Asthma-Chronic Obstructive Pulmonary Disease Overlap

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KEYWORDS

- Asthma • Chronic obstructive pulmonary disease
- Asthma-chronic obstructive pulmonary disease overlap • Disease severity

KEY POINTS

- Asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO), as the term suggests, is comprised of clinical and biologic features of both asthma and COPD.
- ACO represents a distinct disorder with unique underlying pathophysiology.
- ACO is associated with increased disease severity including increased respiratory symptoms, disease exacerbations, and hospitalizations.

Asthma and chronic obstructive pulmonary disease (COPD) are two of the most common chronic respiratory diseases worldwide. The prevalence of asthma and COPD continues to increase, exceeding 358 million and 174 million cases worldwide, respectively.[1] Asthma is a heterogeneous disease characterized by chronic airway inflammation with reversible airflow obstruction that results in respiratory symptoms that vary in intensity over time.[2] Conversely, COPD is characterized by persistent and progressive airflow limitation that results from an abnormal inflammatory response in the lungs caused by chronic exposure to noxious stimuli like cigarette smoke or biomass fuels (GOLD), 2017 #54}.[3] Asthma-COPD overlap (ACO) is a syndrome comprised of clinical and biologic features of both asthma and COPD.[4] Although increasingly recognized as a clinical syndrome associated with high morbidity, a consensus definition of ACO does not yet exist. Generally, ACO applies to a subgroup of patients with asthma and persistent airflow obstruction (defined as postbronchodilator ratio of forced expiratory volume in 1 second [FEV_1] to forced vital capacity [FVC] of less than 70% of predicted) or patients with COPD that may exhibit variable airflow limitation and/or evidence of type 2 inflammation.[5] Additional investigations are needed to determine

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whether ACO represents a distinct disorder with unique underlying pathophysiology, whether ACO patients should be managed differently from those with asthma or COPD, and whether the diagnosis alters long-term outcomes. This article presents data about the clinical features of ACO, current information regarding the underlying pathophysiology of the syndrome, and current understanding of therapeutic options.

DIAGNOSTIC CRITERIA

Patients with persistent airflow obstruction who exhibit features of both asthma and COPD define the subset of individuals with ACO. This subpopulation remains poorly understood, as studies of this condition remain limited. To date, there is no standardized definition of ACO, with varying definitions across studies. Although the term was first used in the 2015 update on asthma management and prevention by the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD), neither organization provided a uniform definition.[4,6] Instead, the guidelines proposed that patients with equal features of asthma and COPD as defined by the age of onset, symptom patterns, lung function, family history of asthma, time course of the illness, and chest radiograph findings were subjects who had ACO.[4,6] Characteristics of ACO include: persistent airflow limitation (post-bronchodilator FEV_1/FVC of <70%); (b) FEV_1 improvement greater than 12-15% and greater than 200-400 mLs from baseline after bronchodilator therapy; and asthma diagnosis, atopy, exposure to harmful environmental agents, sputum neutrophilia or eosinophilia, and age older than 40 years (**Table 1**).

In 2016, a global expert panel proposed an operational definition for ACO consisting of several criteria. In order to have ACO, patients must have all major and at least 1 minor criteria. The 3 major criteria are: (1) persistent airflow limitation (postbronchodilator FEV_1/FVC <0.70 or the lower limit of normal) in patients at least 40 year old; (2) at least 10 pack/years of tobacco smoking or biomass fuel exposure; (3) documented history of asthma before the age of 40 years or bronchodilator responsiveness in FEV_1 greater

Table 1
Key criteria for asthma-chronic obstructive pulmonary disease overlap definition

Major Criteria	Definition	Number of Criteria Needed
Age	<40 y	3
Persistent airflow limitation	Postbronchodilator FEV_1/FVC <0.7 or lower limit of normal	
Smoking history	≥10 pack/year or equivalent indoor/outdoor air pollution exposure	
Asthma history	Documented history of asthma before 40 y of age or bronchodilator reversibility >400 mLs in FEV_1	
Minor Criteria	**Definition**	**Number of Criteria Needed**
Allergy history	History of atopy or allergic rhinitis	1
Bronchodilator reversibility	FEV_1 ≥ 200 mLs and 12% from baseline on ≥ visits	
Eosinophilia	Peripheral blood eosinophil count ≥300 cells/mL	

Adapted from Sin DD, Miravitlles M, Mannino DM, et al. What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion. Eur Respir J 2016; 48: 664–673.

than 400 mLs. The minor criteria include: (1) a documented history of atopy or allergic rhinitis; (2) bronchodilator response of FEV_1 of at least 200 mLs and 12% from baseline values on two or more visits; or (3) peripheral blood eosinophil count of at least 200 cells/mL.[7] In spite of having this expert panel definition of ACO, most studies to date have used a myriad of alternative diagnostic criteria. Several alternative definitions of ACO from previously published studies include

- Diagnosis of COPD with airway hyper-responsiveness or reversibility of airflow obstruction[8]
- Diagnosis of COPD with a history of asthma diagnosed before the age 40 years of age[9,10]
- COPD with at least one of the following: bronchodilator response of at least 12%, bronchial hyper-responsiveness, or a decrease in FEV_1 of at least 15% after exercise[11]

The variability in ACO definition across studies has resulted in conflicting epidemiologic and mechanistic studies for this subset of patients and highlights a large knowledge gap in the understanding of the pathobiologic mechanisms that underlie this clinical entity. Furthermore, the recent workshop statement from the American Thoracic Society (ATS) and the National Heart, Lung, and Blood Institute (NHLBI) determined that ACO should be considered an airway disease phenotype of mixed features and argued that there is a critical need for additional epidemiologic and mechanistic studies in the patient population.[12]

EPIDEMIOLOGY

Because of the differences in definition of ACO, the reported prevalence of ACO across studies has been variable. Estimates of ACO in the general population are between 2% and 3% worldwide.[13,14] In compiled data from 4 population-based studies conducted in developing countries (Peru, Argentina, Chile, Uruguay, Bangladesh, and Uganda), the population prevalence of ACO was 3.8% overall, varying from 0% in rural Peru to 7.8% in Bangladesh.[15] In studies of patients with airflow obstruction, the prevalence of ACO is much higher, ranging from 15% to 56%.[16] Population-based studies of adults with asthma suggest similar ACO prevalence rates (15% to 55%).[5,11,17] It has also been shown that up to one-fourth of patients previously diagnosed with COPD actually have features more consistent with ACO.[12,18]

RISK FACTORS

Risk factors for the development of ACO in subjects without pre-existing respiratory disease include older age, male sex, and a history of tobacco smoking.[14,19] However, compared with COPD patients, those with ACO are more likely to be female, younger, have less smoking exposure, and have higher rates of several comorbidities such as allergic rhinitis, anxiety, obesity, gastroesophageal reflux disease, and osteoporosis.[14,15,20] Notably, age, pack-years of smoking, lower education, and biomass exposure were risk factors for ACO compared with asthma, nonobstructed, and general population groups, while higher body mass index (BMI) was protective.[15]

NATURAL HISTORY OF ASTHMA-CHRONIC OBSTRUCTIVE PULMONARY DISEASE OVERLAP

Research on the association of ACO with clinical outcomes has produced inconsistent findings, although they tend to show the same or worse outcomes for ACO compared

with either asthma or COPD alone. In a large cross-sectional study of 5044 subjects participating in the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study, ACO was associated with decrements in lung function (FEV_1 and FVC) compared with asthma and COPD.[21] Although lung function normally declines every year after early adulthood, in patients with obstructive airway diseases, the rate of decline in lung function over time can be greater than what is expected because of age alone.[22–24] However, the association of ACO with lung function decline has been inconsistent across studies. In a longitudinal study of 6984 young European adults, the rate of decline in FEV_1 over the 9-year follow up study in ACO was similar to that of asthma, but less than with COPD.[25] In a smaller study of patients with obstructive lung disease, Fu and colleagues[16] reported similar rates of decline in FEV_1 for ACO compared with asthma and COPD. Although the impact of ACO on lung function decline is not yet known, the results of previous studies suggest that additional investigation on the impact of ACO on longitudinal lung function is warranted.

Epidemiologic studies demonstrate a more consistent association of ACO with increased disease severity including frequent exacerbations,[26] poor quality of life,[26] and increased use of health care resources[27] including emergency department visits and hospitalizations.[28] One study reported that ACO patients were hospitalized for breathing difficulty at greater frequency than those with other respiratory disorders (6.6% of ACO patients compared with 1.9% of asthma and 0.5% of COPD) in 1 year.[15] In the COPD Genetic Epidemiology (COPDGene) study, subjects with ACO (based on self-reported asthma history in subjects diagnosed with COPD) had a higher exacerbation frequency and had more airway wall thickening on quantitative analysis with computed tomography (CT) scan when compared to patients with COPD.[10] Mortality studies in ACO are also variable, with some demonstrating increased mortality,[29] while others demonstrate decreased [30] mortality; some other studies showed no difference in mortality between ACO and asthma or COPD.[31,32] Because these data demonstrate the significant impact of ACO on morbidity and health care utilization, an understanding of the mechanisms of disease is essential to reducing the health care burden associated with it.

BIOLOGICAL DETERMINANTS AND BIOMARKERS OF ASTHMA-CHRONIC OBSTRUCTIVE PULMONARY DISEASE OVERLAP

The pathophysiologic mechanisms underlying ACO, and indeed the question of its very existence, remain poorly understood. Mechanistic pathways that might otherwise emerge from randomized controlled trials (RCTs) are unavailable for ACO, as most RCTs on asthma or COPD trials exclude patients with overlapping features of these 2 diseases.

Biomarker studies in ACO are limited and have not been replicated in more than 1 population. In the COPD Genetic Epidemiology (COPDGene) study, participants with a history of self-reported asthma were considered to have ACO. In these subjects, immunoglobulin E (IgE) levels were higher in ACO subjects than in those with COPD alone.[10] Furthermore, ACO subjects also had at least 1 positive specific IgE titer compared with COPD controls.[10] Sputum cell counts have also been used as a noninvasive biomarker of airway inflammation and have been extensively studied in the context of asthma and COPD.

In a study sputum cell counts, patients with ACO had increased eosinophil counts compared with COPD patients, but similar levels of sputum eosinophils as those with asthma.[33] Unfortunately, the sputum cell counts did not correlate with the degree of airflow obstruction or bronchial hyperresponsiveness.[33] Thus, the role of sputum

cytokines as a biomarker of ACO remains unclear. In another study of sputum inflammatory biomarkers, the level of neutrophil gelatinate-associated lipocalin (NGAL) in sputum differentiated ACO subjects from those with asthma and COPD.[34] Furthermore, sputum NGAL levels correlated independently with the percentage of prebronchodilator FEV_1.[34]

There are 2 potential additional serum biomarkers that have shown promise for differentiating patients with ACO: periostin, a matricellular protein highly expressed in allergic disease,[35] and YKL-40, a glycoprotein secreted by airway epithelial cells.[35,36] In a small study investigating these serum biomarkers in ACO, serum periostin levels were increased in both asthma and ACO, but not COPD, whereas YKL-40 was high in ACO and COPD, but not asthma.[36] Notably, periostin and YKL-40 were significantly increased in ACO compared with asthma and COPD.[36] Finally, metabolites associated with enhanced energy and metabolic burden are dysregulated in ACO patients when compared with both asthma and COPD.[37] Although these biomarkers are of interest in ACO, additional investigations into these biomarkers in well-phenotyped cohorts are needed to identify replicable biomarkers in ACO (**Table 2**).

Several additional biologic mechanisms have also been proposed to impact ACO susceptibility. In asthmatics, exposure to noxious stimuli, like cigarettes or biomass fuel, can cause fixed airflow obstruction over time[38] due to progressive airway remodeling. Previous studies have demonstrated that cigarette smoke exposure results in increased neutrophilic inflammation in asthmatics who smoke.[39–41] These changes result in airway remodeling leading to fixed airflow obstruction that is characteristic of ACO.[42] Although few data are available to elucidate the biologic mechanisms underlying ACO, several pathways known to be involved in the pathogenesis of asthma and COPD may be implicated in the development of ACO. Mechanistic studies in asthmatic subjects demonstrate a role for interleukin (IL)-6, IL-8, and IL-17A in neutrophil chemotaxis in the airway of smokers with asthma.[40] Also, smoking may result in the proliferation of CD8+ T-cells in the asthmatic airway,[43] which is similar to that demonstrated in the airway of subjects with COPD.[44,45] These mechanisms have been implicated in the development of persistent airflow obstruction[46] and may play a role in the development of ACO.

Air pollution, which is associated with the development of asthma and COPD,[47] could also play a role in ACO, as suggested by a study in asthmatic adults, in which increased exposure to particulate matter $PM_{2.5}$ resulted in an increased risk of the development of this condition.[48] However, additional investigations are needed to determine if these exposures are indeed a risk factor for ACO.

Previous studies have also demonstrated the role of Th2-mediated inflammation in a subset of COPD patients that may also be important in the understanding of ACO. COPD is generally characterized by neutrophil-predominant airway inflammation,[49]

Table 2
Potential blood biomarkers that differentiate asthma-chronic obstructive pulmonary disease overlap

Biomarker	Type	Asthma	ACO	COPD
Periostin[35,36]	Blood	High	High	Low
YKL-40[35,36,55]	Blood	Low	High	High
NGAL[35,36,55]	Blood	Low	High	High
Immunoglobulin E[10]	Blood	High	High	Low

Data from Refs[10,35,36,55].

but a subset of COPD patients have eosinophilic disease,[50] suggesting that this subset may be particularly prone to the development of ACO. These mechanisms are worthy of additional investigation in a well-characterized cohort of ACO patients to identify the biologic underpinnings of this emerging condition.

POSSIBLE THERAPEUTIC OPTIONS

Aside from complicating the effort to determine ACOS pathophysiology, the exclusion of individuals with overlapping features of asthma and COPD from clinical trials[51] has also limited the understanding of how best to treat these patients. In addition to smoking cessation and discussing the importance of vaccinations, evidence-based treatment recommendations for patients with ACO based on existing evidence remain sparse. The recent COPD guidelines suggest that for patients with symptoms of COPD alone, treatment should include long-acting beta-agonist (LABA) therapy. In contrast, inhaled corticosteroids are reserved for those with evidence of asthmatic features.[51] The previously convened consensus panel recommended the use of inhaled corticosteroid (ICS)/LABA treatment for patients with ACO who demonstrate evidence of increased sputum eosinophils.[7] Other recommendations suggest that ACO patients should initially start on ICS therapy with step-up therapy, including LABA and or long-acting muscarinic agents (LAMAs).[24]

The studies of ICS treatment in ACO are conflicting. In an observational study of 125 patients with ACO, treatment with ICS did not decrease exacerbation rates or reduce the decline in lung function caused by ACO.[52] However, in a study of 127 subjects with ACO of varying severity, treatment with inhaled budesonide was shown to improve lung function, decrease sputum eosinophilia, and reduce exhaled nitric oxide (FeNO) in patients of all severity categories.[53] Compared with COPD patients, ACO patients may have an improved response to ICS/LABA combination therapy in improving FEV_1.[54] Thus, they should be considered for treatment with these options. However, well-powered studies are needed to determine the optimum treatment options for subjects with ACO.

SUMMARY

This article highlighted the existing literature regarding ACO epidemiology, risk factors, mechanisms of disease, and treatment options. ACO represents a subgroup of patients with features of both asthma and COPD, who have an increased risk of morbidity and mortality. Additional investigations into the underlying pathophysiology of ACO and inclusion of these patients in RCTs are essential to improve the understanding of ACO and to determine the appropriate therapeutic modalities for these patients.

CLINICS CARE POINTS

- Patients with persistent airflow obstruction who exhibit features of both asthma and COPD define the subset of individuals with ACO.
- Risk factors for the development of ACO in subjects without pre-existing respiratory disease include older age, male sex, and a history of tobacco smoking.
- ACO is associated with increased disease severity including increased respiratory symptoms, disease exacerbations, and hospitalizations.
- Apart from general recommendations of smoking cessation and immunization, evidence to guide specific pharmacotherapy for patients with ACO remains sparse.

DISCLOSURE

The authors have nothing to disclose that is, related to this work.

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