

Advances in adult asthma diagnosis and treatment in 2013

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In 2013, several themes emerged: (1) a dedicated search for new therapies using new mechanisms; (2) the importance of the plasticity of the immune system (eg, that molecules that mediate inflammation in one setting can promote its resolution and return to homeostasis in other circumstances); (3) the complex role of viruses in asthma exacerbations; (4) the similarities and differences among asthma, asthma in smokers, and chronic obstructive pulmonary disease; and (5) the importance of understanding asthma phenotypes and their stability over time. Once new therapeutics pass the initial clinical trials, patient-oriented and real-world research will be needed. (J Allergy Clin Immunol 2014;133:49-56.)

Key words: Asthma, adults, inhaled corticosteroids, asthma management

For several years, it has been my task to review the advances in clinical asthma in adults¹ alongside Dr Szefer's corresponding and excellent reviews of advances in pediatric asthma.² This assignment allows me to identify themes that have evolved over the past year based on the collective thoughts of the investigators and to get a glimpse of where their research is headed. In 2013, several themes emerged: (1) a dedicated search for new therapies using new mechanisms; (2) the importance of the plasticity of the immune system (eg, that molecules that mediate inflammation in one setting can promote its resolution and return to homeostasis in other circumstances); (3) the complex role of viruses in asthma exacerbations; (4) the similarities and differences among asthma, asthma in smokers, and chronic obstructive pulmonary disease (COPD)³; and (5) the importance of understanding asthma phenotypes and their stability over time. These themes organize this review.

MECHANISMS OF DISEASE

In recent years, there have been few commercially available new drugs with novel mechanisms for treating asthma. Thus studies of mechanisms are important for their potential therapeutic implications. For example, protectin D1 is an anti-inflammatory lipid mediator that promotes resolution of inflammation by stimulating clearance of apoptotic cells and debris.

Abbreviations used

ACQ:	Asthma Control Questionnaire
C _{alv} NO:	Alveolar fraction of exhaled nitric oxide
COPD:	Chronic obstructive pulmonary disease
CRTH2:	Chemoattractant receptor homologous molecule expressed on T _H 2 cells
EBC:	Exhaled breath condensate
FENO:	Fraction of exhaled nitric oxide
ICS:	Inhaled corticosteroid
LABA:	Long-acting β -agonist
OA:	Occupational asthma
PGD ₂ :	Prostaglandin D ₂
PROM:	Patient-reported outcome measure
SLIT:	Sublingual immunotherapy
TLR:	Toll-like receptor
WEA:	Work-exacerbated asthma
WRA:	Work-related asthma

Previously, it was found to attenuate eosinophilic inflammation in a mouse model. Studying eosinophils from peripheral blood of asthmatic and healthy subjects, Miyata et al⁴ observed that protectin D1 is produced by human eosinophils and its production is impaired in patients with severe asthma. This finding has implications for protectin D1 both as a biomarker and a potential therapeutic agent.

T-cell influences on asthma are understood to be complex, involving several T-cell subsets and their many cytokines, all with genetic variation, and are influenced by the microenvironment, which determines phenotypic plasticity and the resulting heterogeneity of response to therapeutics (Fig 1).⁵ One such is IL-22, which was previously shown to have proinflammatory and anti-inflammatory properties in mice but has not been extensively studied in human lung disease for its therapeutic potential. Pennington et al⁶ found that IL-22 might have a tissue-restricted anti-inflammatory role: it antagonized the effect of IFN- γ on human bronchial epithelial cells from healthy and asthmatic subjects. Interestingly, Nanzer et al,⁷ examining PBMC cultures from patients with severe asthma, found increased levels of T_H17 cytokines, including IL-22 and IL-17A, which were inhibited by 1,25(OH)₂D₃. They proposed a possible steroid-enhancing role of vitamin D in asthmatic patients, particularly in this phenotype.

The *IL33* gene was first described in the setting of cedar pollinosis. IL-33 promotes IL-4, IL-5, and IL-13 production and eosinophilic airway inflammation. Grotenboer et al⁸ review the mechanisms by which variants of genes for IL-33 and its receptor can increase asthma susceptibility. Gabriele et al⁹ have developed a murine model of allergic asthma to cypress pollen that links it to the T_H2-polarizing activity of dendritic cells involving IL-33 and its receptor. This model could be adapted for testing the dendritic cell- and IL-33-modulating effects of potential treatments for allergic asthma.

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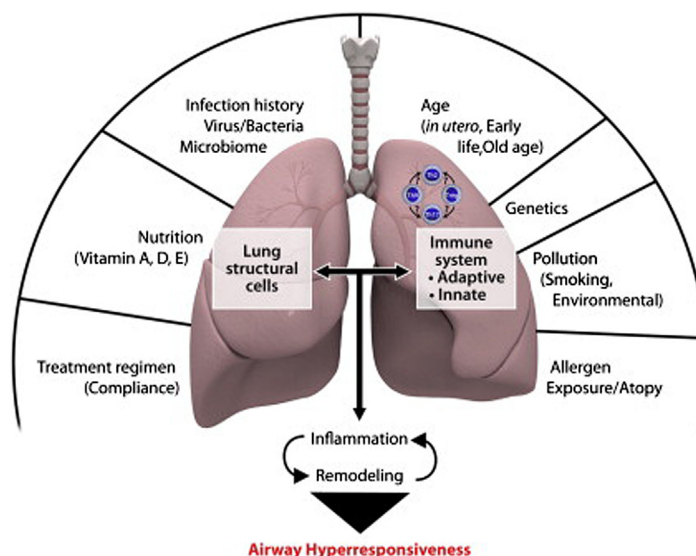


FIG 1. Interplay between environmental exposures, lung structural cells, and immune cells in determining asthma pathophysiology. The lungs are continuously exposed to numerous environmental exposures, which determine responses from both lung structural cells (primarily epithelial cells) and immune cells in a susceptible asthmatic patient. The microenvironment seems critical in determining T effector cell function and likely contributes to alterations in T-cell phenotype and determines development of T_H lineage plasticity. Reprinted with permission from Lloyd and Saglani.⁵

Viruses play a role in asthma inception and exacerbations and might contribute to atopic development.¹⁰ In this year's *Journal*, Kaiko et al¹¹ identified a new defect in the mouse Toll-like receptor (TLR) 7 gene. Because TLR7 is a product of plasmacytoid dendritic cells, the host's immediate source of type I interferon in response to virus, defects in TLR7 can increase T_H2 responsiveness, suggesting another venue by which virus-related asthma exacerbation can be studied in human subjects and possibly treated. Campbell-Harding et al¹² found that IFN- β upregulates IL-13 receptor $\alpha 2$ and suppresses responsiveness to IL-13 in fibroblasts exposed to double-stranded RNA used as an *in vitro* mimic of a viral respiratory tract infection. Thus enhancing IL-13 receptor $\alpha 2$ activity could have therapeutic benefit in asthmatic patients. In another study closer to clinical relevance and also informed by response to viral infection, Beeh et al¹³ conducted a randomized, controlled double-blind, phase II study of the TLR9 agonist QbG10 (bacteriophage Q β -derived virus-like particle with CpG-motif G10 inside). QbG10 is a recombinant viral protein shell filled with DNA and a ligand for TLR9. It is postulated to stimulate T_H1 and suppress T_H2 responsiveness. QbG10 or placebo was administered to 63 patients whose symptoms were stable with inhaled corticosteroids (ICSs). Patients were maintained on ICSs for 4 weeks and then entered an 8-week period of ICS withdrawal. QbG10 was associated with improved asthma control. FEV₁ remained constant while worsening in the control group.

Finally, Barnes¹⁴ reviewed mechanisms of corticosteroid resistance in asthmatic patients that might include alteration of glucocorticoid receptor activities, which are detailed by Oakley and Cidlowski¹⁵ and likely have future therapeutic relevance.

GENETIC INFLUENCES OF CLINICAL RELEVANCE

Li et al¹⁶ conducted meta-analyses of genome-wide association studies of lung function measured as FEV₁ percent predicted in

1544 patients from 4 white populations of European origin whose asthma severity ranged from mild to severe. They confirmed 7 of 28 previously identified lung function loci and also found that genes involved in airway structure and remodeling were associated with lung function in the general population and those with asthma. Interestingly, 4 of 32 identified loci associated with FEV₁ were T_H1 or IL-12 (stimulator of IFN- γ production) cytokine genes participating in antiviral/bacterial immune responses.

Microchimerism is the presence of small numbers of non-self cells in a subject. Maternal microchimerism, the presence of maternal cells in offspring, occurs in up to 55% of healthy children and has been associated with autoimmune disease. Thompson et al¹⁷ found lower rates of asthma development among subjects with maternal microchimerism, suggesting the opposite effects of the accompanying immune dysregulation on autoimmunity and asthma.

Telomeres are terminal regions of chromosomes, and their shortening is associated with cell senescence and apoptosis. In a brief report Kyoh et al¹⁸ noted that leukocytes of asthmatic patients, as in patients with COPD, demonstrate accelerated aging, as judged based on telomere length.

ENVIRONMENTAL EXPOSURES: INNER AND OUTER

Research on the association of microbes and asthma has until now focused on a limited number of organisms identified by means of culture or PCR techniques. Marri et al¹⁹ used metagenomic methods to analyze the entire lower respiratory tract microbiome. Using induced sputum from 10 young asthmatic and 10 nonasthmatic adults, they found those with mild asthma had an altered microbial composition similar to that of patients with more severe asthma and different from that seen in nonasthmatic subjects. Organisms from the Proteobacteria phylum (which includes the gram-negative species *Escherichia coli*, *Proteus*,

Haemophilus, and *Moraxella*) were overabundant in asthmatic subjects, whereas organisms from the Firmicutes (gram-positive species, including *Bacillus*, *Staphylococcus*, and *Streptococcus*) and Actinobacteria phyla were not. Therefore the Proteobacteria might play a proinflammatory role in the development of asthma. The sputum samples of asthmatic subjects showed greater microbial diversity as well. However, only 60% of the bacteria could be assigned to a bacterial family, suggesting others found in sputum have not yet been characterized. Because the asthmatic patients had mild disease and were not taking ICSs, the difference between groups was not attributable to corticosteroid therapy. These tantalizing findings and techniques are in need of further exploration for potential diagnostic and therapeutic implications.

Work-related asthma (WRA) includes occupational asthma (OA) related to a sensitizing substance or irritant at work, and work-exacerbated asthma (WEA), pre-existing or coincidental asthma exacerbated at work. WEA has received less attention than OA. Lemiere et al²⁰ conducted a prospective study of the clinical, functional, inflammatory, and cost-of-treatment differences between patients with WEA and those with OA compared with patients with non-WRA. They followed 154 subjects for 2 years: 53 with WEA, 68 with OA, and 33 with non-WRA. Those with WEA required more frequent prescriptions of ICSs, had a trend toward lower FEV₁, and were more likely to be smokers than those with OA. Moreover, induced sputum of subjects with WEA had less evidence of eosinophils. Patients with WEA and OA were more likely to change jobs and suffer loss of income than those with non-WRA, and their health care use and costs were 10-fold higher.

Although both cockroach and mouse allergens have been associated with inner-city asthma morbidity, a prospective study by Ahluwalia et al²¹ found mouse-specific IgE to be more strongly and consistently associated with asthma morbidity in 144 children living in Baltimore. Children were grouped by sensitization and exposure status (exposure measured as allergen in bed dust and bedroom floor dust). The mouse-specific IgE level, a measure of both sensitivity and exposure, was associated with acute care visits, decreased FEV₁/forced vital capacity ratios, fraction of exhaled nitric oxide (FENO) values, and bronchodilator reversibility. Cockroach sensitivity/exposure was associated with acute care visits and bronchodilator reversibility only when exposure was defined based on bedroom floor allergen levels. (Mouse allergen levels were higher in bed dust samples compared with cockroach allergen levels.) As noted in Ownby's commentary,²² these findings have potentially important public health implications for asthma management in urban and also nonurban settings where mouse allergen exposure is prevalent, particularly if it can be demonstrated that reducing exposure reduces asthma morbidity. An interesting caveat comes from Mueller et al,²³ who, by better defining the structure of the Bla g 1 cockroach allergen, anticipate improved standardization of assays and understanding of the function and allergenic potential of the protein.

Exposure to community violence is associated with increased asthma burden in children,²⁴ their caretakers,²⁴ and also adults with asthma.²⁵ In a prospective study Coogan et al²⁶ add to what we know about the toxicity of such exposures and their continued effects by showing abuse during childhood increases the risk of adult-onset asthma in African American women. The authors hypothesized that the persistent emotional and physiologic stress caused by abuse predisposes to asthma.

Finally, Felix et al²⁷ report that the zest of an orange contains allergen and that exposure might be associated with the generation of specific IgE and bronchospasm in susceptible subjects.

COURSE OF ASTHMA AND INFLUENCES ON ITS COURSE

Donohue et al²⁸ examined the alterations of lung structure, as determined by means of computed tomographic imaging in patients (mean age, 65 years) given a diagnosis of asthma as children (age up to 18 years) or young adults (19–45 years) or after age 45 years, by using data from the Multi-Ethnic Study of Atherosclerosis Lung Study. Asthma onset in childhood or young adulthood was associated with larger decreases in FEV₁, increased mean airway wall thickness, and narrower segmental airway lumens. Among those who smoked, there was greater lung attenuation, a measure of emphysematous change and hyperinflation.

Asthma is heterogeneous; hence defining distinct phenotypes might lead to a better understanding of asthma mechanisms, clinical course, and outcome of therapy and improved management.^{3,29,30} To do this, clinical characteristics are defined, and then subjects fitting the phenotype are examined for underlying immunologic characteristics. For example, the phenotype of childhood-onset asthma with reversible obstruction associated with T_H2 inflammation is perhaps the best studied; there is less known about the adult phenotypes. Amelink et al³¹ examined 176 patients with adult-onset asthma, 78 with severe disease, and 98 with mild-to-moderate disease. Patients with severe asthma were defined as having an Asthma Control Questionnaire (ACQ) score of greater than 1.5, had at least 2 exacerbations within the past year despite high-dose ICSs, and required a second controller medication. The researchers found that subjects with this severe disease phenotype were more likely to be nonatopic and to have more nasal symptoms and polyposis and higher levels of exhaled nitric oxide, blood neutrophil counts, and sputum eosinophilia. No significant differences were detected in sex, age, asthma duration, body mass index, or sputum neutrophil counts between the severe and less severely affected groups. Longitudinal studies are needed to better understand phenotypic stability.^{3,30}

Role of small airways in subjects with acute asthma

Small-airways dysfunction is receiving attention for its role in asthma.³² Thompson et al³³ used an inert gas washout technique to assess ventilation heterogeneity measured as convection and diffusion. The researchers examined acinar air ventilation heterogeneity and conductive ventilation heterogeneity in 18 hospitalized subjects compared with stable control subjects. These techniques are described in detail in an accompanying editorial by Kaminsky.³⁴ Thompson et al³³ determined that of these measures of small airway function, both acinar ventilation (diffusion) and ventilation conductance (convection) impairments are associated with unstable asthma, but acinar function is far more important and correlated with airflow obstruction and treatment requirements, supporting the importance of the contribution of peripheral lung function to asthma control. Additional support for the importance of the peripheral airways comes from Scichilone et al,³⁵ who measured the alveolar fraction of exhaled nitric oxide (C_{alv}NO) in 78 adults with mild untreated asthma. They found higher C_{alv}NO levels associated with a lack of asthma control. Among a subgroup of 55 subjects who underwent extrafine

ICS therapy thought to be more likely to reach the more peripheral airways, there was a significant improvement in the Asthma Control Test score correlating with baseline $C_{alv}NO$ levels.

Influence of tobacco smoke

Patients with mild-to-moderate asthma who smoke have worse control. Using data from the British Thoracic Society Severe Asthma Registry, Thomson et al³⁶ examined asthma control in 760 patients with severe asthma and found that current smokers have different sputum and blood inflammatory profiles and worse outcomes when compared with former smokers and those who never smoked. Current smokers had reduced proportions of sputum eosinophils and lower FENO values. Exsmokers had increased proportions of sputum neutrophils and similar proportions of sputum eosinophils and FENO values compared with never smokers, who were most likely to have the highest serum IgE levels to common environmental allergens. In a longitudinal study Perret et al³⁷ examined the interplay between the effects of lifetime asthma, smoking, and atopy on the development of fixed airflow obstruction in middle age. As a risk factor for fixed airflow obstruction in middle age, early-onset current clinical asthma was equivalent to a 33-pack-year history of smoking compared with a 24-pack-year history of smoking for late-onset current clinical asthma. Importantly, the investigators found active smoking and current clinical asthma both increased the risk of fixed airflow obstruction in middle age, particularly among those who are atopic. The children of smokers also have worse respiratory status. Kalliola et al³⁸ conducted a study of 3- to 7-year-old children with multiple-trigger wheeze and abnormal lung function and found that 43% were exposed to environmental tobacco smoke based on parental report. Among steroid-naïve children with multiple-trigger wheeze, maternal smoking was linked to a dose-dependent increase in FENO values and poorer lung function, as assessed by using impulse oscillometry.

Finally, adding to what is known about various phenotypes, in a population-based incident case-control study from South Finland, Lajunen et al³⁹ demonstrated that subjects with a family history of asthma were considerably more likely to have adult-onset asthma if exposed to secondhand tobacco smoke in a dose-dependent fashion: adjusted odds ratios were 1.97 (95% CI, 1.12-3.45) for exposure to secondhand smoke, 2.64 (95% CI, 1.65-4.24) for parental asthma, and 12.69 (95% CI, 3.44-46.91) for the joint effect.⁴⁰

Influence of physical training

Whether exercise has an effect on asthma course has been debated. In a Cochrane Review, Carson et al⁴¹ examined randomized trials of asthmatic patients over 8 years and found that exercise training was associated with improved cardiopulmonary fitness but not with other measures of pulmonary function, such as FEV₁. However, physical training was well tolerated, and the authors recommended encouragement of regular exercise in patients with stable asthma.

MANAGEMENT

Biomarkers for assessing clinical course and success of interventions

Management involves monitoring patients, and thus there is an ongoing interest in biomarkers as measures of process or

mechanism and of outcomes. Saito et al⁴² found that sputum and serum hydrogen sulfide levels might be useful biomarkers of neutrophilic inflammation and chronic airflow obstruction. Hydrogen sulfide, which is produced by many cell types, is a vasodilator and induces smooth muscle relaxation while inhibiting myocyte proliferation and IL-8 release. Sputum levels were negatively correlated with FEV₁ percent predicted and reversibility to albuterol and positively associated with increased sputum neutrophil percentages.

Kazani et al⁴³ measured levels of anti-inflammatory lipoxins and proinflammatory leukotrienes in exhaled breath condensate (EBC) as noninvasive biomarkers of asthma severity. Lipoxins were studied because they antagonize the effects of leukotrienes and help restore tissue homeostasis and promote immune defense. The researchers found higher concentrations of lipoxin A₄ and leukotriene B₄ in EBC of asthmatic patients in comparison with healthy control subjects, and the lipoxin/leukotriene ratio decreased with increasing asthma severity. Pinkerton et al⁴⁴ proposed using EBC to detect differential expression of microRNAs (small noncoding RNA nucleotides) as biomarkers of inflammation in patients with asthma and COPD compared with healthy adults. Thus EBC is becoming a useful source of markers of asthma and asthma severity in clinical research and might eventually have clinical application.

Bronchoprovocation tests were examined and discussed in *Journal* reports.⁴⁵ Guan et al⁴⁶ proposed a combination of an LTD₄ bronchoprovocation test and a methacholine bronchoprovocation test for identifying leukotriene-responsive asthmatic patients. More practically, Brannan et al⁴⁷ found that, like methacholine, the diagnostic sensitivity of inhaled mannitol is reduced in patients taking regular ICSs.

Sputum eosinophil and neutrophil percentages predict airway inflammation and asthma exacerbations.⁴⁸ Hastie et al⁴⁹ used data from the Severe Asthma Research Program to correlate additional accessible biomarkers (blood eosinophil counts, total serum IgE levels, FENO values, and FEV₁ percent predicted) with these cell percentages. They found that despite significant statistical associations, these biomarkers did not accurately predict sputum eosinophil and neutrophil percentages. This is a very interesting observation because, as Nair⁵⁰ points out, tests of potential agents against eosinophilic or neutrophilic inflammation must be implemented in patients with eosinophil- or neutrophil-driven disease, and as Hastie et al have shown, these patients might be difficult to identify. This is also fascinating when considering the study of Malinovschi et al,⁵¹ who, using a large sample from National Health and Nutrition Examination Survey, found intermediate and high FENO values and blood eosinophil counts independently associated with asthma diagnosis, wheeze, and asthma attacks but only weakly associated with each other. Of note, only intermediate or high blood eosinophil counts were independently associated with emergency department visits. These 2 biomarkers, FENO values and blood eosinophil counts, together provided additive information, suggesting markers of local and systemic eosinophilic inflammation are necessary in studying airways disease and that they might reflect different aspects of T_H2 inflammation.⁵² Clearly more research is needed, particularly as biologic therapies targeting T_H2 pathways become available for clinical trials.

Serum periostin is another biomarker generating much interest as an indirect measure of eosinophilic inflammation. Periostin is an extracellular matrix protein secreted by airway epithelial cells

and lung fibroblasts stimulated by IL-4 and IL-13. Periostin contributes to subepithelial thickening of the airways and remodeling. It has been found to be a predictor of airway eosinophilia in patients with severe asthma who remain symptomatic despite ICS therapy.⁵³ Kanemitsu et al⁵⁴ found higher serum periostin levels associated with a decrease in FEV₁ in patients receiving ICSs. They also found that polymorphisms of *POSTN*, the gene that encodes periostin, are related to higher serum periostin levels and a decrease in FEV₁. They conclude that serum periostin might be a useful biomarker for the development of airflow limitation in patients taking ICSs.

Measuring outcomes

Noting that asthma control is the primary goal of asthma management, Jia et al⁵⁵ compared 2 frequently used measures of asthma control: the Asthma Control Test (ACT) and the ACQ, with its 7-item (ACQ-7) and 6-item (ACQ-6) versions. The ACT and ACQ require the taker to recall, respectively, over 4 weeks and 1 week. The investigators examined data from 21 studies of 11,141 subjects who completed the ACT and 12,483 subjects who completed the ACQ. They found that although the ACT had good diagnostic accuracy for assessment of controlled asthma, neither questionnaire was useful for assessment of uncontrolled asthma: the ACT had poor accuracy, and the cutoff point for the ACQ has not been established. Understanding the role of questionnaires for measuring asthma control in clinical care and research requires further exploration.

Nonpharmacologic interventions

The efficacy and safety of bronchial thermoplasty are under investigation because it is a promising therapy for the 5% of asthmatic patients whose disease is severe. Wechsler et al⁵⁶ report on 162 of 190 treated patients completing 5 years of follow-up. In these patients respiratory adverse events and respiratory-related hospitalizations remained unchanged from years 2 through 5, and FEV₁ was stable. There was an 18% reduction in ICS dose. The original report of a randomized bronchial thermoplasty or sham-controlled trial showed improvement in quality of life in both groups.⁵⁷ Efficacy and safety require further investigation, but this is good news.

Literacy skills might influence a patient's ability to manage a chronic disease, such as asthma. Apter et al⁵⁸ assessed health literacy, which was measured as reading and numeracy skills, in adults with moderate or severe asthma. They then prospectively followed patients for the effect of literacy skills on electronically monitored ICS adherence and asthma outcomes. Although in unadjusted analyses better literacy skills were associated with better adherence, the adjusted analysis found only an association of higher literacy measures with better quality of life and asthma control. Thus interventions that account for and address the literacy needs of patients are required and might operate in ways other than strictly influencing ICS adherence.

Obesity is speculated to induce an inflammatory state that is implicated in asthma initiation and control. Fernandez-Boyanapalli et al⁵⁹ presented evidence that airway macrophages from obese adults have impaired efferocytosis, the clearance of apoptotic inflammatory cells, associated with inflammation measured by increased oxidant levels and decreased glucocorticoid responsiveness. This finding suggests weight control as a nonpharmacologic intervention.

Among asthmatic patients who smoke, Price et al⁶⁰ found that montelukast and fluticasone increased asthma control. They studied 1019 patients randomized to one of these medications or placebo with a mean smoking exposure of approximately 13 pack years and 0.79 packs per day. The percentage of asthma control days over 6 months was 45% (95% CI, 40.6% to 49.3%) for montelukast, 49.2% (95% CI, 44.9% to 53.5%) for fluticasone, and 39.1% (95% CI, 34.7% to 43.5%) for placebo. Those who smoked less than 11 pack years tended to demonstrate more benefit with fluticasone, whereas those with a longer smoking history tended to have more benefit from montelukast. The design included a 3-week, single-blind, placebo run-in period; thus smokers who were least adherent were likely to be excluded. This interesting study does not discount that the most important intervention in these patients is nonpharmacologic.

Therapeutics now and in the future

Sublingual immunotherapy for asthma. Sublingual immunotherapy (SLIT) has great therapeutic potential for allergic rhinitis and allergic asthma. It is convenient and safer than subcutaneous immunotherapy, but its effectiveness and duration of effect require study.⁶¹⁻⁶³ Lin et al⁶⁴ evaluated 63 randomized controlled trials involving 5131 patients from 4 to 74 years of age. They found strong evidence for improvement in asthma symptoms and moderate evidence for its decreasing rhinitis or rhinoconjunctivitis compared with the comparator and found reduced requirements for other medications. No life-threatening adverse events were observed. The investigators note more research is needed to identify optimal dosing strategies, duration of treatment, and relative benefits of single-compared with multiple-allergen therapy. Adherence also requires study.^{62,63} Kiel et al⁶⁵ were among the first to assess adherence and predictors of adherence. This study of 6486 patients with allergic rhinitis living in The Netherlands found adherence better in the group receiving subcutaneous immunotherapy than in the group receiving SLIT, although it was low in both groups. In addition to adherence, the effectiveness of SLIT in asthmatic patients requires study. One would anticipate it would be particularly useful for patients with seasonal allergic asthma.

Biologics. Omalizumab, a human anti-IgE mAb, has been approved and found effective in the treatment of moderate-to-severe asthma. Gevaert et al⁶⁶ conducted a randomized (2:1 omalizumab/placebo), double-blind, placebo-controlled trial of omalizumab in 24 allergic and nonallergic adults with asthma and nasal polyps. The primary end point was the endoscopic nasal polyp score, a measure of polyp size, after 16 weeks. Polyp scores decreased. There was no change in spirometry, but asthma-related quality of life improved more and report of wheeze decreased in the omalizumab group. Outcomes were independent of atopic status. Although potential for efficacy in the treatment of nasal polyps is suggested, this trial is limited by small size, dropout, short duration, and the need to study long-term adverse effects, as well as benefits of the biologic agent. In an editorial Kern⁶⁷ notes that this study prompts investigations of other biologic agents that target eosinophils, basophils, and mast cells for the treatment of chronic sinusitis with nasal polyps.

Speaking of mast cells, severe asthma might have a contribution from these cells through prostaglandin D₂ (PGD₂)

synthesis. Chemoattractant receptor homologous molecule expressed on T_H2 cells (CRTH2) is a G protein-coupled receptor expressed by T_H2 lymphocytes, eosinophils, and basophils. CRTH2 mediates the activation and chemotaxis of these cell types in response to PGD₂, the major prostanoid produced by mast cells. Fajt et al⁶⁸ found levels of PGD₂, its enzyme (hematopoietic prostaglandin D synthase), and its receptor, CRTH2, are increased in patients with severe poorly controlled asthma and in association with T_H2 inflammation. However, Busse et al⁶⁹ report that AMG 853, a potent selective, oral, dual antagonist of human D-prostanoid and CRTH2 was safe but not effective in a dose-ranging 12-week trial of adults 18 to 65 years old with moderate-to-severe asthma receiving ICSs. It is likely we will hear more about the potential for therapeutic targets along this PGD₂ pathway.

Other biologic agents show promise. Dupilumab, a fully human mAb to the α subunit of the IL-4 receptor was tested as a weekly subcutaneous injection in a randomized controlled trial of 104 patients with moderate-to-severe asthma and increased eosinophil levels by Wenzel et al.⁷⁰ After week 4, ICSs were tapered and then discontinued. Patients were followed for 12 weeks or until an asthma exacerbation, the primary end point. There were fewer exacerbations in the dupilumab-treated group.

Lebrikizumab is a humanized IgG₄ mAb that blocks IL-13. Dosed at 250 mg/mo subcutaneously for 6 months, it was associated with improved lung function (increased FEV₁ of 5.5% over placebo) in a randomized, double-blind, placebo-controlled trial.⁷¹ These studies used periostin, which is induced by IL-13 as a marker of IL-13 activity. In 2013, Noonan et al⁷² reported a randomized trial of placebo versus lebrikizumab at a range of doses in monthly injections for 12 weeks and an 8-week follow-up in asthmatic patients not receiving ICSs. They found numeric but not clinically meaningful changes in FEV₁ between groups. Laviolette et al⁷³ report a phase I safety study of benralizumab, a humanized afucosylated mAb targeting eosinophils by binding IL-5 receptor α , resulting in reduced eosinophil counts in sputum, bone marrow, and peripheral blood, although not significantly in the airway.

Other investigations of therapeutics. In a study from The Netherlands, Zetstra-van der Woude et al⁷⁴ found that during pregnancy many asthmatic women stop receiving prescriptions, including long-acting bronchodilators, thereby running the risk of reduced asthma control. Whether medications are not prescribed or not filled requires investigation. Rank et al⁷⁵ found stopping low-dose ICSs increased the risk for an asthma exacerbation. Up to 1 in 5 patients who stopped ICSs were expected to have an exacerbation in the next 6 months attributable to stopping ICSs, but there was no increase in emergency department visits or hospitalizations. There is an inevitable risk in attempting to step down to find the minimal necessary required asthma medication.⁷⁶

The Asthma Clinical Research Network found FEV₁ response to albuterol predicted a positive response to tiotropium and salmeterol.⁷⁷ A study by Colice et al⁷⁸ funded by Teva Pharmaceuticals found increased odds of achieving asthma control with extrafine hydrofluoroalkane-beclomethasone compared with fluticasone administered through a metered-dose inhaler in 10,312 patients with asthma age 12 to 80 years receiving their first ICS. The investigators hypothesize this is a result of the ability of the extrafine ICS formulation to improve total airway

deposition and penetration to the small peripheral airways.³² Control was uniquely defined as no hospitalizations, oral corticosteroids, or antibiotics for lower respiratory tract infection and a less than 2 puffs per day requirement of short-acting β -agonist. Costs were lower for hydrofluoroalkane-beclomethasone.

Whether leukotriene receptor antagonists or long-acting β -agonists (LABAs) added to ICSs are more therapeutic is an important question. Real-world population-based studies are needed. Sadatsafavi et al⁷⁹ analyzed administrative databases of British Columbia, Canada, from 1997 to 2006 in asthmatic patients age 12 to 45 years. They conducted an intention-to-treat analysis and an uninterrupted treatment analysis that followed subjects for as long as they continuously dispensed their "index" medication. Subjects were more adherent to ICS plus LABA therapy. ICS plus LABA therapy was associated with better asthma outcomes, even controlling for adherence differences. However, uninterrupted treatment at the end of the first year was only 9% in those taking ICSs plus LABAs and 3% for those receiving ICSs plus leukotriene receptor antagonists. As O'Byrne⁸⁰ comments in an editorial, we still need a better understanding of barriers to adherence.

There is increased emphasis on real-world research, which studies patients in settings as close to their everyday lives as possible, capturing their perspectives and preferences. Patient-reported outcome measures (PROMs) are increasingly used to understand the relevance of research findings. Frew et al⁸¹ studied the level of patient involvement in the development of 24 asthma-specific PROMs. They found involvement in only 10 and less involvement in the more recently developed PROMs, and this involvement took the form of consultation with no active collaboration or patient control or management of the research. It is important for readers to assess the characteristics of PROMs in reports of patient-oriented research.

Short et al⁸² re-examined whether β -blockers had a deleterious effect in asthmatic patients. They conducted a double-blind, randomized, placebo-controlled crossover trial of 8 weeks of propranolol in patients with mild-to-moderate asthma receiving ICSs. There was no change in ACQ or Asthma Quality of Life Questionnaire results. There were no effects on methacholine or histamine airway hyperresponsiveness, with only a partial attenuation of recovery with albuterol after histamine challenge. No beneficial effects were seen, and although further research is needed, this study suggests that the risk of a β -blocker might not be as much as previously thought for patients who need both β -blocker and asthma medications. Finally, Buehring et al⁸³ provided an update on the management of glucocorticoid-induced osteoporosis.

CONCLUSION

Research on mechanisms, biomarkers, and biologic agents suggests the future will see new therapies based on biologic pathways. The study of phenotypes also involves a search for mechanisms to inform therapeutics. Nonpharmaceutical interventions should not be neglected. Once these new therapeutics pass the initial clinical trials, patient-oriented and real-world research will be needed.

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Key findings in the care of adults with asthma reported in the 2013 *Journal of Allergy and Clinical Immunology*

- The generation of proresolving mechanisms to restore homeostasis accompanies the activation of inflammatory processes, and these molecules can be easily measured in EBC.⁴³
- The respiratory microbiome differs between asthmatic and nonasthmatic subjects.¹⁹
- WEA is a significant cause of morbidity and health care cost.²⁰
- Small-airway dysfunction plays a role in asthma control; biomarkers and therapeutics targeting the small airways are in development.^{32-35,78}
- Serum periostin might be a useful biomarker for airway eosinophilia and decrease in FEV₁ in asthmatic patients despite ICSS.⁵⁴
- New biologic agents of the T_H2 pathway, such as dupilumab, lebrikizumab, and benralizumab, have potential as therapeutic agents.⁷⁰⁻⁷³
- Exposure and sensitivity to mouse allergen was found to be more strongly associated with poor asthma outcomes than cockroach allergen.²¹
- PROMs need input from patients in development.⁸¹
- Investigation of the literacy demand on patients and relevance to health is needed.⁵⁸
- SLIT holds promise, but adherence issues must be addressed.⁶²⁻⁶⁵
- Subjects with a family history of asthma are more likely to have adult-onset asthma, with further increased risk if exposed to secondhand smoke.^{39,40}

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