

Is It Asthma, COPD, or Something In Between, and Does it Matter?

Asthma and COPD are the most common obstructive pulmonary diseases of adults. Although differences exist in the genetics, pathogenesis, histopathology, cellular characteristics, and clinical features of these 2 diseases, both disorders are heterogeneous and share a number of features that may be more or less characteristic of one than the other. Because of these overlapping features, as many as 25–50% of older adults have been diagnosed with both of these obstructive disorders.¹ Using data from the National Health and Nutrition Epidemiologic Survey III (NHANES III), Soriano et al reported that 30.2% of survey participants with a self-reported physician's diagnosis of chronic bronchitis and/or emphysema had also been informed by their physician that they had asthma as well.²

This degree of overlap reflects the frequent difficulty in clinically distinguishing between the 2 diseases. Since no one clinical feature is absolutely discriminatory, and since no validated biomarker has yet been identified that allows one definitively to differentiate asthma from COPD, the diagnosis is dependent on a consideration of several features that may be more characteristic of one than the other disorder. A couple of exceptions include the fact that a defining feature of COPD is “not fully reversible air-flow obstruction,”³ so that fully reversible air-flow obstruction (namely, a ratio of FEV₁ to FVC < 70% or less than the lower limit of normal that improves into the normal range in response to a bronchodilator) points to asthma and not COPD, although asthma itself is sometimes not fully reversible. Another exception is very young age, since asthma is usually diagnosed in childhood, whereas COPD is rarely diagnosed under the age of 30 years, with the possible exception of emphysema due to alpha-1 antitrypsin deficiency. On the other hand, asthma may present for the first time in older age, and not infrequently recurs in adulthood after having apparently gone into remission earlier in life.

Several other clinical features may help clinicians distinguish between the 2 diseases, although considerable overlap exists. The vast majority of patients with COPD are current or former smokers, but some COPD patients have never smoked,³ while some asthmatics have a smoking history. Patients with asthma often have a family history of asthma, although familial clustering may also be present with COPD, reflecting the importance of genetic factors in both diseases. While the vast majority of asthma has an allergic basis,⁴ some COPD patients also have atopy, a condition that is not uncommon in the general population.

Chronic productive cough is common in COPD, whereas in asthma cough is usually episodic rather than chronic, although chronic cough is more likely to be present in asthmatics who smoke, a condition that has been referred to as “asthmatic bronchitis.” Shortness of breath with exertion is the cardinal symptom of COPD, whereas breathlessness is more variable and episodic in asthma. Night-time awakenings with dyspnea and/or wheezing are more common in asthma than in COPD, although the latter may also be associated with sleep disturbances. Symptoms of asthma are highly variable in frequency both within and between days, whereas symptoms of COPD are more chronic and persistent; however, the clinical course of COPD is generally punctuated by one or more episodes per year of increased symptoms that are classified as exacerbations.⁵

COPD is defined as a progressive disease characterized by an excessive rate of decline in lung function with age.^{3,6} However, the annual rate of decline in lung function in adult asthma has also been shown to exceed that in healthy individuals, even after smoking history is taken into account,⁷ although the annual rate of loss is generally less in asthma than in COPD. Most but not all asthmatics respond well to inhaled corticosteroids, with the major exceptions of patients with severe asthma⁸ and asthmatics who smoke, while COPD is generally associated with a comparatively poor response to inhaled corticosteroids, presumably related to oxidative stress.⁹ The nature of the underlying inflammation differs between asthma and COPD, the former being dominated by T-helper type-2 lymphocytes, eosinophils, and mast cells; and the latter by activated alveolar macrophages, neutrophils, and cytotoxic T lymphocytes. On the other hand, in patients with severe asthma, neutrophils may dominate,⁸ and, conversely, during an exacerbation, patients with COPD may show elevated eosinophils, as well as neutrophils, in their sputum.¹⁰

The feature on which many clinicians mostly rely to distinguish asthma from COPD or, at least, to determine whether COPD is associated with an “asthmatic” component, is the response to a bronchodilator, which is characteristically greater in asthma than COPD. However, as pointed out by Kesten and Rebuck¹¹ and discussed further below, the response to a bronchodilator is neither a sensitive nor specific distinguishing feature. Similarly, while nonspecific airway hyper-responsiveness is a hallmark of asthma, a large percentage of patients with COPD also

demonstrate hyper-responsiveness to methacholine in the asthma range.¹² Interestingly, while the hyper-responsiveness in asthma is independent of the baseline level of air-flow obstruction,¹³ the hyper-responsiveness in COPD is directly proportional to the pre-methacholine degree of obstruction,¹² suggesting differing mechanisms underlying this phenomenon in the 2 diseases.

It is not generally appreciated that most patients with established COPD respond substantially to a bronchodilator, so bronchodilator responsiveness is not a reliable distinguishing characteristic. The response in asthma follows an inverted U-shaped curve, such that those with normal or minimal air-flow obstruction, who have relatively little room for improvement, show little response, those with mild to moderate obstruction show the greatest response, and those with severe obstruction show less response, presumably because obstruction in the latter is more related to airway wall thickness and variable occlusion of the lumen with mucus than to reversible bronchospasm.¹⁴ Indeed, in NHANES III, 30% of patients with a physician diagnosis of asthma did not have a positive response to an inhaled bronchodilator.¹⁵ Similarly, in COPD, those with only mild air-flow obstruction, as demonstrated in the Lung Health Study, show relatively little response to a bronchodilator,¹⁶ while those with moderate obstruction show the greatest response, and those with severe to very severe obstruction show diminishing responses in terms of FEV₁.¹⁷ Among nearly 6,000 patients with moderate to very severe COPD participating in a clinical trial, 65% fulfilled American Thoracic Society/European Respiratory Society criteria for a substantial response to a bronchodilator,¹⁷ although the response varies from one day to another.^{18,19} Interestingly, COPD subjects tend to show a greater volume (FVC) than flow (FEV₁) response to a bronchodilator,²⁰ while the reverse is true in asthma. Moreover, in COPD, the volume response to a bronchodilator, unlike the flow response, does not diminish as the severity of air-flow obstruction increases.^{17,21}

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The study by Kim et al in this issue of *RESPIRATORY CARE*²² describes the clinical features of a relatively small proportion of patients (~5%) out of those with diagnosed asthma or COPD who were given a diagnosis of overlapping COPD and asthma (“intermediate type”) by Korean specialists (pulmonologists and allergists). Not unexpectedly, compared to the patients with asthma, those with COPD were older, had a lower body mass index, were more often heavy, long-term smokers, had more severe air-flow obstruction, and made more frequent visits to the emergency department, while those given the diagnosis of the “intermediate type” generally had features in-between

the patients with asthma or COPD alone. Interestingly, the proportion of patients responding positively to a bronchodilator and the percent increase in FEV₁ in response to a bronchodilator were higher in COPD than in asthma, the response to a bronchodilator being in-between in the intermediate type. However, since a positive response to a bronchodilator was framed in terms of the percentage improvement in FEV₁ over baseline (a positive response being defined as $\geq 15\%$ without taking the absolute improvement in FEV₁ into account), these results were biased toward showing a greater response in those with more severe air-flow obstruction (namely, those more likely to have COPD or the intermediate type than asthma), due to the influence of the lower denominator on this percentage.

The diagnosis of the “intermediate type” between asthma and COPD by the specialists caring for the patients included in the study of Kim et al was most likely based on a synthesis by these clinicians of various demographic, clinical, and physiological features, as well as the preconceptions of these physicians regarding which of these features might be more characteristic of one or the other disorder, the “intermediate type” being diagnosed in those with the most overlapping characteristics. Querying the individual specialists regarding which factors led them to arrive at one or the other of these diagnoses would have provided a deeper insight into the differential diagnostic process in the “real world.” Moreover, since the authors confined their study to patients seen by allergists or pulmonologists, while a large proportion of patients with asthma and COPD are seen by non-specialists, it is not clear how generalizable their findings are to the primary care setting.

In summary, COPD and asthma coexist to a varying degree for reasons that, while not entirely clear, might include:

- To some extent, they could share a common pathogenetic basis.
- Asthma has been shown in prospective population-based studies to be a risk factor for the subsequent development of COPD.²³
- A variable proportion of patients with persistent asthma develop a fixed component of air-flow obstruction due to airway wall remodeling,²⁴ thus fulfilling part of the definition of COPD as a “not fully reversible” obstructive disorder.
- Asthma and COPD are both relatively common disorders that could overlap by chance.

Since both conditions have overlapping features and no validated biomarker exists that can lead to a definitive diagnosis, physicians must rely on an assessment of a variety of clinical features to arrive at a diagnosis. Given

this diagnostic challenge, it is not surprising that some patients with features common to both disorders will be diagnosed with an intermediate type. The importance of distinguishing between asthma and COPD and identifying an intermediate type is that treatment approaches as well as prognosis may differ.

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