



EDITORIAL

Diagnosis of asthma-COPD overlap: Is it possible a global definition?



Although the existence of individuals who present a chronic respiratory disease with some characteristics of asthma and some of chronic obstructive pulmonary disease (COPD) has been recognised for many years, the interest in the precise definition of this so-called asthma-COPD overlap (ACO) has emerged only recently.¹ The reason of this interest is the recognition that there is an excessive use of inhaled corticosteroids (ICS) in COPD and the findings of different studies, which suggest that only COPD patients with some characteristics of asthma or with a particular type of inflammation, predominantly eosinophilic, will respond to ICS.² Moreover, the long-term use of ICS in COPD is associated with an increased risk of side effects, including, but not limited, to pneumonia. Therefore, the concept of adequate use of ICS in COPD has emerged as one of the new paradigms in COPD management.³ In this context, the concept of an ACO phenotype that includes patients with COPD and characteristics that predict response to ICS has been used in guidelines to help clinicians in the adequate use of ICS,⁴ but a universally accepted definition of ACO is still missing. In contrast, the diagnosis of ACO does not have any significant therapeutic implication in asthma, because the initial therapy is not different between pure asthmatics and overlap patients.

Most of the proposed definitions of ACO are not based on pathological descriptions or imaging; rather they include different number and associations of risk factors, clinical manifestations, pulmonary function tests and/or inflammatory characteristics, sometimes combined in major or minor criteria.^{1,5–7} Unfortunately, no validation of these definitions exists and the application of one or another may result in different classification of patients and very different prevalence of ACO in a given population.⁸

Until a validated definition of ACO can be accepted and implemented, it is important to recognise the opinion of experienced clinicians and use their opinion to challenge existing definitions and even develop new ones that can be

used in a particular context. Padrao et al.⁹ have developed a survey following the Delphi methodology to assess the need for recognition of ACO in the Portuguese medical community, and more importantly, to achieve consensus on the diagnostic criteria and management. A total of 190 experts were invited to participate, including pulmonologists, general practitioners and immunoallergists. Interestingly, the first result of this survey was that up to 87% of the clinicians considered relevant the definition of ACO,⁹ which is similar to the 84% of Spanish specialists that recognised the existence of ACO and the relevance of a proper definition.¹⁰

Even more interesting is the consensus reached on the diagnostic criteria of ACO. These criteria included two mandatory components: (a) simultaneous clinical characteristics of asthma and COPD, and (b) fixed airflow obstruction (FEV1/FVC < 0.7), presumably post-bronchodilator, although it is not mentioned in the publication. In addition to these criteria, the patient must fulfil 2 major and 1 minor additional criteria selected from: previous history of asthma, significant smoking (or biomass) exposure, or a positive bronchodilator test in more than one occasion, as major; and age older than 40 years, history of atopy, peripheral eosinophilia, elevated IgE and positive skin tests, as minor.⁹

These diagnostic criteria of ACO, as all others,^{1,5–7,11} have some pros and cons. Among the pros, they have been agreed by a group of experienced clinicians, include easy to obtain characteristics and, therefore, they should be easy to use in clinical practice and finally they include the most widely recognised characteristics associated with ACO. Among the cons we must indicate some aspects: (a) the definition of “simultaneous clinical characteristics of asthma and COPD” may be ambiguous, in particular for unexperienced clinicians, (b) the use of major and minor criteria, although methodologically correct, has been difficult to implement in clinical practice in other countries, such as Spain.¹² Consequently another more simple strategy without this differentiation of criteria has recently been adopted^{6,11};

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(c) not including age > 40 years and, particularly smoking, as mandatory criteria may induce some misdiagnosis of ACO. As an example, a 20 years-old male, never smoker, with cough and dyspnea on exercise (clinical symptoms of COPD), some wheezing (clinical symptom of asthma), airflow obstruction, a previous history of asthma, two positive bronchodilator tests and history of atopy would fulfil the Portuguese criteria for ACO, but this patient is clearly an asthmatic and nothing else than an asthmatic. In fact, obstructive asthma in a never smoker is different from ACO^{13,14} and this is one of the five commandments of ACO; i.e. "A patient with asthma may develop non-fully reversible airflow obstruction, but this is not COPD, not even ACO, it is obstructive asthma".¹⁵ However, this possible misclassification will not have any particular consequence for the patient, because the proposed treatment for ACO is exactly the same as for asthma; i.e. combination of long-acting bronchodilator and ICS, but it may create confusion in clinicians and contribute to the perception that ACO is more frequent than it really is.

Another controversial aspect of the definition is the minor role of the peripheral eosinophil count. It is clear that no definitive role of the blood eosinophil counts in predicting response to ICS in COPD has been established yet; however, peripheral eosinophilia is the single criterion most widely studied as marker of Th2 inflammation in COPD and several studies have found a good predictive value of blood eosinophils for response to ICS.^{2,16} In fact, recent definitions of ACO are based on two types of patients: smoking asthmatics that develop chronic airflow limitation and eosinophilic COPD.^{5,6,11,17} These two types of patients may have very different characteristics, but from a practical perspective they share their increased response to ICS compared with the remaining patients with COPD and justify their inclusion under the umbrella term of ACO.

The authors of the Portuguese survey have to be applauded for their initiative, because this brings the concept of ACO high in the agenda of the clinicians implicated in the care of these patients and provide a different point of view over this complex concept.⁹ Their conclusions are similar to other initiatives,^{12,18} but with some significant differences and this brings into question if there will ever be a global definition of ACO universally accepted. This may not have any consequences in the field of asthma, because, as previously mentioned, the treatment for ACO and adult asthma is basically the same; but it is urgently needed in COPD, where there is a need of clear guidance for the adequate use of ICS.³ However, it is possible that, if the role of blood eosinophils as predictor of ICS response in COPD is confirmed in prospective studies, the concept of ACO may no longer be useful for the clinician and will be substituted by the eosinophilic COPD as a clinical phenotype (or endotype) that identifies ICS responders in COPD. In the meantime, we need initiatives such as the one presented by Padrao et al.⁹ to increase the awareness of ACO and improve the care of patients with chronic airflow obstruction in the community.¹⁹

References

1. Barrecheguren M, Esquinas C, Miravittles M. The asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS): opportunities and challenges. *Curr Opin Pulm Med.* 2015;21:74–9.
2. Christenson SA, Steiling K, van den Berge M, Hijazi K, Hiemstra PS, Postma DS, et al. Asthma-COPD overlap: clinical relevance of genomic signatures of Type 2 inflammation in COPD. *Am J Respir Crit Care Med.* 2015;191:758–66.
3. D'Urzo A, Donohue JF, Kardos P, Miravittles M, Price D. A re-evaluation of the role of inhaled corticosteroids in the management of patients with COPD. *Expert Opin Pharmacother.* 2015;16:1845–60.
4. Miravittles M, Soler-Cataluña JJ, Calle M, Molina J, Almagro P, Quintano JA, et al. Spanish COPD guidelines (GesEPOC) 2017. Pharmacological treatment of stable chronic obstructive pulmonary disease. *Arch Bronconeumol.* 2017;53:324–35.
5. Sin DD, Miravittles M, Mannino DM, Soriano JB, Price D, Celli BR, et al. What is asthma-COPD overlap syndrome (ACOS)? Towards a consensus definition from a roundtable discussion. *Eur Respir J.* 2016;48:664–73.
6. Miravittles M, Alvarez-Gutierrez F, Calle M, Casanova C, Cosío BG, López-Viña A, et al. Algorithm for identification of ACO: consensus between the Spanish COPD and asthma guidelines. *Eur Respir J.* 2017;49, pii:1700068.
7. Araújo D, Padrão E, Morais-Almeida M, Cardoso J, Pavão F, Leite RB, et al. Asthma-chronic obstructive pulmonary disease overlap syndrome – literature review and contributions towards a Portuguese consensus. *Rev Port Pneumol.* 2017;23:90–9.
8. Bonten TN, Kasteleyn MJ, de Mutsert R, Hiemstra PS, Rosendaal FR, Chavannes NH, et al. Defining asthma-COPD overlap syndrome: a population-based study. *Eur Respir J.* 2017;49, pii:1602008.
9. Padrao E, Araujo D, Todo Bom A, Robalo Cordeiro C, Correia de Sousa J, Cardoso J, et al. Asthma-COPD overlap: a Portuguese survey. *Rev Port Pneumol.* 2018.
10. Miravittles M, Alcázar B, Alvarez FJ, Bazús T, Calle M, Casanova C, et al. What pulmonologists think about the asthma-COPD overlap syndrome (ACOS). *Int J Chron Obst Pulm Dis.* 2015;10:1321–30.
11. Plaza V, Alvarez F, Calle M, Casanova C, Cosío BG, López-Viña A, et al. Consensus on the Asthma-COPD Overlap Syndrome (ACOS) between the Spanish COPD Guidelines (GesEPOC) and the Spanish Guidelines on the Management of Asthma (GEMA). *Arch Bronconeumol.* 2017;53:443–9.
12. Soler-Cataluña JJ, Cosío B, Izquierdo JL, López-Campos JL, Marín JM, Agüero R, et al. Consensus document on the overlap phenotype COPD-asthma in COPD. *Arch Bronconeumol.* 2012;48:331–7.
13. Tammola M, Ilmarinen P, Tuomisto LE, Lehtimäki L, Haanpää J, Niemelä O, et al. Differences between asthma-COPD overlap syndrome (ACOS) and adult-onset asthma. *Eur Respir J.* 2017;49, pii:1602383.
14. Slats A, Taube C. Asthma and chronic obstructive pulmonary disease overlap: asthmatic chronic obstructive pulmonary disease or chronic obstructive asthma? *Ther Adv Respir Dis.* 2016;10:57–71.
15. Miravittles M. Diagnosis of asthma-COPD overlap: the five commandments. *Eur Respir J.* 2017;49, pii:1700506.

16. Barnes NC, Sharma R, Lettis S, Calverley PM. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. *Eur Respir J*. 2016;47:1374–82.
17. Joo H, Han D, Lee JH, Rhee CK. Heterogeneity of asthma-COPD overlap syndrome. *Int J Chron Obstruct Pulmon Dis*. 2017;12:697–703.
18. Cataldo D, Corhay JL, Derom E, Louis R, Marchand E, Michils A, et al. A Belgian survey on the diagnosis of asthma-COPD overlap syndrome. *Int J Chron Obstruct Pulmon Dis*. 2017;12:601–13.
19. García-García MC, Hernández-Borge J, Barrecheguren M, Miravittles M. The challenge of diagnosing a mixed asthma-COPD (ACOS) phenotype in clinical practice. *Ther Adv Respir Dis*. 2016;10:175–8.

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