Advances in asthma 2015: Across the lifespan

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In 2015, progress in understanding asthma ranged from insights to asthma inception, exacerbations, and severity to advancements that will improve disease management throughout the lifespan. 2015's insights to asthma inception included how the intestinal microbiome affects asthma expression with the identification of specific gastrointestinal bacterial taxa in early infancy associated with less asthma risk, possibly by promoting regulatory immune development at a critical early age. The relevance of epigenetic mechanisms in regulating asthma-related gene expression was strengthened. Predicting and preventing exacerbations throughout life might help to reduce progressive lung function decrease and disease severity in adulthood. Although allergy has long been linked to asthma exacerbations, a mechanism through which IgE impairs rhinovirus immunity and underlies asthma exacerbations was demonstrated and improved by anti-IgE therapy (omalizumab). Other key molecular pathways underlying asthma exacerbations, such as cadherin-related family member 3 (CDHR3) and orosomucoid like 3 (ORMDL3), were elucidated. New anti–IL-5 therapeutics, mepolizumab and reslizumab, were US Food and Drug Administration approved for the treatment of patients with severe eosinophilic asthma. In a clinical trial the novel therapeutic inhaled GATA3 mRNA-specific DNAzyme attenuated early- and late-phase allergic responses to inhaled allergen. These current findings are significant steps toward addressing unmet needs in asthma prevention, severity modification, disparities, and lifespan outcomes. (J Allergy Clin Immunol 2016;138:397-404.)

Key words: *asthma, exacerbation, chronic obstructive pulmonary disease, pregnancy, allergen sensitization, allergy, genetics, epigenetics, transcriptome, microbiome, disparities, race/ethnicity, rhinovirus, respiratory syncytial virus, fungi/mold, IL-5, IgE, IFN-α, eosinophil, T_H2, ORMDL3, CDHR3, GATA3*

Abbreviations used

ACOS: Asthma–chronic obstructive pulmonary disease overlap syndrome
ACQ: Asthma Control Questionnaire
CDHR3: Cadherin-related family member 3
COPD: Chronic obstructive pulmonary disease
DNAzyme: DNA enzyme
FDA: US Food and Drug Administration
HRV: Human rhinovirus
ICS: Inhaled corticosteroid
OR: Odds ratio
ORMDL3: Orosomucoid like 3
RSV: Respiratory syncytial virus

In previous years, we provided separate reviews of pediatric and adult asthma publications in the previous year.[1,2] This year, we directed our attention to asthma across the lifespan by combining these 2 age groups. Early-life events and exposures, even *in utero*, can play a significant role in the natural history of asthma, emerging into persistent, problematic, and/or chronic obstructive pulmonary disease (COPD) in certain subjects. Identifying these at-risk subjects at the earliest possible time for early intervention could optimize lifespan outcomes. In asthmatic patients this relates to prevention of asthma exacerbations, lung function decrease, and even disease onset.

In 2015, the *Journal* included more than 200 publications related to asthma. Because we cannot give each of these important publications appropriate attention, we have focused this review on 4 key areas that inform and will reshape asthma research and management in the coming years, and included relevant publications from other journals that help put these contributions into perspective: (1) inception, (2) exacerbations, (3) severity, and (4) selected topics, including disparities and asthma during pregnancy.

INCEPTION

Environmental determinants

Several recent articles have discussed potential environmental influences on asthma inception. In a longitudinal birth cohort associations between infant over-the-counter antipyretics (acetaminophen and ibuprofen) and increased risk of childhood asthma were lost or attenuated when adjusted for upper respiratory tract infections, which themselves were a stronger risk factor for childhood asthma, and demonstrated the importance of adjusting for upper respiratory tract infections in such studies.[3] In another

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Disclosure of potential conflict of interest: A. H. Liu serves on the board for GlaxoSmithKline and receives payment for lectures from Merck. D. A. Searing receives payment for manuscript preparation from the *Journal of Allergy and Clinical Immunology* and received travel support from the Inner City Asthma Consortium and the American Academy of Pediatrics. S. J. Szefler serves as a consultant for Roche, AstraZeneca, Aerocrine, Daiichi Sankyo, Boehringer-Ingelheim, Merck, Genentech, Novartis; and has grant support from GlaxoSmithKline. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 18, 2016; revised June 21, 2016; accepted for publication June 23, 2016.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2016.06.013

birth cohort prenatal maternal urinary bisphenol A and high-molecular-weight phthalate metabolites increased the relative risk of self-reported wheeze, chest infections, and bronchitis.[4]

Microbiome

Knowledge regarding the establishment, constituents, critical time periods, and disruption of the external, intestinal, and respiratory microbiome in relationship to asthma and atopy inception continued to be a strong thematic area of research in 2015. The epidemiologic observations behind the hygiene hypothesis were linked to the evolving microbiome story in a review by Liu.[5] A Current perspectives article by Huang and Boushey[6] focused on airway microbiome differences in asthmatic patients, as well as the association of different microbiome environments and asthma development. The article reviewed the concept of the "common mucosal response," which suggests stimulated immune responses at one mucosal site can influence alternative mucosal sites. The same group looked at features of the bronchial microbiome in patients with severe and mild-to-moderate asthma and healthy control subjects.[7] Differences in airway bacterial composition in patients with severe asthma were found: Proteobacteria was associated with worsening Asthma Control Questionnaire (ACQ) scores and total sputum leukocyte values, an abundance of Bacteriodetes/Firmicutes was positively correlated with body mass index, and Actinobacteria was associated with improving/stable ACQ scores. Davis et al[8] analyzed 2001-2004 National Health and Nutrition Examination Survey data for associations between *Staphylococcus aureus* nasal colonization and asthma outcomes and found *S aureus* colonization was associated with asthma prevalence, symptoms, and exacerbations in children and young adults but not in adults older than 30 years. Although most data detail bacteria at the mucosal interface, helminths, viruses, and fungi represent other possible microbiome constituents affecting asthma outcomes. Viral infections have frequently been discussed in the context of wheezing and/or asthma exacerbations. By surveying twice-weekly nasal samples for 10 weeks in a group of asthmatic children, Tovey et al[9] demonstrated that rhinovirus detection was also associated with increased day-to-day asthma symptoms. This accounted for 6% to 10% of the population-attributable risk in symptoms and suggests that other factors are also important to day-to-day symptom variability.

Understanding how the microbiome in infancy affects early immune development was furthered by current research. A prospective cohort study of the nasal microbiota in healthy infants using biweekly sampling demonstrated the personalized and dynamic nature of the nasal microbiota and put forth age and seasonality as key factors contributing to microbial composition.[10] A review by Holt[11] on mechanisms of allergic disease focused specifically on the infant respiratory microbiome and atopic asthma development, covering background immunology with a useful historical perspective. The development of allergen sensitization, as well as the intersection between respiratory tract infections and the nasopharyngeal microbiome, on the development of persistent wheeze were included in this review.

The concept of critical windows for immune development and gut microbiome establishment during infancy were reinforced in an analysis of the gut microbiota of infants enrolled in the Canadian Healthy Infant Longitudinal Development (CHILD) longitudinal birth cohort study.[12] Three hundred nineteen children were selected for gut microbiome analysis at 3 and 12 months of age. Comparisons of relative taxa abundance according to 4 clinical phenotypes (patients with atopy plus wheeze, patients with atopy only, patients with wheeze only, and control subjects) were performed. The group with the highest risk for asthma (atopy plus wheeze) displayed lower abundances of the genera *Faecalibacterium*, *Lachnospira*, *Rothia*, and *Veillonella* exclusively at 3 months. To test the potentially protective microbial taxa, germ-free mice in an asthma model were inoculated with infant stool collected at 3 months of age from a patient with "atopy plus wheeze" or with the same stool supplemented with the 4 bacterial genera listed above. The progeny of the supplemented mice showed reduced airway inflammation.[12] Another intriguing observation in this study was the reduced level of fecal acetate in 3-month stool samples from participants with "atopy plus wheeze." Acetate and other short-chain fatty acids are nutrients capable of protecting against airway inflammation through stimulation of regulatory T cells and dendritic cells, which can prevent T_H2-type immune responses.[13] A protective gut microbiome might promote regulatory immune development and prevent airway inflammation by altering nutrient metabolism. For further reading regarding techniques of microbiome assessment, the establishment and modulation of the infant gut microbiome, as well as future directions in microbiome research, the reader is directed to the recent review by West et al.[14]

Sensitization patterns to allergen components

Although select allergens have surfaced as seemingly more important drivers of asthma morbidity than others, narrowing attention to only those exposures perceived to be most relevant overlooks the real-life experience of innumerable host-exposure interactions occurring simultaneously. Levels of serum IgE specific for 112 molecular components from 51 allergen sources were measured in 11-year-old participants of a population-based birth cohort to assess how complex multiallergen sensitization can influence atopic disease.[15] Latent variable modeling revealed that allergen component sensitizations clustered into 3 groups (predominantly pollen, dust mite, and animal/food allergen groupings). Asthma was most strongly associated with sensitization to the animal/food allergen group; in particular, sensitization to lipocalins was associated with asthma. Although limited by its cross-sectional design, this study suggests specific sensitization patterns can influence or predict disease manifestations in patients with atopy.

Epigenetics

Methylation of CpG sequences in specific genes is one of the epigenetic mechanisms that alter gene expression. The epigenetic contribution to asthma expression can be appreciated in a genome-wide study of the methylation differences in PBMCs of black atopic asthmatic children compared with nonatopic nonasthmatic control subjects.[16] Atopic asthmatic children had 81 differentially methylated gene loci, including hypomethylation of T-lymphocyte genes (eg, *IL13*, *RUNX3*, and *TIGIT*), and their related overexpression. Genetic variation in the orosomucoid like 3 *(ORMDL3)* gene is linked with rhinovirus-induced exacerbations, as discussed below.[17,18] Differential methylation of CpG sites in *ORMDL3* was also associated with asthma and affected *ORMDL3* expression.[19] In this study both *ORMDL3*