Asthma Phenotypes and Endotypes: An Evolving Paradigm for Classification

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Abstract: Asthma is a common chronic disease characterized by intermittent chest symptoms, variable airways obstruction, and bronchial hyperresponsiveness. Research performed over the past one to two decades has sought to better understand the heterogeneous clinical nature of asthma. Whereas older attempts at phenotyping asthma emphasized the duality of allergic vs. non-allergic asthma, more recent non-biased analyses have attempted to cluster patients by a multitude of possible features, including age of onset, atopy, severity of airways obstruction, and requirement for medication. Examples of these phenotypes include early-onset mild allergic asthma, later-onset asthma associated with obesity, and severe non-atopic asthma with frequent exacerbations. The elucidation of asthma phenotypes has been further refined by including information regarding pathophysiologic mechanisms present in different groups. These groups, called endotypes, include examples such as aspirin-exacerbated respiratory disease and allergic bronchopulmonary mycosis. A growing understanding of these mechanistically distinct groups, along with the identification of relevant cellular or molecular biomarkers, is already showing promise as a way of predicting clinical response to various asthma therapies. As the number of targeted treatments for asthma continues to grow, physicians will have the opportunity to practice an individualized approach to diagnosis and treatment, which will hopefully improve asthma outcomes and quality of life for these patients.

Introduction
The term “asthma” has been used to refer to a disease process characterized by intermittent chest symptoms (usually wheezing, tightness, cough, and dyspnea), reversible airways obstruction, and bronchial hyperresponsiveness (NAEPP, 2007). However, physicians have long suspected that patients with asthma can be separated into subgroups based upon clinical, physiologic, and pathologic characteristics. More recently, investigators have sought to correlate these generalizable clinical and laboratory traits with molecular biomarkers. In the following review, asthma phenotypes and endotypes will be defined and discussed, with an emphasis on diagnosis and treatment.

**Phenotyping of Asthma: the Search for Differentiating Characteristics**

A phenotype represents the outward manifestation of an individual’s underlying genetics, and may change over time in response to new environments. Disease phenotype may significantly affect choice of diagnostic tests and long-term prognosis, and most importantly predict responsiveness to specific pharmacotherapies.

Over the years, many different clinical subgroups of asthma have been described. These phenotypes may be classified into broad categories based upon a single variable, including symptomatic triggers, patterns of airflow obstruction, and disease severity. The most widely used parameter for classifying asthma has been the separation of patients based upon atopic status. Approximately 50% of adult asthmatics are identified as being allergic to common and relevant airborne allergens (Pearce *et al.*, 1999). While this strategy of phenotyping has identified patients who benefit significantly from both specific allergen immunotherapy (Abramson *et al.*, 2003) and anti-IgE antibody therapy (Tan and Corren, 2011), there are others, particularly those with severe disease, who may not fully respond to these approaches. Thus, the selection of a single dominant characteristic to categorize a given patient often leads to an inherent bias which may ignore the overlap between groups, making accurate generalizations difficult.

**Cluster Analyses**

Hierarchical cluster analysis is a statistical method which attempts to identify relatively homogeneous groups of patients based upon selected characteristics. By definition, this approach attempts to exclude bias in categorizing patients by avoiding *a priori* assignment of severity ratings.
Three recent large analyses performed in Europe (Haldar et al., 2008; Siroux et al., 2011) and the United States (Moore et al., 2010) developed clusters based upon age of onset of asthma, gender, allergic status, asthma symptoms, and lung function as well as other factors that varied between the 3 studies. It is noteworthy that phenotypes identified in all 3 analyses overlapped despite differences in patient populations, study designs, and lists of selected variables. All three studies identified a phenotype composed of subjects with early-onset allergic asthma and another phenotype which consisted mainly of females with late-onset, nonatopic disease, and higher percentages of sputum neutrophils (Table 1). Both Haldar et al. and Siroux et al. also identified groups with mild asthma. The groupings which emerged from these investigations confirm impressions widely held by practicing physicians for many years; early-onset asthma is highly associated with allergy while patients with later-onset disease have more severe airflow limitation and less allergy.

A single cluster analysis has also been conducted in children (6-17 years) with asthma across a range of severities (Fitzpatrick et al., 2011). All 4 of the clusters were strongly associated with histories of atopic dermatitis and atopy, although the degree of atopy as measured by number of positive allergy skin tests and total serum immunoglobulin E (IgE) did differ significantly between groups. Major determinants of asthma phenotype included disease duration, the number of asthma controller medications, baseline lung function, and exhaled nitric oxide concentrations.

Phenotyping Based Upon Inflammatory Biomarkers

While the cluster analysis approach has provided non-biased information regarding certain phenotypes, identification of biologic markers reflecting the underlying disease process is equally important. Towards this end, a number of biomarkers have been examined as potential sources of information regarding response to therapy.

Inflammatory cells. Blood eosinophilia is identified in many patients with asthma, and markedly elevated blood eosinophil counts have been associated with a severe form of late-onset asthma (van Veen et al., 2009). T helper 2 (Th2) cells are thought to be largely responsible for stimulating eosinophilic infiltration into the airways, and the principal cytokines involved in the influx of eosinophils includes interleukin-4 (IL-4), IL-5, and IL-13. While IL-5 is instrumental in the differentiation, survival, and chemotaxis of eosinophils (Takatsu, 2011), IL-4 and IL-13 both upregulate adhesion molecules (e.g., vascular cell adhesion molecule 1, or VCAM-1) and facilitate the entry of eosinophils into tissue sites of inflammation (Luzina et al., 2012; Ingram and Kraft, 2012). Therefore, identification of blood or sputum eosinophils is usually evidence of Th2-type inflammation in the lungs.
Most work regarding the diagnostic utility of eosinophilia has employed sputum analyses. A recent investigation sought to determine the presence of sputum eosinophils in a group of 995 adult asthmatics (McGrath et al., 2012). Sputum eosinophilia (defined as ≥2% eosinophils) was found in 36% of inhaled corticosteroid (ICS)-naive subjects and 17% of ICS-treated subjects. In a longitudinal analysis of ICS-naive patients in this study, 22% had persistent sputum eosinophilia, 31% had intermittent eosinophilia, and 47% had no eosinophilia. Therefore, data from this large study suggests that approximately half of asthmatics have evidence of sputum eosinophilia.

**Proteins.** Th2 cytokines are generally not detectable in the bloodstream of patients with asthma and are difficult to measure in sputum samples. While they can be assayed from bronchial washings, this is not a practical approach to determining the molecular phenotype of a patient. Recently investigators have sought to identify bronchial-derived proteins that are associated with Th2 airway inflammation, which may then be used as surrogate markers for that phenotype. In a recent study of mild, corticosteroid-naive asthmatics, investigators analyzed airway epithelial brushings for the expression of three genes upregulated by the Th2 cytokine interleukin-13 (IL-13) including POSTN, which encodes periostin; CLCA1, which encodes calcium-activated chloride channel regulator 1; and SERPINB2, which encodes serpin peptidase inhibitor, clade B, member 2 (Woodruff et al., 2009). Approximately 50% of the patients had elevations of one or more of these markers in their airway epithelial tissue. Elevation of these proteins correlated with higher amounts of bronchial tissue IL-13 and IL-5 mRNA and greater numbers of eosinophils and mast cells. Importantly, subjects who had elevated levels of these Th2-associated proteins had better responses to inhaled ICS therapy, whereas the TH2-low group did not, suggesting that this distinction is predictive of corticosteroid-responsiveness. These findings are consistent with and help explain a wealth of clinical data indicating that a significant proportion of asthmatics do not improve with ICS treatment.

These observations have been extended to a new experimental therapy for asthma. Lebrikizumab, a humanized monoclonal antibody directed against IL-13, was studied in a randomized, placebo-controlled trial of patients with poorly-controlled asthma despite treatment with ICS or ICS/long-acting beta-agonist (LABA) combination (Corren et al., 2011). While lebrikizumab therapy caused minimal changes in forced expiratory volume in 1 second (FEV1) in the group at large, a subset of patients whose serum periostin was higher than the median for the group demonstrated statistically significant and clinically relevant FEV1 improvements. These results suggest that patients with an unmitigated Th2 phenotype with probable excess of IL-13 activity can be identified with a serum protein test, and that these patients respond to a therapy targeted at the specific defect.
Exhaled nitric oxide. Nitric oxide (NO) is produced by all tissues in the body, including the lung. Exhaled NO has been shown to correlate moderately with bronchial and blood eosinophilia in patients with asthma (van den Toorn et al., 2001; Jones et al., 2001). NO is produced by the enzyme NO synthase, which is under the direct control of the Th2 cytokine IL-13 (Chibana et al., 2008). Elevated concentrations of exhaled NO therefore reflect increased IL-13 activity, and indicate the presence of a Th2 phenotype. Exhaled NO has been shown to predict the likelihood of steroid responsiveness more consistently than spirometry, bronchodilator response, peak flow variation, or airway hyperresponsiveness to inhaled methacholine (Smith et al., 2005). Smith et al. correlated exhaled NO values with FEV1 improvement following treatment with ICS and found that the optimum discriminating level of NO was 47 ppb. In studies, exhaled NO was highly predictive of a positive response to ICS at concentrations higher than 33 ppb (Cowan et al., 2010) while levels less than 22 ppb predicted the likelihood of successful discontinuation of ICS (Zacharasiewicz et al., 2005). While these data were collected in patients with mild to moderate asthma, it is unclear whether these findings can be generalized to more severe groups of asthmatics.

Asthma Endotypes

An “endotype” is proposed to be a subtype of a condition defined by a distinct pathophysiological mechanism. In order to define possible endotypes, a recent group of experts selected 7 parameters, including clinical characteristics, biomarkers, lung physiology, genetics, histopathology, epidemiology, and treatment response and proposed that each endotype should form a distinct entity based on these parameters (Lotvall et al., 2010).

Allergic asthma. Allergic asthma usually begins in childhood or adolescence and is defined by evidence of hypersensitivity to airborne allergens. Allergic asthma is most often a Th2-dominant inflammatory process and both airway and blood eosinophilia are common but not universal. Although patients may manifest substantial differences in severity, cluster analyses of asthma phenotypes support the existence of allergic asthma as a distinct asthma endotype (Moore et al., 2010). In patients with more severe allergic asthma, inhaled corticosteroids tend to be less effective, necessitating the use of therapies which specifically antagonize IgE (i.e., omalizumab).

Aspirin-exacerbated respiratory disease (AERD). This endotype usually begins in adulthood and consists of asthma, chronic rhinosinusitis with nasal polyps, and acute respiratory reactions following the ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs). In addition, these patients usually have marked blood and sputum eosinophilia. Pathophysiologically, AERD has been associated with increased cysteinyl leukotriene production and increased expression of leukotriene C₄ synthase (Cowburn et al., 1998). As might be
expected, cysteinyl leukotriene receptor antagonists (e.g., montelukast) and 5-lipoxygenase inhibitors (e.g., zileuton) both have been shown to have beneficial effects in patients with AERD (Dahlen et al., 1998).

Allergic bronchopulmonary mycosis (ABPM). ABPM is an unusual and severe presentation of asthma caused by a hypersensitivity reaction to the colonization of the airways by fungi, most commonly Aspergillus fumigatus and occasionally other species. In addition to fungal-specific IgE and IgG, this asthma endotype is characterized by markedly elevated blood eosinophil counts and total IgE levels and a mixed pattern of neutrophilic and eosinophilic airway inflammation (Greenberger, 2001). In the absence of treatment, patients with ABPM may develop bronchiectasis and fixed airflow obstruction. Therapy with oral (not inhaled) corticosteroids and oral antifungal agents are directed at the 2 principal components of the disease process.

Late-onset asthma. Studies of individuals with late-onset asthma in adulthood have identified a distinctive subgroup of patients with a pattern of recurrent severe exacerbations (Miranda et al., 2004). Pulmonary function in these patients is often lower than in allergic asthmatics, marked eosinophilia may be present in both blood and sputum, and atopy is much less common (Haldar et al., 2008). A significant proportion of these patients are not well-controlled on inhaled corticosteroids and require oral corticosteroids on a recurring or chronic basis. As IL-5 has been implicated in these patients, anti-IL-5 antibody therapy has been suggested as a possible treatment for this endotype (Haldar et al., 2009).

Cross country skiing-induced asthma (CCSA). Exposure to cold, dry air combined with intense exercise is believed to provoke wheezing in this endotype. While most cases of exercise-induced asthma are noteworthy for being sensitized to common air-borne allergens, CCSA patients are not usually allergic and the inflammatory cell infiltrate is characterized by increased numbers of lymphocytes, macrophages, and neutrophils, but seldom eosinophils. In addition, these patients have evidence of airway remodeling with thickening of the basement membrane (Sue-Chu et al., 1998). Unlike exercise-induced asthma, CCSA is not usually responsive to treatment with inhaled glucocorticoids.

Effects of Comorbidities and Patient Behavior on Asthma Phenotypes

Asthma is associated with a number of comorbid conditions which may occur as part of the phenotype but may also interact with clinical symptoms across phenotypes. Patient behavior may also play important roles in modulating phenotypic expression.
Rhinitis. Allergic rhinitis is ubiquitous in patients with allergic asthma, and is an important characteristic of the allergic asthma phenotype. Recent investigations have demonstrated that allergic and nonallergic upper airway disease are both risk factors for developing asthma and are present in the majority of patients with asthma. There is some evidence that uncontrolled rhinitis can augment bronchial hyperresponsiveness and asthma severity, primarily via the spread of inflammation through the systemic circulation to the lung (Corren et al., 1992; Braunstahl et al., 2001). Along with these laboratory observations, population-based studies have also shown that treatment of rhinitis may beneficially affect asthma outcomes, including emergency room visits and hospitalizations for asthma (Corren et al., 2004). Thus, both the presence and treatment of rhinitis may significantly affect the asthma phenotype.

Obesity. As noted above, obesity has been identified as a key feature in specific asthma phenotypic clusters. However, obesity has also been to be a risk factor for developing asthma in individuals with and without allergy (Ronmark et al., 2005). Furthermore, it is known that obesity may worsen preexisting asthma, through both biochemical and mechanical effects, and potentially impair response to treatment.

Gastroesophageal reflux disease (GERD). It is estimated that more than 75% of patients with asthma also experience GERD, while people with asthma are twice as likely to have GERD as people who do not have asthma, especially those with treatment-resistant asthma (Leggett et al., 2005). There is a complex interplay between the two conditions, as GERD may occasionally worsen asthma symptoms, and asthma and some medications for asthma may worsen manifestations of GERD.

Vitamin-D deficiency. Most, but not all, studies have shown that low vitamin D levels increase the risk for asthma and allergies. Results from small trials of short duration suggest that vitamin D supplementation decreases the risk for asthma exacerbations. This may in part relate to the importance of vitamin D in regulating corticosteroid-responsiveness of immune cells (Sutherland et al., 2010). Thus, deficiency of this pleiotropic hormone may prevent usual therapies from being effective and cause the severity level of asthma to increase.

Patient behavior. Patient behaviors, including compliance with treatment, smoking, and psychiatric disease, may influence asthma severity. Smoking is particularly problematic, as it functionally renders patients corticosteroid-resistant (Chalmers et al., 2002). High adherence to treatment may improve disease outcomes and lead to a milder phenotype (Sumino and Cabana, 2013) while poor adherence, smoking, and psychologic problems may all severely complicate and worsen pre-existing asthma.
Practical Approach to Phenotyping of Asthma

Establishing a phenotype in an individual with asthma is most important in a patient with moderate to severe disease who is not controlled with usual therapy. Of course, alternative explanations for severe symptoms [e.g., vocal cord dysfunction (Newman et al., 1995)] and the presence of comorbidities should be thoroughly considered as well.

The clinical history should always include the age of onset of asthma, the severity level (using a system such as the NAEPP guideline), prior responses to therapies, aggravation of asthma by NSAIDs, and prior and current histories of atopic dermatitis, food allergy, allergic rhinitis, chronic rhinosinusitis, and gastroesophageal reflux disease. Diagnostic testing should include spirometry, before and after inhaled bronchodilator, a skin or blood test panel for specific IgE to common regional airborne allergens (including Aspergillus fumigatus, if ABPM is a possible consideration), a peripheral blood eosinophil count, and serum vitamin D level. These tests will contribute additional information to the categorization of phenotype, including determination of fixed airflow obstruction, an assessment of atopic sensitization, classification as eosinophilic (and thus Th2) or noneosinophilic asthma, and vitamin D status. If the blood eosinophil count is higher than 3%, it is very helpful in establishing that the patient has eosinophilic (Th2 phenotype) asthma. In the absence of blood eosinophilia, exhaled NO is an easily performed test, the elevation of which (greater than 25 ppb) strongly indicates Th2-type asthma. While this analysis is not yet widely available, a growing number of asthma specialists and pulmonary function laboratories are acquiring the equipment required to perform this test. Another test which may help clarify asthma phenotype is the sputum eosinophil count; however, this is a difficult test for the patient and the laboratory, except by facilities that do it routinely.

The determination of a Th2 or non-Th2 phenotype plays an important role in predicting response to treatments. Blood eosinophilia and elevated exhaled NO suggest that patients will be more likely to respond beneficially to corticosteroids. Severe asthma, while reportedly taking an ICS or ICS/LABA combination, should prompt a search for noncompliance with therapy. If the patient is adequately adhering to treatment, it would suggest that corticosteroid resistance is present, encouraging the physician to use maximal doses of ICS/LABA therapy, a leukotriene modifier and, if the patient has a relevant allergic trigger, omalizumab. Poor asthma control with a non-Th2 phenotype poses an even greater therapeutic challenge. In the presence of sputum neutrophilia, options include chronic macrolide therapy (Brusselle et al., 2013) and, in the case of very obese patients, aggressive attempts at weight loss (Boulet et al., 2010).
Future Directions

As new molecular targets, such as cytokines, emerge as possible causes of asthma, researchers have developed strategies for inhibiting those targets. In addition to IL-13 and IL-5, noted above, IL-17 is another molecule which may play an important role in certain subgroups of asthma (Petersen and Lukacs, 2012). In concert with the work of creating new therapeutic antagonists, molecular biomarkers are being developed which accurately correlate with the underlying pathophysiology. As periostin has been demonstrated to identify patients with a Th2 phenotype and probable excess IL-13 activity, similar markers will be sought which will identify patients with other defects.

Summary

Classification of subgroups of patients with asthma has made a great deal of progress in the last decade. While physicians have tried for many years to categorize patients by apparent clinical characteristics, such as atopy, this approach may be inclined towards bias. Hierarchical cluster analysis has demonstrated that there are at least 5 phenotypic groups which segregate according to age of onset, atopy, pulmonary function, requirement for medications, and a number of other factors. Investigators have now attempted to merge these clinical divisions with pathophysiologic considerations through the generation of endotypes. Towards this end, both cellular and molecular biomarkers, such as serum periostin and exhaled NO, have been shown to predict responsiveness to asthma therapy. Finally, evidence of comorbid disease states and aberrant patient behaviors should be carefully sought, as these may have powerful effects on the expression of lung function and symptom severity.

Disclosure

Dr. Corren is a consultant with Pfizer, Genentech, Vectura, and Merck. Dr. Corren has performed clinical trials (in the past year) with Array, TEVA, Genentech, Boehringer-Ingelheim, and ONO. Neither he nor his family owns any stock in any pharmaceutical company nor does he serve as an officer for any pharmaceutical company.

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