MAYO CLINIC

Chronic Obstructive Pulmonary Disease Phenotypes: Implications for Care

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CME Activity

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Abstract

Chronic obstructive pulmonary disease (COPD) phenotyping can help define clusters of patients with common characteristics that relate to clinically meaningful outcomes. In this review, we describe 7 clinically meaningful COPD phenotypes that can be identified by primary care physicians as well as specialists and that have specific management and prognostic implications: (1) asthma-COPD overlap phenotype, (2) frequent exacerbator phenotype, (3) upper lobe–predominant emphysema phenotype, (4) rapid decliner phenotype, (5) comorbid COPD phenotype, (6) physical frailty phenotype, and (7) emotional frailty phenotype.

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The Merriam-Webster dictionary defines *phenotype* as the "observable properties of an organism that are produced by the interaction of the genotype and the environment." There are probably as many "phenotypes" as there are patients with chronic obstructive pulmonary disease (COPD) worldwide. The 1995 American Thoracic Society guidelines recognized airway disease phenotypes in the Venn diagram illustrating the overlap between asthma, chronic bronchitis, and emphysema. However, the limited therapeutic tool kit available at the time rendered distinction along these pathways unproductive from the patient's or clinician's point of view.[1] In 2010, Han et al[2]

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proposed the following definition of COPD phenotypes: "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, the rate of disease progression, or death)." In 2011, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines took a stride toward COPD phenotyping by incorporating the impact of COPD on activity and exacerbation, with the recently published 2017 guidelines further refining recommendations for pharmacotherapy based on symptoms and exacerbations independent of airflow limitation.[3]

In this concise review, we chose to address 7 COPD phenotypes that can help individualize care. These are chosen based on implications regarding outcomes and day-to-day management, and not defined by delineation along anatomic, physiologic, or pathologic schema (Figure 1). Therefore, an overlap between phenotypes is expected and is likely the natural norm, and inclusion into one phenotype is not to the exclusion of the others. Although the asthma-COPD overlap phenotype, the frequent exacerbator phenotype, and the upper lobe–predominant emphysema phenotypes are well established in the COPD literature, the rapid decliner and comorbid phenotypes have been defined via cluster analysis.[4] Physical frailty and emotional frailty traits, although not well defined in patients with COPD, have long been recognized as having direct and independent therapeutic implications for management, in addition to substantially impacting quality of life, prognosis, and health care utilization (Table).

ASTHMA-COPD OVERLAP PHENOTYPE

Asthma and COPD are regarded as separate conditions with differing underlying pathophysiology. Although their individual clinical presentations may be "typical" and easily recognizable, in many patients, especially older people and smokers, determination of the etiology of chronic respiratory symptoms and airflow limitation as originating from asthma, smoking-related COPD, or both can be challenging.[5] The hallmark of the asthma-COPD overlap phenotype is the coexistence of increased variability of airflow in a patient with incompletely reversible airway obstruction. Based on the definition used and the population under study, the prevalence of the asthma-COPD overlap phenotype in patients with COPD has been reported to range from 12% to 55%.[6]

The attempt to define this overlap of phenotypes was prompted by an association with a higher symptom burden, poorer outcomes (including more frequent and severe exacerbations), and diagnostic and therapeutic uncertainties, because this set of patients was excluded from clinical trials that used strict definitions to identify patients with COPD or asthma.[5,7-10] The entity itself and its definition remain controversial because of a lack of broad consensus. However, until such time that obstructive airway diseases, including COPD and asthma, are categorized on the basis of genotypes and endotypes, identifying patients with this overlap retains clinical utility in choosing pharmacological therapy.

In 2012, a consensus-based guideline proposed that the diagnosis of the "overlap phenotype COPD-asthma" be made when 2 major criteria or 1 major and 2 minor criteria are met. The major criteria are (1) a very positive bronchodilator test result (increase in forced expiratory volume in the first second of expiration [FEV_1] of $\geq$15% of predicted and $\geq$400 mL), and (2) sputum eosinophilia and personal history of asthma. The minor criteria are (1) high total IgE level, and (2) personal history of atopy and positive bronchodilator test result (increase in FEV_1 of $\geq$12% of predicted and $\geq$200 mL) on 2 or more occasions.[11] To aid further research efforts in patients with overlap, a 2015 joint Global Initiative for Asthma–GOLD "description," instead of a "definition," of asthma-COPD overlap syndrome was put forth in the form of features that are likely to identify this entity.[12]

The age at which features of the overlap phenotype manifest also appears to be important. Patients with onset of asthma-COPD overlap after age 40 years (likely stemming predominantly from COPD with later onset of asthmalike features) seem to do worse compared with those who have the onset of asthma-COPD overlap before age 40 (likely stemming from asthma) regarding lung function decline, health care utilization, and mortality.[9]