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Asthma Across the Ages: Knowledge Gaps in Childhood Asthma Prepared for the 2014 theme issue in the Journal of Allergy and Clinical Immunology

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Abstract

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 (BPCA). The overall goal of the BPCA Program is to improve pediatric therapeutics through preclinical and clinical drug trials that lead to drug labeling changes.

While 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

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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. Since asthma often begins in early childhood, it is incumbent upon us to continue to address the primary questions raised in this review and carefully evaluate 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.

Keywords

Asthma; asthma natural history; asthma progression; asthma biomarkers; childhood asthma; asthma pharmacotherapy

INTRODUCTION

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (**NICHD**) convened an Asthma Group in response to the Best Pharmaceuticals for Children Act (**BPCA**). The overall goal of the BPCA 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 regards to etiology, 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 four 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 four classes of drugs that merit close attention due to frequent use and lack of appropriate dosage information by age. This information is intended to inform future studies by the NIH, the U.S. Food and Drug Administration (**FDA**) and pharmaceutical firms to advance pediatric asthma care.

I. 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 develop asthma later in life (1). Gender 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 who develop multiple early aeroallergen sensitization 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 may 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 pre-term infants suggests that prevention of severe RSV infection in infancy may 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 (Figure 1), which may be present even when symptoms are absent. The eosinophilic predominance seen on bronchoalveolar lavage (**BAL**) in older individuals is less pronounced in infants (15). However, some children may develop a noneosinophilic or neutrophilic form of asthma. These patients may 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 asthma, as it is unclear what predisposes young children to develop 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 the development of asthma (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 individual determines whether asthma will develop.

Progression of Asthma

The progression of asthma is variable both between, and within, individuals. The National Heart, Lung and Blood Institute's Severe Asthma Research Program (**SARP**) has focused on the clinical, physiologic, and biologic heterogeneity of asthma. To identify potential clinical asthma phenotypes, 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 *a priori* bias (20). Similarly, a cluster analysis of 300 children (ages 6–17 years)

identified marked heterogeneity (21) 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 people with asthma develop some form of airway remodeling regardless of phenotype. Remodeling, which is characterized by epithelial cell injury, thickening of the reticular basement membrane (RBM), sub-basement 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 may 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 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 3 years develop lung function abnormalities by age 6 that persist (23). In another birth cohort study, children diagnosed with asthma by age 7 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 may 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), similar to what has been reported in older children and adults (25, 29, 30). It has recently been reported that airway smooth muscle thickness may increase at a much earlier age than previously thought. Children who have asthma at school age have increased airway smooth muscle as pre-school aged children (31). These findings suggest that some of the pathologic changes in asthma once thought to occur only in patients with long-standing inflammation may 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 healthcare costs. Moreover, recent studies suggest that exacerbations may lead to progressive loss of lung function (32, 33). While 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 and declines 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 (34, 35). There also appears 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 respiratory viral infections. Exacerbations are most commonly caused by HRV in children with concomitant allergic sensitization (7, 40). HRV 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 beta-agonists. However, the validity of such definitions is unknown as such definitions may 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 asthma natural history and pathophysiology include the following:

- What inflammatory phenotypes are present in children, what is their long-term stability, and how do they relate to airway remodeling?
- What factors are responsible for triggering asthma onset?
- What factors are associated with progressive disease?
- What is the influence of gender on asthma in relation to inception, prevalence, persistence, remittance, and response to therapy?
- How do asthma exacerbations contribute to long-term outcomes?

II. 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 less than 5 years have difficulty performing reproducible spirometry according to ATS 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 “super-normal” spirometry readings outside of exacerbations which further renders diagnosis challenging (43–45).

Determination of lung volumes by 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 may be useful in young children who cannot perform spirometry (48). Hyperpolarized helium may 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 immunoglobulin E (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.

FeNO—Measurement of fractional exhaled nitric oxide (**FeNO**) is often used as a surrogate for airway inflammation. It has been purported to be associated with airway iNOS expression and eosinophils, but with varying relationships (49, 50). Inflammatory factors that promote increased FeNO remain unclear, and the coexistence of confounding allergic diseases may further complicate its utility.

Exhaled CO and Pulse CO-Oximetry—In addition to FeNO, carbon monoxide (**CO**) can also be measured in exhaled breath. One meta-analysis demonstrated that exhaled CO (eCO) is 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 (52), are elevated in asthmatics suffering acute exacerbations, return to normal with resolution of symptoms, and are inversely related to lung function in adults (52, 53). While recent work suggests that elevated pulse- CO-Oximeter readings may be associated with asthma control in children(54), further work is needed to understand its potential clinical utility.

Exhaled breath condensate (EBC)—Exhaled breath condensate (**EBC**) is another non-invasive method for the collection of airway secretions. Low EBC pH may be a potential biomarker to identify asthma patients and exacerbations of asthma, but its clinical utility is controversial (55). 8-isoprostane levels are also higher in children with asthma (56) and may be increased as a function of exacerbations and asthma severity (57). Similarly, EBC hydrogen peroxide (**H₂O₂**) concentrations are increased in children with asthma exacerbations and remain elevated despite treatment (58). Other EBC markers include leukotrienes and cytokines/chemokines; however, clinical applications, particularly in children, are not clear at the current time.

Airway inflammatory cells—Less is known about airway inflammation in children compared with adults given age-related research limitations. Most of the existing literature is focused on children with severe asthma where 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) while cytokines and chemokines such as IL-6, IL-13, CXCL1 and IL-8 are increased in children with severe asthma (59). Induced sputum may be more feasibly obtained in children, but at the present time, there are not enough data to determine whether sputum cells may be relevant and practically obtained airway biomarkers in children.

Urinary biomarkers—Urinary leukotriene E4 (LTE4) concentrations are associated with acute exacerbations of asthma (61) and the degree of airflow limitation (62), 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 may be used to predict the risk for 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 in adults is associated with eosinophilic and IL-13 mediated airway inflammation (68–72). However, studies of serum biomarkers in children suggest confounding by bone growth.

CT/MRI—Both CT and MRI 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 which may 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 towards 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?

III. 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,” since it is well recognized that children are not “small adults.” Rather, children are characterized by unique developmental, physiological, biological and behavioral differences which 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” (i.e., 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 0–4 year and 5–11 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 spirometry cannot typically be performed since it is an effort-dependent test that requires developmental maturity and cooperation. While informative, infant pulmonary function testing is not directly comparable to spirometric indices and this test requires sedation and considerable time and effort on behalf of the investigator. Moreover, even in children age 5–11 years, spirometry may be less informative since 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 spirometry data can also be challenging in racially admixed populations and in longitudinal studies given normal physiological 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 may not reflect the true nature of the underlying disease state in children who attend daycare 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 one 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). While there are also no recommended “core” questionnaires of global asthma control for prospective efficacy studies in children, the Childhood Asthma Control Test (cACT), which is completed by both the child and the caregiver, is recommended for baseline characterization of children 5–11 years (83). However, there are no instruments available for children in the 0–4 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 healthcare utilization

Exacerbations are not unique to children, although the frequency of exacerbations may 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 healthcare utilization in children depends on the education level and the personality of the caregiver (84). Therefore, other factors such as emergency healthcare utilization, hospitalization, and/or other unscheduled visits may 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 coping strategies and psychological stress may vary dramatically in children but may be misrepresented by caregivers during the conduct of asthma clinical trials (86). While studies in children typically involve smaller sample sizes in attempts to minimize over-experimentation, this can also result in under-powering of important study outcomes and limited generalizability (87). The issue of placebo control is also more problematic in children and may 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”

may vary according to age (88). Other regulatory issues, including off-label use of study drugs, may also be different in children (87) and may 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?

IV. ASTHMA THERAPEUTICS

Substantial advances in asthma therapeutics have occurred over the last several decades, but extending the benefits of these therapies to pre-school and school-aged 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: first, to improve the methodological tools for conducting appropriate clinical trials and facilitating their translation into clinical care; second, to understand and best apply therapeutic agents which stabilize asthma, reducing and preventing acute exacerbations; third, to identify and apply best therapies for acute severe exacerbations which require hospitalization; and finally, to identify and develop agents which 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 impact.

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 pre-school children, is via the use of pressured metered dose inhaler (pMDI) devices coupled with valved holding chambers (spacers) (89, 90). Only a small fraction of the dose of an inhaled corticosteroid administered by pMDI/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

While inhaled corticosteroids are also effective in children under the age of five 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, while 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 may 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, may 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 beta agonists are the mainstay of treatment for mild to moderate acute exacerbations. Inhaled beta-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 due to acute airway obstruction that limits drug delivery or to disease severity. In these circumstances intravenous magnesium sulfate, intravenous ketamine, and the intravenous adrenergic beta agonist, terbutaline, are commonly used (99). There are no FDA-approved drugs, no pediatric-based formulations, or data that demonstrate the best next-line therapy in acute severe asthma. For all of these options there are numerous gaps in the 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 which 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 beta 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 developing 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 monoclonal antibody, is approved for adults and children greater than 12 years of age with moderate to severe persistent allergic asthma with sensitization to perennial allergens who are not controlled with inhaled corticosteroids (104). It acts by inhibition of IgE binding to the high affinity IgE receptor on mast cells and basophils. By decreasing bound IgE, the activation and release of mediators in the early and late phases of the allergic response is limited. Based on 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 NICHD in response to the Best Pharmaceuticals for Children Act has conducted a thorough review of the core features associated with asthma management including the natural history, diagnostic indicators, biomarkers, outcome measures along with information gaps in the treatment of asthma. While 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. Since asthma often begins in early childhood, it is incumbent upon us to continue to address the primary questions raised in this review and to appropriately evaluate 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 may not show an effect in older children and adults. Therefore, we must be on the alert for new treatment strategies that may 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 felt there were several areas that require additional information to move the management of childhood asthma forward. In regards to the natural history of asthma it would be useful to develop a registry of ongoing cohorts in order to develop 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 regards 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 regards 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 since no treatment to date has been shown to alter progressive loss in pulmonary function, especially that related to the emergence of severe asthma. Further, 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 as well as the associated morbidity as reflected in urgent care needs and altered quality of life for children with asthma.

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ABBREVIATIONS

API	Asthma Predictive Index
BAL	Bronchoalveolar lavage
BPCA	Best Pharmaceuticals for Children Act
CO	Carbon monoxide
EBC	Exhaled breath condensate
eCO	Exhaled carbon monoxide
FDA	Food and Drug Administration
FeNO	Fractional exhaled nitric oxide
FEV₁	Forced expiratory volume in one second
H₂O₂	Hydrogen peroxide
HRV	Human rhinovirus
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
iNOS	Inducible nitric oxide synthase
LTE₄	Leukotriene E ₄
NICHHD	National Institute of Child Health and Human Development

pMDI	Pressurized metered dose inhaler
RBM	Reticular basement membrane
RSV	Respiratory syncytial virus
SARP	NIH/NHLBI Severe Asthma Research Program
Th2	T helper type 2

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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 since no treatment to date has been shown to alter progressive loss in pulmonary function, especially that related to the emergence of severe asthma.

Figure 1.

Airway inflammation in asthma. The orange box represents activities in the lymph node. The DC processes antigens, migrates to the lymph node, and associates with TH0, which then differentiates and migrates back to the airway. Figure A demonstrates non-eosinophilic/neutrophilic asthma, and Figure B demonstrates eosinophilic asthma. Remodeling occurs in all forms of asthma, but is only shown in Figure B.

Table 1

Natural history and pathophysiologic changes of asthma by age

	Age in years			
	< 5	5–11	13–17	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
Reticular basement membrane 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 years but may not be present in those who began wheezing in later childhood	Progressive decline in lung function may occur; Irreversible airway obstruction may also be seen
Incidence of exacerbations	++++	+++	++	++