7. Asthma and chronic obstructive pulmonary disease

7.1 Concept and definitions

C Asthma and chronic obstructive pulmonary disease (COPD) are two highly prevalent diseases that may coexist in the same patient (the so-called mixed COPD/asthma phenotype or mixed COPD/asthma disease or asthma-COPD overlap syndrome [ACOS]). In the COPDGene cohort, the asthma-COPD overlap syndrome was present in 12% of cases[473].

C The prognosis and the therapeutic attitude influence upon the clinical relevance of the coexistence of COPD and asthma in a single patient. No data are available showing a higher mortality when both diseases are associated, although COPD patients who are also asthmatics have a higher risk for exacerbations (OR 3.55 in the study of Hardin et al.[473], 3.01 in the study of Menezes[474]). This risk is even higher (OR 3.79) for a patient with COPD in whom a specific IgE against a perennial allergen is detected[475]. On the other hand, persistent airflow obstruction is associated with a greater severity of asthma severity[476].

C The clinical consequences of asthma and COPD should be based on the presence, in an individual patient of the characteristics inflammatory pattern of each disease (or at least some features of these patterns). While COPD is characterized by an inflammatory response in which CD8+ lymphocytes, neutrophils and macrophages predominate, an eosinophilic response mostly mediated by Th2 lymphocytes is observed in asthma. Different studies have shown that the presence of a significant sputum eosinophilia is predictive of a good response to glucocorticoids in patients with COPD[477,478], as well as in patients with coexistent asthma and COPD[479]. On the other hand, the presence of neutrophils in sputum in patients with asthma is associated with a higher disease severity[480]. Possibly current rigid compartments distinguishing between COPD and asthma patients will be overcome in the future, leading to an integrated concept of airway disease where, for each patient, a distinct inflammatory pattern would be associated with clinical manifestations, prognostic determinants and more effective specific therapies[481].

D According to currently available data, the asthma-COPD overlap syndrome could be defined as the presence of a scarcely reversible airflow obstruction in a smoker (or former smoker) patient showing clinical manifestations of asthma associated with: positive bronchodilatation, or bronchial hyperresponsiveness, or either systemic or bronchial eosinophilia.

7.2 Diagnosis and evaluation

Since some symptoms are common to both disorders, distinguishing asthma from COPD is challenging in clinical practice, and deciding on which disorder contributes the most to the patient's clinical status is also not easy. There are no symptoms, functional impairment (bronchial obstruction, bronchial hyperresponsiveness, significant bronchodilation) o cytological patterns in the induced sputum that can be considered pathognomonic of either disease.

Symptoms that allow suspecting the coexistence of asthma in a patient with COPD are: onset of symptoms before 40 years of age, previous diagnosis of asthma, family history of asthma, great variability of symptom severity, nighttime symptoms, intolerance to NSAID and upper airway involvement (rhinosinusitis with or without polyps).

D Diagnosis should be based on the presence of a persistent (at least at two consecutive visits) airflow obstruction (FEV_1/FVC < 70%) in a smoker or ex-smoker (> 10 packs-year). If the obstruction persists after a bronchodilator test, a trial with oral glucocorticoids (30 mg of prednisone daily for 2 weeks) should be performed. The resolution of airflow obstruction will exclude COPD and confirm the presence of asthma.

D In addition to asthma symptoms and a fixed airflow obstruction, a positive result from a bronchodilator test (FEV_1 increase of 12% and at least 200 ml) or a bronchial hyperresponse (PC_{20} FEV_1 methacholine < 4 mg/ml) should be demonstrated[83]. However, some patients with COPD and without concomitant asthma may also exhibit positivity of these tests[482,483].

C If the results of the above tests were negative or uncertain (or if tests were unfeasible), the presence of systemic eosinophilic inflammation (blood eosinophil count > 300/mm^3[146,484], or bronchial eosinophilic inflammation (eosinophils in induced sputum > 3%[485] or FE_{NO} > 50 ppb[86]) should be confirmed. Also, assessment of blood biomarkers of Th2 inflammatory response, such as periostin[486] has been proposed, although the evidence is insufficient to recommend its use in clinical practice.

D The recommended diagnostic algorithm for the diagnosis of asthma-COPD overlap syndrome is shown in figure 7.1.

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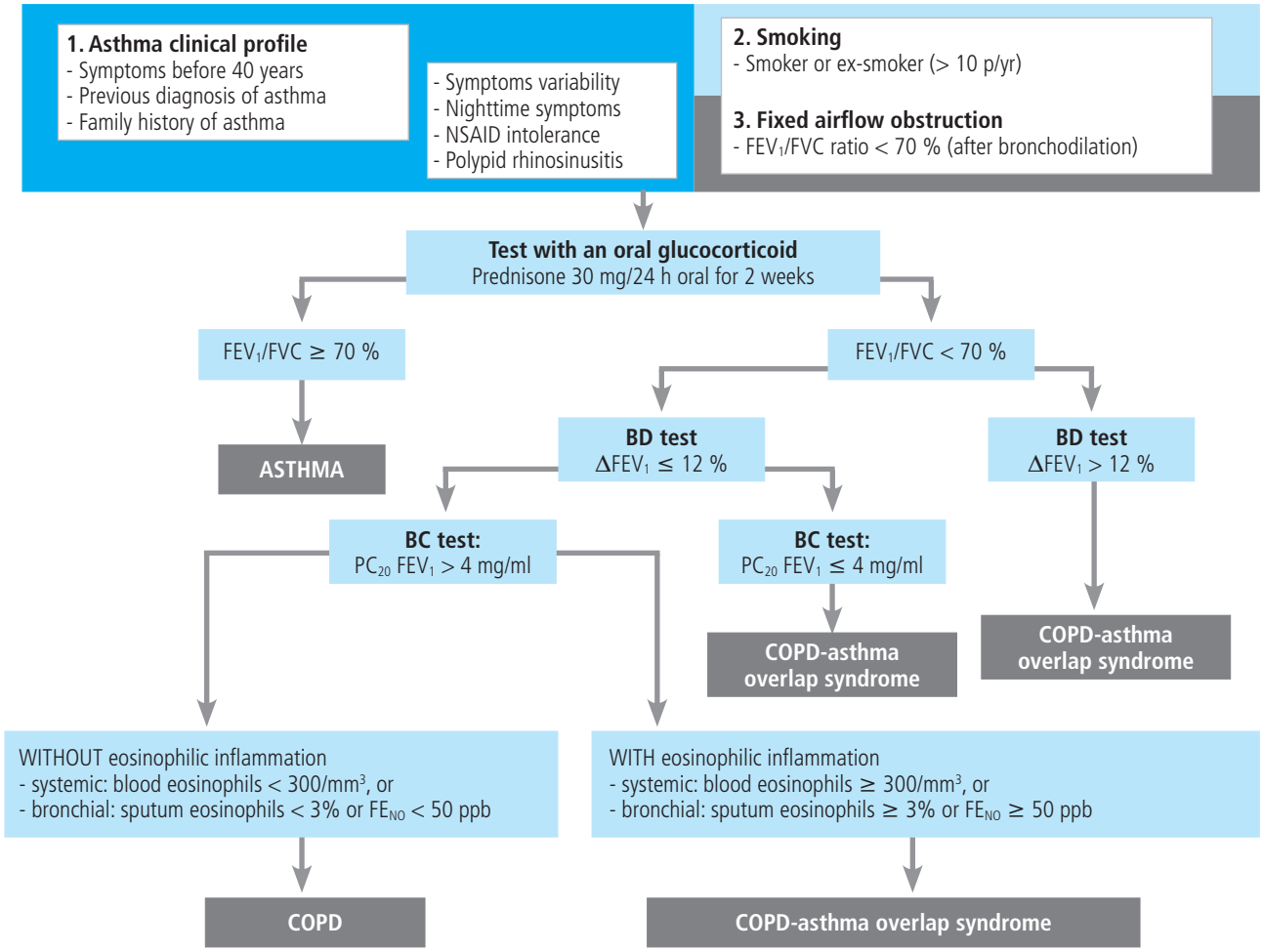

BC: bronchoconstrictor; BD: bronchodilator; FE_{NO}: fractional exhaled nitric oxide; $PC_{20}FEV_1$: concentration of methacholine that causes a 20% fall of FEV_1; p/yr: pack-years.

Figure 7.1. Diagnostic algorithm of asthma-COPD overlap syndrome.

7.3 Treatment

B The first goal of treatment is to prevent exacerbations. Therefore, patients with asthma-COPD overlap syndrome should be prescribed IGCs. The most appropriate IGC for this group of patients has not yet been identified, although these drugs have been reported to achieve a 69% increase in the risk of severe pneumonia, particularly when high doses are administered[487]. Therefore, the minimal clinically effective dose should be used to prevent exacerbations.

A Tiotropium reduces exacerbations in patients with COPD[488] and asthma (in 21% of patients insufficiently controlled with a combination of an IGC and a long-acting β_2-agonist [LABA])[489].

A Biologic agents, such as omalizumab, mepolizumab o dupilumab have been found to be effective in reducing exacerbations in patients with severe asthma. However, since heavy smokers have been excluded from clinical trials, the usefulness of these drugs in the asthma-COPD overlap syndrome remains unknown and, at the present time, the use of these drugs cannot be recommended.

C Treatment of mild-moderate asthma with roflumilast has shown a similar efficacy in improving pulmonary function and relieving symptoms to that of beclomethasone at low doses[490]. In patients with severe COPD and clinical criteria for chronic bronchitis, roflumilast significantly reduced exacerbations[491]. This agent is thus indicated in patients with asthma-COPD overlap syndrome with clinical criteria of chronic bronchitis, FEV_1 values < 50% and lack of efficacy (in the prevention of exacerbations) after receiving a combination of IGC/LABA and tiotropium.

B Vilanterol is available in combination with fluticasone furoate, and it has been shown that the administration of this drug when given once daily, both in asthma and COPD patient, offers a similar efficacy to that observed at 12 hours with the use of fluticasone propionate and salmeterol[492,493].

Little experience is available to date for other recently marketed bronchodilators, such as glycopyrronium, aclidinium, indacaterol and olodaterol, although they might find their place in the treatment of this syndrome in the future.

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Treatment will also be aimed at relieving symptoms and improving lung function. LABAs (inhaled formoterol, salmeterol and vilanterol) are the first-line option in both COPD and asthma patients. On the other hand, tiotropium has been shown to improve pulmonary function in patients with persistent airflow obstruction despite treatment with an IGC/LABA combination, although the impact on symptoms and quality of life was not clinically relevant[489].

In summary, patients with the asthma-COPD overlap syndrome should be initially treated with an IGC/LABA combination, adjusting the IGC dose as much as possible. If exacerbations persist despite using an IGC at medium/high doses, then tiotropium will be added. In case this approach fails, roflumilast may be tried in patients with severe obstruction and clinical criteria for chronic bronchitis. If the aim of treatment is to improve pulmonary function and if exertional dyspnea is clinically significant, tiotropium could also be included in the combination.

RECOMMENDATIONS

7.1.	The asthma-COPD overlap syndrome is defined as an irreversible airflow obstruction in a smoker (or ex-smoker) patient, with clinical manifestations of asthma associated with positive bronchodilatation or bronchial hyperresponse or eosinophilic inflammation (either systemic or bronchial).	**R1**
7.2.	The diagnosis of an asthma-COPD overlap syndrome will be made in a smoker or ex-smoker (> 10 pack-year), with past history or suspected symptoms of asthma and fixed airflow obstruction (post-bronchodilator FEV1/FVC < 70%) (at two consecutive visits), as well as a positive bronchodilator test (12 % increase in FEV_1) or bronchial hyperresponsiveness (PC_{20} FEV_1 methacholine < 4 mg/ml) or either systemic eosinophilic inflammation (blood eosinophils > 300/mm^3) o bronchial eosinophilic inflammation (eosinophils in induced sputum > 3% or FE_{NO} > 50 ppb).	**R2**
7.3.	The first-line therapy for the asthma-COPD overlap syndrome is the combination of an IGC and LABA. In case of insufficient response, tiotropium will be added.	**R1**

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