REVIEW ARTICLE

The Asthma–COPD Overlap Syndrome

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APPROXIMATELY 1 IN 12 PEOPLE WORLDWIDE ARE AFFECTED BY ASTHMA or chronic obstructive pulmonary disease (COPD)[1,2]; once regarded as two distinct disease entities, these two conditions are now recognized as heterogeneous and often overlapping conditions.[3] The term "asthma–COPD overlap syndrome" (ACOS) has been applied to the condition in which a person has clinical features of both asthma and COPD.[1,2]

Asthma is an inflammatory disease that affects the large and small airways. It typically develops in childhood and is often accompanied by allergies, although asthma develops in adulthood in a subgroup of patients.[1] Patients with asthma have bouts of breathlessness, chest tightness, coughing, and wheezing that are due to generalized airway obstruction, which is manifested as decreased flow rates over the entire vital capacity and a diminished forced expiratory volume in 1 second (FEV_1) that usually reverts completely after the attack. This airway obstruction results predominantly from smooth-muscle spasm (Fig. 1), although airway mucus and inflammatory infiltrates also contribute. Bronchial hyperresponsiveness, an enhanced bronchoconstrictor response to inhaled stimuli, is a common and core feature of asthma but is not sufficiently specific to establish a firm diagnosis.[1]

COPD is also an inflammatory airway disease, one that affects the small airways in particular.[2] In chronic bronchitis, there are inflammatory infiltrates in the airways, especially the mucus secretory apparatus, whereas in emphysema, there are clusters of inflammatory cells near areas of alveolar-tissue breakdown (Fig. 1). Chronic bronchitis and emphysema often coexist, although there are patients in whom one phenotype predominates. COPD usually becomes symptomatic with breathlessness in persons older than 40 to 45 years of age and is frequently associated with chronic cough, phlegm, wheezing, or a combination of these. Airway obstruction results from smooth-muscle contraction, airway mucus, tissue breakdown, or a combination of these, with loss of lung elastic recoil leading to airway closure. This form of airway obstruction is progressive in many patients. COPD is caused primarily by smoking, although passive smoking, air pollution, and occupational exposures can cause the condition as well.[2]

Airway inflammation in asthma differs from that in COPD. Asthma is characterized predominantly by eosinophilic inflammation and inflammation involving type 2 helper T (Th2) lymphocytes, whereas COPD is characterized predominantly by neutrophilic inflammation and inflammation involving CD8 lymphocytes.[1,2] The clinical extremes of asthma and COPD are easily recognized in differences in symptoms and in the age of the patients. Particularly in older patients, the presentation of asthma and COPD may converge clinically and mimic each other (Table 1). Irreversible airway obstruction develops over time in some patients with asthma owing to airway remodeling, with the result that these patients with asthma resemble those with COPD (Fig. 1 and Table 1). In contrast, reversible airway obstruction can occur in patients with COPD, with the result that these patients with COPD
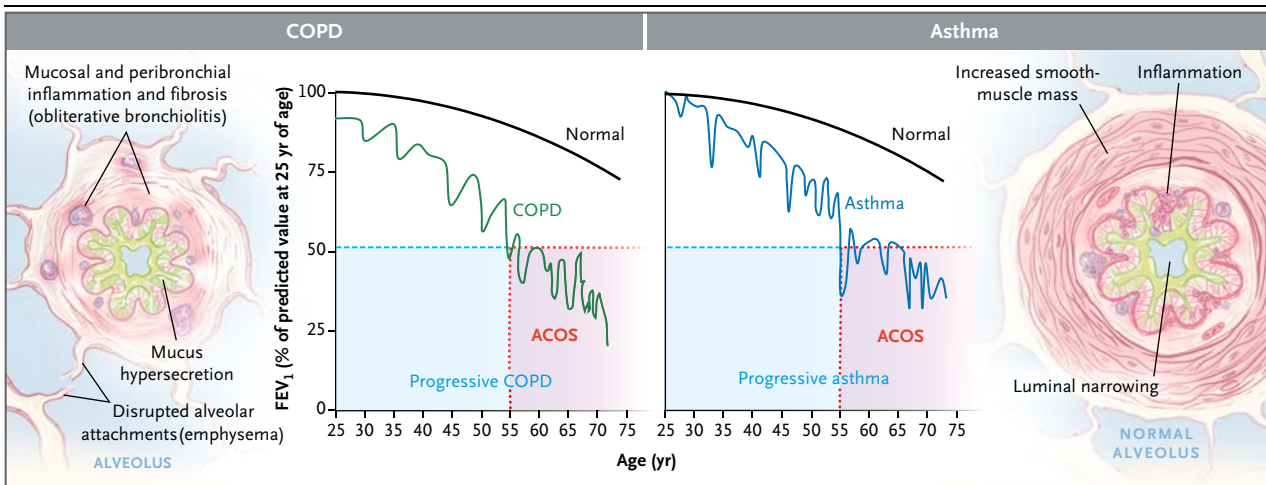
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Figure 1. Hypothetical Course of Lung Function in Chronic Obstructive Pulmonary Disease (COPD) and Asthma.

COPD is an inflammatory disease of the small airways in particular and involves chronic bronchitis and tissue breakdown (emphysema). The disease may start with a low level of lung function as early as 25 years of age, followed by an accelerated decline in forced expiratory volume in 1 second (FEV_1) as compared with the normal decline. FEV_1 may decrease to 50% of the predicted (normal) value at 60 years of age and may go as low as 25% of the predicted value. During exacerbations, FEV_1 falls; the fall and recovery are more gradual than in asthma. In asthma, airway obstruction results predominantly from smooth-muscle spasm and hypersecretion of mucus. Exacerbations may accompany an accelerated decline in FEV_1 as well, with a rapid fall and more rapid recovery than in COPD. Progression of disease may occur in a subgroup of persons with asthma, leading to an FEV_1 of 50% of the predicted value at 60 years of age. FEV_1 seldom decreases to the low levels that occur more frequently in COPD. On the basis of an FEV_1 of 55% of the predicted value at 60 years of age, one cannot differentiate asthma from COPD. ACOS denotes the asthma–COPD overlap syndrome.

Table 1. Four Examples of Patients with Obstructive Airway Disease.*

Characteristic	Patient with "Easy" Asthma	Patient with "Easy" COPD	Patient with ACOS Stemming from Asthma	Patient with ACOS Stemming from COPD
Age (yr)	21	65	45	45
Atopy	Yes	No	Yes	Yes
Current smoker	No	Yes	No	Yes
Pack-years	0	95	0	20
Dyspnea	Recurrent	Chronic	Chronic with flares	Chronic with flares
Wheezing	Yes	No	Yes	Yes
Reversible airway obstruction	Yes	No	No	Yes
Bronchial hyperresponsiveness	Yes	No	Yes	Yes or no

* "Easy" asthma and "easy" COPD are the easily recognized extremes of asthma and COPD. The two patients with the asthma–COPD overlap syndrome (ACOS) have a similar age, and both have atopy. Despite not being a smoker, the patient with ACOS stemming from asthma has irreversible airway obstruction, which is accompanied by chronic dyspnea and flare-ups of wheezing and bronchial hyperresponsiveness. The patient with ACOS stemming from COPD has some reversibility of airway obstruction after bronchodilator use, chronic dyspnea, and flare-ups of wheezing, which may or may not be accompanied by hyperresponsiveness. In the two patients with ACOS, whether the syndrome stems from asthma or from COPD cannot be easily distinguished by their phenotype.

resemble those with asthma. Recently, the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) issued a joint document (available at www.ginasthma.org/local/uploads/files/ACOS_2015.pdf or www.goldcopd.org/uploads/users/files/GOLD_ACOS_2015.pdf) that describes ACOS as a clinical entity and proposes that clinicians

should assemble the features for asthma and for COPD that best describe the patient and compare the number of features in favor of each diagnosis. In practice, if three or more features of either asthma or COPD are present, that diagnosis is suggested; if there are similar numbers of features of asthma and COPD, the diagnosis of ACOS should be considered. The relevant variables are age at onset, pattern and time course of symptoms, personal history or family history, variable or persistent airflow limitation, lung function between symptoms, and severe hyperinflation.

According to a case definition of ACOS that has been widely promulgated, the syndrome is estimated to be present in 15 to 45% of the population with obstructive airway disease, and the prevalence increases with age.[4,5] However, despite this presumed high prevalence, no double-blind, prospective studies have been conducted to provide information on how to treat these types of patients. Indeed, studies of COPD have excluded nonsmokers and patients with some bronchodilator reversibility, whereas studies of asthma have excluded smokers and patients without substantial bronchodilator reversibility. Thus, the most effective treatment of patients with ACOS remains unknown.

In this review, we address the following two questions: How does one determine in a patient whether a diagnostic label of asthma, COPD, or ACOS is appropriate? And what treatment should patients with ACOS receive? The answer to these questions cannot be evidence-based, because studies addressing ACOS as a disease entity and exploring relevant treatment strategies have yet to be conducted.

PROGRESSIVE AIRWAY OBSTRUCTION

The human lung grows steadily from birth to early adulthood; growth stops in the third decade of life. Lung growth leads to increasing lung volumes and improved lung function as measured by the FEV_1. From early adulthood, FEV_1 normally declines by approximately 25 to 50 ml annually.[6] In patients with obstructive airway disease, the decrease can be greater — up to 80 ml per year in some patients with asthma and up to 150 ml per year in some patients with COPD.[7,8] However, there is no convincing evidence that

the rate of FEV_1 decline can be used to distinguish between asthma and COPD (Fig. 1).

The global trend of increasing life expectancy shifts the median age of the population with asthma upward. This increases the probability of overlap with COPD as defined by FEV_1; the estimated prevalence of ACOS is indeed highly age-dependent.[4] The potential overlap populations with an asthma background are thus patients with long-standing asthma (with onset in either childhood or adulthood)[5] and those with severe asthma.

BRONCHIAL HYPERRESPONSIVENESS

The increased bronchoconstrictor response that signifies bronchial hyperresponsiveness[9] may be specific to allergens but can also be nonspecific, such as the response to cold and dry air or to bronchoactive agents such as histamine or methacholine. Bronchial hyperresponsiveness has long been regarded as a hallmark of asthma and is indeed very common in asthma and a risk factor for disease development (Fig. 2). It is currently not part of the definition of asthma,[1] because it does not definitively distinguish asthma from COPD.[9,10] Bronchial hyperresponsiveness is driven by multiple factors, such as reduced airway diameter, increased airway-wall thickness, increased smooth-muscle mass and smooth-muscle reactivity, increased (peri)bronchial vascularity, loss of elastic recoil, airway inflammation, epithelial injury, and increased neurogenic activity.[9] In patients with asthma, there is good evidence that the degree of bronchial hyperresponsiveness is related to underlying eosinophilic inflammation[11] and phenotypic and functional alterations of airway smooth muscle (particularly increased proliferation),[12] altered glucocorticoid response,[13] and small-airway dysfunction.[14] It is debatable whether bronchial hyperresponsiveness is associated with accelerated FEV_1 decline in patients with asthma,[15] but bronchial hyperresponsiveness has been shown to be reduced greatly after 3 months of treatment with inhaled glucocorticoids,[16] which is not convincingly the case in patients with COPD.[17,18] Notably, long-term treatment with inhaled glucocorticoids may even normalize bronchial hyperresponsiveness in patients with asthma.[16]

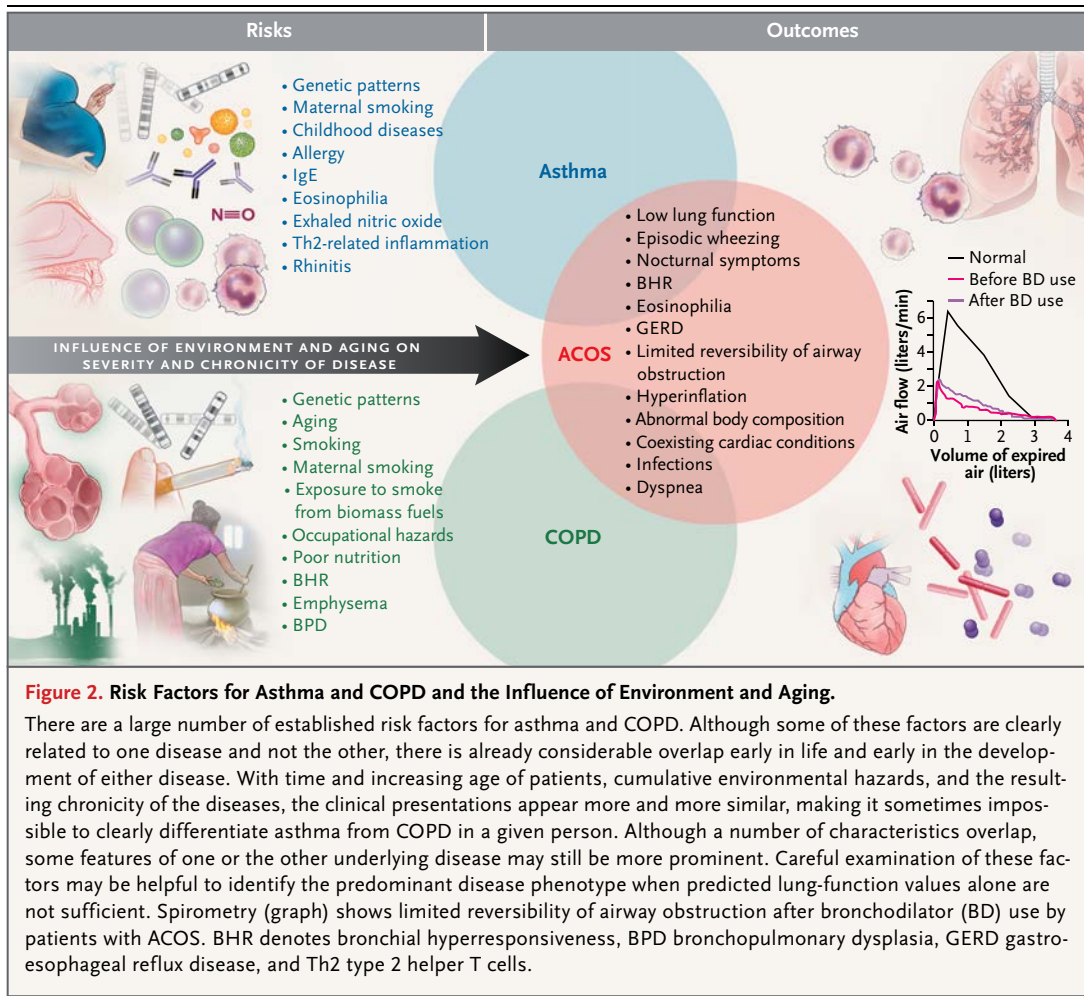Bronchial hyperresponsiveness is also a risk

Figure 2. Risk Factors for Asthma and COPD and the Influence of Environment and Aging.

There are a large number of established risk factors for asthma and COPD. Although some of these factors are clearly related to one disease and not the other, there is already considerable overlap early in life and early in the development of either disease. With time and increasing age of patients, cumulative environmental hazards, and the resulting chronicity of the diseases, the clinical presentations appear more and more similar, making it sometimes impossible to clearly differentiate asthma from COPD in a given person. Although a number of characteristics overlap, some features of one or the other underlying disease may still be more prominent. Careful examination of these factors may be helpful to identify the predominant disease phenotype when predicted lung-function values alone are not sufficient. Spirometry (graph) shows limited reversibility of airway obstruction after bronchodilator (BD) use by patients with ACOS. BHR denotes bronchial hyperresponsiveness, BPD bronchopulmonary dysplasia, GERD gastroesophageal reflux disease, and Th2 type 2 helper T cells.

factor for the development of COPD[19] (Fig. 2). The prevalence of bronchial hyperresponsiveness among patients with COPD has been reported to be 60%,[20] and it may occur even in patients with mild disease, in whom the baseline level of FEV_1 should minimally influence the measurement of bronchial hyperresponsiveness.[20] One study showed bronchial hyperresponsiveness in 90% of patients with COPD who did not have a history of asthma.[21] A recent study showed that more severe bronchial hyperresponsiveness is associated with higher residual volume (a measure of air trapping that is related to small-airway dysfunction) in COPD.[22] In addition, bronchial hyperresponsiveness is associated with airway inflammation — that is, increased levels of neutrophils, macrophages, and lymphocytes in sputum and bronchial-biopsy specimens[22] and increased levels of CD8 lymphocytes and eosinophils in periph-

eral lung tissue[23] — in patients with COPD. The association of increased eosinophil levels with bronchial hyperresponsiveness was once thought to be limited to patients with asthma.[11]

What are the clinical implications of bronchial hyperresponsiveness in COPD? Studies have shown that the decline in FEV_1 is accelerated in patients with COPD who have bronchial hyperresponsiveness,[24,25] and that the decline is even more prominent in smokers.[25] Thus, the association of bronchial hyperresponsiveness with the course of lung-function change and with response to inhaled glucocorticoids differs between COPD and asthma. Bronchial hyperresponsiveness is a risk factor for death from COPD in the general population.[26,27] Thus, bronchial hyperresponsiveness is a marker for more severe disease in both asthma and COPD, but there are not adequate data to indicate whether there is a long-term

benefit to reducing bronchial hyperresponsiveness and, if so, how to achieve this in patients with both asthma and COPD.

REVERSIBILITY OF AIRWAY OBSTRUCTION

Reversibility of airway obstruction after inhalation of a bronchodilator drug such as albuterol is a hallmark in early asthma and has long been regarded as a criterion to distinguish asthma from COPD. However, the amount of reversibility can diminish or even disappear with long-standing asthma.[1] It is well established that lung function can be normalized after inhalation of bronchodilator drugs[1] or after the use of inhaled glucocorticoids[16] in milder forms of asthma. In contrast, there may be limited reversibility in more severe asthma; thus, lack of full reversibility does not rule out an asthma diagnosis.

Reversibility of airway obstruction is frequently present in COPD as well[28-31]; in two studies, reversibility was observed in up to 44%[30] and 50%[31] of patients with COPD. Reversibility is not significantly associated with the risk of exacerbation, hospitalization, or death in patients with COPD.[29] Studies of the association between reversibility and FEV_1 decline have shown contrasting findings,[16,25] but overall, no significant association was found when baseline FEV_1 was taken into account.[27] Notably, studies have suggested that reversibility occurs in the larger airways of patients with COPD but in a more widespread fashion in patients with asthma.[32,33]

ATOPY IN ASTHMA AND COPD

Atopy is a risk factor for asthma (Fig. 2), and most people with asthma are atopic.[1] Allergic asthma generally responds to treatment with inhaled glucocorticoids. Atopy can also be present in COPD, and it is even a risk factor for COPD development.[34] Two studies have investigated cohorts of persons with COPD for the presence of atopy and have shown prevalences of 18% and 30%.[35,36] The European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP),[35] a prospective randomized, controlled trial of the long-term efficacy of inhaled glucocorticoids in mild-to-moderate COPD, showed that approximately 18% of the patients had atopy. Patients with atopy were somewhat younger, were more likely to be male, and had a higher body-mass index (BMI) than those without atopy. Male sex and high BMI were also associated with blood eosinophilia, a marker of atopy, in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, a 1-year observational study involving patients with mild-to-severe COPD.[36] In EUROSCOP, atopy was not significantly associated with the baseline severity of airway obstruction or the rate of FEV_1 decline,[35] but atopy was associated with cough and phlegm in those receiving placebo, and patients with atopy who received budesonide treatment had fewer such symptoms than did those without atopy. This observation is consistent with the results of an earlier study that suggested that patients with COPD who have atopy benefit most from glucocorticoid treatment.[37]

AIRWAY INFLAMMATION IN ASTHMA AND COPD

There is broad consensus that asthma typically has an eosinophilic and a Th2-driven cytokine pattern of inflammation,[38] whereas neutrophilic inflammation dominates in COPD. Bronchial-biopsy studies, sputum studies, and exhaled-breath studies have provided evidence of substantial heterogeneity in mucosal inflammation.[39] Patients with asthma who have severe or late-onset disease or chronic infections or who smoke may also exhibit neutrophilic inflammation[39,40] and CD8 cells in the airways,[40] both of which were once believed to be hallmarks of COPD.[2] Because the number of neutrophils in the airways increases with age,[41] this inflammatory pattern may mimic COPD in older persons with asthma. Recent data suggest that eosinophil recruitment is governed by several pathways other than the classical Th2 pathway[42] — pathways that involve type 2 innate lymphoid cells, interleukin-33, GATA-3,[43] and receptors for CRTH2. This implies that inflammatory changes and markers are probably more diverse than once thought in asthma. It is important to note that an absence of eosinophilia and the lack of a response to inhaled glucocorticoids in a patient does not rule out asthma.[16,38]

A Th2 inflammatory signature can also be present in COPD. For example, interleukin-13 (a Th2 cytokine) was expressed in more T cells

in bronchoalveolar-lavage fluid in patients with COPD than in those without COPD. In a subgroup of patients with COPD, a Th2 inflammation–related gene-expression signature was upregulated in biopsy specimens of airway walls, a finding similar to that in patients with asthma.[44] This gene-expression profile was also associated with eosinophilic inflammation in COPD. The Th2 profile was, however, not associated with an FEV_1 response to inhaled glucocorticoids,[44] as in asthma, but rather was associated with a decrease in the ratio of residual volume to total lung capacity, a marker of hyperinflation. These findings show the complexity and shortcomings of translating an asthma phenotype that is based on Th2 or eosinophilic inflammation to a pattern of response to inhaled glucocorticoids in COPD.

Eosinophils are present in 15 to 40% of patients with stable COPD — in sputum, bronchoalveolar lavage, and lung tissue — even after careful exclusion of patients with reversibility of airway obstruction, bronchial hyperresponsiveness, atopy, or a childhood history of asthma; eosinophil activation is associated with disease severity.[3] Eosinophil levels can also be increased in the sputum of patients with COPD exacerbations.[3] In the ECLIPSE study, 37.4% of the 1483 patients with COPD had persistent blood eosinophilia (eosinophil level >2%) during 3 years of follow-up.[45] As compared with patients without eosinophilia, those with eosinophilia were less likely to be current smokers, were slightly older, were more likely to be male, and had fewer symptoms, a better quality of life, a higher fat-free mass index, and higher FEV_1 values. In another study, patients with COPD who had higher blood eosinophil counts, though mostly in the normal range, maintained FEV_1 values at follow-up, whereas those with lower blood eosinophil counts had accelerated declines in postbronchodilator FEV_1.[46]

Patients with asthma or COPD who have sputum eosinophilia have a better response to inhaled glucocorticoids than those who do not have eosinophilia.[3,29] Targeted treatment with inhaled glucocorticoids to reduce eosinophil levels in patients with COPD has been shown to prevent exacerbations and hospitalizations, and glucocorticoids have been shown to be effective in treating exacerbations accompanied by eosinophilia.[29] These data suggest that eosinophilic inflammation in blood, sputum, or lung tissue signifies an endotype of COPD with more severe disease as reflected by exacerbations but less severe disease when assessed by FEV_1 decline.

EXHALED NITRIC OXIDE IN ASTHMA AND COPD

Exhaled nitric oxide (FeNO) has been described as a marker of asthmatic airway inflammation.[47] FeNO may serve to establish an asthma diagnosis, although its role in the monitoring of the disease, especially in children,[48] is still being debated. FeNO levels are lower in smokers than in nonsmokers, which makes measurements of FeNO levels less useful for differentiating asthma from COPD.[48] FeNO levels associate with sputum (and blood) eosinophilia in asthma; whether this is true in COPD is not known. Although FeNO levels in patients with asthma can decrease dramatically after treatment with inhaled glucocorticoids, some patients have persistent elevations despite treatment with high-dose oral glucocorticoids. In these cases, pathways other than the classical Th2 pathway may be operative (as discussed above).

IS ACOS RELEVANT FOR CLINICAL PRACTICE?

Even though overlaps between asthma and COPD are a clinical reality (Fig. 2), GINA and GOLD documents have not given a specific definition of ACOS and have stated that more evidence on "clinical phenotypes and underlying mechanisms" is needed.[1,2] The danger of seeing ACOS as a disease entity is that we may blur the lines between asthma and COPD, because studies addressing the patient population with ACOS specifically are lacking, which could lead to overtreatment, particularly with inhaled glucocorticoids. Another problem is that different ACOS definitions are being applied in various studies (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), thus precluding firm conclusions regarding clinical severity, management, and prognosis for ACOS. Inconsistent definitions used in treatment studies make it almost impossible to determine the most effective therapy for an individual patient. Therefore, we suggest extensive phenotypic characterization of individual patients before inclusion in clinical trials.

CURRENT TREATMENT OF ASTHMA AND COPD

GINA and GOLD provide well-defined treatment and management plans for clear cases of asthma and COPD, respectively.[1,2] For example, for the patient with "easy" asthma (Table 1), a stepwise approach is recommended on the basis of disease severity, with the clinical aim of disease control and future risk reduction. The main pillars of treatment are inhaled glucocorticoids in combination with bronchodilator drugs, in particular short-acting beta-agonists and long-acting beta-agonists (LABAs). Leukotriene-receptor antagonists are an alternative choice in milder disease.[1] For severe allergic asthma with appropriate IgE levels, anti-IgE treatment is an approved option; long-acting muscarinic antagonists (LAMAs) have been shown to work in controlled trials and are now included in the treatment of severe asthma[1] but are not approved by the Food and Drug Administration for this use.

For the patient with "easy" COPD (Table 1), a stepwise treatment approach is also recommended, with a focus on reduction of symptoms and exacerbations and acknowledgment of the role of coexisting conditions. The main emphasis is on smoking cessation and the use of LABAs and LAMAs. The role of inhaled glucocorticoids has been debated for years and is limited to patients with more severe disease and those with frequent exacerbations.[2]

PATIENTS WITH ASTHMA AND SIGNS OF CONCOMITANT COPD

Given the lack of randomized intervention studies of ACOS, it is difficult to provide firm treatment guidance for patients with the syndrome (Table 1). We believe that treatment with inhaled glucocorticoids should be continued in patients with long-standing asthma even if a component of irreversible airway obstruction develops; leukotriene modifiers may be of value in those with atopy. Combination therapy with a LAMA and a LABA is a well-established treatment and is a reasonable approach for patients with more severe asthma or COPD or with overlapping conditions. However, given the ongoing debate on the safety of LABAs in people with asthma, any suspicion of an asthmatic component in a given person should definitely prompt the use of inhaled glucocorticoids.

PATIENTS WITH COPD AND SIGNS OF CONCOMITANT ASTHMA

Traditionally, COPD is characterized by a relevant smoking history, persistent and progressive airway obstruction, lack of reversibility of airway obstruction, and neutrophil infiltration in the airways. As noted above, we now appreciate that reversibility, eosinophilia, and bronchial hyperresponsiveness may be present in patients with COPD. We think that patients who have any of these asthmalike features might benefit from inhaled glucocorticoids. This approach should be evaluated in large clinical-effectiveness studies with extensive phenotyping at baseline. Notably, such studies need to expand on alternative outcome measures, because patients with COPD and concomitant signs of asthma may not have easily measured changes in FEV_1 in response to treatment and over a short period of time.[44]

CONCLUSIONS

The current debate on ACOS is not new. In 1961, a "Dutch hypothesis," presented by Orie and colleagues,[49] acknowledged the frequent problems in differentiating between asthma and COPD. The clinicians and researchers who developed this hypothesis may have been far ahead of their time: they suggested that asthma and COPD may differ in their extremes but that in adults, the clinical expression depends on age, sex, and environmental factors (Fig. 2). They proposed not labeling a disease on the basis of the clinical impression but rather defining it on the basis of agreed-upon and measured criteria. This was undoubtedly a forerunner of current phenotyping approaches and is in line with what we propose today.

On the basis of information presented in the current review, we believe that it is premature to recommend the designation of ACOS as a disease entity in primary and specialist care. More research is needed to better characterize patients and to obtain a standardized definition of ACOS that is based on markers that best predict treatment response in individual patients We suggest that health professionals keep clear records with objective measures on every patient, including symptoms, exacerbations, lung function, and response to treatments. We hope that these observational data, along with data from yet-to-be-performed clinical trials, will guide our hand in

treating patients with a suspected overlap between asthma and COPD.

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