Chapter 9

# Asthma-COPD Overlap Syndrome (ACOS): Current Understanding and Future Perspectives

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**Abstract**

This chapter resumes our current understanding of asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS), pretending to offer a comprehensive approach for the practicing physician, and provides some future perspectives on this entity.

Although different studies recognize the presence of ACOS, the detection, diagnosis, and treatment of these patients in clinical practice are not always simple and are subject to different interpretations. These patients are of special interest, because they are usually excluded from clinical trials with new medications, and also represent a clinically very important and quite prevalent population, with particular characteristics: more respiratory symptoms, frequent exacerbations, and worse health-related quality of life. They are also characterized by an increase in comorbidity and a greater consumption of health care resources compared to patients with only asthma or COPD alone.

There are currently no universally accepted, validated criteria for the diagnosis of ACOS. The differences between clinical guidelines are discussed here (GINA 2014, GEMA 2015, and GOLD 2014). However, to obtain clear and validated criteria, we think that further research about the underlying mechanisms is needed.

Several potential pathways that might lead to the adult presentation of ACOS are revised. The therapeutic recommendations of the Spanish consensus guideline for patients with overlap phenotype COPD–asthma are provided, and other possible future therapies are discussed in this chapter.

**Keywords:** ACOS, ACOS criteria, ACOS treatment, asthma, COPD

## 1. Introduction

Although different studies recognize the presence of asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS), the detection, diagnosis, and treatment of these patients in clinical practice are not always simple and are subject to different interpretations and controversies. These patients are of special interest, because they are usually excluded from clinical trials with new medications for asthma and also represent a clinically very important and quite prevalent population, apparently with particular characteristics: more respiratory symptoms, frequent exacerbations, and worse health-related quality of life [1–5]. They are also characterized by an increase in comorbidity and a greater consumption of health care resources compared to patients with only asthma or COPD alone. There are currently no universally accepted, validated criteria for the diagnosis of ACOS. Also, clinical trials are necessary to verify the response to treatments of this group of patients.

## 2. Definition of ACOS

ACOS is the coexistence of two distinct diseases in the same individual: asthma and COPD. Whether this concept is clinically relevant or not depends on its capacity to describe an entity with differentiated pathogenic mechanisms, prognostic particularities, and potentially specific treatment options. The recently updated Spanish COPD guidelines [6] acknowledge the existence of a syndrome that overlaps characteristics of COPD and asthma, and it proposes a differential treatment.

When considering how to define this entity, existing definitions of asthma and COPD should be taken into account. The new definition of COPD according to GOLD 2014 includes subtle changes regarding the previous definitions, integrating the findings of recent evidence [7]. For instance, there is no longer mention of reversibility, and it emphasizes the role of exacerbations and comorbidities. Thus, COPD is a common, preventable and treatable disorder, defined by persistent airflow obstruction that is mostly progressive, characterized by a chronic inflammatory response in the airways and lungs to noxious particles and gases; exacerbations and comorbidities generally contribute to the severity of the disease in individual patients.

On the other hand, in 2014, GINA [8] defined asthma as "a heterogeneous disease, usually characterized 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". The similarities between asthma and COPD definitions are obvious, but none of their features are pathognomonic, and all of them might be present in individual patients.

For operative purposes, in 2014, GINA and GOLD published a joint document on ACOS [9]. ACOS was defined as the presence of persistent airflow limitation with several features usually associated with asthma and others usually associated with COPD. The document presents the characteristics of asthma and COPD listed separately and suggests that ACOS may be the

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diagnosis when a similar number of characteristics of both asthma and COPD are identified in a given patient. The joint task force also recommends a stepwise approach to the diagnosis. It uses clinical, spirometric and radiographic findings to help delineate if an adult patient is most likely suffering from asthma or COPD or fulfills enough shared features to be considered within ACOS. This definition and the diagnostic criteria differ from other guidelines, for instance, the Spanish expert report from 2012 [10].

The different diagnostic criteria proposed so far are discussed in Section 5. However, to obtain any clearer and validated criteria, further research about underlying mechanisms is needed.

## 3. Prevalence of ACOS

The exact prevalence of ACOS is unknown. In general, the literature on ACOS has been mostly retrospective and observational, and the studies focused on asthma or COPD populations. It is well known that studies on asthma are usually performed in populations of children or young adults, where the prevalence of COPD is negligible, whereas studies on COPD are usually performed in elderly populations, where the prevalence of asthma is low. The COPDGene study found a prevalence of 13% of ACOS [2]. These patients may have a different clinical natural history, with more frequent and severe exacerbations (odds ratio [OR] 3.55), and different treatment response, which led to recommend early introduction of inhaled corticosteroids (ICS) in these patients. These figures are similar to those reported in the PLATINO study [11]: 12% prevalence for the ACOS phenotype and more risk of exacerbations in these patients (OR 3.01). The inconsistencies and discrepancies that exist upon reported data on prevalence can be in part explained by the absence of a consistent definition and diagnostic standards. In comparison to previous studies that have considered selected groups of patients, such as COPD patients, the study published by de Marco et al [12] assessed the prevalence of ACOS in the general population. They found that this prevalence ranged from a minimum of 1.6% (95% confidence interval (CI): 1.3%–2.0%) in the 20–44 years old age group to 4.5% (95% CI: 3.2%–5.9) in the 60–84 years old age group.

## 4. Pathogenic mechanisms

Several potential pathways might lead to the presentation of ACOS in adults. One such pathway begins in early-onset asthma. Smoking habit later in life might lead to development of fixed airflow limitation and COPD in many of these patients. A second potential pathway recognizes patients with a lifetime smoking history, subsequent COPD, and late-onset features of asthma (adult-onset eosinophilic asthma and aspirin-exacerbated respiratory disease) (see also Figure 1).

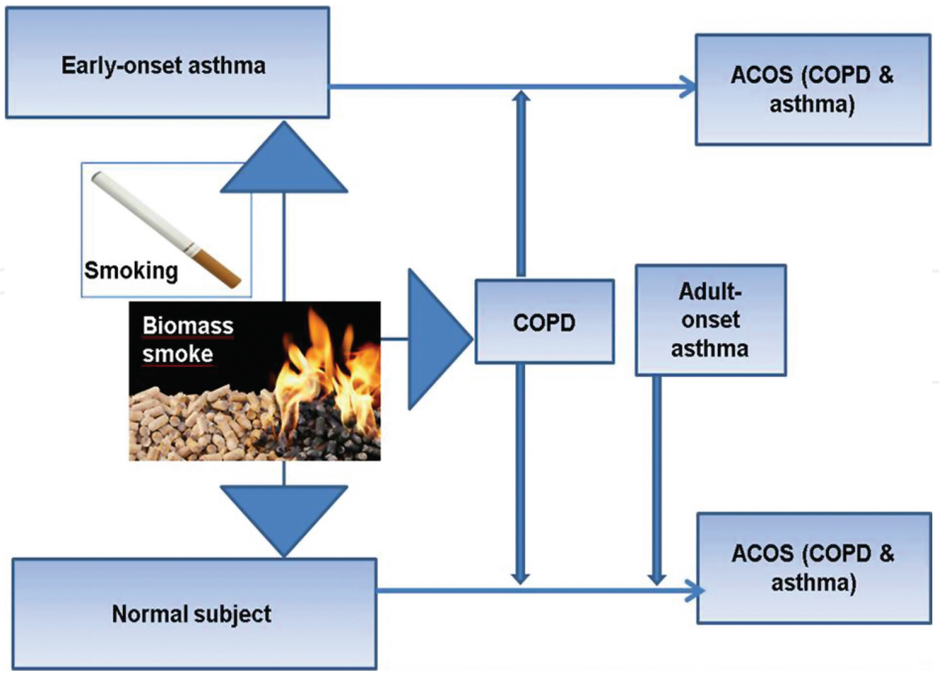


**Figure 1.** Pathogenic pathways leading to ACOS development.

Although no previous studies have addressed the underlying mechanisms of inflammation in ACOS, there is convincing evidence that eosinophils play a pivotal role, similar to what it is found in asthma with a Th2-high profile. Different studies have demonstrated that the presence of significant eosinophilia in an induced sputum sample predicts a good response to ICS, both in patients with COPD and ACOS [13–15]. On the other hand, the presence of more number of neutrophils in sputum has been recently associated with a worse prognosis in asthmatics [16]. Since both asthma and COPD are inflammatory diseases that affect the bronchial tree, it is to be expected to find, in patients with ACOS, some evidence of the Th-1 pattern (characteristic of COPD) and some evidence of Th-2 pattern (characteristic of asthma). The current search for reliable biomarkers of Th1 and Th2 inflammation hopefully will provide additional information in the upcoming years.

Previous studies defined two new asthma molecular phenotypes, namely Th2 high and Th2 low [17]. The Th2–high gene signature includes chloride channel accessory protein 1 (CLCA1), SERPINB2, and periostin (encoded by POSTN), a secreted 90-kDa extracellular matrix protein that is induced by interleukin (IL)-4 and IL-13 in airway epithelial cells and lung fibroblasts. All three genes are induced in bronchial epithelial cells by recombinant IL-13 treatment in vitro, and the expression of these genes correlates with IL-13 and IL-5 expression in the bronchial mucosa, airway and peripheral eosinophilia, airway remodeling, and clinical responsiveness to ICS treatment, but not with atopy. Even more so, periostin seems to become an emerging noninvasive biomarker associated with eosinophilic inflammation, Th2-high molecular phenotype, and airway remodeling, and has potential utility in patient selection for emerging asthma therapeutics targeting Th2 inflammation. A study by Jia et al. [18] identified serum periostin as a systemic biomarker of airway eosinophilia in severe, uncontrolled

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asthmatics belonging to the BOBCAT cohort (Bronchoscopic Exploratory Research Study of Biomarkers in Corticosteroid-refractory Asthma). In a logistic regression model, serum periostin was the single best predictor of sputum and tissue eosinophilia, showing superiority to blood eosinophils, IgE, and FeNO. Mean periostin levels were significantly higher in "eosinophil-high" when compared with "eosinophil-low" patients, as defined by sputum or tissue eosinophil measurements. Using 25 ng/mL serum periostin as an arbitrary cutoff, eosinophil-low and eosinophil-high patients from the BOBCAT study were effectively differentiated, with a positive predictive value of 93% [18]. Moreover, in 62 patients diagnosed with severe asthma, Bobolea et al. [19] found that periostin levels were higher in patients with fixed airflow limitation than in patients with variable airflow limitation (69.76 vs 43.84 ng/ml, $p < 0.05$) and in patients with eosinophilic phenotype than in patients with mixed granulocytic phenotype (61.58 vs 37.31 ng/ml, $P < 0.05$). However, in a cohort of patients with a broad spectrum of asthma severities, Wagener et al. [20] found that blood eosinophils had the highest accuracy in the identification of sputum eosinophilia. In this study, serum periostin was not able to distinguish eosinophilic from noneosinophilic airway inflammation. Therefore, in view of the differing positions, the exact role of periostin in the diagnosis of Th2 bronchial inflammation remains to be determined.

## 5. Diagnosis of ACOS

The specific criteria for diagnosis of this special syndrome had never been established until 2012, when an expert panel meeting of Spanish key opinion leaders agreed unanimously to confirm the existence of this patient profile and to establish a set of criteria for its diagnosis [10], which has been posteriorly adapted within the Spanish COPD Guideline, although not yet validated. The initial definition of ACOS proposed by the Spanish consensus group is as follows: the diagnosis of ACOS is made when two major criteria or one major and two minor criteria are met. The major criteria include a very positive bronchodilator (BD) test (increase in forced expiratory volume in 1 second [FEV1] >15% and >400 mL), eosinophilia in sputum, and personal history of asthma. Minor criteria include high total IgE, personal history of atopy, and positive BD test (increase in FEV1 >12% and >200 mL) on two or more occasions.

The new Finnish guidelines for the treatment of COPD proposed the same criteria for the diagnosis of ACOS as the Spanish guidelines, with the addition of an elevated FeNO higher than 50 parts per billion as a major criterion and a peak flow follow-up typical for asthma as an additional minor criterion [21]. The latest Czech Republic guidelines, published in 2013, also include ACOS with its own diagnostic criteria, similar to the Spanish recommendations [22]. These are, however, quite restrictive criteria and represent a very conservative approach until more evidence about the characterization of ACOS becomes available from large clinical trials or prospective studies. In fact, two recent studies in Spain, using the previous criteria, identified that only between 5% and 6% of the patients fulfilled the criteria for ACOS, in patients with smoking-related COPD [23, 24]. This percentage is clearly below the expected number of individuals sharing the characteristics of asthma and COPD, according to epidemiological data.

In fact, in a Spanish survey performed among pulmonology specialists, selected as experts in asthma and COPD, aimed at collecting their opinions about ACOS and their attitudes in regard to some case scenarios of ACOS patients, only 34.6% of the specialists surveyed were in agreement with the Spanish criteria, and 30.8% were in an intermediate position between agreement and disagreement. The main aspect highlighted by 76.9% of the specialists was that these criteria had to be validated in prospective studies [25].

On the other hand, the GINA–GOLD approach to diagnosis of ACOS [9] is deliberately descriptive and perhaps not very suitable for clinical applications, but recognizes that this entity, just like asthma and COPD, comprises a heterogeneous group of disorders.

The characteristics that might support the diagnosis of ACOS according to GINA–GOLD are as follows:

**1.** – Usually age 40 years or older, but may report symptoms in childhood or early adulthood.

**2.** – Respiratory symptoms, including exertional dyspnea, are persistent, but variability may be prominent.

**3.** – Airflow limitation that is not fully reversible, but often with evidence of significant current or historical variability.

**4.** – Persistent airflow limitation.

**5.** – Frequently, a history of doctor-diagnosed asthma (current or previous), allergies and a family history of asthma, and/or a history of noxious exposures, as seen in COPD.

**6.** – Symptoms are partly but significantly reduced by treatment. Progression is usual, and treatment needs are high.

**7.** – Exacerbations may be more common than in COPD, but are reduced by treatment.

**8.** – Comorbidities can contribute to clinical and functional impairment.

**9.** – COPD-like findings on the chest X-ray.

**10.** – Typically eosinophilia (with or without associated neutrophilia) in sputum.

Taking into consideration all these previously proposed criteria, the most recent Spanish guideline on the management of asthma (GEMA 2015) [26] proposes an algorithm designed to guide physicians in their routine clinical practice. The existence of patients who fulfill the criteria for COPD – adult smokers with respiratory symptoms and post-BD FEV1/FVC <0.7 – and who present characteristics of asthma, such as high reversibility of airflow, signs of bronchial and systemic eosinophilic inflammation, history of atopy, or even a previous diagnosis of asthma before the age of 40 years, has been definitely recognized. This approach also includes, as a novelty when compared with all the others, an oral corticosteroid test with prednisone to assess reversibility of the bronchial obstruction. If FEV1/FVC remains below 70% after a BD test, a methacholine test and the presence or absence of biomarkers of Th2 inflammatory response should help the clinician to distinguish between COPD and ACOS [17]. The algorithm is summarized in Figure 2.

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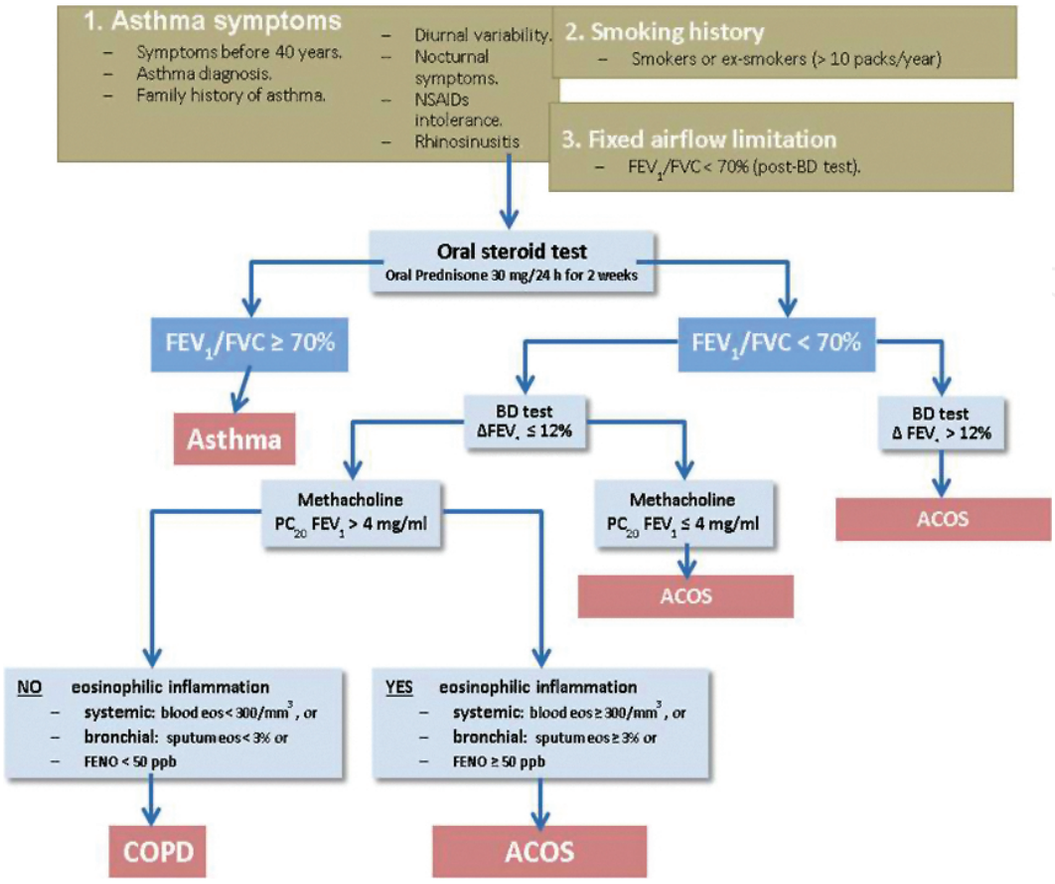


**Figure 2.** Diagnostic algorithm for ACOS according to GEMA 2015 [26].

*BD-test: bronchodilator test; eos: eosinophils.*

## 6. Prognostic implications

It has been reported that patients with ACOS have more frequent exacerbations, are more likely to have a severe exacerbation requiring hospitalization, use more respiratory medications, and have the highest reported pulmonary symptoms. More importantly, patients with ACOS also report worse quality of life than those with either disease alone [27, 28].

However, other authors found that the ACOS phenotype was not clinically different at baseline, in other than the specific criteria used to define it, than patients with no criteria for ACOS. Interestingly, survival after 1 year of follow-up was significantly better in patients with ACOS [29]. To explain such a discrepancy, it should be mentioned that this population included 72% of patients with mild-to-moderate disease, which differs from previous publications with more severe COPD, and of note, 63% of patients with ACOS were receiving ICS, which likely contributed to ameliorate the clinical differences, when compared to the non-ACOS group.

The prognostic significance of having a diagnosis of ACOS must be further assessed in the light of a prospective cohort study, designed to compare the outcomes of COPD patients, asthmatics, and individuals with both diseases.

## 7. Treatment of ACOS

The present approach to pharmacotherapy for ACOS includes trial and error and extrapolation from results of investigations, in particular subpopulations of asthma or COPD patients. The first option recommended by the Spanish consensus guideline for patients with overlap phenotype COPD-asthma is to add ICS to the treatment for COPD [10], as it is also indicated in the Finnish and Czech guidelines [21, 22]. The GINA–GOLD document also indicates that the default position in the case of ACOS should be to start treatment accordingly for asthma, and recommends the LABA/ICS combination, with special attention to avoid the use of LABAs in monotherapy. In the Spanish survey among expert pulmonologists mentioned before [25], 88.5% of the participants agreed that ACOS requires a different treatment compared to COPD, starting with LABA/ICS and stepping up to triple therapy (LABA/ICS+LAMA) in severe cases.

However, these and other recommendations are not based on high-quality data, because patients with ACOS have been classically excluded from pharmacological clinical trials both in asthma and in COPD. As a consequence, there is no clear information about the response of these patients to most of the current pharmacological therapies. The only clinical trial performed to date in patients with ACOS studied the spirometric effects of tiotropium in individuals with concomitant COPD and asthma. Improvement in lung function and a reduction in rescue medication were observed with tiotropium [30].

However, the main interest in differentiating ACOS from COPD lies in the different response to ICS.

Kitaguchi et al. [15], in a retrospective study with a small sample size, found that COPD patients with asthmatic symptoms had high peripheral and sputum eosinophil counts and better reversibility response to treatment with ICS. These findings reproduce those of other studies, in which COPD patients with a positive BD test, or with a positive hyperreactivity test, or with sputum eosinophilia, have been shown to be more responsive to ICS than those without these features [31–36]. Therefore, it seems logical to consider ICSs as the cornerstone of treatment in ACOS with the addition of long-acting β-agonists in those patients who remain symptomatic or suffer recurrent exacerbations.

In addition to the only clinical trial of Magnussen et al., more recent literature has demonstrated the efficacy of long-acting muscarinic antagonists (LAMA), such as tiotropium, in people with asthma with persistent bronchial obstruction [37, 38]. With all these recent data in mind, the Spanish guideline GEMA 2015 recommends the combination of an ICS with a long-acting β-agonist as the first therapeutic choice in patients with ACOS, leaving open the option to add a LAMA if the patients remain uncontrolled [26].

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Biological treatments that target Th2-related pathways (omalizumab, anti–IL-5, and perhaps anti–IL-4/-13) might also be effective in ACOS, and they warrant further investigation. This is also the case for drugs that target predominantly neutrophil-driven mechanisms, such as roflumilast.

## 8. Discussion: ACOS as a phenotype or endotype of obstructive airway disease.

Asthma and COPD are themselves heterogeneous disorders that comprise several phenotypes and endotypes. If we admit that ACOS should be characterized by the presence of inflammatory features of both COPD (mainly Th1) and asthma (mainly Th2), we could argue that COPD patients with sputum eosinophilia and with asthma, with a mixed neutrophilic–eosinophilic pattern are, in fact, patients with ACOS, regardless of their clinical presentation. So changing our point of view, from an initial clinically based classification of obstructive airways diseases to another centered on inflammatory underlying mechanisms (endotypes), would allow us to tailor and optimize treatments, leaving behind the rigid categorization of patients into existing diagnostic labels of either asthma or COPD, which do not fully recognize the molecular and clinical heterogeneity of chronic obstructive airway diseases [39].

We need to move toward a new taxonomy of airway diseases that takes into account the underlying pathogenic mechanisms. In this new scenario, ACOS would be an endotype, like early-onset allergic asthma or emphysema. However, things are not so straightforward, and there are several important issues that complicate the settling-in of this new approach:

- Sputum cell count, the method of reference to measure and identify bronchial inflammation, is technically complex and time consuming. At this moment, we do not have substitute reliable biomarkers to identify the bronchial underlying inflammatory mechanisms in a particular patient.
- There is not a complete identification between a particular and well-recognized clinical phenotype (e.g. late-onset eosinophilic asthma) and an exclusive inflammatory pattern (e.g. eosinophilic). In a large cross-sectional study of patients with airway disease, D'Silva et al. [40] reported the cellular profile of over 4,000 induced or spontaneous sputum samples. In the ACOS group, eosinophilic bronchitis was seen in 35%, neutrophilic bronchitis in 19%, and a mixed inflammatory pattern in 10%. In COPD, the phenotypes were respectively 18%, 34%, and 7% and, in asthma alone, 26%, 14%, and 6%. These data bring to the table the heterogeneous nature of airway inflammation in asthma and COPD.
- The inflammatory pattern can vary over time, either spontaneously or as a result of treatment.

It is to be expected that in a near future, advances in the identification of inflammatory patterns can help us to adequately classify patients with chronic obstructive airway disease and offer them the best therapeutic option in each case.

## 9. Conclusions

ACOS is the coincidence of asthma and COPD in the same individual. Prospective studies are required to analyze the underlying inflammatory mechanisms in this entity. So we think that longitudinal studies are required to validate the diagnostic criteria and identify biomarkers of the disease. It also remains to be determined if it has different prognostic and therapeutic implications. If so, perhaps in the future, ACOS will be considered a distinct endotype of chronic obstructive airway disease. There is also a lack of studies to further clarify the best therapeutic options for patients with ACOS. At this moment, it seems reasonable to consider the combination of an ICS and a long-acting β-agonist as the first-choice therapy for these patients.

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## References

[1] Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax* 2009; 64:728–735.

[2] Hardin M, Silverman EK, Barr RG, et al. The clinical features of overlap between COPD and asthma. *Respir Res* 2011; 12:127.

[3] Miravitlles M, Soriano JB, Ancochea J, et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. *Respir Med* 2013; 07:1053–1060.

[4] Pleasants RA, Ohar JA, Croft JB, et al. Chronic obstructive pulmonary disease and asthma – patient characteristics and health impairment. *COPD* 2014; 11:256–266.

[5] Rhee CK, Yoon HK, Yoo KH, et al. Medical utilization and cost in patients with overlap syndrome of chronic obstructive pulmonary disease and asthma. *COPD* 2014; 11:163–170.

[6] Miravitlles M, Soler-Cataluna JJ, Calle M, Molina J, Almagro P, Quintano JA et al. Spanish COPD Guidelines (GesEPOC): pharmacological treatment of stable COPD. *Arch Bronconeumol* 2012; 48(7): 247–257.

[7] Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Update 2014. www.goldcopd.com.

[8] GINA. Global strategy for asthma management and prevention. 2014. http://www.ginasthma.org.

[9] Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS). GINA 2014 reports are available at http://www.ginasthma.org.

[10] Soler-Cataluna JJ, Cosio B, Izquierdo JL, Lopez-Campos JL, Marin JM, Aguero R et al. Consensus document on the mixed asthma-COPD phenotype in COPD. *Arch Bronconeumol* 2012; 48:331–337.

[11] Menezes AM, Montes de Oca M, Pérez-Padilla R, et al; PLATINO team. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-Asthma. *Chest* 2014; 145 (2):297–304.

[12] de Marco R, Pesce G, Marcon A, et al. The coexistence of asthma and chronic obstructive pulmonary disease (COPD): prevalence and risk factors in young, middle-aged and elderly people from the general population. *PLoS One* 2013; 10; 8 (5):e62985.

[13] Brightling CE, McKenna S, Hargadon B, et al. Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease *Thorax* 2005; 60:193–198.

[14] Fujimoto K, Kubo K, Yamamoto H, et al. Eosinophilic inflammation in the airway is related to glucocorticoid reversibility in patients with pulmonary emphysema. *Chest* 1999; 115:697–702.

[15] Kitaguchi Y, Konatsu Y, Fujimoto K, et al. Sputum eosinophilia can predict responsiveness to inhaled corticosteroid treatment in patients with overlap syndrome of COPD and asthma. *Intern J COPD* 2012; 7:283–289.

[16] Moore WC, Hastie AT, Li X, et al; National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Sputum neutrophil counts are associated with more severe asthma phenotypes using cluster analysis. *J Allergy Clin Immunol* 2014; 133 (6):1557–1563.

[17] Woodruff PG, Modrek B, Choy DF, Jia G, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med*. 2009; 180:388–395.

[18] Jia G, Erickson RW, Choy DF, et al. Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. *J Allergy Clin Immunol* 2012; 130(3):647–654.

[19] Bobolea I, Barranco P, Del Pozo V, et al. Sputum periostin in patients with different severe asthma phenotypes. *Allergy* 2015; 70(5):540–546.

[20] Wagener AH, de Nijs SB, Lutter R, et al. External validation of blood eosinophils, FE(NO) and serum periostin as surrogates for sputum eosinophils in asthma. *Thorax* 2015; 70(2): 115–120.

[21] Kankaanranta H, Harju T, Kilpeläinen M, et al. Diagnosis and pharmacotherapy of stable chronic obstructive pulmonary disease: the Finish guidelines. *Basic Clin Pharmacol Toxicol* 2015; 116:291–307.

[22] Kovlizek V, Chlumsky J, Zindr V, et al. Chronic obstructive pulmonary disease: official diagnosis and treatment guidelines of the Czech Pneumological and Phthisiological Society; a novel phenotypic approach to COPD with patient-oriented care. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2013; 157:189–201.

[23] Golpe R, Sanjuán López P, Cano Jiménez E, et al. Distribution of clinical phenotypes in patients with chronic obstructive pulmonary disease caused by biomass and tobacco smoke. *Arch Bronconeumol*. 2014; 50:318–324.

[24] Miravitlles M, Huerta A, Fernández-Villar JA, et al. Generic utilities in chronic obstructive pulmonary disease patients stratified according to different staging systems. *Health Qual Life Outcomes*. 2014; 12:120.

[25] Miravitlles M, Alcázar B, Alvarez FJ, Bazús T, Calle M, Casanova C, et al. What pulmonologists think about the asthma-COPD overlap syndrome. *Int J Chron Obstruct Pulmon Dis* 2015; 10:1321–1330.

[26] GEMA 4.0. Guía Española para el manejo del asma. 2015. Available at http://www.gemasma.com.

[27] Andersen H, Lampela P, Nevanlinna A, et al. High hospital burden in overlap syndrome of asthma and COPD. *Clin Respir J* 2013; 7(4):342–346.

[28] Kauppi P, Kupiainen H, Lindqvist A, et al. Overlap syndrome of asthma and COPD predicts low quality of life. *J Asthma* 2011; 48(3):279–285.

[29] Cosio BG, Soriano JB, López-Campos JL, et al. Defining the asthma-COPD overlap syndrome in a COPD cohort. *Chest* 2016; 149(1): 45–52.

[30] Magnussen H, Bugnas B, van Noord J, Schmidt P, Gerken F, Kesten S. Improvements with tiotropium in COPD patients with concomitant asthma. *Respir Med* 2008; 102:50–56.

[31] Kerstjens HA, Overbeek SE, Schouten JP, et al. Airways hyperresponsiveness, bronchodilator response, allergy and smoking predict improvement in FEV1 during long-term inhaled corticosteroid treatment. Dutch CNSLD Stud Group. *Eur Respir J* 1993; 6(6):868–876.

[32] Weiner P, Weiner M, Azgad Y, et al. Inhaled budesonide therapy for patients with stable COPD. *Chest* 1995; 108(6):1568–1571.

[33] Leigh R, Pizzichini MM, Morris MM, et al. Stable COPD: predicting benefit from high-dose inhaled corticosteroid treatment. *Eur Respir J* 2006; 27(5):964–971.

[34] Bleecker ER, Emmett A, Crater G, et al. Lung function and symptom improvement with fluticasone propionate/salmeterol and ipratropium bromide/albuterol in COPD: response by beta-agonist reversibility. *Pulm Pharmacol Ther* 2008; 21(4): 682–688.

[35] Leuppi JD, Tandjung R, Anderson SD, et al. Prediction of treatment-response to inhaled corticosteroids by mannitol-challenge test in COPD. A Proof Concept. *Pulm Pharmacol Therap* 2005; 18(2): 83–88.

[36] Kunisaki KM, Rice KL, Janoff EN, et al. Exhaled nitric oxide, systemic inflammation, and the spirometric response to inhaled fluticasone propionate in severe chronic obstructive pulmonary disease: a prospective study. *Ther Adv Respir Dis* 2008; 2(2): 55–64.

[37] Peters SP, Bleecker ER, Kunselman SJ, et al. Predictors of response to tiotropium versus salmeterol in asthmatic adults. *J Allergy Clin Immunol* 2013; 132(5):1068–1074.

[38] Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010; 363(18):1715–1726.

[39] Vanfleteren LE1, Kocks JW, Stone IS, et al. Moving from the Oslerian paradigm to the post-genomic era: Are asthma and COPD outdated terms? *Thorax* 2014; 69(1):72-79.

[40] D'Silva L, Hassan N, Wang HY, et al. Heterogeneity of bronchitis in airway diseases in tertiary care clinical practice. *Can Respir J* 2011; 18(3):144–148.

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