Advances in pediatric asthma in 2014: Moving toward a population health perspective

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Last year's "Advances in pediatric asthma in 2013: Coordinating asthma care" concluded that, "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." This year's summary will focus on further advances in pediatric asthma related to prenatal and postnatal factors altering the natural history of asthma, assessment of asthma control, and new insights regarding the management of asthma in children as indicated in *Journal of Allergy and Clinical Immunology* publications in 2014. A major theme of this review is how new research reports can be integrated into medical communication in a population health perspective to assist clinicians in asthma management. The asthma specialist is in a unique position to convey important messages to the medical community related to 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. By enhancing communication among patients, parents, primary care physicians, and specialists within provider systems, the asthma specialist can provide timely information that can help to reduce asthma morbidity and mortality. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

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

Journal of Allergy and Clinical Immunology publications in 2014 serve as a base for identifying age-related factors that can affect the course of asthma. Attention is now directed at preventing asthma exacerbations and also prevention of the disease. Last year's "Advances in pediatric asthma in 2013: Coordinating asthma care" included a discussion of new insights on understanding factors that influence asthma control, methods to assess and communicate levels of control, and new immunomodulators that address targets considered important in asthma severity.[1] Also, both last year's and this year's review by Andrea Apter on adult asthma focused on new developments in medications that relate to asthma management in adults.[2,3] It is apparent that the health care system is rapidly changing, and the specialist now must find a place in what is being called the "medical neighborhood."[4] To do this, the asthma specialist must transform day-to-day practice in seeing referral and ongoing care patients into looking at the disease as a whole within the medical system, a feature of population health management. This review will highlight areas in which the *Journal* has published reports on asthma as related to the management of children. Asthma specialists can serve a pivotal role in applying new techniques in managing asthma in children across their medical systems.

A series of reviews within a theme issue entitled "Asthma across the ages" opened the year of publications and profiled current directions in studies of pediatric and adult asthma.[5-8] 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.[5] Areas to address include prevention of asthma exacerbations in children and prevention of asthma progression. Identification of effective strategies to prevent the onset of asthma is also a major gap to fill. Sutherland and Busse,[6] on behalf of the National Heart, Lung, and Blood Institute's AsthmaNet, summarized current and future work conducted in the National Institutes of Health's AsthmaNet research network, which combines clinical studies in children and adults, including cross-age, mechanistic, and proof-of-concept studies. Cabana et al[7] summarized challenges that the National Heart, Lung, and Blood Institute'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[8] provided a review on pharmacogenetics as it relates to race and ethnicity on defining genetic profiles for personalized medicine. They addressed a number of key issues for analyzing mixed ethnic groups participating in clinical studies

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Supported in part by Public Health Services research grants AI-90052, ES-18181, and HL-98075; the Denver Post Charities, a McCormick Foundation; and the Colorado Cancer, Cardiovascular, and Pulmonary Disease Program (14 FLA 62707). Supported in part by Colorado CTSA grant UL1 RR025780 from the National Center for Research Resources/National Institutes of Health (NIH) and UL1 TR000154 from the NIH/National Center for Advancing Translational Sciences.

Disclosure of potential conflict of interest: S. J. Szefler has received consultancy fees from Merck, Boehringer Ingelheim, GlaxoSmithKline, and Genentech; has received research support from GlaxoSmithKline (FLV 116794); has received lecture fees from Merck; and has a patent with the National Heart, Lung, and Blood Institute's CARE Network.

Received for publication November 21, 2014; revised December 29, 2014; accepted for publication December 29, 2014.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2014.12.1921

Abbreviations used
ACQ: Asthma Control Questionnaire
ACT: Asthma Control Test
C-ACT: Childhood Asthma Control Test
ICS: Inhaled corticosteroid
LABA: Long-acting β-adrenergic agonist
LTRA: Leukotriene receptor antagonist
SARP: Severe Asthma Research Program

to detect and replicate the novel pharmacogenetic loci necessary in development of individualized treatment strategies.

This review will highlight 2014 *Journal* publications that bring forth new information to help identify prenatal and postnatal factors that contribute to the natural history of asthma, new techniques to assess asthma control, and new insights into management techniques that could be used to improve asthma control. Important theme issues in the *Journal* over the past year included asthma across the ages, immunotherapy, nutrition and allergy, neural immune pathways, allergens and the innate immune system, pollution and allergy, and establishment of school-centered asthma programs. Also, a new version of the Global Initiative for Asthma was published in May 2014.[9] A commentary regarding the differences between Global Initiative for Asthma guidelines and our current national asthma guidelines will be published later in 2015.

NEW INFORMATION ON THE DEVELOPMENT OF ASTHMA

Prenatal factors

There is great interest in evaluating the role of *in utero* exposure on the initiation and development of asthma. In a mouse model Manners et al[10] drew an association between diesel exhaust particle exposure with asthma susceptibility in offspring. Development of asthma was dependent on natural killer cells and associated with increased transcription from aryl hydrocarbon receptor– and oxidative stress–regulated genes. In an accompanying editorial Finkelman[11] commented that the work of these investigators paves the way for further mechanistic studies and provides evidence for the importance of timing in diesel exhaust particle exposure. Additional concern was raised by other investigators that exposures to 2 classes of endocrine-disrupting chemicals, namely prenatal exposure to phthalates and early childhood exposure to bisphenol A, were associated with an increased risk of asthma in inner-city children.[12]

Another feature associated with an increased risk of childhood asthma development appears to be maternal second-hand smoke exposure, even if the mother does not smoke actively during pregnancy.[13] Furthermore, maternal smoking during pregnancy was reported to increase the risk for asthma and wheeze, which persists into adolescence.[14] Another study reported that maternal adverse life events during the second half of gestation increased the risk for development of atopic disorders, asthma, and eczema.[15] On a similar note, another study reported that maternal psychological distress during pregnancy was associated with increased odds of wheezing in children during the first 6 years of life independent of paternal psychological distress and maternal and paternal psychological distress after delivery.[16] A possible intrauterine programming effect of maternal psychological distress leading to respiratory morbidity in the infant was proposed.[16] In a protective direction, Straubinger et al[17] demonstrated that helminth infection during pregnancy could reduce the susceptibility of offspring to allergic airway inflammation in a mouse model. These findings might provide insights into potential mechanisms that explain the variability in clinical expression of allergic diseases.[18]

Prediction tools

There is also great interest in identifying clinical markers, genetic markers, and biomarkers associated with the development of asthma in children that can be applied to the prediction of disease development. One cell of interest is the T_H17 cell. T_H17 cells develop before the age of 3 months and retain a propensity to become regulatory T cells until the age of at least 12 months. This might be an important pathway in the maintenance of tolerance toward allergens.[19] It is also reported that children with asthma by school age exhibit an aberrant immune response to pathogenic bacteria in infancy with the suggestion that this might lead to chronic airway inflammation and childhood asthma.[20]

Efforts have also been made to identify genetic links that might be associated with asthma. Kerkhof et al[21] reported the involvement of at least 3 chronic obstructive pulmonary disease genes in lung development and lung growth, with associations pointing toward reduced airway caliber in early childhood. Chronic obstructive pulmonary disease genes might also be involved in the infant's lung response to smoke exposure *in utero* and in early life.[21] This same group also identified *IL33*–IL-1 receptor–like 1 *(IL1RL1)* pathway polymorphisms associated with asthma and specific wheezing phenotypes in early childhood.[22]

There has been considerable interest in the role of BCG vaccination in protecting against childhood asthma. Reports from the Manchester Community Asthma Study indicated that any protective effect of BCG vaccination on childhood asthma is likely to be transient.[23] However, other investigators found younger gestational age at birth and higher infant weight gain were associated with childhood asthma outcomes.[24] Another group reported that prematurity is strongly associated with atopic asthma in Puerto Rican children and that perhaps prematurity might explain, in part, the high prevalence of atopic asthma in this ethnic group.[25] Another feature of interest reported was an association of winter birth in inner-city children with asthma and an increased risk of food allergen sensitization.[26] Thus there are many interacting features between the development of asthma and allergy that could be playing a role in age-related disease development.

Diet, stress, and the environment also play a role as risk factors in allergy and asthma development. Chiu et al[27] reported that prenatal community violence and air pollution can contribute to respiratory health in urban children. Furthermore, psychosocial stressors might affect host resistance, such that physical pollution can result in adverse effects, even at relatively low levels. Other investigators reported that less food diversity during the first year of life might increase the risk for asthma and allergies in childhood.[28] In a brief report, another set of investigators found that a higher proportion of a certain fatty acid, eicosapentaenoic acid, was associated with a decreased risk of asthma when cow's milk allergy was taken into account as a putative confounder.[29] All of these studies raise important questions about the role of dietary and environmental modifiers related to asthma and allergy development.