

The chronic obstructive pulmonary disease–asthma overlap syndrome

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ABSTRACT

When asthma and chronic obstructive pulmonary disease (COPD) occur together the term COPD–asthma overlap syndrome has been applied. To date, there is no universally accepted definition of this overlap syndrome, just as there is no blood test or other technologic assessment that provides a simple way to distinguish asthma from COPD. One practical approach to the overlap diagnosis has been to include patients with a diagnosis of COPD by Global Initiative for Chronic Obstructive Lung Disease criteria and asthma defined by subject report of a physician diagnosis of asthma before the age of 40 years. Alternatively, it includes patients who meet criteria for COPD (fixed airflow obstruction) and who also have typical features of asthma (wheezing, atopy, eosinophilia, and positive bronchodilator response on spirometry). Compared with patients with COPD alone, the overlap patients are younger with less smoking intensity, have higher health-care utilization, have a worse disease-related quality of life, and have a higher mortality. Treatment with corticosteroids earlier in the course of the disease compared with the patient with only COPD has been recommended.

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Asthma and chronic obstructive pulmonary disease (COPD) are both inflammatory diseases of the airways. The clinical expression of these two conditions is usually quite distinct. The former more often affects children and younger adults and is frequently associated with atopy and “eosinophilic bronchitis.” The latter, a disease of “neutrophilic bronchitis,” usually affects adults >50 years of age, and unlike asthma that is associated with aeroallergen exposure, COPD is caused mostly by cigarette smoke and combustion products of biomass fuels. However, in recent years it has been increasingly recognized that these stereotypes do not encompass all patients with COPD and asthma and that at times the phenotypic expression of some patients makes it difficult to make a correct diagnosis. In fact, the American Thoracic Society/European Respiratory Society guidelines for the diagnosis and treatment of COPD state, “Some patients with asthma cannot be distinguished from COPD using the current diagnostic tests.”¹ To compound this diagnostic dilemma, many asthmatic patients smoke cigarettes and when they present with symptoms they likely have features of both conditions. These patients are thought to experience an overlap syndrome of asthma and COPD.

To date, there is no blood test or other technologic assessment that provides simple criteria for the diag-

nosis of asthma versus COPD. There is a growing consensus that neither asthma nor COPD are a single disease at all, but rather a composite of multiple separate, but overlapping, syndromes with varying phenotypic expressions.^{2–5} This article will explore the similarities and differences of asthma and COPD and how they might help distinguish the subgroup of patients with the overlap syndrome of asthma combined with COPD.

ARE ASTHMA AND COPD THE SAME DISEASE?

This question at first glance seems to have a simple answer: No. However, there are so many similarities in the clinical and physiological expressions of these two conditions, many feel that this is an unanswered question. In 1961, Orie,⁶ in discussing the interrelationships of obstructive lung diseases, first proposed that asthma and COPD had a common genetic origin and that COPD is a clinical expression of asthma. He suggested that asthma and bronchial hyperreactivity predispose patients to develop COPD later in life and, ultimately, these features determine the clinical expression of lung disease depending on host (genetics; *e.g.*, atopy) and environmental (smoking, allergen exposure, and pollution) influences. Although this theory, called the “Dutch Hypothesis,”⁶ has not been ruled out, the presence or severity of bronchial hyperreactivity has not been definitely linked to the pathogenesis of COPD. Although there is some evidence that COPD outcomes such as the accelerated decline of lung function and mortality are associated with bronchial hyperresponsiveness, this is still a matter of debate.

Asthma and COPD are diseases of the airways that are caused by widespread inflammation resulting from

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a complex interaction of cells, mediators, and cytokines.^{1,7} Many of the clinical and physiological features overlap, making a correct diagnosis, at times, difficult. The typical symptoms of asthma including wheezing, dyspnea, and attacks of shortness of breath with wheeze, occur frequently in COPD patients, including those with emphysema.⁸ An acute change in symptoms caused by sudden bronchoconstriction, typical of asthma, is also seen with COPD. In both conditions, environmental irritants, allergens, and respiratory viruses can cause this sudden change. As a result of these similarities, a substantial number of patients are likely to be diagnosed with both asthma and COPD at some point in their history of respiratory illness⁸ and, especially, after age 50 years.⁹ For example, asthma is the most common respiratory diagnosis in patients with α -1-antitrypsin deficiency before the diagnosis of hereditary emphysema.¹⁰

There are three cardinal physiological features of asthma: diffuse airflow obstruction in both large and small airways, reversibility of the airflow obstruction, and bronchial hyperresponsiveness.⁷ These have also been described in patients with COPD. Airflow obstruction is determined by decreases in the forced expiratory volume at 1 second (FEV₁) and FEV₁/forced vital capacity (FVC) ratio. The reduced FEV₁ in asthma patients is typically reversible ($\geq 12\%$ and a 200-mL increase in FEV₁ from baseline) after an inhaled bronchodilator.¹¹ In most asthmatic patients, complete bronchodilator reversibility to normal values can be shown at some point in the course of their illness. This can provide a key differentiation because COPD, by definition, is never completely reversible.

Although the improvement in FEV₁ after bronchodilator use is, on average, greater in asthma patients than in COPD patients (16% versus 11%, respectively), the diagnostic usefulness of spirometry has not proven useful in practice.¹² The acute responses of FEV₁ and FVC after a standard dose of inhaled bronchodilator are neither sufficiently sensitive nor sufficiently specific to differentiate asthma from COPD. Using a threshold bronchodilator FEV₁ change of 15%, Kestin *et al.*¹² showed a 44% sensitivity for detecting asthma and a 72% specificity in distinguishing asthma from COPD. A surprisingly large percent of COPD patients have a brisk bronchodilator response. In the Understanding Potential Long-term Impacts on Function with Tiotropium trial, relatively large doses of a short-acting anticholinergic and β -agonist inhaler (80 mcg of ipratropium and 440 mcg of albuterol) caused a 12% and >200 -mL improvement in FEV₁ in 53.9% of the COPD study patients.¹³

The third cardinal feature of asthma is bronchial hyperresponsiveness. This can be shown with bronchoprovocation testing after the inhalation of agonists such as methacholine.^{14,15} It is a useful test in confirm-

ing the diagnosis of asthma when the clinical suspicion of asthma is high and, more importantly, in ruling out asthma when the test is negative (no bronchial hyperresponsiveness). However, bronchial hyperresponsiveness is a major, but not necessarily a unique, feature of asthma and it has not proven useful in distinguishing asthma from COPD. In the U.S. Lung Health study, a clinical trial of early intervention in COPD, over 5700 smokers with spirometric evidence of airflow obstruction underwent methacholine challenges. A positive methacholine challenge was found in 68% of patients with COPD (85% of women and 59% of men). High levels of bronchial hyperresponsiveness were associated with lower pulmonary function and also with greater rates of decline in lung function over time in continuing smokers.¹⁶

There are also characteristic pathological features described for both asthma and COPD. The discriminatory power of these features has been systematically tested on endobronchial biopsy specimens. Three pathologists, in a double-blind manner, showed discordance in the interpretation of the biopsy material, resulting in a disappointing sensitivity and specificity.¹⁷ The characteristic features were not sufficiently discriminatory. Persistent inflammation in the airways of asthmatic patients and those with chronic bronchitis and COPD can result in hypertrophy of smooth muscle, microvascular leakage, stimulation of mucus-secreting cells, disruption of the ciliated epithelium, and collagen deposition. Although the presence of eosinophils biased the pathological diagnoses in favor of asthma, the estimated prevalences of eosinophils in asthma biopsy (11–37%) and COPD biopsy (13–41%) specimens were similar. Features such as metaplasia and epithelial inflammation tended to be more specific to COPD whereas epithelial desquamation and basement membrane thickening were more associated with asthma, although these changes can be seen in both conditions.

Despite these overlapping features and the frequent confusion in diagnosis, the clinical and pathophysiological extremes of COPD and asthma can be easily separated into distinct categories of disease (Table 1). These extremes argue for a “no” answer to the question: Are asthma and COPD the same disease? There is also little evidence that asthma and COPD share similar genetic factors. To date, large genomewide association studies have failed to identify common genetic loci related to asthma and COPD.¹⁸ Clinically, the extremes are distinct. Asthma is a disease usually beginning in childhood or young adulthood,¹⁹ often associated with atopy, and marked by periods of remission and acute exacerbations.⁷ COPD is a disease presenting in later years,²⁰ usually after the age of 50 years and is marked by a slow progressive decline in lung function, exercise tolerance, and quality of life.¹ Unlike most asthmatic patients, COPD patients have persistent

Table 1 Clinical and pathophysiologic features that help distinguish asthma and COPD

Asthma	COPD
Symptoms begin in childhood or <35 yr of age	Symptoms begin later adulthood (>50 yr)
Positive family history of asthma	Active smoker (>20 pack-yr)
History of allergic rhinitis and eczema	Radiographic evidence of emphysema
Postbronchodilator lung function returns to normal	Postbronchodilator lung function never becomes normal
Normal or high diffusing capacity	Low diffusing capacity
Prolonged periods of remission	Slow progressive decline in lung function over years
Elevated blood or sputum eosinophil level	Sputum neutrophils present; alveolar macrophages increased
Higher CD4 ⁺ /CD8 ⁺ ratio of T cells	Higher CD8 ⁺ /CD4 ⁺ ratio of T cells
Greater density of CD45 ⁺ lymphocytes in the outer adventitial region	CD45 ⁺ lymphocytes higher in inner adventitial region
Selected mediators: IL-4, IL-5, IL 9, IL-13, TNF- α , and GM-CSF	Selected mediators: IL-8, LTB ₄ , serine proteases, MMP-9, TNF- α , and TGF- β -1
COPD = chronic obstructive pulmonary disease; GM-CSF = granulocyte macrophage colony-stimulating factor; LTB ₄ = leukotriene B ₄ ; MMP = matrix metalloproteinase; TGF = transforming growth factor.	

shortness of breath on exertion and a progressive decline in their functional status. Noxious particles or gases cause the inflammatory response of the lungs of COPD patients, and in the developed world this is mainly caused by cigarette smoking. In many underdeveloped countries, the noxious particles and gases come from burning fossil fuels indoors.^{21–23}

Physiologically, asthma can be distinguished by reversibility of airflow obstruction to normal levels immediately after an inhaled bronchodilator or after a more prolonged course of treatment. COPD patients never show complete reversibility with treatment and this is incorporated into the definition. If significant emphysema is present, the surface for lung diffusion is reduced and the single breath diffusing capacity may be significantly decreased. This does not occur with asthma. If emphysema is present, the chest radiograph may show evidence of emphysema and the computed tomography (CT) scan can further define the features of panacinar and centrilobular emphysema. These changes are not seen with asthma. In clinically stable patients with chronic persistent asthma, Gelb and Zamel²⁴ have shown a significant loss of lung elastic recoil, a feature associated with COPD. This unexpected finding presumably reflects unexplained physiological lung parenchymal abnormalities that can not be accounted for by emphysema or loss of alveolar-capillary surface area because their patients showed normal high-resolution, thin-section CT lung scans and normal diffusing capacities. The authors speculated that tissue forces or stress relaxation associated with chronic bronchoconstriction and hyperinflation could be causative.

PROGRESSIVE IRREVERSIBLE AIRFLOW OBSTRUCTION WITH ASTHMA: IS THAT COPD?

Airflow obstruction that returns to normal lung function after a short-acting bronchodilator is seen in most asthmatic patients, and especially those at a younger age. However, longitudinal studies of adult asthmatic patients and some younger asthmatic patients suggest the rate of decline in lung function over time in patients with asthma is greater than that in the nonasthmatic population.^{25–28} In patients with long-standing asthma and asthma that is acquired at an advanced age, normalization of lung function may not be present, even after maximum treatment. In these asthmatic patients, spirometry may show a fixed or “irreversible” obstruction to airflow.^{29–32} This phenomenon has been referred to as “remodeling of the airways.”³³ This phenotype of asthma is mainly seen in those with long-standing asthma, atopic asthma, and those with more severe persistent asthma. It is thought that structural changes including thickening of the epithelial cell layer with goblet cell hyperplasia and mucus gland enlargement, subepithelial fibrosis, an increase in the mass of airway smooth muscle, and angiogenesis cause this apparent “irreversible” airflow obstruction. It has been suggested that the persistent airway inflammation seen in these asthmatic patients can lead to these pathological alterations of airway structure.

Data obtained from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study, a large-scale observational study of patients with severe or difficult-to-treat asthma, 60% had

evidence of persistent, “fixed” airflow limitation.³⁴ In a report of 300 elderly asthmatic patients >65 years of age, ~20% of these patients had FEV₁ values of <50% predicted, and ~80% had values <80% predicted.³¹ Although those studies included some smokers or former smokers, other studies on nonsmoking adults have shown that fixed airflow obstruction is common in older asthmatic patients, especially those with longstanding disease.^{30,35} Fixed airflow obstruction has been identified in very young asthmatic patients also. In patients who have asthma onset before 25 years of age and persistent airflow limitation in adult life, the bulk of the FEV₁ deficit is already established before the age 25 years.³⁶ In a study by Vonk *et al.*³⁷ of 228 asthmatic patients aged 13–44 years, studied after a mean of 28 years, 16% of the group showed persistent airflow obstruction and absence of reversibility after this time period. Fifty percent of these patients had some history of smoking and asthma and cigarette smoking to cause an accelerated decline in lung function. However, other longitudinal studies such as those by Ulrick *et al.*³⁸ showed that 23% of lifelong nonsmokers with asthma (mean age, 37 years; range, 18–64 years; duration of asthma, 16 years; range, 2–60 years) showed irreversible airflow obstruction at a 10-year follow-up.

Do asthmatic patients with “fixed” airflow obstruction have COPD? Physician-diagnosed COPD is common in the asthmatic population. Using data from an asthma call-back phone survey of >70,000 U.S. asthmatic patients, Mirabelli *et al.* found that physician-diagnosed COPD was made in 29% of the entire asthmatic population.³⁹ There was a higher prevalence of COPD in those with active asthma (34.6%) and especially as current smokers (53%). However, 23% of lifetime nonsmokers with active asthma also reported that they had physician-diagnosed COPD. COPD was also reported as a diagnosis in those with inactive asthma (14.7%) and age was an important factor in a COPD diagnosis. The majority of patients with active asthma >75 years of age (58.2%) had a diagnosis of COPD whereas 20.4% of patients with active asthma between the ages of 18 and 35 years reported a diagnosis of COPD. What is clear from this national survey is that many physicians, likely using subjective criteria, call asthma “COPD” even when it is unlikely that the patient has this diagnosis, in *e.g.*, the 18–35-year-old population and with the nonsmokers (Table 2). To compound the problem, there are estimates that ~10–12% of patients with COPD have never smoked⁴⁰ and longitudinal studies have suggested that asthma may develop into COPD.⁴¹ The diagnosis of COPD, however, in this latter study, like the national survey, was established by a physician diagnosis and abnormal pulmonary function studies⁴¹ that could be the result of asthmatic airway remodeling and not COPD. In

cross-sectional studies of smokers and nonsmokers with COPD using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of COPD,⁴² features suggesting a diagnosis of asthma were almost universal among the nonsmokers. This was supported by a higher prevalence of atopy and eosinophilic inflammation in the nonsmokers. Fabri *et al.*⁴³ studied a group of older adults >50 years of age with fixed airflow obstruction and a history of either asthma or COPD to determine whether there were distinct pathological and functional characteristics for each group. Despite similar degrees of fixed airflow obstruction and airway hyperresponsiveness, these older subjects with asthma had distinct characteristics compared with subjects with a history of COPD. Asthmatic patients had significantly more eosinophils in peripheral blood, sputum, bronchoalveolar lavage, and airway mucosa; fewer neutrophils in sputum and bronchoalveolar lavage fluid; a higher CD4⁺/CD8⁺ ratio of T cells infiltrating the airway mucosa; and a thicker reticular layer of the epithelial basement membrane. They also had significantly lower residual volume, higher diffusing capacity, higher exhaled nitric oxide, lower high-resolution CT scan emphysema score, and greater reversibility to bronchodilator and steroids. It appears, therefore, that patients with COPD and those with asthma and “fixed” airflow obstruction due to remodeling represent two distinct groups and it remains a matter of definition as to whether the latter group is considered a phenotype of COPD. Because current definitions of COPD include causation linked to an abnormal inflammatory response of the lung to noxious particles or gases, asthmatic patients with fixed airway disease that do not have these exposures should not be classified as having COPD.

THE COPD–ASTHMA OVERLAP SYNDROME

Asthma and COPD are both common diseases according to 2012 statistics: the percentage of children with asthma is 9.3% and for adults is 8%⁴⁴; the prevalence of COPD varies considerably by state, from <4% in Washington and Minnesota to >9% in Alabama and Kentucky.⁴⁵ Therefore, the likelihood of acquiring both conditions together is substantial. However, establishing the exact prevalence of these two conditions together has been difficult. This is because there is no universally accepted definition of the COPD–asthma overlap syndrome. In various patient groups that met COPD criteria it has been defined by various additional criteria: asthma symptoms worsening at night or in the early morning,⁴⁶ a history of wheezing and bronchodilator reversibility,⁴⁷ the presence of partial reversibility and reduced diffusing capacity,⁴⁸ and a series of major and minor criteria including a very positive bronchodilator test (increase in FEV₁ ≥ 15%

Table 2 Criteria used to define overlap syndrome of asthma and COPD

Authors	Source	Criteria
Soler-Cataluna <i>et al.</i> ⁴⁹	Nationwide consensus of COPD experts, Spain	Positive bronchodilator response, eosinophilia in sputum, personal history of asthma before age 40 yr, high total IgE level, and a personal history of atopy; COPD criteria not listed
Hardin <i>et al.</i> ⁵¹	COPDGene® study group, United States	Greater than 10 pack-yr smoking; GOLD criteria for COPD; asthma before the age of 40 yr
Menezes <i>et al.</i> ⁴⁷	Platino Team, South America	GOLD criteria for COPD; wheezing in the last 12 mo; postbronchodilator increase in FEV ₁ or FVC of 200 mL and 12%
Kitaguchi <i>et al.</i> ⁶³	Research cohort, Japan	GOLD criteria for COPD; asthma symptoms such as episodic breathlessness, wheezing, cough, and chest tightness worsening at night or in the early morning
Iwamoto <i>et al.</i> ⁶²	Research cohort, Finland	ATS/ERS criteria for COPD; clinical history of asthma; plus either a postbronchodilator increase in FEV ₁ of >12%, diurnal variation of >20% in peak expiratory flow, moderate-to-severe bronchial hyperreactivity, or a decrease in FEV ₁ of >15% postexercise
Gibson and Simpson ⁶⁶	Review, Australia	COPD: incompletely reversible airflow obstruction and asthma: episodic respiratory symptoms; variable airflow obstruction occurring spontaneously or with treatment (FEV ₁ increases >200 mL and >12% baseline or after provocation (such as methacholine challenge)

COPD = chronic obstructive pulmonary disease; ATS/ERS = American Thoracic Society/European Respiratory Society; FEV₁—forced expiratory volume at 1 s; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

and ≥ 400 mL), eosinophilia in sputum, personal history of asthma, total IgE, and a personal history of atopy.⁴⁹ Others have preferred the following major criteria: a physician diagnosis of asthma and COPD in the same patient; history or evidence of atopy, *e.g.*, hay fever; elevated total IgE, age ≥ 40 years; smoking >10 pack-years; postbronchodilator FEV₁ < 80% predicted; and FEV₁/FVC < 70%. Minor criteria included a $\geq 15\%$ increase in FEV₁ or $\geq 12\%$ and a ≥ 200 -mL increase in postbronchodilator treatment with albuterol.⁵⁰

A simplified but practical approach to this definition “quandary” has been taken by the COPDGene investigators.^{51,52} The overlap syndrome is defined in patients with a diagnosis of COPD by Global Initiative for Chronic Obstructive Lung Disease criteria⁴² and asthma is defined by subject report of a physician diagnosis of asthma before the age of 40 years. This definition avoids mislabeling COPD as asthma because COPD would not likely be seen before age 40 years.

One exception is in those with hereditary emphysema and a smoking history. Such patients are often mislabeled with a diagnosis of asthma and a blood test for an α -1-antitrypsin level can lead to the correct diagnosis. This definition, however, would eliminate the late-onset asthmatic patients who also has developed COPD. It is likely that the COPDGene definition would include a phenotype of COPD patients with increased reversibility and eosinophils found in the sputum and/or smoking asthmatic patients with fixed airflow obstruction, the later often having elevated neutrophils in their airways, similar to COPD.⁵³ Patients with COPD who show more bronchodilator reversibility have higher numbers of sputum eosinophils and concentrations of exhaled nitric oxide and greater responsiveness to inhaled corticosteroids, suggesting that they have asthma, have the overlap syndrome.^{54–56} Similarly, asthmatic patients with a smoking history who have fixed airflow obstruction, exhibit higher

numbers of neutrophils in bronchoalveolar lavage fluid and biopsies, have the COPD–asthma overlap syndrome.^{57,58}

Despite the lack of a universal definition, worldwide clinical attention has been directed to the COPD–asthma overlap syndrome^{47–53,59} and, recently, novel genetic variants associated with the syndrome have been described.⁵³ CT scans have shown less emphysema and greater airway wall thickness.⁵² Compared with patients with COPD alone,⁵¹ the overlap patients have been described as a bit younger and with less smoking intensity and a worse disease-related quality of life. They are more likely to have more severe and more frequent COPD exacerbations and have a higher mortality.⁶⁰ A study of Medicaid utilization outcomes showed that patients with asthma and COPD cost five times more for total medical services than asthma alone and three times more for COPD alone.⁶¹ Because of the need to improve outcomes for this distinctive phenotype, there have been recent attempts to improve diagnostic accuracy with biomarker detection. One study by Iwamoto *et al.*,⁶² showed that increased induced sputum levels of neutrophil gelatinase–associated lipocalin might be a characteristic feature of overlap. The authors suggested that enhanced neutrophilic airway inflammation and/or airway epithelial injury occurs distinctively in the COPD–asthma overlap compared with those with asthma or COPD alone.

In view of these recent findings regarding the COPD–asthma overlap syndrome, greater physician attention to this phenotype of airway disease is needed. Because studies have shown improvement in lung function with inhaled corticosteroids in patients the overlap syndrome compared with COPD,^{63,64} some national guidelines are recommending this treatment earlier in the disease.⁶⁵ Because these patients have been previously excluded from both COPD and asthma pharmacologic clinical trials, further studies of this unique group of patients are needed to identify optimal treatment strategies.

SUMMARY

Asthma and COPD are two distinct inflammatory diseases affecting the respiratory system. When they are combined, the term COPD–asthma overlap syndrome applies. Although there is no established definition of the syndrome, such patients show features of the asthma phenotype, have substantial exposure to cigarette smoke or other noxious particles or gases, and show fixed airflow obstruction. It can be identified in COPD patients who show features of asthma: eosinophilia in the blood and sputum, significant reversibility to a bronchodilator, and improvement of lung function with inhaled corticosteroids. Identification of this phe-

notype is important because such patients are more likely to have more severe COPD exacerbations and a higher mortality. Because these patients have been excluded from previous pharmacologic studies, further research is needed to identify the ideal therapeutic approach.

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