



Asthma/obstructive pulmonary disease overlap: update on definition, biomarkers, and therapeutics

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Purpose of review

Asthma/chronic obstructive pulmonary disease overlap (ACO) continues to be a poorly understood condition. This review discusses newly proposed criteria and potential biomarkers in ACO, to aid in diagnosis and research studies, and prudent therapeutic approaches.

Recent findings

A global expert panel proposed an operational definition consisting of major and minor criteria as a step toward defining ACO. Serum periostin and YKL-40 may serve as biomarkers for ACO. Clinically, a reasonable therapeutic approach to ACO is the early addition of a long-acting β -agonist (LABA) and/or a long-acting muscarinic antagonist (LAMA) to an inhaled corticosteroid (ICS).

Summary

Both the proposed criteria and the described biomarkers for ACO can help guide clinicians in identifying this condition as well as aid researchers in designing much needed future studies. In the meantime, clinicians can treat potential ACO patients using the above approach, until therapeutic studies in clearly defined ACO patients are performed.

Keywords

asthma/chronic obstructive pulmonary disease overlap, asthma/chronic obstructive pulmonary disease overlap syndrome, asthma, chronic obstructive pulmonary disease

INTRODUCTION

Patients with persistent airflow obstruction who exhibit features of both asthma and chronic obstructive pulmonary disease (COPD) are categorized into a group called asthma/COPD overlap (ACO) [1,2]. To date, ACO continues to be poorly understood as studies of this condition are lacking. This is a consequence of having no clear definition of ACO, hindering the ability of investigators to truly study it; along with clinical trials solely enrolling pure populations of either asthma or COPD patients, excluding those with overlapping features [3,4]. The inclusion of such patients is critical in understanding ACO, as it is uncertain whether ACO represents a distinctly different disorder from asthma and COPD, whether a diagnosis of ACO alters treatment options, and whether disease-related outcomes for ACO differ from asthma-only or COPD-only. Though uncertainty remains, it is argued that ACO is actually a unique entity. Two arguments for this position are that various proposed diagnostic criteria and studies of potential biomarkers distinguish ACO from both asthma and COPD [4]. Moreover, it is also argued that the presence of

ACO does affect treatment choices, as is exemplified by the current treatment recommendations set forth by COPD guidelines for patients with COPD symptoms only (treat with LABA only) versus COPD with an asthma component (add ICS). Finally, currently it seems ACO does affect clinical outcomes as it is reported to be associated with more frequent exacerbations, poorer quality of life, more rapid decline in lung function, higher mortality, and greater healthcare utilization compared to asthma or COPD [4,5,6]. This review will cover the prevalence/natural history, disease mechanism, influencing factors, potential biomarkers, proposed criteria, and therapeutic approaches with regard to ACO.

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KEY POINTS

- The 2016 global expert panel proposal of an operational definition of ACO, consisting of major and minor criteria, will enable clinicians to better diagnose ACO and aid researchers to design ACO-specific studies.
- Elevation in both serum periostin and YKL-40 levels may suggest the presence of ACO.
- Consider the early addition of a LABA and/or a LAMA to an ICS in ACO.

EVOLUTION OF A DEFINITION

Defining ACO has been a challenge as the condition likely represents a spectrum of disease and phenotypes/endotypes. Currently, there is a notable lack of consensus regarding how to define ACO, and thus no accepted definition exists. However, to attempt to define ACO, one must first define and understand asthma and COPD.

Asthma is a chronic disorder of the small and large airways characterized by inflammation, reversible obstruction, and bronchial hyperresponsiveness [1,3]. It typically presents in childhood or young adulthood, and is commonly seen in patients with allergic disease. It is a heterogeneous disease with different phenotypes/endotypes (e.g., exercise-induced asthma, aspirin-exacerbated respiratory disease, allergic asthma, and eosinophilic asthma). Although lung function usually normalizes between episodes in most, a subset of patients do demonstrate fixed obstructive patterns over time, particularly in those with sub-optimally-treated disease.

Like asthma, COPD is also an inflammatory respiratory disorder, but mostly of the small airways [2,3]. Patients have persistent respiratory symptoms and airflow limitation (post-bronchodilator ratio of forced expiratory volume in one second [FEV₁] to forced vital capacity [FVC] < 0.7). It is generally diagnosed in older individuals who have significant history of tobacco smoking. COPD has two main phenotypes (chronic bronchitis and emphysema), and is progressive despite treatment.

It is particularly difficult to distinguish asthma from COPD in smokers as well as older adults. Some patients easily fit one diagnosis, but there exists a subset of patients who have overlapping features of both illnesses, raising the possibility of ACO.

Currently, it is unclear how to best define ACO; that is, by clinical features, biomarkers, or a combination of these. The 2018 Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) have not defined

ACO, but instead have put forth a description for clinical use [1,2]. Per GINA and GOLD, ACO is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD.

Though a formal definition is lacking, in 2016 an expert panel has proposed a reasonable starting point for defining ACO using major and minor criteria [7^{***}]. This will be discussed in further detail below.

PREVALENCE AND NATURAL HISTORY

As there is no clear definition of ACO, true prevalence remains unknown, though has been reported to range from as low as 12% to as high as 61% of patients with lower respiratory illness [7^{***}]. Diagnosis is highly age-dependent with the diagnosis more likely to be made in older patients or in smokers [3]. Van Boven *et al.* [8] found that in comparison to patients with COPD ($n = 22\,778$), patients with ACO ($n = 5093$) were more frequently women, younger, had less smoking exposure, and had higher rates of certain comorbidities such as allergic rhinitis, anxiety, gastroesophageal reflux disease, and osteoporosis.

As for prognosis, the Copenhagen City Heart Study ($n = 8382$) found that patients with ACO and late-onset asthma had higher rates of FEV₁ decline and exacerbations, with poorer prognosis [5]. Meanwhile, Cosio *et al.* [9] found that ACO patients were predominantly men, receiving ICS, and had a better 1-year prognosis than clinically similar patients with COPD only. The significant disparity in findings among these studies further reinforces the need to better define and stratify ACO.

DISEASE MECHANISM

Likely, the overlap seen clinically in ACO is related to the overlap in the underlying inflammatory pathophysiologic mechanisms of both asthma and COPD [3]. Traditionally, the inflammation associated with asthma is considered to be mediated by T₂ high cytokines. However, some patients (who often have the most severe or recalcitrant disease) do not respond to T₂ high-targeted therapeutics. These patients are instead thought to have neutrophilic or pauci-granulocytic pattern of inflammation.

Meanwhile, the inflammation associated with COPD is generally considered to be mediated by neutrophils. However, increasing evidence suggests that some COPD patients have T₂ high phenotype. Eosinophils (in sputum, bronchoalveolar lavage, and lung tissue) have been reported in 15–40% of patients with stable COPD [10–12].

Furthermore, a cluster analysis by Ghebre *et al.* [13] examining sputum from patients with obstructive lung disease found three clusters: asthma predominant (eosinophilic), COPD predominant (mixed eosinophilic and neutrophilic), and ACO (neutrophilic). Such findings further highlight the need to study the inflammatory milieu present in ACO.

The heterogeneity in mucosal inflammation in asthma and COPD described above likely manifests as the various phenotypes observed clinically in both diseases.

INFLUENCING FACTORS

Although the underlying mechanisms of inflammation influence the development of ACO, environmental factors such as tobacco smoking, infections, pollutants, and diet likely also play a role [3]. Two of the best studied of these exposures are cigarette smoke and pollution.

Though definitely a driving factor in COPD, smoking is a habit seen in asthma patients as well [14]. It is uncertain whether tobacco exposure contributes to irreversible airway remodeling in asthma as it does in COPD. Of note, even in COPD, similar amount of tobacco exposure does not necessarily lead to the same outcome with regard to decline in lung function in all patients [3,15]. Moreover, smoking not only leads to increased symptoms in asthmatics, but it also decreases corticosteroid responsiveness [16–18]. Furthermore, active smokers have a more rapid annual rate of lung function decline, which may be mitigated by smoking cessation [19]. Currently, it is unknown whether asthmatics who smoke and progress to ACO represent the same phenotype as their nonsmoking counterparts [3].

As for air pollution, exposure has been linked to the development of asthma and COPD [3]. However, its role in the development of ACO is unknown. In their study of asthmatic adults ($n = 6040$), To *et al.* [20] did find that higher cumulative exposure to fine particulate matter and ozone had nearly a three-fold greater odds of developing ACO.

POTENTIAL BIOMARKERS

Two biomarkers that may be of utility in identifying ACO are serum periostin and YKL-40 (Table 1). Periostin is a matricellular protein highly expressed in allergic diseases [21,22[•]]. YKL-40 is a glycoprotein that is secreted by inflammatory and airway epithelial cells, and is upregulated in COPD [21,22[•]]. In a study of Japanese patients with asthma ($n = 177$), ACO ($n = 115$), and COPD ($n = 61$), Shirai *et al.* [22[•]]

Table 1. Potential asthma/COPD overlap biomarkers

	Serum periostin	Serum YKL-40
Asthma	high	low
COPD	low	high
ACO	high	high

ACO, asthma/COPD overlap; COPD, chronic obstructive pulmonary disease.

found that serum periostin is high in both asthma and ACO, but not in COPD. Meanwhile, YKL-40 is high in both COPD and ACO, but not in asthma. Moreover, the proportion of patients with both high serum periostin and YKL-40 levels is significantly greater in ACO than in asthma or COPD. These findings suggest that ACO has both hallmarks of asthma (T2 high inflammation) as well as COPD (neutrophilic inflammation), and thus a combined assessment using these two biomarkers may help in the diagnosis of ACO.

However, as discussed by Izuhara and Barnes [21] serum periostin and YKL-40 are not always upregulated in asthma or COPD. As such, periostin and YKL-40 are not biomarkers of asthma and COPD, but rather biomarkers of subtypes of asthma and COPD. Furthermore, they point out that Shirai *et al.*'s [22[•]] findings ultimately suggest that combined assessment of these two biomarkers alone is not sufficient to diagnose ACO accurately.

Regarding another possible biomarker, Iwamoto *et al.* [23] found that sputum levels of neutrophil gelatinase-associated lipocalin (neutrophil-derived inflammatory molecule) was significantly elevated in ACO compared to both asthma and COPD, suggesting potential utility in distinguishing ACO as a distinct entity.

Ultimately, further studies are needed to clarify the utility of combined assessment of serum periostin and YKL-40 in ACO, as well as to look for other potential biomarkers like sputum neutrophil gelatinase-associated lipocalin.

PROPOSED CRITERIA FOR ASTHMA/CHRONIC OBSTRUCTIVE PULMONARY DISEASE OVERLAP

Despite a lack of a formal definition, there is at least general agreement regarding some of the key features of ACO. Pulmonary specialty organizations from several countries, including the Czech Republic, Australia, Japan, and Spain, have published diagnostic criteria for ACO, with each varying somewhat [4[•]]. In 2016 a global expert panel, comprised of specialists and generalists from North America, Western Europe, and Asia, agreed that to advance

Table 2. Proposed major and minor criteria for asthma/COPD overlap

Major criteria	Minor criteria
Persistent airflow limitation in patients ≥ 40 years old	Personal history of atopy or allergic rhinitis
≥ 10 pack years tobacco smoking or equivalent air pollution exposure	Bronchodilator response of FEV1 ≥ 200 ml and 12% from baseline values on ≥ 2 more visits
Asthma before 40 years old or bronchodilator response of >400 ml in FEV1	Blood eosinophil count of ≥ 300 cells

Source: table derived from Sin *et al.*

FEV1, forced expiratory volume in one second.

ACO as a unique entity, a universally accepted definition is required (even an imperfect one) [7[■]]. The panel proposed an operational definition consisting of major and minor criteria (Table 2). They defined three major criteria that must be present for the diagnosis of ACO. These included: persistent airflow limitation (post-bronchodilator FEV1/FVC < 0.70 or lower limit of normal) in patients at least 40 years old, at least 10 pack-years of tobacco smoking or equivalent indoor or outdoor air pollution exposure (e.g., biomass), documented history of asthma before the age of 40 years old or bronchodilator responsiveness in FEV1 of more than 400 ml. They also proposed three minor criteria, of which only one is necessary for diagnosis. These include: documented history of atopy or allergic rhinitis, bronchodilator response of FEV1 at least 200 ml, and 12% from baseline values on two or more visits or peripheral blood eosinophil count of at least 300 cells/ml. Although arbitrary and requiring validation, this definition may enable clinicians to better diagnose ACO and aid researchers to design studies that can further provide meaningful knowledge about ACO.

THERAPEUTIC APPROACHES

Currently, no firm therapeutic approach exists for ACO. It has been argued that clinicians do not actually have the scientific information necessary to make specific treatment recommendations as studies in clearly defined patient populations of ACO have yet to be performed [4[■]]. With that said, clinical decision making with regard to ACO is simply guided by a clinician's overall impression of whether a patient has more asthma-like or COPD-like disease [3]. Physicians are then left to choose a treatment approach without substantiated evidence of efficacy in this specific group.

Despite the above, there are reasonable default approaches that should be considered. These include smoking cessation and pulmonary rehabilitation when indicated [3]. Moreover, stressing the importance of vaccinations (such as influenza and pneumococcal pneumonia) will be paramount for

potential ACO patients given their predisposition to increased morbidity. In addition, as described by Postma *et al.* [10] the recommended default position in ACO seems to be to start therapy for asthma (usually with an ICS), with step-up therapy often adding a LABA, LAMA, or LABA/LAMA combination possibly earlier in the treatment algorithm than would be considered for asthma. The previously discussed 2016 expert panel proposed that ICS combined with a LABA may be reasonable for ACO patients, especially in those with elevated serum or sputum eosinophils [7[■]]. This recommendation is reinforced by a study by Pascoe *et al.* [24] who found that the short-term benefits of ICS for COPD patients are greater in those with evidence of a T2 high phenotype (as indicated by elevated blood eosinophil counts $\geq 2\%$). Similarly, Siddiqui *et al.* [25] found that peripheral blood eosinophilia in COPD patients was associated with a favorable response to ICS and LABA therapy. As such, ACO patients could possibly derive similar benefits. Of note, as there is concern for the use of LABAs in patients with asthma, the presence of an asthmatic component warrants concomitant use of ICS [26]. However, this does raise the concern of possible adverse effects of ICS (especially when overused), as ICSs have been associated with an increased risk of pneumonia in patients with COPD [27].

As for LAMAs, though historically used mostly for COPD, this class of drugs has established a therapeutic role in step-up therapy in asthma. Peters *et al.* [3] found that the addition of tiotropium to a LABA and ICS combination improved symptoms and lung function in patients with uncontrolled asthma [28]. Moreover, leukotriene modifiers may be of value in those with atopy.

For potential ACO patients, the prudent approach may be to avoid monotherapy with LABA or LAMA alone. ICS should concomitantly be used so that symptoms are not simply masked by the LABA or LAMA, but instead the underlying inflammatory disease is appropriately treated with the ICS. In summary, until formal therapeutic trials are performed, it is reasonable to consider the early addition of a LABA and/or a LAMA to an ICS in ACO,

while considering potential adverse effects of each of these agents upon choosing therapy.

CONCLUSION

Currently, a consensus definition of ACO is lacking, but reaching one is necessary in order for meaningful studies to be performed. Potential areas of study include identifying ACO biomarkers as well as determining phenotypes and endotypes. Additionally, the efficacy of current therapies (ICS, LABA, and LAMA) need to be investigated, along with other drugs that have shown benefit in asthma and/or COPD (e.g., biologics and roflumilast [phosphodiesterase inhibitor]) [29–33]. As research indicates ACO to be an illness with significant prevalence, and one that leads to increased morbidity/mortality and healthcare utilization, further studies of this entity are certainly warranted.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

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The proposed criteria for ACO are a start at defining this entity. This will help clinicians diagnose ACO and aid researchers in designing ACO-specific studies.

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