



CME Review

Elucidating asthma phenotypes and endotypes: progress towards personalized medicine



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- Describe the heterogeneity of asthma
- Recognize new approaches to identifying asthma phenotypes and endotypes and how this may help tailor asthma therapy

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Introduction

Over time, there has been a shift in the paradigm of asthma, from a single-disease concept toward a greater recognition of asthma as a complex, chronic disease with marked clinical heterogeneity. Physicians have long suspected that patients with asthma belong to phenotypes based on observed differences in clinical presentation and response to therapy. The study of asthma phenotypes is evolving, with increased investigation into their genetic underpinnings and corresponding biomarkers. Until the past decade or so, limited therapeutic options were available, including anti-inflammatory and bronchodilator medications, which were tried by most, if not all, patients irrespective of phenotype. With the emergence of biologic agents, there is renewed interest in the identification of clinically meaningful phenotypes and endotypes using noninvasive biomarkers. This approach may help stratify patients and identify those most likely to experience benefit. Our attempts to select targeted asthma therapies for patients with the greatest likelihood of treatment response will pave the way for the delivery of tailored, personalized asthma care and perhaps lead to improved outcomes and patient care.

Definitions

Patients can present with asthma in a myriad of ways, with some of or all the following characteristics: variable, recurring symptoms (including wheezing, cough, dyspnea); reversible airflow obstruction (which can progress to a fixed obstruction over time); and bronchial hyperresponsiveness as a consequence of underlying airway inflammation.¹ This has led to the question of whether asthma is a single disease with a variable presentation or a syndrome with several disease variants.

A disease *phenotype* describes observable characteristics (clinical, physiologic, morphologic, biochemical, and response to treatment) without a relation to the underlying pathology. A person's asthma phenotype is a manifestation of the interaction between genes and environment and can change over time. Significant overlap can exist between phenotypes, making it difficult to classify

patients. A disease *endotype* is a specific biological pathway (defining an etiology and/or a consistent pathophysiologic mechanism) that explains the observable properties of a phenotype.^{2,3} Recent studies using nonbiased molecular approaches have identified some groups that likely represent endotypes, such as aspirin-exacerbated respiratory disease (AERD) and allergic bronchopulmonary mycosis (ABPM).

Experts have suggested that asthma is really a syndrome of multiple illnesses and proposed that, by stratifying asthma based on specific phenotypes or endotypes, better outcomes might be achieved. The elucidation of asthma phenotypes and endotypes is paralleled by a quest for noninvasive molecular biomarkers to identify these groups easily. The subset of patients with severe asthma refractory to standard medical therapy serves as an impetus for developing better models of improving phenotypic identification and tailoring therapy. In this review, we discuss perspectives on asthma classification and explore evolving asthma phenotypes and endotypes, with an emphasis on their use to tailor asthma therapy to improve patient outcomes.

Classifications of Asthma Phenotypes

There have been shifts in our perspective on asthma through time, as shown in Figure 1. A review of the literature shows that during some periods physicians embraced the concept of asthma as a single disease, but overwhelmingly we have resisted this approach and have struggled to dissect the heterogeneity of asthma.

Early Concepts of Heterogeneity

Early attempts at phenotyping asthma focused on the duality of allergic (extrinsic) vs nonallergic (intrinsic) asthma.⁴ This classification was widely accepted but its inadequacies in explaining the complexity of asthma presentation have been clear for a long time. In 1941, Rackemann and Mallory⁵ published a descriptive analysis of patients with asthma from the Massachusetts General Hospital; they described subsets of patients with intrinsic asthma but with very different sets of triggers (aspirin, respiratory infections) and

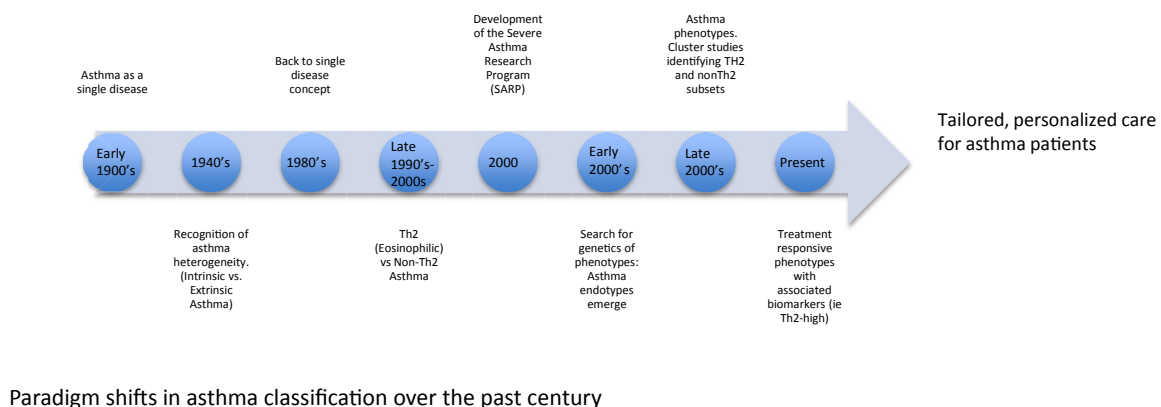


Figure 1. Perceptions of asthma through time: moving toward personalized medicine. TH2, T-helper cell type 2.

variations in time to death caused by exacerbation. Their observations show that, even 75 years ago, some physicians resisted a simplistic model of asthma and attempted to stratify patients with asthma.

Other methods of classifying asthma based on a single clinical or demographic variable have included early- vs late-onset asthma, exercise-induced asthma, obesity-related asthma, and smoking-related asthma; however, these have been poorly characterized and lack supporting longitudinal studies.⁶ Although differentiating asthma based on a single variable such as atopy might be conceptually helpful, its usefulness has been questioned repeatedly over time. Currently, there is a shift away from using the terms *intrinsic* and *extrinsic* asthma toward stratifying illness based on severity and level of control.¹ This is likely to change as we make further advances in clinical phenotyping and biomarker use.

Inflammatory Phenotypes

Since the early 19th century, it has been appreciated that airway eosinophilia is often seen in asthma.⁷ A broad classification scheme used to describe asthma is eosinophilic vs non-eosinophilic.⁸ In the

late 1990s and early 2000s, a resurgence of interest in defining asthma subsets led to increased research regarding inflammatory cell types within the asthmatic airway. In particular, patients with severe asthma refractory to standard care provided an impetus for asthma specialists to explore inflammatory markers in an attempt to explain variations in treatment response. A 2006 study by Simpson et al⁹ that examined eosinophil and neutrophil percentages in induced sputum found 4 inflammatory subtypes: eosinophilic, neutrophilic, mixed granulocytic, and pauci-granulocytic asthma. Through this and other studies, it became increasingly evident that a process not mediated by T-helper cell type 2 (TH2) might be the driving force in certain cases of asthma. The role of neutrophils in asthma remains unclear, but increased neutrophils have been reported in severe asthma and sudden-onset fatal asthma.^{10,11}

There has been longstanding evidence that patients with eosinophilic asthma (>2% eosinophils in sputum) have greater responsiveness to steroids compared with those with neutrophilic asthma.¹² This makes sense given the known apoptotic effects of inhaled corticosteroid (ICS) on eosinophils. Although identification of airway eosinophilia appears to play an important role in

Table 1
Select data from several representative cluster studies

	Haldar et al ¹⁶ (United Kingdom, 2008)	Moore et al ¹⁷ (SARP, 2010)	Wu et al ²⁰ (SARP, 2014)	Siroux et al ¹⁸ (Europe, 2011)	Fitzpatrick et al (2011) ¹⁹
Methodology	k-means cluster analysis	cluster analysis	cluster analysis, characterization with machine learning approach	latent class analysis	cluster analysis
Population	(1) mild to moderate in primary care, adults; (2) refractory in secondary care, adults	range of severity, adults (SARP)	range of severity, adults	range of severity, applied to 2 large epidemiologic studies with adult patients	children 6–17 y old from SARP
Subjects	primary care (n = 184), secondary care (n = 187)	n = 726	n = 378 (only SARP patients with data on inflammatory variables including healthy controls)	sample 1 (n = 641), sample 2 (n = 1,895)	n = 161 children
Variables	16	34 core	112	19	12
Clusters identified	clusters in primary care: (1) early-onset atopic asthma; (2) obese non-eosinophilia; (3) benign asthma	early-onset atopic asthma (normal lung function with <2 controller medications)	mostly healthy, normal lung function	sample 1: (1) actively treated allergic childhood-onset asthma; (2) actively treated adult-onset asthma; (3) inactive or mild untreated allergic asthma; (4) inactive or mild untreated nonallergic asthma	late-onset symptomatic asthma with normal lung function
	clusters in secondary care: (1) and (2) as above; (3) early symptom predominant; (4) inflammation predominant	early-onset atopic asthma (normal lung function with >2 controller medications)	mostly mild asthma, early onset, less asthma symptoms, near normal FEV ₁	sample 2: (1) and (2) as above; (3) inactive or mild untreated allergic childhood-onset asthma; (4) inactive or mild untreated adult-onset asthma	early-onset atopic asthma with normal lung function
		adult onset, obese, primarily women, low lung function	predominantly Hispanic women, atopy, high symptoms, near normal FEV ₁		early-onset atopic asthma with mild airflow limitation
		early-onset asthma with severe obstruction, some reversibility early-onset asthma, severe obstruction, without reversibility	predominantly female sex, high BMI, frequent symptoms, early onset mostly severe, older, less atopy, more nasal polyps, sinusitis early-onset severe asthma, high symptoms, lowest lung function, high BAL eosinophils, high FeNO, high corticosteroid use		early-onset atopic asthma with advanced airflow limitation

Abbreviations: BAL, bronchioalveolar lavage; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; SARP, Severe Asthma Research Program.

predicting response to therapy, some have argued that the view of characterizing asthma as eosinophilic and non-eosinophilic is limited. Significant heterogeneity in response to therapy exists even within eosinophilic asthma, as exemplified by patients with eosinophilic asthma that is refractory to medical therapy with steroids.¹³ In addition, it does not account for overlap between groups. There is mounting evidence for discrete sub-phenotypes of eosinophilic and non-eosinophilic asthma, which was nicely described by Wenzel⁸ in a 2006 *Lancet* article. This has led to a search for phenotypes with clinically useful measurements based on newer, more sophisticated, and less biased approaches.

Newer Approaches to Characterizing Asthma Phenotypes and Endotypes

Severe Asthma Research Program and Severe Asthma Phenotypes

In 2000, the National Heart, Lung, and Blood Institute sponsored a workshop on severe asthma, which affects 5% to 10% of people with asthma.¹⁴ This workshop identified an unmet need for research in this group of patients with asthma, which catalyzed the National Heart, Lung, and Blood Institute to fund the Severe Asthma Research Program (SARP), a collaborative approach to studying severe asthma that consists of 9 sites in the United States and 1 site in the United Kingdom.¹⁴ SARP researchers enrolled patients with severe asthma and compared them with patients with mild and moderate asthma who acted as controls. They performed comprehensive phenotypic characterization of subjects that included questionnaires, determination of atopy, pulmonary function testing, blood tests, and exhaled nitric oxide.¹⁵

By enrolling patients across multiple institutions, SARP has gathered valuable information about this often difficult-to-treat cohort of patients that has shed light on the many aspects of disease behavior in this group. For example, Moore et al,¹⁵ in a 2007 article, reported that decreased forced expiratory volume in 1 second, a history of pneumonia, and no atopy were the strongest independent risk factors for severe asthma. Also, a higher incidence of sinus disease, aspirin sensitivity, and gastroesophageal reflux disease was observed in severe asthma. Further insight into clinical characteristics of patients with severe asthma will allow for earlier identification and appropriate therapy, which is extremely important in this group in light of their high morbidity and health care usage. As such, SARP researchers continue to gather data and are performing advanced analyses in the hope of identifying phenotypes of severe asthma, as discussed below.

Cluster Analysis

Hierarchical cluster analysis is a new, less biased, statistical method that attempts to cluster patients by a wide range of pre-selected variables, such as age of onset, atopy, sex, severity of obstruction, and others. As noted by Haldar et al,¹⁶ cluster analysis uses multivariate mathematical algorithms to accomplish 2 functions: (1) quantification of similarities between subjects within a group based on prespecified variables and (2) grouping into clusters such that similarities are strong between subjects in the same cluster and weak in relation to subjects in other clusters. Several large cluster analyses have been performed, in Europe and in the United States, including a cluster analysis of the SARP data. It should be noted that particular variables, including the number of variables chosen in the studies, have varied but have consistently included age of onset, sex, and atopy.

Select data from several representative cluster studies are presented in Table 1.^{16–20} Haldar et al¹⁶ performed the first such study in 2008 in Leicester, United Kingdom. They performed this analysis on a group of patients with mild to moderate asthma and a group with severe asthma by examining 16 variables and identified several

clusters in each group. In 2010, Moore et al¹⁷ published a cluster analysis study of subjects with asthma in the SARP sample using 32 core variables and identified 5 asthma clusters. Siroux et al¹⁸ performed latent class analysis, a model-based clustering approach, on 2 large European cohorts and found 4 clusters in each cohort. Despite differences in study design and a range of variables examined, all 3 of these cluster studies identified 2 similar phenotypes. The first was a cluster with early-onset allergic asthma and the second was a cluster of mostly women with late-onset disease who generally did not have atopy and had a high body mass index.

Other cluster studies have been performed on specific populations, such as children and patients with severe asthma.^{19,20} A review of the literature shows a burgeoning of more cluster studies, highlighting the importance of using methods that are computational and less biased to confirm the inherent heterogeneity of asthma. Although most of these studies have not been replicated, en masse they provide evidence of clinically distinct phenotypes such as early-onset allergic and late-onset eosinophilic asthma. Rather than create an ever-expanding list of specific phenotypes, future directions will likely focus on dissecting out the clinically relevant ones.

Moving Beyond Phenotype

There is likely significant overlap between phenotypes; thus, not surprisingly, classification of patients can be difficult. To understand asthma heterogeneity better, researchers are investigating the underlying genetic mechanisms responsible for an observed phenotypic trait.

Genetic Studies of Asthma Susceptibility

Genetic studies, including large-scale genomewide association studies (GWASs), have identified several genetic loci that might influence asthma susceptibility. This method searches the genome for single-nucleotide polymorphisms (SNPs) that occur more frequently in people with a particular disease compared with those without the disease. This approach allows researchers to pinpoint genes that might contribute to the risk of developing asthma. For example, a European study showed a reproducible association between childhood-onset asthma and markers near the *ORMDL3* gene on chromosome 17q21.²¹ Despite the discovery of potentially meaningful SNPs, genetic associations of susceptibility genes have lacked consistency and reinforce that further longitudinal studies are needed.

Clustering Approaches Using Genetics

New techniques are being applied to study the genetic basis of observed phenotypes. One study used gene expression to identify transcriptional asthma phenotypes. Baines et al¹³ identified 3 asthma phenotypes (eosinophilic, neutrophilic, and paucigranulocytic) on a transcriptional level using unsupervised hierarchical clustering of induced sputum gene expression profiles. The inflammatory phenotypes had upregulation of various genes related to immune defense and inflammatory responses. Another new technique is the application of a GWAS to phenotypes identified by a nonbiased clustering method. Moving beyond identifying clinical clusters, Siroux et al²² used latent class analysis to identify adult asthma phenotypes and then conducted a GWAS to identify genetic variants. Asthma SNPs identified by previous GWASs were found in the active allergic asthma phenotype, and several other associations of genomewide significance were noted. The literature will likely grow with such studies that attempt to identify genetic variants within refined asthma phenotypes.

Table 2
Clinical Features of asthma phenotypes and evolving endotypes

	Natural history	Clinical features	Genetic pathway	Pathobiology	Potential biomarkers	Response to therapy
Early-onset allergic	early onset, range of severity	symptoms with allergen exposure, associated with other allergic diseases	T _H 2 pathway	allergen-specific IgE, T _H 2 cytokines	sputum eosinophils, FeNO, periostin, positive skin prick test reaction or serum specific IgE level	corticosteroid responsive, T _H 2-targeted biologics (such as: anti-IgE, anti-IL-13, anti-IL-5)
Late-onset eosinophilic	adult onset	tends to be more severe, less atopy, more sinus disease	T _H 2 pathway, LT pathway	refractory eosinophilia, IL-5 activity	sputum eosinophils, peripheral blood eosinophilia	antibody to IL-5, cys-LT modifiers
AERD	adult onset	tends to be more severe, sinusitis with nasal polyposis, NSAID allergy	T _H 2, LT pathway gene polymorphisms	increased cys-LT production, increased LT c4 synthase	often eosinophilic, increased IgE	cys-LT modifiers
ABPM	adult onset, can occur with cystic fibrosis	tends to be more severe, increased cough, mucus, central bronchiectasis	T _H 2 pathway	mixed adaptive immunity, eosinophilia	blood and sputum eosinophilia, fungus-specific IgE and IgG	corticosteroids, antifungal medications, possible role for anti-IgE
EIB		intermittent symptoms with exercise	component of T _H 2, LT pathway	T _H 2 cytokines, cys-LTs		cys-LT modifiers, β -agonists
Neutrophilic		decreased lung function, difficult to treat	non-T _H 2 pathway	neutrophils, T _H 17 pathways, IL-8, possible innate immune activation	sputum neutrophils	unknown, possibly responsive to macrolide antibiotics
Extensive remodeling		accelerated lung function decrease with irreversible or only partly reversible obstruction		damaged epithelial cells, release of pro-fibrotic cytokines		
Obesity related	adult onset	more common in women	innate, non-T _H 2 pathways	lack of atopy, oxidative stress	lack of T _H 2 biomarkers	weight loss, possibly hormonal

Abbreviations: ABPM, allergic bronchopulmonary mycosis; AERD, aspirin-exacerbated respiratory disease; cys-LT, cysteinyl leukotriene; EIB, exercise-induced bronchoconstriction; FeNO, forced exhaled nitric oxide; IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; LT, leukotriene; NSAID, nonsteroidal anti-inflammatory drug; T_H2, T-helper cell type 2.

Blank fields represent areas where much uncertainty exists and further data is needed to better refine and understand the phenotype or endotype.

Proposed Endotypes

An endotype is recognized “wherein a specific biological pathway is identified that explains the observable properties of a phenotype.”⁶ Several endotypes have been proposed, with mounting evidence that conditions such as AERD and ABPM in fact represent a true endotype. To define other possible endotypes, Lötvall et al³ selected 7 parameters in their Practall consensus, including clinical characteristics, biomarkers, lung physiology, genetics, histopathology, epidemiology, and treatment response and proposed that endotypes should form distinct entities based on these parameters. The consensus report proposed the following endotypes based on these parameters: (1) aspirin-sensitive asthma, (2) ABPM, (3) allergic asthma (adults), (4) asthma predictive index positivity in preschool child with wheezing, (5) severe late-onset hyper eosinophilic, and (6) asthma in cross-country skiers. However, there remains a lack of consensus among experts regarding which ones represent true endotypes, as there is limited confirmatory data.⁶

Asthma Phenotypes and Evolving Endotypes

The acceptance of various phenotypes is evolving, and as discussed earlier, several endotypes have been proposed but none have been agreed to. Large-scale longitudinal studies are needed to determine whether phenotypes with proposed distinct biologic pathways represent true endotypes. A complete list of proposed endotypes is beyond the scope of this review; however, highlights of several important phenotypes and endotypes are discussed below. Features of these phenotypes and evolving endotypes are listed in Table 2.

T_H2-Mediated Asthma

Asthma has largely been viewed as a T_H2-mediated process strongly linked to atopy and eosinophilic inflammation. Phenotyping studies have identified an early-onset allergic asthma

phenotype and several late-onset T_H2-related phenotypes. Increased levels of eosinophils in the sputum, bronchioalveolar lavage, or blood characterize eosinophilic asthma.

Early-Onset Allergic T_H2 Asthma

Allergic asthma is the most studied asthma phenotype, accounting for approximately 50% of subjects with asthma.²³ This process begins in childhood or adolescence in most cases, with evidence of hypersensitivity to environmental allergens. Early-onset allergic asthma is linked with other allergic diseases, including allergic rhinitis and atopic dermatitis, and can range from mild to severe.

From a pathobiologic standpoint, this phenotype is linked with high T_H2 cytokines, including increased total serum immunoglobulin E (IgE) and allergen-specific IgE. There appears to be a probable genetic component to early-onset asthma, as evidenced by the presence of a strong family history of asthma in this group. Other biomarkers for T_H2 asthma include increased forced exhaled nitric oxide, sputum eosinophils, and serum periostin levels. Newer molecules, and perhaps a combination of inflammatory markers, could emerge as potential biomarkers to identify this T_H2 phenotype and aid in the stratification of illness.

Late-Onset Persistent Eosinophilic Asthma

Studies of subjects with severe asthma have identified a distinct group of patients with recurrent exacerbations, marked eosinophilia, less atopy, and later onset of asthma.⁶ The key drivers of inflammation in this group are unknown but believed to be unrelated to allergic triggers. These patients with asthma tend to have decreased pulmonary function and persistent sputum eosinophilia despite corticosteroid use compared with subjects with allergic asthma. Airway eosinophilia is associated with thickening of the sub-basement membrane and high transforming growth factor- β

expression.²⁴ Unfortunately, biomarkers in this group have not been validated. Because these patients tend to represent a more severe cohort with frequent exacerbations and poor control with ICS therapy, they have been considered for targeted therapy with anti–interleukin (IL)-5 biologics but more data are needed.

Aspirin-exacerbated respiratory disease is a sub-phenotype of persistent eosinophilic asthma and is believed by most to be an endotype. It consists of asthma, chronic rhinosinusitis with nasal polyposis, and respiratory reactions after ingestion of nonsteroidal anti-inflammatory drugs. There is intense eosinophilic inflammation of nasal and bronchial tissues. Pathophysiologically, AERD is characterized by increased cysteinyl leukotriene production and increased expression of leukotriene c4 synthase. Kim et al²⁵ in a Korean population found that a genetic variant of tandem repeat in the soluble enzyme 5-lipoxygenase promoter was associated with severity of airway hyperresponsiveness in patients with aspirin-intolerant asthma. This makes sense from a biological standpoint because soluble enzyme 5-lipoxygenase and protein 5-lipoxygenase-activating protein are crucial for cysteinyl leukotriene production.²⁵ Further, as would be expected, cysteinyl leukotriene receptor antagonists (eg, montelukast) and 5-lipoxygenase inhibitors (eg, zileuton) have been shown to have beneficial effects in patients with AERD.

Allergic Bronchopulmonary Mycoses

Allergic bronchopulmonary mycoses is classified as an endotype of severe asthma caused by a hypersensitivity reaction to fungal colonization of the airways, typically by *Aspergillus fumigatus*. It involves the propagation of fungi along the airway. There is an association with cystic fibrosis, suggesting that an abnormality in epithelial function could predispose to this condition. This endotype is associated with bronchiectasis, mucus production, increased mold-specific IgE and IgG, eosinophilia, and obstructive lung physiology. Little is understood about the genetics of ABPM. Systemic corticosteroids remain the mainstay of therapy; anti-IgE therapy and antifungal therapy have shown benefit in case series.^{26,27}

Exercise-Induced Bronchoconstriction

Exercise-induced bronchoconstriction is bronchoconstriction triggered by exercise, mostly representing a mild phenotype of asthma.²⁸ This phenotype is typically associated with a younger age of onset, is more common in athletes with atopy, and has variable eosinophilic inflammation. The genetic and inflammatory nature of this phenotype is poorly understood but is believed to be, at least in part, mediated by T_H2. No distinct genetic predisposition or biomarker has been identified thus far.

Non-T_H2–Mediated Asthma

Non-T_H2–mediated asthma likely represents a significant proportion of all asthma cases, but it is not as well understood as T_H2-mediated asthma. These patients tend to respond poorly to corticosteroid therapy,¹² and currently, there have been no large-scale successful therapeutic trials in this group.²⁹

Neutrophilic Asthma

There are data to support a neutrophil-predominant asthma phenotype, but these data are mixed. Lung airway neutrophilia might be associated with lower lung function, more air trapping, and thickening airway walls.⁶ In fact, sputum neutrophilia has been reported in severe asthma and sudden-onset fatal asthma.^{10,11} However, it is important to note that sputum neutrophilia can be seen in patients as a consequence of treatment with corticosteroids. Novel mechanisms implicated in this form of asthma include

activation of immune responses to bacteria, viruses, or diet; activation of neutrophil elastase; and impaired nuclear recruitment of histone deacetylase.³⁰ Corticosteroids are less effective in this phenotype. Clinical trials in this group are limited and most, such as one looking at anti–tumor necrosis factor- α therapy, failed to show any improvement.³¹ One study suggested that neutrophilic asthma might be more responsive to macrolide antibiotics.³²

Extensive Remodeling Asthma

Another possible phenotype of asthma is extensive remodeling asthma, which is characterized by an accelerated decrease of lung function and irreversible or only partly reversible airflow obstruction. Remodeling of the airway can occur anywhere from the large to the small airways. Its pathogenesis involves epithelial damage, collagen deposition in the subepithelial reticular basement membrane, smooth muscle hyperplasia and hypertrophy, increased smooth muscle mass, mucus gland hypertrophy, and angiogenesis.

The concept of the epithelial-mesenchymal trophic unit points to the epithelium as the key tissue in remodeling.³³ Release of pro-fibrotic cytokines, such as epidermal growth factor and transforming growth factor- β , from damaged epithelial cells leads to fibroblast proliferation and myofibroblast activation.³⁴ Transforming growth factor- β , IL-11, and IL-17 have been implicated in the formation of subepithelial fibrosis. Early studies indicated that early intervention with ICS could mitigate the remodeling process; however, more recent studies have challenged this notion. These studies have identified the presence of a subset of patients who might be predisposed to remodeling despite treatment with ICS.^{35–37} Given the irreparable lung damage seen in this subset, it is important to identify biomarkers of remodeling and new targets for therapy.

Comorbidities

Genetics alone might not explain the diversity of asthma; in fact, many believe asthma is a manifestation of genetic and environmental interactions. Factors such as smoking, hormonal changes, infection, and obesity are comorbidities and possible confounders that can alter asthma phenotypes and their stability over time. Epigenetics might mediate the gene-by-environment interactions seen in asthma. Epigenetic phenomenon, such as DNA methylation, histone modifications, and microRNA changes, which affect gene expression, are being studied in attempt to explain the variability seen in asthma.³⁸

For patients with asthma, smoking is linked with increased symptoms, accelerated decrease of lung function, and impaired responsiveness to corticosteroids.^{39,40} In a British study of smokers with asthma, 6 weeks of smoking cessation was associated with improved lung function and decreased sputum neutrophilia compared with control active smokers.³⁹ A small study by Lazarus et al⁴⁰ found that smokers with mild asthma had an attenuated response to ICS but not to montelukast. Such evidence highlights the importance of considering patient comorbidities when evaluating and treating asthma.

The relationship between obesity and asthma remains controversial; it is unclear whether obesity is a mere confounder or a principal component of an asthma phenotype. Obesity can lead to changes in respiratory dynamics that mimic symptoms of asthma or lead to a generalized proinflammatory state.⁴¹ Cluster studies performed by Haldar et al¹⁶ and Moore et al¹⁷ provided evidence for the existence of an adult-onset, non-T_H2–related phenotype of women who were mostly obese, had minimal atopy, and had a large burden of symptoms. Further evidence of a possible obesity-driven phenotype comes from a study by Dixon et al⁴² who demonstrated that, after bariatric surgery, patients had improvement in airway hyperresponsiveness to methacholine challenge.

Applications of Phenotypes and Endotypes and Future Directions

Alongside the “disentangling” of asthma phenotypes and endotypes described earlier is a quest for corresponding noninvasive and useful biomarkers of asthma. Bronchial biopsy examinations and induced sputum looking for eosinophils are exceedingly cumbersome to perform and thus are impractical for routine clinical practice. As such, we have witnessed over the past decade a burgeoning of literature regarding noninvasive surrogate biomarkers of eosinophilic asthma. The hope is that in the near future these biomarkers will help identify phenotypes with clinical ease that might preferentially respond to specific emerging biologic therapies.

Biomarkers

According to Agache et al,³⁰ successful endotypes should be useful and cost efficient in daily clinical practice. To this end, noninvasive biomarkers of underlying genetic processes are being developed. Potential biomarkers for T_H2-mediated disease include measurements of sputum eosinophils, peripheral blood eosinophils, forced exhaled nitric oxide, and periostin, among others. Serum periostin was shown in one study of 59 patients with moderate to severe asthma to be the single best predictor of airway eosinophilia.⁴³ A recent study published in *Lancet Respiratory Medicine* suggested that peripheral blood eosinophil counts might serve as a surrogate marker of poor asthma control and exacerbations.⁴⁴ Such positive studies have fueled major interest in the quest for the identification and optimal use of noninvasive biomarkers. However, data to support the use of these biomarkers in clinical practice currently remain mixed.⁴⁵ It is unclear whether a single biomarker or a combination of biomarkers will prove to be most useful and reliable. Fewer potential biomarkers have been proposed for non-eosinophilic disease, but there is clearly a need for an easy means to identify this population with asthma that is often refractory to ICS.

Composite Phenotypes

Inhaled corticosteroids are a cornerstone of therapy for asthma; thus, understandably, much study has focused on predicting ICS responsiveness based on phenotype. In a recent study by Clemmer et al,⁴⁶ a more “holistic” approach rather than a focus on single phenotypes was used. They constructed a composite corticosteroid responsiveness phenotype using principal component analysis and found that this composite phenotype was more accurate than individual phenotypes in predicting a corticosteroid-responsive endophenotype. It remains to be seen whether individual phenotypes or composite phenotypes with corresponding biomarkers will become the most clinically useful in the future. Either way, we know that treatment response phenotypes will likely receive increased attention moving forward.

Personalized Care with Biologics

Recently, investigators have been taking a second look at phenotypes to discover meaningful classifications that allow for targeted treatment with biologics. Biomarkers are being used to identify patients most suitable for treatment with monoclonal antibodies, such as biologics targeted to IgE, IL-5, IL-4 receptor- α , and thymic stromal lymphopoietin. This approach is very well exemplified by the literature on mepolizumab, which was one of the first biologic drugs to be applied to a targeted population in double-blinded, placebo-controlled trials. Initial studies seemed to show no significant effect on asthma control with this agent, but when patients with an eosinophilic phenotype were preselected for trials, intravenous mepolizumab was effective in decreasing the rate of asthma exacerbations.^{47–50} This response seems plausible from a mechanistic standpoint, because IL-5 is the key driver of eosinophil expansion.

Rather than identify a very specific sub-phenotype, a biomarker or a group of biomarkers can be used to identify a pattern of inflammation that might have good predictive value. For example, periostin has been proposed as a biomarker for a more general “T_H2-high phenotype.”⁵¹ Woodruff et al⁵² performed a molecular phenotyping analysis of people with mild corticosteroid-naïve asthma. They used 3 signature genes (*POSTN* encoding for periostin, *CLCA1*, and *SERPINF2*) to identify subjects with the T_H2-high phenotype, which was found in 50% of the cohort. This phenotype was found to respond better to ICS therapy. Expanding on this concept, investigators of the anti-IL-13 monoclonal antibody lebrikizumab in severe asthma performed a subgroup analysis of treatment effectiveness in subjects based on high vs low serum periostin levels.⁵³ This analysis showed that patients with high periostin levels had greater improvement in lung function with lebrikizumab treatment than did the group with low periostin levels, thereby demonstrating that clinically useful biomarkers might help stratify patients and predict responsiveness to therapy. Likewise, Hanania et al,⁵⁴ in the Exploring the Effects of Omalizumab in Allergic Asthma study, identified a biomarker-high group (using forced exhaled nitric oxide, peripheral blood eosinophil count, and serum periostin) that had a greater decrease in exacerbation rate with omalizumab therapy compared with the biomarker-low group.

Lessons learned from clinical trials will likely translate from the research setting to clinical practice in the near future. Moving forward, it will be important in clinical practice to preselect patients with the greatest likelihood of benefiting from the therapy, particularly given issues such as the high cost of new biologics and the potential for side effects.

Conclusion

Until the past decade, the treatment of asthma was limited to several maintenance medications (anti-inflammatory drugs and bronchodilators) that were generally used in all patients irrespective of differences in disease characteristics. With the continued presence of severe refractory asthma and the emergence of new biologics, there is a resurgence of interest in identifying treatment-responsive phenotypes. Although various phenotype clusters and endotypes have been proposed, there is still much unknown about gene expression, the effect of environment and comorbidities, the stability of phenotypes over time, and the appropriate use of biomarkers.

Recent studies have successfully grouped patients as having a T_H2-high phenotype based on at least 1 biomarker or created composite phenotypes to predict responsiveness to drugs.

It may be that teasing apart discrete phenotypes could become less important and finding clinically meaningful classifications that predict treatment response will trump all further stratification. This remains to be seen. During the past century, there have been swings in the literature moving from stratification to simplification. This merely underscores the complexity of this heterogeneous disease known as asthma.

The current hope is that a better understanding of asthma heterogeneity will allow us to select treatments based on the greatest likelihood of therapeutic response, thereby improving asthma control and quality of life for patients. As the number of biologics for asthma continues to grow, physicians will have the opportunity to practice a more personalized approach to asthma care.

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