# Do we really need asthma–chronic obstructive pulmonary disease overlap syndrome?

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**The association of asthma and chronic obstructive pulmonary disease (COPD) in the same patient, which is designated as mixed asthma-COPD phenotype or overlap syndrome (ACOS), remains a controversial issue. This is primarily because many conflicting aspects in the definition of ACOS remain, and it is extremely difficult to summarize the distinctive features of this syndrome. Furthermore, we are realizing that asthma, COPD, and ACOS are not single diseases but rather syndromes consisting of several endotypes and phenotypes and, consequently, comprising a spectrum of diseases. The umbrella term ACOS blurs the lines between asthma and COPD and allows an approach that simplifies therapy. However, this approach contradicts the modern concept according to which we must move toward more targeted and personalized therapies to treat patients with these diseases. Therefore we argue that the term ACOS must be abandoned and ultimately replaced when new phenotypes and underlying endotypes are identified and a new taxonomy of airway diseases is generated. (J Allergy Clin Immunol 2016;138:977-83.)**

***Key words:*** *Asthma, chronic obstructive pulmonary disease, asthma–chronic obstructive pulmonary disease overlap syndrome, definition, prevalence*

*Abbreviations used*
ACOS: Asthma-COPD phenotype or overlap syndrome
COPD: Chronic obstructive pulmonary disease
GINA: Global Initiative for Asthma
GOLD: Global Initiative for Chronic Obstructive Lung Disease
ICS: Inhaled corticosteroid

For some time, we have been debating whether asthma and chronic obstructive pulmonary disease (COPD) are manifestations of the same disease[1] or completely distinct disease entities.[2] In the majority of cases, the principal characteristics and pathophysiology differ significantly between asthma and COPD, which permits differentiating between the 2 and providing appropriate treatment.[3] However, there are patients, especially those who are elderly, who present with features of both diseases. The presentations of asthma and COPD can converge and mimic each other, making it difficult to give these patients a diagnosis of either condition.[4] There are asthmatic patients, commonly smokers with severe asthma, who have fixed airway obstruction primarily as a result of airway remodeling in addition to a neutrophilic pattern and, in this manner, resemble those with COPD. In contrast, many patients with COPD have a good reversibility of airway obstruction and increased eosinophil counts, and consequently, they can be confused with asthmatic patients.

The association of asthma and COPD in the same patient has been designated as mixed asthma-COPD phenotype or overlap syndrome (ACOS),[3] but the exact definition of this syndrome remains ambiguous, and the existence of ACOS *per se* is still a controversial issue.[4] In the overview below, we will explain why we believe that the term ACOS should be abandoned.

## WHAT IS THE DEFINITION OF ACOS?

Many conflicting aspects regarding the definition of ACOS remain. This results in variations in the definition itself that, consequently, describe different clinical pictures. In a remarkable review of the literature published to date on ACOS, Slats and Taube[5] reported that individual studies used 13 different definitions of the syndrome (Table I).[6-20] This makes the identification of ACOS challenging and of questionable utility. However, these definitions also highlight the large percentage of patients who do not have "pure" forms of asthma or COPD to such an extent that, for example, 15% of a cohort of Spanish patients with COPD presented with the criteria Cosio et al[6] suggested to set the diagnosis of ACOS (Table I). Intriguingly, these criteria were useful in identifying the group of patients with a better 1-year prognosis.

The recent Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) report on ACOS,[3] which was written to shed light on this syndrome, describes it as a clinical condition characterized by persistent airflow limitation with several features usually associated with asthma and other features typically associated with COPD. Regarding a definition of ACOS, it states the

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**TABLE I.** Definition of ACOS per study

| Reference | Definition |
|---|---|
| 8 | Self-reported asthma and COPD |
| 9 | Combination of asthma and COPD |
| 10 | $FEV_1$/FVC ratio <0.7, self-reported wheezing |
| 11 | Previous diagnosis of asthma, postbronchodilator $FEV_1$/FVC ratio <0.7 |
| 7 | History of asthma, postbronchodilator $FEV_1$/FVC ratio <0.7, previous positive bronchodilator response, <5 pack-year smoking history |
| 12 | History and symptoms of COPD and asthma, postbronchodilator $FEV_1$/FVC ratio <0.7 and $FEV_1$ <80%, >30 pack-year smoking history |
| 13, 14 | Previous diagnosis of asthma before age 40 y, postbronchodilator $FEV_1$/FVC ratio <0.7, postbronchodilator $FEV_1$ <80%, >10 pack-year smoking history |
| 15 | Symptoms of wheezing, postbronchodilator $FEV_1$/FVC ratio <0.7, bronchodilator response >12% + 200 mL |
| 16 | History of asthma, positive bronchodilator response ≥15%, $FEV_1$ <75% predicted despite ICSs or oral steroids, <10 pack-year smoking history |
| 17 | Chronic symptoms of asthma, postbronchodilator $FEV_1$ <50%, previous variation obstruction >15% either spontaneously or with treatment, persistent obstruction (postbronchodilator $FEV_1$ had not varied by >10% when repeated within 3-6 mo) |
| 18 | Physician's diagnosis of asthma at age <30 y, diagnosis of COPD, postbronchodilator $FEV_1$/FVC ratio <0.7, post bronchodilator $FEV_1$ <80% of predicted value, documented bronchodilator response ($FEV_1$ ≥200 mL and 12%), ICSs in previous year, >10 pack-year smoking history |
| 19 | Diagnosis of obstructive airway disease, postbronchodilator $FEV_1$/FVC ratio <0.7, postbronchodilator $FEV_1$ <80% of predicted value, with airway hyperresponsiveness (≥15% $FEV_1$ decrease from baseline after inhalation of 4.5% hypertonic saline) or bronchodilator response ($FEV_1$ ≥200 mL and 12%) |
| 20 | History of asthma, postbronchodilator $FEV_1$/FVC ratio <0.7, bronchodilator response >12% in $FEV_1$ or >15% in PEF, >20% diurnal variation in PEF, airway hyperresponsiveness, long-term smoking |
| 6 | *Major criteria*: previous history of asthma, $FEV_1$ >15% and 400 mL after salbutamol; *minor criteria*: IgE >100 IU, history of atopy, 2 separated bronchodilator responses to salbutamol >12% and 200 mL, blood eosinophils >5%; among patients with COPD, ≥1 major or 2 minor criteria needed to set the diagnosis of ACOS |

*PEF*, Peak expiratory flow.

following: "A specific definition for ACOS cannot be developed until more evidence is available about its clinical phenotypes and underlying mechanisms."

## DISTINGUISHING FEATURES OF ACOS

The lack of a precise definition of ACOS makes it difficult to categorize the contrasting distinctive features of this syndrome, at least those derived from different studies (Table II).[7,9-17,20-23] Proof of variable airflow limitation is usually considered a fundamental feature of ACOS,[3] but the diagnostic differentiation between asthma and COPD is not a simple matter of reversibility of airway obstruction induced by a bronchodilator. In fact, a documented bronchodilator response can be found in a considerable proportion of patients with COPD.[24] Furthermore, a previous clinical diagnosis of asthma, COPD, chronic bronchitis, or emphysema, another fundamental feature of ACOS,[25] is not fully reliable, particularly in family practice, where the diagnostic process is primarily based on symptoms and signs presented by the patient.[25]

Slats and Taube[5] derived several features and parameters that can be considered characteristic of ACOS. They also correctly emphasized that not all studies compared ACOS with both asthma and COPD. Consequently, these studies, although using the same methods, produced divergent results. Furthermore, studies of the same features and parameters that used different definitions for ACOS generated opposing results. All of this leads us to believe that the evidence to characterize ACOS is not strong enough and therefore is of limited value.

## CONTRASTING INFORMATION IN THE RECOMMENDATIONS OF GUIDELINES AND INITIATIVES

As appropriately stressed by Fernández-Villar and López-Campos,[26] the lack of validated features and parameters to assist in the characterization of ACOS explains the contrasting information in the recommendations of various guidelines and initiatives.

These recommendations have been derived from the consensus of expert opinion. They predominantly cast COPD as a starting point. They then suggest identifying features typically associated with asthma, such as bronchodilator reversibility, peripheral blood and sputum eosinophilia, atopy, early onset of airways disease, childhood asthma and adult smoking, asthma with neutrophilic bronchitis, and a score of several asthma characteristics,[26] and then assign an arbitrary weight to these to determine whether a person has asthma-COPD overlap.[27]

Apart from a personal history of asthma and a positive bronchodilator test result (postbronchodilator $FEV_1$ ≥200 mL and ≥12%), the lack of features and parameters in common between recommendations led Fernández-Villar and López-Campos[26] to the strong presumption that rather than ACOS, we face COPD-asthma overlap syndrome (CAOS). Looking at the exact spelling of the term used, we might surmise that the authors had intended to state CHAOS, erroneously using the Spanish form. In any case, if a history of asthma had presumably preceded the development of cigarette-related COPD, the term ACOS is the right term for this condition, but if COPD was the starting point, perhaps it would be more appropriate to define this syndrome the CAOS.

## PREVALENCE ESTIMATES FOR ACOS

The prevalence of ACOS holds potential significance because asthma and COPD are not single diseases and the term ACOS identifies the multitude of patients without a pure form of asthma or a pure form of COPD. However, the prevalence estimates available vary considerably (Table III).[8,9,13,15,19,28-31] As a result of the lack of a specific formal definition, validated common features and parameters, and certain diagnostic criteria for ACOS, studies have used different criteria depending on the study design and population.[32]

**TABLE II.** Features of ACOS, as described by the GINA/GOLD report on ACOS and derived from different studies

| Feature | GINA/GOLD report on ACOS | ACOS derived from studies | Compared with: | Reference |
|---|---|---|---|---|
| Symptoms | Respiratory symptoms, including exertional dyspnea, are persistent, but variability can be prominent. | More wheezing and dyspnea (not cough or sputum production)<br>More cough and sputum production | COPD alone<br>Asthma alone | 11<br>15 |
| Lung function | Airflow limitation is not fully reversible but often with current or historical variability. | Similar lung function, 6 MWT<br>Faster lung function decrease<br>Worse lung function<br>Better lung function<br>More reversibility<br>No difference in reversibility<br>More hyperresponsiveness | COPD alone<br>Asthma without fixed airflow obstruction but not to COPD alone<br>Normal decrease but not to asthma without fixed airflow obstruction<br>To COPD alone, not to asthma alone<br>Both to COPD and asthma alone<br>To asthma alone but not to COPD alone<br>To COPD alone but not to asthma alone<br>To COPD alone but not to asthma alone<br>Both COPD and asthma alone<br>COPD alone<br>COPD alone | 11, 12<br>7<br>16<br>15<br>10<br>9<br>9<br>15<br>20<br>11-13<br>21 |
| Exacerbations | Exacerbations might be more common than in patients with COPD but are reduced by treatment. | More (severe) exacerbations<br>Similar number of exacerbations | COPD alone (similar lung function, less pack years)<br>Asthma without fixed airflow obstruction but not to COPD alone<br>COPD alone | 11, 13, 15<br>7<br>22 |
| Allergy | There is frequently a history of doctor-diagnosed asthma (current or previous) or allergies, a family history of asthma, and/or a history of noxious exposures. | More allergic rhinitis<br>Higher blood IgE levels<br>Same blood IgE levels<br>More atopy | COPD alone<br>COPD alone<br>COPD alone<br>COPD alone | 9, 20<br>20<br>12<br>23 |
| Inflammation | Eosinophils and/or neutrophils in sputum | Higher sputum neutrophil counts<br>More sputum eosinophils<br>More blood eosinophils<br>Increased exhaled NO levels | Asthma alone but not COPD alone<br>Nonsmoking asthma without fixed airflow obstruction<br>Healthy smokers and COPD alone but not asthma alone<br>COPD alone<br>Asthma alone<br>Asthma alone | 20, 23<br>16<br>20<br>12<br>17<br>17 |
| Chest x-ray | Similar to COPD | Increased bronchial wall thickening on HRCT | COPD alone | 12, 14, 17 |
| Comorbidities | Comorbidities can contribute to impairment. | Higher comorbidity index | COPD alone | 11 |

*HRCT*, High-resolution computed tomography; *6 MWT*, 6 minutes walking test; *NO*, nitric oxide.

Even the use of very basic criteria for the identification of ACOS does not prevent substantial variation in ACOS prevalence estimates. Wurst et al[33] explored the effect of 4 different simple disease definitions on prevalence estimates by reviewing the English-language literature published from 2000 to 2014. The 4 classification schemes for defining ACOS were as follows: (1) a reported physician's diagnosis of asthma and a reported physician's diagnosis of COPD at any point in a patient's life; (2) a reported physician's diagnosis of asthma and spirometry-defined COPD; (3) both spirometry-defined asthma and spirometry-defined COPD; and (4) International Classification of Disease codes to determine both asthma and COPD diagnoses among patients. The ACOS prevalence among patients with COPD fluctuated between 12.1% and 32.9% when a reported physician's diagnosis of asthma and spirometry-defined COPD were used as criteria, 13.0% and 55.2% when both spirometry-defined asthma and spirometry-defined COPD were used as criteria, 25% and 41.4% when a reported physician's diagnosis of asthma and a reported physician's diagnosis of COPD at any point in a patient's life were used as criteria, and 26% and 54.6% when International Classification of Diseases codes used to determine both asthma and COPD diagnoses among patients were used. Similarly, there was wide variability in the prevalence estimates of ACOS among patients with asthma, but in this case the most notable variability (16.0% to 61.0%) was recorded when a reported physician's diagnosis of asthma and a reported physician's diagnosis of COPD were used as the chosen criteria.

## PROBLEMS IN DIFFERENTIATING BETWEEN ASTHMA AND COPD OR IN RECOGNIZING THE OVERLAP OF THE 2

We know that although asthma and COPD can differ in their extremes, in an adult population age, sex, and environmental factors can influence the clinical expression of chronic inflammatory airway obstructive diseases, and the 2 diseases can

**TABLE III.** Prevalence of ACOS depending on the type of population studied and the diagnostic criteria used

| Type of population | Diagnostic criteria | Prevalence | Reference |
|---|---|---|---|
| General population | COPD (postbronchodilator $FEV_1$/FVC ratio <0.70) + criteria for asthma (wheezing in the last 12 mo + postbronchodilator increase in $FEV_1$ or FVC of ≥200 mL and ≥12%) | 1.8% | 15 |
| | Positive response to both of the following questions: "Has a doctor ever told you that you have asthma?" and "Has a doctor ever told you that you have chronic bronchitis or emphysema?" | 2.7% | 8 |
| With pre-existing diagnosis of COPD | COPD stage 2-4 (postbronchodilator $FEV_1$/FVC ratio <0.70 and $FEV_1$ <80%) + >10 pack years of smoking + self-report of physician-diagnosed asthma before age 40 y | 13% | 13 |
| | COPD (postbronchodilator $FEV_1$/FVC ratio <0.70) + any criteria for asthma (postbronchodilator increase in $FEV_1$ ≥15%, peak flow variability >20% during 1 wk of testing and a physician's diagnosis of asthma in conjunction with current symptoms or inhaler use in last 12 mo) | 55% | 28 |
| | *Major criteria*: postbronchodilator test with an increase in $FEV_1$ of >15% and >400 mL, FENO >40 ppb, and personal history of asthma. *Minor criteria*: increased IgE level in blood, personal history of atopy, and postbronchodilator $FEV_1$ increase ≥12% and ≥200 mL over baseline on ≥2 occasions | 5.0% for tobacco; 21.3% for biomass | 29 |
| | Two major criteria or 1 major criterion and 2 minor criteria | | |
| With pre-existing diagnosis of asthma | Self-report of physician-diagnosed asthma + self-report of physician-diagnosed COPD | 16% to 61% | 30 31 |
| | Documented physician-diagnosed asthma + classical symptom of chronic bronchitis and/or DLCO <80% | 29% | |
| With diagnosis of obstructive lung disease (either asthma or COPD) | Patients with COPD (postbronchodilator $FEV_1$/FVC ratio <0.70 or postbronchodilator $FEV_1$/FVC ratio <88% of predicted value, long-term smoking) with any criteria for asthma (postbronchodilator increase in $FEV_1$ of ≥12%, bronchodilator response of ≥15% or diurnal variation of ≥20% in PEF, moderate-to-severe bronchial hyperreactivity, and decrease in $FEV_1$ of ≥15% on the exercise test) | 14.6% | 9 19 |
| | Compatible respiratory symptoms, increased airflow variability (positive airway hyperresponsiveness to hypertonic saline and/or postbronchodilator $FEV_1$ ≥200 mL and 12%) and incompletely reversible airflow obstruction (postbronchodilator $FEV_1$/FVC ratio <70% and postbronchodilator $FEV_1$<80%) | 56% | |

*FENO*, Fraction of exhaled nitric oxide.

overlap.[4] Accordingly, we are currently classifying these diseases using the terms asthma, COPD, and ACOS.[3]

However, Reddel[34] elegantly suggests that ACOS cannot be understood as a single disease or a single phenotype. Instead, a patient's susceptibility (genetic makeup) and exposures (including smoking, infections, pollutants, and diet) contribute to the development of specific molecular or pathologic disease pathways. In turn, these interact over time with the effects of aging, exposures, infections, treatments, and psychosocial factors to produce a range of overlapping clinical phenotypes. Differing symptoms, physiologic features, and/or biomarkers identify these phenotypes.

Two crucial studies published by Fabbri et al[35] and Contoli et al[7] have led us to believe in the existence of only 2 fundamental distinct nosological diseases, asthma and COPD (Table IV),[7,35] with different etiopathogenic bases, diagnostics, and therapeutic and prognostic characteristics. It is important to note that both Fabbri et al[35] and Contoli et al[7] enrolled patients with different phenotypes of asthma and COPD who were all characterized by fixed obstruction of the airways. Consequently, their data have led to the erroneous conclusion that we must remain focused on these 2 nosological entities, regardless of any further evaluation.

We recognize that although current routine diagnosis and management of asthma and COPD are based on clinical/pulmonary function parameters, pathologic evaluation of bronchial biopsy specimens has an added value to help differentiate asthma from COPD.[36] In fact, pathologists reproducibly recognize histological characteristics in bronchial biopsy specimens, although the differentiation based on histopathology between asthma and COPD is difficult without information about inhaled

**TABLE IV.** Features that differentiate asthma from COPD in the presence of fixed airflow obstruction

| | History of asthma | History of COPD | Reference |
|---|---|---|---|
| Eosinophils | | | |
| In sputum and BAL | +++ | + | 35 |
| In sputum over time | +++ | 0/+ | 7 |
| Correlations between $FEV_1$ decrease rate and percentage of sputum eosinophils | ++ | 0 | 7 |
| Neutrophils | | | |
| In sputum and BAL fluid | + | +++ | 35 |
| In sputum over time | ++ | +++ | 7 |
| Correlations between $FEV_1$ decrease rate and percentage of sputum neutrophils | 0 | ++ | 7 |
| $CD4^+CD8^+$ ratio of T cells infiltrating airway mucosa | +++ | + | 35 |
| Residual volume (% predicted) | | | |
| Increased | + | ++ | 35 |
| Increase over time | 0/+ | ++ | 7 |
| $K_{CO}$ (% predicted) | | | |
| Decreased | + | +++ | 35 |
| Decrease over time | + | +++ | 7 |
| Inverse correlation between baseline $K_{CO}$ values and $FEV_1$ decrease rate | 0 | ++ | 7 |
| $F_{ENO}$ (ppb) | | | |
| Greater than normal | ++ | 0/+ | 35 |
| Change over time | 0 | 0 | 7 |
| High-resolution computed tomographic scan emphysema score | 0 | + | 35 |
| Positive correlation between emphysema score and $FEV_1$ decrease rate over time | 0 | ++ | 7 |
| Reversibility to bronchodilators and steroids | ++ | 0 | 35 |
| Inverse correlation between baseline reversibility to bronchodilator and $FEV_1$ decrease rate | ++ | 0 | 7 |
| Rate of decrease in $FEV_1$ | + | + | 7 |
| Exacerbation rate | | | |
| No. of exacerbations per patient-year | + | + | 7 |
| Percentage of exacerbations requiring hospitalization | 0/+ | ++ | 7 |
| Correlations between frequency of exacerbations and percentage of sputum eosinophils | ++ | 0 | 7 |
| Correlations between frequency of exacerbations and percentage of sputum neutrophils | 0 | + | 7 |
| Correlations between frequency of exacerbations and $FEV_1$ decrease rate | 0 | ++ | 7 |
| Correlations between frequency of exacerbations and patients' self-reported comorbidities | 0 | + | 7 |
| Comorbidities | | | |
| No. of coexistent illnesses | + | ++ | 7 |
| Positive correlation between baseline Charlson Index and $FEV_1$ decrease rate | 0 | ++ | 7 |
| Positive correlation between no. of comorbidities and percentage of neutrophils in sputum at baseline | 0 | ++ | 7 |

*BAL*, Bronchoalveolar lavage; *DLCO*, diffusing capacity of the lung for carbon monoxide; *FENO*, fraction of exhaled nitric oxide; *$K_{CO}$*, diffusing capacity.

corticosteroid (ICS) use. Unfortunately, bronchial biopsy specimens are not a routine approach in everyday practice, and their use is limited. Therefore we still have difficulties in differentiating between asthma and COPD and in recognizing the overlap of the 2.

Furthermore, our knowledge today indicates that the real problem does not lie in differentiating asthma from COPD or in the recognition of their overlap. We are realizing that both asthma and COPD are not single diseases but rather syndromes consisting of several endotypes and phenotypes, consequently comprising a spectrum of diseases that must be recognized and adequately treated with targeted therapy.[37,38]

## SHOULD THE TERM ACOS BE ABANDONED?

Previous work has been done, although indirectly, in an attempt to answer the crucial question of whether the term ACOS should be abandoned.

According to the opinion of Gibson and McDonald,[27] a precise and useful definition of asthma-COPD overlap is impossible because the condition itself appears to comprise several different subphenotypes. Therefore addressing disease components through a multidimensional approach to assessment and management of obstructive airway diseases should be useful in managing the heterogeneity of these conditions. Reddel[34] ultimately highlighted the recognized need for more phenotype-driven research to directly dissect this clinical entity. Postma and Rabe[4] emphasized that the danger of seeing ACOS as a disease entity is that we might blur the lines between asthma and COPD, and this could lead to overtreatment, particularly with ICSs. They stressed that it is premature to recommend the designation of ACOS as a disease entity in primary and specialist care. Furthermore, they suggested that there is a need to better characterize patients to obtain a standardized definition of ACOS based on markers that best predict treatment response in individual patients.

The recent view of Agusti et al,[39] according to which patients with airway disease must be managed based on those treatable traits present in each subject, is much stronger but roughly in line with previous opinions. Abandoning the traditional diagnostic labels better reflects the clinical and biological complexity of airway diseases and might eventually result in better patient management than the current "label-based" approach.[39] More simply, Slats and Taube[5] suggested that instead of using the label ACOS for a patient with features of both asthma and COPD, it would be preferable to describe a patient with

COPD in as much detail as possible with regard to characteristics that determine treatment response (eg, eosinophilic inflammation) and prognosis (eg, smoking status, exacerbation rate, fixed airflow limitation, hyperresponsiveness, and comorbidities).

Together, these authoritative opinions lead us to believe that the term ACOS must be abandoned and ultimately replaced when new phenotypes and underlying endotypes are identified and a new taxonomy of airway diseases is generated.[40]

In the meantime, the umbrella term ACOS is allowing and will allow a simplified approach that directs the clinician's therapeutic decision: no real choice, one supplier, one problem, and one solution. In other words, one size fits all, although it is well known that one size does not fit all. This basically means that we will continue to prescribe ICSs to all patients with chronic inflammatory airways diseases, despite the frequent and potentially inappropriate use of ICSs in many patients with COPD.[41] The fact that more than 70% of patients with COPD are treated with high doses of ICSs[42] is something that should make us think. Although we recognize that marketing activities of pharmaceutical companies can influence the prescribing behavior of physicians, we also fully agree with the concept that there is room for the use of ICSs in patients with COPD, at least in some subtypes of COPD. We strongly believe that the right question is not whether ICSs should not be used at all unless patients have concomitant asthma but instead which patient with COPD can benefit from a therapy with ICSs. Unfortunately, however, the number of studies that have investigated the clinical features that can predict corticosteroid response in patients with COPD is still inadequate.

Definitively, for many patients, asthma and COPD are outdated terms that do not fully recognize molecular and clinical heterogeneity. There is an absolute need for a new taxonomy of chronic inflammatory airways diseases, which is the right direction toward more targeted and personalized approaches to patients with these diseases. This means that we should use a precision medicine strategy for the management of patients with airway diseases that is "label free" and based on the identification of "treatable traits" in each patient. In contrast, the use of the term ACOS generates an apparent oversimplification in our clinical activity that does not take into account the fact that diseases with different phenotypes and underlying endotypes might require different therapeutic strategies.

## CONCLUSION

One could argue that ACOS is a suitable interim solution until biomarkers for asthma/COPD endotype characterization are identified and all associated regulatory and fiscal issues are regulated. However, we are firmly convinced that, until such new knowledge is incorporated into the clinical management of asthma or COPD, we must treat our patients by personalizing therapy on the basis of the not-insignificant information that is already available: the treatable traits present in each subject. Regarding the suggestions of the GINA/GOLD report on ACOS,[3] our focus should lie on the part that describes the treatable traits.

Certainly, the GINA/GOLD report on ACOS[3] tries to offer suggestions to improve the therapeutic approach to patients who lack classic features of either asthma or COPD, but these suggestions are too general and do not always fit with the numerous different features we have to deal with in our everyday practice. This is a problem common to all guidelines and initiatives for the treatment of asthma or COPD that have been developed based on the findings of research studies with strict exclusion criteria: current and often former smokers excluded from most asthma trials, patients with excessive bronchodilator reversibility excluded from COPD trials, and those with minimal reversibility excluded from asthma trials.[43] It is questionable whether such data can be extrapolated to a larger, real-life population of patients with obstructive lung disease.

The GINA/GOLD report on ACOS states, "There is an urgent need for more research on this topic, in order to guide better recognition and appropriate treatment."[3] In our view this is a clear acknowledgment, although indirect, that the term ACOS must be abandoned. In fact, a disease must not be labeled on the basis of clinical impression but rather on the basis of agreed upon and measured criteria,[1] and ACOS does not identify a clearly independent disease entity.

## REFERENCES

1. Orie NGM, Sluiter HJ, De Vries K, Tammeling GJ, Witkop J. The host factor in bronchitis. In: Orie NGM, Sluiter HJ, editors. Bronchitis. Assen (The Netherlands): Royal Van Gorcum; 1961. pp. 43-59.
2. Vermeire PA, Pride NBA. "Splitting" look at chronic nonspecific lung disease (CNSLD): common features but diverse pathogenesis. Eur Respir J 1991;4:490-6.
3. Global Initiative for COLD. Joint project of GOLD and GINA 2014. Global strategy for asthma management and prevention 2014. Diagnosis of diseases of chronic airflow limitation: asthma, COPD and asthma-COPD overlap syndrome (ACOS). Global Initiative for Asthma, Global Initiative for Chronic Obstructive Lung Disease. Available at: http://www.ginasthma.org and http://www.goldcopd.org. Accessed March 20, 2016.
4. Postma DS, Rabe KF. The Asthma-COPD overlap syndrome. N Engl J Med 2015; 373:1241-9.
5. 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.
6. Cosio BG, Soriano JB, López-Campos JL, Calle-Rubio M, Soler-Cataluna JJ, de-Torres JP, et al. Defining the Asthma-COPD overlap syndrome in a COPD cohort. Chest 2016;149:45-52.
7. Contoli M, Baraldo S, Marku B, Casolari P, Marwick JA, Turato G, et al. Fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease: 5-year follow-up. J Allergy Clin Immunol 2010;125:830-7.
8. Diaz-Guzman E, Khosravi M, Mannino D. Asthma, chronic obstructive pulmonary disease, and mortality in the U.S. population. COPD 2011;8:400-7.
9. Kauppi P, Kupiainen H, Lindqvist A, Tammilehto L, Kilpelainen M, Kinnula V, et al. Overlap syndrome of asthma and COPD predicts low quality of life. J Asthma 2011;48:279-85.
10. Chung J, Kong K, Lee J, Lee S, Ryu Y, Chang J. Characteristics and self-rated health of overlap syndrome. Int J Chron Obstruct Pulmon Dis 2014;9:795-804.
11. Miravitlles M, Soriano J, Ancochea J, Munoz L, Duran-Tauleria E, Sanchez G, et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. Respir Med 2013;107:1053-60.
12. Kitaguchi Y, Komatsu Y, Fujimoto K, Hanaoka M, Kubo K. Sputum eosinophilia can predict responsiveness to inhaled corticosteroid treatment in patients with overlap syndrome of COPD and asthma. Int J Chron Obstruct Pulmon Dis 2012; 7:283-9.
13. Hardin M, Silverman E, Barr R, Hansel N, Schroeder J, Make B, et al. The clinical features of the overlap between COPD and asthma. Respir Res 2011;12:127.
14. Hardin M, Cho M, McDonald M, Beaty T, Ramsdell J, Bhatt S, et al. The clinical and genetic features of COPD-asthma overlap syndrome. Eur Respir J 2014;44: 341-50.
15. Menezes AM, Montes de Oca M, Perez-Padilla R, Nadeau G, Wehrmeister FC, Lopez-Varela MV, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. Chest 2014;145: 297-304.
16. Boulet L, Turcotte H, Turcot O, Chakir J. Airway inflammation in asthma with incomplete reversibility of airflow obstruction. Respir Med 2003;97:739-44.
17. Bumbacea D, Campbell D, Nguyen L, Carr D, Barnes P, Robinson D, et al. Parameters associated with persistent airflow obstruction in chronic severe asthma. Eur Respir J 2004;24:122-8.

18. 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;102:50-6.
19. Fu JJ, Gibson PG, Simpson JL, McDonald VM. Longitudinal changes in clinical outcomes in older patients with asthma, COPD and asthma-COPD overlap syndrome. Respiration 2014;87:63-74.
20. Iwamoto H, Gao J, Koskela J, Kinnula V, Kobayashi H, Laitinen T, et al. Differences in plasma and sputum biomarkers between COPD and COPD-asthma overlap. Eur Respir J 2014;43:421-9.
21. De Marco R, Accordini S, Cerveri I, Corsico A, Anto J, Kunzli N, et al. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. Am J Respir Crit Care Med 2007;175: 32-9.
22. Izquierdo-Alonso J, Rodriguez-Gonzalezmoro J, de Lucas-Ramos P, Unzueta I, Ribera X, Anton E, et al. Prevalence and characteristics of three clinical phenotypes of chronic obstructive pulmonary disease (COPD). Respir Med 2013;107:724-31.
23. Gibson P, Simpson J. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax 2009;64:728-35.
24. Calverley PM. A lbert P, Walker PP. Bronchodilator reversibility in chronic obstructive pulmonary disease: use and limitations. Lancet Respir Med 2013;1:564-73.
25. Cazzola M, Puxeddu E, Bettoncelli G, Novelli L, Segreti A, Cricelli C, et al. The prevalence of asthma and COPD in Italy: a practice-based study. Respir Med 2011; 105:386-91.
26. Fernández-Villar A, López-Campos JL. Mixed COPD-asthma phenotype: ACOS or CAOS? A reflection on recent guidelines and recommendations. Arch Bronconeumol 2016;52:277-8.
27. Gibson PG, McDonald VD. Asthma–COPD overlap 2015: now we are six. Thorax 2015;70:683-91.
28. Marsh SE, Travers J, Weatherall M, Williams MV, Aldington S, Shirtcliffe PM, et al. Proportional classifications of COPD phenotypes. Thorax 2008;63:761-7.
29. Golpe R, Sanjuan Lopez P, Cano Jimenez E, Castro Anon O, Perez de Llano LA. Distribution of clinical phenotypes in patients with chronic obstructive pulmonary disease caused by biomass and tobacco smoke. Arch Bronconeumol 2014;50:318-24.
30. de Marco R, Pesce G, Marcon A, Accordini S, Antonicelli L, Bugiani M, 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;8:e62985.
31. Milanese M, Di Marco F, Corsico AG, Rolla G, Sposato B, Chieco-Bianchi F, et al. Asthma control in elderly asthmatics. An Italian observational study. Respir Med 2014;108:1091-9.
32. Tho NV, Park HY, Nakano Y. Asthma-COPD overlap syndrome (ACOS): a diagnostic challenge. Respirology 2016;21:410-8.
33. Wurst KE, Kelly-Reif K, Bushnell GA, Pascoe S, Barnes N. Understanding asthma-chronic obstructive pulmonary disease overlap syndrome. Respir Med 2016;110:1-11.
34. Reddel HK. Treatment of overlapping asthma-chronic obstructive pulmonary disease: Can guidelines contribute in an evidence-free zone? J Allergy Clin Immunol 2015;136:546-52.
35. Fabbri LM, Romagnoli M, Corbetta L, Casoni G, Busljetic K, Turato G, et al. Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003;167:418-24.
36. Fattahi F, Vonk JM, Bulkmans N, Fleischeuer R, Gouw A, Grünberg K, et al. Old dilemma: asthma with irreversible airway obstruction or COPD. Virchows Arch 2015;467:583-93.
37. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med 2012;18:716-25.
38. Segreti A, Stirpe E, Rogliani P, Cazzola M. Defining phenotypes in COPD: an aid to personalized healthcare. Mol Diagn Ther 2014;18:381-8.
39. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J 2016;47: 410-9.
40. Bateman ED, Reddel HK, van Zyl-Smit RN, Agusti A. The asthma-COPD overlap syndrome: towards a revised taxonomy of chronic airways diseases? Lancet Respir Med 2015;3:719-28.
41. Vestbo J, Vogelmeier C, Small M, Higgins V. Understanding the GOLD 2011 Strategy as applied to a real-world COPD population. Respir Med 2014;108:729-36.
42. Barnes PJ. Inhaled corticosteroids in COPD: a controversy. Respiration 2010;80: 89-95.
43. Bell MC, Busse WW. Is it asthma or is it COPD: The overlap syndrome. J Allergy Clin Immunol Pract 2015;3:641-2.