Advances in pediatric asthma in 2013: Coordinating asthma care

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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 prenatal 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. (J Allergy Clin Immunol 2014;133:654-61.)

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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 not only to prevent exacerbations but also to alter the progression of the disease that might 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[2] on adult asthma focused on new developments in medications, as well as gene-environment interactions.

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 Working Group summarized the gaps in information that must be filled to advance appropriate labeling of medications that are used to manage pediatric asthma, especially for use in early childhood.[3] Sutherland and Busse,[4] on behalf of the National Heart, Lung, and Blood Institute (NHLBI)'s AsthmaNet, summarized current and future work conducted in the National Institutes of Health's AsthmaNet research network that combines clinical studies in children and adults, including cross-age, mechanistic, and proof-of-concept studies. Cabana et al[5] summarized challenges that the NHLBI's 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 logistic 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 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 prenatal 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.

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Abbreviations used
ERK: Extracellular signal-regulated kinase
ICS: Inhaled corticosteroid
LABA: Long-acting β-adrenergic agonist
NHLBI: National Heart, Lung, and Blood Institute
PD1: Protectin D1
RSV: Respiratory syncytial virus

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 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 influences 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 might protect against the development of asthma. Chandra Pandey et al[9] provided information to show that different Toll-like receptor 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 outcomes for offspring. Tegethoff et al[10] reported on a wide spectrum of diseases in offspring 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 that strategies to safely control asthma during pregnancy are needed. Harpsoe et al[12] examined the effect of body mass index 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 risk score at different ages and in different 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 because we do not yet have accurate screening tests that use 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 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 Trousseau Asthma Program cohort, used cluster analysis and concluded that remission is most frequently observed in patients with mild early viral wheeze and that no remission is observed in patients with 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, with Kang et al[22] indicating a relationship between acetaminophen use and risk of asthma based on a cross-sectional survey of preschool children and suggesting 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 was significantly associated with childhood lower respiratory tract illness and that temporal changes in viral prevalence occur that can be used for designing preventative and treatment strategies. Papi et al[24] provided evidence that rhinovirus 16 infection of human airway epithelium induced glucocorticoid resistance. In studying the association of rhinovirus-related 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 there were consistent findings in 2 representative US populations and 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. On the basis of 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, an mAb 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