

Advances in adult asthma diagnosis and treatment in 2014

Andrea J. Apter, MD, MSc, MA Philadelphia, Pa

In 2014, new biologic therapies are emerging for severe asthma based on identification of relevant phenotypes. The exploration of nutritional supplements to treat asthma has been less successful. (J Allergy Clin Immunol 2015;135:46-53.)

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

Journal of Allergy and Clinical Immunology articles published in 2013 on adult asthma focused on its phenotypes, both their definitions and causes.^{1,2} In 2014, this interest continued, leading to important potential applications for new therapies for severe asthma. Key advances in 2014 are summarized in Table I.³⁻¹⁸

MECHANISMS OF DISEASE GUIDE THERAPEUTIC INNOVATIONS

Asthma research in 2014 has emphasized the role of T_H2-like immunity. One focus has been on innate lymphoid cells (ILCs),¹⁹ innate non-T, non-B effector cells for which animal studies have implicated a role in regulating asthma. Type 2 ILCs (ILC2s), which were previously called nuocytes, produce IL-5, IL-9, and IL-13 in response to IL-33 and IL-25 (Fig 1).¹⁹ Extending this research to the study of human ILC2s, Bartemes et al²⁰ cultured PBMCs from patients with allergic asthma (n = 18), patients with allergic rhinitis (n = 16), or healthy control subjects (n = 18) with IL-25 or IL-33. Innate type 2 responses and ILC2 numbers increased in those with asthma but not in those with allergic rhinitis or control subjects, suggesting a unique role for innate immunity in patients with allergic asthma and a potential future therapeutic target.

Traister et al²¹ found increased expression of ST2L, the epithelial receptor for IL-33 (itself an IL-1 family cytokine), in endobronchial brushings and biopsy specimens from asthmatic adults and association of ST2L and its gene, *IL1RL1*, with severe T_H2-like asthma. T_H2-like asthma was assessed with a composite score reflecting blood eosinophil numbers, fraction of exhaled nitric oxide (FENO) values, epithelial calcium-activated chloride channel regulator 1 (CLCA1), and eotaxin 3. The importance of

Abbreviations used

AERD:	Aspirin-exacerbated respiratory disease
CLCA1:	Calcium-activated chloride channel regulator 1
COPD:	Chronic obstructive pulmonary disease
FENO:	Fraction of exhaled nitric oxide
GP:	General practitioner
GWAS:	Genome-wide association study
ICS:	Inhaled corticosteroid
ILC:	Innate lymphoid cell
IRF:	Inhaler reminders and feedback
LABA:	Long-acting β -agonist
NSAID:	Nonsteroidal anti-inflammatory drug
PAD:	Personalized adherence discussion
PGE ₂ :	Prostaglandin E ₂
RDBPCT:	Randomized, double-blind, placebo-controlled trial
SLIT:	Sublingual immunotherapy
Treg:	Regulatory T
TRPV1:	Transient receptor potential vanilloid 1

IL-33, which was noted above for its role in promoting ILC2s, gains further traction from a study in mice showing that *Altemaria* species-derived serine proteases can activate IL-33 release and T_H2-like inflammation with exacerbation of allergic airway disease.²² Extrapolating from animal studies, Kinoshita et al²³ hypothesized that the regulatory T (Treg) cell response is insufficient to overcome T_H2 inflammation in patients with allergic asthma. In their analysis of induced sputum specimens from adults with mild allergic asthma, those who experienced both an early and late response to allergen challenge had a reduced ratio of CD4⁺ forkhead box protein 3–positive Treg cells to total CD4⁺ cells compared with those with only an immediate response. Further study is needed to determine whether the reduced Treg cell/total CD4⁺ cell ratio was a cause or an effect of the biphasic inflammatory response and whether this will improve insight into T_H2-like asthma mechanisms and treatment possibilities.

New findings regarding clinical presentations and pathways governing aspirin-exacerbated respiratory diseases (AERDs) and a clinical review of management appeared in the *Journal* during 2014.²⁴ Using latent class analysis, Bochenek et al²⁵ identified 4 clinical AERD subphenotypes, suggesting that AERD might involve heterogeneous mechanisms and benefit from targeted therapies. Laidlaw et al²⁶ found granulocytes from patients with AERD generated more leukotriene B₄ and cysteinyl leukotrienes than those of patients with aspirin-tolerant asthma or control subjects. Compared with nonasthmatic control subjects, granulocytes from patients with AERD had similar levels of E prostanoic acid and prostaglandin E₂ (PGE₂)–mediated cyclic AMP but were resistant to PGE₂ suppression of leukotriene generation. Impaired protein kinase A function leading to failure of suppression of

From the Division of Pulmonary, Allergy, & Critical Care Medicine, Department of Medicine, Perelman School of Medicine, University of Pennsylvania.

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

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TABLE I. Key findings in the care of adults with asthma reported in 2014

• Cluster analysis is being widely used to identify distinct and clinically relevant phenotypes. ^{4-10,13}
• Definition of phenotype can lead to individualized treatments. ^{3,8,10,13,16,17}
• Distinguishing eosinophilic from noneosinophilic inflammation has led to new therapeutics. ^{16,17}
• Mepolizumab is associated with decreased exacerbations of eosinophilic asthma. ^{16,17}
• Severe childhood asthma and childhood allergic rhinitis predict asthma presence and morbidity at age 50 years. ^{11,12}
• Vitamin D3 supplementation in symptomatic asthmatic adults with vitamin D deficiency did not reduce the rate of first treatment failure or exacerbation. ¹⁴
• In a small study an anti-thymic stromal lymphopoietin antibody attenuated the late decrease in FEV ₁ after allergen challenge. ¹⁵
• A postmarketing study of the safety of omalizumab found no evidence of increased risk of malignancy. ¹⁸

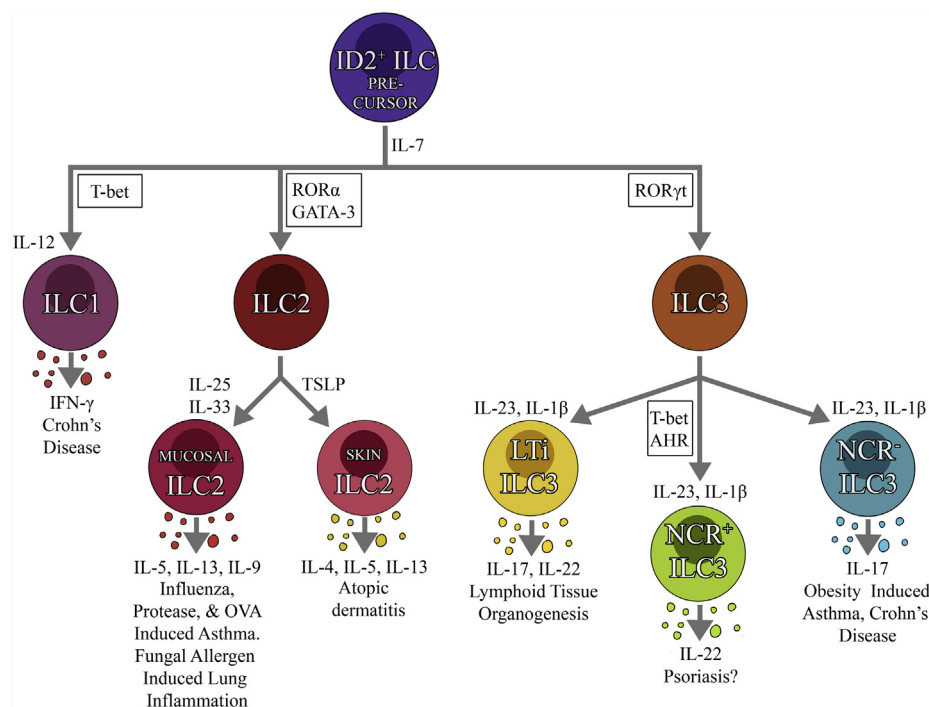


FIG 1. Development and function of ILCs. All ILCs develop from a common precursor cell characterized by expression of the transcriptional repressor inhibitor of DNA binding 2 (*ID2*), expression of the common cytokine receptor γ chain (not shown), and dependence on IL-7 for development. ILC1s produce IFN- γ on stimulation with IL-12, depend on T-bet for their development, and are involved in the pathogenesis of Crohn disease. ILC2s depend on the transcription factors GATA-3 and retinoic acid-related orphan receptor (*ROR*) α for their development. They produce IL-5, IL-13, and IL-9, although skin ILC2s are reported to produce IL-4, IL-5, and IL-13. ILC2s are activated by stimulation with IL-33, IL-25, and IL-2 and participate in the development of some forms of asthma. Different from mucosal ILC2s, the skin ILC2 response is elicited by thymic stromal lymphopoietin (*TSLP*) and promotes atopic dermatitis. ILC3s require the transcription factor *ROR* γ t for their development and respond to IL-23 and IL-1 β . ILC3s include 3 different subsets: lymphoid tissue inducer (*LTi*) ILC3s, natural cytotoxicity receptor (*NCR*)⁺ ILC3s, and *NCR*⁻ ILC3s. *LTi* ILC3s play an important role in lymphoid tissue organogenesis and produce IL-17 and IL-22. *NCR*⁻ ILC3s express CCR6, produce IL-17 and sometimes IL-22, and are critical in the development of obesity-induced asthma and inflammatory bowel disease. *NCR*⁺ ILC3s produce IL-22 and also depend on the aryl hydrocarbon receptor (*AHR*) and T-bet for their function. Some ILC3s downregulate *ROR* γ t and transform into ILC1s. *NCR*⁺ ILC3s might contribute to the development of psoriasis. *OVA*, Ovalbumin. The figure and figure legend are used with permission from Yu et al.¹⁹

5-lipoxygenase activity by PGE₂ was a factor. These findings were corroborated in part by mouse studies.²⁷

Using a mouse model to study allergic airway disease, Hatchwell et al²⁸ observed that salmeterol exerts anti-inflammatory effects by increasing levels of protein phosphatase 2A, which attenuates the chemotactic response to rhinovirus and subsequent exacerbation. This finding is likely to attract clinical attention.

GENETIC INFLUENCES OF POTENTIAL CLINICAL RELEVANCE

Personalized asthma management will require an understanding of genetic influences on disease and medication efficacy derived from studies of diverse populations with differing genetic variability and admixture, as well as differing environmental exposures. This is discussed by Ortega and Meyers,²⁹ who note the need to expand research beyond European white subjects, who

have less genetic variation than other populations. In 2014, there have been several studies of non-European populations. Galanter et al³⁰ conducted a genome-wide association study (GWAS) and admixture mapping of asthma-associated genetic loci in a Latino population recruited from Puerto Rico, New York, Chicago, Houston, and San Francisco. They identified the association at 17q21 previously recognized in Latinos and a novel locus at 6p21. Leung et al³¹ ascertained differences in allele frequencies and haplotype blocks of asthma loci in Chinese subjects compared with other ethnic groups. In another study Ortega et al³² found rare variants of the β -adrenergic receptor gene (*ADRB2*) associated with severe asthma exacerbations during long-acting β -agonist (LABA) therapy in a diverse population of African Americans, non-Hispanic whites, and Puerto Rican asthmatic patients. Replication of some of the variant associations was accomplished in additional non-Hispanic white patients, but further study is needed.

Ferreira et al³³ conducted a meta-analysis of GWASs of persons of European ancestry having both asthma and hay fever compared with those with neither disease to determine genetic risk factors for allergic asthma. Subjects were from Australia, the United Kingdom, and a United States–based personal genome service. Two novel variants, zinc finger and BTB domain containing 10 (*ZBTB10*) and C-type lectin domain family 16, member A (*CLEC16A*), and 9 known variants were identified. Of the latter, gasdermin A (*GSDMA*) and thymic stromal lymphopoietin (*TSLP*) variants were stronger risk factors for asthma than for allergic rhinitis. In a study by Dizier et al³⁴ fine-scale mapping of the 1p31 region revealed a strong association of the nuclear factor I/A gene *NFIA* with asthma plus allergic rhinitis in French nuclear families, which was replicated in French-Canadian and United Kingdom family cohorts.

Elucidating the genes that influence response to inhaled corticosteroids (ICSs) and other asthma therapies among diverse populations is of major importance. Wu et al³⁵ conducted a GWAS of 581 white children with asthma from the Childhood Asthma Management Program with a replication cohort of 227 white asthmatic adults from the Leukotriene Modifier or Corticosteroid or Corticosteroid-Salmeterol Trial. Using a gene-environment analysis, the investigators found that variable expression of the chromosome 19 zinc finger protein gene *ZNF432* modulates the response to ICSs. However, Hosking et al³⁶ were unable to replicate an association between glucocorticoid induced transcript 1 (*GLCCI1*) and treatment response to ICSs in non-Hispanic whites.³⁷ The GWAS of Childhood Asthma Management Program data conducted by Park et al³⁸ identified a single nucleotide polymorphism within the intron region of F-box and leucine-rich repeat protein 7 (*FBXL7*) associated with improved responsiveness to ICSs. This was replicated in a pediatric but not an adult cohort.

Measuring gene expression might guide future phenotyping and therapeutic interventions. Already, phenotypes of asthma have been characterized as “ T_H2 -high” versus “ T_H2 -low” based on expression of the genes upregulated in airway epithelial cells by IL-13: periostin, chloride channel accessory 1 (*CLCA1*), and Serpin $\beta 2$ (*SERPINB2*).^{39–41} This bronchoscopy-requiring characterization has had therapeutic implications. Peters et al⁴¹ demonstrated that it is feasible and more convenient to measure expression of *IL4*, *IL5*, and *IL13*, as well as periostin, *CLCA1*, and *SERPINB2*, in induced sputum and that expression profiling of *IL4*, *IL5*, and *IL13* can be used to classify asthma into T_H2 -high and T_H2 -low variants. As Sterk and Lutter⁴² comment in the accompanying editorial on this hypothesis-driven approach,

hypothesis-independent high-throughput technologies will allow identification of additional and possibly unexpected “molecular profiles,” enabling further subphenotyping and individualized patient management.

ENVIRONMENTAL EXPOSURES

Environmental exposures affecting asthma range from psychosocial stressors to infectious agents to allergens. Rosenberg et al³ review how stress-induced responses alter neuroendocrine, autonomic, and immunologic function at the cellular, epigenetic, and genetic levels and might influence airway hyperreactivity and response to environmental exposures and therapy. Juhn⁴³ considers whether a variety of infectious agents, including gram-positive and gram-negative bacteria, viruses, and mycobacteria, have a possible bidirectional causal relationship in asthmatic patients, such as infection-triggered asthma exacerbations and asthma-associated increased infection risk. Both he and Busse and Gern⁴⁴ in an accompanying editorial stress the importance of vaccinations against pneumococcus, pertussis, influenza, and other preventable infections for asthmatic patients.

To explore the relationship between indoor environmental fungal diversity and respiratory health risk, Sharpe et al⁴⁵ conducted a meta-analysis and systematic review, scanning 10 databases to identify 17 studies of medium quality. Current asthma symptoms were associated with indoor presence of *Penicillium*, *Aspergillus*, *Cladosporium*, and *Alternaria* species. Limitations included the difficulty of mold measurement and possible publication bias: searches with negative results are not generally published.

Gómez-Casado et al⁴⁶ reported that occupational asthma accounts for 10% of adult asthma and that baker's asthma is the most common occupational respiratory disease in the West. These investigators found sensitivity to wheat allergens did not vary by local environment, whereas IgE to the lipid transfer protein Tri a 14 was exclusively associated with wheat-induced allergy by means of inhalation and diagnostically valuable. Lemiere et al⁴⁷ found that a less than 2% change in sputum eosinophil counts after specific inhalation challenge in patients with occupational asthma might signify a worse prognosis.

The persistent pernicious effects of tobacco were explored by several investigators. Westerhof et al⁴⁸ studied 200 adult smokers with new-onset asthma. Of 128 who could be assessed 2 years later, greater pack-year exposure at baseline was independently associated with an increased asthma severity score based on medications, symptoms, and FEV₁ reduction. Pugmire et al⁴⁹ found exposure to parental smoking in childhood to be associated with persistence of respiratory symptoms into young adult life in their population-based cohort study. In another longitudinal study of the Multicenter Allergy Study birth cohort from Germany, Grabenhenrich et al⁵⁰ found asthma incidence up to age 20 years was higher in subjects with prenatal smoke exposure.

PHENOTYPES OF SEVERE ASTHMA

In 2014, cluster analyses were used to define phenotypes of severe asthma with potential for targeted therapy. Moore et al⁴ used cluster analysis of blood and inflammatory cell data from the Severe Asthma Research Program. They found 4 phenotype clusters and determined that neutrophil-predominant or mixed granulocyte inflammation was associated with a more severe asthma phenotype, which is similar to another brief report by Nagasaki et al.⁵

In another unsupervised cluster analysis using Severe Asthma Research Program data from 378 patients with severe asthma and healthy control subjects, Wu et al⁶ selected 51 clinical, physiologic, and inflammatory variables for a machine-learning approach that identified 6 subject clusters. The clusters included subjects with early-onset allergic asthma, severe systemic corticosteroid dependence, and late-onset nasal polyps and eosinophilia and a cluster of predominantly women with early-onset symptom predominance who had some overlap with other clusters.^{4,5,7}

Schatz et al⁸ used a hierarchic clustering algorithm on data from subjects within The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study to characterize phenotypes with severe or difficult-to-treat asthma. There were 5 clusters distinguished by sex, atopic status, nonwhite race, and aspirin sensitivity, with the cluster of nonwhite race having the highest proportion of patients with abnormal baseline pulmonary function and lowest mean FEV₁/forced vital capacity ratio values, whereas the cluster with aspirin sensitivity had the highest proportion of exacerbations.

Sputum eosinophilia has been associated with asthma severity and favorable response to corticosteroid therapy. In a study from the United Kingdom based on induced sputum from 97 patients with severe asthma followed for 6 years, Newby et al⁹ found 3 patient clusters defined by the presence of eosinophils. Those patients with variable levels of eosinophils in sputum had an accelerated FEV₁ decrease compared with those without significant eosinophil counts or with high eosinophil levels but low variation in eosinophil counts. Ghebre et al¹⁰ used cluster and factor analyses of clinical and physiologic characteristics and sputum mediators to compare the distinct and overlapping characteristics of physician-defined patients with severe asthma and moderate-to-severe chronic obstructive pulmonary disease (COPD). Interestingly, they found an asthma cluster characterized by eosinophil-predominant sputum, an asthma/COPD overlap cluster characterized by neutrophilic sputum, and a COPD cluster with a mixed eosinophilic and neutrophilic sputum profile. Such sputum profiling may predict the success of emerging specific anti-inflammatory therapies.

To describe the natural history of childhood asthma, Tai et al¹¹ used longitudinal data from the Melbourne Asthma Study, a community-based prospective study of children with a history of wheezing who were recruited at age 7 years. Of 484 original subjects, 197 provided data. Severe childhood asthma and childhood hay fever predicted asthma at age 50 years; however, the reduced lung function was established in childhood, and the rate of lung function decrease was not greater in patients with severe asthma compared with that seen in those with no asthma or mild asthma.

Investigating the pathophysiology of persistent airflow obstruction in patients with moderate-to-severe asthma, Gelb et al⁵¹ found evidence of mild emphysema in 10 nonsmoking adults with lifelong asthma. This is consistent with an analysis by Savage et al¹² who examined the association between asthma and allergic disease and mortality in a cohort with more than 30 years of follow-up from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. They found an association of asthma with increased respiratory and all-cause mortality but not with cardiovascular or cancer mortality.

BIOMARKERS

Biomarkers are needed for assessing clinical course, suggesting potential interventions, and judging their success. They are

the markers of phenotypes that can individualize care. FENO is a biomarker of eosinophilic inflammation in asthmatic patients, but Haccurria et al⁵² discovered that FENO is susceptible to alteration by decreases in airway caliber. In 15 asthmatic patients with mite allergy challenged with house dust mite allergen, both FENO and FEV₁ values decreased in the early airway response to mite allergen challenge, presumably before significant eosinophil involvement, indicating that FENO is not a discrete indicator of eosinophilic inflammation but rather a complex function of eosinophil activation and airway caliber.

Also, considering airway caliber, Gupta et al¹³ used quantitative computed tomography to determine 3 phenotype clusters in 65 patients with severe and mild-to-moderate asthma and 30 healthy control subjects. Cluster 1 had the most impaired lung function and severe air trapping, with increased bronchus wall and lumen volumes suggestive of bronchiectasis. Cluster 2 had the least impaired lung function, despite higher wall volume and moderate air trapping, implying airway thickening. Cluster 3 had severe lung function deficit and air trapping; its subjects tended to be more obese and had more airway remodeling, as evidenced by increased bronchial wall volumes and narrowed airway lumens. As noted in an accompanying editorial, although these clusters do not correspond to previously described clinical phenotypes, a biomarker like quantitative computed tomography might add to our understanding of the pathophysiology of remodeling and allow assessment of the efficacy of therapeutic interventions, such as bronchothermoplasty.⁵³

Baines et al⁵⁴ identified 6 gene biomarkers from induced sputum with expression levels that distinguished asthma inflammatory phenotypes and treatment responses. Included were genes for Charcot-Leyden crystal protein (*CLC*); carboxypeptidase A3 (*CPA3*); deoxyribonuclease I-like 3 (*DNASE1L3*); IL-1 β (*IL1B*); alkaline phosphatase, tissue-nonspecific isozyme (*ALPL*); and chemokine receptor 2 (*CXCR2*). Expression of *CLC*, *CPA3*, and *DNASE1L3* was increased in patients with eosinophilic asthma and reduced by ICSs, whereas expression of *IL1B*, *ALPL*, and *CXCR2* was increased in patients with neutrophilic asthma. This discovery analysis involved 47 asthmatic patients, was validated on 59 subjects, and then was analyzed for reproducibility and robustness in 50 additional asthmatic patients and control subjects.

The 2010 national Asthma Outcomes Workshop recommended that quality-of-life instruments be developed for patient-centered research, which focuses on patients' perceptions of the effect of asthma on their lives and not symptoms or functioning.⁵⁵ Sherbourne et al⁵⁶ report the validity of 2 short forms derived from the RAND Negative Impact of Asthma on Quality of Life item bank to accomplish this task. Their analysis relied on data from 2032 fairly highly educated adults aged 18 to 99 years of diverse race/ethnicity. The short measures, one with 4 items and one with an additional 8 items, correlated with other measures of quality of life and asthma control and differentiated adults by perceived severity, level of control, presence of exacerbations, and comorbidities.

MANAGEMENT Adherence

In measuring asthma control, Slejko et al⁵⁷ used the nationally representative Medical Expenditure Panel Surveys and found that among those with recent exacerbations, only 29% used daily preventive medication and 54% had never used a long-term

controller medication. This finding could reflect lack of prescription, lack of access, or poor adherence. Zafari et al⁵⁸ used Markov models, a procedure explained in an editorial by Chinchilli and Wang,⁵⁹ to assess the effect of full adherence with controller medications on cost and quality-adjusted life years in adults. They found that compared with the status quo, full adherence reduced weeks of uncontrolled asthma by 31% and the rate of exacerbations by 40%. Such interventions were unlikely to be cost-saving but were likely cost-effective.

Foster et al⁶⁰ report a 6-month, cluster-randomized, 2×2 factorial intervention trial in 43 general practitioner (GP) practices to improve adherence and asthma control; 143 patients with moderate-to-severe asthma aged 14 to 65 years were enrolled. Adherence was measured with electronic monitors attached to patients' ICS/LABA inhalers. One intervention comprised personalized adherence discussions (PADs) between the GP and the patient. The other consisted of inhaler reminders and feedback (IRF) in which patients set and received twice-daily reminders to take ICSs/LABAs while their GPs received an automated monthly graph of their patients' medication use. All GPs received "usual care" training in the use of an action plan and inhaler technique/education. Adherence in the IRF group was higher than in the non-IRF groups ($73\% \pm 26\%$ vs $46\% \pm 28\%$). There was no difference between the PAD and non-PAD groups. Asthma control improved overall, with no significant changes in FEV₁ percentages among the groups, including those receiving only usual care but with a trend toward fewer severe exacerbations in the IRF groups. With the potential for low-cost monitoring, IRF might become practical. It is important to realize that monitoring patients, which changes behavior, and provision of medication necessary for monitoring are both interventions.

Dietary supplements

Nonpharmaceutical approaches to asthma management, including behavioral and nutritional interventions, need exploration. The National Institutes of Health Asthma Research Network (AsthmaNet) was organized to encourage innovative cross-age studies and is described in 2 articles in the *Journal*.^{61,62} One of AsthmaNet's first contributions is a study of vitamin D3 supplementation in adults with symptomatic asthma and low (<30 ng/mL) serum 25-hydroxyvitamin D levels concurrently treated with ICSs.¹⁴ Vitamin D3 supplementation did not reduce the rate of first treatment failure or exacerbations nor did it improve asthma control, as hypothesized.

Other studies of vitamin D in adults with asthma published in the *Journal* in 2014 have failed to establish unequivocal benefit of supplementation or harm from deficiency.⁶³ Zhang et al⁶⁴ showed vitamin D exerts anti-inflammatory and corticosteroid-enhancing effects *in vitro* in peripheral blood monocytes of steroid-sensitive and steroid-resistant asthmatic patients. However, a study of new employees at a mouse facility found no increase in IgE sensitivity among those with low serum 25-hydroxyvitamin D levels.⁶⁵ In 23 patients with severe glucocorticoid-resistant asthma, Nanzer et al⁶⁶ found no difference in FEV₁ percent predicted values after a 4-week course of vitamin D supplementation. In a large cross-sectional study from Korea, Cheng et al⁶⁷ found no increase in asthma risk among adults with vitamin D insufficiency, although they did find an association with atopic dermatitis.

Other nonpharmacologic/dietary supplements have been tested for benefit in asthmatic patients. In the mouse allergy study above, Keet et al⁶⁵ found evidence that higher folate serum levels increased the risk of new IgE sensitivities. Wendell et al⁶⁸ reviewed the role of dietary fatty acids in inflammation and concluded that the role of dietary interventions in these pathways has not demonstrated efficacy. The review by Moreno-Macias and Romieu⁶⁹ found little longitudinal data and no large clinical trials to support the use of antioxidant supplements and nutrients in asthmatic patients. In a complementary review Sharma and Litonjua⁷⁰ present possible mechanisms of how dietary supplements and nutrients, including methyl donors, such as folate and choline, might act, such as through epigenetic methylation. However, they caution that these effects might extend to other pathways and that the intestinal microbiome must be considered as well for its role in metabolism and production of B vitamins and other nutrients.

Therapeutics: ICSs and β -agonists

Beasley et al⁷¹ advocate testing alternative schedules of ICS/ β -agonist combinations that could include symptom-driven use of an ICS/short-acting β -agonist or an ICS/LABA or of a combination ICS/ β -agonist (short-acting β -agonist or LABA) as reliever therapy.

Special asthmas: AERD, *Aspergillus*-sensitized, capsaicin-induced cough

Woessner and White²⁴ review aspirin desensitization in patients with AERD, noting there are few blind controlled studies of its benefits. Swierczynska-Krepa et al⁷² conducted a small randomized, double-blind, placebo-controlled trial (RDBPCT) in patients with aspirin-intolerant compared with patients with aspirin-tolerant asthma, all with polypoid rhinosinusitis, randomized after aspirin challenge to aspirin or placebo desensitization for 6 months. Only aspirin-intolerant patients reported improvement with desensitization in terms of improved ability to smell, reduced sneezing, diminished nasal congestion, and improved asthma control. However, FEV₁ did not change, and 4 of 12 patients in the aspirin-intolerant group undergoing aspirin desensitization dropped out.

Morales et al⁷³ conducted a systematic review of blind placebo-controlled clinical trials in which patients with AERD were challenged with selective nonsteroidal anti-inflammatory drugs (NSAIDs), such as meloxicam or COX-2 inhibitors. They found that COX-2 inhibitors, such as celecoxib, are well tolerated and can be used in place of NSAIDs in patients with stable mild-to-moderate asthma with AERD. There was a small risk of respiratory symptoms with selective NSAIDs. In patients with mild allergic asthma, Daham et al⁷⁴ found COX-2 inhibition with etoricoxib did not exacerbate airway inflammation or obstruction after allergen or methacholine challenge.

Agbetile et al⁷⁵ conducted an RDBPCT of voriconazole in patients with moderate-to-severe asthma and *Aspergillus fumigatus*-specific IgE but not otherwise meeting the diagnostic criteria for allergic bronchopulmonary aspergillosis. Three months of voriconazole, which lacks the corticosteroid-enhancing effect of itraconazole, was not effective in patients with *A. fumigatus*-associated asthma.

Activation of transient receptor potential vanilloid 1 (TRPV1) is the cause of capsaicin-induced cough and is possibly implicated

in refractory asthma.⁷⁶ It has been proposed that tiotropium modulates some of TRPV1's effects.⁷⁷ Khalid et al⁷⁸ tested an antagonist to TRPV1 but found no improvement in objective 24-hour cough frequency, patient-reported cough severity, urge to cough, or cough-related quality of life.

Sublingual immunotherapy for asthma

With the first US Food and Drug Administration approvals of sublingual immunotherapy (SLIT) for grass and ragweed immunotherapy in 2014, other allergens are being studied for safety and efficacy. Wood et al⁷⁹ examined the cockroach-specific IgE and IgG₄ response to cockroach immunotherapy administered as subcutaneous and sublingual formulations in children and adults in 4 pilot studies. They found these immunotherapies to be safe overall, with a more robust immunologic response to subcutaneous rather than sublingual administration. Efficacy was not evaluated. Mosbech et al⁸⁰ examined the efficacy and safety of a standardized house dust mite SLIT in an RDBPCT of 604 patients aged 14 years or older with mite-induced allergic rhinitis and mild-to-moderate asthma. After a year of treatment, those with the highest active dose of mite SLIT were able to reduce daily ICSs by about 81 μ g more than those receiving placebo; no other differences in asthma parameters were observed. The most common adverse events were local reactions involving the mouth.

Biologics

Biologics for severe asthma are in development. De Boever et al⁸¹ conducted a multisite 12-week RDBPCT of monthly intravenous anti-IL-13 in 237 adults with refractory asthma after improvement in lung function was noted in preliminary studies of this mAb. Although well tolerated, the investigators observed no clinical improvement or change in total serum IgE levels or blood eosinophil counts. However, patients were not selected according to baseline levels of these biomarkers, and the authors postulate that identifying the relevant inflammatory phenotype might make a difference.

Gauvreau et al¹⁵ report that an anti-thymic stromal lymphopoietin mAb reduced allergen-induced bronchoconstriction and airway inflammation before and after allergen challenge in both the early and late asthmatic response after 5 to 12 weeks of monthly infusions delivered in an RDBPCT of 31 adults with mild allergic asthma. Further evaluation of the clinical effects and mechanism of this promising mAb is needed.⁸²

Beck et al⁸³ reported that dupilumab, an mAb directed against the α subunit of the IL-4 receptor, which blocks signaling from both IL-4 and IL-13 with therapeutic efficacy in asthmatic patients,⁸⁴ also showed benefit in atopic dermatitis.

Mepolizumab, an anti-IL-5 mAb that inhibits eosinophilic inflammation, was shown to have efficacy in asthmatic patients in 2 studies. Ortega et al¹⁶ reported a multicenter phase 3 RDBPCT of 576 patients aged 12 to 82 years with recurrent asthma exacerbations despite high-dose ICSs. Asthmatic adults with evidence of eosinophilic inflammation (eosinophil count ≥ 150 cells/ μ L in peripheral blood at screening or ≥ 300 cells/ μ L in the previous year) were randomized to either 75 mg of intravenous or 100 mg of subcutaneous mepolizumab or placebo every 4 weeks for 32 weeks. Mean baseline FEV₁ was about 60%, and approximately one fourth of the subjects used oral steroid maintenance therapy. Mepolizumab reduced exacerbations and improved quality of life, asthma control, and FEV₁ significantly. In a related RDBPCT

of 135 patients with severe eosinophilic asthma requiring daily oral glucocorticoids, Bel et al¹⁷ found those randomized to 100 mg of mepolizumab administered subcutaneously every 4 weeks for 20 weeks were able to reduce steroids a median of 50% compared with no change in the placebo group and had reduced exacerbations and improved asthma control. In an accompanying editorial, Nair⁸⁵ points out that only when biomarkers that identified the relevant phenotype, in this case eosinophilic asthma, were used was mepolizumab found to be clinically effective. These studies illustrate the importance of determining phenotypes for effective individualized treatment. Nair⁸⁵ also observes that in the study by Ortega et al,¹⁶ the placebo group also improved, indicating that close monitoring of asthma is itself an intervention that in some patients would obviate the need for an expensive mAb. These and earlier studies also provide preliminary evidence of the short-term safety of mepolizumab.

Relevant to safety, Haldar et al⁸⁶ compared changes in blood and sputum eosinophil counts and asthma control in a 12-month observational study of 56 adults with refractory eosinophilic asthma who discontinued mepolizumab or placebo after 12 months of administration during participation in a clinical trial. Subjects were evaluated at 3-month intervals. Blood eosinophil counts were increased in the first 6 months, as were sputum eosinophil counts in the first 3 months, and there was a small decrease in mean asthma control in those stopping mepolizumab but not in the placebo group over the 12 months of observation. Asthma exacerbations, which were preceded by an increase in eosinophil counts, increased in the mepolizumab group, but by 6 months were not different from those in control subjects.

Also concerning the safety of mAbs, Long et al¹⁸ found no increased risk of malignancy from omalizumab among patients aged 12 years or older with moderate-to-severe asthma and hypersensitivity to a perennial aeroallergen. The study used 2 cohorts in a 5-year postmarketing commitment to the US Food and Drug Administration: one cohort (n = 5007) was prescribed omalizumab, and one cohort (n = 2829) was left unexposed. The omalizumab cohort had a higher proportion of patients with severe asthma compared with the non-omalizumab cohort (50.0% vs 23.0%). The adjusted hazard ratio for time to first confirmed malignancy for omalizumab versus no omalizumab was 1.09 (95% CI, 0.87-1.38).

Conclusion

Improvements in asthma phenotyping that combine clinical with immunologic and genetic information are leading to therapeutic innovation.

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