Clinical reviews in allergy and immunology

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Clinical phenotypes of chronic obstructive pulmonary disease and asthma: Recent advances

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Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Brendan J. Carolan, MD, and E. Rand Sutherland, MD, MPH

Activity Objectives

1. To understand phenotyping studies that lend additional information to the clinician when assessing the diagnosis, severity, and treatment of 2 clinically similar airflow limitation diseases (chronic obstructive pulmonary disease [COPD] and asthma).
2. To appreciate how exacerbation phenotyping and radiologic phenotyping in patients with COPD can guide prevention and treatment strategies.
3. To understand clinical phenotypes related to the progression of COPD and asthma.
4. To understand how clinical phenotyping relates to asthma progression, outcomes, and treatment strategy.

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Asthma and chronic obstructive pulmonary disease (COPD) are prevalent obstructive lung diseases, both of which are characterized by airflow limitation. Although both represent distinct pathogenic entities, there can be significant clinical and physiologic overlap between the 2 disorders, creating potential management difficulties for clinicians. Although practice guidelines for both conditions outline diagnostic and management strategies, asthma and COPD are highly heterogeneous, and the symptoms of many patients remain poorly controlled despite adherence to current guidelines. Recent advances in phenotyping studies have elucidated heterogeneity in these airway diseases and might represent the best opportunity to enhance diagnosis, predict outcomes, and personalize treatments in patients with asthma and those with COPD. This review will focus on recent advances in describing phenotypic heterogeneity in asthma and COPD, including the evaluation of multiple clinical variables, molecular biomarkers, physiologic and radiologic data, and factors associated with disease progression and frequent exacerbations. (J Allergy Clin Immunol 2013;131:627-34.)

Key words: *Biomarker, biopsy, cluster analysis*

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Together, asthma and chronic obstructive pulmonary disease (COPD) comprise the 2 most prevalent chronic lung diseases worldwide.[1,2] One of the essential challenges facing clinicians caring for patients with these 2 disorders is that although both share a spectrum of signs and symptoms and are characterized physiologically by expiratory airflow limitation, they represent distinct entities with apparently distinct pathogeneses. Thus, particularly in older patients, clinicians must carefully consider a number of variables in determining a correct diagnosis and appropriate treatment strategy. Clinical practice guidelines have attempted to differentiate between the 2 diseases in clinically meaningful ways, typically

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Abbreviations used
BMI: Body mass index
BODE: Body mass index, airflow obstruction, dyspnea, and exercise capacity
CAMP: Childhood Asthma Management Program
COPD: Chronic obstructive pulmonary disease
CT: Computed tomography
ECLIPSE: Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
FVC: Forced vital capacity
GOLD: Global Initiative for Chronic Obstructive Lung Disease
HR: Hazard ratio
ICS: Inhaled corticosteroid
OR: Odds ratio
SARP: Severe Asthma Research Program
SGRQ: St George's Respiratory Questionnaire

incorporating some combination of epidemiologic and clinical characteristics to help differentiate the 2 disorders. However, there can be significant clinical and physiologic overlap between asthma and COPD, and therefore distinguishing between the 2 diseases and integrating clinical, physiologic, and inflammatory data to optimize outcomes remains a challenge.

One area of clinical investigation with the potential to have great clinical impact is the study of airways disease phenotypes. Phenotyping studies typically evaluate the interrelationship of multiple clinical, physiologic, inflammatory, and radiographic variables of disease (rather than focusing primarily on one physiologic variable, as is the case with current guidelines), and there has been a recent proliferation of data and scholarly reviews in the area of airways disease phenotyping.[3,4] Herein, we focus on emerging data in this regard, with a particular focus on studies that have the potential to enhance efforts to diagnose, predict outcomes in, and refine treatments for patients with chronic airway diseases. These data will be applied to important disease characteristics of both asthma and COPD, including phenotypes related to underlying disease biology, radiologic manifestations, disease progression, and exacerbations.

GUIDELINE-BASED APPROACHES TO DIFFERENTIATING ASTHMA AND COPD

Guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) state that a clinical diagnosis of COPD should be considered in adult patients with dyspnea, chronic cough, sputum production, and a history of significant tobacco exposure. Typically, patients will present with cough, sputum production, or shortness of breath, and once such patients are identified, the diagnosis of COPD further necessitates the presence of a postbronchodilator FEV_1/forced vital capacity (FVC) ratio of less than 0.70 to demonstrate expiratory airflow limitation. The initial assessment of COPD is directed at determining disease severity by using airflow limitation, evaluating the effect of symptoms, and predicting disease course with regard to events such as exacerbations, hospital admissions, or death. Treatment is then linked to disease severity, with the goals of reducing symptoms, reducing exacerbation frequency and severity, and improving exercise tolerance and overall health status.[2]

Guidelines from the Global Initiative for Asthma indicate that asthma is a chronic airway inflammatory disorder with clinical manifestations that can be controlled with appropriate anti-inflammatory treatments. Patients typically present with symptoms such as episodic breathlessness, wheezing, chest tightness, and cough, and as in patients with COPD, evaluation of lung function is useful in assessing disease severity. In addition to measures of lung function, severity is based on assessment of daytime and nocturnal symptoms and frequency of bronchodilator use, and unlike COPD, asthma is described as being episodic in nature, both from the standpoint of symptoms and lung function impairment. As with COPD, treatment is linked to disease severity, with the ultimate goal being the achievement of clinical control of asthma, as reflected by the elimination of exacerbations, minimal symptoms and rescue β-agonist use, and maximal levels of activity and lung function.[1]

Although practice guidelines are useful in applying general principles to large numbers of patients in primary care settings, specialty physicians are often expected to provide expertise in circumstances in which the guidelines do not apply or where there is question about the appropriate diagnosis, treatment, or both, a phenomenon that often arises because of the potential heterogeneity of the 2 disorders. Heterogeneity in asthmatic patients has long been recognized in a number of features, including degree of airflow limitation, bronchodilator responsiveness, frequency of exacerbations, and response to therapies, particularly inhaled corticosteroids (ICSs). Recently, phenotype-based approaches to asthma have moved to include features such as airway inflammatory cell types and various molecular pathways in concert with clinical characteristics. COPD also represents a heterogeneous disorder, with at least 2 clinical subgroups (chronic bronchitis and emphysema) having been recognized for decades.[5] COPD can be further characterized by other factors, such as the degree, type, and distribution of emphysema, or nonspirometric physiologic parameters, such as diffusing capacity and hyperinflation. As with asthma, novel investigations to classify COPD phenotypes based on exacerbation frequency, radiologic parameters, and inflammatory biomarkers are currently underway.

CLINICAL PHENOTYPING IN PATIENTS WITH COPD AND PREDICTION OF MORTALITY

One approach to phenotyping in patients with COPD involves the use of clinical, physiologic, and radiologic data to elucidate factors that dictate disease heterogeneity and therefore might be relevant to diagnosis, prognosis, or both. The application of analytic approaches, such as cluster analysis, has advanced the study of phenotypes, facilitating the identification of unique groups of related variables in an attempt to identify factors that might relate to both underlying disease biology and clinically relevant outcomes.[6] Such approaches are typically hypothesis independent and use data obtained from large cohorts of well-characterized patients to identify relationships between clinical variables and outcomes.

In one example of such an approach, Burgel et al[7] used principal component analysis to assess the relationship between 8 COPD-related variables in a cohort of 322 French patients: age, smoking history, FEV_1 percent predicted, body mass index (BMI), exacerbation frequency, shortness of breath (evaluated by using the modified Medical Research Council scale), overall health status (measured by using the St George's Respiratory Questionnaire [SGRQ]), and depressive symptoms (measured by using the hospital anxiety and depression scale). The study population was 77% male, with a median age of 65 years and a