

Review Article

Asthma Chronic Obstructive Pulmonary Disease Overlap Syndrome (ACOS): Where We Stand

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Abstract: Asthma-Chronic obstructive pulmonary disease overlap syndrome (ACOS) or ASCOS is a frequently encountered clinical syndrome. It is identified by the clinical features that it shares with asthma and COPD. There is no clear consensus definition yet for this medical syndrome. ACOS has not been extensively studied partly because of the absence of clarity of its clinical significance and because of the lack of a clear definition for this syndrome. ACOS is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with chronic obstructive pulmonary disease (COPD). It has been described and named differently by different authors. Some of the commonly encountered names are asthmatic bronchitis, asthma of the elderly, patients with COPD and a prominent asthmatic component, asthma that complicates COPD, asthma with permanent obstruction, COPD with a reversible component and asthma-COPD overlap syndrome. In most obstructive lung disease trials patients with overlap syndrome are excluded because they are not strictly asthmatic per the study inclusion criteria or they are not strictly chronic obstructive pulmonary disease patients. With no clear consensus on the definition and few studies on its genetics or pathophysiology, it is difficult to create management guidelines for this group of patients. Patients with ACOS have been found to have higher risk not only for exacerbations, but also for hospitalizations. Global Initiative for Chronic Obstructive Lung Disease (Gold) and the Global Initiative for Asthma (GINA) have suggested a stepwise diagnostic and management criteria for patients with ACOS.

Keywords: Asthma COPD Overlap Syndrome (ACOS), Definition, Pathophysiology, Approach, Management

1. Introduction

Asthma-COPD overlap syndrome is a frequently encountered clinical condition which has not been precisely defined by the pulmonary community partly due to inadequate clinical studies. Most clinical trials strictly address asthma in which case COPD is one of the criteria for exclusion or COPD is being addressed and asthma is one of the exclusion criteria. American Thoracic Society first attempted to characterize this syndrome decades ago, and they described it as asthmatic bronchitis.¹ For several years after the initial definition, no studies to the best of our knowledge were completed to better understand ACOS. In the past decade or so, several attempts have been made in the United States, Spain, Japan, Greece, and Canada to better define and classify ACOS.^{2,3,4}

Asthma which is a reversible obstructive lung disease and COPD, which is a non-reversible obstructive lung disease have been clearly defined and studied, but in clinical practice, there is a hybrid disease between asthma and COPD. Patients with the hybrid disease are known to have asthma, smoke, and do not have complete reversibility to treatment as expected, or they are known to have COPD, but respond with partial reversibility to treatment.⁵ In some guidelines, these patients are described as patients with COPD and a prominent asthmatic component or as asthma that complicates COPD. Due to the wide range of response to treatment in these patients with obstructive lung disease, there is a need to throw more light on the range of syndromes that are encountered in clinical practice. Soriano et al. analyzed data from NHANES and found that ACOS is common among older patients from

the general population, particularly in adults aged ≥ 50 years.⁶ ACOS is identified by the features that it shares with both asthma and COPD.

2. Definition

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.⁷

COPD is a common preventable and treatable disease, characterized 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.⁸

Asthma-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 is therefore identified by the features that it shares with both asthma and COPD.

A definition of ACOS remains elusive since there is no consensus in the available studies.

Asthma COPD overlap syndrome has been defined as a syndrome in which older people with a significant smoking history and chronic obstructive airway disease, manifest asthmatic features.² Patients with overlap are either smokers with asthma or nonsmokers with long-standing asthma which is progressing toward COPD.

Miraville et al.⁹ established Spanish COPD guidelines and proposed four COPD phenotypes that determine differential treatment: nonexacerbation with emphysema or chronic bronchitis, mixed COPD–asthma, exacerbation with emphysema and exacerbation with chronic bronchitis. This group defined Asthma COPD overlap syndrome as an airflow obstruction that is not completely reversible, accompanied by symptoms or signs of an increased reversibility of the obstruction. The American Thoracic Society identified 11 airflow obstruction syndromes ranging from asthma, through chronic bronchitis and emphysema to COPD, and they found that 6 of these 11 syndromes overlap with each other.¹⁰

Soler-Cataluña et al. established major and minor criteria to define asthma-COPD overlap syndrome. The major criteria include very positive bronchodilator test (increase in FEV1 $\geq 15\%$ and ≥ 400 ml), eosinophilia in sputum and personal history of asthma. Minor criteria include high total IgE, personal history of atopy and positive bronchodilator test (increase in FEV1 $\geq 12\%$ and ≥ 200 ml) on two or more occasions. The diagnosis of Asthma COPD syndrome is made when 2 major criteria and 2 minor criteria are met.¹¹ These criteria are non-specific since there are patients who have COPD with eosinophilia and by the same token most COPD patients respond by 15% or more to bronchodilators.¹²

Louie et al. established another set of major and minor criteria for ACOS. The major criteria are: a physician diagnosis of asthma and COPD in the same patient, history or

evidence of atopy, elevated total IgE, age 40 years or more, smoking >10 pack-years, post-bronchodilator FEV1 $<80\%$ predicted and FEV1/FVC $<70\%$. The minor criteria are: a $\geq 15\%$ increase in FEV1 or $\geq 12\%$ and ≥ 200 mL increase in post-bronchodilator treatment with albuterol.¹³

Genetic studies have been conducted on asthma¹⁴ and COPD¹⁵ but the lack of definition for ACOS makes it hard to link it to any particular gene. The consensus-based description of Asthma-COPD Overlap Syndrome (ACOS) by GOLD and GINA is intended to stimulate further studies on the character of ACOS and treatments for this common clinical problem.⁸

3. Epidemiology

The few studies that have evaluated ACOS report an estimated prevalence of 20-24%.^{2,6,16} This is approximately half the prevalence of asthma which is the most prevalent type of airway disease (about 43%). This prevalence is comparable with that of COPD which is 23.3% in the same study by Zeki A et al.¹¹

Marsh et al. estimated the prevalence of asthma in a COPD cohort to be 55.2% using a composite definition of asthma being a post-bronchodilator increase in FEV1 $> 15\%$, or peak flow variability $> 20\%$ during 1 week of testing, or physician diagnosis of asthma, in conjunction with current symptoms.¹⁷ The comparison of different estimates is inconsistent because of the different definitions of ACOS. However, the majority of patients with moderate-to-very-severe chronic obstructive pulmonary disease demonstrate meaningful increases in lung function following administration of inhaled anticholinergic plus sympathomimetic bronchodilators.¹⁸

ACOS accounts for approximately 15-25% of obstructive airway diseases and patients experience worse outcomes compared with asthma or COPD alone.¹³ Patients with ACOS who have the combined risk factors of smoking and atopy are generally younger than patients with COPD and experience acute exacerbations with higher frequency and greater severity than lone COPD. ACOS is more prevalent in older adults, as the population ages, the prevalence of overlap syndrome increases in each decade, the highest prevalence being in those >60 years of age.^{2,3,4} There is an estimated prevalence of $<10\%$ in patients younger than 50 years and $>50\%$ in patients aged 80 years or older.⁶ De Marco et al.¹⁸ through a screening questionnaire, showed that the prevalence of asthma-COPD overlap was 1.6%, 2.1% and 4.5% in the 20-44, 45-64, 65-84 age groups, respectively.¹⁷

A consensus is needed on the definition of ACOS by the pulmonary community. This definition and specific characteristics of ACOS can then be used to design prospective, randomized clinical trials to evaluate specific drug interventions on important outcomes such as lung function, acute exacerbations, quality of life, and mortality. One certainty is that the overlap syndrome is clinically relevant since it has $>20\%$ prevalence in populations with airway diseases.¹³

In a study focusing on health-related quality of life (HRQoL), a patient population of 1,546 subjects was divided

into three groups: (I) asthma only; (II) COPD only; (III) asthma-COPD overlap. In the overlap group, HRQoL was the poorest of all. In the logistic regression model, with the asthma group as the reference, both the overlap and the COPD group showed a higher risk for low HRQoL with an odds ratio (OR): 1.9; 95% CI: 1.2-3.2; and OR: 1.8; 95% CI: 1.0-3.2; respectively. ACOS was clearly associated with low HRQoL, when compared with asthma or COPD only.¹⁹

In the EPI-SCAN study, an epidemiology study in Spain, data was analyzed from 3,885 subjects who had been previously diagnosed with asthma, 17.4% of them were classified as the asthma-COPD overlap phenotype. These patients were found to have more dyspnea, wheezing, exacerbations, reduced levels of physical activity and worse respiratory-specific quality of life (11.1 units on the St. George's Respiratory Questionnaire-SGRQ, 95% CI: 4.88-17.36).²⁰

Menezes et al. evaluated the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study population, and found that patients with ACOS had more respiratory symptoms, had worse lung function, used more respiratory medication, had more hospitalizations and exacerbations, and had worse perceptions of general health status.²¹ In a Finnish population study on patients with primary or secondary diagnosis of asthma or COPD, the average number of treatment periods during 2000-2009 was 2.1 in asthma, 3.4 in COPD and 6.0 in overlap syndrome.²²

Patients with coexisting asthma and COPD manifest the signs and symptoms of obstructive lung disease as would patients who have just asthma or COPD, but patients with overlap syndrome tend to have worse lung function, more respiratory symptoms, and a lower health-related quality of life than either asthma or COPD alone.^{19,23} They are 2-6 times more expensive to take care of as compared to patients with asthma or COPD alone.²⁴ They experience more frequent and severe respiratory exacerbations despite younger age and reduced lifetime smoking history.²⁵ Overlap patients had more evidence of air trapping on chest CT than those with COPD.²⁴

4. Pathophysiology

There are still several unanswered questions with regards to the pathophysiology of ACOS. Questions like: is ACOS a progression of asthma into COPD? Does it have a completely separate pathophysiology from asthma or COPD? Is this a disease of older adults with asthma? According to "The Dutch Hypothesis," asthma and bronchial hyperresponsiveness in childhood predispose to COPD later in life. Also, asthma, COPD, chronic bronchitis, and emphysema are different expressions of a single airway disease. What is expressed is influenced by the host and environmental factors.²⁶

The main components of obstructive pulmonary disease are bronchial hyperresponsiveness, airway inflammation, and airway obstruction.²⁷ Exposure of airways and the lungs to noxious particles or gases like tobacco smoke lead to smooth muscle dysfunction and small airway inflammation in patients with ACOS causing exacerbation (Table 1).

Table 1. Effects of small muscle dysfunction and small airway inflammation.

Smooth muscle dysfunction	Small airway inflammation
<ul style="list-style-type: none"> • Bronchoconstriction • Bronchial hyperresponsiveness • Inflammatory mediator release 	<ul style="list-style-type: none"> • Inflammatory cell infiltration • Inflammatory Mediator release • Mucosal edema
<ul style="list-style-type: none"> • Smooth muscle hyperplasia • Smooth muscle hypertrophy 	<ul style="list-style-type: none"> • Epithelial damage and mucus hypersecretion • Basement membrane thickening

Most asthmatic patients have CD4-eosinophilia driven inflammation while most COPD patients have CD8-neutrophilic driven inflammation, but patients with ACOS have both eosinophilia and neutrophilia driven inflammation. Neutrophilia driven inflammation is more resistant to steroids.²⁸ Smoking asthmatics have more neutrophils in their airways, and thus more resistance to steroids as compared to asthmatics that do not smoke or eosinophilic asthmatics. The amount of neutrophils found in the airways of patients with asthma has been directly linked to a decline in the FEV1.²⁹ At some point, these patients develop ACOS. This is not a one-way correlation. Eosinophilic inflammation has been found in some COPD patients and these patients are more responsive to steroids.²⁸

Patients with ACOS have increased airway wall thickness due to remodeling consisting of mucosal edema, inflammation, hypersecretions, mucus plugs hypertrophy and hyperplasia of airway smooth muscles.³⁰ This results in airway obstruction. This is similar to the pathological airway changes that are seen in asthma and COPD. The structures that are remodeled are the same, but there is a difference in the degree of remodeling of each of the structures in asthma, COPD, and ACOS.³¹ A longitudinal study completed by Vonk et al. showed that 16% of the asthmatic patients enrolled in this study developed incomplete airway reversibility after 21-33 years of follow up.³²

Some have suggested that in order to recognize ACOS in COPD patients with airflow obstruction, we can use provocation tests with agents that do not cause direct airway smooth muscle contractions like adenosine, mannitol or antihistamines.²⁷ All patients with asthma have airway hyperreactivity especially during acute exacerbations, and up to two-thirds of patients with COPD have airway hyperreactivity.²⁹

Iwamoto et al. discovered that the biomarker neutrophil gelatinase-associated lipocalin (NGAL) was significantly increased in the sputum of patients with ACOS, compared to patients with COPD. They suggested that NGAL could be used to differentiate ACOS from COPD. This means that elevated induced sputum levels of NGAL should point to a diagnosis of ACOS suggesting enhanced neutrophilic airway inflammation or airway epithelial injury in overlap syndrome.³³

ACOS has three times the rate and severity of exacerbations as compared to patients with asthma or COPD alone.^{5,34} Exacerbations are mainly caused by viral or bacterial infections and can lead to accelerated loss of lung function.²¹ Harden et al.⁴ suggested that systemic inflammation with an increase in IL6 and C-reactive proteins may be a contributing

factor to the morbidity associated with ACOS. Older adults with asthma tend to have more fixed obstructions and more severe symptoms than younger patients partly due to the natural deterioration in lung function that comes with age.^{35,36} Therefore older adults with asthma may manifest like patients with COPD.

5. Diagnosis

A stepwise approach (Figure 1) is recommended by GINA and GOLD for the diagnosis and management of ACOS.^{7,8}

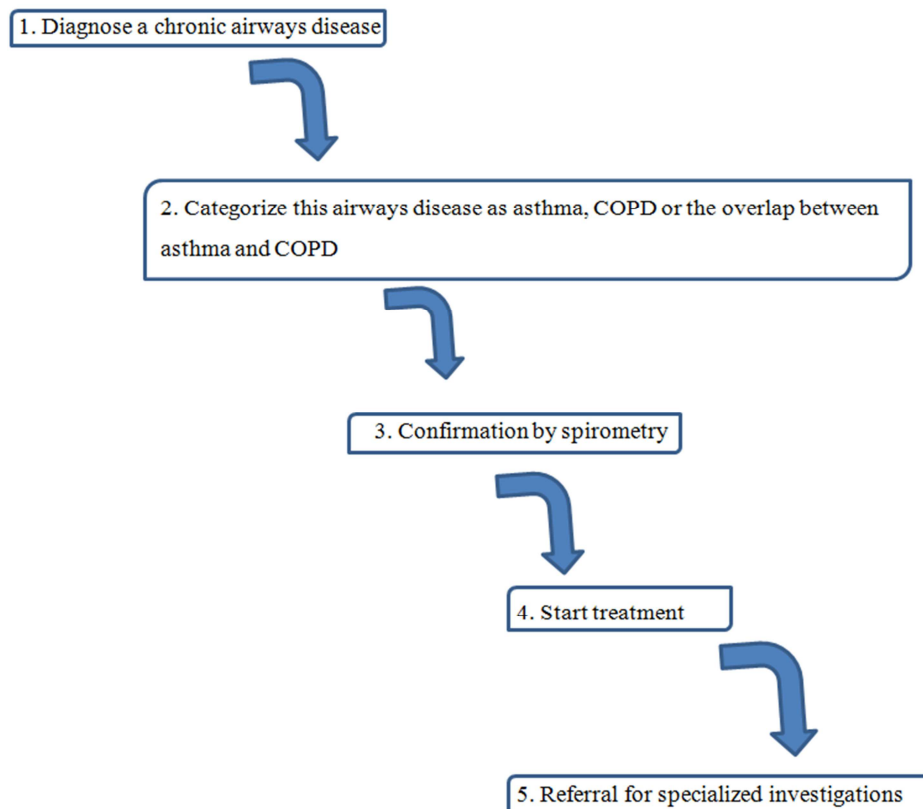


Figure 1. Stepwise approach to patients with ACOS.

Since the outcome for ACOS is worse than the outcome for COPD or asthma alone, referral for confirmatory investigations is encouraged.

The first step in the diagnoses of ACOS (Figure 2) is to identify patients at risk of having a chronic airways disease or patients who have a high likelihood of having chronic airways disease, and to exclude other potential causes of respiratory symptoms. Other potential causes of the presenting symptoms have to be excluded by a thorough medical history, physical examination, laboratory studies, imaging and any other warranted investigations.

The medical history should elicit exposures to tobacco, occupational exposures, environmental hazards, and domestic exposures to airborne pollutants. A past medical history should include a history of atopy or use of inhaled medications, and diagnosis of COPD or asthma. A history of chronic or recurrent cough, sputum production, dyspnea wheezing, and repeated acute lower respiratory tract infections should warrant a complete investigation.⁶

The physical examination should focus on looking for features of chronic lung disease or respiratory insufficiency, wheezing and/or crackles.

Laboratory studies usually have nonspecific findings or

may be normal. Chest X-ray or CT scan findings may include hyperinflation, airway wall thickening, air trapping, hyperlucency, bullae or other features of emphysema. Imaging may help eliminate some of the differential diagnoses like bronchiectasis, interstitial lung diseases, heart failure or infections such as tuberculosis.

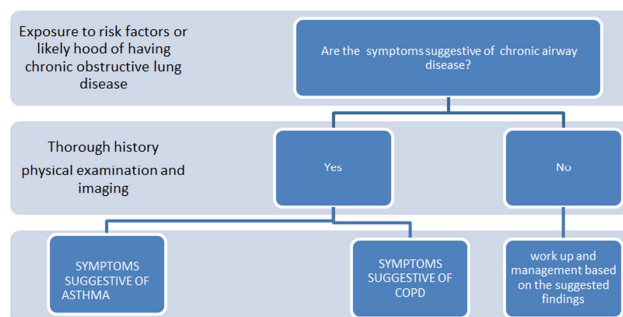


Figure 2. First diagnostic step for ACOS.

The next step is to categorize the airways disease as asthma, COPD or ACOS. In order to do this, the clinical characteristics of the disease have to be thoroughly assembled and all the factors that favor the diagnosis of asthma or COPD have to be

compared (Table 2). Based on how many factors favor asthma or COPD, a diagnosis is made. If a patient has a similar number of features of both asthma and COPD, a diagnosis of

ACOS may be more appropriate. Depending on the level of certainty, treatment may be initiated.

Table 2. Diagnostic features to be compared^{8, 35}.

Features in favor of a diagnosis of asthma	Features in favor of a diagnosis of COPD
<ul style="list-style-type: none"> Onset before 20 years of age Symptoms vary over time Variable airflow limitations by spirometry/peak flow History of a diagnosis of asthma or other allergic conditions Normal lung function between symptoms Family history of asthma and other allergic conditions Symptoms do not get worse over time Short-acting bronchodilators may provide immediate relief 	<ul style="list-style-type: none"> Onset after 40 years of age Symptoms persist even after treatment Persistent airflow limitations with post-bronchodilator FEV1/FVC<0.7 History of COPD, chronic bronchitis or emphysema. Lung function is abnormal between symptoms
<ul style="list-style-type: none"> The chest x-ray is usually normal 	<ul style="list-style-type: none"> Heavy exposure to risk factors: tobacco, smoke, occupational exposures, environmental hazards, and domestic exposures to airborne pollutants. Symptoms slowly worsen over time Short-acting bronchodilators provide only limited relief The chest x-ray usually shows hyperinflation

ACOS patients frequently have a history of doctor-diagnosed asthma, allergies and a family history of asthma, and/or a history of noxious exposures.¹³ They are often ≥ 40 years old at diagnosis, but may have had symptoms in childhood or early adulthood.^{38, 39} Respiratory symptoms including exertional dyspnea are persistent but variability may be more prominent in these patients.⁸ The airway limitation in ACOS is persistent, not fully reversible, but often variable. Symptoms are partly but significantly reduced by treatment. The usual progression and treatment needs in ACOS are higher than in either COPD or asthma alone. Exacerbations may be more common than in COPD but are reduced by treatment. They usually have higher hospitalization rates as compared to asthma or COPD alone.²¹ Comorbidities can contribute to impairment. ACOS has eosinophils and/or neutrophils in the sputum. The chest x-ray may show severe hyperinflation and other changes of COPD. ACOS has less extensive emphysema and a different distribution as compared to COPD. Also, ACOS has a greater post-bronchodilator variation in air trapping as compared to COPD.⁴⁰

The third step in the diagnosis is confirmation with spirometry.^{7,8} Every patient with suspected chronic disease of the airways needs a before and after the trial of treatment spirometry at the initial or subsequent visit.^{7,8} Spirometry confirms chronic airflow limitation but is of more limited value in distinguishing between asthma with fixed airflow obstruction, COPD, and ACOS. Early confirmation of diagnosis is cost saving, in terms of the patient's quality of life, the trial of other costly medications or delays in initiating other investigations.

Spirometry at a single visit is not always confirmatory of a diagnosis. Make sure the patient is not yet on treatment. Inhaled corticosteroids and long-acting bronchodilators influence results, so a long withhold period is required prior to performing spirometry. Further tests might, therefore, be necessary either to confirm the diagnosis or to assess the response to initial and subsequent treatment.

Other than spirometry, peak expiratory flow (PEF) measurements on the same meter over a period of 1–2 weeks

may demonstrate excessive variability, which could be seen in asthmatics or some patients with ACOS.

Once the results of spirometry and investigations are available, together with the presentation and clinical examination findings, this information should be assessed and a diagnosis should be suggested.

Asthmatics usually have an FEV1 $\geq 80\%$ of predicted, but an FEV1 $< 80\%$ of predicted can also be observed. FEV1 $< 80\%$ of predicted is a risk factor for asthma exacerbation. In patients with asthma, there is an increase in FEV1 of $>12\%$ post-bronchodilator and 400ml from baseline. FEV1/FVC < 0.7 is required for a diagnosis of COPD.⁸

6. Treatment

When in doubt, treat for asthma. If initial assessments suggest asthma, ACOS, or too much uncertainty, start inhaled corticosteroids in order to prevent morbidity and even death in patients with uncontrolled asthma symptoms. This is especially true for patients with asthma who even though may present with seemingly milder symptoms compared to those of moderate or severe COPD, might indicate significant risk of a life-threatening attack.^{7, 8}

A long-acting beta2-agonist (LABA) should also be started. If there are features of asthma, patients should not be treated with LABA without inhaled steroids.⁷ If the syndromic assessment suggests COPD, appropriate symptomatic treatment with bronchodilators or combination therapy should be commenced, but not inhaled corticosteroids alone.⁸

Both GINA and GOLD reports advise that therapeutic strategies should always include:

- Smoking cessation
- Pulmonary rehabilitation
- Vaccinations
- Treatment of comorbidities

As noted in table 3, there are several medications that could be added on to the treatment of ACOS. There are also several emerging treatments for ACOS, but until this clinical condition is clearly defined, it will be challenging to pinpoint the optimal treatment.

Table 3. Add on pharmacotherapies and emerging treatments for the management of ACOS.

Add on pharmacotherapies for the treatment of ACOS may include either of the following. ^{9,41-47}	Emerging treatment for ACOS.
<ul style="list-style-type: none"> Long-acting beta 2 agonists (LABA) or long Acting muscarinic receptor agonist (LAMA) Leukotriene receptor agonist (LTRA) Roflumilast Theophylline Omalizumab Prednisone Intrabronchial devices Lung transplantation 	<ul style="list-style-type: none"> Newer bronchodilators Triple therapy Mediator antagonists like anti-IL 5, 8 and 13 monoclonal antibodies Mucoregulators like carbocysteine Azithromycin and moxifloxacin Metalloproteinase inhibitors Antioxidants Vitamin C Vaccines Necrotizing factors inhibitors P38 MAPK inhibitors CRTH2 receptor antagonists

7. Referral for Further Investigations and Management

Patients with suspected ACOS should be referred for further investigations and management at a relevant point of their care, given that it is associated with worse outcomes and greater health care utilization.^{6,7,22}

Requesting expert consultation in the management of patients with ACOS is necessary in the following situations:

- Persistent symptoms despite treatment
- Recurrent exacerbations
- Diagnostic uncertainties
- Patients with suspected asthma or COPD in whom atypical or additional symptoms or signs suggest an additional pulmonary diagnosis
- When chronic airways disease is suspected but syndromic features of both asthma and COPD are few
- Patients with comorbidities that may interfere with the assessment and management of their airways disease
- When issues arise during an appropriate management of asthma, COPD or ACOS

Some of the investigations completed by the specialists include:

- Lung function tests, carbon monoxide diffusing capacity (DLCO)
- Arterial blood gases
- Airway hyperresponsiveness (AHR)
- A high-resolution CT scan
- Inflammatory biomarkers to test for atopy (specific IgE and/or skin prick tests)
- Fractional exhaled nitric oxide (FENO), which is high in nonsmokers
- Blood eosinophilia
- Sputum inflammatory cell analysis

8. Conclusion

The fact that older people with asthma or asthmatics who are smokers have a lower response to corticosteroids may just be one of the reasons why there is a need for more studies on

ACOS. ACOS has a high prevalence but very few studies have focused on this condition. Studying ACOS may allow a better understanding of the disease development and progression of COPD, the development of treatment that could completely arrest or slow down the progression of COPD or stop the development of COPD in the first place. There is a need for a drug study on obstructive lung disease that includes ACOS as its own separate entity since this syndrome may need to be managed completely differently. Current data on the treatment of ACOS is an extrapolation from asthma and COPD guidelines. It is really unclear if these are the most appropriate drugs for the treatment of this condition. ACOS patients suffer from significantly more exacerbations, up to 2 or 2.5 times as many as those with lone COPD. With the aging population and the increase prevalence of ACOS in older adults, there is an absolute need for the pulmonary community to appropriately define and address this condition with clinical studies.

Conflict of Interest

None declared.

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