

The asthma – COPD overlap syndrome: ACOS, CAOS or CHAOS?

**Stelios Loukides,
Petros Bakakos,
Kostas Kostikas**

Editorial board Pneumon

The GINA and GOLD guidelines provide information in regard to both asthma and COPD definition. Asthma is 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 limitation¹. COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients².

Both definitions share some common characteristics: the airway obstruction and the chronic inflammatory process. However both characteristics significantly differ between the two diseases. Inflammatory process in asthma is mainly characterized by a Th2 response while airway obstruction is usually reversible. On the other hand COPD is mainly characterized by non-Th2 response and non-reversible airway obstruction. 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 COPD³. The above definition is mainly characterized by what we called generality. It is critical to define the direction that drives the ACOS. So is it asthma or COPD? The second arising question comes from the possible relationship between smoking habit and the presence of ACOS. Do we consider smoking as a major requirement in order to define ACOS? Finally and most important how critical is it to define the presence of airway obstruction? The latter is the critical step in order to build some characteristics that drive or are driven by ACOS. These characteristics are summarized in table 1. If we retrieve some information from the above features we may speculate that all of them are in favor of asthma than of COPD. A recently published consensus from Spanish experts provides some evidence in regard to ACOS⁴. The consensus clearly supports that the presence of some features suggestive of asthma in a patient with existing COPD can lead to the diagnosis of ACOS. Which are these features? Eosinophilic inflammation, atopy, high IgE levels and, finally, spirometric reversibility with an increase of FEV₁ 15% and 400 ml after the administration of β_2 agonists⁴. The main difference of the above consensus compared to both GINA & GOLD guidelines is the pre-existing

Correspondence to:

Stavros V. Konstantinides, MD, FESC
Department of Cardiology
Democritus University of Thrace
University General Hospital
68100 Alexandroupolis, Greece
e-mail: skonst@med.duth.gr

COPD irrespective of the presence of possible asthma features. Taking all the above into consideration it is somehow clear that the most difficult procedure is the confirmation of the ACOS syndrome. This means that the diagnostic process is complicated and consists of many pitfalls which might affect the final diagnosis.

Three parameters drive the diagnostic process: first and most important the clinical history, second the functional status with main representative the spirometry, and final the inflammatory biomarkers.

A careful medical history that takes into consideration age, symptoms and particularly the onset of these symptoms, progression, variability, seasonality or persistence, may provide an initial clinical direction. Past history, family history and social factors like smoking must always be taken into consideration. Finally symptoms in relation to treatment responses are a hallmark feature that might identify either an asthma or a COPD-like profile. However, the absence of any of these features has a smaller predictive value, and does not rule out the diagnosis of either disease. For example, a history of atopy increases the probability of asthma but cannot confirm it.

If we consider the GINA and GOLD recommendations, a patient who shares features of both asthma and COPD can be diagnosed as ACOS. However from a clinical point of view how easy is to exclude this patient from being a smoking asthmatic or/and a severe asthmatic with diminished response to treatment regimens? To our knowledge and based on our clinical experience we have to support the Spanish consensus which solves the above issues by starting the diagnostic procedure in a pre-existing diagnosis of COPD. Supportive evidence comes from their suggestions/criteria which are all features that characterize asthma and not COPD.

Moving towards the spirometry issue, it is completely clear that the presence of airflow obstruction is the major criterion for the identification of ACOS. Two further indications could positively predict the presence of ACOS: The repeatable reversibility of airway obstruction and the clinical and spirometric response after the initiation of specific treatments like ICS. How do we define the term reversibility? Using the Spanish theory an improvement of FEV₁ over 15% and 400 ml after administration of β_2 agonists is a main criterion for the identification of ACOS. Alternatively, an increase of FEV₁ over 12% and 200 ml in two independent measurements is considered as a minor criterion. It is difficult and simultaneously provocative to establish a strong level of certainty for the above functional issues. We have to provide a strong weight of

evidence and not simple expert opinion. Furthermore we have to consider that, irrespective of the absence of repeatability, reversibility could also be a feature of COPD⁵. A criterion that favors the asthmatic component might be a functional reversibility after the initiation of a maintenance treatment which involves ICS⁶. However a recently published article supports that the additive effect of ICS on long-acting bronchodilators may be less effective than expected. In the above study the authors used as a major outcome the annual decline of FEV₁⁷.

Both asthma and COPD are characterized by particular inflammatory processes. The discrimination procedure in most cases is simple. It becomes problematic in patients with asthma who smoke and those with severe disease and predominant neutrophilic inflammation. If we consider the theory of pre-existing COPD then the presence of eosinophilic inflammation increases the probability of asthma. Despite the fact that some patients with COPD might have an eosinophilic profile, eosinophilic inflammation still represents the major inflammatory feature of asthma. Either sputum eosinophils or/and increased levels of FeNO in non-smokers are the biomarkers that clearly characterize eosinophilic inflammation. Interestingly, recently published evidence using the methodology of cluster analysis identified three clusters⁸: the first cluster was the predominant asthma with increased levels of Th2 derived cytokines, the second was the ACOS one with mixed sputum cellular population and the last one was the predominant COPD with a pure neutrophilic profile. The above evidence seems to come from the old-fashioned inflammatory profiles where identification does not rule out any underlying disease. The existing efforts in the direction of inflammatory discrimination do not seem to be supported by published data since a significant overlapping within diseases and biomarkers exist^{9,10}. Possibly a combined assessment of biomarkers might clearly discriminate ACOS from its components.

Summarizing the above diagnostic procedures, it is clear that the diagnosis of ACOS is based on recommendations that avoid clarifying the basis of this syndrome. It seems that the existing criteria may not be easily applicable in clinical practice. Two are the main challenges: the first one to our point of view is the wide acceptance that ACOS is based on preexisting COPD with asthmatic features and the second one whether these asthmatic features are different from the classically accepted. If that is the case, perhaps we should be talking about the COPD-asthma Overlap Syndrome or CAOS for that purpose. The latter is partially supported by evidence that ACOS syndrome

is characterized by an increase severity which is mainly attributed to increased rates of exacerbations, increased needs for treatment and finally increased mortality¹¹. Someone would expect that the presence of asthma and the effective response to ICS might be protective against the harmful effects of COPD. The reality is completely different and a possible resistance to ICS may exist⁷.

In conclusion, we have to intensify our efforts in order to clarify all the possible mechanisms that are implicated in ACOS or CAOS. Simultaneously we have to be very strict in our diagnostic procedures in order to avoid the intensively discussed ACOS or CAOS entity in order to avoid creating CHAOS for the practicing clinician.

REFERENCES

1. Reddel HK, Hurd SS, FitzGerald JM. World Asthma Day. GINA 2014: a global asthma strategy for a global problem. *Int J Tuberc Lung Dis* 2014;18:505-6.
2. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report, February 2014 at <http://www.goldcopd.com/>.
3. 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.
4. Soler-Cataluña JJ, Cosío B, Izquierdo JL, et al. Consensus document on the overlap phenotype COPD-asthma in COPD. *Arch Bronconeumol* 2012;48:331-7.
5. Albert P, Agusti A, Edwards L, et al. Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. *Thorax* 2012;67:701-8.
6. Bateman ED, Reddel HK, Eriksson G, et al. Overall asthma control: the relationship between current control and future risk. *J Allergy Clin Immunol* 2010;125:600-8.
7. Lim HS, Choi SM, Lee J, et al. Responsiveness to inhaled corticosteroid treatment in patients with asthma-chronic obstructive pulmonary disease overlap syndrome. *Ann Allergy Asthma Immunol* 2014; 113:652-7.
8. Ghebre MA, Bafadhel M, Desai D, et al. Biological clustering supports both "Dutch" and "British" hypotheses of asthma and chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2014 Aug 13. pii: S0091-6749(14)00951-8. doi: 10.1016/j.jaci.2014.06.035. [Epub ahead of print].
9. Fu JJ, McDonald VM, Gibson PG, Simpson JL. Systemic Inflammation in Older Adults With Asthma-COPD Overlap Syndrome. *Allergy Asthma Immunol Res* 2014;6:316-24.
10. Iwamoto H, Gao J, Koskela J, et al. Differences in plasma and sputum biomarkers between COPD and COPD-asthma overlap. *Eur Respir J* 2014;43:421-9.
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;145:297-304.