Advances in asthma in 2016: Designing individualized approaches to management

William C. Anderson III, MD,[a] Andrea J. Apter, MS, MA, MSc,[b] Cullen M. Dutmer, MD,[a] Daniel A. Searing, MD,[a] and Stanley J. Szefler, MD[c] *Aurora, Colo, and Philadelphia, Pa*

In this year's Advances in Asthma review, we discuss viral infections in asthmatic patients and potential therapeutic agents, the microbiome, novel genetic associations with asthma, air quality and climate effects on asthma, exposures during development and long-term sequelae of childhood asthma, patient-centered outcomes research, and precision medicine. In addition, we discuss application of biomarkers to precision medicine and new information on asthma medications. New evidence indicates that rhinovirus-triggered asthma exacerbations become more severe as the degree of sensitization to dust mite and mouse increase. The 2 biggest drivers of asthma severity are an allergy pathway starting with allergic sensitization and an environmental tobacco smoke pathway. In addition, allergic sensitization and blood eosinophils can be used to select medications for management of early asthma in young children. These current findings, among others covered in this review, represent significant steps toward addressing rapidly advancing areas of knowledge that have implications for asthma management. (J Allergy Clin Immunol 2017;140:671-80.)

Key words: *Air quality, airway hyperreactivity, allergen immunotherapy, allergen sensitization, allergy, asthma, biomarkers, climate, chronic obstructive pulmonary disease, eosinophils, exacerbation, exhaled nitric oxide, genetics, ligelizumab, medication adherence, microbiome, patient-centered outcomes, pregnancy, prenatal exposures, respiratory syncytial virus, rhinovirus, roflumilast, tiotropium*

Abbreviations used

AHR:	Airway hyperresponsiveness
APIC:	Asthma Phenotypes in the Inner City
BAL:	Bronchoalveolar lavage
COPD:	Chronic obstructive pulmonary disease
DENND1B:	Differentially expressed in normal and neoplastic cells domain 1B
DEP:	Diesel exhaust particle
FDA:	US Food and Drug Administration
FEF_{25-75}:	Forced expiratory flow between 25% and 75% of forced vital capacity
FVC:	Forced vital capacity
HDM:	House dust mite
ICS:	Inhaled corticosteroid
ILC2:	Innate lymphoid cell
JACI:	*Journal of Allergy and Clinical Immunology*
LABA:	Long-acting β-agonist
miRNA:	MicroRNA
NIH:	National Institutes of Health
PCORI:	Patient-Centered Outcomes Research Institute
PEF:	Peak expiratory flow
RSV:	Respiratory syncytial virus
SNP:	Single nucleotide polymorphism
TET1:	Ten-eleven translocation 1
TLR:	Toll-like receptor
TRAP:	Traffic-related air pollution

Last year's Advances in Asthma focused on asthma across the lifespan and reported on some key observations related to asthma inception, the microbiome, and the epigenome. In addition, some aspects of predicting and preventing asthma exacerbations were featured.[1] It is now clear that scientific advances are being made in many areas related to asthma, such as epidemiology, immunology, microbiology, genetics, biomarkers, and new medications, so much so that it is a challenge for those writing asthma guidelines and strategies to synthesize this work and rapidly apply it to clinical practice. Therefore reviews of key discoveries are important to keep the clinician abreast of these findings, so that they can be considered in the clinical setting while they await integration into asthma guidelines. This year, we discuss new findings reported in the *Journal of Allergy and Clinical Immunology* (JACI) and other publications that relate to respiratory tract infections, air quality, factors that influence long-term outcomes, patient-centered outcomes research, precision medicine, and new observations related to medications and asthma management.

VIRAL INFECTIONS IN ASTHMATIC PATIENTS AND THE PROMISE OF THERAPEUTIC TARGETS

Respiratory viruses remain a key trigger of asthma exacerbations, providing insight into the evolution and pathophysiology of asthma. In a prospective observational cohort study involving 183 asthmatic children aged 6 to 17 years, Kantor et al[2] found that

From [a]the Allergy & Immunology Section and [c]the Breathing Institute and Pulmonary Medicine Section, Children's Hospital Colorado and University of Colorado School of Medicine, Aurora, and [b]the Section of Allergy & Immunology, Perelman School of Medicine, University of Pennsylvania, Philadelphia.

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Corresponding author: Stanley J. Szefler, MD, Pediatric Asthma Research Program, the Breathing Institute, Section of Pulmonary Medicine, Children's Hospital Colorado, 13123 E 16th Ave, Box 395, Aurora, CO 80045. E-mail: Stanley.Szefler@childrenscolorado.org.

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subjects with rhinovirus infection had more severe exacerbations than those participants with virus-negative exacerbations. In this cohort rhinovirus-triggered asthma exacerbations became more severe as the degree of sensitization to dust mite and mouse increased. Akin to the more severe exacerbations appreciated in the rhinovirus-infected children in the aforementioned study, Ducharme et al[3] performed a large, prospective, multicenter cohort study in emergency departments, revealing that viral detection was associated with failure of symptom management. Analyses from a large prospective cohort of adults enrolled in an influenza surveillance study revealed that rhinovirus infection is prevalent in adults, with 11% of nasal/throat swabs testing positive for rhinovirus in adults presenting to the hospital, emergency department, or outpatient clinic with acute respiratory illness or fever.[4]

In 2016, there was elucidation into the immune response induced by virus-triggered asthma exacerbations, identifying or further characterizing potential therapeutic targets. Han et al[5] illustrated the role of Toll-like receptor (TLR) 2–expressing macrophages in the airway inflammatory response to rhinovirus, noting that $TLR2^+$ macrophages were required for early stages of airway inflammation in their murine model. Additionally, transfer of wild-type macrophages to *Tlr2* knockout mice was sufficient to confer airway inflammation after rhinovirus infection. When IL-4–treated macrophages were similarly transferred, features akin to rhinovirus-infected mice with allergic airways disease were observed. Assessing the role of resident alveolar macrophages in respiratory syncytial virus (RSV) infection, Naessens et al[6] devised a post–allergic airway inflammation murine model in which treatment with GM-CSF abrogated RSV-induced inflammation and airway hyperreactivity by means of maturing an apparent immature phenotype appreciated in the post–allergic airway inflammation resident alveolar macrophage population. Through repeated inoculation of mice with low-dose virus and cockroach allergen, Lynch et al[7] showed that coexposure of respiratory virus and cockroach allergen induced a biphasic IL-33 response and impaired antiviral interferon production. Furthermore, IL-33 negatively regulated TLR7 signaling. Studying effects of RSV infection on group 2 innate lymphoid cells (ILC2s), another murine model showed proliferation and activation of IL-13–producing ILC2s through thymic stromal lymphopoietin–dependent mechanisms.[8]

CHARACTERIZATION OF THE AIRWAY MICROBIOME

Through detailed assessments of the airway microbiome, key differences between asthmatic patients, nonasthmatic subjects, and those at risk for asthma have been characterized. Regarding at-risk populations, the nasopharyngeal microbiota in more than 1000 infants with bronchiolitis was analyzed as part of a large multicenter study.[9] In this prospective cohort infants with bronchiolitis caused by RSV had a high abundance of Firmicutes and the genus *Streptococcus* and a low abundance of Proteobacteria and the genera *Haemophilus* and *Moraxella*, whereas infants with bronchiolitis caused by rhinovirus had the opposite pattern. It is not clear whether viral infections increase certain bacterial populations within a community, microbial community populations create environments suitable for viruses, or both.[9]

Addressing older subjects with established atopic phenotypes, a study orchestrated by AsthmaNet obtained bronchial brushings from 42 steroid-naive adults with atopic asthmatic, 21 nonasthmatic but atopic adults, and 21 healthy control adults.[10] By profiling samples through 16S rRNA gene sequencing, distinct differences in the bronchial bacterial microbiomes were appreciated in the 3 groups. Among asthmatic adults, the bronchial microbiome at baseline differed according to their responsiveness to inhaled corticosteroid (ICS) treatment. In a cross-sectional retrospective study assessing adult asthmatic patients who were not steroid naive, Denner et al[11] noted significant differences in the bronchial microbiome based on corticosteroid treatment. Further still, Sverrild et al[12] found that the level of eosinophilic airway inflammation correlates with variations in the microbiome across asthmatic patients.

NOVEL GENETIC ASSOCIATIONS WITH ASTHMA AND THE BIOLOGIC EFFECT OF KNOWN GENE VARIANTS

Through discovery of new associations and demonstration of the biologic effects of known gene variations, the link between genetic changes and asthma expanded in 2016 (Table I).[13-16] Doublesex and mab-3–related transcription factor 1 (DMRT1) emerged as a novel candidate to potentially explain sex-specific asthma effects during childhood.[13] A single nucleotide polymorphism (SNP) on chromosome 8 was associated with early lung function decrease in 2 asthma cohorts and was also associated with chronic obstructive pulmonary disease (COPD).[14] Exploring the mechanism by which SNPs at the differentially expressed in normal and neoplastic cells domain 1B *(DENND1B)* locus might lead to the development of asthma in young children, a *Dennd1b* knockout mouse model demonstrated the role of *DENND1B* in T-cell receptor downmodulation in T_H2 cells.[17] A new locus associated with time to asthma onset was identified at position 16q12.[15] Investigating the role of the previously reported 17q21 locus in asthma, a study by Schmiedel et al[18] detailed the deleterious effects exerted by asthma risk variants on T cells. By analyzing the asthma risk variant Glu-to-Arg substitution at position 576 of human IL-4 receptor α, new insights into the role of regulatory T cells and development of T_H2-T_H17 inflammation were presented.[19] Further assessing the known Gly-to-Arg substitution at the 16 position in the β_2-adrenoceptor gene, asthmatic children recruited from 5 cross-sectional studies identified the increased risk of asthma exacerbation with use of long-acting β-agonists (LABAs) in children carrying 1 or 2 alleles of the aforementioned substitution.[16]

INFLUENCE OF AIR QUALITY AND CLIMATE ON ASTHMA

Annesi-Maesano[20] provided an overview of allergy-specific health issues emerging because of climate change, as well as future directions regarding climate-related health. Worldwide, only 12% of urban populations breath air that complies with World Health Organization Air Quality Guidelines. Citing NASA data, we learn not only that the earth has experienced a 0.8°C/1.4°F average global temperature increase since the 1880s but also that two thirds of this warming has occurred since 1975. Components and consequences of this change, such as air