

Pediatric Asthma

Guidelines-Based Care, Omalizumab, and Other Potential Biologic Agents



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KEYWORDS

• Asthma • Asthma management • Pediatric asthma • Biologics • Omalizumab

KEY POINTS

- Current step-up asthma therapy is sufficient for most children with asthma, although physicians must work to ensure medication compliance.
- Phenotypic and genotypic variability in asthma are becoming increasingly important in asthma management, particularly with regard to the use of biologics.
- The future of asthma in children will include earlier diagnosis and even prevention as more is learned about the development of this disease.

INTRODUCTION

Asthma affects more than 6 million children, making it one of the most common chronic diseases of childhood, and the prevalence continues to increase.¹ Asthma accounts for more than 14 million school absences each year and is the leading cause of hospitalizations among children.^{2–4} However, advances in medical therapy have reduced the number of asthma-related deaths and improved overall quality of life for many asthmatics.^{1,2} Effective management guidelines now exist, with substantial supporting evidence from clinical trials in asthmatic children.⁵ However, over the past decade there has been a rapid increase in novel therapies for asthma management and few of these have been studied in children.

Further complicating pediatric asthma management is the diagnosis of asthma. There is significant heterogeneity among children who wheeze, and only a subset of all children who wheeze go on to develop asthma.^{6–8} Several studies have evaluated both children who wheeze and those who subsequently develop asthma and have clustered children into distinct phenotypes.^{6–9} This phenotypic variability is only a small part of the heterogeneity among asthmatics, as can be seen with the range of

Funding: NIH/NIAID K24 AI106822.

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Immunol Allergy Clin N Am 35 (2015) 129–144

<http://dx.doi.org/10.1016/j.iac.2014.09.005>

immunology.theclinics.com

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responses to guidelines-based therapy. Although this heterogeneity causes some difficulty in the diagnosis and management of asthma in children, it also poses the unique opportunity for targeted asthma therapy. In the era of biologics, targeted therapy may become increasingly important and fundamental to management.

This article focuses on (1) the evidence supporting the current guidelines-based therapies, with an emphasis on phenotypic heterogeneity; (2) promising novel therapeutics that have not yet been incorporated into standard care; and (3) potential opportunities for prevention of pediatric asthma.

MEDICATION ADHERENCE

Once the diagnosis of asthma is established, ensuring medication adherence becomes a fundamental component of asthma management.^{5,10,11} Poor adherence leads to increased morbidity and unnecessary escalation of treatment regimens.^{10,11} In children with asthma, noncompliance with inhalers is a significant problem in all disease severity categories, with some studies citing adherence rates of less than 60%.^{12–15}

The reasons for nonadherence are many and differ depending on the child and family.^{15–18} Cost, lack of knowledge about asthma, and patient motivation have been cited in multiple studies as the most critical barriers to adherence.^{17,18} In several analyses, education of the parent or caregiver on the importance of medication and impact on the underlying disease was a major factor toward improving child medication adherence.^{17,18} Providers also play a key role, because appointment time constraints, changes in providers, and barriers to scheduling appointments have all been shown to worsen medication compliance.^{17,18} Implementation of the guidelines-based therapy and the development of novel therapies for the refractory asthmatic (discussed later) are only of benefit if clinicians address adherence as a primary component of asthma management.

INHALED CORTICOSTEROIDS

Based on several large trials, inhaled corticosteroids have become the first-line agent in the management of asthma and remain the preferred treatment choice for all levels of persistent asthma in children.^{19,20} However, in spite of improving asthma control, inhaled corticosteroids have not been shown to alter the progression of asthma. In a large randomized controlled trial from the childhood asthma management program (CAMP) group, budesonide was not shown to preserve lung function compared with placebo.^{21,22} The prevention of early asthma in kids (PEAK) trial showed that inhaled corticosteroids decreased wheezing episodes and need for supplemental inhalers in young children with a positive modified Asthma Predictive Index, but this effect did not last once the inhaled corticosteroids were discontinued.²⁰ Inhaled corticosteroids similarly have not been shown to alter the progression of intermittent to persistent wheezing in infants.²³ In addition, there is evidence to suggest that well-controlled asthmatic children on inhaled corticosteroids with normal spirometry continue to have abnormalities in lung clearance indices, suggesting that abnormalities persist despite not being detectable using standard office measurements.²⁴

Newer data suggest that inhaled corticosteroids may hold greater benefit in certain subpopulations. Numerous studies have shown heterogeneity in response to inhaled corticosteroids.^{20,25–28} For example, some studies have shown that treatment with fluticasone propionate has greatest benefit in children with frequent symptoms, family history of asthma, and a positive Asthma Predictive Index.^{20,25} Another study found better outcomes with inhaled corticosteroids in white children, boys, and those with aeroallergen sensitization.²⁷ More recently, benefit from fluticasone propionate has been associated with specific genetic polymorphisms.^{26,28}

Furthermore, the newer generation of inhaled corticosteroids may improve control for the asthmatic population. The newer inhaled corticosteroids ciclesonide and mometasone generate smaller particles and thus better reach the peripheral airways at lower doses. Although there is evidence to suggest that children on traditional long-term inhaled corticosteroids may have increased risk for delayed growth, studies support that most children achieve their predicted adult heights when treated with recommended doses.^{22,29} Nevertheless, studies suggest that the newer generation of inhaled corticosteroids have a smaller side effect profile because of lower daily doses.^{16,30–35} However, a 2013 Cochrane Review found no difference in control of asthma symptoms, exacerbations, or side effects between ciclesonide, budesonide, and fluticasone.³⁶ An additional potential benefit of these newer agents is that both ciclesonide and mometasone are effective as once-daily dosing, and thus may improve medication adherence.^{16,34,37}

ALTERNATIVES TO INHALED CORTICOSTEROIDS

Other agents, including cromolyn and leukotriene receptor antagonists, have also shown some benefit in children but overall have not performed as well as inhaled corticosteroids and thus are not considered first-line therapy.^{5,38–44} As with inhaled corticosteroids, there may be some phenotypic variability in response to leukotriene receptor antagonists. Evidence suggests that the differential response to inhaled corticosteroids and leukotriene receptor antagonists is greatest in children with lower lung function, allergic airway inflammation, and increased FeNO levels, and children with higher ratios of urinary leukotriene E4 to FeNO may respond better to leukotriene receptor antagonists.^{38–45} The data are inconsistent and thus these biomarkers have not yet been included in the guidelines for clinical practice.⁵

Theophylline, an agent with a long history in the management of asthma, has been shown to be inferior to inhaled corticosteroids and inferior to montelukast as add-on therapy.^{46,47} One small trial showed that the addition of theophylline to inhaled corticosteroids resulted in improvement in peak expiratory flow, but did not improve forced expiratory volume in 1 second (FEV₁) or bronchial reactivity.⁴⁸ Given the lack of substantial supporting evidence, potential toxicity, and need for frequent monitoring, theophylline is not part of first-line therapy for children with asthma and is not recommended for children less than 5 years of age.⁵

STEP-UP THERAPY

If inhaled corticosteroids do not adequately manage a child's asthma, the guidelines suggest that the next step in therapy should be the addition of a long-acting beta agonist.⁵ The addition of a long-acting beta agonist to inhaled corticosteroids has been shown to improve lung function for most children, but many studies have shown that there is significant variability in response and resulting asthma control.^{44,49–54} The Best Add-On Giving Effective Response (BADGER) study showed that, although the addition of long-acting beta agonists to low-dose inhaled corticosteroids was most likely to reduce exacerbations and improve FEV₁ and the number of asthma control days compared with medium-dose inhaled corticosteroids or the addition of a leukotriene receptor antagonist, the study also showed that there was significant variability among the children with regard to these results.⁵⁴ As many as 26.7% of children in the study responded better to a medium dose of inhaled corticosteroids and 29.2% to leukotriene receptor antagonists.⁵⁴ In a recent post-hoc analysis of the BADGER study, Rabinovitch and colleagues⁴⁴ identified phenotypic variables that differentiate these populations of children. Higher impulse oscillometry reactance area, suggesting peripheral airway

obstruction, corresponded with better response to the addition of long-acting beta agonists to low-dose inhaled corticosteroids than increasing the dose of inhaled corticosteroids or adding a leukotriene receptor antagonist.⁴⁴ In addition, higher urinary leukotriene E₄ levels predicted better response to the addition of leukotriene receptor antagonists.⁴⁴ Additionally, genetic variants have been identified in certain populations that lead to differential responses to bronchodilators.^{55–57} Thus, as with inhaled corticosteroids and leukotriene receptor antagonists (discussed earlier), there is phenotypic variability in response to beta agonists. Further work is needed before genetics or biomarkers are used to guide asthma management in clinical practice.

NOVEL USES FOR OLD THERAPIES

Macrolides have been broadly studied in adult chronic pulmonary diseases as well as in children with cystic fibrosis, and have shown significant benefits in some patients.^{16,58–61} The observed improvement is thought to be related to the immunomodulatory role of macrolides and resulting decrease in airway neutrophils.^{16,58–61} Initial optimism surrounding the benefit of macrolides in management of refractory asthma was moderated by the discovery that many macrolides decrease the clearance of steroids.^{16,62,63} More recently, several small studies have suggested that the use of macrolides in children with asthma may reduce bronchial hyperresponsiveness and airway neutrophils, and shorten the duration of symptoms.^{64,65} There is also some evidence to suggest that asthmatics with colonization by *Chlamydia pneumoniae* or *Mycoplasma pneumoniae* may have more benefit from macrolides.^{16,66,67} Some clinicians have argued that, given the low risk nature of macrolides, a trial of therapy in refractory asthmatics is reasonable, although this recommendation has yet to become part of the US guidelines for pediatric asthma management.^{5,10} The National Heart, Lung and Blood Institute (NHLBI) AsthmaNet is currently investigating whether azithromycin initiated at the start of upper respiratory infection in preschool children who wheeze will alter the development of lower respiratory illness and exacerbation (NCT01272635).

Vitamin D is also known to have immunomodulatory effects and may play a role in the management of asthma.^{16,68,69} Vitamin D has been shown in vitro to stimulate T-regulatory cells and the production of interleukin (IL)-10 in response to steroids, which then inhibits allergen-specific Th2 cells.^{16,68} Furthermore, a study from the Childhood Asthma Management Program found that children with vitamin D deficiency were likely to have poorer lung function and less response to inhaled corticosteroids.⁶⁹ A recent study published in the *Journal of the American Medical Association* found that vitamin D did not reduce the rate of exacerbation in adults with asthma.⁷⁰ Further analysis is needed to determine the utility of vitamin D supplementation in asthmatic children as well as other specific subgroups.⁷⁰

THE ERA OF BIOLOGICS

A subset of asthmatics remains severely symptomatic despite the therapies discussed earlier, and before the introduction of biologics, these patients were relegated to long-term oral corticosteroids. With the advent of biologics, there is now hope that these severe steroid-dependent asthmatics may have alternative options for treatment.

Furthermore, biologics provide the perfect opportunity to selectively choose therapy based on asthma phenotype. The first of these agents to be accepted in the national guidelines is omalizumab. Omalizumab, an anti-immunoglobulin (Ig) E monoclonal antibody, is now recommended by the most recent guidelines from the National Asthma Education and Prevention Program for children 12 years of age and older with moderate to severe asthma. These recommendations are supported by more than a

decade of work showing that omalizumab reduces the frequency of asthma exacerbations, emergency department visits, and hospitalizations, and decreases the need for rescue medications and steroids in children with asthma.^{71–77} There are limited data at this point on the safety and efficacy of long-term use; some of the longest studies have shown that the medication was tolerated for at least 3 years with improvement in both symptoms and lung function.⁷⁸ In addition, data are limited for children less than 12 years of age.

Omalizumab has been further studied in specific patient populations and has shown significant benefit for asthmatics of certain phenotypes. A major randomized controlled trial of omalizumab in inner-city children with asthma of any severity showed significant reduction in asthma exacerbations and symptoms.⁷⁹ Omalizumab had the greatest benefit in children with sensitization and exposure to cockroach and dust mites.⁷⁹ Post-hoc analysis further supported the concept that anti-IgE therapy may be of particular benefit in children with seasonal exacerbations.⁷⁹ Studies of omalizumab in other clinical phenotypes that are thought to be Th2 driven, including patients with chronic rhinosinusitis and those with nasal polyps, have shown promise as well.^{80,81} Given the cost of omalizumab, many clinicians have argued for the importance of identifying populations that will have significant benefit and of using the drug selectively in those groups, although newer indications in other allergic diseases, including the recent new indication for chronic urticaria, may expand its utility and control costs.^{79,82,83} In the past, the populations identified have been those with increased IgE levels and more severe asthma, although recent work has begun to investigate the impact of anti-IgE on specific biomarkers in allergic asthmatics, including FeNO, eosinophilia, and periostin.^{79,84–87} In the future, anti-IgE therapy may even play a role in asthma prevention, as is discussed in more detail below.⁸⁸

Although omalizumab is the only biologic that has been approved for asthma in children, there are several others that have shown promise in clinical trials in adults and thus may eventually be incorporated into pediatric asthma management as well. In addition, there are ongoing clinical trials for many of biologics in adolescents aged 12 years and older. Many of these newer biologics target T cells or T-cell cytokines. The role of T cells in asthma is well established and is discussed in detail elsewhere.⁸⁹ This article discusses several of the newer biologics, but this list is only intended to be illustrative of the numerous and varied biologics in existence for asthma and is not meant to be a comprehensive list of all biologics trialed in asthma to date.

One such biologic targeting T cells is keliximab, a monoclonal antibody to the CD4 receptor. In phase II trials, keliximab seemed to improve peak expiratory flow, but resulted in diminished CD4 counts.^{90,91} Several of the other biologics under investigation target the cytokines involved in Th2-mediated allergic and asthmatic inflammation, including IL-2, IL-5, IL-4, and IL-13. IL-2 leads to the activation of Th2 cells, and symptomatic asthmatics have long been known to have increased levels of the IL-2 receptor.⁹² Daclizumab, a monoclonal antibody to the IL-2 receptor, has been shown in phase II trials to improve lung function in adults with moderate to severe asthma on inhaled corticosteroids.⁹³ No trials have been done on daclizumab in children or adolescents with asthma.

There are several new monoclonal antibodies targeting IL-5, a cytokine linked directly with sputum eosinophilia and airway hyper-responsiveness in asthma.⁹⁴ Mepolizumab, a monoclonal antibody targeting IL-5, has had very promising results thus far.^{95,96} IL-5 is a cytokine that has been linked directly with sputum eosinophilia and airway hyper-responsiveness in asthma.⁹⁴ Early work showed that mepolizumab reduced exacerbations and improved quality of life scores in adults with eosinophilic asthma in phase III clinical trials.^{97–99} Two studies recently published in the *New England Journal of*

Medicine showed that mepolizumab reduced asthma exacerbations, improved asthma morbidity, and had a significant steroid-sparing effect in subjects with eosinophilic asthma.^{95,96} While both of these studies included adolescent asthmatic patients, the total number of children in these studies was small. There are ongoing clinical trials recruiting children ages 12 and older, including NCT01842607, designed to examine the long-term safety of this drug. Reslizumab, another monoclonal antibody to IL-5, has shown promise in phase II trials in improving asthma quality of life scores and lung function.^{100,101} Interestingly, the greatest benefit was seen in those patients with asthma and nasal polyps.¹⁰¹ The efficacy and safety of reslizumab in children ages 12 and older with eosinophilic asthma is currently being examined in the following clinical trials: NCT01270464, NCT01287039, NCT01285323, and NCT01290887.

IL-4 and IL-13 are directly involved in IgE-mediated mast cell degranulation and mucus hypersecretion and plays a role in airways remodeling in asthma.¹⁰² Dupilumab, a human monoclonal antibody to IL-4, has been shown to reduce the frequency of asthma exacerbations and improve lung function in adults with persistent moderate to severe asthma and increased sputum eosinophil levels.¹⁰³ No trials have been done on dupilumab in children or adolescents with asthma. Pitrakinra, a recombinant form of IL-4 that blocks IL-4 receptor signaling, decreased asthma exacerbations and symptoms in patients with specific IL-4 receptor polymorphisms.¹⁰⁴ No trials have been done on pitrakinra in children or adolescents. Lebrikizumab, a monoclonal antibody to IL-13, has been shown in a phase II trial to improve lung function in adult asthmatics, particularly those with increased serum periostin levels.¹⁰⁵ Periostin, a matricellular protein, is secreted by bronchial epithelial cells in response to IL-13 and results in airway remodeling.¹⁰⁶ Lebrikizumab is currently being studied in children in several different clinical trials, including adolescents aged 12 to 17 years on both an inhaled corticosteroid and a second controller agent, steroid-dependent children aged 12 years and older, and steroid-dependent children aged 12 years and older with a trial design focused on changes in biomarkers. Another anti-IL-13 antibody, tralokinumab, was found in phase IIa trials to also improve lung function, and most dramatically in those with high levels of airway eosinophils.¹⁰⁷ Tralokinumab is currently undergoing pharmacokinetic studies in children aged 12 to 17 years.

POTENTIAL THERAPEUTIC TARGETS

In addition to the cytokines mentioned earlier, numerous other cytokines have been suggested as targets for biologics in the treatment of asthma (**Table 1**).^{108,109} Studies in mice suggest that IL-9 may play a role in airway hyperresponsiveness, airway eosinophilia, and mucus secretion.¹¹⁰ Medi-528, a monoclonal antibody to IL-9, is under investigation, and has reached phase 2 trials with some promise.¹¹¹ Work is also ongoing to develop an anti-IL-25 antibody for use in allergic asthmatics, because IL-25 plays a role in the activation of Th2 lymphocytes and the development of allergic asthmatic traits.¹¹² IL-33 was also recently identified as an important potential target, because it was found to promote airway remodeling in pediatric patients with steroid-resistant asthma.¹¹³ Preclinical studies have shown that anti-IL-33 can prevent the development of allergic asthma in mice.¹¹⁴ Tumor necrosis factor (TNF) alpha, which has shown great success in many chronic inflammatory diseases, is known to be upregulated in the airways of severe asthmatics.^{115,116} However, anti-TNF agents, such as infliximab and golimumab, have not had significant success in asthma secondary to significant risk with limited benefit.^{117,118}

Tyrosine kinase inhibitors, which have become part of the standard of care in the management of many malignancies, have recently come under investigation for use

Table 1
Potential therapeutic targets and ongoing studies to establish their roles in asthma

Therapeutic Target	Role in Asthma	Current Investigation
IL-9	AHR, airway eosinophilia, mucus secretion ¹¹⁰	Medi-528, phase II trials ¹¹¹
IL-25	Activation of Th2 cells, allergic asthma ¹¹²	Preclinical studies, ¹¹² development of anti-IL-25 antibody
IL-33	Airway remodeling ¹¹³	Preclinical studies ¹¹⁴
Tyrosine kinase inhibitors	Inflammatory gene expression ^{16,119}	Masitinib, ¹¹⁹ phase III clinical trial currently recruiting (NCT01449162)
CCR3	Airway eosinophilia, airway remodeling ^{123,124}	GW766994, phase II clinical trial (NCT01160224)
CCR4	Airway inflammation ^{108,125}	AMG 761, phase I clinical trial (NCT01514981)

Abbreviation: AHR, airway hyperresponsiveness.

in asthma given their role in inflammatory gene expression.^{16,119} A preliminary study of masitinib, a c-kit/platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitor, showed promise in reducing asthma symptoms in severe steroid-dependent asthmatics.¹¹⁹ Further work is needed to determine whether the benefits outweigh the potential side effects of such therapy, and a phase III clinical trial of masitinib in severe steroid-dependent asthmatics is currently underway.

Chemokines involved in the homing of inflammatory cells have also attracted attention as being potential targets in the treatment of asthma.¹⁰⁸ C-C chemokine receptor type 3 (CCR3) and eotaxin are involved in eosinophil infiltration in the airways, and their presence and level in induced sputum correlates with asthma severity.^{120,121} Furthermore, additional work suggests that CCR3 may play a role in smooth muscle remodeling in asthmatic airways.¹²² There has been some investigation into CCR3 and eotaxin antagonists, and results of a clinical trial of a CCR3 receptor antagonist in adults with mild to moderate asthma are currently pending publication.^{123,124} CCR4 is overexpressed in Th2 lymphocytes in asthma, and RS-1748, a CCR4 antagonist, has been shown to reduce airway inflammation in animal models.^{108,125} Another CCR4 antagonist, AMG 761, is currently undergoing phase I clinical trials in asthmatics. Other chemokines may eventually be targeted for asthma therapy as well.

There are many other potential targets under investigation, including phospholipase A2, 5'-lipoxygenase, phosphodiesterase-4, thymic stromal lymphopoietin, OX40 ligand, and tissue kallikrein-1. Discussion of these targets is beyond the scope of this article, but are discussed in more detail elsewhere.^{16,108}

PREVENTION

Prevention is the goal of any chronic disease management, including for asthma, and there is currently no known agent that has been proven modify disease progression in early disease or even prevent the onset of disease. With tools such as the Asthma Predictive Index to predict which children will develop asthma, improved asthma phenotyping, and even asthma genotyping, prevention may be a possibility for the future.¹²⁶ One phenotype that has been targeted for prevention already is the allergic atopic phenotype. There is a strong association between exposure to allergen sensitization and asthma, and early exposure to allergens in sensitized atopic children has been shown to reduce lung function.^{127,128} Prophylactic interventions have thus been aimed

at reducing allergen exposure and inducing tolerance. The Inner City Asthma Study showed that reducing cockroach and dustmite allergen in the home significantly reduced asthma symptoms in inner-city asthmatic children.¹²⁹ Jacobsen et al showed that open label treatment with subcutaneous specific immunotherapy potentially altered the course of asthma in atopic children.^{130,131} Sublingual immunotherapy may also have similar effects, but the results have been mixed.^{132–136} Omalizumab (anti-IgE), is a well-established therapy for asthma and being extensively evaluated in children. With its role in complete blockade of all IgE regardless of idiotype, given the critical role of atopy and the atopic march in asthma development and persistence, it is still in need of evaluation in its role in potential prevention and disease modification of asthma in young children.⁸⁸

There is also a strong association between RSV bronchiolitis, other viral respiratory infections, and the development of asthma.^{127,137–141} Palivizumab, an anti-RSV monoclonal antibody, has been shown to reduce wheezing in premature infants, suggesting that perhaps it may prevent the development of asthma in this population.^{142,143} The impact of palivizumab on wheezing in term infants remains to be determined. Other anti-virals could also be considered, but none of the available agents so far have proven consistent effectiveness in lower respiratory disease. Furthermore, the Inner City Asthma Consortium demonstrated that the use of omalizumab during the common cold season reduced rates of exacerbation.⁷⁹ Clinical trial NCT01430403 investigating the role of omalizumab in prevention of asthma exacerbations in asthmatic children during the fall season has been completed and is awaiting publication. As discussed in detail elsewhere, perhaps in the future, anti-IgE may be used during the cold season to prevent the development of asthma in at risk populations.⁸⁸

In addition, given the growing evidence for the role of gut flora in the development of allergic and atopic disease, probiotics have become of interest in preventing not only asthma, but other allergic diseases as well. Unfortunately, the data have not supported the use of probiotics in the prevention of asthma thus far. Multiple studies have had limited if any positive results and a recent meta-analysis of trials of probiotic supplementation in pregnancy and infancy found no evidence that probiotics prevented the development of asthma.^{144,145} Some studies suggest that there may be a role for probiotics in preventing asthma in children that are otherwise atopic, although further work is needed in this area.¹⁴⁶ Clinical trials of probiotics to prevent asthma in infants are currently ongoing: NCT00113659, NCT01285830. Further, a killed bacterial lysate, OM-85 BV, has been demonstrated to decrease the frequency and duration of wheezing episodes in young children, and could also be considered in prevention.¹⁴⁷

SUMMARY

The management of asthma is becoming more patient specific as more is learned about the biology of the development and progression of asthma. The future of asthma management is likely to involve phenotypic characterization and potentially even genotypic characterization in certain cases to determine appropriate therapy. Until that time, the current therapies are sufficient for most pediatric asthmatic patients and the focus should remain on ensuring adherence to the guidelines through education of both patients and providers.

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