Asthma Phenotypes: Understanding Distinct Subgroups of Asthma Patients

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Asthma is a heterogeneous disease with respect to clinical features, cellular components of airway inflammation, and response to prescribed treatment. To better understand patients who remain symptomatic despite standard treatment with anti-inflammatory drugs and bronchodilators, investigators are exploring the molecular, genetic, and environmental determinants of asthma phenotypes in adults and children with asthma. The goal is to be able to classify patients by asthma phenotype and provide patients with treatment that is most likely to fit their individual needs.

Asthma Phenotypes in Children

Children who are referred to specialist care for difficult-to-control asthma despite standard firstline therapy are a heterogeneous group. Some children may have an incorrect diagnosis and therefore require a detailed assessment to exclude alternative conditions. Other children may have comorbid conditions that exacerbate asthma symptoms and interrupt asthma drug delivery. Children with true therapy-resistant asthma remain symptomatic even when their basic treatment needs are met. Anne M. Fitzpatrick, PhD, Emory University School of Medicine, Atlanta, Georgia, USA, described new efforts to understand variations in asthma severity and inflammatory responses in children.

The National Institutes of Health/National Heart, Lung, Blood Institute (NIH/NHLBI) Severe Asthma Research Program (SARP) is a new initiative that is designed to identify the clinical attributes that define distinct subgroups of childhood asthma severity. Toward this goal, SARP will undertake a detailed clinical characterization (phenotyping) and genetic analysis (genotyping) of children with asthma to understand the range of mechanisms that define the disorder.

Preliminary findings from SARP studies are already shedding light on the natural history of asthma in children. In one recent study of 161 children, SARP investigators identified four distinct subgroups of patients, defined by asthma severity, asthma duration, lung function, and other factors. In Group 1 (n=48), children had nearly normal lung function and minimal atopy. In Group 2 (n=52), children had slightly reduced lung function, more atopy, increased symptoms, and increased medication use. Children in Group 3 (n=32) were more likely to have comorbidities, increased bronchial responsiveness, and worse lung function. Finally, children in Group 4 (n=29) had the lowest lung function, most frequent symptoms, and greatest medication use. Each group included children with severe asthma, and no group corresponded fully to the definitions of asthma severity that are provided in current clinical guidelines [Fitzpatrick AM et al. *J Allergy Clin Immunol* 2011]. Other SARP studies are focused on the molecular phenotypes of severe asthma in children, with an emphasis on identifying novel biomarkers of inflammation and treatment response.

For decades, childhood asthma was regarded as a homogenous disorder with a common inflammatory mechanism, a direct association between inflammation and symptoms, and a uniform response to corticosteroid therapy. Findings from SARP studies may refine these assumptions and lead to new definitions of asthma subgroups that benefit from different management strategies.

Highlights from the
American Thoracic Society 2011 International Conference

Molecular Determinants of Asthma Phenotypes

T-helper (Th2) cytokines are major factors that control allergic airway inflammation for many patients with asthma. However, alternative pathways of inflammation or airway obstruction are also active in other patients, leading to pronounced heterogeneity in the molecular mechanisms that underlie reversible airway obstruction. Prescott Woodruff, MD, MPH, University of California, San Francisco, California, USA, discussed the emerging biomarkers that are used to identify distinct molecular phenotypes of asthma and predict response to treatment.

With current technology, molecular phenotyping requires tissue samples and therefore is more complex than phenotyping by sputum cell counts or other measures of airway pathology. However, molecular phenotyping offers several advantages over less invasive testing. Phenotyping by gene expression analysis identifies specific genes that contribute to the inflammatory and pathological process and therefore serve as targets for therapy. Gene expression analysis also identifies specific proteins that characterize the phenotype and may be developed into simpler diagnostic tests for future use.

In 2009, Woodruff and colleagues described 2 major molecular phenotypes of asthma, defined by degree of Th2 inflammation. Patients can be classified as having Th2-high and Th2-low asthma, based on gene expression analysis of Th2 cytokines, including IL-5 and IL-13, in bronchial biopsies. Asthma patients with high Th2 levels were more likely to respond to treatment with inhaled steroids, whereas those with non-Th2-driven asthma typically failed to respond to inhaled steroids [Woodruff PG et al. *Am J Respir Crit Care Med* 2009]. In the future, molecular phenotypes that are defined by Th2 levels may be used to guide treatment selection in patients with asthma.

Environmental Determinants of Asthma Phenotypes

While some investigators explore the microscopic determinants of asthma, others are looking to environmental factors to understand the heterogeneity of asthma. Louis-Philippe Boulet, MD, Université Laval, Québec City, Quebec, Canada, discussed recent research on the environmental determinants of asthma phenotypes.

The "allergic asthma" phenotype is the major phenotype that is defined by environmental factors. Compared with patients with nonallergic asthma, patients with allergic asthma have an earlier age of disease onset, are less likely to develop nasal polyps, and have increased levels of allergen-specific IgE, and total IgE, Th2 cells, and airway eosinophils are similarly involved.

There are, however, many other phenotypes that are related to the influence of microorganisms, smoking, and air pollutants.

Occupational asthma is another well-defined phenotype that arises after exposure to allergens or toxins in the workplace and must be managed accordingly. Even athletes seem to have specific clinical features of asthma, which may differ according to the sport that is performed, probably due to the characteristics of the air that is breathed during training and its content (cold air, chlorine derivatives, etc). For example, swimmers with asthma have fewer total respiratory symptoms (more frequent asymptomatic airway hyperresponsiveness) than athletes who participate in winter sports, such as snow skiing, for which symptoms such as cough predominate.

Certain medical comorbidities also shape the natural history of asthma and, as such, can be used to define asthma phenotypes. For instance, obesity has specific adverse effects on pulmonary function, including decreased expiratory reserve volume. Obesity is also associated with rapid shallow breathing and loss of bronchoprotection from deep inspiration. Obese patients with asthma often show reduced response to standard therapy, particularly with inhaled corticosteroids.

The goals of defining asthma phenotypes are to understand the pathophysiology, prognosis, and underlying determinants of the disease and ultimately to improve clinical decision-making. By understanding the unique influences of genetic, environmental, and other factors on asthma symptoms, physicians will be able to provide treatment that is tailored to each patient's asthma phenotype.

The editors would like to thank the many members of the American Thoracic Society presenting faculty who generously gave their time to ensure the accuracy and quality of the articles in this publication.