

Advances in adult asthma diagnosis and treatment in 2012: Potential therapeutics and gene-environment interactions

Andrea J. Apter, MD, MSc Philadelphia, Pa

In the *Journal of Allergy and Clinical Immunology* in 2012, research reports related to asthma in adults clustered around mechanisms of disease, with a special focus on their potential for informing new therapies. There was also consideration of the effect of the environment on health from pollution, climate change, and epigenetic influences, underlining the importance of understanding gene-environment interactions in the pathogenesis of asthma and response to treatment. (*J Allergy Clin Immunol* 2013;131:47-54.)

Key words: Asthma, adults, inhaled corticosteroids, biomarkers, long-acting β -agonist, gene-environment interaction

Last year's review of advances in adult asthma diagnosis and treatment noted how old questions continued developing new answers.¹ In the companion review of 2011 advances in pediatric asthma, Szefer² wondered whether it was time to revise the guidelines and about the role of the electronic medical record. This year's adult asthma topics cluster around mechanisms of disease, with a focus on their potential for informing new therapies. There was also consideration of the effects of environmental pollution, climate change, and other factors affecting epigenetics in asthma, underlining the importance of understanding gene-environment interactions in the pathogenesis of asthma and its response to treatment, topics that will continue to pose challenges in the coming year.

MECHANISMS OF DISEASE

New mechanisms suggesting new biomarkers and therapeutic targets

Noteworthy studies in human subjects in 2012 revealed new mechanisms of disease and potential biomarkers and therapeutics, as outlined in the following 4 reports. Farah et al³ adapted a noninvasive multiple-breath nitrogen washout technique previously used in patients with other lung diseases to study small-airways ventilation heterogeneity in 105 adults with asthma. They found that the unevenness of small-airways ventilation correlated with poor asthma control measured by using the Asthma Control Questionnaire (ACQ) and that treatment of a subgroup of 50 subjects with high-dose inhaled corticosteroids (ICSs)

Abbreviations used

ACQ:	Asthma Control Questionnaire
ASMC:	Airway smooth muscle cell
BAFF:	B cell-activating factor of the TNF family
COPD:	Chronic obstructive pulmonary disease
EPR-3:	Expert Panel Report 3
FLG:	Filaggrin
GWAS:	Genome-wide association study
ICS:	Inhaled corticosteroid
LABA:	Long-acting β -agonist
MAPK:	Mitogen-activated protein kinase
MCT:	Methacholine challenge test
MMP:	Matrix metalloproteinase
TSLP:	Thymic stromal lymphopoietin

decreased ventilation heterogeneity and improved ACQ scores. These findings suggest small-airways ventilation unevenness is a therapeutic target.

Chang et al⁴ investigated whether airway smooth muscle cells (ASMCs), which proliferate and produce more chemokines in patients with severe asthma, also exhibit corticosteroid insensitivity, as previously observed in macrophages and T cells. The researchers compared cytokine expression of ASMCs in bronchial biopsy cultures from 10 adults with nonsevere asthma, 10 adults with severe asthma, and 12 control subjects. They found that in patients with severe asthma, ASMC TNF- α -induced phosphorylated p38 mitogen-activated protein kinase (MAPK) levels were increased, and suppression by dexamethasone of TNF- α -induced release of CCL11 and CXCL-8 (IL-8) was reduced; however, the inhibitory effect of dexamethasone was augmented by a p38 MAPK inhibitor. These findings suggest that ASMC corticosteroid insensitivity in patients with severe asthma correlates with p38 MAPK levels and that a p38-MAPK inhibitor might have therapeutic benefit.

Meyer et al⁵ studied the interaction of vascular endothelial growth factor, which stimulates angiogenesis in airway remodeling, with IL-32, a newly described cytokine with both proinflammatory and anti-inflammatory properties. They observed that IL-32 was induced by IFN- γ , TNF- α , T_H1 cells, and rhinovirus in normal human bronchial epithelial cells. IL-32 decreased vascular endothelial growth factor production and angiogenesis, and IL-32 expression increased with improved asthma control; thus IL-32 is a potential biomarker and predictor of treatment response.

Jones et al⁶ used a mouse model to study IL-9, which is produced by T_H9 cells and associated with T_H2 cytokines and mast cell activation in the allergic response.⁷ Inhibiting IL-9 suppressed T_H2 expression and tissue remodeling. Furthermore, activin A, a member of the TGF- β family, promoted T_H9 activity, suggesting inhibition of IL-9 or blockers of activin A as additional new potential biomarkers or therapeutic targets in patients with allergic asthma.

Three reports helped to elucidate the increased morbidity in patients with asthma associated with respiratory tract infection. Bauer et al⁸ observed enhanced caspase-1-dependent activation

From the Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Pennsylvania.

Disclosure of potential conflict of interest: The author declares that she has no relevant conflicts of interest.

Received for publication November 9, 2012; accepted for publication November 12, 2012.

Corresponding author: Andrea J. Apter, MD, MSc, 829 Gates Building, Hospital of the University of Pennsylvania, 3600 Spruce St, Philadelphia, PA 19104. E-mail: apter@mail.med.upenn.edu.

0091-6749/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2012.11.020>

of the inflammasome and innate immune signaling in response to influenza A in human bronchial epithelial cells from asthmatic compared with nonasthmatic volunteers. These effects were not seen in caspase-1-deficient mice. Caspase-1 is necessary for the proteolytic processing of pro-IL-1 β and pro-IL-18 and therefore might be an important link between airway viral infection and asthma exacerbation. Hernandez et al⁹ observed a blunted innate immune response in allergic asthmatic but not healthy volunteers challenged with inhaled endotoxin (LPS), a ubiquitous pathogen-associated molecular pattern found in gram-negative bacteria, ambient air particles, and tobacco smoke. Increases in absolute sputum leukocyte and neutrophil counts and in sputum IL-6 and TNF- α levels occurred in both groups after LPS challenge, but levels were significantly lower in the allergic asthmatic subjects. Moreover, sputum IL-1 and IL-18 levels and sputum cell-surface expression of Toll-like receptors 4 and 2 were significantly increased only in the healthy volunteers. Conceivably, the blunted innate inflammatory response to LPS in patients with allergic asthma might increase susceptibility to infection in this group. Kumar et al¹⁰ analyzed data obtained from 3 large cohorts of self-identified African American subjects and determined that the rs17564816 (allele A) intronic single nucleotide polymorphism in the gene for B cell-activating factor of the TNF family (*BAFF*) was associated with higher serum levels of BAFF and asthma exacerbations in 2 of these cohorts. The researchers speculated that increased BAFF levels lead to more aggressive innate and adaptive immune responsiveness to viruses, thereby contributing to the asthma exacerbations and suggesting that along with socioeconomic factors, genetic variations play a role in asthma disparities.

Two studies focused on the interrelationship of atopy and asthma. Berg et al¹¹ confirmed that genetic defects in filaggrin gene (*FLG*), which is known to be associated with atopic disease (particularly atopic dermatitis) and increased serum IgE levels, further increase the risk of asthma. However, carriers of *FLG*-null mutations, particularly nonatopic carriers, were more susceptible to the bronchoconstrictive effects of smoking on asthma. Arbes¹² considered whether asthmatic patients with atopy had atopic asthma, an intriguing question with important therapeutic implications. Using National Health and Nutrition Examination Survey data, he calculated the attributable risk proportion (ie, the proportion of disease [asthma] among the exposed [atopic subjects: specific IgE ≥ 0.35 kU/L to at least 1 of 15 aeroallergens and 4 foods] caused by the exposure [atopy]) and ascertained that only 57% of asthma cases among atopic subjects were due to atopy. An implication of this analysis is that the remaining 43% of atopic patients with asthma will not benefit from treatment aimed at atopy control. Limitations included the cross-sectional design, how good the survey questions were at diagnosing asthma, and whether the allergen-specific IgE selection and assessment reliably defined atopy.

Vitamin D deficiency has been linked with asthma development and severity in some studies. In addition, variations in vitamin D receptor genes have been associated with asthma susceptibility. A genome-wide association study (GWAS) of gene–vitamin D interactions in asthma exacerbations was carried out in subjects from the Childhood Asthma Management Program and replicated in a Costa Rican cohort.¹³ Variants in the class I MHC-restricted T cell-associated molecule gene (*CRTAM*) were associated with an increased rate of asthma exacerbations based on the presence of vitamin D levels. Although the

mechanism by which *CRTAM* might affect the relationship between vitamin D and asthma exacerbation is not known, the researchers argue these findings support the need for clinical testing of whether vitamin D has therapeutic value in asthma.

Severe asthma: Identifying the mechanism to inform therapy

Severe asthma that does not respond to conventional anti-inflammatory therapy continues to challenge patients, practitioners, and investigators. Tsitsiou et al¹⁴ investigated the role of activated CD8⁺ T cells by using transcriptomic analysis. The transcriptome is the set of all RNA molecules. The researchers compared 12 patients with severe asthma (needing frequent oral corticosteroids, continuous high-dose ICSs, or both), 4 patients with nonsevere asthma, and healthy control subjects. Using microarrays and quantitative real-time PCR, the investigators found changes in the mRNA and noncoding RNA expression in circulating CD8⁺ but not CD4⁺ cells of patients with severe asthma. The specific mRNAs upregulated were chitinase 3 protein 1 and arginase, which are possible potential therapeutic targets.

Thymic stromal lymphopoietin (TSLP), a cytokine released from airway epithelial cells in response to inflammatory cytokines and Toll-like receptor 3 stimulation, promotes asthma. TSLP's many activities and potential roles in patients with asthma and allergic diseases were reviewed by Ziegler¹⁵ in the October issue. Shikotra et al¹⁶ found that TSLP expression was increased in patients with severe asthma despite corticosteroid therapy, particularly where there was evidence of T_H2 inflammation and IL-13-expressing nuocytes. TSLP is another potential target for intervention, especially in patients with severe asthma.

Matrix metalloproteinases (MMPs) are extracellular matrix proteolytic enzymes that participate in normal growth and repair of airway remodeling; however, some MMPs, such as MMP-12, have excessive activity in patients with chronic obstructive pulmonary disease (COPD) and asthma. Chaudhuri et al¹⁷ compared disease severity with MMP-12 concentrations and activity in a cross-sectional analysis in patients with asthma, patients with COPD, and healthy control subjects. They found greater sputum concentrations of MMP-12 in patients with COPD and smokers with asthma than in healthy nonsmokers. In sputum from patients with COPD, MMP-12 concentration and activity were associated with the extent of emphysema. Thus a blocker of MMP-12 is identified as another potential therapeutic target for severe asthma, particularly when smoking is a factor.

GENETIC INFLUENCES OF CLINICAL RELEVANCE

Noting that asthma and autoimmune disease appear to be mediated by dichotomous immunologic mechanisms (eg, T_H2 vs T_H1), Li et al¹⁸ hypothesized that genes associated with protection in asthmatic patients might, in contrast, be linked to exacerbation of autoimmune disease. They conducted a GWAS of asthma in a large population of non-Hispanic white subjects from the Severe Asthma Research Program and the Chicago Asthma Genetics Study and identified a new candidate gene, *TNFAIP3* interacting protein 1 (*TNIP1*), which is associated with asthma risk. Although the identified allele of *TNIP1* was a minor protective allele in asthmatic patients, it was previously

recognized as a risk allele for systemic lupus erythematosus and systemic sclerosis in non-Hispanic white subjects. The study also identified other genes, such as *IL13* and *HLA-DRA*, which are known to have opposite associations in patients with asthma and autoimmune disease. For example, identified *IL13* and *HLA-DRA* alleles associated with asthma risk were previously found to be protective in patients with psoriasis and ulcerative colitis, respectively. However, identified genes involved in T-cell regulation had homologous effects. Such insights might yield therapeutic applications.

However, the findings of GWASs cannot always be replicated in new populations. To address this, the EVE Consortium, a National Institutes of Health-funded consortium of investigators who have conducted GWASs of asthma, has as its main objective a meta-analysis to identify asthma susceptibility loci.¹⁹ In a replication study they identified 2 novel single nucleotide polymorphism associations with asthma in European American but not African American or Latino subjects. The investigators emphasized the importance of attention to recruitment strategies, environmental risk factors, and correction for admixture when designing GWASs.

Genetic influences and gene-environment interactions

As noted by the EVE Consortium, the risk of asthma has both genetic and environmental contributions. Their interactions are the subject of active study. Kauffmann and Demenais²⁰ provide a salient perspective on the evolution of the concept of gene-environment interaction in the cause of human disease from the nature-versus-nurture theory of the 19th century. Importantly, these authors also incorporate time in their model (Fig 1).

Several studies focused on gene-environment interactions. Using data from 3 Canadian family-based studies and 1 Australian population-based case-control study, Daley et al²¹ found interactions between innate immunity genes with viral infections in early life and susceptibility to asthma.

Wegienka et al²² considered the interaction of socioeconomic with genetic factors on asthma susceptibility. They assessed adult women from the Detroit area as part of a birth cohort study of their children for the prevalence of allergic history and serum specific IgE for aeroallergens and egg. Black women were more likely than white women to be sensitized to at least 1 allergen, to have higher total IgE levels, and to have a doctor's diagnosis of asthma and eczema but not hay fever. After adjusting for socioeconomic and environmental variables, these associations persisted for total serum IgE levels, having at least 1 sensitization to allergen, and eczema. The investigators concluded that racial differences and gene-environment interactions deserve further study to determine the causes of health disparities and prevent them. Rumpel et al²³ assessed the genetic ancestry of 392 African American subjects with asthma by using ancestry informative markers and found an interaction between ancestry and sex: the risk of asthma exacerbations was higher with increasing African ancestry among male but not female subjects. They, too, concluded that a portion of risk of asthma exacerbations is gene dependent and deserves further study.

ENVIRONMENTAL EXPOSURES

The *Journal* devoted the January 2012 issue to a review of the deleterious effects of ambient air pollution and the importance of

the Clean Air Act,^{24,25} drawing attention to the effects of pollution on respiratory and allergic disease worldwide.^{26,27} Of particular interest was the natural experiment that occurred in Beijing when a government-mandated reduction in pollution for the 2008 Olympics was followed by fewer outpatient visits for asthma. Bauer et al²⁸ reviewed the innate immune system response to pollutants and respiratory pathogens and particularly the role of Toll-like and NOD-like receptor-dependent signaling. Ji and Khurana Hershey²⁹ described the genetic and epigenetic modifications associated with ambient air pollution, specifically particulate matter, in genetic susceptibility on the development of allergic disorders. Areas in which research is needed to better elucidate epigenetic mechanisms in the development of asthma, particularly associated with environmental exposures were discussed by Yang and Schwartz.³⁰

Several perspectives considered how plant and microbial environments influence respiratory disease. Ziska and Beggs³¹ describe what is known about the human or anthropogenic influence on climate, particularly global warming and the increasing concentration of atmospheric CO₂, and their effects on plant biology and allergen exposure. For example, global warming and CO₂ generation stimulate plant photosynthesis, altering growth and pollen production, whereas climate and weather changes modify pollen dispersal and exposures to fungi. Knutsen et al³² review the contribution of sensitization to fungi in patients with severe asthma and allergic lower respiratory tract diseases, including allergic bronchopulmonary mycoses. Heederik and von Mutius speculate on the possible protective effects of environmental microbial exposures against allergy and asthma.^{33,34} They point out that higher exposure to bacterial endotoxins, β -glucans, and muramic acid correlates with reduced risk of allergy and asthma in both rural and urban populations and suggest a research agenda for understanding these interrelationships. Finally, these authors and the perspective by Ursell et al³⁵ describe the diversity of the internal environmental microbial populations or microbiome and its variation with anatomic site, including the airways, and of external environmental differences related to geographic or cultural factors. Whether microbial diversity at various stages of life protects against asthma or contributes to its development is an area of active research.

In a very different consideration of the environment, Bougault et al³⁶ investigate the environment of swimmers. Their concern is that high and sustained levels of ventilation required by athletes causes dehydration and mechanical stress on the airways. In addition, increased ventilation might promote exposure to pollutants, irritants, and allergens. These investigators studied 23 elite swimmers during and outside of the training season, with an extensive evaluation that included bronchial biopsy, comparing them with patients with mild asthma and healthy control subjects. Among the elite swimmers, 12 had airway hyperresponsiveness to methacholine, and 9 had exercise-induced bronchospasm. Compared with either control group, these swimmers had increased airway mucosa eosinophil and mast cell numbers, as well as greater mucin expression, submucosal collagen expression, and goblet cell hyperplasia, although exhaled nitric oxide levels, responsiveness to methacholine, and eucapnic voluntary hyperpnea did not correlate with these inflammatory and remodeling changes. It can be argued that limiting exposure to chlorine and pool chemicals is advisable, and more and longer-term study of these athletes is warranted.

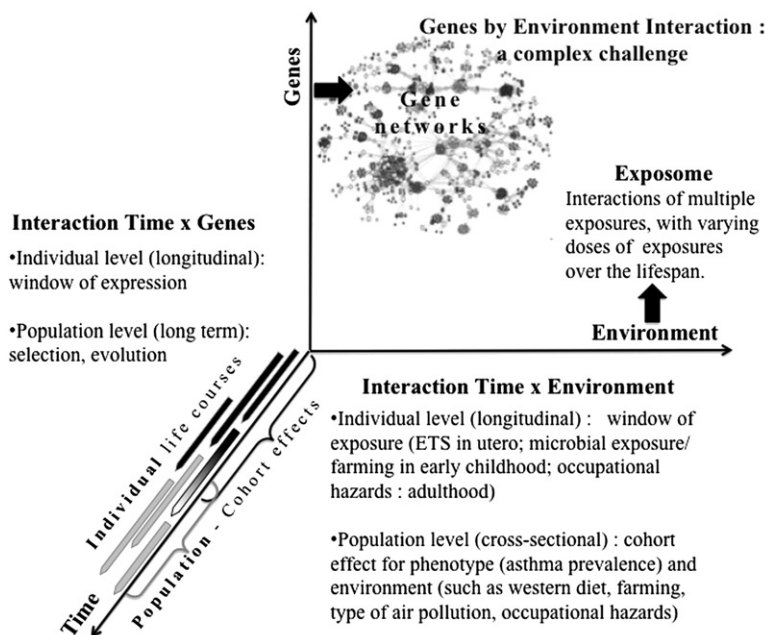


FIG 1. Gene-environment-time interactions (printed with permission from Kauffmann and Demeais²⁰). The time axis represents individual life courses, with changes in environment corresponding to cohort effects (*black and light gray lines*). Within their life course, some subjects might experience acute environmental changes in case of migration or changes that might occur in developing countries with the new availability of clean water. With time, protective factors (eg, modification of the microbiome) or emergence of deleterious factors (eg, new occupational cleaning agents) can occur. The gene effect on disease can vary with time; this can occur in relation to lung growth or modification of epigenetic marks or during the course of asthma development or the aging process.

THE COURSE OF ASTHMA AND INFLUENCES ON ITS COURSE

Elements that influence the course of asthma were considered by several authors in 2012. Why the course of asthma is so variable, remitting and relapsing in some patients, resolving for others, and never remitting in still others, remains unexplained. Gershon et al³⁷ conducted a longitudinal retrospective study of asthmatic patients followed over 15 years using a Canadian administrative database. Of 613,934 subjects, 58% were older than 18 years on enrollment, and 82% had active asthma. Seventy-five percent experienced a gap of at least 2 years in asthma activity. Previous asthma claims, older and younger age, and a diagnosis of COPD correlated with greater asthma activity. The effect of atopic diseases, including asthma, on sleep disturbances and thus on quality of life and functioning and disease course were reviewed by Koinis-Mitchell et al.³⁸

HIV

HIV-infected patients, including those with asthma, are living longer thanks to combination antiretroviral therapy and other advances, presenting an opportunity to reassess what we know about asthma in this setting. Gingo et al³⁹ examined asthma prevalence and bronchodilator reversibility of 223 HIV-infected patients aged 18 years or older and evaluated at the University of Pittsburgh Medical Center between 2007 and 2010 in a cross-sectional analysis. Twenty-one percent had doctor-diagnosed asthma, and 9% had a bronchodilator response, more than double the reported prevalence in the general population.

Asthma was associated with female sex, obesity, a history of pneumonia, not taking antiretroviral therapy, and a family history of asthma. High sputum eosinophil percentages were more likely in those with asthma or bronchodilator response, increased sputum IL-4 and RANTES levels were more common in those with asthma, and bronchodilator response was associated with high plasma macrophage inflammatory protein 1 α and high sputum macrophage inflammatory protein 1 β levels. The researchers concluded that asthma and β -agonist responsiveness were both prevalent among HIV-infected cohorts, and the associated risk factors suggested mechanisms for further investigation.

MANAGEMENT

Measuring outcomes

Clinical research is needed to improve asthma management. This research requires standardized outcomes so that findings can be compared across studies. The March 2012 supplement reports the work of the Asthma Outcomes Workshop convened by the National Institutes of Health and the Agency for Healthcare Research and Quality to accomplish this task.⁴⁰⁻⁴⁸ Seven categories of outcome were considered: biomarkers, symptoms, composite scores of asthma control, exacerbations, quality of life, pulmonary physiology, and health care utilization and costs. Mediators of asthma outcomes were also considered.

In 2012, the *Journal* reported research evaluating some of these outcome elements. Two biomarkers were considered: methacholine and periostin. Sumino et al⁴⁹ conducted a cross-sectional cohort-control study in 126 persons between the ages of 12 and 69 to investigate the ability of the methacholine challenge test (MCT)

to distinguish asthmatic from nonasthmatic subjects. The asthmatic participants had stable disease, used controller medications within the preceding 12 months, but had no exacerbation in the 4 weeks before evaluation. The sensitivity (probability of a positive test result in asthmatic patients) of the MCT was 77% and the specificity (probability of a negative MCT result in healthy patients) was 96% with a threshold PC₂₀ of 8 mg/mL. The sensitivity was lower in white than in African American participants (69% vs 95%, $P = .015$) and higher in atopic compared with nonatopic participants (82% vs 52%, $P = .005$). The performance characteristics of the test did not vary by changing the PC₂₀ threshold from 8 to 16 mg/mL. In this population or those generalizable to it, for white or nonatopic patients, a negative MCT result does not exclude the presence of asthma.

The second biomarker examined was periostin as a potential indicator of eosinophilic inflammation. Eosinophilic inflammation of the airways is one mechanism among several responsible for the pathogenesis of asthma.⁵⁰ Asthma resulting from eosinophilic T_H2-driven inflammation is steroid responsive and might also respond to antibodies directed against T_H2 cytokines, such as IL-5, whereas other types of asthma might not respond as well. Directly sampling airway eosinophils is technically difficult and might not be feasible in clinical settings. Therefore a noninvasive biomarker of airway eosinophilic inflammation would be useful for patient selection in clinical research and as an indicator of responsiveness to therapy, particularly in the small but important set of patients who are steroid resistant.⁵¹ Jia et al⁵² found that levels of serum periostin, a matricellular protein associated with fibrosis the levels of which correlate with bronchial IL-13 and IL-5 expression, is a biomarker of airway eosinophilia. Indeed, serum periostin was recently used as a surrogate for IL-13 activity in blood and airways in a recent study of lebrikizumab, an mAb to IL-13.⁵³ Jia et al⁵² found that serum periostin concentrations were higher in asthmatic patients with airway hypereosinophilia. Although periostin levels did not correlate with ACQ scores or FEV₁, the investigators noted they were better discriminators than blood eosinophil counts or fraction of inhaled nitric oxide. However, an accompanying editorial cautions that periostin is not specific to asthma or airway epithelium and might be related to other processes, including cancer in other organs.⁵¹

Goleva et al⁵⁴ considered products of PBMCs as biomarkers that might distinguish steroid-responsive versus steroid-resistant patients with severe asthma. The PBMCs of steroid-resistant patients had higher baseline levels of the mitogen-induced kinase phosphatase 1, IL-8, and glucocorticoid receptor β but were less responsive to the suppression of dexamethasone by TNF- α and IL-8. The significance of these observations awaits further investigation.

In 2012, there were several assessments of patient-reported asthma outcome measures. Bime et al⁵⁵ further assessed the reliability, validity, and responsiveness to change of the Asthma Symptom Utility Index, the most widely used recall questionnaire of symptoms, which is considered promising by the Asthma Outcomes Workshop. The data analyzed were from 1648 asthmatic adults participating in 2 trials conducted by the American Lung Association Asthma Clinical Research Centers. The researchers also determined a minimal important difference of 0.09.

New composite measures were among these patient-reported outcomes. Composite measures describe several constructs and, as such, have the potential to contribute more information than any of the components alone if they are succinct and not

burdensome to patients or researchers.⁵⁶ Greenberg et al⁵⁷ proposed and validated an Asthma Disease Activity score, both a 6-item and a 4-item version, to gauge response to treatment. This study used data from montelukast phase III trials. As a composite measure, the authors note it has the advantage of capturing several aspects of disease activity, and these component variables can be weighted. Investigators from the National Institutes of Health–supported Inner City Asthma Consortium developed and validated the Composite Asthma Severity Index for use in children and adolescents.⁵⁸ The tool was developed to measure composites of severity as described in the Expert Panel Report 3 (EPR-3) “Guidelines for the diagnosis and management of asthma”⁵⁹: impairment and risk of exacerbations and the amount of medication to achieve control.

The Asthma Outcomes Workshop also considered possible mediators of outcome: environmental, social, or individual factors that might influence patient self-management. Rosas-Salazar et al⁶⁰ described the effect of health literacy, a possible mediator, on patient-provider communication and proposed a conceptual model linking health literacy and asthma outcomes. Patel et al⁶¹ reported the 6-month validation of an electronic monitoring device, the Smartinhaler (Nexus6 Limited, Auckland, New Zealand), for measuring inhaled steroid adherence, a potentially important mediator of asthma outcomes. The monitor can also record β -agonist use as a measure of symptoms.

Using information technology and more on biomarkers

Management involves potential new therapeutics, the use of biomarkers, and, increasingly, the use of information technology. The electronic health record, with its patient portals and platforms for communication between health care providers and patients, holds great potential for personalizing and improving medical care.⁶² Information technology also allows rapid sequencing and interpretation of genomic information in ways that will have increasing clinical applicability and increasing potential for personalizing medicine.⁶² Use of technology will also allow increasing use of gene biomarkers to identify patients and access care.

Pertinent to the discussion on biomarkers above, this year, the Best Adjustment Strategy for Asthma in the Long Term (BASALT) randomized controlled trial was published.⁶³ Sponsored by the National Heart, Lung, and Blood Institute’s Asthma Clinical Research Network, it was a comparison of physician-based, biomarker-based (exhaled nitric oxide), or symptom-based (as needed inhaled steroid) strategies for the adjustment of ICS therapy in adults with mild-to-moderate asthma. The primary outcome was time to first exacerbation of asthma. In 36 weeks of observation, the use of biomarker-based or symptom-based adjustment of ICSs was not superior to physician assessment and treatment according to standard care based on guidelines from the EPR-3. This report also adds to our knowledge of when ICSs can be used intermittently according to symptoms.

Therapeutics

As noted above, mechanistic studies inform the next generation of asthma therapeutics. Emphasizing the immunologic mechanisms, new current and future therapeutics were reviewed by Barnes.⁶⁴ New approaches to current therapeutics include development of ICSs designed to have fewer systemic and local side

effects, once-daily β -agonists, and the adaptation from COPD of the use of long-acting muscarinic antagonists (eg, tiotropium) as a possible effective addition in patients with severe asthma to ICSs and β -agonist bronchodilators.⁶⁵ The drugs in development should target specific inflammatory mechanisms and be steroid sparing, such as the IL-5 blocking mAbs mepolizumab and reslizumab as inhibitors of T_H2 -like inflammation in asthmatic patients.^{64,66} A recent multicenter trial enrolled patients with evidence of eosinophilic inflammation requiring at least 2 bursts of steroids in the past year; 616 subjects were randomized to mepolizumab at 3 different doses or placebo for 12 months. The mepolizumab-treated patients had fewer asthma exacerbations and lower blood and sputum eosinophil counts, but their FEV₁, Asthma Quality of Life Questionnaire scores, and ACQ scores did not significantly differ. Thus there is more to learn about identifying the best patients for each drug, the long-term effectiveness and safety of the therapeutics, and their potential role in related diseases, such as other eosinophilic diseases.⁶⁷ As noted earlier, this is also relevant to studies of vitamin D in asthma. Goleva et al⁶⁸ measured serum 25-OH-vitamin D and IgE levels in asthmatic adults and children, more than 75% using ICSs, and showed that vitamin D levels were inversely associated with serum IgE levels and daily ICS doses among the pediatric but not adult patients. Whether vitamin D supplementation will improve asthma control in children or adults remains unresolved.

Adverse reactions

Postmarketing surveillance of medications is essential because pre-US Food and Drug Administration approval experience is relatively limited, and thus adverse drug reactions associated with a drug might not be apparent before marketing. There had been concern that the use of omalizumab might be associated with an increased risk of malignancy. To address this concern, Busse et al⁶⁹ pooled data from 67 phase I to phase IV clinical trials involving 11,459 patients, 7,789 receiving omalizumab, for more than 2000 patient years. The primary analysis was of 32 randomized controlled trials, in which 4254 patients received omalizumab. Malignancies were observed in 14 of these patients and in 11 of the 3178 patients receiving placebo. Thus it is reassuring that no association was found between omalizumab treatment and risk of malignancy, although, as the authors note, longer follow-up of patients is needed, including postmarketing surveillance data.

The safety of montelukast was examined in 2 reports in 2012, one focusing on birth defects and another on cardiovascular risk. Reassuring was a report by Nelsen et al,⁷⁰ who reviewed insurance claims in more than 50,000 pregnancies and found no evidence to support a causal relationship between montelukast and limb reduction or other birth defects. Leukotriene inhibitors inhibit the leukotriene pathway that has been associated with increased risk of cardiovascular disease. Ingelsson et al⁷¹ examined a Swedish population-based cohort and found no association of montelukast with either myocardial infarction or stroke. In a *post hoc* analysis the authors found lower risk of recurrent myocardial infarction in male subjects prescribed montelukast, but the analysis does not adjust for other comorbidities (ie, whether those prescribed montelukast were healthier).

Most important among questions of drug safety, is the controversy surrounding the safety of long-acting β -agonists (LABAs) described by Szeffler and Busse.⁷² They note the recent meta-analysis of Brozek et al⁷³ reporting worse asthma quality of

TABLE I. Key advances in the care of adults with asthma reported in the *Journal of Allergy and Clinical Immunology* in 2012

- Periostin has potential as a systemic marker of eosinophilic airway inflammation in asthmatic patients.⁵²
- *FLG*-null mutations are associated with asthma, and asthmatic patients with these defects, especially those with nonatopic asthma, might be especially predisposed to the adverse effects of tobacco smoking.¹¹
- Gene-environment interactions, including a time variable, help explain the determinants and prevalence of diseases like asthma.²⁰
- Composite measures used in asthma studies have potential for providing unique patient-centered information.⁵⁶⁻⁵⁸
- Management of disease increasingly will be informed by the use of information technology for applications as diverse as the electronic health record and rapidly sequencing and interpreting genomic information.⁶²
- Competitive swimmers who swim in chlorinated pools have increased risk of airway responsiveness to methacholine and exercise-induced bronchospasm and of having inflammatory and remodeling changes on bronchial biopsy.³⁶
- A meta-analysis found discontinuing LABA therapy in adults with asthma controlled by combination ICSs and LABAs was associated with a decrease in asthma quality of life and asthma control and fewer symptom-free days.⁷³
- A pooled analysis of clinical trials found no association between omalizumab treatment and risk of malignancy.⁶⁹
- In a retrospective analysis of insurance claims of live births, no association was found between montelukast and limb reduction or other birth defects.⁷⁰

life, asthma control, and fewer symptom-free days in patients whose LABAs were discontinued after asthma control was achieved with an ICS-LABA combination. It is noteworthy that the investigators found only 5 trials among 1492 screened that satisfied their study criteria of randomized controlled trials of patients of at least 4 years of age with asthma requiring treatment with an ICS and a LABA and with discontinuation of a LABA compared with continued use of a LABA and an ICS. Szeffler and Busse,⁷² respectively, chair the pediatric and adult steering committees of the ongoing large US Food and Drug Administration-requested study of LABA safety in children and adults. They worry that this unresolved issue is impairing development and approval of newer asthma medications. These authors provide a number of suggestions for clinicians that allow more flexibility and individualization and tailoring of regimens for patients while awaiting the results of the large studies. These include consideration of the variability of the disease, the risk benefits of changing either the ICS or the LABA, the time of year when making changes, patient education and action plan, the ability to assess and the reliability of various biomarkers, and the availability and risk/benefit ratio of alternate therapies. They conclude that in the meantime there are no data to support a change from the EPR-3 approach for selecting therapy and that current research does not guide how best to step down therapy. At least 1 study does not support withdrawing the LABA.⁷³

CONCLUSION

The future is likely to bring new management and therapeutic interventions as the relevant immunology and gene-environment-time interactions are better understood (Table I).

I gratefully acknowledge Anita T. Gewurz, MD, for her careful review and invaluable and insightful suggestions.

REFERENCES

1. Apter AJ. Advances in adult asthma diagnosis and treatment and health outcomes, education, delivery, and quality in 2011: what goes around comes around. *J Allergy Clin Immunol* 2012;129:69-75.
2. Szefer SJ. Advances in pediatric asthma in 2011: moving forward. *J Allergy Clin Immunol* 2012;129:60-8.
3. Farah CS, King GG, Brown NJ, Downie SR, Kermode JA, Hardaker KM, et al. The role of the small airways in the clinical expression of asthma in adults. *J Allergy Clin Immunol* 2012;129:381-7.e1.
4. Chang PJ, Bhavsar PK, Michaeloudes C, Khorasani N, Chung KF. Corticosteroid insensitivity of chemokine expression in airway smooth muscle of patients with severe asthma. *J Allergy Clin Immunol* 2012;130:877-85.e5.
5. Meyer N, Christoph J, Makrinioti H, Indermitte P, Rhyner C, Soyka M, et al. Inhibition of angiogenesis by IL-32: possible role in asthma. *J Allergy Clin Immunol* 2012;129:964-73.e7.
6. Jones CP, Gregory LG, Causton B, Campbell GA, Lloyd CM. Activin A and TGF- β promote T(H)9 cell-mediated pulmonary allergic pathology. *J Allergy Clin Immunol* 2012;129:1000-10.e3.
7. Munitz A, Foster PS. T(H)9 cells: in front and beyond T(H)2. *J Allergy Clin Immunol* 2012;129:1011-3.
8. Bauer RN, Brighton LE, Mueller L, Xiang Z, Rager JE, Fry RC, et al. Influenza enhances caspase-1 in bronchial epithelial cells from asthmatic volunteers and is associated with pathogenesis. *J Allergy Clin Immunol* 2012;130:958-67.e14.
9. Hernandez ML, Herbst M, Lay JC, Alexis NE, Brickey WJ, Ting JP, et al. Atopic asthmatic patients have reduced airway inflammatory cell recruitment after inhaled endotoxin challenge compared with healthy volunteers. *J Allergy Clin Immunol* 2012;130:869-76.e2.
10. Kumar R, Williams LK, Kato A, Peterson EL, Favoreto S Jr, Hulse K, et al. Genetic variation in B cell-activating factor of the TNF family (BAFF) and asthma exacerbations among African American subjects. *J Allergy Clin Immunol* 2012;130:996-9.e6.
11. Berg ND, Husemoen LL, Thuesen BH, Hersoug LG, Elberling J, Thyssen JP, et al. Interaction between flaggrin null mutations and tobacco smoking in relation to asthma. *J Allergy Clin Immunol* 2012;129:374-80, e1-2.
12. Arbes SJ Jr. Do all asthmatics with atopy have atopic asthma? *J Allergy Clin Immunol* 2012;130:1202-4.
13. Du R, Litonjua AA, Tantisira KG, Lasky-Su J, Sunyaev SR, Klanderman BJ, et al. Genome-wide association study reveals class I MHC-restricted T cell-associated molecule gene (CRTAM) variants interact with vitamin D levels to affect asthma exacerbations. *J Allergy Clin Immunol* 2012;129:368-73, e1-5.
14. Tsitsiou E, Williams AE, Moschos SA, Patel K, Rossios C, Jiang X, et al. Transcriptome analysis shows activation of circulating CD8+ T cells in patients with severe asthma. *J Allergy Clin Immunol* 2012;129:95-103.
15. Ziegler SF. Thymic stromal lymphopoietin and allergic disease. *J Allergy Clin Immunol* 2012;130:845-52.
16. Shikotra A, Choy DF, Ohri CM, Doran E, Butler C, Hargadon B, et al. Increased expression of immunoreactive thymic stromal lymphopoietin in patients with severe asthma. *J Allergy Clin Immunol* 2012;129:104-11, e1-9.
17. Chaudhuri R, McSharry C, Brady J, Donnelly I, Grierson C, McGuinness S, et al. Sputum matrix metalloproteinase-12 in patients with chronic obstructive pulmonary disease and asthma: relationship to disease severity. *J Allergy Clin Immunol* 2012;129:655-63.e8.
18. Li X, Ampleford EJ, Howard TD, Moore WC, Torgerson DG, Li H, et al. Genome-wide association studies of asthma indicate opposite immunopathogenesis direction from autoimmune diseases. *J Allergy Clin Immunol* 2012;130:861-8.e7.
19. Myers RA, Himes BE, Gignoux CR, Yang JJ, Gauderman WJ, Rebordosa C, et al. Further replication studies of the EVE Consortium meta-analysis identifies 2 asthma risk loci in European Americans. *J Allergy Clin Immunol* 2012 [Epub ahead of print].
20. Kauffmann F, Demenais F. Gene environment interactions in asthma and allergic diseases: challenges and perspectives. *J Allergy Clin Immunol* 2012 [Epub ahead of print].
21. Daley D, Park JE, He JQ, Yan J, Akhabir L, Stefanowicz D, et al. Associations and interactions of genetic polymorphisms in innate immunity genes with early viral infections and susceptibility to asthma and asthma-related phenotypes. *J Allergy Clin Immunol* 2012 [Epub ahead of print].
22. Wegienka G, Joseph CL, Havstad S, Zoratti E, Ownby D, Johnson CC. Sensitization and allergic histories differ between black and white pregnant women. *J Allergy Clin Immunol* 2012;130:657-62.e2.
23. Rumpel JA, Ahmedani BK, Peterson EL, Wells KE, Yang M, Levin AM, et al. Genetic ancestry and its association with asthma exacerbations among African American subjects with asthma. *J Allergy Clin Immunol* 2012 [Epub ahead of print].
24. Ledford DK, Burks AW, Ballou M, Cox L, Wood RA, Casale TB. Statement regarding "The public health benefits of air pollution control." *J Allergy Clin Immunol* 2012;130:24.
25. Li J, Ewart G, Kraft M, Finn PW. The public health benefits of air pollution control. *J Allergy Clin Immunol* 2012;130:22-3.
26. Laumbach RJ, Kipen HM. Respiratory health effects of air pollution: update on biomass smoke and traffic pollution. *J Allergy Clin Immunol* 2012;129:3-13.
27. Leung TF, Ko FW, Wong GW. Roles of pollution in the prevalence and exacerbations of allergic diseases in Asia. *J Allergy Clin Immunol* 2012;129:42-7.
28. Bauer RN, Diaz-Sanchez D, Jaspers I. Effects of air pollutants on innate immunity: the role of Toll-like receptors and nucleotide-binding oligomerization domain-like receptors. *J Allergy Clin Immunol* 2012;129:14-26.
29. Ji H, Khurana Hershey GK. Genetic and epigenetic influence on the response to environmental particulate matter. *J Allergy Clin Immunol* 2012;129:33-41.
30. Yang IV, Schwartz DA. Epigenetic mechanisms and the development of asthma. *J Allergy Clin Immunol* 2012 [Epub ahead of print].
31. Ziska LH, Beggs PJ. Anthropogenic climate change and allergen exposure: the role of plant biology. *J Allergy Clin Immunol* 2012;129:27-32.
32. Knutsen AP, Bush RK, Demain JG, Denning DW, Dixit A, Fairs A, et al. Fungi and allergic lower respiratory tract diseases. *J Allergy Clin Immunol* 2012;129:280-93.
33. Heederik D, von Mutius E. Does diversity of environmental microbial exposure matter for the occurrence of allergy and asthma? *J Allergy Clin Immunol* 2012;130:44-50.
34. von Mutius E. A fascinating look at the world with a new microscope. *J Allergy Clin Immunol* 2012;129:1202-3.
35. Ursell LK, Clemente JC, Rideout JR, Gevers D, Caporaso JG, Knight R. The interpersonal and intrapersonal diversity of human-associated microbiota in key body sites. *J Allergy Clin Immunol* 2012;129:1204-8.
36. Bougault V, Loubaki L, Joubert P, Turmel J, Couture C, Laviolette M, et al. Airway remodeling and inflammation in competitive swimmers training in indoor chlorinated swimming pools. *J Allergy Clin Immunol* 2012;129:351-8.e1.
37. Gershon A, Guan J, Victor JC, Wang C, To T. The course of asthma activity: a population study. *J Allergy Clin Immunol* 2012;129:679-86.
38. Koinis-Mitchell D, Craig T, Esteban CA, Klein RB. Sleep and allergic disease: a summary of the literature and future directions for research. *J Allergy Clin Immunol* 2012 [Epub ahead of print].
39. Gingo MR, Wenzel SE, Steele C, Kessinger CJ, Lucht L, Lawther T, et al. Asthma diagnosis and airway bronchodilator response in HIV-infected patients. *J Allergy Clin Immunol* 2012;129:708-14.e8.
40. Busse WW, Morgan WJ, Taggart V, Togias A. Asthma outcomes workshop: overview. *J Allergy Clin Immunol* 2012;129(suppl):S1-8.
41. Akinbami LJ, Sullivan SD, Campbell JD, Grundmeier RW, Hartert TV, Lee TA, et al. Asthma outcomes: healthcare utilization and costs. *J Allergy Clin Immunol* 2012;129(suppl):S49-64.
42. Cloutier MM, Schatz M, Castro M, Clark N, Kelly HW, Mangione-Smith R, et al. Asthma outcomes: composite scores of asthma control. *J Allergy Clin Immunol* 2012;129(suppl):S24-33.
43. Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA Jr, Gern J, et al. Asthma outcomes: exacerbations. *J Allergy Clin Immunol* 2012;129(suppl):S34-48.
44. Krishnan JA, Lemanske RF Jr, Canino GJ, Elward KS, Kattan M, Matsui EC, et al. Asthma outcomes: symptoms. *J Allergy Clin Immunol* 2012;129(suppl):S124-35.
45. Rand CS, Wright RJ, Cabana MD, Foggs MB, Halterman JS, Olson L, et al. Mediators of asthma outcomes. *J Allergy Clin Immunol* 2012;129(suppl):S136-41.
46. Szefer SJ, Wenzel S, Brown R, Erzurum SC, Fahy JV, Hamilton RG, et al. Asthma outcomes: biomarkers. *J Allergy Clin Immunol* 2012;129(suppl):S9-23.
47. Tepper RS, Wise RS, Covar R, Irvin CG, Kercsmar CM, Kraft M, et al. Asthma outcomes: pulmonary physiology. *J Allergy Clin Immunol* 2012;129(suppl):S65-87.
48. Wilson SR, Rand CS, Cabana MD, Foggs MB, Halterman JS, Olson L, et al. Asthma outcomes: quality of life. *J Allergy Clin Immunol* 2012;129(suppl):S88-123.
49. Sumino K, Sugar EA, Irvin CG, Kaminsky DA, Shade D, Wei CY, et al. Methacholine challenge test: diagnostic characteristics in asthmatic patients receiving controller medications. *J Allergy Clin Immunol* 2012;130:69-75.e6.
50. Ingram JL, Kraft M. IL-13 in asthma and allergic disease: asthma phenotypes and targeted therapies. *J Allergy Clin Immunol* 2012;130:829-42.
51. Nair P, Kraft M. Serum periostin as a marker of T(H)2-dependent eosinophilic airway inflammation. *J Allergy Clin Immunol* 2012;130:655-6.
52. Jia G, Erickson RW, Choy DF, Moscoso S, Wu LC, Solberg OD, et al. Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. *J Allergy Clin Immunol* 2012;130:647-54.e10.

53. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011;365:1088-98.
54. Goleva E, Jackson LP, Gleason M, Leung DY. Usefulness of PBMCs to predict clinical response to corticosteroids in asthmatic patients. *J Allergy Clin Immunol* 2012;129:687-93.e1.
55. Bime C, Wei CY, Holbrook JT, Sockrider MM, Revicki DA, Wise RA. Asthma Symptom Utility Index: reliability, validity, responsiveness, and the minimal important difference in adult asthmatic patients. *J Allergy Clin Immunol* 2012;130:1078-84.
56. Wilson SR. Adding measures to the asthma outcome measurement toolbox: new findings, new issues. *J Allergy Clin Immunol* 2012;130:1085-6.
57. Greenberg S, Liu N, Kaur A, Lakshminarayanan M, Zhou Y, Nelsen L, et al. The Asthma Disease Activity Score: a discriminating, responsive measure predicts future asthma attacks. *J Allergy Clin Immunol* 2012;130:1071-7.e10.
58. Wildfire JJ, Gergen PJ, Sorkness CA, Mitchell HE, Calatroni A, Kattan M, et al. Development and validation of the Composite Asthma Severity Index—an outcome measure for use in children and adolescents. *J Allergy Clin Immunol* 2012;129:694-701.
59. Expert Panel Report-3: guidelines for the diagnosis and management of asthma. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed October 18, 2012.
60. Rosas-Salazar C, Apter AJ, Canino G, Celedon JC. Health literacy and asthma. *J Allergy Clin Immunol* 2012;129:935-42.
61. Patel M, Pilcher J, Chan A, Perrin K, Black P, Beasley R. Six-month in vitro validation of a metered-dose inhaler electronic monitoring device: implications for asthma clinical trial use. *J Allergy Clin Immunol* 2012 [Epub ahead of print].
62. Weiss ST. New approaches to personalized medicine for asthma: where are we? *J Allergy Clin Immunol* 2012;129:327-34.
63. Calhoun WJ, Ameredes BT, King TS, Icitovic N, Bleecker ER, Castro M, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA* 2012;308:987-97.
64. Barnes PJ. Severe asthma: advances in current management and future therapy. *J Allergy Clin Immunol* 2012;129:48-59.
65. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012;367:1198-207.
66. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.
67. Hashimoto S, Bel EH. Targeting IL-5 in severe asthma: a DREAM come true? *Lancet* 2012;380:626-7.
68. Goleva E, Searing DA, Jackson LP, Richers BN, Leung DY. Steroid requirements and immune associations with vitamin D are stronger in children than adults with asthma. *J Allergy Clin Immunol* 2012;129:1243-51.
69. Busse W, Buhl R, Fernandez Vidaurre C, Blogg M, Zhu J, Eisner MD, et al. Omalizumab and the risk of malignancy: results from a pooled analysis. *J Allergy Clin Immunol* 2012;129:983-9.e6.
70. Nelsen LM, Shields KE, Cunningham ML, Stoler JM, Bamshad MJ, Eng PM, et al. Congenital malformations among infants born to women receiving montelukast, inhaled corticosteroids, and other asthma medications. *J Allergy Clin Immunol* 2012;129:251-4, e1-6.
71. Ingelsson E, Yin L, Back M. Nationwide cohort study of the leukotriene receptor antagonist montelukast and incident or recurrent cardiovascular disease. *J Allergy Clin Immunol* 2012;129:702-7.e2.
72. Szeffler S, Busse W. The LABA controversy in asthma: troublesome times. *J Allergy Clin Immunol* 2012 [Epub ahead of print].
73. Brozek JL, Kraft M, Krishnan JA, Cloutier MM, Lazarus SC, Li JT, et al. Long-acting beta2-agonist step-off in patients with controlled asthma: systematic review with meta-analysis. *Arch Intern Med* 2012 [Epub ahead of print].