UPDATE ARTICLE

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Understanding the Asthma-COPD Overlap

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Introduction

Clinically, in the last century – and till recently – asthma and chronic obstructive pulmonary disease (COPD) have been labelled as separate disease entities with unique epidemiological features and pathophysiological mechanisms. For the internist, asthma and COPD are the most common pulmonary disorders characterised by airway inflammation, airflow obstruction, and tissue remodelling[1-4]. A frequent scenario is an older patient with a current or past smoking history, a history of atopy and asthma, with fixed airflow obstruction or partial reversibility, exhibiting overlapping features of asthma and COPD[5-7].

The entity of asthma-COPD overlap (ACO) is not a syndrome. Why? Simply because it is a heterogeneous disorder and does not describe a single disease entity. ACO has concomitant features of both asthma and COPD with patients presenting with different forms of airways disease (phenotypes) caused by a range of different underlying mechanisms. Wherease airway obstruction is common to both asthma and COPD, it is intermittent and reversible in asthma, but not so in COPD.There is always a subset of patients who exhibit overlapping features, i.e., unremitting airflow obstruction in severe asthma, or limited reversibility of airflow obstruction in COPD[8,9].

As early as 1962,"Asthmatic bronchitis"was mentioned as an entity by the American Thoracic Society. However, the existence of ACO was not documented because all published research focussed either on asthma or on COPD as different entities. It is important to look at ACO as a uniquely different entity requiring management which is to some extent different from both asthma and COPD. Moreover, the natural course of ACO is also different from both asthma and COPD considered separately. Hence, for all practical purposes, the co-existence of asthma and COPD in a patient needs to be recognised as asthma-COPD overlap (ACO).

Definition

Patients diagnosed to be having both asthma and COPD together are labelled as ACO. If the same patient has been diagnosed as a case of asthma by one physician and as COPD by another, it can be considered as ACO.The scientific committee consisting of both GINA (Global Initiative for Asthma) and GOLD (Global Initiative for Chronic Obstructive Lung Disease) define ACO as "persistent airflow limitation [forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio of < 70%] with several features usually associated with asthma and several usually associated with COPD"[3,10-12].

Incidence/prevalence

Due to growing awareness amongst clinicians, the recognition of ACO as a disease entity has of late seen the light of day, accounting for 15 to 25% of the obstructive airway diseases with patients experiencing worse outcomes compared with either of the conditions alone[4,13,14]. Different studies have shown wide variations in incidence. The incidence of ACO increases with age. It starts increasing from 40 + years to 70 + years. It is < 10% in those below 50 years of age, but > 50% in those over 80 years. In diagnosed cases of asthma, the incidence of ACO was noted to be 16% (20 - 44 years age group), 30% (45 - 64 years age group), and 60% (65 - 84 years age group). On the other hand, in diagnosed cases of COPD, it was 33% (20 - 44 years age group), 27% (45 - 64 years age group), and 25% (65 - 84 years age group)[15]. The pooled prevalence of ACO in the COPD population has been found to be 27% and 28% in population and hospital-based studies, respectively[3].

Aetio-pathogenesis of asthma-COPD overlap

The pathogenesis of ACO may be mediated by inflammatory mechanisms and/or structural alterations that are mainly characterised by airway obstruction and bronchial hyper-responsiveness. Classically, chronic inflammation is mostly eosinophilic and driven by CD4 cells in asthma, whereas in COPD it is mainly driven by neutrophils and CD8 cells. It has been noted that patients with severe asthma and smokers show higher numbers of neutrophils as compared to those with mild and moderate asthma. Patients with COPD – particularly those with acute disease exacerbations – frequently show tissue eosinophilia. It is evident that the gradual shift of a patient

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features of both asthma and COPD may necessitate various physiological modifications[2, 13,16,17].

Progression from asthma to asthma-COPD overlap

Asthma is considered a disease of variable airflow obstruction, usually in response to allergen hypersensitivity. On the other hand, obstruction in COPD is supposed to be incompletely reversible and the outcome of exposure to noxious inhalants, e.g., cigarette smoke or biomass fuel. It is proposed that patients with asthma who are exposed to the usual inhalants that cause COPD could develop this degree of fixed obstruction over time. Individuals with asthma who are exposed to higher levels of air pollution are at increased risk of developing ACO.

Exposures to noxious inhalants lead to neutrophilic inflammation, cytokine release, oxidative stress, DNA methylation changes, and matrix metalloproteinase-mediated proteolysis. These changes may redirect the asthmatic airway to features of COPD, including fixed airway obstruction and emphysema[16,18] (Fig.1).

Progression from COPD to Asthma-COPD Overlap

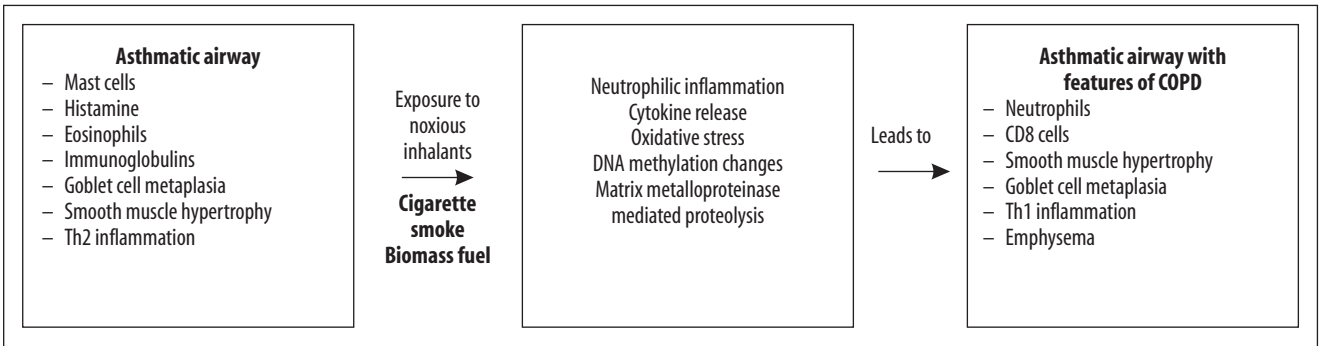
For a patient of COPD to develop features of asthma, the development of three key features is necessary, i.e., allergen sensitisation, airway hyper-responsiveness, and eosinophilic and type 2 (Th2) mediated airway inflammation. Patients with COPD – especially the elderly – are known to have allergen sensitisation, and more than one-fourth of patients with COPD report allergic upper airway symptoms or exhibit IgE sensitisation to perennial allergens. Also, allergen sensitisation has been associated with faster decline in lung function among smokers, and with increased respiratory symptoms and COPD exacerbations among patients with COPD. Also, presence of airway hyper-responsiveness and eosinophilic/Th2 mediated inflammation is seen in patients with COPD. Moreover, COPD patients also have thickening of the airway wall, involving the epithelium, reticular basement membrane, airway smooth muscle (ASM), and mucous glands that over time may contribute to airway narrowing in this cohort of patients[2,16].

Contributing factors

1. **Age:** Incidence of ACO is quite rare below age 40 years and above 85 years.
2. **Gender:** Women have an increased risk of developing ACO.
3. **Smoking:** Smokers (active and passive) and ex-smokers have a greater chance of developing ACO. Though vehicular smoke is known to contribute to the development of COPD, it is not a high risk factor for the development of ACO.
4. **Pre-existing respiratory illnesses:** Pulmonary tuberculosis, bronchiectasis, and long-standing asthma predispose to the development of ACO.

Clinical features

- Breathlessness and wheezing with subsequent development of cough and sputum production.
- Some cases report late night or early morning chest tightness.
- Excerbations are more frequent in ACO than in COPD, thus leading to compromised respiratory function, mandating hospitalisation.
- Clinically, there is lengthening of the expiratory time, diffuse wheezing (rhonchi), and diffuse crepitations (crackles).



Adapted from: 1. Leung JM. Asthma–COPD overlap syndome: pathogenesis, clinical features, and therapeutic targets. *BMJ* 2017; 358: j3772.
2. To T, Zhu J, Larsen K *et al.* Progression from Asthma to Chronic Obstructive Pulmonary Disease. Is Air Pollution a Risk Factor? *Am J Respir Crit Care Med* 2016; 194 (4): 429-38.

Fig. 1: *Mechanism for the progression of asthma to asthma-COPD overlap.*

- Pulmonary function test reveals reduction in FEV_1, FEV_1/FVC and PEFR.
- Reduction in oxygen saturation (presenting as cyanosis) is seen in acute conditions.
- Limited reversibility of the airway obstruction – which is not as complete as in asthma – can be demonstrated.

Phenotyping of asthma-COPD overlap

ACO may be suspected in many patients with airway disease, as it encompasses features of both asthma and COPD, but a clear definition is lacking[19].

A study by Ghebre *et al*[20] evaluated clinical findings and also determined the expression of cytokines in the sputum in ACO patients with either severe asthma or mild-to-moderate COPD. This study revealed three distinct groups:-

Group 1: Patients with predominant eosinophilic asthma presentation with Th2 cytokine expression.

Group 2: Patients with both asthmatic and COPD symptoms, with raised levels of proinflammatory cytokines and a higher incidence of bacterial colonisation. The airway inflammation is predominantly neutrophilic, which is postulated to be a consequence of bacterial airway infection.

Group 3: Patients with predominant features of COPD. There is an increased level of proinflammatory cytokines, but in comparison to group 2, a lower incidence of bacterial colonisation. This suggests that inflammation may be a primary abnormality with a major role in the development and progression of the disease. The airway inflammation may be either neutrophilic or eosinophilic.

This study found that patients with overlapping features (group 2) could be differentiated from the other groups with the following biomarkers: sputum cytokine IL-1Beta and tumour necrosis factor (TNF) at a cut-off point of 130 pg/m and 5 pg/ml, respectively.

Rhee[21] has proposed four phenotypes of ACO according to eosinophilic inflammation, history of allergy, smoking history, and emphysema. Each phenotype has a different underlying pathophysiology and requires different medications:-

Phenotype A

- Predominant clinical features of allergic asthma, usually since childhood.
- Non-smokers.
- May have other systemic allergies.
- A more favourable prognosis compared with patients with other ACO phenotypes.

Phenotype B

- Severe noneosinophilic asthma.
- Non-smokers.
- Poor lung function.
- A higher risk of COPD in the long-term as compared with patients with non-severe asthma.

Phenotype C

- Features of both asthma and COPD present.
- History of asthma present.
- Eosinophilic lung inflammation.
- History of other allergic disease.
- History of long-term smoking.
- In patients with predominent features of asthma, prognosis is poorer in smokers compared with nonsmokers.
- Patients with predominent features of COPD, but with overlapping allergic phenotype, have an increased risk of poor clinical outcome.

Phenotype D

- Predominant features of COPD.
- No history of asthma or allergic diseases.
- History of smoking present.

The clinical validity of the proposed classification by Rhee was established by a study by Joo *et al*[19], wherein patients with ACO were classified into four phenotype categories based on blood eosinophils and history of smoking:-

Group A: Patients with history of smoking < 10 pack-years and with blood eosinophil counts > 300/µl.

Group B: Patients with history of smoking < 10 pack-years and with blood eosinophil counts < 300/µl.

Group C: Patients with history of smoking > 10 pack-years and with blood eosinophil counts > 300/µl.

Group D: Patients with history of smoking > 10 pack-years and with blood eosinophil counts < 300/µl.

Clinical characteristics were analysed and compared among other groups. The most important finding of this study was that phenotype C had the most frequent exacerbations, but this was not necessarily correlated with a worse pulmonary function. This study showed that the four groups had differing characteristics and prognosis. Therefore, phenotypical categorisation of patients with obstructive

airway diseases, in particular ACO, may result in better design of clinical trials leading to improved understanding of clinical concepts and treatment with evidence-based pharmacotherapy[19].

Diagnosis of asthma-COPD overlap (ACO) – a clinical dilemma

Due to the overlap between asthma and COPD, it is quite a challenge to differentiate between the two. To arrive at a proper diagnosis, one needs to take a thorough history, do a physical examination, and go for relevant investigations followed by analysis of the symptoms to distinguish between asthma, COPD, and ACO. Symptoms of airway obstruction and non-reversible airway inflammation in middle-aged individuals are the hallmarks of ACO (Fig. 2).

In a nutshell, the following features go in favour of a diagnosis of ACO

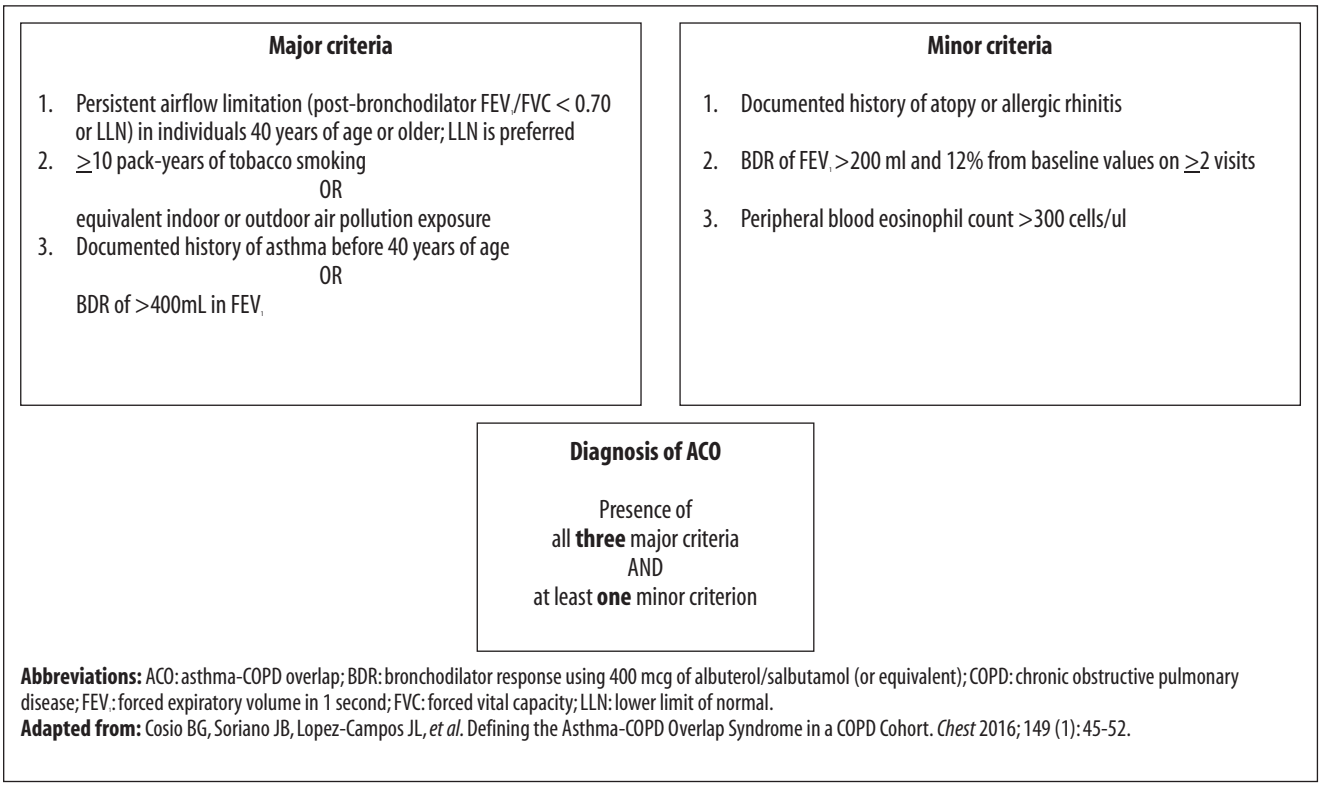
- Age > 40 years.
- Active or former smoker (~10 pack-years).
- Persistent airflow (chronic) obstruction.
- Persistent dyspnoea; however, it may vary.
- Post-bronchodilator FEV_1/FVC ratio < 0.70.
- History of asthma, allergies, or family history of asthma.
- Chest X-ray showing hyperinflation with other features of COPD.
- Frequent exacerbations than COPD, but reduced by treatment.
- Marked eosinophilia (> 300 eosinophils/μl) and/or elevated neutrophils in sputum.

History

- History of chronic or recurrent cough, sputum production, dyspnoea, wheezing, or repeated acute lower respiratory tract infections.
- History of smoking tobacco (or other substances).
- History of prior treatment with inhaled medications.
- Family history of COPD.

Physical examination

- It may reveal normal results.
- Evidence of hyperinflation and other features of chronic lung disease or respiratory insufficiency.
- Wheezing and crackling sounds on auscultation.



Abbreviations: ACO: asthma-COPD overlap; BDR: bronchodilator response using 400 mcg of albuterol/salbutamol (or equivalent); COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; LLN: lower limit of normal.
Adapted from: Cosio BG, Soriano JB, Lopez-Campos JL, *et al*. Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort. *Chest* 2016; 149 (1): 45-52.

Fig. 2: *Diagnostic criteria for asthma-COPD overlap.*

Investigations

- Radiological findings of chest X-ray or CT scan include hyperinflation, airway wall thickening, bullae, or other features of emphysema.
- Blood tests: Complete blood count to look for anaemia or polycythemia.

Analysis of symptoms to distinguish between COPD, asthma, and ACO

Differentiating characteristics of COPD and asthma are shown in Table I. If the patient presents with similar number of features (in each column) of both the diseases, diagnosis of ACO should be considered.

Table I: Differentiating characteristics of chronic obstructive pulmonary disease and asthma.

Characteristics	Chronic obstructive pulmonary disease	Asthma
Age	• > 35 years	• < 20 years
Symptom pattern	• Chronic cough and sputum precedes onset of dyspnoea, regardless of triggers • Good and bad days but daily symptoms and exertional dyspnoea always present	• Episodes related to triggers such as exercise, emotions including laughter, dust or exposure to allergens • Symptoms worsen during night or early morning
Lung function	• Persistent airflow limitation	• Variable airflow limitation
Time course	• Symptoms gradually worsen over time • Limited relief can be provided by rapid-acting bronchodilator treatment	• Seasonal variation in symptoms present • Demonstrates immediate response to bronchodilator or to inhaled corticosteroid over weeks

Quality-assured spirometry

For confirmation of the diagnosis and severity of the disease, quality assured spirometry is required. The degree of airflow limitation is assessed using spirometry (FEV_1 predicted):

- Mild: > 80%
- Moderate: 50 - 79%
- Severe: 30 - 49%
- Very severe: < 30%

Difficulties in the diagnostic differentiation of asthma-COPD overlap

Since a unified definition of ACO is still lacking, clinicians might make use of some key features to identify this condition. Presence of variable airflow limitation is usually considered an essential feature of ACO. However, the diagnostic differentiation between asthma and COPD may not just be a matter of reversibility of airway obstruction induced by a bronchodilator, since a sizeable proportion of patients with moderate-to-very severe COPD also exhibit a known bronchodilator response. In patients with asthma, ACO usually corresponds to those who smoke and develop non-fully reversible airway obstruction. However, it should be noted that the presence of chronic non-fully reversible airflow obstruction in an individual with asthma is not necessarily ACO, since patients with severe asthma are known to develop non-reversible airflow limitation without any characteristics of COPD. Moreover, in the absence of a known history of asthma, the diagnosis of ACO may be difficult due to lack of specific biomarkers[5,22,23].

Identifying a patient with ACO is important in that it may affect the clinical course, long-term prospect, and therapeutic response. Effective management of patients with ACO necessitates a definitive diagnosis of the condition. The frequently used approaches for clinical assessment including history, exposure, and bronchodilator reversibility are not concrete. Thus, considering that patients with ACO represent a significant clinical challenge, further research is warranted to define this entity, to facilitate its identification in clinical practice, and to devise an effective management approach[22,24].

Diagnostic role of Fractional exhaled nitric oxide (FeNO)

NO gas is produced by bronchial epithelial cells in response to local production of interleukin-4 and interleukin-13 by eosinophils, mast cells, and Th2 cells. Therefore, an elevated level of exhaled NO is indicative of an eosinophilic airway inflammation[25]. Asthma and COPD are characterised by inflammation of the airways with limitation of airflow. It has been established that FeNO is associated with eosinophilic airway inflammation, especially in asthmatic patients[26]. In contrast, patients with COPD do not exhibit significantly raised FeNO value because the inflammation has different characteristic, with the predominantly inflammatory cells being neutrophils[27]. However, FeNO level is elevated in a subset of COPD patients having concomitant asthmatic features, and may serve as a biomarker to differentiate between COPD and the ACO. This also has implications in the management of these patients as inhaled corticosteroids (ICS) are indicated in the treatment of ACO but are avoided in patients with COPD due to a higher risk of complications, such as pneumonia[28]. A study by Chen *et al*[28] showed that the level of FeNO is higher in patients with ACO as compared with patients of COPD.

Biomarkers in asthma-COPD overlap

Biomarkers of ACO are being sought to facilitate diagnosis, clinical classification, and targeted pharmacotherapy as there is yet no universally accepted criteria for establishing a diagnosis of ACO. The GOLD 2015 COPD guidelines outline the biomarkers for patients with asthma and COPD, but there is paucity of research on biomarkers delineating ACO[29]. However, a few biomarkers for ACO have been identified.These are inflammatory biomarkers and sputum biomarkers:-

1. Inflammatory biomarkers

In allergic asthma, there is a raised level of fractional exhaled Nitric Oxide (FeNO), blood eosinophils, and allergen specific immunoglobulin E (IgE) level[30]. Eosinophilic inflammation is a characteristic feature of asthma, whereas neutrophilic inflammation is present in COPD[26]. Both FeNO and IgE have potential as inflammatory biomarkers to distinguish asthma from COPD[31]. However,the importance of these biomarkers in the diagnosis of ACO is yet to be determined.

A study by Kobayashi *et al*[32] showed that the mean FeNO level was significantly elevated in patients with ACO as compared with patients with COPD alone. Blood eosinophil count and percentage were also increased in patients with ACO. Additionally, the total IgE level was also raised. The results of this study indicated that inflammatory biomarkers provide additional diagnostic information for ACO. A combination of these biomarkers increases the specificity for a diagnosis of ACO[32].

2. Sputum biomarkers

Gao *et al*[33] evaluated five biomarkers with the potential to differentiate ACO from asthma and COPD. These were interleukin (IL)-13, myeloperoxidase (MPO), neutrophil gelatinase-associated lipocalin (NGAL), chitinase-like protein (YKL-40), and IL-6, based on the hypothesis that the sputum biomarkers known to be raised in airway inflammation in asthma (IL-13), COPD (MPO, NGAL), or in both asthma and COPD (YKL-40, IL-6) could be used to differentiate ACO from asthma ($P < 0.001$).

A study by Iwamoto *et al*[34] showed that patients with asthma had a lower level of sputum myeloperoxidase levels as compared with patients with ACO and COPD. In addition, levels of sputum NGAL were found to be raised in patients with ACO as compared with COPD alone.

Comprehensive management of asthma-COPD overlap

Any therapeutic approach for ACO should address both asthma and COPD. Considering its severity relative to both asthma and COPD alone, ACO requires more intensive treatment.

1. Identification and minimising exposure to risk factors

- Allergens
- Air pollutants
- Smoking
- Airway infections

2. Pharmacologic intervention (Table II, Fig. 3)

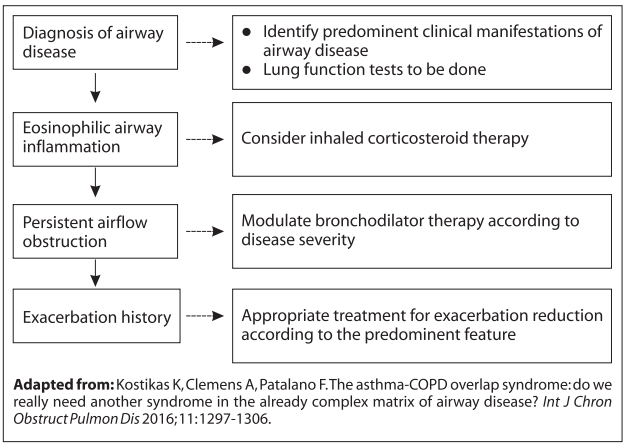
According to the GINA and GOLD guidelines, ACO should be treated according to the dominant presenting feature. Combine pharmacotherapy along with risk reduction (cessation of smoking). As such, ACO management requires treatment of both asthma and COPD conditions.This includes:

- Optimal use of bronchodilators
- Appropriate dose of inhaled corticosteroids (ICS), long-acting beta 2 agonists (LABA), and long-acting muscarinic receptor antagonist (LAMA) in varying combinations according to disease severity[29,35]. Growing data suggests the use of LABA/ICS combination therapy in these patients.
- The use of 'triple' therapy including LAMA, LABA, and ICS may be considered in patients with more severe symptoms, particularly in the presence of frequent exacerbations[36,37].
- Short-acting reliever medication such as short-acting beta-agonist (SABA) can be administered and continued at all stages.
- Long-acting muscarinic antagonist (LAMA) can be administered for the prevention of exacerbations.
- Second- and third-line medications include terbutaline, inhaled aclidinium bromide, inhaled glycopyrronium bromide, formoterol (12 mcg), salmeterol or LAMA + LABA combination inhaler/LABA + ICS combination inhaler.
- Check for inhaler technique used by the patient as well as adherence.

Table II: Therapeutic options for asthma-COPD overlap.

Primary treatment	ICS (low/medium/high dose) ± LAMA ± LABA
Additional treatment	• Methylxanthine • LTRA • Anti-IgE antibody • Oral corticosteroid • Macrolides* • Expectorants*

Abbreviations: COPD: Chronic obstructive pulmonary disease; ICS: Inhaled corticosteroid; LAMA: Long-acting muscarinic antagonist; LABA: Long-acting beta-2 agonist; LTRA: Leukotriene receptor antagonist. *in case of mucus hypersecretion.
Adapted from: Kondo M, Tamaoki J. Therapeutic approaches of asthma and COPD overlap. *Allergol Int* 2017; pii: S1323-8930 (17) 3136-3.



Adapted from: Kostikas K, Clemens A, Patalano F. The asthma-COPD overlap syndrome: do we really need another syndrome in the already complex matrix of airway disease? *Int J Chron Obstruct Pulmon Dis* 2016;11:1297-1306.

Fig. 3: *A proposed management model in patients with asthma-COPD overlap.*

3. Non-pharmacologic intervention

In addition to pharmacotherapy, ACO management necessitates the following:-

- Improvement of the patient's environment.
- Patient education.
- Smoking cessation.
- In order to review quality of life (QOL), degree of breathlessness, pulse oximetry, COPD assessment test (CAT) score should be evaluated using Medical Research Council (MRC) scale.
- Pulmonary rehabilitation should be offered to patients with MRC score 2 and above, who consider themselves functionally disabled by their condition or breathlessness, recent hospitalisation for exacerbation, or significant functional deterioration.
- Vaccinations against influenza and pneumococcus.
- Nutritional therapy: Review body mass index (BMI) and nutritional status, and encourage physical activity to optimise function.
- Oxygen therapy.
- Ventilator assistance.
- Assessment and treatment of comorbidities, e.g., cardiovascular diseases, bronchiectasis, lung cancer, osteoporosis, skeletal muscle dysfunction, metabolic syndrome, anxiety and depression[37,38].

Management of ACO according to phenotype

Rhee[21] has proposed a management regimen varying according to phenotype:-

Phenotype A

Standard treatment here is asthma medication, especially inhaled corticosteroids. Since these patients have lower lung function, a long-acting beta agonist (LABA) can be added. If these patients have a suboptimal response to ICS + LABA, a long-acting muscarinic antagonist (LAMA) can be added as it has been shown to decrease asthma exacerbations. Other asthma medications, e.g., a leukotriene antagonist (LTRA) can also be given.

Phenotype B

ICS + LABA can be considered as a first-line therapy as these patients are usually associated with severe asthma. However, those with severe noneosinophilic asthma may not respond satisfactorily, and a LAMA may need to be added. In patients with severe asthma and a noneosinophilic phenotype, tiotropium may be effective. Other medications which reduce the concentrations of neutrophils and interleukin-8, and reduce exacerbations are macrolides, clarithromycin, and azithromycin.

Phenotype C

Best response in these patients of phenotype C has been seen with ICS + LABA. There is more increase in forced expiratory volume in 1 s (FEV_1) with ICS treatment in ACO as compared with patients with only COPD. Since phenotype C patients have a history of both asthma and smoking, LTRAs are also beneficial.

Phenotype D

Since the airway inflammation is neutrophilic and these patients do not have asthma, treatment should be as per the COPD guidelines. Moreover, since these patients are prone to lose lung function relatively rapidly, the aim of treatment should be to prevent decline in lung function. Salmeterol plus fluticasone has been shown to reduce the rate of decline of FEV_1 in patients with moderate to severe COPD. In patients with GOLD stage II COPD, tiotropium reduces deterioration of post-bronchodilator FEV_1. Excerbations may be reduced with the addition of roflumilast or azithromycin as patients with phenotype D have neutrophilic inflammation.

Prognosis

Patients with ACO fare worse than those with COPD since they have more frequent exacerbations and hospitalisations. Acute exacerbations are 2 - 3 times more frequent than COPD cases. They have a worse quality of life in comparison to either asthma or COPD alone[39]. Frequency of hospital/ICU admission, and visitations to the emergency department/ward were higher than COPD cases[40]. The costs of treatment incurred by patients of ACO were nearly 5-times more than those of asthma.

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