The asthma-COPD overlap syndrome (ACOS): hype or reality?

That is, a curiosity for the media or an opportunity for physicians?

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Summary

Asthma-COPD Overlap Syndrome (ACOS) has been recently defined as a new pathological entity. Most studies support a large difference in the pathophysiology of bronchial asthma and chronic obstructive pulmonary disease (COPD). However, there is evidence of an increasing prevalence of patients in whom the two diseases coexist or in which one condition evolves into the other, leading to the pathological condition named ACOS. This occurs mainly in individuals with long-standing asthma, especially if also current or former-smokers. Indeed, epidemiological studies show that aging is one of the main risk factors for ACOS, creating the basis for the two entities to converge on the same subject. It is important not to forget the history of asthma, even when the patient develops functional and radiological features suggestive of COPD, because of the therapeutic implications. Patients with ACOS have poorer health related quality of life and higher exacerbation rate then subjects with asthma or COPD alone. Whether ACOS is a distinct nosological entity with genetic variants, or whether it is rather a condition of concomitant diseases that overlap is still a matter of debate. The challenge is to solve this issue.

KEY WORDS: asthma; COPD; lung function; airway inflammation; quality of life; acute exacerbations.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are chronic diseases with high prevalence in the general population. Asthma affects 25 million Americans (18 million adults and 7 million children) (1), while about 14.2 million Americans are diagnosed with COPD and 9.8 million are estimated to have COPD that is undiagnosed (2, 3). A variable degree of airway inflammation, airway obstruction, and airway hyperresponsiveness are common pathophysiological features of both diseases (4, 5). Several studies described different inflammatory cells recruitment, mediators production, and responses to therapy in asthma and COPD. Airway obstruction is typically intermittent and reversible in asthma while it is progressive and largely poor reversible in COPD (6). Although COPD and asthma are two different and independent diseases, COPD can coexist with asthma with features of irreversible airflow limitation (7).

In 1995, the guidelines on chronic obstructive pulmonary diseases by the American Thoracic Society (ATS) described eleven syndromes, including asthma, chronic bronchitis, emphysema, COPD and airflow obstruction, and an overlap at 6 of these was observed (8). More than 40% of patients with COPD report a history of asthma, and asthma is recognized as a risk factor for COPD (9). Increasing evidence suggests that the two diseases may coexist in the same individual; however, only in recent years an asthma-COPD overlap syndrome (ACOS) has been described. Epidemiological studies showed that the prevalence of overlapping diagnoses increased in older populations (10-12). The pathologic and functional overlap between asthma and COPD has been estimated to be <10% in patients younger than 50 years and >50% in patients aged 80 years or older (10). Similar results on the age distribution were found in the Italian individuals (13), in whom asthma and COPD coexist in a substantial proportion of subjects. In this study, the prevalence of asthma-COPD overlap was 1.6%, 2.1% and 4.5% in the 20-44, 45-64, 65-84 age groups, respectively. Pride et al. (14), in a study on the application of diagnostic labels for obstructive airway showed that a vast proportion of clinicians extended the diagnostic label beyond asthma to indicate the presence of other clinical features, using additional terms such as asthma with chronic bronchitis, asthma with permanent

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obstruction, chronic obstructive bronchitis and COPD with a reversible component.
The crucial question is whether ACOS can be envisaged as a distinct nosological entity, or whether it is rather a condition of concomitant diseases that overlap. This is not a trivial issue, since the diagnostic and therapeutic approaches may considerably vary. If one disease (i.e. asthma) is the driving pathological condition and the other (i.e. COPD) occurs at some stages because of causal factors (i.e. smoking exposure), then the diagnostic procedures should aim at recognizing the primary nosological condition (i.e. reversibility test), and the pharmacological management would therefore follow current guidelines (i.e. inhaled combination treatment). Similar reasoning (with different conclusions) applies when the primary disease is COPD. In this scenario, the "overlap" state is by no means different from other overlapping conditions, such as COPD and sleep apnea syndrome, COPD and bronchiectasis, or asthma and rhinosinusitis, asthma and gastroesophageal reflux. The concept can be extended to extra-respiratory diseases (i.e. cardiovascular diseases) or even physiological abnormalities (i.e. obesity). On the other hand, the identification of a single genetic origin, together with common physiological abnormalities, lead to the description of a new nosological entity, which is not asthma nor COPD, but resembles features of both. The reason why this entity is being increasingly recognized only in recent years could be attributed to the increased life expectancy, since this condition is predominant in the most advanced ages. The challenge is to answer the question of whether ACOS is a hype or a reality.

Historical background of asthma and COPD

In 850 before Christ, when the term COPD was far from being conceived, Homer in the Iliad described the difficulty in breathing of Hector by using for the first time the term "asthma". After this definition, dating back to ancient Greece, other historical descriptions of patients with respiratory problems were proposed in the following centuries. However, up to the Middle Ages and pre-industrial era, the average median survival did not exceed 40 years of age and cigarette smoking was almost absent; therefore, it could be assumed that a disease with the typical features of COPD did not exist (and consequently the asthma-COPD overlap). However, a median survival of 40 years does not imply that elderly people did not exist. Indeed, until a couple of centuries ago, life expectancy was drastically reduced by the frequent infant and neonatal deaths. Seneca (4 BC - 65 AD), is an example of a 60-year-old man who lived about 2000 years ago, suffering from respiratory problems. In describing his illness, Seneca highlighted two of the peculiar characteristics of asthma: the reversibility and recurrence of the breathlessness attacks. Moreover, Seneca realized that year after year, his breathing tended to worsen, identifying what would have been scientifically shown much later, that is, asthma being responsible for an accelerated decline in lung function (15). This may sometimes result in a not fully reversible airflow limitation, which is one of the features used in the current definition of COPD (16). However, the first description of emphysema as "voluminous lungs" was made in 1679 by Bonet (17), and only in 1789 the works by Baillie suggested that emphysema could be part of a more complex disease (18). Much later, in 1814, Badham (19) used the word "catarrh" to refer to the chronic cough and increased mucus secretion as symptoms of bronchiolitis and chronic bronchitis. In 1821 Laënnec, the inventor of the stethoscope, described a combination of emphysema and chronic bronchitis (20). Two breakthroughs in the diagnosis of COPD came in 1846, when John Hutchinson invented the spirometer (21) and in 1947, when Tiffeneau and Pinelli added the concept of timed vital capacity as a measure of airflow (22). Finally, the first definition of COPD was proposed in the CIBA Guest Symposium (1959) (23) and the American Thoracic Society Committee on Diagnostic Standards (1962) (24).

When the two diseases overlap

Over the years, several researchers have claimed a common origin for asthma and COPD. According to this hypothesis (the so-called Dutch hypothesis), the two diseases are two expressions of a single "non-specific chronic lung disease" (25). This would assume different clinical and functional connotations in relation to different environmental factors involved in the same individual. With the progress of knowledge, several elements have emerged in favor of a substantial difference between asthma and COPD (26). Most authors currently consider asthma and COPD as two separate diseases, in which different and specific risk factors concur to determine two different pathological conditions, with different pathogenetic mechanisms, and also requiring different therapeutic approaches. However, there is evidence that aging sets the basis for the coexistence of the two diseases in the same individual (6). This occurs mainly in elderly patients suffering from asthma for a long time, especially if smokers.
It has been estimated that in most developed countries approximately 25% of adults with asthma are current cigarette smokers (27). Cigarette smoking may modify the inflammatory features that are associated with asthma. Active cigarette smoking in asthmatics is responsible for more severe symptoms, accelerated decline in lung function, greater need for rescue medication, worse indices of health status, and impaired short-term therapeutic response to corticosteroids when compared with never-smokers (28-32).

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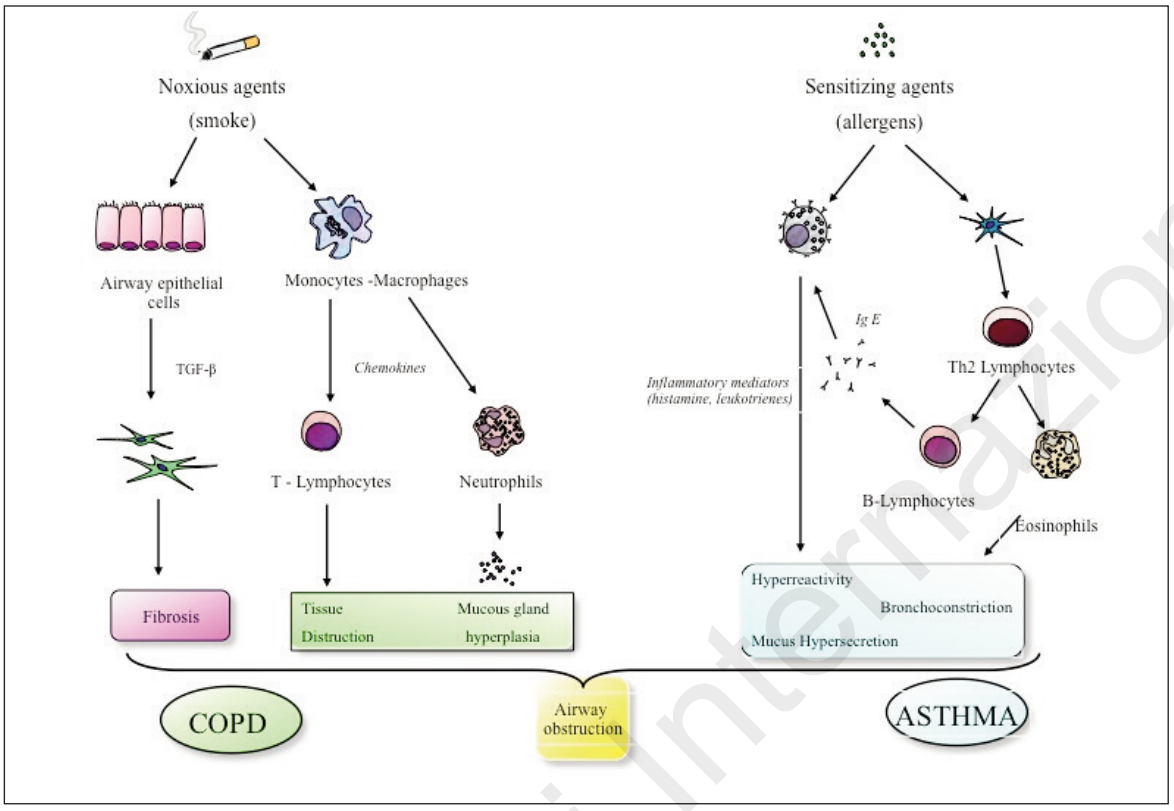

Figure 1 - Inflammatory mechanisms and immune cells involved in chronic airways diseases.

The longitudinal observation of the Tucson cohort showed that asthmatic subjects were 12 times more likely to develop COPD than healthy individuals. COPD was diagnosed either as not fully reversible airflow limitation, or as a reduction in diffusing capacity of the lung for carbon monoxide (DLCO) (33). Therefore, there is a general consensus that asthma in some cases may progress to COPD (25). Authors who are engaged with the genetic aspects of obstructive airway diseases are questioning whether COPD begins in childhood (34, 35). The Dutch Hypothesis supports the concept that asthma and airway hyperresponsiveness (AHR) predispose patients to develop COPD later in life (25) and that asthma and COPD are different expressions of a single disease with a common genetic background. The COPD Gene study enrolled >10000 subjects performing quantitative chest computed tomography (CT) analysis and genome-wide genotyping, to better characterize the clinical, radiographic and genetic features of the ACOS group (36). Subjects with both COPD and asthma demonstrated greater airway wall thickness and less emphysema than subjects with COPD alone. Several variants associated with ACOS were found in the genetic analyses (36). The two most significant associations among non-Hispanic white overlap subjects included variants from the CSMD1 gene, which has been associated with emphysema, and within the SOX5 gene, which has been correlated with COPD and may play a role in lung development. On the contrary, in non-Hispanic white and African-American subjects several variants in the GPR65 gene were associated with the overlap syndrome.

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Several factors, such as, infections, atopy, and tobacco-smoking exposure, in addition to genetic susceptibility, low birth weight and incomplete lung growth may contribute to the origin of ACOS since childhood. A portion of neversmokers asthmatics who develop ACOS may be explained by the extensive use of wood (or other) combustion, for cooking and heating, in poorly ventilated spaces. This make the “abnormal inflammatory response of the lung to noxious particles or gases” not uncommon in certain social contexts even in the absence of cigarette smoking.

Plasma and sputum biomarkers: what is in common?

Chronic airway inflammation in COPD is different than in asthma (Figure 1). Asthma is usually characterized by airway hyperresponsiveness and eosinophilic inflammation that affects all the airways but not lung

parenchyma. However, smoker asthmatic patients develop pathological features similar to COPD (27, 37), and COPD patients may demonstrate features of asthma (38), such as a mixed inflammatory pattern with increased eosinophils (39) and sputum eosinophilia, which has been reported to be related to an improvement in FEV_1 using treatment with inhaled corticosteroids (ICS) (40). It was hypothesized that patients with overlap syndrome may have different clinical characteristics such as sputum eosinophilia, and as a consequence better responsiveness to treatment with ICS. Kitaguchi et al. (41) performed a study with the aim to clarify the features of COPD patients with asthmatic symptoms, such as episodic breathlessness, wheezing, cough, and chest tightness worsening at night or in the early morning, compared with those of COPD patients without asthmatic symptoms. Authors showed that the increases in FEV_1 in response to treatment with ICS, the peripheral eosinophil counts, the sputum eosinophil counts and the prevalence of patients with bronchial wall thickening on high resolution CT were significantly higher in the COPD subjects with asthma-like symptoms. Therefore ICS should be considered earlier as a potential treatment in such patients, and high sputum eosinophil counts a good predictor of response to ICS. No significant difference was found in the increases in FEV_1 in response to β2-agonist between the two groups. On the other hand, a study on adults with stable obstructive airway disease (asthma and/or COPD) underlined that sputum total cells and neutrophils were highest in ACOS subjects than in asthmatics and healthy controls. Instead, sputum eosinophils were not different between the groups with airway disease (42). Therefore, the inflammatory component of ACOS still remains to be fully elucidated, and studies should be designed to properly address this issue.

Sputum total cells and neutrophils were highest in ACOS subjects than in asthmatic and healthy controls.

It is well known that in COPD subjects, systemic inflammation with chronic low-grade elevation of circulating pro-inflammatory mediators such as C-reactive protein (CRP) and interleukin 6 (IL-6) is associated with accelerated disease progression. The systemic inflammation and its association with clinical characteristics and inflammatory mediators were investigated in asthma-COPD overlap syndrome (43). Data identified a high prevalence of systemic inflammation in older people with the asthma-COPD overlap syndrome, resembling COPD in terms of systemic inflammation. Patients with ACOS had significantly higher IL-6 levels compared with healthy controls and asthmatics. Systemic levels of IL-6 were strongly associated with the magnitude of lung function impairment and with cardiovascular diseases. These findings suggested that IL-6 is a pivotal inflammatory mediator that may be involved in airflow obstruction and cardiovascular disease, and may perhaps be an independent treatment target. Acay et al. (44) performed an evaluation of serum paraoxonase (PON1) and arylesterase (AE) activities in subjects with asthma and COPD. PON1 and AE enzymes appeared to protect HDL from oxidation, thus showing antiatherogenic, antioxidant, and antiinflammatory properties. The authors concluded that, although asthma and COPD are two different conditions, PON1 and AE activities cannot be markers of differential diagnosis as they overlap.

There is a high prevalence of systemic inflammation in older people with the asthma-COPD overlap syndrome, similarly to the systemic inflammation frequently seen in ageing COPD.

Differential diagnosis between asthmatics and COPD subjects

Asthmatics are likely to be younger, non-smokers, and have atopy and/or allergies and reversible airway limitation; COPD patients are older, smokers, and have persistent and progressive airflow obstruction. Preserved carbon monoxide diffusion capacity (DLCO) and a higher ratio of airway-to-lung parenchymal abnormalities by HRCT may also distinguish asthma from COPD. Relevant differences exist between asthma and COPD in terms of structural and inflammatory features: elevated IgE, induction of Th2 cells, eosinophilic infiltration, smooth muscle hyperplasia, reticular basement membrane thickening are generally found in asthmatics, while increased neutrophils, induction of Th1 and Th17 cells, TGF -induced small airway fibrosis, goblet cell hyperplasia, and elastic tissue destruction are typically found in COPD.

Features of airway remodeling and a role of inflammatory process in the small airways may be a key point to understand the pathology of ACOS.

In clinical practice, some patients with asthma also develop poorly reversible airway limitation, whereas in the elderly with COPD a condition of variable airway obstruction is commonly observed (45). In addition, in COPD subjects increased AHR correlates with increased rate of exacerbations and overall mortality (46). Studies have shown that prevalence of AHR in COPD patients is increased as much as three times in the elderly compared to non-elderly patients (47), and that 50% of the elderly with airway disease have airflow variability with some degree of irreversible airway obstruction (42, 48). Irreversible obstruction is reported to occur in 23% of chronic asthmatics (49), and smoking and long history of asthma are important risk factors for irreversible asthma. Based on the clinical and physiological testing used to differentiate the two conditions, Bellia et al. estimated that 20% of elderly COPD patients are actually suffering from irreversible asthma (50). This finding is supported by studies that used physiological tests, CT scan and bronchial biopsy to differentiate irreversible asthma and COPD (51-53).

Differential diagnosis can be a difficult task for clinicians. Beeh et al. (54) developed a questionnaire to differentiate asthma and COPD symptoms. On a scale of 1 to 15, the questionnaire performed best at a cut-off of 7 with a sensitivity of 87.6% for COPD, though some 20% of patients had overlap features (scores 6-8). Authors encountered smokers with irreversible airflow obstruction, labeled as COPD patients. However, based on normal transfer coefficient (KCO) calculated as carbon monoxide diffusion capacity/alveolar volume (DLCO/VA), and bronchial histology, they shifted the diagnosis to irreversible asthma and used anti IgE therapy, omalizumab, a treatment that would not have been considered with the diagnostic label of COPD, inducing a significant improvements in FEV_1 and dyspnea (55).

Although the well known importance of differential diagnosis between COPD and irreversible asthma, the available physiological and radiological tests are not sufficient to clearly differentiate the two conditions. Increased airway wall thickness is an important feature in obstructive airway diseases, due to inflammation, increased airway wall fibrosis and increased thickness of the smooth muscle (42, 56). There are significant histologic differences between asthma and COPD; however, endobronchial biopsy cannot be widely used in the work-up and management of obstructive lung disease due to the unfavorable risk-benefit profile (53). Therefore, the possibility of overlap syndrome should be considered when managing elderly patients with asthma with persistent airway limitation or COPD patients with variability in symptoms and reversibility of lung function limitation. Recent data show that ACOS is recognized by the coexistence of incompletely reversible airway obstruction; features of airway remodeling and a role of inflammatory process in the small airways may be a key point to understand the pathology of ACOS. Every effort should be made to better define the disease with the aim to understand the exact nature of the asthma-COPD overlap syndrome: genetic or other reasons?

Proposed diagnostic approaches to ACOS

Patients with ACOS are mainly smokers with history of asthma or nonsmokers with long-standing asthma who developed a non completely reversible airflow obstruction (57). The Spanish COPD guidelines propose four COPD phenotypes that determine differential treatment: 1) nonexacerbator with emphysema or chronic bronchitis, 2) mixed COPD-asthma, 3) exacerbator with emphysema and 4) exacerbator with chronic bronchitis (58). The mixed COPD-asthma phenotype was defined as an airflow obstruction that is not completely reversible accompanied by symptoms or signs of an increased reversibility. However, the ACOS is not only a phenotype of COPD; likewise it could be considered a phenotype of asthma. In fact, other authors have described two possible types of patients with ACOS: 1. a subject with known asthma + not fully reversible airflow obstruction, with or without emphysema or reduced DLCO; 2. a subject with known COPD and emphysema + partially reversible airflow obstruction with or without environmental allergies or reduced DLCO (59). For diagnostic purposes, the Spanish group has proposed, in patients who have already been diagnosed with COPD, two major and two minor criteria (60). Major criteria include a very positive bronchodilator test (increase in FEV_1 ≥15% and ≥400 mL), and eosinophilia in sputum and personal history of asthma. Minor criteria include high total IgE, personal history of atopy, and positive bronchodilator test (increase in FEV_1 ≥12% and ≥200 mL) on 2 or more occasions.

The mixed COPD-asthma phenotype was defined as an airflow obstruction that is not completely reversible accompanied by symptoms or signs of an increased reversibility.

Different criteria for the diagnosis of ACOS were proposed by Louie et al. (61). They considered as major criteria: 1) The physician-diagnosis of asthma and COPD in the same patient, 2) History or evidence of atopy, (e.g. hay fever, elevated total IgE), 3) Age 40 years or more, 4) Smoking with >10 pack-years, 5) Postbronchodilator FEV_1 <80% predicted, and 6) FEV_1/FVC <70%. Minor criteria were increase in FEV_1 ≥15%, or ≥12% and ≥200 mL in post-bronchodilator treatment with albuterol (62). Zeki et al. (59) described two clinical phenotypes for the definition of the overlap syndrome: 1) allergic disease consistent with asthma, that is, variable airflow obstruction or AHR that is incompletely reversible (with or without emphysema or reduced carbon monoxide diffusion capacity (DLCO); 2) COPD with emphysema accompanied by reversible or partially reversible airflow obstruction (with or without an allergic syndrome or reduced DLCO).

The last GINA and GOLD guidelines (2014) dedicated a joint chapter to ACOS to underline the clinical importance of the overlap syndrome (16, 62). They suggested a stepwise approach to diagnosis of patients with respiratory symptoms:

Step 1. Assess the presence of a chronic airway disease. This can be done through the clinical history, physical examination, and other investigation such as radiology or screening questionnaires. Chronic cough, sputum, dyspnea, wheezing, and recurring acute lower respiratory tract infections are the main features that suggest a chronic airways disease. A significant history of smoking is the main factor associated with the suspicion of COPD, whereas atopy is more frequently observed in asthma. Chest X-ray or CT scan may reveal characteristic abnormalities, such as hyperinflation, airway thickening, air trapping, hyperlucency, bullae or other features of emphysema.

Step 2. Assemble the features in favor of a diagnosis of asthma or COPD. The GINA and GOLD documents listed the main characteristics of asthma and COPD: if a patient presents with several (three or more) characteristics of one but not the other disease, the diagnosis of asthma or COPD will be most likely the correct one. If the patient shows the same number of asthma and COPD features, the likelihood that he/she has ACOS is very high (Figure 2).

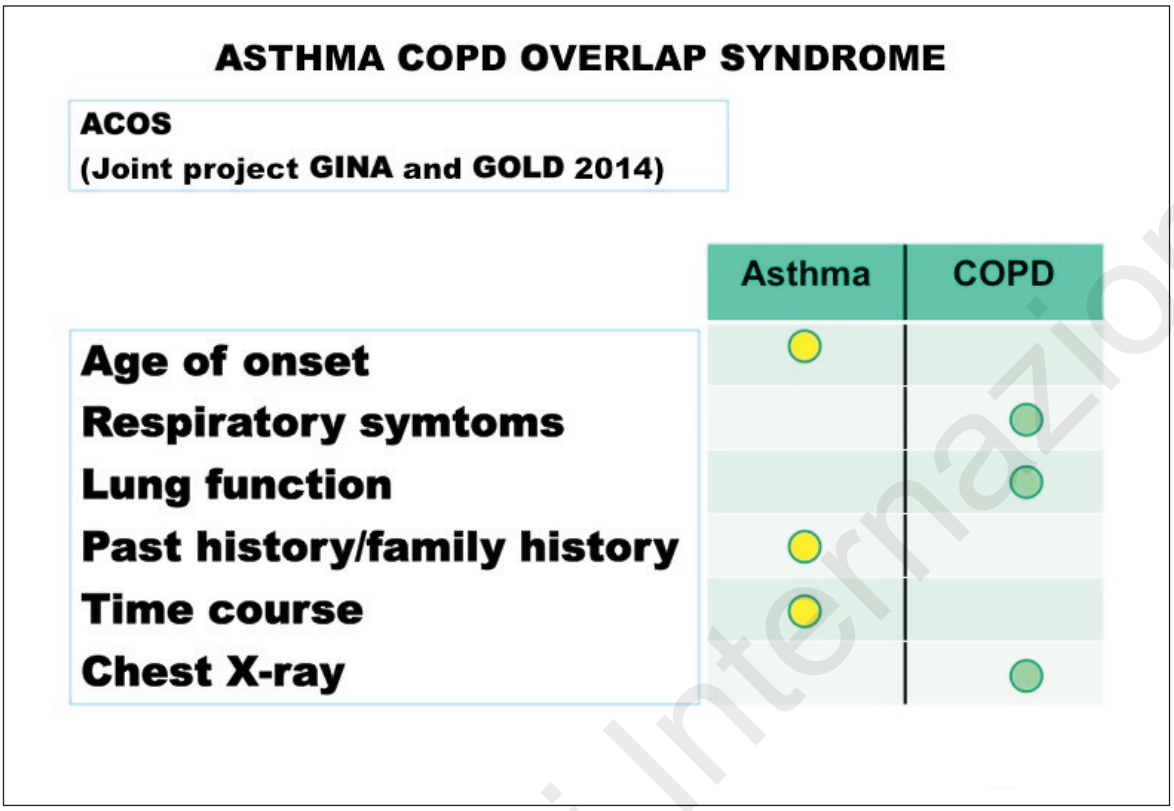

Figure 2 - Example of a diagnosis of ACOS based on the responses to the main features suggested to characterize chronic airway diseases.

Step 3. Perform spirometry, preferably before and after bronchodilator. A normal FEV_1/FVC pre- or post bronchodilator is compatible only with the diagnosis of asthma, while it excludes the presence of COPD or ACOS. A reduced FEV_1/FVC may occur with asthma, COPD, or ACOS. A significant post-bronchodilator increase in FEV_1 (≥ 12% and 200 ml) is frequent in asthma; it may be absent if asthma is well-controlled, whereas it may also occur in COPD. If reversibility is marked (increase in FEV_1 >12% and 400 ml from baseline), asthma is highly likely. If airflow limitation is not fully reversible, COPD is the most probable diagnosis, and ACOS may be considered according to the clinical history.

Step 4. Commence initial therapy. If ACOS is suspected, the treatment should be started accordingly for asthma, due to the widely recognized key role of inhaled glucocorticoids in reducing morbidity and mortality in patients with uncontrolled asthma. Indeed, differently from COPD, even mild symptoms in asthma may involve a significant risk of a life-threatening attack.

Is ACOS worse than asthma and COPD?

Patients with ACOS have the combined risk factors of smoking and atopy (61). They have a worse health-related quality of life, significantly higher frequency of respiratory symptoms (13), more rapid disease progression, increased co-morbidities and health care utilization, more severe and more frequent respiratory exacerbations than alone COPD or asthma (10, 63, 64), greater airway wall thickness compared to subjects with COPD alone. A recent study analyzed medical utilization and cost in patients with overlap syndrome, showing that in ACOS patients both medical utilization and cost were higher than in COPD patients without asthma (65). Kauppi et al. showed that overlap syndrome of asthma and COPD predicts low quality of life. The study population consisted of 1546 patients divided into three groups: asthmatics, COPD patients, and overlap syndrome group. Patients with overlapping asthma and COPD differed from those patients with asthma or COPD only and overlap syndrome was associated with low health-related quality of life (HRQoL). Moreover, female gender, obesity, duration of disease, disability pension, and coexisting cardiovascular disease were associated with low HRQoL (66). Andersen described the hospital impact and characteristics of patients with overlap syndrome (67). The author observed that patients with asthma were younger than patients with COPD and overlap syndrome, while the age distribution was very similar in COPD and overlap syndrome patients. ACOS patients had an increased hospitaliza-

Patients with overlapping asthma and COPD differed from those patients with asthma or COPD only and overlap syndrome was associated with low health-related quality of life.

Compared to the other groups, subjects in the overlap syndrome group were more likely to have low lung function, high proportion of smokers, low socioeconomic status, shorter education duration.

tion in term of access to the hospital and days of hospitalisation.

An Italian observational study (68) explored the level of asthma control in elderly subjects, and factors influencing it. Twenty-nine percent of patients was classified as having ACOS due to the presence of chronic bronchitis and/or CO lung diffusion impairment. This subgroup of patients had lower mean Asthma Control Test scores and more exacerbations compared to the asthmatic patients. In addition Modified Medical Research Council dyspnea (mMRC) scores and airway obstruction were more severe in ACOS than in asthma, without any difference in responses to salbutamol. The authors highlight the need to evaluate the coexistence of features of COPD in elderly asthmatics, as a factor that worsens asthma control. A recent study (69) investigated characteristics of overlap syndrome and their effect on self-rated health (SRH) in four groups: COPD group, asthma group, overlap syndrome group and non-obstructive disease (NOD) group. Compared to the other groups, subjects in the overlap syndrome group were more likely to have low lung function, high proportion of smokers, low socioeconomic status, shorter education duration. Metabolic syndrome and osteoarthritis were most prevalent in the overlap syndrome group. In addition female sex, age >60 years, low education level, low economic status, smoking history and other comorbidities were also associated with lower SRH. Therefore overlap syndrome was accompanied by high morbidity and was independently associated with lower SRH, which needs more appropriate care. Finally, Fu et al. (70) in a recent study examined the prognosis of obstructive airway diseases (OADs) including asthma, COPD and ACOS in older adults and identified potential determinants for longitudinal changes in clinical outcomes. They showed that COPD patients had a poor prognosis compared with other groups and that the BODE index is a prognostic indicator in older adults with OADs. The change in 6MWD was lower in the asthma-COPD overlap group; indeed, the airflow reversibility was associated with a reduced decline in 6MWD.

Therapeutic choices for ACOS

Randomized controlled clinical trials on efficacy of treatment excluded smoker asthmatics and patients with overlapping asthma and COPD: therefore, the data on efficacy of treatment in this clinical populations are lacking. Statements on proposed therapeutic algorithms and strategic approaches are only speculative and extrapolated from studies which are not representative of the ACOS population. Caution should therefore be made when interpreting and translating to the ACOS patients findings from clinical trials. It is mandatory to expand the knowledge on ACOS in order to establish adequate guidelines and recommendations for its diagnosis and treatment. Prospective randomized clinical trials should be performed including overlap syndrome to evaluate drug efficacy on primary outcomes such as lung function, rate of exacerbations, quality of life and mortality (61).

The Spanish society has proposed (60) treatment recommendations for ACOS. ACOS patients may benefit from a treatment similar to that of asthma as they have clinical characteristics that suggest greater effectiveness of the anti-inflammatory treatment. Thus, the document recommends using ICS early on in all patients with overlap syndrome, and adjusting the dose according to symptoms, lung function and/or the presence of eosinophils in sputum. However, due to the nature of COPD itself, unlike asthma, in all cases the use of ICS should be associated with long-acting beta2-agonist bronchodilators (LABA). In cases of worsened symptoms, the consensus also recommends assessing the triple association of ICS, LABA and also long-acting muscarinic antagonists (LAMA). Welte et al. (71) demonstrated significant functional and clinical benefit following the use of triple therapy in patients with severe COPD. In addition, consensus was reached to use caution when withdrawing ICS in these patients, as this could cause new exacerbations, although a recent paper shows the opposite (72). Several authors recommend a symptom-targeted approach (59), while controversial remains on the use of LAMA alone or in combination with LABAs in overlap syndrome. Smoking cessation, oxygen supplementation, pulmonary rehabilitation, and vaccines are all reasonable interventions.

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