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 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; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, 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 beta2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; mMRC, modified Medical Research Council; PEF, peak expiratory flow; SABA, short-acting beta2-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.1,2 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.3 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.4 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.’4 This description is intuitive but difficult to apply to daily clinical practice.

Since ACOS has overlapping characteristics of asthma and COPD,5 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.6,7 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 definitively8,9 and is known by different names, including overlap syndrome of asthma and COPD,10 mixed asthma–COPD phenotype,11 asthma combined with COPD,12 coexistence of asthma and COPD13 or COPD with asthmatic features.14 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).10–13,15–24 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 (DLCO).15 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 years16 and increased up to 55% when the patients met any criteria for asthma.20 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 1.16 In the general population, the prevalence of ACOS was 1.8% in the PLATINO study if ACOS was diagnosed based on symptoms and spirometry.23 It was 2.7% in the US population if ACOS was diagnosed based on self-reported, physician-diagnosed asthma and COPD.12

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,22 leading to higher healthcare costs due to the fact that hospitalizations account for the largest proportion of the total healthcare costs for COPD.25 A retrospective study has shown that patients with ACOS incur higher healthcare costs because they use more health-care services than those with COPD alone.24 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.27 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.28 The average annual medical cost was higher for ACOS ($14 914) than for asthma ($2307) or COPD ($4879).28

Disability

Because ACOS is common in the elderly, patients with ACOS experience multiple clinical problems that adversely impact their health.29 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.24,30,31 A multicentre study showed that COPD patients with atopy, a feature of ACOS, were associated with a higher prevai-
Table 1  The prevalence of ACOS from different study populations with different diagnostic criteria

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligible age</th>
<th>Diagnostic criteria</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>From the population of patients with asthma</td>
<td></td>
<td>Documented physician-diagnosed asthma + classical symptom of chronic bronchitis and/or DLCO &lt; 80%</td>
<td>29%</td>
</tr>
<tr>
<td>Milanese et al., 2014</td>
<td>≥65 years</td>
<td>Self-reported, physician-diagnosed asthma + self-reported, physician-diagnosed COPD</td>
<td>16–61%</td>
</tr>
<tr>
<td>de Marco et al., 2013</td>
<td>20–84 years</td>
<td>At least 2 major criteria or 1 major plus 2 minor criteria. Major criteria: post-BD FEV1 increase ≥15% and ≥400 mL over baseline, FENO &gt; 40 ppb, and personal history of asthma. Minor criteria: elevated serum IgE, personal history of atopy, and post-BD FEV1 increase ≥12% and ≥200 mL over baseline on 2 or more occasions.</td>
<td>5.0% for tobacco; 21.3% for biomass</td>
</tr>
<tr>
<td>From the population of patients with COPD</td>
<td></td>
<td>Similar to Golpe et al. except 'FENO &gt; 40 ppb' is replaced with 'eosinophilia in sputum'.</td>
<td>6.5%</td>
</tr>
<tr>
<td>Golpe et al., 2014</td>
<td>≥40 years</td>
<td>COPD stage 2–4 (post-BD FEV1/FVC &lt; 0.70 and FEV1 &lt; 80%) + self-reported symptoms like asthma (episodic dyspnea, wheezing, cough, and chest tightness worsening at night or in the early morning)</td>
<td>27%</td>
</tr>
<tr>
<td>Miravitlles et al., 2014</td>
<td>≥40 years</td>
<td>COPD stage 2–4 (post-BD FEV1/FVC &lt; 0.70 and FEV1 &lt; 80%) + self-reported, physician-diagnosed asthma before the age of 40</td>
<td>13%</td>
</tr>
<tr>
<td>Kitaguchi et al., 2012</td>
<td>71 ± 1 years</td>
<td>COPD (post-BD FEV1/FVC &lt; 0.70 or FEV1/FVC &lt; 88% predicted) + any criteria for asthma (a post-BD increase in FEV1 of ≥12%, a bronchodilator response of ≥15% or diurnal variation of ≥20% in PEF, and a decrease in FEV1 of ≥15% in the exercise test)</td>
<td>55%</td>
</tr>
<tr>
<td>Hardin et al., 2011</td>
<td>45–80 years</td>
<td>Compatible respiratory symptoms + positive airway hyper-responsiveness and/or positive reversibility testing + post-BD FEV1/FVC &lt; 70% and post-BD FEV1 &lt; 80%</td>
<td>56%</td>
</tr>
<tr>
<td>Marsh et al., 2008</td>
<td>&gt;50 years</td>
<td>Any treatment for asthma + any treatment for COPD during the follow-up</td>
<td>16.1%</td>
</tr>
<tr>
<td>From the population of patients with a diagnosis of obstructive lung disease (either asthma or COPD)</td>
<td></td>
<td>COPD (post-BD FEV1/FVC &lt; 0.70 or post-BD FEV1/FVC &lt; 88% predicted) + any criteria for asthma (a post-BD increase in FEV1 of ≥12%, a bronchodilator response of ≥15% or diurnal variation of ≥20% in PEF, and a decrease in FEV1 of ≥15% in the exercise test)</td>
<td>14.6%</td>
</tr>
<tr>
<td>Fu et al., 2014</td>
<td>&gt;55 years</td>
<td>COPD (post-BD FEV1/FVC &lt; 0.70 or post-BD FEV1 &lt; 80%) + criteria for asthma (wheezing in the last 12 months + post-BD increase in FEV1 or FVC of ≥200 mL and ≥12%)</td>
<td>1.8%</td>
</tr>
<tr>
<td>Andersen et al., 2013</td>
<td>&gt;34 years</td>
<td>FEV1/FVC &lt; 0.70 + a history of self-reported wheezing or whistling in the last 12 months</td>
<td>2.3%</td>
</tr>
<tr>
<td>Kauppi et al., 2011</td>
<td>18–85 years</td>
<td>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?’</td>
<td>2.7%</td>
</tr>
<tr>
<td>From the general population</td>
<td></td>
<td>COPD (post-BD FEV1/FVC &lt; 0.70) + criteria for asthma (wheezing in the last 12 months + post-BD increase in FEV1 or FVC of ≥200 mL and ≥12%)</td>
<td>1.8%</td>
</tr>
<tr>
<td>Menezes et al., 2014</td>
<td>&gt;40 years</td>
<td>FEV1/FVC &lt; 0.70 + a history of self-reported wheezing or whistling in the last 12 months</td>
<td>2.3%</td>
</tr>
<tr>
<td>Chung et al., 2014</td>
<td>&gt;19 years</td>
<td>FEV1/FVC &lt; 0.70 + a history of self-reported wheezing or whistling in the last 12 months</td>
<td>2.7%</td>
</tr>
<tr>
<td>Diaz-Guzman et al., 2011</td>
<td>≥25 years</td>
<td>FEV1/FVC &lt; 0.70 + a history of self-reported wheezing or whistling in the last 12 months</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

ACOS, asthma-COPD overlap syndrome; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lung for carbon monoxide; FENO, fractional expiratory nitric oxide; FEV1, 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.32 Another observational study showed that patients with ACOS had a higher modified Medical Research Council (mMRC) dyspnoea grade (1.26 ± 0.98 vs 0.99 ± 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.15

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).21 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).12

PATHOPHYSIOLOGY OF ACOS

There are genetic, pathological and functional overlaps between asthma and COPD.33 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.33

Pathologically, structural changes in the small airways contribute to the phenotypic overlap between asthma and COPD.34 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.34 HRCT of the chest reflects these structural changes. Patients with ACOS had greater gas trapping on expiratory CT scans,19 less severe emphysema and a thicker airway wall on inspiratory CT scans than patients with COPD alone.30

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.35–37 In adults, asthma and chronic exposure to cigarette or biomass smoke may interact to increase the risk of airway obstruction,38–40 an important feature of ACOS. Cigarette smoking can alter airway inflammation in asthma from being eosinophilic to neutrophilic with increased CD8+ cells, thus becoming similar to that seen in COPD.41 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.42 Moreover, ACOS becomes more prevalent in the elderly.13,26,27 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.43

A STEP-WISE APPROACH TO DIAGNOSING ACOS

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

The diagnosis of ACOS is challenging because there are no specific biomarkers to differentiate it from asthma or COPD.5 Since a single factor, such as a respiratory symptom or a spirometric parameter, is unable to differentiate between asthma, COPD and ACOS,5 especially in the elderly46 and in current or former smokers,47 major and minor criteria have been suggested to diagnose ACOS.16,17 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,35 long-standing asthma without taking ICS,48 adult-onset asthma49 and severe or difficult-to-treat asthma.50

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 beta2-agonist (LABA) plus add-on medications to optimize lung function and to exclude reversible airflow limitation.1 ICS-naive 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-
A step-wise approach to ACOS

Because patients with ACOS are generally excluded from randomized controlled trials for either asthma or COPD, their response to therapy is largely smokers with long-standing asthma should be assessed for a history of occupational exposure to inorganic dust or chemical irritants. Chest HRCT and DLCO may help differentiate ACOS from asthma. However, the cut-off point for the level of emphysema on HRCT or for DLCO 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. 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. 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. 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. 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. 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. 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 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.

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. However, induced sputum testing for eosinophilia has limited availability, and a profile of sputum cell counts may change over time.

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. In principle, ACOS has similar goals of treatment as asthma and COPD: 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. Treatment may comprise the following components: patient education, smoking cessation, allergen avoidance, flu vaccination, pulmonary rehabilitation and management of any comorbidity.

Patients with ACOS may benefit from a combination therapy of ICS/LABA. 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). However, the benefits of ICS/LABA in ACOS should be confirmed in randomized controlled 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). 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 (FEV1) and the number of days with controlled asthma.

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.

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. 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.

Another example of individualized management is that current smokers with ACOS may require a higher dose of ICS than ex-smokers with ACOS. 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.

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, it is still hampered by poor cooperation in this population. 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.

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, what are the molecular pathways of ACOS? By using genome-wide association studies, a recent study identified several novel genetic variants that are associated with ACOS. 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. The annual rate of post-bronchodilator FEV1 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). However, given that abnormal lung growth affects fixed airway disease development later in life, 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.

CONCLUSIONS
ACOS may be an interim term applicable to patients in whom it is difficult to distinguish between asthma...
and COPD. An alternative approach to chronic obstructive airway disease is to describe rather than to categorize the disease, this allows the physician to build a complete picture of the disease and to start to think about individual disease phenotypes and treatments. 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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