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Asthma across the ages: Knowledge gaps in childhood asthma

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The Eunice Kennedy Shriver National Institute of Child Health and Human Development convened an Asthma Group in response to the Best Pharmaceuticals for Children Act. The overall goal of the Best Pharmaceuticals for Children Act Program is to improve pediatric therapeutics through preclinical and clinical drug trials that lead to drug-labeling changes. Although significant advances have been made in the understanding and management of asthma in adults with appropriately labeled medications, less information is available on the management of asthma in children. Indeed, many medications are inadequately labeled for use in children. In general, the younger the child, the less information there is available to guide clinicians. Because asthma often begins in early childhood, it is incumbent on us to continue to address the primary questions raised in this review and carefully evaluate the medications used to manage asthma in children. Meanwhile, continued efforts should be made in defining effective strategies that reduce the risk of exacerbations. If the areas of defined need are addressed in the coming years, namely prevention of exacerbations and progression of disease, as well as primary intervention, we will see continuing reduction in asthma mortality and morbidity along with improved quality of life for children with asthma. (*J Allergy Clin Immunol* 2013;■■■:■■■-■■■.)

Key words: Asthma, asthma natural history, asthma progression, asthma biomarkers, childhood asthma, asthma pharmacotherapy

The Eunice Kennedy Shriver National Institute of Child Health and Human Development convened an Asthma Group in response to the Best Pharmaceuticals for Children Act. The overall goal of the Best Pharmaceuticals for Children Act Program is to improve pediatric therapeutics through preclinical and clinical drug trials that lead to drug-labeling changes (<http://bpca.nichd.nih.gov>). The task of the Asthma Group was to discuss differences between childhood and adult asthma to define specific knowledge gaps related to current asthma management. Two broad issues were discussed: (1) challenges with drug delivery in children, especially in relation to age, and (2) differences in outcome measures between pediatric and adult studies.

The Asthma Core Group evaluated these issues over the past year by (1) developing responses to high-level questions on disease progression and manifestation in children and adults; (2) summarizing individual responses in each area in regard to

Abbreviations used

CO: Carbon monoxide
 EBC: Exhaled breath condensate
 FENO: Fraction of exhaled nitric oxide
 HRV: Human rhinovirus
 RBM: Reticular basement membrane
 RSV: Respiratory syncytial virus
 SARP: Severe Asthma Research Program

cause, diagnosis, pathophysiology, outcomes, and therapeutics; (3) identifying and justifying major issues, knowledge gaps, and short- and long-term objectives in each area; and (4) summarizing these observations for this report.

These findings are presented in 4 broad areas: natural history and pathophysiology, diagnostics and biomarkers, outcome measures, and therapeutics. Each section summarizes the relevant issues, identifies the important information gaps, and presents short- and long-term objectives to fill identified gaps. The section on therapeutics further identifies 4 classes of drugs that merit close attention because of the frequent use and lack of appropriate dosage information by age. This information is intended to inform future studies by the National Institutes of Health, the US Food and Drug Administration, and pharmaceutical firms to advance pediatric asthma care.

NATURAL HISTORY AND PATHOPHYSIOLOGY

Asthma, which typically begins in childhood and occurs throughout life, has common clinical manifestations but many different “phenotypes” that are associated with variable disease courses. Not all children who wheeze early in life will have asthma later in life.¹ Sex also influences the natural history of asthma, with a shift in severity and prevalence biased toward women after puberty.² In this section differences across the ages in natural history and pathophysiology as they relate to the inception, progression, and exacerbations of asthma are reviewed (Table I).

Inception of asthma

Asthma results from the interaction between the host’s genetics and environment. Exposures to environmental stimuli lead to alterations in inflammatory pathways that trigger wheezing illnesses and the development of asthma. Birth cohort studies have identified risk factors (allergic sensitization and wheezing with viral infections) for asthma inception. Allergic sensitization early in life is an important risk factor for persistent wheezing and asthma development.^{1,3-5} Children with multiple early aeroallergen sensitizations are at increased risk of morbidity associated with childhood asthma.⁶

Wheezing with viral infections is the most common presentation of asthma in early life. Preschool children have an intermittent pattern of disease and are often well between episodes. Viruses, human rhinovirus (HRV), respiratory syncytial virus (RSV), influenza virus, and metapneumovirus are identified in approximately 90% of children younger than 3 years with acute wheezing.^{3,7} Pathogenic bacteria also might play a role in recurrent wheezing.⁸ Wheezing associated with RSV in infancy, particularly those episodes requiring hospitalization, increase the risk of recurrent wheezing and asthma.⁹⁻¹² Wheezing

associated with HRV has been identified as a strong risk factor for persistent asthma.^{3,13} It is unclear whether RSV and HRV cause asthma or uncover an underlying predisposition to disease. However, a recent trial of palivizumab in healthy preterm infants suggests that prevention of severe RSV infection in infancy might prevent recurrent wheeze.¹⁴ Whether these findings hold true for prevention of childhood asthma remains an open and important question.

Intermittent viral infections trigger an exaggerated inflammatory response (Fig 1), which might be present even when symptoms are absent. The eosinophilic predominance seen on bronchoalveolar lavage in older subjects is less pronounced in infants.¹⁵ However, some children might have a noneosinophilic or neutrophilic form of asthma. These patients might not respond to corticosteroids, although it remains controversial whether airway neutrophilia represents a true asthma inflammatory phenotype or whether it represents exposure to higher doses of corticosteroids. Biomarker development to distinguish inflammatory phenotypes in children will be a major advance in the treatment of asthma because it is unclear what predisposes young children to have one asthma phenotype over another. Moreover, the temporal stability of these phenotypes is not understood.

In addition to viral infection and allergen exposure, other environmental factors influence the development of asthma, including maternal depression, psychological stress, and exposure to air pollution. Prenatal and postnatal maternal depression, anxiety, and distress and exposure to psychological stress have been associated with the development of asthma.^{16,17} In addition, exposure to both indoor and outdoor air pollution also appears to influence asthma development.^{18,19} The relative contribution of each of these environmental factors in the inception of asthma is unknown. It is likely that exposure to a combination of these and other environmental factors at a specific time in the maturation of the immune response in a genetically susceptible subject determines whether asthma will develop.

Progression of asthma

The progression of asthma is variable both between and within subjects. The National Heart, Lung, and Blood Institute’s Severe Asthma Research Program (SARP) has focused on the clinical, physiologic, and biologic heterogeneity of asthma. An unsupervised hierarchical cluster analysis of adult SARP participants with the full spectrum of disease allowed for grouping of patients based on similarities free from an *a priori* bias to identify potential clinical asthma phenotypes.²⁰ Similarly, a cluster analysis of 300 children (ages 6-17 years) identified marked heterogeneity²¹ and identified distinct clusters from the SARP adult studies. Although distinct clinical phenotypes were identified, the airway inflammatory response underlying those phenotypes is less distinct. Most asthmatic patients have some form of airway remodeling regardless of phenotype. Remodeling, which is characterized by epithelial cell injury, thickening of the reticular basement membrane (RBM), subbasement fibrosis, smooth muscle hypertrophy and hyperplasia, and angiogenesis, is presumed to result in abnormalities in lung function, including persistent airflow limitation and increased airway hyperresponsiveness. Airflow obstruction might be permanent or only partially reversible. Lung function changes seen in children are different than those seen in adults who experience a loss of lung function over time. In children 5 to 11 years old, the magnitude

TABLE I. Natural history and pathophysiologic changes of asthma by age

	Age (y)			
	<5	5-11	12-17	≥18
Prevalence by sex	M > F	M > F	Before puberty: M > F After puberty: F > M	F > M
Predominant effector cell	Neutrophil Eosinophil	Eosinophil	Eosinophil	Eosinophil Significance of neutrophils in some patients controversial phenotypes
RBM thickening	Begins after the first birthday	Not as thick as adults	Thickening approaches that seen in adults	Established
Lung function findings	Lung function measures difficult to obtain	Lung function changes associated with duration of asthma symptoms	Lung function deficits present in those patients who began wheezing before age 3 y but might not be present in those who began wheezing in later childhood	Progressive decrease in lung function can occur; irreversible airway obstruction might also be seen
Incidence of exacerbations	++++	+++	++	++

F, Female; M, male.

of airflow limitation and air trapping is less than in adults and correlates with structural changes.²² Although lung function is maintained for most children, longitudinal studies have shown that many children with asthma symptoms before age 3 years have lung function abnormalities by age 6 years that persist.²³ In another birth cohort study, children given a diagnosis of asthma by age 7 years already had decreased airflow and increased bronchial hyperresponsiveness as neonates, and their lung function deficits were progressive.²⁴ Most of what is known about airway remodeling derives from adult studies, which must be interpreted with caution because airway remodeling in adults might be different than that in children and is likely influenced by many environmental and genetic interactions that occur over a lifetime. Although airway inflammation is a prominent feature of asthma, it is not understood how inflammation leads to remodeling. Indeed, it remains controversial to what degree airway inflammation must be present for remodeling to occur. RBM thickening appears to occur early, although it is typically absent in wheezy infants.²⁵ Significant RBM thickening has been described in biopsy specimens from children with severe asthma, even in the absence of eosinophils or neutrophils.²⁶⁻²⁸ These findings occur after the first year of life in atopic children with severe recurrent wheeze,²⁹ which is similar to what has been reported in older children and adults.^{25,29,30} It has recently been reported that airway smooth muscle thickness can increase at a much earlier age than previously thought. Children who have asthma at school age have increased airway smooth muscle as preschool-age children.³¹ These findings suggest that some of the pathologic changes in asthmatic patients once thought to occur only in patients with long-standing inflammation might be present early in life. Factors associated with progression of airway remodeling remain unclear.

Importance of asthma exacerbations

Asthma exacerbations, which consist of narrowing of the airway lumen from increased hyperresponsiveness, inflammation, and mucus plugging, are common during the early school years and lead to significant morbidity and substantial health care costs. Moreover, recent studies suggest that exacerbations can

lead to progressive loss of lung function.^{32,33} Although current therapies are effective in controlling daily asthma symptoms, they are only partially effective in preventing exacerbations. The frequency of exacerbations is greatest in children younger than 5 years and decreases throughout childhood, with boys more affected than girls. Puberty appears to be a transition point, such that the risk of an asthma exacerbation is doubled in women after the age of 14 years.^{34,35} There also appear to be seasonal influences. Exacerbations in children occur more frequently in autumn but more commonly in winter in adults.³⁶⁻³⁹ Why does this occur? This likely relates to interactions among the start of school, allergen exposure, and viral respiratory tract infections. Exacerbations are most commonly caused by HRV in children with concomitant allergic sensitization.^{7,40} HRVs have been detected in up to 90% of exacerbations in children.⁴¹ Prior exacerbations appear to be the best predictor of subsequent exacerbations.⁴² However, the ability to predict the risk of exacerbations is limited.

Although most clinicians are able to identify an asthma exacerbation, the definition of what constitutes an exacerbation, particularly as it relates to a clinical trial, remains elusive. Most definitions rely on a combination of symptoms and medication changes, such as the prescription of systemic corticosteroids and increased use of short-acting β -agonists. However, the validity of such definitions is unknown because they can vary by study participant and investigator. Furthermore, the relative importance of an exacerbation in the natural history of the disease is unknown. Is there a cumulative effect of exacerbations such that a patient with more frequent exacerbations is more likely to experience increased morbidity later in life? Does the severity of the exacerbation matter? The answers to these questions are unknown.

Unanswered questions

Primary unanswered questions related to the natural history and pathophysiology of asthma include the following:

- What inflammatory phenotypes are present in children, what is their long-term stability, and how do they relate to airway remodeling?

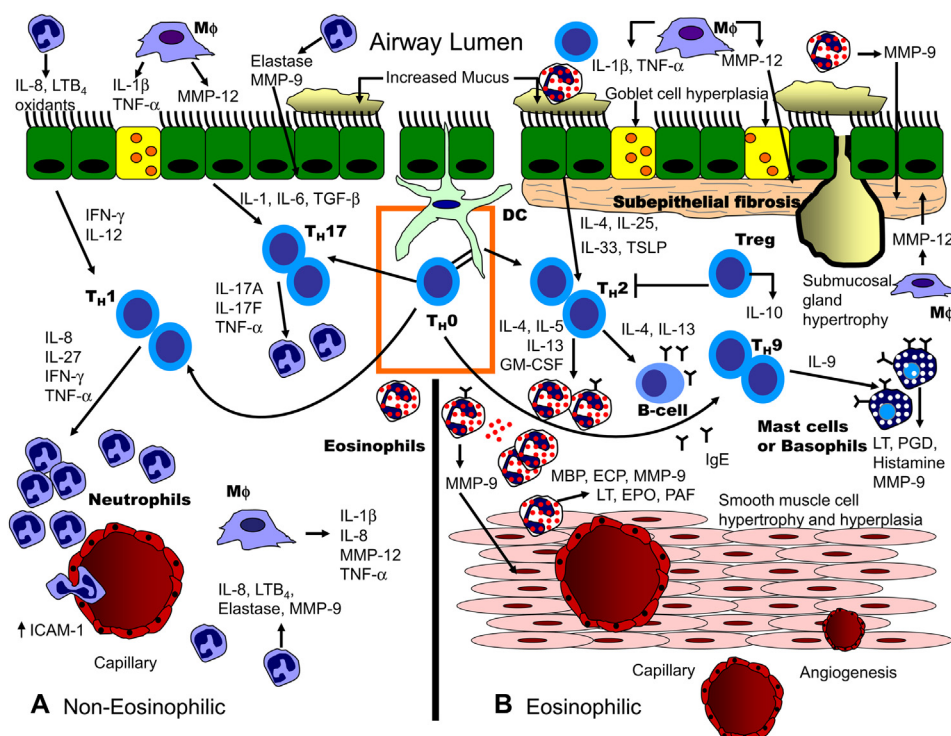


FIG 1. Airway inflammation in the setting of asthma. The *orange box* represents activities in the lymph node. The dendritic cell (DC) processes antigens, migrates to the lymph nodes, and associates with T_H0 , which then differentiates and migrates back to the airway. **A**, Noneosinophilic/neutrophilic asthma, **B**, Eosinophilic asthma. Remodeling occurs in patients with all forms of asthma but is only shown in Fig 1, *B*. *EPO*, Eosinophil peroxidase; *ICAM-1*, intercellular adhesion molecule 1; *LTB₄*, leukotriene B₄; *Mφ*, macrophage; *MBP*, major basic protein; *MMP*, matrix metalloproteinase; *PAF*, platelet-activating factor; *Treg*, regulatory T cell; *TSLP*, thymic stromal lymphopoietin.

- What factors are responsible for triggering asthma onset?
- What factors are associated with progressive disease?
- What is the influence of sex on asthma in relation to inception, prevalence, persistence, remittance, and response to therapy?
- How do asthma exacerbations contribute to long-term outcomes?

DIAGNOSTICS AND BIOMARKERS

Substantial advances in asthma therapeutics have occurred over the last several decades, but extending the benefits and role of these therapies to children has been slow. Asthma diagnosis is primarily based on respiratory symptoms and evidence of airway bronchodilator reversibility or airway hyperresponsiveness in response to specific triggers. Because children younger than 5 years have difficulty performing reproducible spirometry according to American Thoracic Society guidelines, asthma diagnosis in younger children is typically based on the presence of symptoms and specific risk factors, such as family history and atopy. Furthermore, many school-age children demonstrate normal or even “supernormal” spirometric readings outside of exacerbations, which further renders diagnosis challenging.^{43–45}

Determination of lung volumes by using plethysmography for the evaluation of air trapping and hyperinflation consistent with obstruction of the airways is often helpful in characterizing older children with asthma.⁴⁶ Additionally, electromagnetic inductance

plethysmography can be used to measure tidal breathing in preterm and term infants.⁴⁷ Emerging techniques, such as impulse oscillometry, to evaluate small airways has recently gained interest and might be useful in young children who cannot perform spirometry.⁴⁸ Hyperpolarized helium might also be useful for asthma diagnosis through visualization of ventilated and unventilated airways. However, the comparative efficacies of these techniques versus standard spirometric or symptom-based approaches to diagnosis remain unclear. Further work is necessary to determine the role of standard and newer diagnostic approaches as they relate to symptomatology.

Biomarkers

Given the challenges associated with lung function testing in children, specific biomarkers of disease and progression with high clinical and practical utility are needed but are lacking in children. Currently, only IgE and specific IgE as a measure of allergic sensitization are routinely used outside of research settings. The following summarizes key features of potential biomarkers for use in children.

Fraction of exhaled nitric oxide. Measurement of the fraction of exhaled nitric oxide (FENO) is often used as a surrogate for airway inflammation. It has been purported to be associated with airway inducible nitric oxide synthase expression and eosinophil counts but with varying relationships.^{49,50} Inflammatory factors that promote increased FENO values remain unclear,

and the coexistence of confounding allergic diseases might further complicate its utility.

Exhaled carbon monoxide and pulse carbon monoxide oximetry. In addition to FENO, carbon monoxide (CO) can also be measured in exhaled breath. One meta-analysis demonstrated that exhaled CO levels are increased in both adults and children with asthma, irrespective of corticosteroid treatment, disease severity, or level of asthma control.⁵¹ Similarly, arterial carboxyhemoglobin levels, which correlate with exhaled CO levels,⁵² are increased in asthmatic patients with acute exacerbations, return to normal with resolution of symptoms, and are inversely related to lung function in adults.^{52,53} Although recent work suggests that increased pulse CO-oximeter readings might be associated with asthma control in children,⁵⁴ further work is needed to understand its potential clinical utility.

Exhaled breath condensate. Exhaled breath condensate (EBC) is another noninvasive method for the collection of airway secretions. Low EBC pH might be a biomarker to identify asthmatic patients and exacerbations of asthma, but its clinical utility is controversial.⁵⁵ 8-Isoprostane levels are also higher in children with asthma⁵⁶ and might be increased as a function of exacerbations and asthma severity.⁵⁷ Similarly, EBC hydrogen peroxide concentrations are increased in children with asthma exacerbations and remain increased despite treatment.⁵⁸ Other EBC markers include leukotrienes and cytokines/chemokines; however, clinical applications, particularly in children, are not currently clear.

Airway inflammatory cells. Less is known about airway inflammation in children compared with that seen in adults given age-related research limitations. Most of the existing literature is focused on children with severe asthma in whom invasive assessments are clinically indicated.^{59,60} These studies suggest that more abundant eosinophils, neutrophils, and epithelial cells are found in children with persistent asthma,⁶⁰ whereas levels of cytokines and chemokines, such as IL-6, IL-13, CXCL1, and IL-8, are increased in children with severe asthma.⁵⁹ Induced sputum might be obtained more feasibly in children, but at the present time, there are not enough data to determine whether sputum cells might be relevant and practically obtained airway biomarkers in children.

Urinary biomarkers. Urinary leukotriene E₄ concentrations are associated with acute exacerbations of asthma⁶¹ and the degree of airflow limitation⁶² and appear to change with age and severity.⁶³ Similarly, urinary bromotyrosine (a marker of eosinophil activation) has also been associated with asthma control and can be used to predict the risk of an asthma exacerbation.⁶⁴

Serum biomarkers. In adults serum and airway YKL-40 levels have been associated with subepithelial basement membrane thickness and clinical indexes of disease severity, including airflow limitation and exacerbations.⁶⁵⁻⁶⁷ Similarly, serum periostin levels in adults are associated with eosinophilic and IL-13-mediated airway inflammation.⁶⁸⁻⁷² However, studies of serum biomarkers in children suggest confounding by bone growth.

Computed tomography/magnetic resonance imaging. Both computed tomography and magnetic resonance imaging can be used to measure structural airway changes. However, asthma likely has a regional distribution within the airways whereby some areas are more affected than others.⁷³ There appears to be some persistence to this distribution that

might explain the observed patterns of airway remodeling and provide targets for localized therapies, such as bronchial thermoplasty, which is currently unavailable for children.⁷⁴

Unanswered questions

Although there have been significant efforts toward diagnostics and biomarkers in asthma, diagnostics (including biomarkers) that can help us fully understand the natural course of pediatric asthma and related symptoms are greatly needed. Unanswered questions in diagnostics and biomarkers include the following:

- Are there acceptable alternative approaches to lung function testing in young children?
- What biomarkers can be used to predict asthma progression in young children?
- What are the performance characteristics of available biomarkers, including ease of collection and stability and long-term validity across the age spectrum?

OUTCOME MEASURES

A significant challenge associated with the design and conduct of pediatric research is the selection of appropriate outcome measures for both the characterization of the study population and determination of therapeutic efficacy. Although a recent asthma outcomes workshop provided recommendations for core, supplemental, and emerging outcomes for asthma clinical trials,⁷⁵ children were not the primary focus of this initiative. Further complicating the issue of outcome measurement in children is the operational definition of the term “child” because it is well recognized that children are not “small adults.” Rather, children are characterized by unique developmental, physiologic, biological, and behavioral differences that render assessment and treatment challenging.⁷⁶ This section addresses asthma outcome measures in children, as well as other considerations for the conduct of pediatric clinical trials.

Biomarkers

Despite increased understanding of the biological determinants of asthma, biomarkers for diagnosis and treatment have remained elusive given the heterogeneity of the disorder and the variability of individualized therapeutic responses. Thus there are currently no recommended “core” (ie, required) outcomes for prospective efficacy studies in children. Only serologic multiallergen screen (IgE) testing is recommended for baseline characterization.⁶³ This test is easily performed in both the 0- to 4-year and 5- to 11-year age groups, although it is recognized that age does affect IgE levels.⁷⁷

Spirometry

Although spirometry is recommended as both a core efficacy outcome and characterization variable in asthma clinical trials involving children 5 years and older,⁷⁸ spirometry poses several challenges. In children less than 5 years of age, spirometry cannot typically be performed because it is an effort-dependent test that requires developmental maturity and cooperation. Although informative, infant pulmonary function testing is not directly comparable with spirometric indices, and this test requires sedation and considerable time and effort on behalf of the investigator.

Moreover, even in children age 5 to 11 years, spirometry might be less informative because children tend to have less airflow limitation, regardless of disease severity.^{44,79} Furthermore, there is often discordance between pulmonary function, symptoms, and other asthma impairment in children. Although age-appropriate reference equations are available, interpretation of spirometric data can also be challenging in racially admixed populations and in longitudinal studies given normal physiologic changes associated with lung growth.

Composite questionnaires for asthma symptoms, asthma control, and asthma-related quality of life

Although there are a number of available questionnaires for asthma assessment, use of these questionnaires in children is troublesome. Because these instruments require caregiver assistance for completion, the recorded answers might not reflect the true nature of the underlying disease state in children who attend day care or school. Young children also have more episodic disease patterns,⁸⁰ but most asthma questionnaires are focused on chronic disease burden over a period of 1 to several weeks. Many of these instruments also assume that asthma diagnosis is firmly established and that caregivers are familiar with treatment approaches. Thus most asthma questionnaires are focused on the global concept of asthma control, which incorporates both current symptoms and risk of future impairment, and therefore there are no recommended core questionnaires for specific asthma symptoms or asthma-related quality of life.^{81,82} Although there are also no recommended core questionnaires of global asthma control for prospective efficacy studies in children, the Childhood Asthma Control Test, which is completed by both the child and the caregiver, is recommended for baseline characterization of children 5 to 11 years of age.⁸³ However, there are no instruments available for children in the 0- to 4-year age group. Thus the major ongoing challenge with pediatric questionnaire development is the inclusion of developmentally appropriate language and concepts, as well as the nature and capabilities of the respondent.

Asthma exacerbations and health care use

Exacerbations are not unique to children, although the frequency of exacerbations might differ across the age span as a function of specific triggers and altered innate and adaptive immune responses. Independent of age, the asthma outcomes workshop recommended that asthma exacerbations be defined as “worsening of asthma requiring the use of systemic corticosteroids to prevent serious outcomes.”⁸⁴ It was further recommended that asthma exacerbations be considered core outcomes for both prospective efficacy analyses and baseline characterization in all age groups, although it was recognized that the threshold for symptom identification and health care use in children depends on the education level and personality of the caregiver.⁸⁴ Therefore other factors, such as emergency health care use, hospitalization, and/or other unscheduled visits, might be informative in the assessment of pediatric populations.⁸⁵ Other unique factors to consider in pediatric studies include absenteeism from school, parental absence from work, and “presenteeism” (or impairment of performance while at work or school), which also influence cost-effectiveness analyses.⁸⁵

Other general considerations for outcome assessment

Asthma outcome measures in children can also be influenced by other developmentally unique factors. For example, behaviors, such as medication administration, medication adherence, and general asthma-related coping strategies and psychological stress, might vary dramatically in children but could be misrepresented by caregivers during the conduct of asthma clinical trials.⁸⁶ Although studies in children typically involve smaller sample sizes in attempts to minimize overexperimentation, this can also result in underpowering of important study outcomes and limited generalizability.⁸⁷ The issue of placebo control is also more problematic in children and might ultimately result in a higher threshold for statistical significance as opposed to adult-oriented placebo-controlled studies, particularly if best available practice is used as the comparator. At the same time, the “placebo response” might vary according to age.⁸⁸ Other regulatory issues, including off-label use of study drugs, could also be different in children⁸⁷ and might be further complicated by unique safety-related issues and adverse event profiles as a function of developmental maturation.

Primary unanswered questions include the following:

- Should outcome measures for pediatric studies be the same as for adults?
- Should composite measures be preferred in children over single outcomes, such as lung function or exacerbations?

ASTHMA THERAPEUTICS

Substantial advances in asthma therapeutics have occurred over the last several decades, but extending the benefits of these therapies to preschool- and school-age children has been slow. Extrapolation of new findings and therapeutic advances in adults cannot readily be made because of differences in underlying respiratory function, immune biology, and disease pathogenesis. Four prominent needs in the treatment of childhood asthma must be addressed to reduce the health burden in children: (1) to improve the methodological tools for conducting appropriate clinical trials and facilitating their translation into clinical care; (2) to understand and best apply therapeutic agents that stabilize asthma symptoms, reducing and preventing acute exacerbations; (3) to identify and apply best therapies for acute severe exacerbations that require hospitalization; and (4) to identify and develop agents that will prevent, ameliorate, or otherwise alter the course of asthma development and progression. This section focuses on gaps in the evidence base for asthma therapeutics in children, concentrating on specific priorities that will have the most direct and widespread effect.

Challenges with drug delivery in children

Effective and consistent drug delivery to the airways is a significant challenge in children. The most common means of chronic corticosteroid administration, even in preschool children, is through the use of pressurized metered-dose inhaler devices coupled with valved holding chambers (spacers).^{89,90} Only a small fraction of the dose of an inhaled corticosteroid administered through a pressurized metered-dose inhaler/spacer or nebulizer reaches the distal airway, resulting in variability of

drug effect between subjects. Additional pharmacokinetic studies in young children are needed to determine the optimum means of drug administration, quantify systemic absorption and elimination, define the efficacy of treatment, and define the risk of adverse effects on development.

Long-term suppression of asthma exacerbations

Although inhaled corticosteroids are also effective in children less than 5 years of age in reducing wheezing episodes when compared with placebo,⁹¹⁻⁹⁴ their use is associated with some adverse effects, including decreased growth velocity from systemic exposure.⁹² Therefore although daily inhaled corticosteroids are efficacious in infants and young children, their place as preferred first-line therapy for persistent asthma in this age group requires further study. Alternative therapeutic approaches that might be equally efficacious and safer, including intermittent administration, are being explored.^{95,96}

The development of controller medications other than corticosteroids is highly desirable. Recent studies in preschool children suggest similar effectiveness between daily inhaled corticosteroids and leukotriene receptor antagonists, as measured by the time to first additional asthma medication.^{91,97} Anticholinergic agents, particularly tiotropium, might provide baseline bronchodilation and therefore prevent lower airway obstruction. However, there are few studies in children, and currently available anticholinergic agents are not approved for use in children. Studies are needed to establish dose-response relationships, efficacy, safety, and adverse effects.

Acute therapy: Severe exacerbations requiring intensive care

Self-administered inhaled β -agonists are the mainstay of treatment for mild-to-moderate acute exacerbations. Inhaled β -adrenergic agonists combined with systemic corticosteroids are also the initial drugs of choice for severe acute asthma.⁹⁸ However, inhaled agents in the acute setting can be ineffective, possibly because of acute airway obstruction that limits drug delivery or disease severity. In these circumstances intravenous magnesium sulfate, intravenous ketamine, and the intravenous adrenergic β -agonist terbutaline are commonly used.⁹⁹ There are no US Food and Drug Administration–approved drugs, no pediatric-based formulations, and no data that demonstrate the best next-line therapy in patients with acute severe asthma. For all of these options, there are numerous gaps in clinical pharmacology, therapeutic uncertainty, unknown risks of use, and significant variability in clinical practice.

Intravenous terbutaline has demonstrated activity as a bronchodilator, but its use in the pediatric setting lacks pharmacologic data. The risk of side effects, including pulmonary edema, are not adequately defined for the pediatric population. Efficacy and safety studies are needed, as are studies defining the age-dependent pharmacokinetics and pharmacodynamics.

Additionally, there is no pediatric formulation of intravenous terbutaline. Thus pediatric ICU physicians and pediatric pulmonologists who choose this option must use adult formulations that are much more dilute than desired. Administration of a weight-appropriate dose (usually extrapolated from adult studies) requires administration of large fluid volumes, which carries the risk of acute fluid overload, exacerbating the risk of pulmonary edema.

Ipratropium has been shown in adults and children to be a useful addition to short-acting β -agonists in relieving bronchoconstriction in the emergency department, thereby preventing hospitalization.^{100,101} The use of this agent outside these settings requires further study.

Disease prevention and change in progression

Asthma is the most prevalent chronic disease in children,¹⁰² highlighting the need for asthma prevention studies in at-risk children and development of approaches to alter progression in those with established disease. Existing drugs have not been evaluated with these goals in mind except for the studies with inhaled corticosteroids mentioned previously.^{92,103} Identification of the ability of specific drugs to exert preventive or disease-modifying effects would be significantly enhanced by the development of age-effective means to measure pulmonary function or other important asthma-related outcomes.

Childhood asthma frequently has an environmental antigen-triggered IgE component, either causative or contributory. Environmental modification and allergen desensitization are potential approaches to asthma disease modification or trajectory alteration but are potentially costly and time-consuming. Additionally, effectiveness varies dramatically among patients.

Omalizumab, an anti-IgE mAb, is approved for adults and children greater than 12 years of age with moderate-to-severe persistent allergic asthma with sensitization to perennial allergens whose symptoms are not controlled with inhaled corticosteroids.¹⁰⁴ It acts through inhibition of IgE binding to the high-affinity IgE receptor on mast cells and basophils. By decreasing levels of bound IgE, the activation and release of mediators in the early and late phases of the allergic response is limited. On the basis of this biology, the possibility that omalizumab could prevent the development or modify the course of asthma if given in early childhood to at-risk infants is a reasonable hypothesis. Further study is warranted.

Unanswered questions

Primary unanswered needs in asthma therapeutics include the following:

- Identify the age-appropriate inhaled drug administration technique that provides optimal lung delivery of medications.
- Determine which treatment strategies are effective in preventing and modifying the course of asthma.
- Identify the studies that should be conducted to appropriately label medications for the management of acute asthma exacerbations in children.
- Develop age-appropriate formulations for therapeutic agents, especially those used in the hospital setting.

SUMMARY

The Asthma Group formed by the National Institute of Child Health and Human Development in response to the Best Pharmaceuticals for Children Act has conducted a thorough review of the core features associated with asthma management, including natural history, diagnostic indicators, biomarkers, and outcome measures, along with information gaps in the treatment of asthma. Although significant advances have been made in the

understanding and management of asthma in adults with appropriately labeled medications, less information is available on the management of asthma in children. Indeed, many medications are inadequately labeled in children. In general, the younger the child, the less information there is available to guide clinicians. Because asthma often begins in early childhood, it is incumbent on us to continue to address the primary questions raised in this review and to appropriately evaluate the medications most frequently used to manage asthma in children. There are several new medications on the horizon, including a number in the biologic modifier category. Perhaps one or a combination of treatments will be effective in preventing the onset and progression of asthma. It is possible that the same strategy might not show an effect in older children and adults. Therefore we must be on the alert for new treatment strategies that might prove more effective in children than adults and perhaps hold the key for interventions that alter the natural history of asthma and lead to a cure of this disease.

After discussing the gaps in information, the Working Group believed there were several areas that require additional information to move the management of childhood asthma forward. In regard to the natural history of asthma, it would be useful to develop a registry of ongoing cohorts to form the basis of a collaborative effort at understanding the early origins of asthma, especially as related to asthma progression, and to define a profile that is associated with the development of severe asthma. This would be useful information for designing prevention studies. In regard to biomarkers, it is important to identify clusters of biomarkers that are associated with or reflect disease activity that can easily be used in a research setting for studies in children, especially young children. For outcome measures, it is important to focus attention on validating outcome markers for symptoms assessment in children, especially young children. This should be accompanied by efforts to define reliable measures of pulmonary function. In regard to therapeutics, efforts should be made to develop clinical trials for early intervention, including dose-ranging and pharmacokinetics/pharmacodynamic studies, which could be useful in primary prevention. Defining therapeutic strategies that could alter progression of disease is also a high priority because no treatment to date has been shown to alter progressive loss in pulmonary function, especially that related to the emergence of severe asthma. Furthermore, age-specific drug formulations should be developed. Meanwhile, continued efforts should be made in defining effective strategies that reduce the risk of exacerbations. If these areas of need are addressed in the coming years, namely prevention of exacerbations, progression of disease, and primary intervention, we will continue to see a reduction in mortality related to asthma and the associated morbidity as reflected in urgent care needs and altered quality of life for children with asthma.

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What do we know?

- Asthma, which typically begins in childhood and occurs throughout life, has common clinical manifestations but many different “phenotypes” that are associated with variable disease courses.
- Exposures to environmental stimuli lead to alterations in inflammatory pathways that trigger wheezing illnesses and the development of asthma.
- Asthma diagnosis in younger children is typically based on the presence of symptoms and specific risk factors, such as family history and atopy.
- Substantial advances in asthma therapeutics have occurred over the last several decades, but extending the benefits of these therapies to children has been slow.

What is still unknown?

- Given the challenges associated with lung function testing in children, specific biomarkers of disease and progression with high clinical and practical utility are needed but are lacking in children.
- A significant challenge associated with the design and conduct of pediatric research is the selection of appropriate outcome measures for both the characterization of the study population and determination of therapeutic efficacy.
- Continued efforts should be made in defining effective strategies that reduce the risk of exacerbations.
- Defining therapeutic strategies that could alter progression of disease is also a high priority because no treatment to date has been shown to alter progressive loss in pulmonary function, especially that related to the emergence of severe asthma.

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