

THE ASTHMA–COPD OVERLAP SYNDROME: WHAT IS IT AND HOW SHOULD WE TREAT IT?

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ABSTRACT

Asthma and COPD are two distinct diseases but may overlap, especially in older patients. Typically, asthma patients have marked variability in their airflow obstruction with significant reversibility in response to both bronchodilator and corticosteroid therapy. However, it has become increasingly clear that many patients with asthma may develop fixed airflow obstruction, whereas many patients with COPD exhibit some bronchodilator reversibility. The term 'Asthma–COPD Overlap Syndrome' (ACOS) has been coined to describe patients who have features of both but, as yet, there is no validated definition for the combination of features. Patients with ACOS have worse outcomes than those with asthma or COPD alone: more frequent exacerbations, poorer quality of life, more rapid decline in lung function, higher mortality and greater healthcare use. The Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) have recently published guidelines for the diagnosis and treatment of patients with asthma, COPD or ACOS.

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INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) represent two distinct diseases with differing pathogenesis, histology and risk factors. They do share certain clinical characteristics and these may overlap.¹ Several population studies have shown that a significant number of adult patients with obstructive lung disease are diagnosed with more than one condition.^{2–4} This can be shown graphically in a non-proportional Venn diagram (see Figure 1). Typically, COPD has an onset from the fifth decade, has constant symptoms of dyspnoea and cough and is marked by slow progression. A history of significant smoking (greater than ten pack-years) or some

other exposure (occupational or biomass fuel exposure) is usually a factor.⁵ On the other hand, asthma usually but not always starts at a young age, is often associated with other atopic disease, has classically episodic symptoms with diurnal or day-to-day variability and has a good response to therapy.⁶ Asthma and COPD can coexist in the same patient: many asthmatics smoke – not all develop COPD but most have an accelerated fall in lung function. In addition, poorly treated asthmatics may develop fixed disease, so-called 'remodelling'. The diagnosis of asthma rests on characteristic symptoms combined with tests showing variable airflow obstruction, airway hyper-responsiveness and bronchodilator reversibility.

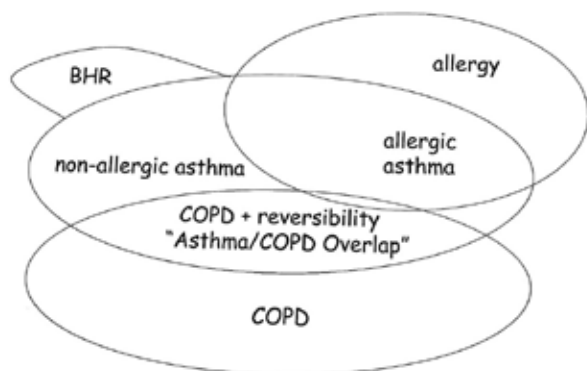


Figure 1: Non-proportional Venn diagram of obstructive lung disease
Abbreviations: BHR = bronchial hyper-responsiveness, COPD = chronic obstructive pulmonary disease

BRONCHODILATOR REVERSIBILITY

Bronchodilator (BD) reversibility response remains the hallmark of the diagnosis of asthma. It has been used historically as a tool for distinguishing reversible from irreversible airway obstruction, although this distinction has become somewhat blurred. In the SATS and GINA Guidelines, the definition of bronchodilator reversibility is stated as an increase from baseline in the FEV₁ of both >12% and 200 ml, 10–30 min following the inhalation of 200–400 µg of salbutamol, or a 20% improvement in PEF (peak expiratory flow) from baseline.^{6,7} In 2015, the GINA Guidelines added that a >15% and >400 ml increase in the FEV₁ gives greater confidence in asthma diagnosis.⁷ However, most asthmatics will not exhibit reversibility at each assessment, particularly those on treatment, and the

test therefore lacks sensitivity. Repeated testing at different visits is advised. This frequent absence of BD reversibility in patients with physician-diagnosed asthma has been shown in several studies in different countries,^{8–10} including South Africa,¹¹ where almost half of young non-smoking asthmatics did not have a significant BD response at their first assessment at a tertiary referral centre. Possible reasons for this low incidence of reversibility include a temporary phenomenon due to severe viral or allergic airway inflammation (which may change after a course of oral or inhaled corticosteroids), recent BD use, inadequate BD dose, permanent airway remodelling and an incorrect asthma diagnosis.

Not only do many asthmatics not always show BD reversibility but it is not uncommon for COPD patients to have significant reversibility. In the UPLIFT study, >50% of the COPD patients enrolled had significant reversibility.¹² Using the GOLD severity stages, reversibility generally decreases as COPD severity increases.¹³ However, a lack of acute BD reversibility does not predict a lack of response to long-term treatment with BDs (although acute responders usually show greater long-term improvements in PFTs).¹³

ASTHMA–COPD OVERLAP SYNDROME (ACOS)

As discussed by Gibson and Simpson in their 2009 article, data from large population studies show that 17–19% of patients had more than one condition.¹⁴ This is more common in older people, in whom epidemiological studies show that >50% with obstructive airway disease may have overlapping diagnoses of asthma and COPD. At a physiological level, patients with ACOS have evidence of incompletely reversible airflow obstruction that can be detected by a decreased post-BD FEV₁ but, in addition, have increased variability of airflow. This may be determined by enhanced BD responsiveness.

Overlap groups include:

- Subjects with asthma who develop fixed airflow obstruction (remodelling).
- Subjects with either asymptomatic bronchial hyper-responsiveness (BHR) or asthma who smoke or have other COPD risk factors (biomass fuel, occupational, previous chest infections, especially tuberculosis).

ASTHMA WITH FIXED AIRFLOW OBSTRUCTION (REMODELLING)

Longitudinal studies show that at the start of adulthood, lung function is lower in asthmatics.¹⁴ Moreover, a longitudinal study has shown that 16% of asthmatics develop incomplete airflow reversibility after 20–30 years of follow-up.¹⁵ They also are at increased risk of death from airway disease.¹⁴ This fixed airflow obstruction that develops is thought to be due to structural remodelling of the airways due to inflammation, subepithelial fibrosis and increased smooth muscle thickness.¹⁶ This results in bronchial wall

thickening and luminal narrowing, which can be seen on high-resolution computer tomography (HRCT).¹⁷

BRONCHIAL HYPER-RESPONSIVENESS OR ASTHMA AND EXPOSURE TO COPD RISK FACTORS

Bronchial hyper-responsiveness (BHR) is defined by a drop in PEF or FEV₁ after challenge (exercise or chemical).⁷ BHR is present in 10–20% of the population and is usually associated with clinical asthma but up to 50% may be asymptomatic. However, even asymptomatic BHR is associated with an increased risk of developing asthma or COPD after more than ten years' follow-up.¹⁸ BHR is also associated with an increased decline in lung function. There is significant interaction with smoking, with a mean additional decline in FEV₁ of 12 ml/yr in smokers versus 4 ml/yr in non-smokers.¹⁸ Therefore active smokers with BHR or asthma are at particular risk for the development of COPD and patients with ACOS are commonly ex-smokers.

ACOS PATIENTS

Several papers have looked at the profile of patients with Asthma–COPD Overlap. In the COPD Gene study, 13% of 915 COPD patients reported a previous doctor diagnosis of asthma. The COPD and Asthma subgroup had a 41% ATS-defined positive BD response versus 36% in those with COPD alone. They also had a worse quality of life with more frequent and severe exacerbations despite younger age and a lower smoking history.¹⁹

In the Finnish NIHW Registry, the health records of the entire population (5.3 million) were studied and those of >34 years with a principal and secondary diagnosis asthma and COPD from 2000–2009 were focused on. It was found that 16% of this population had Asthma–COPD Overlap. These patients were of a similar age to those with COPD alone but had had more treatment periods (6 versus 2 in asthma and 3 in COPD) and more hospitalisations.²⁰

TABLE I: DOES THE PATIENT HAVE CHRONIC AIRWAYS DISEASE?

HISTORY:

- chronic or recurrent cough, sputum, dyspnoea or wheezing, or repeated lower respiratory tract infections;
- previous doctor diagnosis of asthma and/or COPD;
- previous treatment with inhaled medications;
- history of smoking tobacco and/or other substances;
- exposure to environmental hazards, for example airborne pollutants.

PHYSICAL EXAMINATION:

- may be normal;
- evidence of hyperinflation or respiratory insufficiency;
- wheeze and/or crackles.

RADIOLOGY (CXR OR HRCT SCAN PERFORMED FOR OTHER REASONS):

- may be normal, especially in early stages;
- may show hyperinflation, airway wall thickening, bullae;
- may identify or suggest an alternative or additional diagnosis, for example bronchiectasis, tuberculosis, interstitial lung disease, cardiac failure.

In the PLATINO multi-centre population-based study in five Latin American cities with 5 044 subjects >50 years, 594 (12%) of the total population were classified as COPD (defined as post-BD FEV₁/FVC <70%), 84 (1.7%) as Asthma (defined as positive ATS BD response) and 89 (1.8%) as Asthma–COPD Overlap. Of those with obstructive lung disease, 12% had Asthma COPD–Overlap. Overlap patients were more likely to have greater symptoms, more exacerbations (PR 2.1), more hospitalisations (PR 4.1), worse quality of life and lower lung function.²¹

In the EPI-SCAN study, a multi-centre population-based study in Spain, involving 3 885 subjects between 40 and 80 years of age, 385 (10%) were diagnosed with COPD (post-BD FEV₁/FVC <70%) and 67 of these (17%) were classified with Asthma–COPD Overlap. ACOS patients were more likely to be female and were again more likely to have worse dyspnoea and wheeze, more exacerbations, worse health-related quality of life and lower physical activity.²²

ACOS has been specifically looked at in a special chapter in the 2015 GINA Global Strategy for Asthma Management and Prevention Guideline.⁷ An important point is made that ACOS is not a single disease and that it is likely that a range of different underlying mechanisms and origins will be identified.

The reported prevalence of ACOS varies between 15% and 55% of patients with chronic airways disease, depending on the population studied (as it varies with age and gender) and also the definitions used for ‘asthma’ and ‘COPD’.

Asthma is defined as a heterogeneous disease, usually

characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.⁷

COPD is defined as a common preventable and treatable disease, characterised by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory responses in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.²³

Asthma–COPD Overlap Syndrome (ACOS) is characterised 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. However, a specific definition for ACOS cannot be developed until more evidence is available about its clinical phenotypes and underlying mechanisms.⁷

DIAGNOSTIC AND THERAPEUTIC APPROACH

It is suggested that when an adult presents with respiratory symptoms, the healthcare provider should ask if the patient has chronic airways disease (see Table I).⁷ If so, they should make a provisional syndromic diagnosis of asthma, COPD or ACOS (see Table II). They should assemble the features that most favour a diagnosis of typical asthma or COPD and compare the number of features on each side. If the patient has ≥3 features of either asthma or COPD, there is a strong likelihood that this is the correct diagnosis. They should also consider the level

TABLE II: SYNDROMIC DIAGNOSIS OF ASTHMA, COPD OR ACOS

Several positive features (≥3) for either asthma or COPD suggest that diagnosis. If there are a similar number for both asthma and COPD, consider diagnosis of ACOS.		
FEATURES (IF PRESENT)	ASTHMA	COPD
Age of onset	Before 20 years.	After 40 years.
Symptom pattern	Variation over minutes, hours or days.	Persistent despite treatment.
	Worse at night or early morning.	Good and bad days but always daily symptoms and dyspnoea.
	Triggered by exercise, emotions, fumes, allergens, etc.	Chronic cough/sputum preceded onset of dyspnoea, unrelated to triggers.
PFTs during symptoms	Record of variable obstruction (spirometry or peak flow rate).	Record of persistent obstruction (FEV ₁ /FVC <70%).
PFTs between symptoms	May be normal.	Always shows obstruction.
Past history or family history	Previous doctor diagnosis of asthma, hay fever or eczema.	Previous doctor diagnosis of COPD, emphysema or chronic bronchitis.
	Family history of asthma, hay fever or eczema.	Heavy exposure to risk factor: tobacco, smoke, biomass fuels, occupation or PTB.
Time course	No worsening of symptoms over time. Variation in symptoms either seasonally or from year to year.	Symptoms slowly worsening over time (progressive course over years).
	May improve spontaneously or have an immediate response to BDs, ICS or oral steroids over weeks.	Short-acting BDs provide only limited relief.
CXR	Normal.	Hyperinflated (normal in early stages).

of certainty surrounding the diagnosis as diagnoses are made on the weight of evidence, and the absence of any of these features does not rule out either diagnosis (e.g. the absence of atopy does not rule out asthma). When a patient has a similar number of features of both asthma and COPD, the diagnosis of ACOS should be considered. Spirometry should be performed. It shows whether chronic airflow limitation is present but is of more limited value in distinguishing between asthma with fixed airflow limitation, COPD and ACOS (especially if medications are taken before testing). Spirometry should be done at the initial visit and subsequent visits and, if possible, before and after a trial of therapy. Peak expiratory flow (PEF) testing is not a substitute for spirometry and a normal PEF does not rule out asthma or COPD, but repeated PEF measurement may confirm excessive variability, found in asthma or in most ACOS patients.

If the syndromic assessment suggests asthma, therapy should be started with twice-daily low-dose inhaled corticosteroids (ICS) and short-acting beta-agonists (SABA) when required. If there is poor control despite good adherence and correct inhaler technique, long-acting beta-agonists (LABA) and/or long-acting anti-muscarinics (LAMA) should be added. Do not give LABA alone without ICS.

If syndromic assessment suggests COPD, start with bronchodilators (BDs) or combination therapy and do not give ICS alone without LABA and/or LAMA.

If the differential diagnosis is equally balanced between asthma and COPD, diagnose ACOS and start treatment as for asthma, pending further tests. This is because if there is an asthmatic component, the underlying inflammation needs regular inhaled corticosteroid treatment; this avoids the reported danger of giving only BDs to these patients.

For all patients with chronic airflow limitation, manage the modifiable risk factors (including advice about smoking cessation and avoiding biomass fuel), treat comorbidities, advise about non-pharmacological strategies (including physical activity, pulmonary rehabilitation and vaccinations), provide appropriate self-management strategies and arrange regular follow-up.

Refer for specialised investigations (e.g. diffusing capacity for carbon monoxide, skin-prick tests, IgE levels, blood or sputum eosinophilia, exhaled nitric oxide, sputum bacteriology, HRCT) if there is diagnostic uncertainty, atypical or additional symptoms or signs (e.g. haemoptysis, weight loss, night sweats, fever, chronic purulent sputum), comorbidities that may interfere with management or the patient has persistent symptoms and/or exacerbations despite your therapy.

CONCLUSIONS

The Asthma–COPD Overlap Syndrome (ACOS) is a work in progress and there is no clear-cut or validated definition. It is not a single disease but more likely represents a range of different underlying conditions. As shown by several studies, patients with ACOS have worse outcomes than those with asthma or COPD alone: more frequent exacerbations, poorer quality of life, more rapid decline in lung function, higher mortality and greater healthcare use. The above diagnostic and therapeutic strategy is an interim practical approach. It should be stressed that whether a patient has asthma, COPD or ACOS may often not be clear at the first or even the second assessment, and that there is great value in reassessment after therapy and over time.

DECLARATION OF CONFLICT OF INTERESTS

Cipla – Member of Inhalant Delivery Device Advisory Board in June 2015; Astra Zeneca: Sponsored speaker (on IPF) at Respiratory Symposium in March 2014.

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