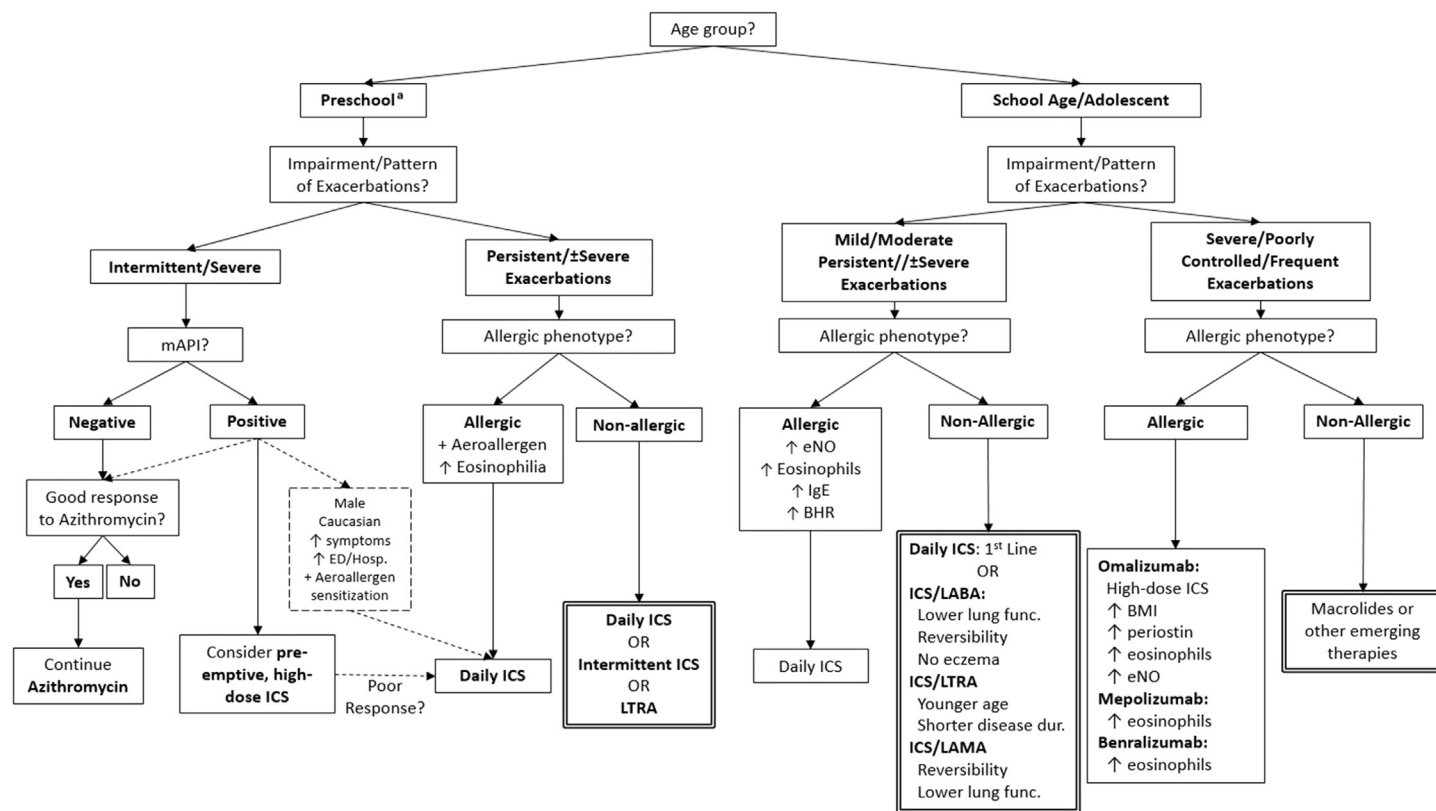


Fig. 1. Phenotype-based algorithm for management of pediatric asthma based on markers of response. ^aLimited evidence for oral corticosteroid use in the preschool age group. Double-lined box = limited evidence for treatment options in the nonallergic phenotypes. ↑, increased; BHR, bronchial hyper-responsiveness; BMI, body mass index; ED/Hosp., emergency department/hospital; eNO, exhaled nitric oxide. (Modified from Beigelman A, Bacharier LB. Management of preschool recurrent wheezing and asthma: a phenotype-based approach. *Curr Opin Allergy Clin Immunol* 2017;17(2):131-8; with permission.)

improved control over both leukotriene receptor antagonist and combination ICS/long-acting beta-agonist therapy.¹⁸

ICS therapy alone has shown improved control for children with the following:

1. Exhaled nitric oxide levels ≥ 25 ppb
2. Peripheral eosinophilia $\geq 5\%$
3. Ig E levels >150 KU/L^{18,19}

A crossover study comparing ICSs with montelukast directly in children between 6 and 17 years old with mild-moderate persistent asthma showed that children with higher exhaled nitric oxide levels, total eosinophil counts, serum IgE levels, serum cationic protein levels, bronchial hyperresponsiveness on methacholine challenge, and lower baseline lung function showed a greater response in forced expiratory volume in 1 second (FEV₁) on ICSs.²⁰

Oral Corticosteroids

A meta-analysis of children 3 years and older presenting to the emergency room with acute asthma symptoms demonstrated that oral corticosteroids given early in the setting of acute exacerbation reduce the need for hospitalization and remain a first-line treatment.²¹ A meta-analysis of children 2 years or older with asthma ranging from mild to severe investigating early initiation of ICSs rather than systemic corticosteroids in an emergency department setting showed insufficient data to favor the use of ICSs alone.²²

Leukotriene Receptor Antagonists (Montelukast)

In the previously described study²⁰ comparing ICSs with montelukast directly through a crossover design in children 6 to 17 years old with mild-moderate persistent asthma, montelukast was shown to have favorable outcomes predicted by younger age and shorter disease duration. However, another review of 2 studies in children from 2 to 14 years old with moderate symptoms has not shown significant factors predicting favorable response to montelukast.²³

Long-Acting Beta-Agonists

Long-acting beta-agonist (LABA) therapy in combination with an ICS is a guideline-recommended step-up therapy for those with poorly controlled asthma on ICSs alone.⁴ A study of children 6 to 17 years old on low-dose ICSs with mild-moderate persistent asthma who stepped-up to either medium-dose ICS, low-dose ICS/LABA, or low-dose ICS/LTRA showed significant improvement across all groups but was most significant in the LABA step-up group.²⁴ This response was most significant in those with lower baseline lung function. Further post hoc analysis showed that those without eczema had the most consistent improvement, whereas those without eczema had variable response depending on race and ethnicity.²⁵ Multiple double-blind, randomized studies examining safety with the combination of LABA and ICS therapies have helped to allay prior concerns.^{26–28}

Long-Acting Muscarinic Antagonists

Tiotropium is a long-acting muscarinic antagonist (LAMA) that has been approved for children 6 years and older. When used in combination with ICSs in children with moderate to severe asthma, it has shown improved lung function and decreased symptom burden.^{29,30} In adults with moderate persistent asthma, there is a greater response in those with lower baseline lung function, higher degree of bronchodilator response,

and higher systemic cholinergic tone³¹; however, there currently are no data suggesting what phenotypic characteristics might predict response in children.

Biological Therapies

Omalizumab

Omalizumab is an injectable recombinant humanized IgG1 monoclonal anti-IgE antibody that can be considered in patients who are poorly controlled despite high doses of standard therapies.³² It is approved for children 6 years or older with moderate to severe persistent asthma, evidence of perennial aeroallergen sensitivity, and inadequate control of symptoms on ICSs.³³ Injections are given every 2 to 4 weeks and there are specific IgE and weight requirements.³³ It has been shown to reduce required ICS dosing and number of exacerbations in children to moderate to severe asthma.^{34,35} It has also been shown to reduce rate of severe exacerbations, emergency department visits, hospitalizations, unscheduled office visits, rescue therapy use, and ICS dose in teenagers and adults with poorly controlled severe persistent asthma.^{1,36–39} In a separate study of inner-city children with moderate to severe persistent asthma it led to improved control, reduction in seasonal peaks in exacerbations, and reduction in need for additional medications.⁴⁰ It is most effective in children and adolescents who require high-dose ICSs and experience frequent exacerbations.^{41,42} A greater response has also been observed in those with higher levels of peripheral eosinophils, higher periostin (a biomarker found to correlate with T2 high inflammatory response), higher exhaled nitric oxide levels, and higher body mass index.^{1,37,43–47}

Mepolizumab

Mepolizumab is a humanized monoclonal antibody against interleukin (IL)-5 aimed at those with severe eosinophilic asthma.^{32,48} It is approved for children older than 12 years as an add-on therapy in those with severe persistent asthma and an eosinophilic phenotype, and it is given subcutaneously every 4 weeks.⁴⁹ It has been showed to increase FEV₁, reduce exacerbations requiring emergency room visits and hospitalizations, and improve control and symptoms.^{50,51} Greater response is related to higher blood eosinophil levels.^{50,51}

Benralizumab

Benralizumab is a humanized monoclonal antibody targeting the alpha subunit of the IL-5 receptor, also aimed at those with severe and poorly controlled eosinophilic asthma.^{32,52} It has been showed to reduce oral glucocorticoid needs and exacerbation rates.⁵³ It was recently approved as an add-on maintenance therapy for children age 12 and older with severe asthma and eosinophilic phenotype, and it is given subcutaneously at 4-week intervals for the first 3 doses and then every 8 weeks.⁵⁴

Emerging Therapies

There are a limited number of studies of children with nonallergic, typically neutrophil predominant, phenotypes. Chronic azithromycin is often used in cystic fibrosis for neutrophilic inflammation. Meta-analysis of azithromycin in adults with severe asthma did not show significant benefit above placebo; however, 2 of the included studies did show possible benefit in noneosinophilic asthma.⁵⁵ A recent randomized, placebo-controlled, double-blinded study in adults with persistent asthma requiring ICSs and long-acting bronchodilators showed that azithromycin treatment resulted in fewer asthma exacerbations and improved quality of life in both eosinophilic and noneosinophilic asthma.⁵⁶ Additional research is needed in the school-age pediatric age group.

Bronchial thermoplasty is a radiofrequency-generated thermal treatment of the airways by flexible bronchoscopy intended to reduce airway smooth muscle mass.⁵⁷

Treatment has been shown to reduce severe exacerbations and reduce emergency department visits in adults with severe, uncontrolled asthma.^{58,59} This treatment is currently approved only for those 18 years and older and there have been no studies in the pediatric or adolescent age groups.⁶⁰

Several studies have looked at additional phenotypic markers that may be useful in the future for stratifying and further tailoring treatment of children with severe asthma. One recent cohort trial of individuals 6 to 18 years old with severe asthma had a number of inflammatory markers followed over a 3-month period. Comparisons between those who were treatment-refractory and those who achieved control showed that sputum neutrophils, IL-10, interferon- γ , tumor necrosis factor- α , and granulocyte-macrophage colony-stimulating factor were higher in the refractory group.⁶¹ There was no difference seen in fractional exhaled nitric oxide (FeNO) in this study. Prior meta-analyses combining adult and pediatric data across a range of asthma severities using both FeNO and sputum eosinophils to dictate medical management showed that likelihood of exacerbations decreased but asthma control based on symptom score and lung function were not impacted.⁶²

Other Considerations for Adolescents

Management of chronic illness in the adolescent population presents unique challenges that differ from the younger, school-age child. A range of environmental, psychosocial, behavioral, and lifestyle factors impact asthma control in this age group.^{63–65} It is important that providers consider these factors when choosing therapies. Multiple studies^{66–68} have shown that incorporating psychosocial interventions through behavioral and cognitive-behavioral approaches in combination with education about the disease and medications has resulted in improved medication adherence, reduced asthma severity, and reduced psychological problems that have been described in association with severe asthma.

Summary of School-Age and Adolescent Age Group

For school-age and adolescent children with mild persistent asthma who have an allergic phenotype marked by elevated eosinophils and elevated IgE levels in addition to increased bronchial hyperresponsiveness and higher levels of exhaled nitric oxide, ICSs remain the first-line treatment, whereas leukotriene receptor antagonists can be considered as first-line treatment in children of younger age or shorter disease duration. Step-up therapies, such as leukotriene receptor antagonists, LABAs and LAMAs, in combination with ICSs have all been shown to have benefit, with ICS/LABA showing greater efficacy than ICS/LTRA, especially in those with lower baseline lung function and in those without eczema. Specific evidence for how ICS/LAMA combinations perform for specific phenotypes and in comparison with other combinations is not yet available in the pediatric age range. For children with severe asthma, frequent or severe exacerbations, and poor control on the therapies described previously, multiple biologic agents are available. All have shown to be more beneficial in children with higher eosinophil levels and omalizumab has been shown to have greater efficacy in those with poor control on high-dose ICSs, higher exhaled nitric oxide levels, higher periostin, and higher body-mass index. Current Food and Drug Administration approvals regarding age range and dosing regimens must be taken into account when tailoring biologic therapy to a specific patient. For children with nonallergic phenotypes, there is less evidence guiding phenotype-specific therapy. Finally, although important in all patients, addressing psychosocial, environmental, behavioral, and lifestyle factors in the adolescent population is crucial to establishing improved asthma control.

SUMMARY

The optimal treatment strategy for a child with asthma is not yet clearly defined. An increase in the number of available therapies for children with asthma coupled with a growing body of evidence on specific phenotypes within this heterogeneous disease suggest a phenotype-based approach will allow for improved asthma management. The evidence reviewed is limited in children and often based on post hoc analyses, so should be regarded as preliminary. Improved understanding of specific asthma phenotypes and research into targeted therapies is likely to significantly improve asthma treatment in the future.

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