The Asthma–Chronic Obstructive Pulmonary Disease Overlap Syndrome: A New Take on an Old Concept

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Problems cannot be solved with the same mindset that created them.

—Albert Einstein

Although asthma and chronic obstructive pulmonary disease (COPD) can be easily distinguished at their extremes, many patients manifest features of both diseases and are referred to by clinicians as having "asthma/COPD." In 1960, N. G. M. Orie, a Dutch pulmonologist, organized an international symposium on "bronchitis" in Groningen, the Netherlands to discuss the similarities and differences between asthma and COPD. Professor Orie and colleagues concluded that while the expression of disease was determined by both endogenous and exogenous factors, asthma and COPD have common origins. Most importantly, they strongly emphasized the need for careful phenotyping of patients before prematurely assigning them a disease label (1). This idea of common disease origins was dubbed "the Dutch hypothesis," and it stimulated a vigorous debate regarding the approach to diagnosing asthma and COPD (2–4).

In recent years, there has been increased recognition of the clinical overlap between asthma and COPD, called asthma–COPD overlap syndrome (ACOS) (5, 6). However, the term ACOS remains controversial (7, 8), without an agreed-upon definition (5). For example, it remains unclear if ACOS is a different disease manifesting in never-smokers with asthma, or instead identifies the evolution of severe asthma over time (9). Despite our limited understanding, ACOS is increasingly recognized as a clinical entity distinct from asthma or COPD, yet with overlapping features (10, 11). Several studies have shown that patients with ACOS have more active or severe disease, greater morbidity and mortality, and lower quality of life (12). These observations provide justification for conducting clinical trials specifically in patients with ACOS, and the need to further refine our understanding of airway disease and its optimal management in the "omics" era.

In this issue of *AnnalsATS*, Cosentino and colleagues (pp. 1483–1489) analyzed a large data set of patients from the COPDGene Study, a multicenter prospective observational study involving 21 clinical centers and more than 10,000 subjects with a history of smoking (13). They defined "ACOS-bronchodilator responsive" (ACOS-BDR) on the basis of a history of asthma or hay fever, the presence of airway obstruction with significant bronchodilator responsiveness, and minimal (<15%) emphysema present on computed tomographic (CT) chest images. "COPD with emphysema" was defined as (*1*) a history of asthma or hay fever, (*2*) airway obstruction without bronchodilator reversibility (post-bronchodilator change in FEV_1: <400 ml and <15%), and (*3*) the presence of emphysema on chest CT imaging (>15% of lung).

Of 10,192 enrolled subjects, 385 met criteria for ACOS-BDR and 620 met criteria for COPD with emphysema. Subjects with ACOS were younger, more likely to be African American, and had higher body mass index (BMI), and were more likely to be current tobacco smokers. The majority of subjects with ACOS met criteria for GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2011 COPD severity grade B.

Although those with ACOS had better lung function, they had similar severity and frequency of exacerbations compared with patients with COPD. Indeed, when adjusted for FEV_1% predicted in addition to age, race, sex, BMI, total pack-years, and current smoking, subjects with ACOS were more likely to experience severe and frequent exacerbations. Therefore, the authors concluded that bronchodilator responsiveness and lack of significant emphysema on CT scanning can identify patients with ACOS, who appear to be a high-risk group with distinct clinical features.

The importance of this study is that it used readily available metrics to define ACOS in a COPD population. Although diffusion capacity was not reported, quantification of emphysema on chest CT scans combined with history and spirometry provide a reasonable approach to distinguishing ACOS-BDR from COPD with emphysema.

Whereas other investigators have attempted to define ACOS in an asthma population on the basis of pathophysiological findings (9), a cluster analysis of the Severe Asthma Research

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Program cohort used clinical criteria to define five distinct groups. As compared with the other four groups, Cluster 5 subjects were more akin to those with COPD than those with asthma (14); they were older with more severe fixed airflow obstruction, had longer disease duration, less atopy, and mixed sputum eosinophilia and neutrophilia. They also had more frequent symptoms and albuterol use, with greater comorbidities, and higher health care use. In many ways, Cluster 5 subjects may actually represent patients who can be better described as having ACOS. Whether a given patient has predominantly COPD with asthma features, or asthma with COPD features, the practicing clinician needs pragmatic means to phenotype patients and determine the most appropriate therapy.

Another important finding in the study by Cosentino and colleagues is related to the GOLD 2011 severity grade. Nearly one-half of subjects with ACOS had grade B disease, indicating a high level of symptoms and disease instability, despite having better expiratory airway function on spirometry as compared to subjects with COPD. Although subjects with COPD had smoked more heavily as measured by cigarette pack-years, subjects with ACOS were much more likely to be current smokers, which could be driving the letter GOLD grade B designation. Subjects with ACOS also had a higher prevalence of comorbidities such as sleep apnea, diabetes mellitus, hypertension, and hypercholesterolemia as compared to patients with COPD. Having a higher BMI, to near obesity (29.6 kg/m^2), and a greater prevalence of gastroesophageal reflux disease raises questions related to diet, lifestyle, and nutrition as potential contributors to ACOS pathophysiology (15). Finally, despite having more severe disease, subjects with ACOS were less likely to be using an inhaled long-acting β-agonist, a long-acting muscarinic antagonist, or a combination inhaled corticosteroid/long-acting β-agonist than those with COPD. Whether (and to what degree) this difference in treatment is contributing to the differences in symptoms and exacerbation severity is not clear from the study.

Several questions remain to be addressed. First, there is a clear need for improved understanding of airway disease pathogenesis and its complex biological networks to help target future personalized therapies. Second, a consensus definition for ACOS, beyond the initial and laudable steps taken by authors of the 2015 GINA guidelines, is necessary to better identify and treat patients with ACOS. This effort could be facilitated by a joint statement on ACOS led by the American Thoracic Society and the European Respiratory Society. Such a document would serve to engage the global respiratory community in conducting much-needed research, pave the way for improved understanding of ACOS, and help inform the design of future clinical trials focused on ACOS.

Until more definitive studies are completed, it is reasonable to speculate that incorporating clinical history, indicators of atopy or allergies (e.g., skin testing, IgE), physiology (e.g., spirometry, bronchodilator response, PC_{20} bronchial challenge, air-trapping), imaging (e.g., chest CT, magnetic resonance imaging with hyperpolarized gases), biomarkers of inflammation (e.g., exhaled nitric oxide, blood and sputum eosinophils, periostin, C-reactive protein), and possibly genetic testing (e.g., alpha-1-antitrypsin) could help define patients as having asthma, COPD, or ACOS. However, challenges remain as not all of these parameters are available for clinicians. Even if they become available, the burden to patients and associated costs may limit their wide implementation in clinical decision-making. Molecular phenotyping (16) is rapidly advancing and may soon offer point-of-care, practical diagnostic tools to aid clinicians in making more specific diagnoses that could inform the pathophysiology of airway disease and help guide its therapy (17).

In the future, the use of diagnostic terms such as "asthma," "COPD," and "ACOS," will likely give way to the more unifying diagnosis of *obstructive airway disease* (*OAD*), as originally proposed by Professor Orie and colleagues. OAD would be further delineated on the basis of molecular phenotyping, genomic, and systems biology approaches, in combination with more traditional clinical and physiological parameters.

In the words of Albert Einstein, this new mindset can help us solve the problem of obstructive airway disease taxonomy and develop not only better treatments, but eventually invent lasting cures—if we are so lucky. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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