

INVITED REVIEW SERIES:  
UNRAVELLING THE MANY FACES OF COPD TO OPTIMIZE ITS CARE  
AND OUTCOMES

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## Asthma–COPD overlap syndrome (ACOS): A diagnostic challenge

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### ABSTRACT

Asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS may be a special phenotype of a spectrum of chronic obstructive airway diseases, in which asthma and COPD are at the two opposite ends. The prevalence of ACOS varies considerably due to differing criteria being applied for diagnosis. Patients with ACOS utilize a large proportion of medical resources. They are associated with more frequent adverse outcomes than those with asthma or COPD alone. ACOS is currently a diagnostic challenge for physicians because there are no specific biomarkers to differentiate ACOS from asthma or COPD. The approach to diagnosing ACOS depends on the population from which the patient originated. The management of ACOS should be individualized to ensure the most effective treatment with minimal side effects. In

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### Summary:

The diagnostic criteria of asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) is advocated by GINA/GOLD, but limited data are available regarding how ACOS patients respond to current medications. We present a case of a 64-year-old man with clinical features of both asthma and COPD. Over 5 years follow-up with combination treatment with inhaled corticosteroids and bronchodilators, he experienced a single episode of moderate exacerbation. However, post-bronchodilator FEV<sub>1</sub> decreased by 240 mL for 4 years (–60 mL/yr), indicating rapid lung function decline. Longitudinal studies are necessary to assess optimal interventions and natural course of ACOS.

### Main teaching points:

- ACOS is a disease of persistent airflow limitation combined with features of both asthma and COPD.
- In addition to inhaled corticosteroids and bronchodilator therapy, it is important to identify and eliminate modifiable risk factors such as smoking.
- The rapid rate of decline in lung function in ACOS patient might be due to the combination of asthma and smoking.

**this paper, we review the diagnostic criteria of ACOS used in previous studies, propose practical approaches to diagnosing and managing ACOS and raise some research questions related to ACOS.**

**Key words:** asthma, asthma-chronic obstructive pulmonary disease overlap syndrome, chronic obstructive pulmonary disease, obstructive airway disease, phenotype.

**Abbreviations:** ACOS, asthma-COPD overlap syndrome; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DL<sub>CO</sub>, diffusing capacity of the lung for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; HRCT, high-resolution computed tomography; ICS, inhaled corticosteroid; LABA, long-acting beta<sub>2</sub>-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; mMRC, modified Medical Research Council; PEF, peak expiratory flow; SABA, short-acting beta<sub>2</sub>-agonist; SAMA, short-acting muscarinic antagonist.

## INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are two of the most commonly encountered chronic lung diseases in clinics.<sup>1,2</sup> They are characterized by chronic inflammation and airway remodeling, but they differ in the patterns of inflammation, the structures affected and the prime anatomic site at which pathological changes occur.<sup>3</sup> These differences are most apparent when young non-smokers with asthma and older smokers with COPD are compared. However, it may be problematic to differentiate asthma from COPD, especially in older adults who currently smoke or have a significant history of cigarette smoking.<sup>4</sup> A joint project of Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) provides a clinical description of asthma-COPD overlap syndrome (ACOS) as follows: 'ACOS is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD'.<sup>4</sup> This description is intuitive but difficult to apply to daily clinical practice.

Since ACOS has overlapping characteristics of asthma and COPD,<sup>5</sup> ACOS may be a special phenotype of a spectrum of chronic obstructive airway diseases, in which asthma and COPD are at the two opposite ends.<sup>6,7</sup> ACOS is poorly characterized in terms of genetic risk factors, underlying mechanisms, pathological findings, clinical features, treatment response and prognosis. In this paper, we review the diagnostic criteria of ACOS used in previous studies, propose practical approaches to diagnosing and managing ACOS and raise some research questions related to ACOS.

## DIAGNOSTIC CRITERIA AND PREVALENCE OF ACOS

ACOS has not been defined definitively<sup>8,9</sup> and is known by different names, including overlap syndrome of asthma and COPD,<sup>10</sup> mixed asthma-COPD phenotype,<sup>11</sup> asthma combined with COPD,<sup>12</sup> coexistence of asthma and COPD<sup>13</sup> or COPD with asthmatic features.<sup>14</sup> However, ACOS has been the most commonly used term.

In reviewing previous studies, the prevalence of ACOS varies considerably because it has been diagnosed using different criteria, which depend on the study design and the population (Table 1).<sup>10-13,15-24</sup> In patients with a pre-existing diagnosis of asthma, the prevalence of ACOS was 29% when they had chronic bronchitis and/or impairment in the diffusing capacity of the lung for carbon monoxide (DL<sub>CO</sub>).<sup>15</sup> In patients with a pre-existing diagnosis of COPD, the prevalence of ACOS was 13% when the patients had self-reported, physician-diagnosed asthma before the age of 40 years<sup>19</sup> and increased up to 55% when the patients met any criteria for asthma.<sup>20</sup> Depending on the exposure type of either tobacco or biomass smoke, the prevalence of ACOS differed from 5% to 21% when the patients met at least two major criteria or one major plus two minor criteria for asthma as shown in Table 1.<sup>16</sup> In the general population, the prevalence of ACOS was 1.8% in the PLATINO study if ACOS was diagnosed based on symptoms and spirometry.<sup>23</sup> It was 2.7% in the US population if ACOS was diagnosed based on self-reported, physician-diagnosed asthma and COPD.<sup>12</sup>

## BURDEN OF ACOS

### Economic burden

Patients with ACOS utilize a large proportion of the available medical resources. They experience more frequent hospitalizations than patients with either asthma or COPD alone,<sup>22</sup> leading to higher health-care costs due to the fact that hospitalizations account for the largest proportion of the total health-care costs for COPD.<sup>25</sup> A retrospective study has shown that patients with ACOS incur higher health-care costs because they use more health-care services than those with COPD alone.<sup>26</sup> A recent study, using the 2009 database pertaining to South Korean National Health Insurance, demonstrated that the percentage of patients who visited emergency departments or were admitted to hospitals or intensive care units was significantly higher in ACOS patients than in patients with COPD alone.<sup>27</sup> In a US Medicaid population, patients with ACOS had a higher rate of utilization of any service (physician office visit, outpatient or inpatient service) than patients with either asthma or COPD alone. Patients were classified as ACOS if they had at least one medical claim for COPD and at least one medical claim for asthma.<sup>28</sup> The average annual medical cost was higher for ACOS (\$14 914) than for asthma (\$2307) or COPD (\$4879).<sup>28</sup>

### Disability

Because ACOS is common in the elderly, patients with ACOS experience multiple clinical problems that adversely impact their health.<sup>29</sup> ACOS is associated with more frequent symptoms of dyspnoea and wheezing, more frequent exacerbations, a lower respiratory-specific quality of life and lower levels of physical activity than COPD alone.<sup>24,30,31</sup> A multi-centre study showed that COPD patients with atopy, a feature of ACOS, were associated with a higher preva-

**Table 1** The prevalence of ACOS from different study populations with different diagnostic criteria

Study	Eligible age	Diagnostic criteria	Prevalence
From the population of patients with asthma Milanese <i>et al.</i> , 2014 <sup>15</sup>	≥65 years	Documented physician-diagnosed asthma + classical symptom of chronic bronchitis and/or DL <sub>CO</sub> < 80%	29%
de Marco <i>et al.</i> , 2013 <sup>13</sup>	20–84 years	Self-reported, physician-diagnosed asthma + self-reported, physician-diagnosed COPD	16–61%
From the population of patients with COPD Golpe <i>et al.</i> , 2014 <sup>16</sup>	≥40 years	At least 2 major criteria or 1 major plus 2 minor criteria. Major criteria: post-BD FEV <sub>1</sub> increase ≥15% and ≥400 mL over baseline, FENO > 40 ppb, and personal history of asthma. Minor criteria: elevated serum IgE, personal history of atopy, and post-BD FEV <sub>1</sub> increase ≥12% and ≥200 mL over baseline on 2 or more occasions.	5.0% for tobacco; 21.3% for biomass
Miravittles <i>et al.</i> , 2014 <sup>17</sup>	≥40 years	Similar to Golpe <i>et al.</i> except 'FENO > 40 ppb' is replaced with 'eosinophilia in sputum'.	6.5%
Kitaguchi <i>et al.</i> , 2012 <sup>18</sup>	71 ± 1 years	COPD stage 2–4 (post-BD FEV <sub>1</sub> /FVC < 0.70 and FEV <sub>1</sub> < 80%) + self-reported symptoms like asthma (episodic dyspnea, wheezing, cough, and chest tightness worsening at night or in the early morning)	27%
Hardin <i>et al.</i> , 2011 <sup>19</sup>	45–80 years	COPD stage 2–4 (post-BD FEV <sub>1</sub> /FVC < 0.70 and FEV <sub>1</sub> < 80%) + self-reported, physician-diagnosed asthma before the age of 40	13%
Marsh <i>et al.</i> , 2008 <sup>20</sup>	>50 years	COPD (post-BD FEV <sub>1</sub> /FVC < 0.70) + any criteria for asthma (post-BD increase in FEV <sub>1</sub> ≥ 15%, peak flow variability > 20% during 1 week of testing, and physician diagnosis of asthma in conjunction with current symptoms or inhaler use in the last 12 months)	55%
From the population of patients with a diagnosis of obstructive lung disease (either asthma or COPD) Fu <i>et al.</i> , 2014 <sup>21</sup>	>55 years	Compatible respiratory symptoms + positive airway hyper-responsiveness and/or positive reversibility testing + post-BD FEV <sub>1</sub> /FVC < 70% and post-BD FEV <sub>1</sub> < 80%	56%
Andersen <i>et al.</i> , 2013 <sup>22</sup>	>34 years	Any treatment for asthma + any treatment for COPD during the follow-up	16.1%
Kauppi <i>et al.</i> , 2011 <sup>10</sup>	18–85 years	COPD (post-BD FEV <sub>1</sub> /FVC < 0.70 or post-BD FEV <sub>1</sub> /FVC < 88% predicted) + any criteria for asthma (a post-BD increase in FEV <sub>1</sub> of ≥12%, a bronchodilator response of ≥15% or diurnal variation of ≥20% in PEF, and a decrease in FEV <sub>1</sub> of ≥15% in the exercise test)	14.6%
From the general population Menezes <i>et al.</i> , 2014 <sup>23</sup>	>40 years	COPD (post-BD FEV <sub>1</sub> /FVC < 0.70) + criteria for asthma (wheezing in the last 12 months + post-BD increase in FEV <sub>1</sub> or FVC of ≥200 mL and ≥12%)	1.8%
Chung <i>et al.</i> , 2014 <sup>24</sup>	>19 years	FEV <sub>1</sub> /FVC < 0.70 + a history of self-reported wheezing or whistling in the last 12 months	2.3%
Diaz-Guzman <i>et al.</i> , 2011 <sup>12</sup>	≥25 years	A positive response to both following questions: 'Has a doctor ever told you that you have asthma?' and 'Has a doctor ever told you that you have chronic bronchitis or emphysema?'	2.7%

ACOS, asthma-COPD overlap syndrome; COPD, chronic obstructive pulmonary disease; DL<sub>CO</sub>, diffusing capacity of the lung for carbon monoxide; FENO, fractional expiratory nitric oxide; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; post-BD, post-bronchodilator.

lence of chronic cough and sputum production than those without atopy.<sup>32</sup> Another observational study showed that patients with ACOS had a higher modified Medical Research Council (mMRC) dyspnoea grade ( $1.26 \pm 0.98$  vs  $0.99 \pm 0.88$ ,  $P = 0.01$ ) and a higher percentage of at least one severe exacerbation in the previous year (42% vs 18%,  $P < 0.01$ ) than patients with asthma alone.<sup>15</sup>

### Mortality

There are inconsistent findings regarding mortality in ACOS. In a 4-year follow-up study, the mortality rate did not differ among patients with ACOS, asthma and COPD ( $P = 0.320$ ).<sup>21</sup> However, this study had a small sample size and relatively short-term follow-up. In another 18-year follow-up study, patients with ACOS had the highest risk of death with a hazard ratio (HR) of 1.83 (95% CI: 1.34–2.49), followed by COPD only (HR 1.44, 95% CI: 1.28–1.62) and asthma only (HR 1.16, 95% CI: 0.94–1.42). These effects were attenuated after adjusting for baseline lung function, but ACOS patients still had the highest risk of death (HR 1.45, 95% CI: 1.06–1.98), followed by COPD only (HR 1.28, 95% CI: 1.13–1.45) and asthma only (HR 1.04, 95% CI: 0.85–1.27).<sup>12</sup>

### PATHOPHYSIOLOGY OF ACOS

There are genetic, pathological and functional overlaps between asthma and COPD.<sup>3,33</sup> ACOS appears to be a unique disease resulting from interactions between these genetic, pathological and functional effects in asthma or COPD.

Christenson *et al.*, using asthma and COPD datasets, showed that asthma-associated gene signatures were increased in COPD without a clinical history of asthma and were associated with asthma-related features.<sup>33</sup>

Pathologically, structural changes in the small airways contribute to the phenotypic overlap between asthma and COPD.<sup>34</sup> Asthma and COPD have common features at the epithelial layer: goblet cell metaplasia and squamous cell metaplasia. At the reticular basement membrane layer, COPD patients with asthma-like features have a thicker basement membrane than COPD patients without these features. There is an increased amount of airway smooth muscle in COPD, but it is less striking than in asthma.<sup>34</sup> HRCT of the chest reflects these structural changes. Patients with ACOS had greater gas trapping on expiratory CT scans,<sup>19</sup> less severe emphysema and a thicker airway wall on inspiratory CT scans than patients with COPD alone.<sup>30</sup>

Clinically, ACOS shares important risk factors with asthma and COPD. Bronchial hyper-reactivity representing asthma has been considered as a risk factor for COPD besides aging and exposure to noxious agents.<sup>35–37</sup> In adults, asthma and chronic exposure to cigarette or biomass smoke may interact to increase the risk of airway obstruction,<sup>38–40</sup> an important feature of ACOS. Cigarette smoking can alter airway inflammation in asthma from being eosinophilic to

neutrophilic with increased CD8<sup>+</sup> cells, thus becoming similar to that seen in COPD.<sup>41</sup> Smokers with asthma had a higher number of goblet cells, a higher number of mast cells, a lower number of eosinophils and a thicker epithelial layer than never smokers with asthma.<sup>42</sup> Moreover, ACOS becomes more prevalent in the elderly.<sup>13,26,27</sup> This might be related to a lifetime exposure to antigens, to extended exposure to environmental stimuli such as atmospheric pollution and environmental tobacco smoke, or to age-related physiological changes in the lungs.<sup>43</sup>

### A STEP-WISE APPROACH TO DIAGNOSING ACOS

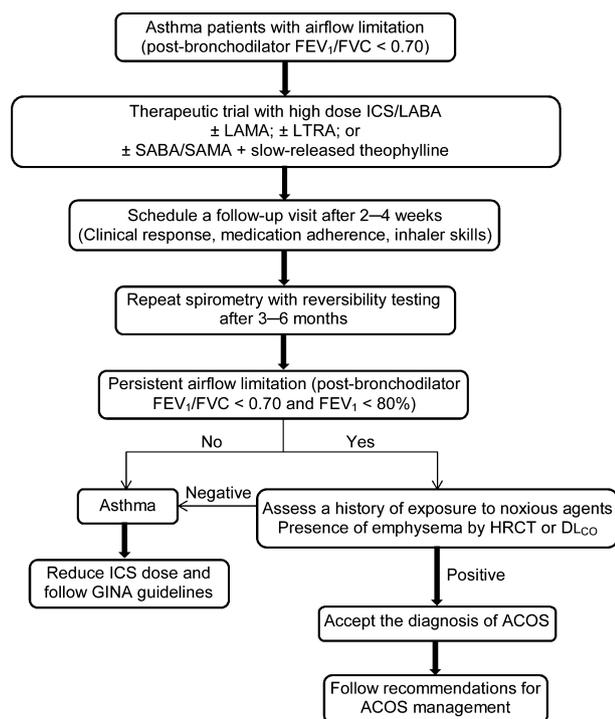
Patients with ACOS are usually diagnosed at the age of 40 years or older.<sup>44</sup> Their respiratory symptoms, such as productive cough, wheezing and dyspnoea, are persistent but may vary over time. These symptoms are partly, but significantly, reduced by treatment with bronchodilators and/or inhaled corticosteroids (ICS).<sup>4</sup> Patients with ACOS usually have a persistent airflow limitation that varies naturally and with treatment.<sup>4</sup>

The diagnosis of ACOS is challenging because there are no specific biomarkers to differentiate it from asthma or COPD.<sup>45</sup> Since a single factor, such as a respiratory symptom or a spirometric parameter, is unable to differentiate between asthma, COPD and ACOS,<sup>5</sup> especially in the elderly<sup>46</sup> and in current or former smokers,<sup>47</sup> major and minor criteria have been suggested to diagnose ACOS.<sup>16,17</sup> Nevertheless, these diagnostic criteria are not definitive and physicians often change diagnosis during follow-up. In addition, physicians may encounter ACOS diagnostic challenges in two clinic populations: patients with asthma who have developed irreversible airflow limitation and patients with COPD with a history of asthma. The following are our proposed practical approaches to diagnosing ACOS from these two populations.

#### In patients with a pre-existing diagnosis of asthma

ACOS should be considered in patients with asthma who have risk factors for developing persistent airflow limitation: childhood asthma with persistent wheeze from the first years of life into adulthood,<sup>35</sup> long-standing asthma without taking ICS,<sup>48</sup> adult-onset asthma<sup>49</sup> and severe or difficult-to-treat asthma.<sup>50</sup>

A step-wise approach can be applied for diagnosing ACOS in asthma patients with persistent airflow limitation (Fig. 1). We suggest that all asthma patients with airflow limitation could undergo a therapeutic trial for 3 to 6 months, which may include a combination of high-dose ICS and a long-acting beta<sub>2</sub>-agonist (LABA) plus add-on medications to optimize lung function and to exclude reversible airflow limitation.<sup>1</sup> ICS-naïve patients may be prescribed a combination of ICS/LABA. Patients that have been taking ICS or a combination of ICS/LABA for at least 3 months before attending may be considered for add-on medications, which may include a long-acting muscarinic antago-



**Figure 1** Flow-chart for diagnosing asthma–COPD overlap syndrome (ACOS) in patients with a pre-existing diagnosis of asthma. DL<sub>co</sub>, diffusing capacity of the lung for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; GINA, global initiative for asthma; HRCT, high-resolution computed tomography; ICS, inhaled corticosteroid; LABA, long-acting beta<sub>2</sub>-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, short-acting beta<sub>2</sub>-agonist; SAMA, short-acting muscarinic antagonist.

nist (LAMA);<sup>51</sup> a leukotriene receptor antagonist<sup>52,53</sup> or a combination of a short-acting beta<sub>2</sub>-agonist and a short-acting muscarinic antagonist plus a slow-released theophylline if no LAMA is available.<sup>1</sup> During follow-up, patients should be reviewed to make sure that they adhere to medications prescribed before repeating a spirometry with reversibility testing. ACOS is a possible diagnosis if the airflow limitation persists after the therapeutic trial. We acknowledge that the medications and the duration proposed in the therapeutic trial are debatable and need to be validated in future studies.

The diagnosis of ACOS is accepted if the patients have a history of exposure to noxious agents<sup>8</sup> and/or present with signs of emphysema on chest HRCT or on DL<sub>co</sub>.<sup>43</sup> It can be debated whether asthma patients with fixed airway obstruction should be labeled as asthma or as ACOS. In our opinion, asthma patients with fixed airway obstruction would be classified as ACOS if they have been exposed to noxious agents such as cigarette or biomass smoke. Otherwise, they should be classified as asthma. The elicitation of a history of exposure to noxious agents is very important. For example, Asian female patients with long-standing asthma should be assessed for a history of passive exposure to cigarette smoke. Male non-

smokers with long-standing asthma should be assessed for a history of occupational exposure to inorganic dust or chemical irritants. Chest HRCT and DL<sub>co</sub> may help differentiate ACOS from asthma. However, the cut-off point for the level of emphysema on HRCT or for DL<sub>co</sub> to differentiate the two diseases has not been established.

### In patients with a pre-existing diagnosis of COPD

Physicians are more likely to label asthma with fixed airway obstruction as COPD than to label COPD with partially reversible airway obstruction as asthma.<sup>54</sup> Therefore, a proportion of patients with a pre-existing diagnosis of COPD have indeed asthma or ACOS; it is necessary to identify them because they have differing specific treatments.<sup>55</sup> The utility of the following features for differentiating ACOS from COPD has been explored.

A history of physician-diagnosed asthma before the age of 40 years has been proposed to diagnose ACOS in patients with COPD.<sup>19</sup> However, a history of self-reported, physician-diagnosed asthma is not reliable in primary care patients aged 40 years or older because it is subject to recall bias and/or lack of confirmation of lung function testing.<sup>56</sup> Furthermore, a history of self-reported asthma is often insufficient to differentiate ACOS from COPD because not all patients with asthma have typical symptoms and respond to ICS—not all asthma patients have had a definitive diagnosis.<sup>9</sup> Physicians might need to elicit a history of childhood asthma from the patient's parents because nearly one half of patients with childhood asthma misclassify their childhood asthma status.<sup>57</sup> A thorough interview reviewing symptoms suggestive of asthma may help confirm a history of asthma before the age of 40 years.

Spirometry with reversibility testing should be performed routinely because positive reversibility testing is one of the criteria to differentiate ACOS from COPD.<sup>4</sup> However, caution should be taken when interpreting reversibility testing results in patients with COPD because the prevalence of positive reversibility testing varies according to the criteria used; COPD patients can also exhibit significant reversibility of lung function following the administration of short-acting bronchodilators.<sup>58</sup>

Induced sputum eosinophil counts may be helpful in differentiating ACOS from COPD. Patients with ACOS have higher sputum eosinophil counts than those with COPD alone.<sup>18,59</sup> However, induced sputum testing for eosinophilia has limited availability, and a profile of sputum cell counts may change over time.<sup>60</sup>

## RECOMMENDATIONS FOR ACOS MANAGEMENT

### General management

Because patients with ACOS are generally excluded from randomized controlled trials for either asthma or COPD, their response to therapy is largely

unknown.<sup>61</sup> In principle, ACOS has similar goals of treatment as asthma and COPD:<sup>62</sup> control and relief of symptoms, a reduction in the frequency of exacerbations, a reduction in the rate of decline in lung function and limiting adverse effects from therapeutic treatments.<sup>63</sup> Treatment may comprise the following components: patient education, smoking cessation, allergen avoidance, flu vaccination, pulmonary rehabilitation and management of any comorbidity.<sup>64–66</sup>

Patients with ACOS may benefit from a combination therapy of ICS/LABA.<sup>67,68</sup> A population-based longitudinal study showed that in COPD patients aged over 65 years with a co-diagnosis of asthma, who made up 28% of COPD patients, the introduction of ICS/LABA combination therapy was associated with a significantly lower risk of the composite outcome of all-cause mortality and COPD hospitalization than the introduction of a LABA alone (HR 0.84, 95% CI: 0.77–0.91).<sup>69</sup> However, the benefits of ICS/LABA in ACOS should be confirmed in randomized control trials.

LAMA may be considered in patients with ACOS with significant dyspnoea (mMRC dyspnoea grade > 1). A 12-week randomized, controlled trial showed that the addition of tiotropium 18 µg once daily to ICS appeared efficacious in COPD patients with concomitant asthma (or ACOS).<sup>70</sup> The percentage of patients with COPD exacerbations was lower in the tiotropium group (5.7%) than in the placebo group (10.7%). Another crossover trial in patients with asthma inadequately controlled by an ICS showed that the addition of tiotropium was superior to doubling the dose of the ICS and was not inferior to the addition of salmeterol with respect to all assessed outcomes, such as morning and evening peak expiratory flow, pre-bronchodilator forced expiratory volume in 1 s (FEV<sub>1</sub>) and the number of days with controlled asthma.<sup>71</sup>

### Individualized management

To optimize the treatment outcome, each patient may require further investigation to detect features that would need specific interventions. This approach is in line with the current trend in which a subset of patients who share clinical characteristics, outcomes and, more importantly, similar responses to existing treatments should be identified.<sup>72</sup>

As an example of individualized management, ICS may be considered in patients with ACOS with significant sputum eosinophilia (eosinophil count ≥ 3%). In a crossover trial, sputum eosinophilia predicts short-term clinical benefit from high-dose ICS treatment in COPD patients with eosinophilic bronchitis.<sup>73</sup> Another study showed that the eosinophil count and the eosinophil cationic protein concentration in bronchoalveolar lavage fluid were significantly higher in responders to prednisone than in non-responders among patients with COPD.<sup>74</sup>

Another example of individualized management is that current smokers with ACOS may require a higher dose of ICS than ex-smokers with ACOS.<sup>41,63</sup> A randomized, double blind, parallel group study showed that smokers with mild asthma had an

impaired response to ICS at low doses. This insensitivity could be overcome by ICS given at a higher dose.<sup>75</sup>

Elderly patients with ACOS may need special attention and careful management. Although spirometry can be adequately performed in more than 90% of older patients with obstructive airway disease, when technicians are appropriately trained and rigorous quality control is used,<sup>76</sup> it is still hampered by poor cooperation in this population.<sup>43</sup> With the lack of lung function data, diagnosis or severity evaluation is often delayed in the elderly. Thus, the initiation of ICS and/or LABA and follow-up monitoring to evaluate symptomatic improvement might be necessary. In addition, repetitive education and review of side effects should be performed because elderly patients usually have poor adherence to prescribed medications and more side effects due to interactions with medications prescribed for other comorbidities.<sup>77</sup>

### FUTURE ACOS STUDIES

Information related to ACOS is limited because ACOS patients have been typically excluded from clinical studies, that is, asthma patients from COPD studies or COPD patients from asthma studies. Long-term observation or prospective studies are required to answer the following research questions. First, which genes are the genetic risk factors for developing ACOS? By using genome-wide association studies, a recent study identified several novel genetic variants that are associated with ACOS.<sup>30</sup> Moreover, this study provided comprehensive information including genetic, clinical and imaging data associated with ACOS. From this initial step, further validation studies and fundamental research to understand the link between genotype and phenotype are necessary. Thus, the second question is what are the molecular pathways of ACOS? We also need to understand the underlying mechanisms of ACOS, identify specific biomarkers for diagnosis and develop target therapies. Third, what is the natural course or prognosis of ACOS? A 5-year follow-up study showed the natural course of ACOS with lung function decline.<sup>78</sup> The annual rate of post-bronchodilator FEV<sub>1</sub> decline in asthma patients with fixed airflow obstruction (−49.7 ± 10.6 mL), with features similar to ACOS, was similar to that in COPD (−51.4 ± 9.8 mL, *P* = 0.71), but worse than that in asthma patients with fully reversible airflow obstruction (−18.1 ± 10.1 mL, *P* < 0.01).<sup>78</sup> However, given that abnormal lung growth affects fixed airway disease development later in life,<sup>79</sup> a prospective cohort study would be necessary from early adulthood. Fourth, what are the optimal interventions for ACOS? Randomized controlled trials should be conducted on well-characterized patients with ACOS, especially in the elderly.<sup>77</sup>

### CONCLUSIONS

ACOS may be an interim term applicable to patients in whom it is difficult to distinguish between asthma

and COPD.<sup>61</sup> An alternative approach to chronic obstructive airway disease is to describe rather than to categorize the disease;<sup>80</sup> this allows the physician to build a complete picture of the disease and to start to think about individual disease phenotypes and treatments.<sup>81</sup> Nevertheless, ACOS is currently a diagnostic challenge for physicians; future studies are required to answer many questions related to this important disease.

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