

Asthma-COPD overlap

Implications for patient management

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Asthma-COPD overlap (ACO) is characterised by persistent airflow limitation with features typically associated with both asthma and chronic obstructive pulmonary disease (COPD). Because there is no universally accepted definition of ACO, reliable data on managing patients exhibiting ACO is lacking. An approach to treating chronic airways disease that targets identifiable clinical traits rather than the disease label is increasingly recommended.

Asthma and chronic obstructive pulmonary disease (COPD) are the most prevalent chronic lung diseases and are responsible for considerable morbidity, mortality and the use of healthcare resources globally.^{1,2} In Australia, up to 11% of the population report a diagnosis of asthma.³ The prevalence of COPD is estimated at 7.5% of Australians over 40 years of age, and this increases to 30% for those over 75 years.⁴ Once managed as distinct diagnoses, it is now increasingly acknowledged that asthma and COPD have

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Key points

- The term asthma-COPD overlap (ACO) was proposed to reflect the overlapping aetiologies and clinical features of asthma and chronic obstructive pulmonary disease (COPD) and the large population of patients who demonstrate features of both.
- Clinical features and underlying inflammatory and physiological mechanisms of asthma and COPD are highly variable and affect the utility of the ACO umbrella in clinical practice. This heterogeneity limits both high-quality research on the subject and treatment recommendations specific to ACO.
- Initiation of inhaled corticosteroids is recommended in patients who clearly demonstrate features of both asthma and COPD, as this is a critical component of asthma control.
- An individualised approach to treatment, with a focus on identifying and treating disease traits is more important than managing disease labels, and will lead to better overall care of the patient with chronic airway disease.

overlapping aetiologies and clinical features that translate to a high likelihood that patients will demonstrate features of both conditions.⁵ Despite this reality, guidelines for both conditions have evolved separately and differ significantly in recommendations for treatment.^{1,2} The term asthma-COPD overlap (ACO) was proposed to assist clinicians resolve this dilemma and provide an approach to treatment; however, there is controversy over whether ACO should be regarded as a separate entity in itself. The alternative is for clinicians to move away from the confinement of disease labels and instead take a 'treatable traits' approach to chronic airways disease and identify important clinical phenotypes and target treatment towards these.⁶ This article discusses ACO its implications for patient treatment.

What is asthma-COPD overlap (ACO)?

Although proposed definitions of ACO differ between respiratory societies, ACO is generally characterised by persistent airflow limitation with features typically associated with both asthma and COPD, such as a history of smoking, a documented history of asthma before the age of 40, a history of atopy and elevated eosinophils on full blood count (FBC; more than $0.3 \times 10^9/L$).^{7,8} This definition is based on expert opinion and does not define ACO as an independent entity based on either pathophysiology or disease outcomes.

In clinical practice, the relative contribution from features of asthma or COPD will differ substantially between patients, resulting in a cohort of patients with the label of ACO who display highly variable disease mechanisms and clinical outcomes. A patient who fits the above definition of ACO may indeed have asthma and COPD concurrently, though they may instead have an atypical manifestation of one of these conditions alone, such as COPD with eosinophilic inflammation, or asthma with irreversible airflow obstruction due to airway remodelling.

The alternative is for clinicians to move away from the confinement of disease labels and instead take a 'treatable traits' approach to chronic airways disease

Pathophysiology and clinical features

Asthma and COPD are conditions that feature airflow limitation and chronic airway inflammation,^{1,2} although each of these chronic airway diseases are themselves heterogeneous conditions with various contributing disease mechanisms and inflammatory processes. This highlights the complexity and lack of utility of the ACO umbrella.

Asthma is defined as an inflammatory airways disease that often, but not exclusively, begins in childhood. Asthma involves the large and small airways, but not the terminal bronchioles or alveoli, and is characterised by airway hyper-responsiveness and reversible airway obstruction.² COPD is also an inflammatory airways disorder

associated with inhaled noxious agents such as tobacco smoke, which usually manifests in people over 40 years of age. COPD predominantly affects the small airways and is associated with varying amounts of alveolar tissue breakdown and mucous hypersecretion. The condition is characterised by progressive and irreversible airway obstruction, loss of lung elastic recoil and hyperinflation, and symptoms of breathlessness, productive cough and wheeze.¹

The inflammatory cells and mediators that drive COPD and asthma broadly differ but there is no pathognomonic inflammatory endotype that defines ACO. COPD is typically characterised by inflammation, referred to as a type 1 (T1) immune response, featuring a predominance of neutrophils, CD8+ T cells, macrophages and inflammatory mediators such as interleukin (IL)-8 and tumour necrosis factor (TNF) alpha-1. Asthma is usually a type 2 immune process characterised by elevated eosinophils, mast cells, CD4+ T cells and cytokines IL-4, IL-5 and IL-13.^{2,9} Type 2 (T2) inflammation refers to a pattern of inflammation driven by T helper 2 cells and other components of the innate immune system, with increased activity of eosinophils and the allergic inflammatory cascade. Active T2 inflammation has been demonstrated to correspond with asthma symptoms, increased exacerbation frequency and lung function decline. T2 inflammation is generally responsive to inhaled corticosteroid (ICS) or oral corticosteroid (OCS) therapy. Neither of these inflammatory processes are specific for either disease. Asthma driven by neutrophilic inflammation is a recognised phenotype in 15 to 20% of people with asthma,¹⁰ and eosinophilic inflammation is recognised in up to 20% of people with COPD.^{2,11}

Similarly, spirometry does not always distinguish between asthma and COPD. Bronchodilator reversibility (BDR) is a defining feature of asthma; however, patients with COPD often and variably demonstrate a significant improvement in forced expiratory volume in one second (FEV₁) with bronchodilators.¹² Conversely, airflow obstruction that is not fully reversible is a defining feature of COPD, but can occur as a result of airway remodelling in cases of asthma alone, particularly in patients with longstanding disease.² Patients with either COPD or asthma can also demonstrate hyper-responsiveness on bronchial provocation testing.¹³

Diagnosing patients with ACO

Box 1 outlines three case studies of patients with aetiologies that fit the description of ACO based on current consensus statements. However, it could be argued these patients have different diseases that will affect their prognosis and response to treatment.

Patient 1 has a history of early-onset asthma with typical symptoms, a history of atopy and elevated biomarkers to suggest active type 2 inflammation. Elevated levels of eosinophils on FBC (particularly when higher than $0.3 \times 10^9/L$) correlate with active T2 inflammation and are a readily available way to assess this. Eosinophils can be elevated due to other causes, such as potential atopy in the case of Patient 1. Although not routinely available in general practice, fractional exhalation of nitric oxide (FeNO) is a more specific and noninvasive method of detecting eosinophilic airway inflammation,

with readings over 50 ppb consistent with this. Despite the patient's features of allergic asthma, his heavy smoking history and CT evidence of emphysema are typically associated with COPD.

Patient 2 has a diagnosis of early-onset asthma and significant airflow obstruction. The incompletely reversible airflow obstruction suggests a diagnosis of COPD, although her smoking history is relatively mild and there is no CT evidence of emphysema. It is likely that the patient's fixed airflow obstruction is a direct result of her longstanding asthma and subsequent airway remodelling, rather than loss of elastic recoil and increased airway resistance as that occurs with COPD associated with an emphysema predominant phenotype. The absence of biomarkers of T2 inflammation suggests a poor response to typical ICS and OCS therapy. A poor response to corticosteroid therapy has been well described in people with neutrophilic asthma.

Patient 3 has a heavy smoking history and clear radiological evidence of emphysema. BDR can exist in COPD alone; however, the magnitude of BDR in this case increases the likelihood that this is true evidence of concurrent asthma. Although eosinophilic inflammation is recognised in COPD, the elevated T2 biomarkers in Patient 3 may suggest a diagnosis of asthma as described above.

The patients described in these case studies will be recognisable to all clinicians and will raise questions including: What treatment paradigm should be followed? Do you treat a disease label, such as asthma, COPD, or ACO, or do you treat the individual treatable traits?

Quality of research on ACO

Prospective intervention trials of patients who meet a definition of ACO are lacking, with most research limited to cohort and case-controlled studies.¹⁴ Data from these studies yield varying and sometimes conflicting results because of the lack of an accepted definition of ACO and inconsistent inclusion criteria.^{7,14} Treatment recommendations for ACO are extrapolated from trials of asthma and COPD alone; however, the inclusion criteria for these same trials would have excluded most patients with ACO.^{7,15-18} For example, asthma trials will often exclude patients with even a minor smoking history or with a past diagnosis of COPD,¹⁹⁻²¹ and most COPD studies will exclude never-smokers or those with a history of asthma.^{16,22}

Epidemiology and natural history

The reported global prevalence of ACO varies between 15 and 55% but is critically dependent on the inclusion criteria in the individual studies.⁸ Patients who meet the definition of ACO are generally younger, have a higher body mass index, are less likely to have a smoking history, have a higher FEV₁ and more healthcare utilisation than patients with COPD alone.¹⁴ Patients with ACO are at increased risk of exacerbations, hospitalisations and a greater number of chronic respiratory symptoms; therefore, outcomes may be worse with ACO compared with asthma or COPD alone.^{5,14} Observations are often inconsistent between studies, which makes it difficult to draw valid conclusions.

1. Case studies. Typical aetiologies for patients with asthma-COPD overlap

Patient 1

Greg is a 68-year-old male who was diagnosed with asthma in childhood. He exhibits typical episodic symptoms, including wheeze and chest tightness, which supports the diagnosis of asthma, and a productive cough consistent with chronic mucous hypersecretion (also known as chronic bronchitis). He has frequent exacerbations of these symptoms – three episodes per year – and a history of atopy.

Greg was a pack-a-day smoker for 30 years (i.e. has a 30 pack year smoking history), but successfully quit 10 years ago.

Spirometry testing reveals that Greg has moderate airflow obstruction (forced expiratory volume in one second [FEV₁] 68% predicted) and significant bronchodilator reversibility (BDR) (200mL and 15% response to salbutamol). Greg's blood eosinophils level is 0.4×10⁹/L and fractional exhaled nitric oxide (FeNO) is 67 ppb. He does not have evidence of lower respiratory tract infections, and there are no organisms isolated on sputum culture. A chest CT scan reveals he has bilateral upper lobe emphysema.

What are the alternative disease labels for Patient 1?

Allergic asthma and emphysema

Patient 2

Susan is 54 years old with a longstanding history of asthma since childhood that has been poorly controlled. She experiences regular cough and purulent sputum. She is often breathless on exertion, such as walking up one flight of stairs.

Her exacerbations are increasing in frequency, with three in the past 12 months, all requiring treatment with antibiotics. She has no history of atopy.

She has a 10 pack year smoking history, but has recently quit.

Susan has severe airflow obstruction (FEV₁ 48% predicted) but no significant BDR (100mL and 5% response to salbutamol). Her blood eosinophils level is 0.1×10⁹/L and FeNO is 13 ppb. Sputum microbiology reveals infection with *Haemophilus influenzae*. Her chest CT scan is clear, with no emphysema or bronchiectasis.

What are the alternative disease labels for Patient 2?

Asthma with non-T2 inflammation

Patient 3

John, 73 years old, has declining exercise tolerance in the last 12 months, which is now limited to 100 m on the flat. He is an active smoker of 40 pack years. He has no previous history of asthma or atopy.

John has frequent exacerbations, with four in the past year, all requiring oral prednisone. He has moderate airflow obstruction (FEV₁ 62% predicted) and significant BDR (400mL and 20% response to salbutamol). John's blood eosinophils level is at 0.3×10⁹/L and FeNO at 55 ppb. He has no lower respiratory tract infection. A chest CT scan reveals widespread centrilobular emphysema.

What are the alternative disease labels for Patient 3?

COPD with eosinophilic inflammation or COPD with bronchodilator reversibility

Table. A treatable traits approach to managing patients with asthma, COPD or asthma-COPD overlap⁴

Treatable trait	Assessment and management in the primary care setting		Advanced options in specialist centre	
	Assessment	Treatment	Assessment	Treatment
Airway smooth muscle hyper-reactivity	Bronchodilator reversibility test	LABA or LAMA ICS	Bronchial provocation challenge	LABA or LAMA ICS
Airflow obstruction	Spirometry testing	Short-acting bronchodilators LABA or LAMA Theophylline	Further assessment with lung plethysmography, forced oscillometry	Short-acting bronchodilators LABA or LAMA Theophylline
Eosinophilic airway inflammation	Blood eosinophils	ICS OCS	Blood eosinophils FeNO Sputum eosinophils	ICS OCS Monoclonal antibodies directed against IL-5
Emphysema and loss of elastic recoil	High-resolution chest CT scan	Smoking cessation	High-resolution chest CT scan Lung plethysmography Transpulmonary (oesophageal) pressure monitoring	Smoking cessation Lung volume reduction surgery Endoscopic lung volume reduction
Chronic bronchitis	History Sputum colour	Smoking cessation	History Sputum total and differential cell count	Smoking cessation Sputum clearance
Deconditioning/exercise intolerance	History COPD activity questionnaires (e.g. COPD assessment test)	Rehabilitation, exercise program	Tests including six-minute walk, shuttle walk, cardiopulmonary exercise, sit to stand	Rehabilitation, exercise program
Chronic hypoxaemia	Pulse oximetry, arterial blood gases	Long-term oxygen therapy	Pulse oximetry Arterial blood gas test	Long-term oxygen therapy
Chronic hypercapnoea	Arterial blood gases Sleep studies	Refer patient for specialist management	Arterial blood gas test In-lab sleep study with CO ₂ monitoring	Noninvasive ventilation
Obesity or sarcopenia	Weight Height Body mass index	Dietary modification Physical activity	n/a	n/a
Upper airway inflammation (chronic rhinosinusitis or nasal polyposis)	Screening questionnaires CT nose and paranasal sinuses	Intranasal steroids, nasal irrigation	n/a	n/a
Vocal cord dysfunction (paradoxical closure of vocal folds during inspiration, commonly coexists with asthma and can mimic its clinical features)	Screening questionnaires	Refer patient for specialist management	Screening questionnaires Direct laryngoscopy	Speech pathology
Dysfunctional breathing (chronic change in breathing pattern with associated dyspnoea, often accompanies severe asthma and COPD, though is not specifically driven by organic pathology)	Screening questionnaires History	Anxiety management	n/a	Anxiety management Breathing retraining Cognitive behavioural therapy
Nonadherence to therapy, poor inhaler technique	History Script refills	Education Self-management support	History Script refills Electronic monitoring devices	Education Self-management support

Abbreviations: COPD = chronic obstructive pulmonary disease; FeNO = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; IL-5 = interleukin 5; LABA = long-acting beta-agonists; LAMA = long-acting muscarinic antagonist; OCS = oral corticosteroid.

Treatment of ACO – negotiating the contrasting inhaler therapies for asthma and COPD

The most common dilemma for the clinician treating a patient with ACO is which inhaler therapy to initiate and when.^{1,2} ICS therapy is the cornerstone of asthma management, and the addition of long-acting bronchodilators is indicated only if insufficient control is achieved with ICS. Bronchodilators – both short- and long-acting – represent a major part of the management of COPD, and ICS is only added in certain circumstances of advanced disease. The recommended management of asthma and COPD, with a focus on inhaler therapy, is briefly outlined below to highlight their sometimes contrasting management.

For adolescents and adults with asthma, including mild asthma, ICS therapy is recommended to decrease the risk of exacerbations and improve control of asthma symptoms.^{2,23,24} Long-acting beta-agonists (LABAs) reduce the frequency of severe asthma exacerbations when combined with ICS therapy and are recommended in combination with ICS therapy if inadequate control is achieved with ICS alone.^{2,20} LABA monotherapy has been linked with increased rates of asthma-related death and is contraindicated in the absence of ICS therapy.^{2,25,26} The long acting muscarinic antagonist (LAMA) tiotropium improves lung function, exacerbation rates and asthma control when added to ICS/LABA combinations, and is recommended only for those with inadequate control and persistent exacerbations despite (high-dose) ICS/LABA combinations.^{2,21}

[A treatable traits] approach emphasises a shift from intensifying treatment targeted towards disease labels, to targeting the treatments to the clinical phenotypes present in the individual patient

Treatment of COPD is similarly based on the management of symptoms and to reduce the risk of exacerbations, but in contrast to asthma, bronchodilator therapy is the preferred first-line therapy, rather than ICS.¹ Long-acting bronchodilator therapy (LAMA alone or in combination with LABA) has been shown to improve lung function and COPD symptoms, and reduce the frequency of exacerbations and hospitalisations.^{16,17,22} The addition of ICS therapy can be considered in the setting of persistent exacerbations despite long-acting bronchodilator therapy.^{1,27,28} As described above, the inflammation in COPD is usually driven by neutrophilic (T1) inflammation, which is less responsive to corticosteroids than the eosinophilic (T2) inflammation associated with asthma. With the increased appreciation of an overlap between our traditional understanding of asthma and COPD inflammatory patterns, there will be a cohort of patients with COPD who demonstrate evidence of eosinophilic airway inflammation, with elevated blood eosinophils (above $0.3 \times 10^9/L$) and elevated FeNO (above 50 ppb) (although FeNO measurement is not necessary to diagnose eosinophilic inflammation in the primary care setting), and are more likely to respond to ICS therapy. It is therefore

important to check for evidence of eosinophilic airway inflammation in patients with COPD, as this will influence treatment options, though it should be noted that the addition of ICS to COPD in the absence of frequent exacerbations or a concurrent diagnosis of asthma constitutes off-label use. The use of ICS in COPD has been linked to an increased risk of pneumonia and tempers enthusiasm for its use in COPD that can be adequately managed with bronchodilator therapy alone, particularly in the majority of patients with COPD who don't demonstrate evidence of eosinophilic inflammation.^{12,29}

Consensus treatment of ACO with inhaled therapy

Evidence to support specific treatment recommendations for ACO as a single disease is limited. Most experts support the initiation of ICS therapy early in the disease course of patients who fit the definition of ACO, as this is an important part of asthma control.^{2,5,8} If a patient with an established diagnosis and treatment regimen for COPD demonstrates features of asthma such as bronchodilator reversibility or eosinophilic inflammation (blood or sputum), the addition of an ICS is supported by expert consensus, although data only supports the use of ICS in those with evidence of eosinophilic inflammation.^{8,30}

Overall care of the patient with ACO: the treatable traits approach

Asthma and COPD are both heterogenous conditions with multiple contributing pathophysiological processes. The classification of patients who display features of both conditions under the umbrella of ACO only risks compounding the complexity of their condition without providing any meaningful value to the individual patient. In 2016, a consortium of physicians proposed that, rather than relying on disease labels for asthma and COPD, they should be viewed as 'a continuum of different diseases that may share biological mechanisms (i.e. endotypes), and present similar clinical, functional, imaging and/or biological features that can be observed (i.e. phenotypes) which require individualised treatment'.⁶ In this treatable traits approach, the focus is on identifying disease traits or clinical phenotypes with treatments that specifically target them. Such clinical phenotypes then are not limited to just asthma or COPD. The Table lists some of the traits or phenotypes that may manifest in a patient with asthma, COPD or ACO, and associated management strategies to consider for each.

Adopting a treatable traits approach to the management of the patients in the three case studies (Box 1) is outlined in Box 2. Such an approach emphasises a shift from intensifying treatment targeted towards disease labels, to targeting the treatments to the clinical phenotypes present in the individual patient.

Conclusions

Asthma-COPD overlap describes an important cohort of patients who demonstrate features typically associated with both asthma and COPD. This description is useful on a population level to highlight the complexity of chronic airways disease and the heterogeneity of the individual diagnoses of asthma and COPD. However, ACO is

2. Applying the treatable traits approach to patient case studies from Box 1

All patient management should include a disease care plan including patient education, a review of inhaler technique and a written action plan in the event of exacerbations.

Patient 1 (ACO or possible allergic asthma and emphysema)

Management approach in primary care

Elevated blood eosinophils suggests type 2 airway inflammation

- treat with ICS
- titrate ICS dose based on symptom response

Airflow obstruction

- treat with long acting bronchodilators (LABA or LAMA alone or in combination)

Screen for comorbidities

- allergic rhinosinusitis as a manifestation of atopy
- treat with nasal steroids and nasal irrigation

Further management options in specialist centres

- Titrate ICS dose based on symptoms, with support from biomarkers (i.e. measured reduction in blood eosinophils or FeNO)
- Consider a macrolide antibiotic for persistent exacerbations
- If the patient has persistent exacerbations or symptoms and persistently elevated biomarkers of T2 inflammation, consider monoclonal antibodies directed against allergic/eosinophilic inflammation – targeting this patient’s allergic asthma traits*

Patient 2 (ACO or possible asthma with non-T2 inflammation)

Management approach in primary care

Inclusion of an ICS is currently the consensus-based recommended treatment for patients with COPD with a childhood history of asthma

- aim for low-dose ICS

Fixed airflow obstruction (associated with future risk of exacerbations)

- step up to long-acting bronchodilator therapy
- use of an ICS/LABA combination
- addition of a LAMA if ongoing frequent exacerbations (more than two per year)

Evaluate for bronchiectasis

- chest CT scan

If chronic mucus hypersecretion

- physiotherapy review for chest clearance

Include antibiotic therapy targeted against *Haemophilus influenzae* during exacerbations

Impaired exercise capacity and breathlessness

- assess for deconditioning. Refer for pulmonary rehabilitation

Further management options in specialist centres

- Further down-titration of ICS is recommended if FeNO confirms the ongoing absence of eosinophilic airway inflammation
- Consider the use of mucolytics if difficult to clear secretions
- Consider a macrolide antibiotic for persistent exacerbations

Patient 3 (ACO or possible COPD with eosinophilic inflammation or bronchodilator reversibility)

Management approach in primary care

Airflow obstruction

- treat with long-acting bronchodilators
- given severe airflow obstruction, begin treatment with LABA/LAMA combination (no role for stepped introduction)

Eosinophilic airway inflammation

- add ICS

Impaired exercise capacity and breathlessness

- assess for deconditioning
- refer for pulmonary rehabilitation

Recommend smoking cessation to

- improve response to ICS
- reduce mucus hypersecretion
- decrease exacerbation frequency
- slow decline in lung function

Further management options in specialist centres

- Titrate ICS dose based on response to FeNO and blood eosinophils
- If the patient has persistent exacerbations and refractory eosinophilic airway inflammation, add monoclonal antibodies directed against anti-IL-5 – targeting this patient’s asthma traits and inflammatory phenotype*
- Evaluate for extrathoracic causes of frequent exacerbations, including chronic rhinosinusitis, vocal cord dysfunction, anxiety or depression, dysfunctional breathing

* This recommendation had not been specifically studied in ACO and is formed by extrapolating evidence for efficacy in patients with asthma.

Abbreviations: ACO = asthma-chronic obstructive pulmonary disease overlap; ICS = inhaled corticosteroid; IL-5 = interleukin 5; FeNO = fractional exhalation of nitric oxide; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist.

clearly not a disease entity in its own right and attempts to fit a label to patients who demonstrate symptoms of both asthma and COPD, and illustrates the limitations with the current approach to chronic airways disease. As we develop a greater understanding of the mechanisms underlying both asthma and COPD, a focus on treating identifiable clinical traits may offer a more targeted approach to therapies to improve symptoms and disease outcomes with fewer side effects. The management of the individual patient who fits the

description of ACO should focus on the traits of chronic airways disease that the patient manifests rather than the disease label. **RMT**

References

A list of references is included in the online version of this article www.respiratorymedicinetoday.com.au.

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