Current perspectives

New and future strategies to improve asthma control in children

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Symptomatic asthma in childhood has lifelong effects on lung function and disease severity, emphasizing the need for improved pediatric asthma control. Control of pediatric risk and impairment domains can be achieved through increased medication adherence or new therapeutic strategies. Developing electronic monitoring device technology with reminders might be a key noninvasive resource to address poor adherence in children and adolescents in a clinical setting. In patients who have persistently poor control despite optimal medication compliance, newly emerging pharmaceuticals, including inhaled therapies and biologics, might be key to their treatment. However, barriers exist to their development in the pediatric population, and insights must be drawn from adult studies, which has its own unique limitations. Biomarkers to direct the use of such potentially expensive therapies to those patients most likely to benefit are imperative. In this review the current literature regarding strategies to improve pediatric asthma control is addressed with the goal of exploring the potential and pitfalls of strategies that might be available in the near future. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Asthma, asthma control, asthma exacerbations, dupilumab, biomarkers, inhaled corticosteroids, lebrikizumab, long-acting ß-adrenergic agonists, mepolizumab, omalizumab, reslizumab, severe asthma, therapeutics*

Abbreviations used

ACQ:	Asthma control questionnaire
BADGER:	Best Add-on Therapy Giving Effective Responses
CAMP:	Childhood Asthma Management Program
COPD:	Chronic obstructive pulmonary disease
DREAM:	Dose Ranging, Efficacy, and Safety with Mepolizumab
EMD:	Electronic monitoring device
EPR3:	Expert Panel Report 3
FDA:	US Food and Drug Administration
FENO:	Fraction of exhaled nitric oxide
FVC:	Forced vital capacity
ICATA:	Inner-City Anti-IgE Therapy for Asthma
ICS:	Inhaled corticosteroid
LABA:	Long-acting β-agonist
MENSA:	Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma
NHLBI:	National Heart, Lung, and Blood Institute
OCS:	Oral corticosteroid
PEF:	Peak expiratory flow
SARP:	Severe Asthma Research Program
SMART:	Single combination budesonide-formoterol inhaler maintenance and reliever therapy
TALC:	Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid Inadequately Controlled on Lower Dose of Inhaled Corticosteroid
TREXA:	Treating Children to Prevent Exacerbations of Asthma

Despite advances in care, asthma still imposes a significant burden on the pediatric population. The Eunice Kennedy Shriver National Institute of Child Health and Human Development Asthma Group raised several questions regarding the natural history, diagnostics, outcome measures, and therapeutics of pediatric asthma.[1] They addressed the pressing need to define effective strategies to prevent exacerbations and progression of disease, especially in younger populations.[1] The age of asthma diagnosis is decreasing, from 4.7 years in 1993 to 2.6 years in 2000.[2] Among children given a diagnosis before age 3 years, by 6 years of age, 35.6% to 45.2% continue to require care for their asthma[2] and most already have lung function abnormalities,[3] suggesting a more persistent disease process. Early-onset asthma has long-lasting effects that can continue throughout childhood into adolescence and adulthood. Patients with mild-to-moderate asthma have an increasing magnitude of airway obstruction over their childhood compared with nonasthmatic subjects.[4] Persistent pediatric wheezing carries a significant risk for both reduced lung function and FEV_1 growth over adolescence.[5] Severe childhood asthma is a risk factor for continued active disease as an adult.[6]

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Given asthma's lifelong effect, prevention of disease development and progression has been investigated, particularly with inhaled corticosteroids (ICSs). Inhaled fluticasone propionate in preschool children with a positive Asthma Predictive Index result did not change the development of asthma symptoms, exacerbations, or lung function once medication was stopped compared with placebo.[7] Maintenance inhaled fluticasone propionate in preschool children with multiple-trigger wheezing did not prevent the development of asthma or change in lung function, FEV_1, and airway reactivity compared with placebo by 5 years of age.[8] To date, no therapy has been able to prevent the development of pediatric asthma. The appropriate time or targets of intervention to prevent pediatric lung remodeling are also unclear.[9] Given the lack of resources to prevent asthma development, focus should be given to asthma control.

The National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report 3 (EPR3) recommendations focus asthma control on 2 primary domains: impairment and risk.[10] Control in both domains is necessary because pediatric patients with persistent asthma symptoms have an increased risk of exacerbations, hospitalizations, emergency department visits, and oral corticosteroid (OCS) use,[11] with exacerbations leading to progressive loss of lung function.[1] Reasons for poor asthma control include controller medication adherence failure, unresponsiveness to available therapies, improper inhalation technique, poor comorbid condition control, psychosocial stressors, and misdiagnosis. In this review we examine current and future approaches of pediatric asthma control, with a focus on adherence and therapeutics in development.

ADHERENCE

Therapeutic adherence should be addressed first when approaching asthma control. Adult and pediatric adherence to controller therapies only ranges from 30% to 70%.[12] In ancillary Childhood Asthma Management Program (CAMP) study data, 75% of children had objective adherence of less than 80%, and 27% of subjects had adherence of less than 50%.[13] Pediatric adherence specifically to ICSs is only 20% to 33.9%, with only 4.7 to 5.5 prescription refills for inhaled fluticasone over 1 year.[14] The ramifications of poor controller adherence in the pediatric population include an increased risk of severe exacerbations, hospitalizations, emergency department visits, and OCS use.[14] Based on refill data, the risk of an asthma exacerbation was 21% to 68% lower for children who were adherent to controller medications.[14]

Even when adherence is assessed, patients are poor self-reporters, with a large discrepancy existing between their reported adherence and their actual medication use.[13,15-17] Evaluation of CAMP data showed 93.6% self-reported adherence on diary cards but only 60.8% objective adherence based on device actuations in 5- to 12-year-olds.[13] Diary cards are limited by patients potentially fabricating data or completing it retrospectively. Only 26.2% of patients 6 to 17 years old kept diary cards regularly for at least 6 months in one study.[18] Although regular diary card users had significantly greater use of daily controller therapies, neither the number of asthma exacerbations, emergency department visits, or hospitalizations nor the patient's FEV_1 or Asthma Control Test scores varied between those who completed diary cards and those who did not, regardless of whether they were completed by the patient or parent.[18] Overall, it is unclear how much symptom diaries or diary cards add to improving asthma control, health care use, or costs.[19]

Multiple reasons exist for poor adherence with medications in the pediatric population, including the complexity of treatment regimens, costs of medications, perceived risk of medication-related side effects, insufficient parental health literacy, lack of parental supervision, familial socioeconomic strain, poor patient perception of disease severity, and possible secondary gain from poor asthma control.[15,20-22] Broadly, this nonadherence can be categorized as either intentional or unintentional.[23]

Intentional nonadherence can result from a patient choosing not to take their medication based on their own needs, knowledge base, or perception of the medication.[15,23] Conversely, unintentional nonadherence can result from the complexity of the treatment regimen or the patient's life, forgetfulness, or understanding of the medication.[15] Nonadherent asthmatic patients are more likely to have unintentional nonadherence and, per the investigators, would likely benefit from reminder systems and patient education.[23]

Electronic monitoring devices (EMDs) are a new approach to achieving disease control and adherence in clinical practice and research.[15,24] EMDs provide accurate, objective, and detailed information on day-to-day patient adherence without significantly disrupting a patient's natural medication-taking behavior.[25] The SmartTouch (formerly SmartTrack; Adherium, Auckland, New Zealand) and Propeller (Propellor Health, Madison, Wis) sensors are 2 of the more advanced devices, with date and time recordings of each actuation, real-time uploading to a Web page or smartphone application, and reminders to prompt adherence.[25] The Propeller sensor also has a Global Positioning System to monitor location of inhaler use.[25] EMDs also overcome the limitation of dose dumping when using remaining doses or canister weight as markers of adherence.[13,16,24,26] EMDs are not without their limitations, which include their cost,[15,27,28] time for patient education[27] and device testing and data download,[28] measurement reliability and potential device failures,[27,28] identification of patients most likely to benefit from this strategy,[24,27] and the need to convince patients to use a device that will supervise their behavior.[28] As more technologically advanced devices come onto the market, the cost is decreasing.[26] Real-world study of the SmartInhaler Tracker (Adherium, Auckland, New Zealand) has demonstrated reliability, with 98.2% of devices passing prestudy checks, only 3.5% being thrown away or lost by patients, and only 1.9% malfunctioning before data upload.[29]

Adults and adolescents given an EMD with an audiovisual reminder function showed a 19% improvement in ICS adherence compared with control subjects.[30] Pediatric and adolescent studies using EMDs with reminders demonstrated a 40% to 54% increase in adherence to controller medications compared with those without reminders.[25,31] The aforementioned studies showed no difference in asthma outcomes,[31] school or caregiver work absenteeism, FEV_1 improvement, or emergency department visits.[25] One reminder group had significantly fewer asthma exacerbations in the first 2 months but without a persistent difference at 4 and 6 months.[25] Possible reasons for lack of improvement include small sample sizes, limited intervention duration, patient awareness of adherence monitoring, or multiple asthma phenotypes requiring different treatment modalities.[24] Pediatric patients with poorly controlled asthma who were provided adherence feedback had overall increased adherence, which continued to increase over the course of the study, compared