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Advances in Pediatric Asthma in 2013: Coordinating Asthma Care

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Abstract

Last year's Advances in Pediatric Asthma: Moving Toward Asthma Prevention concluded that: "We are well on our way to creating a pathway around wellness in asthma care and also to utilize new tools to predict the risk for asthma and take steps to not only prevent asthma exacerbations but also to prevent the early manifestations of the disease and thus prevent its evolution to severe asthma." This year's summary will focus on recent advances in pediatric asthma on pre- and postnatal factors altering the natural history of asthma, assessment of asthma control, and new insights regarding potential therapeutic targets for altering the course of asthma in children as indicated in Journal of Allergy and Clinical Immunology publications in 2013 and early 2014.

Recent reports continue to shed light on methods to understand factors that influence the course of asthma, methods to assess and communicate levels of control, and new targets for intervention as well as new immunomodulators. It will now be important to carefully assess risk factors for the development of asthma as well as the risk for asthma exacerbations and to improve the way we communicate this information in the health care system. This will allow parents, primary care physicians, specialists and provider systems to more effectively intervene in altering the course of asthma and to further reduce asthma morbidity and mortality.

Keywords

airway remodeling; asthma; asthma control; asthma exacerbations; early intervention in asthma; biomarkers; environment; genetics; inhaled corticosteroids; leukotriene receptor antagonists; long-acting ß-adrenergic agonists; personalized medicine; severe asthma; therapeutics

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Introduction

Journal publications in 2013 and early 2014 serve as a base for identifying prenatal and postnatal factors that can affect the course of asthma. Attention is now being directed to not only prevent exacerbations but also alter the progression of the disease that may in fact be intricately related to the occurrence of asthma exacerbations. Last year's "Advances in Pediatric Asthma in 2012: Moving toward asthma prevention" included a discussion of new tools to predict the risks for asthma, steps to prevent asthma exacerbations, and possible methods to prevent the evolution of severe asthma (1). Also last year's review by Andrea Apter on adult asthma focused on new developments in medications as well as gene-environment interactions (2).

A series of reviews in the recent January 2014 theme issue entitled "*Asthma Across the Ages*" profiled current directions in studies of pediatric and adult asthma (3-6). Members of a National Institute for Child Health and Human Development (NICHD) Working Group summarized the gaps in information that must be filled in order to advance appropriate labeling of medications that are used to manage pediatric asthma, especially for use in early childhood (3). Sutherland and Busse on behalf of the National Hearth Lung and Blood Institute (NHLBI) AsthmaNet summarized current and future work conducted in the NIH AsthmaNet research network that combines clinical studies in children and adults including cross age, mechanistic and proof of concept studies (4). Cabana et al (5) summarized challenges that the NHBLI AsthmaNet has faced in designing and conducting cross-age clinical studies including the selection of clinical interventions, appropriate controls, and meaningful outcome measures, along with a discussion of ethical and logistical issues. Finally, Ortega and Meyers (6) provided a review on pharmacogenetics as it relates to race and ethnicity on defining genetic profiles for personalized medicine. They address a number of key issues for analyzing admixed ethnic groups participating in clinical studies in order to detect and replicate novel pharmacogenetic loci necessary in developing individualized treatment strategies.

This review will highlight 2013 Journal publications that bring forth new information to help identify pre- and postnatal factors that contribute to the natural history of asthma, new tools to assess asthma control, and new insights on possible therapeutic targets that could be used to design medications that alter the course of asthma. Important theme issues in the Journal over the past year included clinical phenotypes of pulmonary disease, B-lymphocytes, T cells, the microbiome, and microRNA in relation to understanding asthma.

New information on prevention

Prenatal factors

A review on T cells in asthma was provided by Lloyd and Saglani (7) indicating the role that T cells play in reacting to the genetic and environmental exposures and interacting with structural cells, including epithelial cells, and other cells in the immune system to influence whether inflammation resolves or progresses, and thus influence the pathway of asthma. Thompson et al (8) examined methods of transmission or persistence of maternal cells to children of mothers with asthma compared with children of mothers without asthma and reported that maternal microchimerism may protect against the development of asthma. Chandra Pandey et al (9) provided information to show that different TLR signaling mechanisms might be involved in the pathogenesis of atopic and nonatopic asthma and that post-genome-wide association study analyses of existing data sets with pathway approaches might be a promising way of identifying novel asthma susceptibility loci, adding to the missing heritability of asthma. Maternal health can also play a role in the outcomes of their offspring. Tegethuff et al (10) reported on a wide spectrum of offspring diseases during

childhood suggesting that careful monitoring of women with asthma during pregnancy and their offspring is important. On that note, Zetstra-van der Woude et al (11) reported that many women stop or reduce their use of asthma medications when they become pregnant and strategies to safely control asthma during pregnancy are needed. Harpsoe et al (12) examined the effect of BMI and gestational weight gain and reported that maternal obesity during pregnancy was associated with increased risk of asthma and wheezing in offspring but not with atopic eczema and hay fever. Therefore, some maternal conditions could be modified to affect the course of asthma in the child.

Natural history and pathophysiology

Hafkamp-deGroen et al (13) sought to externally validate the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) risk score at different ages and in ethnic and socioeconomic subgroups of children and concluded that it showed good external validity. However, further studies are needed to test this system in other populations and to assess its clinical relevance. Clinical predictive scores will be particularly important as we design prevention intervention strategies since we do not yet have accurate screening tests that utilize genetic or single biochemical markers (14).

Kiss et al (15) provided a review on the role of lipid-activated nuclear receptors in shaping macrophage and dendritic cell function and concluded that a systematic analysis of the roles of these receptors and their activating lipid ligands will be crucial for the development of new therapies to target these nuclear receptors and alter the course of inflammatory diseases. In addition, O'Reilly et al (16) reported that increased airway smooth muscle at preschool age is associated with those children who have asthma at school age suggesting that changes in smooth muscle might be important in the subsequent development of childhood asthma. This research group also reported that IL-33 is a relatively steroid-resistant mediator that promotes airway remodeling in patients with severe therapy-resistant asthma and is an important therapeutic target (17). A great deal of attention has been directed to understanding the natural history of asthma phenotypes and perhaps cluster analysis of various study populations will prove helpful in linking biologic mechanisms to asthma phenotypes (18).

Just et al (19), based on analysis of the Trousau Asthma Program cohort used cluster analysis and concluded that remission is most frequently observed in mild early viral wheeze and that no remission is observed in atopic multiple-trigger wheeze. Collins et al (20) using a different cohort prompted questions related to the natural history of children who wheeze in the first year of life and whether they are different from those who never wheeze.

Oh et al (21) reported that perhaps exhaled nitric oxide might be a better marker for asthma phenotypes in preschool children than measures of airway hyperresponsiveness and pulmonary function. There is still a high level of interest in acetaminophen as a modifier of disease development for asthma and Kang et al (22) indicate a relationship between acetaminophen use and risk of asthma based on a cross-sectional survey of preschool children and suggest a relationship with eosinophilic inflammation. Therefore, postnatal features of children and medication use could be related to the outcomes of asthma in asthma in children.

Viral infection

Linder et al (23) found that human rhinovirus-C (HRV-C) was significantly associated with childhood lower respiratory illness and that temporal changes in virus prevalence occur that can be used for designing preventative and treatment strategies. Papi et al (24) provided evidence that RV-16 infection of human airway epithelium induced glucocorticoid

resistance. In studying the association of RV wheezing illness and genetic risk of childhood-onset asthma, Caliskan et al (25) found that variants at the 17q21 locus were associated with asthma in children.

There were several new directions and treatments proposed. James et al (26) reported that in two representative US populations there were consistent findings that nearly 50% of the asthma cases in children with a history of infant bronchiolitis during the respiratory syncytial virus (RSV) season were associated with bronchiolitis. Based on their observations related to asthma and RSV, they proposed that the next step will be to determine whether preventing or altering host response to infant RSV infection decreases both the incidence and severity of childhood asthma as a primary asthma prevention strategy. Blanken et al (27) subsequently reported that treatment with palivizumab, a monoclonal antibody shown to prevent severe RSV infection in high-risk infants, resulted in a significant reduction in wheezing days during the first year of life, even after the end of treatment. Given these findings, Lemanske (28) commented that it will be important to evaluate the role of allergic sensitization and 17q21 locus variation or treatment on influencing the natural history of asthma. Yoo et al (29) reviewed recent advances in pulmonary viral infection triggering innate and adaptive immune responses, mechanisms of virus clearance and the consequences of acute viral infection complicating underlying lung diseases including asthma. In a Rostrum review, Dreyfus (30) indicated that atopic patients receiving long term oral corticosteroids for asthma are at increased risk for severe or atypical varicella virus infection. These patients should be treated appropriately with varicella zoster virus immune globulin or antiviral therapy, such as acyclovir, if they are suspected of exposure to the wild type virus.

Environment – air pollution, microbiome, and farming

There is currently great interest in understanding the role of the environment in driving airway inflammation. Brunst et al (31) provided evidence that chronic diesel exhaust particle exposure during childhood is associated with *FOXP3* methylation and increased risk for persistent wheezing and asthma. Donohue et al (32) also reported an association of another environmental agent, bisphenol a, used widely in food container linings, with asthma in children. Figueiredo et al (33) identified distinct immune phenotypes in children living in poor urban neighborhoods in Brazil. Environmental characteristics related to an improved environment and lower exposure to pathogens were associated with a responsive immune phenotype and a greater prevalence of atopy but not asthma. Bringolf-Isler et al (34) demonstrated the importance of objective means of assessing physical activity in children to examine the impact on asthma and allergy development. They also reported that the protective forming effect for asthma and allergies was not due to differences in physical activity levels.

Portnoy et al (35) provided a practice parameter on the assessment and methods to reduce exposure to cockroach allergen. However, Ahluwalia et al (36) observed that in a community with high levels of both mouse and cockroach allergens, mouse allergen appears to be more strongly and consistently associated with poor asthma outcomes than cockroach allergen. In an accompanying editorial, Ownby commented that the available evidence indicates that mouse allergen needs to be more full investigated as a major cause of asthma in urban homes in the hope that better methods of reducing mouse allergen exposure will be associated with less morbidity, especially in urban children (37).

Stress

There is continued interest regarding fetal programming effects of stress on infant wheeze and atopic disease development, however it is also important to recognize that the postnatal

period is a critical period for programming of future health (38). Now there is even great interest in the role of microbe exposure in establishing a biologic system of interaction between the environment and the host. Wright et al (39) reported that maternal prenatal cortisol disruption, as an indicator of altered prenatal maternal hypothalamic pituitary axis functioning, and obesity were independently associated with children's wheeze. Obese women with adverse cortisol profiles were most likely to have children with repeated wheeze. In addition, stress in later childhood is thought to play a role in the development of adult-onset asthma (40). Murphy and Hollingsworth (41) comment on this complex relationship between the external environment and host factors that regulate the pathogenesis of childhood asthma and suggest that perhaps there are epigenetic and genetic alterations that link psychosocial stress to childhood asthma. However, additional studies are needed to provide insight into this complex interrelationship of host genetics and common environmental exposures along with epigenetic programming.

Growth and development

Another environmental factor being closely examined is the role of nutrition on disease development. Nwaru et al (42) reported that early introduction of wheat, rye, oats, and barley cereals; fish; and egg seem to decrease the risk of asthma along with allergic rhinitis and atopic sensitization in childhood. Also, longer duration of exclusive breast-feeding was protective against the development of nonatopic but not atopic asthma, suggesting a potential differing effect of breast-feeding on different asthma phenotypes. Lu et al (43) indicated that being overweight or obese can increase susceptibility to indoor PM2.5 and NO2 in urban children with asthma. They suggest that weight loss or environmental control measures might therefore reduce asthma symptom responses to environmental pollutant exposures. Rzehak et al (44) reported that rapid increase in BMI during the first 2 years of life increased the risk of asthma up to age 6 years. Therefore, longitudinal pre-birth cohort studies will now be able to take advantage of emerging technologies to measure multiple exposures, intermediate genomic and proteomic responses, and physiologic and symptom end points to further delineate pathways linking somatic growth to asthma. These initiatives might provide guidance for regulatory decisions related to environmental exposures that jointly influence early-life growth trajectories and asthma (45). On this note, Halonen et al (46) provided evidence that elevated lipopolysaccharide-induced TNF-alpha production, an indicator of innate immune response, early in life acts as a predictive biomarker for childhood asthma, and excess pregnancy weight gain in the mother seems to contribute to both.

Assessment of established asthma

Asthma control

Belgrave et al (47) investigated whether joint modeling of observations from medical records and parental reports helped to more accurately define wheezing disorders during childhood and whether incorporating information from medical records better characterizes severity. They identified a novel group of children with persistent troublesome wheezing who have markedly different outcomes compared with persistent wheezers with controlled disease. This points to the need to organize data bases in medical care to identify children who benefit from individualized interventions. Clinical tools are extremely useful in monitoring asthma over time. Jia et al (48) explored the diagnostic performance of a comparison between the Asthma Control Test (ACT) and the Asthma Control Questionnaire (ACQ). They concluded that the ACT is preferable to the ACQ in clinical practice. However, they also noted that neither test is useful for the assessment of uncontrolled asthma. Okelo et al (49) examined asthma control questionnaires across a broad range of minority and Spanish-speaking children in an outpatient setting. They concluded that the

Pediatric Asthma Control and Communication Instrument accurately measured asthma control in English- and Spanish-speaking children and it should be useful to clinicians to assess and classify asthma according to current asthma guidelines.

Jang et al (50) reported that although medical costs for patients with asthma increased or remained stable across all age groups over a 10-year period, outcomes did not improve. Therefore, they indicate that continued attention should be focused on asthma management in the United States. One way to do this is to carefully evaluate readmission and revisit rates. However, Bardach et al (51) found that when comparing hospitals' performances to the average, few hospitals that care for children are identified as high- or low-performers for revisits, even for common pediatric conditions, such as asthma. This limits the usefulness of condition-specific readmissions or revisit measures in pediatric quality measurement.

Additional strategies to enhance asthma management are to improve medication adherence and clinician use of available guidelines. McGrady and Hammel (52) reported that reduced medication adherence in pediatric chronic illness is related to increased health care use in children and adolescents who have a chronic condition. Okela et al (53) demonstrated that decision support tools, feedback and audit, and clinical pharmacy support were most likely to improve provider adherence to asthma guidelines, as measured through health care process outcomes.

Pulmonary function

Konstantinou et al (54) indicated that mild episodes of wheeze in preschoolers, aged 4 to 6 years, are characterized by enhanced airway inflammation (measured via exhaled nitric oxide [FeNO]), reversible airflow limitation (in those who could perform spirometry), and asthma-related symptoms. In addition, maternal smoking is associated with increased FeNO and poorer lung function in steroid-naïve preschool children with multiple-trigger wheeze (55). Van der Wiel et al (56) reviewed small airways dysfunction in asthma and suggested that an early recognition of small-airways dysfunction is important because it enables the clinician to start timely treatment to target the small airways. It is therefore important to develop simpler and more reliable tools to assess the presence and extent of small-airways dysfunction in clinical practice. Shi et al (57) indicated that children with controlled asthma who have increased peripheral airway impulse oscillometry indices are at risk of losing asthma control. Van Leeuwen et al (58) also indicated that a jumping castle (an inflatable platform on which children can safely jump) procedure could be used to measure breakthrough exercise-induced bronchoconstriction in young asthmatic children. Tse et al (59) sought to examine the diagnostic accuracy of the bronchodilator response of 12% or greater change in FEV_1 from baseline post-bronchodilator. They concluded that it might not be appropriate to choose a specific bronchodilator cutoff criterion for an asthma diagnosis.

Imaging

Another emerging tool for assessing altered lung structure is computed tomography. Donohue et al (60) observed that asthma examined with computed tomography in later adulthood after onset in childhood or young adulthood was associated with reduced lung function, narrower airways, and among asthmatic patients who smoked, greater percentage of low attenuation area, possibly associated with air trapping, in later life. Cadman et al (61) reported that magnetic resonance imaging with ^3He detected more and larger regions of ventilation and a greater degree of restricted gas diffusion in children with asthma compared with those seen in children without asthma. They suggested that these measures are consistent with regional obstruction and smaller and more regionally variable dimensions of the peripheral airways and alveolar spaces. Castro and Woods (62) commented that quantitative imaging of the lungs is an evolving technology with exciting applications in

understanding the pathophysiology of airway disease early in life and a potential clinical endpoint for interventions.

Interventions

New techniques to target interventions

Biomarkers and mechanisms of disease—A recent Current Perspective summarized the advances in diagnostics in allergy, asthma and immunology in 2013 (63). There are now several biomarkers emerging that hold promise for selecting and monitoring therapy including exhaled nitric oxide, serum IgE, periostin, and urinary leukotrienes. More will follow in the coming years and will be helpful in the selection of patients most likely to respond to the new immunomodulators. Malinovschi et al (64) demonstrated that exhaled nitric oxide, an indicator of local inflammation, and blood eosinophil count, an indicator of systemic inflammation, values offered independent information in relation to the prevalence of wheeze, asthma diagnosis, and asthma events in their population sample. Further information is needed on the application of these biomarkers in phenotyping and individualized treatment. Pavord and Bafadhel in an accompanying editorial (65) stated that we should use these two biomarkers as complementary biomarkers of a clinically important pattern of airway inflammation. Each biomarker might associate with important clinical events and treatment responses.

Guan et al (66) sought to compare 2 tests (leukotriene D4 and methacholine bronchial provocation) and classify leukotriene responsive subtypes in asthmatic patients. They found both tests to be of high diagnostic value and helpful in predicting the response to antileukotriene therapy. An area where biomarkers could be particularly helpful and much needed is steroid resistance in severe asthma. This area of research could be useful in defining treatments for asthma and other chronic inflammatory diseases(67).

Salazar et al (68) provided a Current Perspective on the role of lectins in allergic sensitization and allergic disease including ways of developing therapeutic modalities against newly identified targets including a switch in the response to a protective T_H1 profile. Miyata et al (69) investigated the synthesizing capacity of protectin D1 (PD1), an anti-inflammatory and proresolving lipid mediator. They concluded that activated human eosinophils represent a major source of PD1 whereas the production of PD1 is impaired in patients with severe asthma. Konradsen et al (70) examined the chitinase-like protein YKL-40 which has been related to asthma and airway remodeling. They observed that YKL-40 levels are increased in children with severe, therapy-resistant asthma compared with healthy children, and also compared to children with controlled asthma. Therefore, YKL-40 may be an easily attainable biomarker of asthma severity and airway remodeling in children. Kazani et al (71) examined exhaled breath condensate eicosanoid levels, specifically lipoxin and leukotrienes, and concluded that the proresolving compounds decreases with asthma severity.

Genetics—Granell et al (72) reported that single nucleotide polymorphisms in the 17q21 locus are specific to asthma and specific wheezing phenotypes and are not explained by association with intermediate phenotypes, such as atopy or lung function. Elucidation of causal mechanism has the potential to identify risk factors that might be targets for primary or secondary disease prevention. Pandey et al (73) demonstrated significant associations of polymorphisms in typical and atypical extracellular signal-related kinase (ERK) path genes with asthma and its subphenotypes. The results suggest that genetic variation in ERK pathway genes might play a role in asthma development through novel mechanisms. Replication studies and further functional assessments are necessary next steps to establish the role of ERKs in asthma development.

Microbiome—An NIH/NHLBI Workshop was held on the role of the lung microbiome in health and disease. Current knowledge and the state of research on the lung and related areas of human microbiome investigation were reviewed and discussed (74). A number of issues, such as sample collection, investigative techniques, and future studies were identified as most important to address for the future of lung microbiome research. Reddy Marri et al (75) characterized and compared the microbiome of induced sputum in asthmatic and nonasthmatic adults. They observed that patients with mild asthma have an altered microbial composition in the respiratory tract that is similar to that observed in patients with more severe asthma.

Role of microRNA—The July 2013 theme issue was devoted to a discussion of microRNA. Lu and Rothenberg reviewed the diagnostic, functional and therapeutic roles of microRNA in allergic diseases including asthma (76). Specific microRNAs have been found to have critical roles in regulating key pathogenic mechanisms in allergic inflammation, including polarization of adaptive immune responses and activation of T cells, regulation of eosinophil development, and modulation of IL-13-driven epithelial responses. Rebane and Akdis (77) discussed the roles of microRNAs in the regulation of inflammation and indicated that they could prove to be useful as biomarkers, as well as microRNA-related novel treatment modalities. Khosgoo et al (78) in another review indicated that a number of microRNAs have been demonstrated to play important roles during early and late lung development including lung organogenesis. Nicodemus-Johnson et al (79) reported that the effects on the gene regulatory landscape, likely mediated by microRNAs, in the airways of the mother's children persist into adulthood.

Therapeutic Interventions—A recognition of the limitations of our current treatment should prompt the development of new therapeutic strategies. Beigelman et al (80) reported observations related to the lack of effect of oral corticosteroids during acute lower respiratory tract illnesses in preschool children with recurrent wheeze. They indicated that further studies are needed to verify this observation derived from retrospective analysis of 2 separate cohorts. This information adds to the growing evidence that understanding the phenotype we are treating can help select effective treatment while minimizing side effects (81). We need more information related to the benefit-risk and dose-response of oral corticosteroids in respiratory tract illnesses in young children and, if limited effect is indeed demonstrated, then identification of alternative treatment strategies for treating these children. An alternative strategy is to identify treatments that prevent respiratory tract illness in young children.

Elazab et al (82) conducted a meta-analysis of clinical trials related to the use of probiotics in early life, atopy and asthma. They concluded that prenatal and/or early-life probiotic administration reduces the risk of atopic sensitization and decreases total IgE level in children but may not reduce the risk of asthma/wheeze. Sadatsafavi et al (83) reported that in a real-world clinical setting composed of a population of children 12 years and older and adults, subjects were more adherent to inhaled corticosteroids (ICS) plus long-acting ß-adrenergic agonist (LABA) therapy than ICS and leukotriene receptor antagonist (LTRA) therapy. Therefore, ICS+LABA seems to be more effective than ICS+LTRA, despite accounting for differential adherence. Although results generated from administrative databases have limitations, they allow conclusions that cannot be obtained from randomized controlled trials (84). Kim et al (85) conducted a systematic review of allergen-specific immunotherapy for pediatric asthma and concluded that evidence supports the efficacy of both subcutaneous and sublingual allergen immunotherapy for the treatment of asthma. However, the evidence was stronger for subcutaneous over sublingual routes but that may be due to fewer studies with sublingual immunotherapy. Comparative studies with these two

methods of administration in a real-world setting and at various age groups are needed to verify these preliminary conclusions.

Step-down techniques – limiting exposure to medications—Parents and clinicians are always interested in limiting the exposure of children to medications. Rank et al (86) sought to estimate the risk of asthma exacerbations in patients who stop low-dose ICS compared with those who continue ICS in randomized controlled trials from a systematic review of the literature (86). They concluded that patients with well-controlled asthma who stop regular use of low-dose ICS have an increased risk of an asthma exacerbation compared with those who continue ICS. Of interest, they noted that for every four patients who stop low-dose ICS, one will have an exacerbation in the next 6 months that is attributable to stopping ICS. This observation was evaluated in a pediatric asthma management program and it was recommended that step down be conducted carefully in guideline eligible patients, basically well controlled over the past 3 months, and it should be avoided at certain times of the year, particularly the fall season (87).

New drugs—There are several new drugs in development and currently being evaluated in adults that may see application in childhood asthma in the future. Busse et al (88) reported that AMG 853, a potent, selective, orally bioavailable, small molecule dual antagonist of D-prostanoid and CRTH2, chemoattractant receptor homologous molecule expressed on TH2 cells, added on to ICS therapy demonstrated no associated risks in adults but was not effective at improving asthma symptoms or lung function in patients with inadequately controlled moderate to severe asthma. Noonan et al (89) reported that lebrikizumab, an anti-IL-13 monoclonal antibody, in a dose-ranging study is insufficient to improve pulmonary function but had an effect on prevention of protocol-defined treatment failure. There is a need to develop biomarkers that may be predictive of beneficial effect in certain patients.

Wenzel et al (90) reported that dupilumab, a monoclonal antibody to the alpha subunit of the interleukin-4 receptor, reduced exacerbations when LABAs and ICS were withdrawn. This medication withdrawal was associated with improved pulmonary function, in adults with moderate to severe asthma and blood eosinophils that was at least 300 cells per microliter or a sputum eosinophil level of at least 3% and currently receiving medium-dose to high-dose ICS plus LABA. While the results of this study are promising, additional studies are needed to verify efficacy and assure safety and to identify biomarkers that are associated with beneficial effect, such as the sputum measurements used in the initial report (91). In addition, reassuring long term safety and effectiveness data was provided by Wechsler et al (92) from a 5 year follow-up study of patients receiving bronchial thermoplasty in adults. To date, this procedure has not been evaluated in adolescents to determine whether similar efficacy and safety could be derived.

Phenotype-directed treatment—As indicated above with studies in adults on dupilumab (90), clinical trials are now being directed to select participants based on biomarker criteria or other features. Similarly, Laviolette et al (93) evaluated the effects of benralizumab, a monoclonal antibody designed to target IL-5Ralpha expressed on eosinophils and basophils, in a group of adult subjects with asthma and an elevated sputum eosinophil count. They noted reduced eosinophil counts in airway mucosa/submucosa and sputum and suppressed eosinophil counts in bone marrow and blood. Therapeutic benefits need to be evaluated along with additional safety studies (94). The direction seems to be headed in using eosinophil measures, either blood or sputum, to identify responders to anti-IL5 directed treatment. However, further studies are needed to define the eosinophil phenotype to determine whether it is related to tissue, sputum or even blood eosinophil count and whether a level of eosinophil activity would be helpful (95). Similarly, identifying inadequate levels of vitamin D could be an indicator of a phenotype that would respond to

vitamin D supplementation (96). In addition, it will be important to identify the clinical variables, molecular biomarkers, physiologic and radiologic information that might be useful in differentiating and assessing risks for progression and frequent exacerbations in asthma, as well as chronic obstructive pulmonary disease (97).

Summary

Significant advances have been made in the past 10 years in defining asthma control as well as individuals at risk for asthma exacerbations. We now recognize the limitations of our available treatments and seek new strategies for intervention that will fill those gaps in disease management. Some of those medications, such as the monoclonal antibody immunomodulators, will be expensive at least upon initial approval. Therefore, there will be resistance to their utilization unless cost effectiveness can be demonstrated. In this era of cost containment while moving to strategies of prevention, it will be important to organize health care systems in order to identify patients who are inadequately controlled as indicated by frequent exacerbations, increased medication requirements or loss of pulmonary function over time. A patient profile that combines clinical features along with reliable predictors of beneficial effect to certain treatments will be useful in individualizing treatment plans. These treatment effects may differ in adults and children. Enhanced communication systems will be necessary among parents, clinicians, health care providers and the pharmaceutical industry so that we continue the pathway of understanding the disease and developing new treatments that address the unmet needs of patients who are at risk for severe consequences of unchecked disease persistence or progression.

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Abbreviations

BMI	Body Mass Index
CRTH2	chemoatrractant receptor homologous molecule expressed on TH2 cells
F_ENO	fraction of exhaled nitric oxide (ppb)
Fev1	Forced expiratory volume in one second
FOXP3	forkhead box protein 3
HRV	Human rhinovirus
ICS	inhaled corticosteroid
IL33	interleukin 33
LABA	long acting β-adrenergic agonists
LTRA	leukotriene receptor antagonist
NHLBI	National Heart, Lung and Blood Institute
NICHD	National Institutes of Child Health and Human Development

PIAMA risk score	Prevention and Incidence of Asthma and Mite Allergy risk score
RSV	respiratory syncytial virus
RV	rhinovirus
TNF	tumor necrosis factor
T_H2	T helper cell 2
TLR	Toll-like receptor

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Key Advances in Pediatric Asthma, 2013

- Maternal microchimerism may protect against the development of asthma (8).
- IL-33 is a relatively steroid-resistant mediator that promotes airway remodeling in patients with severe therapy-resistant asthma and is an important therapeutic target (17).
- Treatment with palivizumab, a monoclonal antibody shown to prevent severe RSV infection in high-risk infants, resulted in a significant reduction in wheezing days during the first year of life, even after the end of treatment (27).
- Mouse allergen appears to be more strongly and consistently associated with poor asthma outcomes than cockroach allergen (36).
- Early introduction of wheat, rye, oats, and barley cereals; fish; and egg seem to decrease the risk of asthma along with allergic rhinitis and atopic sensitization in childhood (42).
- The Pediatric Asthma Control and Communication Instrument accurately measured asthma control in English- and Spanish-speaking children and it should be useful to clinicians to assess and classify asthma according to current asthma guidelines (49).
- Magnetic resonance imaging with ^{3}He detected more and larger regions of ventilation and a greater degree of restricted gas diffusion in children with asthma compared with those seen in children without asthma (61).
- Exhaled nitric oxide, an indicator of local inflammation, and blood eosinophil count, an indicator of systemic inflammation, values offered independent information in relation to the prevalence of wheeze, asthma diagnosis, and asthma events in their population sample (64).
- Specific microRNAs have been found to have critical roles in regulating key pathogenic mechanisms in allergic inflammation, including polarization of adaptive immune responses and activation of T cells, regulation of eosinophil development, and modulation of IL-13-driven epithelial responses (76).
- Evidence supports the efficacy of both subcutaneous and sublingual allergen immunotherapy for the treatment of asthma. However, the evidence was stronger for subcutaneous over sublingual routes but that may be due to fewer studies with sublingual immunotherapy (85).