Advances in pediatric asthma in 2012: Moving toward asthma prevention

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Last year's "Advances in pediatric asthma: moving forward" concluded the following: "Now is also the time to utilize information recorded in electronic medical records to develop innovative disease management plans that will track asthma over time and enable timely decisions on interventions in order to maintain control that can lead to disease remission and prevention." This year's summary will focus on recent advances in pediatric asthma on modifying disease activity, preventing asthma exacerbations, managing severe asthma, and risk factors for predicting and managing early asthma, as indicated in *Journal of Allergy and Clinical Immunology* publications in 2012. Recent reports continue to shed light on methods to improve asthma management through steps to assess disease activity, tools to standardize outcome measures in asthma, genetic markers that predict risk for asthma and appropriate treatment, and interventions that alter the early presentation of asthma to prevent progression. We are well on our way to creating a pathway around wellness in asthma care and also to use 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. (J Allergy Clin Immunol 2013;131:36-46.)

Key words: *Airway remodeling, asthma, asthma control, asthma exacerbations, asthma impairment, asthma risk, asthma severity, early intervention in asthma, biomarkers, environment, genetics, inhaled corticosteroids, leukotriene receptor antagonists, long-acting β-adrenergic agonists, omalizumab, personalized medicine, severe asthma, therapeutics, tiotropium*

Abbreviations used
FENO: Fraction of exhaled nitric oxide
HRV: Human rhinovirus
ICS: Inhaled corticosteroid
LABA: Long-acting β-adrenergic agonist
RSV: Respiratory syncytial virus
SNP: Single nuclear polymorphism
Treg: Regulatory T
TSLP: Thymic stromal lymphopoietin

Journal publications in 2011 and 2012 serve as a base for evaluating the current status of asthma and set the stage for looking to the future direction of asthma management. Last year's "Advances in pediatric asthma in 2011: moving forward" included a discussion of studies related to accomplishments in asthma care, new information to supplement the asthma guidelines, and insights that could affect future management.[1] Last year's review by Andrea Apter[2] on adult asthma focused on ways to improve health outcomes by understanding mechanisms of disease, environmental exposures, and new management principles.

A series of *Journal* reviews, entitled "Asthma: current status and future directions" profiled major issues in asthma.[3-9] Dr Jeffrey Drazen, Editor-in-Chief of the *New England Journal of Medicine*, ended the series with an editorial entitled "Asthma: the paradox of heterogeneity." He stated that what we need to do is make progress in understanding the root causes of asthma. For this, we need targeted diagnostics and therapeutics so we can infer causality and design the best treatment for each patient.[10] In addition, Barnett and Nurmagambetov[11] provided a cost analysis of asthma in the United States.

Currently, it is recognized that inhaled corticosteroids (ICSs) are very effective in reducing the risk of asthma exacerbations and that the combination of long-acting β-adrenergic agonists (LABA) and ICSs, both as maintenance and also as rescue therapy, has a significant further beneficial effect on reducing exacerbations and maintaining asthma control.[12] In addition, leukotriene receptor antagonists, omalizumab, sputum eosinophil-adjusted therapy, and anti–IL-5 in patients with sputum eosinophilia can also be used to reduce the risk of an asthma exacerbation.[12]

Better organization of overall asthma care can be used to improve asthma outcomes in large health care systems.[13] Advances in genetic discoveries will help identify patients at risk for asthma and for the development of certain phenotypes of asthma.[14,15] The availability of such tools should lead to a proactive preventative approach to asthma care.

This review will highlight 2012 *Journal* publications that provide new information to identify risk factors for the development of asthma, assess disease activity, prevent asthma exacerbations, and manage severe asthma. Important theme issues in the *Journal* included air pollution, infection, early asthma, and genetics.

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ANALYZING DISEASE ACTIVITY

Indicators of disease activity

Gershon et al[16] set out to examine the course of asthma activity in a population study. They noted that over 15 years, most patients with asthma had active disease that was interspersed with periods of inactivity when they did not require medical attention and were likely in remission. This study should prompt further studies that facilitate prognostication of the course of disease to permit a proactive management approach for patients.

Biologic markers

It would be useful to complement clinical history, spirometry, and measurement of biologic markers to enhance the evaluation of disease activity. One biomarker that has received attention is exhaled nitric oxide. Fuchs et al[17] reported that children living on farms are protected against wheeze independently of atopy and that there was no farm effect on lung function and fraction of exhaled nitric oxide (FENO). Patelis et al[18] studied the IgE antibody profile for a broad spectrum of allergen molecules in asthmatic patients and concluded that FENO, bronchial hyperresponsiveness, and the risk of asthma increase with multiple sensitizations to different allergen groups. In addition, IgE antibodies against food allergens are independently associated with increased FENO levels and increased risk of asthma with simultaneous sensitization to pollen allergens. Gouvis-Echraghi et al[19] reported that in young children FENO values appear to be influenced by poor asthma control and disease severity and then by atopic features.

Jia et al[20] reported that periostin is a systemic biomarker of airway eosinophilia in asthmatic patients and has potential utility in patient selection for emerging asthma therapies targeting T_H2 inflammation. Nair and Kraft[21] comment that a simple blood test would be ideal and potentially clinically very useful. Periostin shows some promise, particularly in patients with severe asthma, but must be further evaluated.

Another promising area of investigation is the area of genetics and epigenetics. Ji and Khurana Hershey[22] summarized recent findings on the genetic and epigenetic regulation of responses to ambient air pollutants, specifically respirable particulate matter, and their association with the development of allergic disorders. Understanding epigenetic markers and how they integrate with genetic influences to translate the biologic effect of particulate exposure could be critical to developing novel preventative and therapeutic strategies for allergic disorders. Furthermore, epigenetic mechanisms provide a promising line of inquiry that might, in part, explain the inheritance and immunobiology of asthma.[23] Hawkins et al[24] reported that the IL-6 receptor *(IL6R)*–coding single nucleotide polymorphism (SNP) rs2228145 (Asp^{358} Ala) could have a pathologic role in the airways that could identify subjects at risk for severe asthma. With anti–IL-6 receptor therapies that block IL-6 transsignaling, there might be a therapeutic value for this treatment in patients with severe asthma. Tantisira et al[25] identified the T gene as a novel determinant of ICS pulmonary response using genome-wide association analysis.

Environment

Bauer et al[26] reviewed current knowledge on how air pollutants modify Toll-like receptor–dependent and nucleotide-binding oligomerization domain–like receptor–dependent signaling and host defense responses in the lung to address the role of air pollutants on innate immunity. Hernandez et al[27] demonstrated that gene expression profiles in sputum cells from atopic asthmatic patients are distinctly different from those of healthy volunteers. Compared with healthy subjects, asthmatic patients showed increased immune signaling, increased proinflammatory cytokine levels, and upregulated expression of the v-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (*ERBB2* [HER-2]) gene network on exposure to ozone.

Cakmak et al[28] reported an association between aeroallergens and hospitalizations for asthma, which was enhanced on days of higher air pollution. These observations suggest that minimizing exposure to air pollution might reduce allergic exacerbations of asthma. Laumbach and Kipen[29] reviewed the respiratory health effects of air pollution and concluded that air pollution from sources such as traffic and burning biomass fuels is a major preventable cause of increased incidence and exacerbations of respiratory disease. Leung et al[30] reviewed the role of pollution in the increasing prevalence and exacerbations of allergic disease in Asia. Interestingly, they found inconsistent evidence regarding the roles of individual pollutants in the initiation of asthma and allergy among Asian children and adults.

Ziska and Beggs[31] reported that anthropogenic climate change and increasing atmospheric carbon dioxide concentrations have the potential to transform almost all spatial and temporal aspects of plant-based aeroallergen (production, allergenicity, and distribution), with subsequent effects on aeroallergen exposure and the severity and prevalence of allergic disease. Darrow et al[32] examined short-term associations between ambient concentrations of various pollen taxa and emergency department visits for asthma and wheeze in Atlanta between 1993 and 2004. They noted that *Poaceae* and *Quercus* species pollen contribute to asthma morbidity in Atlanta. Indeed, the role for the allergist is important in providing appropriate information on environmental control measures that can effectively reduce asthma and allergy symptoms.[33]

Rabinovitch et al[34] examined the health effects of concurrent environmental tobacco smoke and ambient particulate matter exposure in children with asthma. They concluded that concurrent tobacco smoke exposure limits the increase in urinary leukotriene E_4 levels and albuterol use in response to an increase in concentrations of ambient particulate matter up to 2.5 μm in size. Baccarelli and Kaufman[35] commented on these findings and suggested that they raise new questions regarding our understanding of the environmental determinants of asthma. Li et al[36] and Ledford et al[37] provided commentaries on the public health benefits of air pollution control. The difficulty in formulating national policy is that all decisions will affect costs paid by industry or utilities and ultimately paid by the consumer and the public.

Vitamin D and asthma severity

Recently, attention has been directed to vitamin D and its role in asthma management. Several *Journal* publications explored potential cellular mechanisms for vitamin D. Du et al[38] reported on the association of variants of the class I MHC–restricted T cell–associated molecule gene *(CRTAM)* with asthma exacerbations and suggested that this association could be important for predicting patients at risk for exacerbations and a rationale for therapeutic intervention with vitamin D in a proportion of patients with high-risk asthma. Goleva et al[39] provided