



# The many faces of asthma-chronic obstructive pulmonary disease overlap

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## Purpose of review

Asthma and chronic obstructive pulmonary disease (COPD) are common diseases that often overlap. The term asthma-COPD overlap (ACO) has been used to define this entity but there remain several speculations on its exact definition, impact, pathophysiology, clinical features, and management. We reviewed recent publications on ACO to obtain more insight of current knowledge and outline future needs.

## Recent findings

Criteria for ACO vary from one publication to another and the many variable features of these patients underline the need to reconsider the evaluation and approach of patients with overlapping features based on clinical traits and underlying biological mechanisms. Epidemiological studies reveal that ACO patients have generally an increased burden of illness and healthcare use in addition to poorer quality of life (QoL) compared with asthma and higher or equal to COPD. However, their long-term outcome seems better than patients with COPD alone. Various methods have been proposed to evaluate these patients but their usefulness compared to 'classical' investigation of obstructive lung diseases remains speculative and needs further evaluation. Furthermore, there are no formal studies that examined and compared the different treatment strategies of well-characterized patients with ACO as such patients are usually excluded from clinical trials.

## Summary

ACO is a common condition with variable features and a high burden of disease. There is no consensus on its definition, diagnostic, and clinical features and more research should be done on its optimal management and long-term outcomes.

## Keywords

asthma, asthma-chronic obstructive pulmonary disease overlap, chronic obstructive pulmonary disease, phenotypes

## INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are common diseases. Although they have traditionally been viewed as distinct clinical entities, it is estimated that 15–20% of patients with either asthma or COPD have considerable overlapping features. This has recently led clinicians and researchers to revisit this overlap [1] but there seems to be a lack of consensus for a specific definition of this entity. As it would be quite difficult to compare the various types of asthma-COPD overlap (ACO) according to the many definitions used by different authors, we here include data from studies on patients who have some features both of asthma and COPD. Unfortunately, many studies are performed with suboptimal methodology and more rigorous phenotyping of the various categories of ACO will be needed to further explore their characteristics, pathophysiology, and clinical outcomes. Furthermore, many manuscripts use the term asthma-COPD overlap syndrome

('ACOS'), but according to the recent change proposed by the Global Initiative for Asthma (GINA) and the Global Initiative for Obstructive Lung Disease [2,3], we will use 'ACO' as a term for this condition as it is not considered a single entity but a group of phenotypes.

## DEFINITION OF ASTHMA-CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Although there is no current universal definition for ACO, recent review articles and consensus

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KEY POINTS

- ACO is common although there is no consensus on the criteria to define this condition.
- ACO patients generally show an increased burden of the disease compared with asthma and equal burden to COPD.
- There is a need to perform studies of well-characterized phenotypes of ACO, looking at the effects of the available therapies.

statements attempted to define criteria for patients with ACO based on differences in clinical features, radiographic findings, and diagnostic tests including biomarkers (e.g., blood and sputum eosinophils) and physiologic parameters (e.g., acute bronchodilator reversibility) [4<sup>■</sup>,5–8]. A roundtable consensus from an international group [5] suggests using major and minor criteria for the diagnosis of such an entity with the following key features to be included in such a definition: persistent airflow limitation on spirometry despite adequate administration of a short-acting bronchodilator in study participants 40 years of age or older; a ‘significant’ history of cigarette smoking or an equivalent lifetime exposure to biomass; and a physician diagnosis of asthma before 40 years of age (Table 1). More recently, an updated Spanish consensus attempted to simplify such an approach with a diagnostic algorithm that may be used as an initial guide to clinicians to identify such patients (Fig. 1) [4<sup>■</sup>,6,9]. However, a recent study utilizing this algorithm (CHACOS study) demonstrates that patients with a diagnosis of ACO according to these criteria are indistinguishable from nonsmoking asthmatics or COPD patients without eosinophilia [10<sup>■</sup>,11]. These data also support the idea that although the conventional diagnostic categories based on clinical presentation are valid for differentiating clear cases of asthma and COPD, they are, however, insufficient for identifying patient groups

who exhibit mixed or atypical inflammatory or clinical features. This underlines the need for a shift in the evaluation and approach of patients with overlapping features emphasizing on clinical traits and underlying biological mechanisms.

EPIDEMIOLOGY: NATURAL HISTORY

Most published studies on ACO have been observational and revealed that patients with ACO have higher overall burden including more exacerbations and healthcare utilization than those with either asthma or COPD [12–14]. A recent study utilizing data from commercial US health plan enrollees estimated an ACO prevalence of 6% among the 183 521 full study patients [15]. Comorbidities related to ACO were higher than in patients with asthma but similar to those with COPD. Mean total healthcare costs were significantly higher for ACO versus asthma but similar to COPD. However, another study from the United States utilizing the National Health and Nutrition Examination Surveys conducted from 2007 to 2012 suggested that the age-adjusted prevalence of ACO was much lower (1.05%) but reported that this overlap was associated with higher asthma and COPD severity as well as decreased lung function compared with asthma or COPD alone [16]. Another study from South Korea, reported that the prevalence and outcome of ACO were highly dependent on the different diagnostic criteria used which would compromise implementation of ACO interventions until a clear definition is established [17].

The various definitions and diagnostic criteria for both asthma and COPD have allowed focused analysis and characterization of subgroups or special populations with some standardization and reproducibility [12]. Existing evidence suggests that ACO is usually encountered in individuals slightly younger than those with COPD alone but older than those with asthma alone [18]. Most data report that individuals with ACO are between 60 and 68 years of

Table 1. Suggested criteria for Diagnosis of asthma-chronic obstructive pulmonary disease overlap

| Major                                                                                                 | Minor                                                                                  |
|-------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| 1. Postbronchodilator FEV1/FVC <0.7 or LLN in individuals ≥40 years of age                            | 1. Documented history of atopy or allergic rhinitis                                    |
| 2. ≥10 pack/year smoking<br>Or<br>Equivalent indoor or outdoor air pollution exposure (e.g., biomass) | 2. Bronchodilator response of FEV1 ≥200 ml and 12% from baseline on two or more visits |
| 3. Documented history of asthma before age 40<br>Or<br>Bronchodilator reversibility in FEV1 >400 ml   | 3. Peripheral blood eosinophil count ≥300 cells/μl                                     |

Diagnosis of ACO requires presence of all three major criteria and at least one minor criterion for diagnosis of ACO. ACO, asthma-chronic obstructive pulmonary disease overlap; FEV1, forced expiratory volume in first second; FVC, forced vital capacity; LLN, lower limit of normal. Adapted with permission [5].

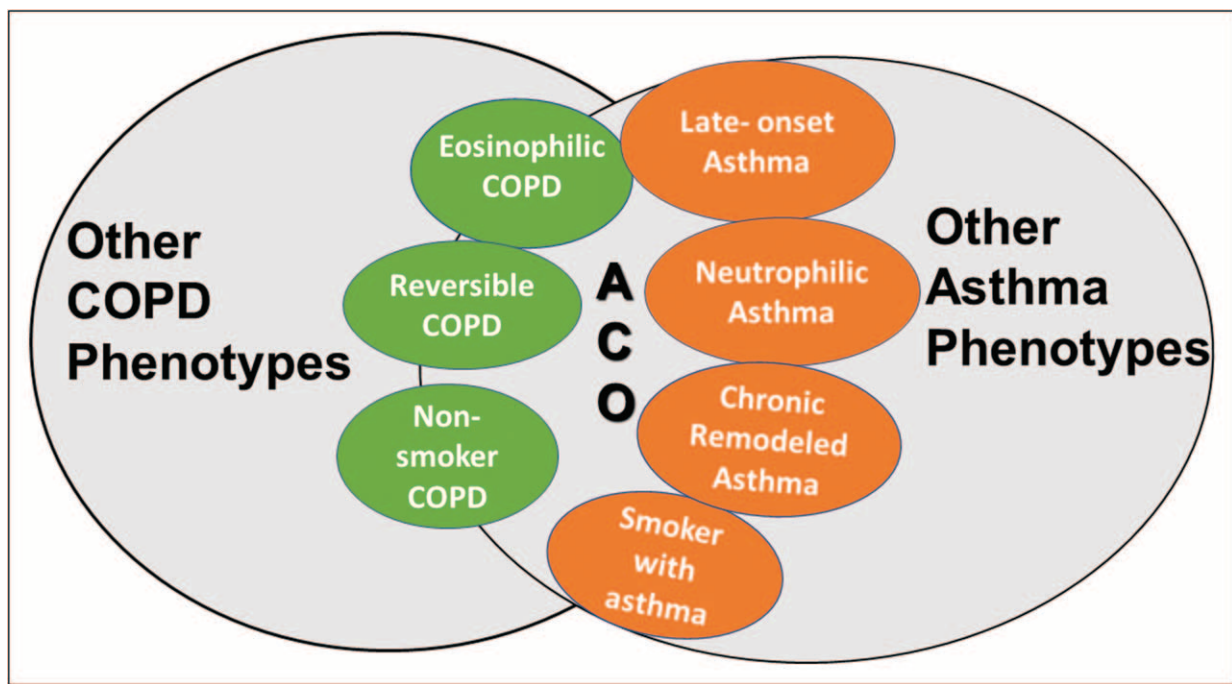


**FIGURE 1.** The multiple phenotypes of asthma-chronic obstructive pulmonary disease overlap.

age, but some information suggests that the incidence of ACO increases as age continues to advance [18]. Conflicting data currently exist in regards to sex and gender specifics in ACO; some reports suggest a higher prevalence of ACO in women, whereas others suggest that men are more often affected [19–23]. The heterogeneous definitions and diagnostic criteria utilized in much of the current ACO data largely accounts for this variability. The reported sex differences in ACO populations likely depend on how the ACO cohorts were gathered and analyzed as well as the diagnostic criterion that was utilized for ACO diagnosis. Cohorts generated from clinics or pools with more asthma patients will likely identify more women, whereas cohorts generated from individuals with more COPD will likely identify more male patients with ACO. A recent Canadian study examined data from the Canadian National Breast Screening Study from 1980 to 1985 [24]. A total of 4501 women with asthma were included of whom, 1701 (42%) developed fixed airflow obstruction meeting the criteria for ACO. The study revealed that risk factors other than cigarette smoke exposure including air pollution may contribute to the incidence of ACO in women. Until further information emerges, it is unknown how sex difference affects rates of ACO in addition to how it may affect therapeutic or management strategies. Although limited, available data from the United States suggest that African Americans make up a higher percentage of individuals with ACO than they do for COPD alone [25,26]. Although there is not enough evidence to

adequately comment on much of the disparity, it is reasonable to assume that the higher prevalence of asthma in this subpopulation accounts, at least in part, for the increased prevalence of ACO based on the way many studies have defined ACO as individuals with a history of reported asthma or asthma international classification of diseases-9 coding who have fixed airflow obstruction. In addition, a sub-analysis of the COPDGene study demonstrated that African Americans have less emphysema but similar amounts of air trapping and airway wall thickness compared with non-Hispanic Whites [26]. This analysis also demonstrated that despite having less smoking exposure and higher forced expiratory volume in first second (FEV<sub>1</sub>) values, African Americans had more reported pulmonary symptoms and less distance during 6-min walk testing. These differences may be in part explained by the fact that African Americans in this analysis had a much higher reported history of asthma [27]. Given the fact that bronchial wall thickening has been associated with more frequent COPD exacerbations as well as chronic bronchitis, one may infer that African Americans are more likely to present with phenotypic characteristics consistent with ACO. Ultimately, more research is needed to fully understand and determine whether race and ethnicity impact ACO.

There are limited long-term follow-up assessments on patients with ACO. In a recent Korean study, patients with ACO showed favorable longitudinal changes in lung function compared with

COPD patients over a median follow-up of 5.8 years [28]. In another study from Spain, patients with ACO defined using major and minor criteria described earlier were followed for 1 year [20]. About 15% of the COPD cohort fulfilled the criteria for ACO, and 98.4% of them sustained these criteria after 1 year. Patients with ACO showed a better 1-year prognosis than clinically similar patients with COPD.

## CLINICAL FEATURES AND PHENOTYPES

It has become increasingly obvious that ACO presents as multiple phenotypes, some including more features of asthma than COPD and the opposite in others [11]. Indeed, clinicians and researchers now realize that ACO is an umbrella term of multiple subphenotypes including patients who have predominant asthma with some COPD features and others with predominant COPD with some asthma features [29]. Three main clinical subphenotypes appear to encompass the majority of patients with ACO; the first includes patients with diagnosis of COPD with physiologic features of asthma (such as significant acute bronchodilator reversibility); the second includes patients with the diagnosis of COPD with biologic features of asthma (e.g., high blood or sputum eosinophils, high immunoglobulin E (IgE)); and the third includes those patients with existing diagnosis of asthma before age 40 but who have been exposed to smoke (or not, according to some authors) and demonstrate partial reversibility of airway obstruction suggestive of COPD. Recent observations show that this condition may present with various characteristics, not only depending of a predominance of asthma or COPD features, but as a result of diagnostic criteria used to determine if some features are related to asthma or COPD [30,31]. As mentioned previously, overall, however, although not universal, ACO is usually associated with an increased disease burden compared with asthma or COPD alone, more frequent exacerbations and poorer QoL [32]. The studies described in this document support this assertion.

### Smoking versus nonsmoking-related asthma-chronic obstructive pulmonary disease

First, some authors consider that the term ACO should be reserved to those who have a significant past history of smoking, whereas for others, the term 'ACO' has also been used in nonsmokers, when they have a component of fixed airway obstruction, corresponding to the initial definition of COPD [9,33]. There is a need, however, to gather more information on smoking versus nonsmoking ACO. [11] In

this regard, Boulet *et al.* [34] recently demonstrated that in patients with a previous diagnosis of asthma, those with a component of incomplete reversibility of airway obstruction (IRAO) associated with smoking had worse asthma control and poorer asthma QoL, higher residual lung volume, and a lower carbon monoxide diffusing capacity ( $D_LCO$ ) corrected for alveolar volume, compared with non-smoking asthmatics with IRAO [34]. However, no significant differences were observed in systemic or lower airway inflammation, a result which can be related to the fact that most previously smoking IRAO asthma patients had stopped smoking for variable time periods.

### Asthma-chronic obstructive pulmonary disease features compared to chronic obstructive pulmonary disease or asthma

Although, as previously reported, data on ACO vary from one study to another, overall, recent publications suggest that ACO patients represent a more severe and troublesome disease than either COPD or asthma. As reported in this section, patients with ACO usually have more respiratory symptoms, worse lung function, more frequent exacerbations, and hospitalizations particularly compared with COPD.

In a cohort of residents from Norway, Henriksen *et al.* [35] showed that participants with self-reported ACO generally had the highest frequency of respiratory symptoms compared with asthma or COPD. Furthermore, Ekerljung *et al.* [14], in a cross-sectional population sample, the West Sweden Asthma Study, reported that ACO patients, defined as doctor-diagnosed asthma or with clinical signs of asthma on examination, but with a  $FEV_1$  over forced vital capacity ( $FEV_1/FVC$ ) less than 0.7, not only had worse lung function than asthma only or COPD only but reported more respiratory symptoms and more respiratory-related emergency visits compared with asthma or COPD. Also, in two Northern European general population surveys, Mindus *et al.* [36] reported that ACO was associated with increased respiratory symptoms.

Park *et al.* [37] reported that in a retrospective review of 1504 patients with COPD from a Korean COPD Subtype Study cohort, ACO was characterized by less severe symptoms [38]. However, in this analysis, the criterion for ACO was only a positive response to a bronchodilator. In an assessment of 1065 study participants aged over 65 years, Sorino *et al.* [39] found that ACO was associated with impaired physical performance and functional ability. Furthermore, Tammola *et al.* [40] reevaluated 188 patients participating to the Seinäjoki Adult Asthma Study (SAAS) with adult-onset asthma,

12 years after diagnosis. They were divided into three groups based on smoking history and postbronchodilator spirometry values: never and ex-smokers with less than 10 smoked pack/years; non obstructive [(FEV<sub>1</sub>/FVC)  $\geq$  0.7] patients with  $\geq$  10 pack/years; and ACO patients with  $\geq$  10 pack/years and FEV<sub>1</sub>/FVC less than 0.7. ACO patients had lower D<sub>L</sub>CO diffusing capacity, higher blood neutrophil levels, and higher interleukin (IL-6) levels compared to the two other groups, in addition to reduced lung function and higher airway obstruction reversibility.

Furthermore, compared to COPD, respiratory-related exacerbations and/or hospitalizations were found either similar or more frequent while exacerbations either less or more frequently severe [37,41–43]. Using 5-year follow-up data from 4915 study participants, Hayden *et al.* [44<sup>■</sup>] reported that a history of childhood asthma or ACO was associated with an increased exacerbation frequency. In a primary care setting, Montes de Oca *et al.* [45] also found that the number of visits to a physician was higher (2.8 times) in ACO, asthma (1.9 times), or COPD (1.4 times) patients compared with those without these respiratory diseases. Another study looking at the prevalence and clinical characteristics of ACO according to various current criteria showed that compared with other criteria, patients with ACO diagnosed according to the modified Spanish criteria [4<sup>■</sup>] had better exercise capacity and lung function at baseline but higher risk of moderate to severe and total exacerbations during at least a 1-year follow-up period, than patients without ACO [46]. Bai *et al.* [47] also found that compared to COPD, ACO patients had greater exacerbation frequency. Patients with ACO tended to have earlier age of onset, longer duration of symptoms, better nutritional status, higher D<sub>L</sub>CO and airway resistance, more exacerbations in the preceding 12 months but shorter lengths of hospitalization [47].

From a retrospective cohort study of patients identified from National Health Insurance claims data in Taiwan in 2009–2011, Shantakumar *et al.* [43] showed that compared with patients with asthma or COPD alone, patients with ACO experienced a greater disease burden such as mean numbers of respiratory-related outpatient and emergency department visits and hospital or ICU admissions. From a database analysis, out of 1 488 613 patients by Wurst *et al.* [48] identified 316 987 with ACO. Patients with ACO had higher disease burden indicators compared with COPD alone and patients with obstructive asthma and COPD tended to be older. The ACO group had the highest proportion among patients over the age of 65 years of oxygen therapy (10.6%), short-acting bronchodilators use (29.3%), inpatient hospital visits (27.2%), oral corticosteroid use (16.1%),

shortness of breath, and emergency department visits (27.1%).

Poorer QoL was also associated with ACO in many studies and asthma-predominant ACO individuals displayed poorer socioeconomic status compared to the COPD-predominant ACO group [41,49,50].

Finally, in a specific type of ACO from occupational origin reported by Ojanguren *et al.* [51], defined as postbronchodilator FEV<sub>1</sub>/FVC less than 70% and smoking history  $\geq$  10 pack/years, these workers were less often atopic than those with ‘classical’ occupational asthma.

## Healthcare costs

Recent reports on healthcare use and medical costs confirm previous reports showing that they are higher in ACO compared to other obstructive diseases [43,52]. These are mainly due to treatment of exacerbations and hospital admissions.

## Long-term outcome and mortality

Here also, we find controversial data. In the study by Park *et al.* [28], patients with ACO showed favorable longitudinal changes in lung function, compared to COPD patients, over a median follow-up of 5.8 years. In the study by Caillaud *et al.* [41], compared to COPD patients, those with ACO had similar elements of prognosis such as mortality compared to COPD patients. Bai *et al.* [47] also suggested that patients with ACO were more likely to have a better prognosis and lower mortality than those with COPD alone.

However, in the Diet, Cancer, and Health cohort, Baarnes *et al.* [53] studied patients with ACO, defined as at least one hospital admission for asthma and one for COPD at different time points, and ‘incident ACO’, as at least one of the diagnoses occurring after enrollment in the study. Mortality rate was higher in ACO compared with COPD and asthma alone. Compared to COPD alone, mortality was higher in women with ACO and the excess mortality rate for ACO patients was most prominent for younger age groups [53]. Furthermore, Sorino *et al.* [39] suggested that individuals with ACO had higher mortality rates than controls. After adjustment for the main confounders, the risk of all-cause mortality remained significantly increased in study participants with ACO or COPD but not asthma.

## Evaluation

Although the optimal evaluation strategy of ACO remains to be determined, we can suggest that overall it should be similar to the evaluation of asthma or

COPD, ideally trying better define their various phenotypes. In this regard, the initial approach to ACO proposed by GINA and the Global Initiative for Obstructive Lung Disease is to evaluate the number of features that favor a diagnosis of asthma or COPD. Baarnes *et al.* [53] suggested that while screening for COPD in general practice among patients with no previous diagnosis of obstructive lung disease, patients with possible ACO could be identified by self-reported wheeze and/or significant bronchodilator reversibility of airway obstruction. However, we know that such reversibility can be found in COPD without past or present evidence of associated asthma and if a marked reversibility could suggest a component of asthma, as suggested in Spanish guidelines, remains a matter of debate [54]. Indeed, Christenson *et al.* [55] previously showed increased bronchodilator reversibility, and steroid-induced improvements in measurements of hyperinflation, in a subset of patients with COPD. So, such features could suggest an ACO component in COPD, although they can also be observed without evidences of an associated asthma-like profile [54].

Otherwise, Metting *et al.* [56], checking the diagnostic accuracy of a decision tree derived from data from 9297 primary care patients with suspicion of an obstructive pulmonary disease, reported that it correctly diagnosed 79% of asthma patients, 85% of COPD patients although only 32% of those with ACO, and suggested it could be incorporated into a computer-assisted diagnostic system. However, the value of such tool remains to be determined.

Furthermore, Wang *et al.* [57] suggested that computer quantification of 'angle of collapse' on maximum expiratory flow volume curve, defined as the upper right angle of the optimal couple of regression lines of the descending branch of the maximal expiratory flow-volume curve, could help diagnosing ACO syndrome. More studies should however be done on such features to determine their usefulness. Finally, in regard to radiologic features, Qu *et al.* [58] suggested that ACO patients have larger postbronchodilator variations of sagittal-lung computerized tomography measurements than patients with pure COPD, although diaphragm flattening and hyperinflation were not significantly different between patients with COPD and patients with ACO.

### Comorbidities

In most studies, comorbidities were increased in ACO compared to other airway obstructive diseases, mainly in smokers [59]. However, depending on the type of ACO, these were often different. For example, in the study by Nadeau *et al.* [60], out of a total

of 199 patients, patients with asthma and complete reversibility of airway obstruction had more comorbidities than asthma with IRAO and COPD although this difference was significant only with non-smokers with IRAO. The prevalence of comorbidities in both IRAO subgroups was intermediate between groups with complete reversibility of airway obstruction and COPD, with significant differences between smoking IRAO and nonsmoking IRAO only for hypertension, nasal polyps, and pneumonia. As expected, typical asthma-associated comorbidities tended to be more prevalent in nonsmoking IRAO patients and COPD-related comorbidities in smoking IRAO patients. Other conditions such as obesity and atopic diseases, and allergic rhinitis seem also more prevalent in ACO [35,41,59]. Looking at radiographic evidence of sinonasal inflammation in ACO, Hamada *et al.* [61] showed that frequency of radiographic evidences of sinonasal inflammation in patients with COPD, asthma, and ACO was 60.0, 94.9, and 72.2%, respectively. However, patients with ACO and COPD had only mild radiographic evidence of sinonasal inflammation, whereas moderate and severe radiographic evidence of sinonasal inflammation were detected only in patients with asthma.

In a series of four publications, Yeh *et al.* [62,63,64,65] suggested that compared to a non-ACO cohort, the risk of depression, of pulmonary embolism, of tuberculosis, and cardiovascular disease was higher in ACO cohorts. Furthermore, Oh *et al.* [66], in a study on osteoporosis in patients with ACO, reported that among patients with COPD and ACO, bone mineral density was negatively associated with the COPD Assessment Test.

Finally, prevalence of sleep disorders, including insomnia and sleep apnea, has been reported to be increased in ACO [14,36].

### PATHOPHYSIOLOGY AND BIOMARKERS

The various predisposing factors to either asthma or COPD may interact in a given individual to determine his/her phenotype of ACO [29]. Needless to say that the various endotypes or mechanisms involved in the different ACO presentations remain to be explored. As mentioned previously, ACO patients will present pathophysiological features both of asthma and COPD at various degrees and it suggests that underlying mechanisms are related in various degrees to either asthma or COPD endotypes. Some will have mainly features of atopy and type 2-type asthma airway inflammation, with eosinophilia, CD4<sup>+</sup> cells, increased IgE levels, involving some key mediators such as IL-4, IL-5, IL-9, and IL-13. Others will have mainly COPD-like features such as airway neutrophilia and increased

CD8<sup>+</sup> cells, involving mediators such as IL-6, IL-8, IL-13, and tumor necrosis factor (TNF- $\alpha$ ) [67].

In regard to airway structural changes, if asthma predominates, we expect to see features such as epithelial desquamation, subepithelial fibrosis, and airway smooth muscle mass, whereas in COPD, squamous cell metaplasia, increased mucus glands and parenchymal destruction may predominate. We previously showed early signs of COPD features on biopsies of smoking asthma study participants, even before the development of a fixed component of airway obstruction. [68] We, however, need studies on airway structural changes in various ACO phenotypes.

Otherwise, Christenson *et al.* [55] previously showed increased type 2-associated gene expression alterations in a COPD subgroup, associated with increased eosinophil levels suggesting type 2-associated inflammation. Also, showing the need to differentiate the various subtypes of ACO when looking at mechanisms, Perez-de-Llano and Cosio [11] reported that in patients with COPD and eosinophilic inflammation and smoking asthmatics with nonfully reversible airflow obstruction severe asthma (SA), the concentrations of IL-5, IL-13, IL-8, IL-6, TNF- $\alpha$  and IL-17 in serum were similar but Th2-related biomarkers such as periostin, fractional exhaled nitric oxide (FeNO), and blood eosinophils median values were higher in COPD and eosinophilic inflammation patients.

Overall, IgE levels of FeNO and sputum eosinophils are usually higher in ACO than in COPD and relatively similar compared to asthma [69–71]. Alcazar-Navarrete *et al.* [72] reported that patients with COPD and ACO characteristics show increased inflammation in the large and small airways and that eosinophil counts are associated with increased values of alveolar from bronchial components of nitric oxide.

GINA suggests that some features of asthma such as FeNO could present as either low or increased in ACO [2]. Duong-Quy *et al.* [73] suggested that the levels of FeNO in study participants with ACO were significantly higher than those in study participants with COPD. Furthermore, Hirai *et al.* [74] showed that the ACO phenotype could be characterized by peripheral blood eosinophilia and higher levels of IgE despite the Th2-low endotype.

Perez-de-Llano *et al.* [11] studied 109 ACO, 89 COPD, and 94 asthma patients. Serum levels of IL-5 were higher in asthma patients than in COPD patients, and IL-8 levels were higher in COPD patients than in asthma patients. Their values in ACO were intermediate between those in asthma and in COPD. The authors conclude that asthma and COPD may overlap in some patients, leading to

a mixed inflammatory pattern, and that IL-13 could be central to the regulation of inflammation in these conditions [10].

A most interesting study was reported by Ghebre *et al.* [75] recently. Based on the observation that exacerbations of asthma and COPD are heterogeneous, they reported three exacerbation biologic clusters. Cluster 1 was COPD predominant, with elevated blood and sputum neutrophil counts, pro-inflammatory mediators (IL-1 $\beta$ , IL-6, IL-6R, TNF- $\alpha$ , TNF-R1, TNF-R2, and vascular endothelial growth factor), and proportion of the bacterial phylum Proteobacteria. Cluster 2 showed increased blood and sputum eosinophil counts, type 2 mediators (IL-5, IL-13, C chemokine ligand (CCL13), CCL17, and CCL26), and proportion of the bacterial phylum Bacteroidetes. Cluster 3 had elevated type 1 mediators chemokine (C-X-C Motif) Ligand (CXCL10, CXCL11, and interferon- $\gamma$ ) and proportions of phyla Actinobacteria and Firmicutes. Each cluster had different percentages of patients with overlapping asthma and COPD [75].

## TREATMENT

It is difficult to determine what is the optimal treatment of ACO as previous studies on asthma or COPD usually excluded these patients and as there are insufficient randomized clinical trials to assess the effect of various therapies on its different phenotypes [76]. It is logical, however, to think that treatment should focus on the predominant features observed, either related to asthma or COPD. Furthermore, although there has been no consensus about the goals of ACO treatment, we can propose that they should include symptoms relief, improvement of functional status and lung function and prevention of exacerbations and loss of pulmonary function. As suggested for both asthma and COPD, prevention of exacerbations, prevention of disease progression, and treatment of comorbidities should be included in the treatment plan [76,77].

Treatment includes nonpharmacological and pharmacological interventions [32]. Smoking cessation, avoidance of contact with pollution or relevant allergens, patient education, and self-management including an action plan for exacerbations as well as regular follow-ups are suggested.

As in asthma, use of an inhaled corticosteroid (ICS) is considered required, and as in COPD, long-acting inhaled bronchodilators, in the form of a long-acting  $\beta$ -2 agonist (LABA) and/or a long-acting muscarinic agent (LAMA) are the mainstay of treatment. Combined therapy with an ICS and either a LABA or LAMA seems the most logical baseline treatment for ACO [3]. Although in some cases with

highly predominant asthma, only an ICS can be sufficient, in many patients it could not. Furthermore, if there is any suspicion of asthma, LABA should not be used as monotherapy [78]. The recently developed triple-therapy combining a LABA, a LAMA, and an ICS in the same inhaler should be of interest for ACO [79,80].

Furthermore, depending of inflammatory phenotypes, new biologics could possibly be useful in some patients with ACO [81]. In this regard, data from the Australian Xolair Registry reported by Maltby *et al.* [82] suggest that omalizumab may provide benefits in the management of severe allergic asthma with a COPD component with improvements in asthma control and QoL. We, however, need more studies on how to determine in whom these agents could be useful [83].

In regard to current practice, Amaral *et al.* [84] reported that regardless of its phenotypic classification, having ACO was significantly associated with  $\geq 2$  controller medications and FEV1 less than lower limit of normal, adjusted for confounding variables. Also, Wurst *et al.* [48] showed a higher ICS/LABA use compared with COPD alone in ACO. In a study by Ding and Small [85], in total, 9042 patients with asthma-only, 7119 patients with COPD-only, and 523 patients with ACO the most commonly prescribed regimens were ICS/LABA and LAMA; (ACOS 30%, asthma 1.4%, and COPD 32%), ICS/LABA (19, 41.5, and 17%, respectively), and LAMA (6, 0.4, and 19%, respectively); 18% of patients with ACOS were not prescribed an ICS.

Using Taiwan's National Health Insurance Research Database, Su *et al.* [86] conducted a nationwide population-based study to evaluate medication effects in patients with COPD and asthma. The use of LAMA or ICS/LABA combinations was associated with a lower risk of acute exacerbation in patients with ACO in this study.

Lee *et al.* [87] defined ACO as a personal history of asthma, irrespective of age, and wheezing in the last 12 months in a self-reported survey and a positive bronchodilator response. Among 152 eligible COPD patients, 45 (29.6%) fulfilled the criteria for ACO. ACO patients with mild-to-moderate airflow limitation showed a greater response in lung function after 3 months of ICS/LABA combination treatment.

## CONCLUSION

The recent publications on ACO stress the fact that its definition varies greatly among authors, and that more studies are needed to determine its optimal assessment and treatment. As reported in the American Thoracic Society/National Heart, Lung, and Blood Institute Asthma-Chronic Obstructive

Pulmonary Disease Overlap Workshop Report, much research remains to be done on ACO [88].

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## Conflicts of interest

There are no conflicts of interest.

## REFERENCES AND RECOMMENDED READING

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

- of special interest
- of outstanding interest

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