Advances in asthma in 2016: Designing individualized approaches to management

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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

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Disclosure of potential conflict of interest: S. J. Szefler serves as a consultant for Roche, AstraZeneca, Aerocrine, Daiichi Sankyo, Boehringer Ingelheim, Merck, Genentech, Novartis, and Teva and receives grant support from GlaxoSmithKline. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 14, 2017; revised June 26, 2017; accepted for publication June 27, 2017.

Available online July 12, 2017.

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0091-6749/$36.00

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http://dx.doi.org/10.1016/j.jaci.2017.06.015

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

TABLE I. Summary of novel genetic associations with asthma and biologic effect

- Doublesex and mab-3–related transcription factor 1 (DMRT1) potentially explains sex-specific asthma effects during childhood.[13]
- An SNP on chromosome 8 was associated with early lung function decrease and COPD.[14]
- A new locus associated with time to asthma onset is at position 16q12.[15]
- Gly-to-Arg substitution at the 16 position in the β_2-adrenoceptor gene in asthmatic children was associated with an increased risk of asthma exacerbation with use of LABAs in children carrying 1 or 2 alleles of this substitution.[16]

pollution, floods, and plant life adaptation, will affect population health, with the most vulnerable areas most effected, as well as our most vulnerable patients, such as the elderly, young, and poor.[20] In the face of evolving climate challenges, new research has helped refine our understanding of how indoor and outdoor environments interact with the immune system and influence pulmonary physiology (Table II).[21-25]

Multiple letters to the editor in the September 2016 edition of the *JACI* examined traffic-related air pollution (TRAP)'s influence on asthma. A median regression analysis of patients in a large birth cohort showed a significant association between increased exposure to traffic nitric oxides in the first year of life and increased adolescent airways resistance and reactance.[21] Adolescent self-reported psychosocial stress also seems to influence the estimated pulmonary effects of TRAP. TRAP was associated with larger negative effects on lung function in households without a father present compared with homes with a father present. The authors speculate that hypothalamic axis modification secondary to stress might modulate immune function and enhance susceptibility to air pollution.[26]

TRAP can also affect steroid sensitivity. In a mouse model of allergen-induced asthma with diesel exhaust particle (DEP) exposure, 4 days of dexamethasone treatment only partially reduced airway hyperresponsiveness (AHR) in mice exposed to both house dust mite (HDM) and DEPs. These HDM plus DEP–exposed mice were noted to have greater airway neutrophilia compared with mice exposed to HDM only. Anti–IL-17A treatment in combination with dexamethasone significantly reduced AHR compared with either treatment alone.[22]

Asthmatic patients experience clinical symptoms quickly when exposed to worsening air quality. Explanations of the mechanism of this rapid sensitivity are now being reported. Many articles, as well as a recent review in the *JACI*,[27] have explained how innate lymphoid cells are emerging as key contributors to the pathogenesis of inflammatory disease. ILC2s produce type 2 cytokines, such as IL-4, IL-5, IL-9, and IL-13, on stimulation with epithelium-derived cytokines, such as IL-33, IL-25, and thymic stromal lymphopoietin.

A recent report by Yang et al[28] revealed that BALB/c allergen-sensitized and allergen-challenged mice had increased eosinophil counts in bronchoalveolar lavage (BAL) fluid after O_3 exposure. IL-5 release occurred within 12 hours after O_3 exposure, notably without increased T_H2 cell numbers in the lung. Importantly, depletion of both innate lymphoid cells and T cells, but not specific depletion of $CD4^+$ T_H cells, abolished IL-5 release in BAL fluid of O_3-exposed mice. These findings confirmed that ILC2s were the major source of IL-5 after O_3 exposure. The group went on to demonstrate a relationship between ILC2s and enhanced AHR in the setting of O_3 exposure.[28] The timeline and pattern of inflammation in this study was as follows: type 2 cytokine release within hours, leading to increased AHR after TRAP, which helps describe how asthmatic patients might experience symptoms quickly and have heightened sensitivity to air pollution.

Previous work has shown that TRAP is associated with DNA methylation variation. Ten-eleven translocation 1 (TET1) enzyme is a promoter of DNA demethylation. Cross-sectional data from nontwin siblings discordant for asthma who were born and raised in the same household showed an association between asthma status and demethylation of a CpG site in the promoter region of the *TET1* gene. In addition, this study showed that methylation of the same CpG site was associated with TRAP exposure.[29] The exact role of *TET1* in influencing these associations remains unknown, and the authors suggest *TET1* warrants further study as a possible systemic biomarker for childhood asthma.

In addition to air pollution's effects, data continue to emerge on specific microbial exposures that can influence asthma development. Fungal and bacterial community characteristics were measured in the main living areas of asthmatic children by using next-generation DNA sequencing technology. Participants were selected at the extremes of asthma severity. Among all children, increased asthma severity was associated with high concentrations of allergenic species, high total fungal concentrations, and increased bacterial richness. In addition, fungal and bacterial community composition shared more similarities in homes of patients with severe asthma compared with those with mild asthma. Although no specific bacterial operational taxonomic units were significantly associated with asthma severity, the fungal genus *Volutella* was found to be associated with asthma severity.[30]

Prior work has shown that children raised on traditional dairy farms demonstrate protection from asthma and allergic disease. Stein et al[31] recently looked at environmental exposures, genetic ancestry, and immune profiles in both Amish and Hutterite US populations. These 2 groups live similar lifestyles, with the notable exception that the Hutterites use more industrialized farming practices. Genome-wide SNPs compared allele frequencies and showed strong similarities between the groups, indicating similar genetic ancestry. Markers of atopy were lower in the Amish group than in the Hutterite group. After 1 month of sampling from electrostatic dust collectors in 10 homes from both groups, Amish homes had endotoxin levels 6.8 times higher than those in Hutterite homes. Amish children had increased proportions of neutrophils, lower proportions of eosinophils, and monocytes with a more suppressive phenotype than Hutterite children. The Amish also had genetic overexpression of components of the innate immune response to microbial stimuli. An ovalbumin mouse model of allergic asthma, after administration of Amish house dust intranasally, demonstrated inhibited AHR, BAL eosinophilia, and ovalbumin-specific IgE.[31] For additional information on the microbiome's influence on early asthma development, readers are directed to the recent review by Erika von Mutius.[32]

TABLE II. New findings related to studies on air quality, pollution, climate, environment, and asthma

- Patients in a large birth cohort showed a significant association between increased exposure to traffic NO_x in the first year of life and increased adolescent airways resistance and reactance.[21]
- A mouse model of allergen-induced asthma with DEP exposure demonstrated that 4 days of dexamethasone treatment only partially reduced AHR in mice exposed to both HDM and DEPs.[22]
- A causal network analysis on an inner-city asthma cohort demonstrated that the 2 biggest drivers of asthma severity appear to be an allergy pathway starting with allergic sensitization and an environmental tobacco smoke pathway.[23]
- Analysis of an Australian longitudinal birth cohort demonstrated that allergic sensitization by 12 months of age was associated with increased risk of wheeze during young adulthood, as well as lower FEV_1, FEV_1/FVC ratio, and FEF_{25-75} at 24 years of age.[24]
- After adjusting for confounders in a pregnancy cohort, a dose-response relationship emerged with an increase in the odds of asthma diagnosis in children for each increase in maternal stress category both prenatally and postnatally.[25]

EXPOSURES DURING DIFFERENT STAGES OF DEVELOPMENT AND LONG-TERM SEQUELAE OF CHILDHOOD ASTHMA

Among the well-described risk factors for asthma, recent research is helping to define the level of influence had by these risk factors. The Inner-City Asthma Consortium conducted a causal network analysis on a conceptual model of 8 potential asthma risk factor domains. They found that the model could explain about 50% of the variance in asthma severity. The 2 biggest drivers of asthma severity were an allergy pathway starting with allergic sensitization and an environmental tobacco smoke pathway. Among the individual domains, pulmonary physiology and rhinitis severity had the largest effects on asthma severity.[23] Analysis of an Australian longitudinal birth cohort demonstrated that allergic sensitization by 12 months of age was associated with increased risk of wheeze during young adulthood, as well as lower FEV_1, FEV_1/forced vital capacity (FVC) ratio, and forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}) at 24 years of age.[24] The contribution of allergic sensitization and respiratory pathogens (both viral and bacterial) was reviewed last year by Jackson et al[33] for the clinical reviews series in the *JACI*.

In a pregnancy cohort the relative importance of prenatal and postnatal stress on asthma was assessed. After adjusting for confounders, a dose-response relationship emerged with an increase in the odds of asthma diagnosis for each increase in maternal stress category both prenatally and postnatally.[25] A meta-analysis found that compared with term-born children, premature children had a lower FEV_1, FEV_1/FVC ratio, and FEF_{75} at a mean age of 8.5 years. Similar findings were seen in children born with low birth weight. Mediation analyses suggested that FEV_1, FEV_1/FVC, and FEF_{75} can explain 7% to 45% of the associations between early growth characteristics and asthma. These associations were present across the full range of early growth, an observation with possible population health implications.[34]

In addition to defining early influencers of airflow obstruction, we are learning more about the long-term effects of airflow obstruction. A latent class analysis of more than 12,000 participants followed from infancy into adolescence identified 6 different wheezing phenotypes. Phenotypes characterized by remitting symptoms in later childhood were associated with lung function deficits in adolescence compared with the never/infrequent wheezing phenotype. All 3 phenotypes with persistent symptoms had strong associations with diagnosed asthma, bronchodilator reversibility, and high exhaled nitric oxide values in adolescence. Late-onset wheezing was not associated with airway obstruction by age 15 years. The associations suggest wheezing illnesses with onset early in life have a greater influence on lung function than wheezing duration.[35] McGeachie et al[36] highlighted long-term deficiencies in lung function in Childhood Asthma Management Program participants followed into the third decade of life. Despite this cohort comprising patients with mild-to-moderate asthma, investigators found that a high proportion (75%) of subjects had reduced lung function as adults. Notably, 11% of participants met the spirometric criteria for COPD.[36]

PATIENT-CENTERED OUTCOMES RESEARCH REFLECTS PATIENT PRIORITIES AND ENGAGES STAKEHOLDERS

The National Asthma Education and Prevention Program Expert Panel Report,[37] which was last updated in 2007, provides guidance for the management of asthma. For the most part, it is informed by efficacy studies. These narrowly defined studies include patients most likely to benefit and who are treated under the most promising conditions. However, a limitation of these well-controlled studies is that the interventions are not always effective when applied in the real world, do not take into account the uniqueness of patients and their environments, and often exclude those with comorbidities. This limitation is particularly evident when applying recommendations to patients from low-income and minority communities, where resources are limited and social barriers to accessing health care and carrying out management recommendations are common.[38]

Additionally, interventions prompting guideline recommendations might not reflect individual patient priorities, such as a patient's concern about taking many medications for a variety of conditions or their cost. Thus patient-centered studies are needed to address health disparities. The December issue of the *JACI* is devoted to patient-centered comparative effectiveness research focusing on research funded by the Patient-Centered Outcomes Research Institute (PCORI). The PCORI's mission is to fund comparative effectiveness research that allows patients and other stakeholders of research to make informed health decisions.[39]

In presenting the PCORI perspective, Anise and Hasnain-Wynia[39] argue for the importance of engaging these stakeholders, which include patients and health care providers, in all aspects of the research: development of the intervention design, selection of outcome measures, and refinement and conduct of the research, analysis, and reporting of the results.[40] Bryant-Stephens et al[41] describe the experiences of community health workers as they make home visits to asthmatic adults in low-income urban

TABLE III. Analyzing predictors of severe asthma from the NIAID Inner-City Asthma Consortium

- Multifactorial interventions, such as exposure to environmental tobacco smoke and allergens, must be used to address asthma severity.[23]
- A cluster analysis methodology was used to define phenotypes of inner-city children with asthma, including one phenotype of severe asthmatic children that is highly allergic.[46]
- Children and adolescents with difficult-to-control asthma defined as requiring high-dose ICSs are distinguishable from those requiring only low-dose ICSs by FEV_1 bronchodilator responsiveness rhinitis severity and atopy.[47]

neighborhoods, many living in 1-room apartments or overcrowded spaces with many family members. Martin et al[42] report the challenges of overcoming barriers in transitioning care for children with asthma from the emergency department to stable consistent outpatient care. An analysis of the methodologies of 8 PCORI-funded studies concludes with recommendations for modifying traditional research methodology to overcome obstacles in patient-centered intervention research. Modifications might include devoting more resources than in a traditional study for recruitment and conduct of the study to maintain enrollment and to minimize but account for missing data.[43]

CLINICAL RISK FACTORS

Wells et al[44] add support to this patient-centered approach by demonstrating that neither self-reported race-ethnicity nor race defined by genetic ancestry predicted ICS response; rather, baseline lung function and self-reported asthma control do, emphasizing the need to find ways to ensure optimal lung function, asthma control, and elimination of barriers to accessing care. Szentpetery et al[45] describe asthma risk factors among Puerto Ricans, including exposure to environmental tobacco, violence, pollution, and psychological stress along with personal risk factors, such as obesity, difficult access to health care, and low health literacy. The authors conclude multifactorial interventions are needed.[45]

Liu et al,[23] in the longitudinal Asthma Phenotypes in the Inner City (APIC) study, analyzed pathways through which risk factors contribute to asthma severity in inner-city children, suggesting that multifactorial interventions, such as exposure to environmental tobacco smoke and allergens, will address asthma severity (Table III).[23,46,47] Their model explained 53.4% of the variance in asthma severity of the cohort of 561 children. The authors illustrated their points using a new *JACI* feature, a graphical abstract.

In another APIC analysis, Zoratti et al[46] used cluster analysis to define phenotypes of inner-city children with asthma, including one phenotype of children with severe asthma who were highly allergic. Also from the APIC Study, Pongracic et al[47] examined children and adolescents with difficult-to-control asthma, which was defined as requiring high-dose ICSs, and found them distinguishable from those requiring only low-dose ICSs based on FEV_1 bronchodilator responsiveness, rhinitis severity, and atopy. Other studies found exacerbations vary by season in inner-city asthmatic children[48] and in youth living in poverty, whether urban or rural.[49,50] The pathways and heterogeneity of risk factors emphasize that in multifactorial intervention studies informed by these analyses, addressing poverty and engaging the children and their caretakers in interventions, is essential.

In considering patient engagement in health care, navigation (ie, the ability to access health care and communicate with providers), is an important skill. Perez et al[51] developed and validated a questionnaire with input from patients to assess navigation. More important than the development of the questionnaire, they found an item of the questionnaire, also routinely a part of a patient-provider interview (eg, "Tell me the names of your asthma medications.") was correlated with more general health literacy. Thus a routine interview question yields much information about the patient.

PRECISION MEDICINE

In January 2015, President Obama proposed a Precision Medicine Initiative[52] considering each patient's uniqueness and the need for tailoring treatment to take into account individual variability in genes, environment, and lifestyle. This initiative aligns with translational and comparative effectiveness research, seeking to understand environmental, clinical, and lifestyle risk factors that characterize phenotypes and identifying the biomarkers to help define the pathophysiologic mechanisms or endotypes to tailor preventive and ongoing medical care for each subject.[53-55]

Berry and Busse[56] review currently used biomarkers. Muraro et al[57] collaborated under PRACTALL, an initiative of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology, to harmonize approaches and summarize endotypes and validation of biomarkers to develop precision medicine for management of asthma and other atopic diseases. With this focus on biomarkers, how exposure to the environment, including the microbiome, and also how the phenotype of poverty[41] result in relevant biomarkers needs to be understood. Thus the contributions of real-world and comparative effectiveness research with participation from stakeholders are essential to complete the translation of research from bench to bedside.[53]

APPLICATION OF BIOMARKERS TO PERSONALIZED MEDICINE

In 2012, the *JACI* published a report from the National Institutes of Health (NIH) Asthma Outcomes Task force to summarize relevant outcomes for NIH asthma research. One of the sections was on physiology and listed various physiologic measures as core (should be included in all asthma research), supplementary (applied in selected research), and exploratory (intended to be evaluated for potential application).[58] AHR by methacholine challenge was listed as a supplemental measure. Pralong et al[59] reported on the predictive value of nonspecific airway responsiveness in bronchial asthma. Based on data from a Canadian database of 1012 cases, they indicated that a negative methacholine challenge result in a patient still exposed to the causative agent at work makes the diagnosis of occupational asthma unlikely.

The outcomes report stated that FEF_{25-75} is not a specific measure of small-airway obstruction but could be chosen as an end point; however, its value is less established.[58] Siroux et al[60]

TABLE IV. Useful biomarkers for personalized medicine for asthma

- In patients with severe uncontrolled asthma 12 years and older, a high blood eosinophil count (≥400 cells/mm^3) was an independent risk factor for ≥2 asthma exacerbations or any asthma emergency department visit or hospitalization but not direct costs.[63]
- In young children with asthma necessitating step 2 treatment, phenotyping with allergen sensitization and a blood eosinophil count of 300 cells/mm^3 or greater identifies children with a high exacerbation probability for whom treatment with a daily ICS is beneficial despite risks of growth suppression.[64]
- A combined high exhaled nitric oxide level and blood eosinophil count is related to a higher likelihood of AHR and uncontrolled asthma in young asthmatic patients.[65]
- Serum periostin levels are not associated with asthma severity but are associated with type 2 immunity in patients who are symptomatic, despite their use of corticosteroids and potential use for assessing greater response to type 2 immunity–based treatment.[66]
- Expression of miRNAs and genes associated with bronchial immune responses were demonstrated to be significantly modulated by diesel exhaust or allergens and thus might be used as biomarkers of exposure to air pollution as an indicator of epithelial wall damage.[67]

studied 337 participants (142 children and 225 adults) for persistence of current asthma and risk for uncontrolled asthma and concluded that decreased FEF_{25-75}, as an indicator of small-airway obstruction, might contribute to long-term persistence of asthma and subsequent risk for poor asthma outcomes independent from effects of the large airways.

Another section of the NIH Outcomes Task Force addressed biomarkers.[56] Berry and Busse[56] provided an updated review on biomarkers in asthmatic patients and indicated that certain biomarkers, such as sputum and blood eosinophils, can help define the specific pathophysiology of different asthma phenotypes and identify potential therapeutic agents. Similarly, Muraro et al[57] indicated that progress has been made in profiling type 2 immune response–driven asthma, but the endotype-driven approach for the non-T2 immune response for asthma is lagging behind. It will be important to define validated and qualified biomarkers for research and precision medicine. Skevaki et al[61] indicated that biomarker discovery and validation in children with disease lag behind those in adults, given the early onset and potential lifelong effect of the disease. The ultimate challenge will be optimization of prevention strategies that can be implemented in children identified as being at risk of a noncommunicable disease, such as asthma, through use of biomarkers.

Blood and sputum eosinophils, along with exhaled nitric oxide were listed as supplementary biomarkers to be considered optional in asthma research (Table IV).[62-69] Zeiger et al[63] reported observations from a Kaiser Permanente Southern California database of patients 12 years and older that a high blood eosinophil count (≥400 cells/mm^3) was an independent risk factor for 2 or more asthma exacerbations or any asthma emergency department visit or hospitalization but not direct costs in patients with severe uncontrolled asthma.

A study conducted in the National Heart, Lung, and Blood Institute AsthmaNet reported that in young children with asthma necessitating step 2 treatment, phenotyping with allergen sensitization, considered a core biomarker in the Asthma Outcomes Report, and a blood eosinophil count of 300 cells/mm^3 or greater, is a useful guide for treatment selection and identifies children with a high exacerbation probability for whom treatment with a daily ICS is beneficial despite risks of growth suppression.[64]

A "Paradigms and perspectives" review[68] summarized key lessons learned for the application of exhaled nitric oxide in clinical practice. Exhaled nitric oxide measurement can be an important tool in the management of asthma, and there is a need for asthma guidelines to define its application so that it can be more readily applied in the primary care setting, where the majority of asthmatic patients are managed. Additional reports demonstrated that a combined high exhaled nitric oxide level and blood eosinophil count were related to a higher likelihood of AHR and uncontrolled asthma in young asthmatic patients.[65]

Michils et al[69] measured exhaled nitric oxide levels in relation to β_2-agonist use and identified 3 exhaled nitric oxide behaviors to identify the site of airway obstruction in asthmatic patients. A note of precaution was provided by Cohen et al,[70] indicating that exhaled nitric oxide levels were not associated with an asthma diagnosis, wheezing symptoms, lung function measures, or prior morbidity in children with sickle cell anemia but were associated with markers of atopy and increased risk of future acute chest syndrome.

Periostin was a newly reported biomarker at the time of the NIH Asthma Outcomes Report and thus was not fully addressed in that report and would have been considered exploratory at the time. Periostin is considered an extracellular matrix protein that is upregulated by the type 2 cytokines IL-4 and IL-13 in bronchial epithelial cells and lung fibroblasts. Johansson et al[66] demonstrated that serum periostin levels are not associated with asthma severity but are associated with type 2 immunity in patients who are symptomatic despite their use of corticosteroids and potential use for assessing greater response to type 2 immunity–based treatment. Noguchi et al[71] reported that periostin upregulates eosinophil functions, such as superoxide anion generation and eosinophil-derived neurotoxin release, along with production of TGF-β and cysteinyl leukotrienes from eosinophils.

As further studies are being conducted, new biomarkers are being discovered. Hinks et al[72] reported on 6 clinicopathobiologic clusters based on blood and induced sputum measures. They implied from their studies that IL-5 production is relatively steroid insensitive, and the expression of chitinase 3–like protein-1 is present in patients with neutrophilic inflammation, along with expression of metalloproteinases in patients with severe asthma.

There is increasing interest in the use of specific microRNA (miRNA) expression profiles with inflammatory cell profiles and disease severity in asthmatic patients. Maes et al[73] reported that expression of miR-223-3p, miR-142-3P, and miR-629-3p is increased in sputum of patients with severe asthma and is linked to neutrophilic airway inflammation, which is perhaps a new way to identify this asthma inflammatory phenotype. Panganiban et al[74] demonstrated that circulating miRNAs are uniquely expressed in patients with allergic rhinitis and asthma and have the potential for use as noninvasive biomarkers to diagnose and characterize these diseases. Expression of miRNAs and genes associated with bronchial immune responses were demonstrated to be significantly modulated by diesel exhaust or allergens and thus might be used as biomarkers of exposure to air pollution as an indicator of epithelial wall damage.[67]

TABLE V. New insights relevant to asthma management

- The mission of the PCORI is to fund comparative effectiveness research that allows patients and other stakeholders of research to make informed health decision.[39]
- Using reimbursement data, only 24% of adults and pediatric patients maintained regular ICS adherence 1 year after a period of regular ICS use.[87]
- *The School-based Asthma Management Program (SAMPRO) was developed to foster multidirectional communication between children, families, clinicians, school-based personnel, and the community to promote better pediatric asthma care.*[88]
- Use of an electronic monitoring device system, decreased short-acting β-agonist (SABA) use, and increased SABA-free days in children and adults were seen.[89]
- A multidisciplinary school-based program can increase the number of asthma action plans, increase rescue and controller medication use in schools, improve asthma knowledge scores, improve inhaler technique, and reduce asthma exacerbations.[90]

There is also great interest in identifying biomarkers that might be reflective of asthma development *in utero*. Magnus et al[75] reported that high maternal levels of neopterin, a marker of cellular immune activation, during pregnancy were positively associated with asthma in offspring, but further studies are needed to identify the mechanism for this observation. There is also interest in using breathomics with the assessment of volatile organic compounds in assessment of asthma and COPD. Large multicenter studies will be needed to validate this noninvasive technology before clinical applications can be made for chronic airways disease assessment, phenotyping, and monitoring.[76]

Another biomarker considered exploratory by the biomarkers committee[56] was airway imaging. This field continues to move along and holds promise for new ways to assess airway disease. Gonem et al[77] used hyperpolarized ^{3}He diffusion magnetic resonance to determine the nature of acinar airway involvement in asthmatic patients. They demonstrated alterations in long-range diffusion within the acinar airways and gas trapping, but the precise anatomic nature and mechanistic role in patients with severe asthma requires further evaluation. Hartley et al,[78] using thoracic quantitative computed tomography, reported that in asthmatic patients and patients with COPD, lung function impairment is strongly associated with air trapping, with a contribution from proximal airway narrowing in asthmatic patients.

Therefore, since the 2012 report on biomarkers for the NIH Asthma Outcomes Task Force, information regarding certain biomarkers has been refined, new biomarkers have been discovered, and information is being rapidly accumulated on the exploratory category of biomarkers to refine their application.

NEW INFORMATION ON ASTHMA MEDICATIONS

In 2016, promising new medications as add-on management for poorly controlled asthma were introduced, and the safety of well-established medications, namely LABAs, was revisited. The addition of roflumilast, a selective phosphodiesterase 4 inhibitor, in conjunction with montelukast to the controller regimen of adults with inadequately controlled asthma despite the use of at least medium-dose ICSs with a LABA resulted in a statistically significant increase in prebronchodilator FEV_1 from baseline, improved morning peak expiratory flow (PEF), and improved daytime symptom scores compared with placebo with montelukast.[79] However, there was no change in prebronchodilator PEF or asthma control questionnaire scores.[79]

QGE031 (ligelizumab), an anti-IgE antibody with a higher binding affinity for IgE than omalizumab, elicited a 3- and 16-fold greater increase in provocative allergen concentrations to decrease the FEV_1 by 15% compared with omalizumab and placebo, respectively, in adults with mild allergic asthma.[80] QGE031 also elicited a suppression of allergen-induced skin prick test responses that was greater than that of placebo or omalizumab.[80]

Once-daily tiotropium delivered through the Respimat Soft Mist inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) in addition to background ICS therapy, with or without a leukotriene receptor antagonist, improved peak and trough FEV_1, FEF_{25-75}, and predose morning and evening PEF values in adolescent patients.[81]

In adults with not well-controlled HDM allergy–related asthma, HDM sublingual immunotherapy improved the time to the first moderate or severe asthma exacerbation, primarily because of an effect on moderate asthma exacerbations, compared with placebo during an ICS reduction phase.[82] HDM sublingual immunotherapy did not change asthma control questionnaire or asthma-related quality-of-life scores compared with placebo.[82]

The benefits of the aforementioned add-on medications primarily center on their ability to improve lung function.[79-81] Additional studies to examine their effect on asthma control, including risk and impairment, would be beneficial because they are explored as novel controller therapies.

The US Food and Drug Administration (FDA) issued a public health advisory on the safety of LABA-containing products in 2005 in response to the Salmeterol Multicenter Asthma Research Trial findings.[83] After this activity, there was a statistically significant decrease in fixed-dose ICS-LABA use in children and adults, with a concurrent increase in ICS and leukotriene modifier use based on prescription database analysis.[83]

Subsequently, the FDA mandated postmarketing safety studies examining the effect of ICS-LABA combination therapy on serious asthma-related events, including death, intubation, and hospitalization.[84-86] In adolescents and adults fixed-dose budesonide-formoterol and fluticasone-salmeterol combination therapies were noninferior to budesonide or fluticasone alone, respectively, for serious-asthma related events.[84,85] Similarly, in pediatric patients fluticasone-salmeterol was noninferior to fluticasone alone for serious asthma-related events.[86] The risk of a severe asthma exacerbation was significantly lower in adults and adolescents treated with combination ICS-LABA therapy compared with ICS therapy alone,[84,85] but this medication effect was not observed in pediatric patients.[86] The effect of these studies on the FDA's overall assessment of fixed-dose ICS-LABA controller therapy safety remains to be seen.

MANAGEMENT

In 2016, emphasis was placed on assessment of medication adherence and creation of comprehensive school-based asthma support networks (Table V).[39,87-90] In a population-based cohort study, only 33% of pediatric patients demonstrated high ICS

TABLE VI. Key advances in 2016

- Rhinovirus-triggered asthma exacerbations become more severe as the degree of sensitization to dust mite and mouse increases.[2]
- Coexposure of respiratory virus and cockroach allergen induced a biphasic IL-33 response and impaired antiviral interferon production.[7]
- 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.[9]
- Cross-sectional data from nontwin siblings discordant for asthma born and raised in the same household showed an association between asthma status and demethylation of a CpG site in the promoter region of the *TET1* gene.[29]
- The 2 biggest drivers of asthma severity were an allergy pathway starting with allergic sensitization and an environmental tobacco smoke pathway.[23]
- Wheezing illnesses with onset in early life have a greater influence on lung function than wheezing duration.[35]
- Precision medicine and patient-centered research, including the contributions of stakeholders, are needed.[40]
- Ability to list asthma medications is associated with higher levels of health literacy.[51]
- Biomarkers, including exhaled nitric oxide levels and eosinophil counts, have potential as indicators of endotypes.[56]
- Allergen sensitization and blood eosinophil counts can be used to select medications for management of asthma in young children.[64]
- In a population-based cohort study only 33% of pediatric patients demonstrated high ICS adherence.[91]
- Use of an acoustic recording device attached to an inhaler found that only 20% of patients used their inhaler in the correct manner at the correct interval, emphasizing the need to address not only the number of actuations but also technique errors.[94]

adherence.[91] Similarly, by using reimbursement data, only 24% of adults and pediatric patients maintained regular ICS adherence 1 year after a period of regular ICS use.[87] The unique barriers for poor medication adherence are age specific, requiring tailored approaches.[92] In addition, inhaled medications pose a unique challenge to adherence, requiring proper technique for adequate drug delivery.[93]

Technological advances are exploring ways to address poor adherence. Use of the Propeller Health Asthma Platform (Propeller Health, Madison, Wis), an electronic monitoring device system, decreased short-acting β-agonist use and increased short-acting β-agonist–free days in children and adults.[89] Use of an acoustic recording device attached to an inhaler found that only 20% of patients used their inhaler in the correct manner at the correct interval, emphasizing the need to address not only number of actuations but also technique errors.[94]

The School-based Asthma Management Program was developed to foster multidirectional communication between children, families, clinicians, school-based personnel, and the community to promote better pediatric asthma care.[88] The School-based Asthma Management Program identified 4 essential components to create this partnership: a circle of support between the aforementioned groups, asthma management plans, comprehensive asthma education for school personnel, and assessment and remediation of school-based asthma triggers.[88]

The benefit of such a multidisciplinary school-based program was highlighted through the Step-Up Asthma Program, which used asthma counselors as a bridge between subspecialty asthma care, primary care providers, school nurses, and families.[90] Over a 2-year period, the program increased the number of asthma action plans, increased use of rescue and controller medications in schools, improved asthma knowledge scores, improved inhaler technique, and reduced asthma exacerbations.[90]

SUMMARY

As indicated in this summary, there are rapid areas of development related to the natural history of asthma and the effect of the environment (Table VI).[2,7,9,23,29,35,40,51,56,64,91,94] There has been no previous era in asthma management that has witnessed the introduction of so many new classes of medications. It will be a challenge for clinicians and those contributing to asthma guidelines to select relevant pieces of information that should be incorporated into clinical practice. Meanwhile, clinicians must keep up with these new findings to provide benefits to patients by implementing strategies that are most likely to be effective. We will continue to monitor this literature and highlight those key findings that have the potential to alter asthma management and report on them in our annual review.

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