Importance of distinguishing between asthma and chronic obstructive pulmonary disease in primary care

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Abstract

Objective To facilitate distinction between asthma and chronic obstructive pulmonary disease (COPD) in day-to-day primary care practice, and provide practical treatment strategies using spirometric cases to outline how to recognize the clinical and spirometric overlap between asthma and COPD.

Sources of information The approaches described here were developed using evidence-based guidelines and the expertise of the authors, including research findings by the authors in the areas of asthma, COPD management, and spirometric testing in primary care.

Main message There are patients with clinical or spirometric features of both asthma and COPD. Both asthma and COPD are associated with some degree of inflammation of the respiratory tract, mediated by the increased expression of inflammatory proteins. However, there are clear differences between asthma and COPD in the pattern of inflammation that occurs in the lungs. Diagnostic confusion between COPD and asthma is most likely to arise in older patients with respiratory complaints, particularly against a background that includes cigarette smoke or workplace exposure. Both asthma and COPD are clinical diagnoses based on patient history, symptoms, physical examination findings, and objective measures of lung function. Postbronchodilator spirometry is always needed to confirm a new diagnosis of COPD and should also be performed prebronchodilator for the diagnosis of asthma. However, in many cases, the interpretation of spirometry results is not straightforward.

Conclusion Understanding the nature and extent of the spirometric overlap between asthma and COPD is critical for tailoring a therapeutic strategy that is based on factors that include medical and family history, signs and symptoms, and a clear interpretation of spirometry data. This information will be leveraged differently for individual patients to arrive at the correct clinical diagnosis and to select the most appropriate therapy.

Editor's key points

- The clinical and spirometric overlap between asthma and chronic obstructive pulmonary disease (COPD) presents important challenges for primary care physicians, who are often faced with substantial time constraints in day-to-day clinical practice.
- Patients with COPD, asthma or asthma-COPD overlap may present with similar clinical symptoms. Furthermore, patients with non–fully reversible chronic asthma may present with spirometric overlap, making distinction of each condition difficult since symptoms such as chronic cough or sputum production are also frequently reported in patients with COPD or asthma-COPD overlap.
- Once spirometric data have been obtained and considered in conjunction with other important clinical information, such as patient history and physical examination findings, clinical uncertainty may be reduced and physicians may be better able to arrive at an accurate clinical diagnosis and appropriate treatment.

With an increasing and aging population worldwide, chronic respiratory diseases (of which chronic obstructive pulmonary disease [COPD] and asthma are the most common) are becoming important causes of mortality and morbidity.[1,2] The Global Burden of Disease study reported that, in 2015, asthma was the most prevalent chronic respiratory disease, affecting an estimated 358.2 million people (an increase in prevalence of 12.6% between 1990 and 2015), with COPD affecting 174.5 million people (an increase in prevalence of 44.2%).[2]

When encountering adult patients with respiratory symptoms who have a history of exposure to noxious particles including cigarette smoke, primary care physicians are potentially faced with the important task of differentiating asthma from COPD. Spirometry remains central to the diagnosis, outcome

prediction, and management of both COPD and asthma.[3,4] Although there are differences in pathophysiology, treatment, expected progression, and outcomes between these 2 conditions,[5-8] there is considerable spirometric and clinical overlap, which makes diagnostic confirmation difficult in day-to-day practice.

This article attempts to help distinguish between asthma and COPD in day-to-day primary care practice by using spirometric cases that outline how to recognize the clinical and spirometric overlap to facilitate a clinical diagnosis.

Cases

Case 1. The patient is a 45-year-old man who has never been a smoker. He has intermittent bouts of shortness of breath and chest tightness and normal findings from cardiovascular workup. His response to asthma therapy was favourable; thus, the diagnosis is consistent with asthma. The prebronchodilator and postbronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratios are 79.2% and 82.4%, respectively, while the FEV_1 improved from 2.92 L to 3.29 L after bronchodilation (increase of 370 mL and 13%) (**Figure 1**).[9]

Case 2. The patient is a 73-year-old man with a 40 pack-year smoking history, no allergies to environmental factors, and a history of progressive shortness of breath over the past 10 years. His medical and family histories were otherwise unremarkable for asthma risk factors. The prebronchodilator and postbronchodilator FEV_1-FVC ratios are 47.8% and 50.3%, respectively. The prebronchodilator and postbronchodilator FEV_1 results are 1.52 L and 1.88 L, respectively (increase of 360 mL and 24%) (**Figure 1**).[9] Because the postbronchodilator FEV_1-FVC ratio remains below 70% and the FEV_1 reversibility criterion is met, the clinician is led to differentiate asthma from COPD using historical data, as the spirometric criteria for asthma and COPD are both met. The historical and spirometric data in this case are consistent with a clinical diagnosis of COPD.

Case 3. The patient is a 36-year-old woman who has never been a smoker. She has numerous environmental allergies and has severe asthma that is well controlled on maintenance therapy. The prebronchodilator and postbronchodilator FEV_1-FVC ratios are 46.7% and 50.3%, respectively. The prebronchodilator and postbronchodilator FEV_1 values are 1.65 L and 1.94 L, respectively (increase of 290 mL and 18%) (**Figure 1**).[9]

Cases 2 and 3 highlight the spirometric overlap between asthma and COPD and the limitations of using FEV_1 reversibility to help distinguish asthma from COPD.

Case 4. The patient is a 19-year-old boy with a history of childhood asthma and β_2-agonist use increasing over several months. The prebronchodilator and postbronchodilator FEV_1-FVC ratios are 63.9% and 77.8%, respectively (**Figure 1**).[9] The prebronchodilator and postbronchodilator FEV_1 values are 2.17 L and 2.74 L, respectively (increase of 570 mL and 26%). These data exclude a spirometric diagnosis of COPD based on the normal postbronchodilator FEV_1-FVC ratio, and the increase in FEV_1 is consistent with a spirometric diagnosis of asthma.

Sources of information

The approaches described here were developed using evidence-based guidelines and the expertise of the authors, including research findings by the authors in the areas of asthma, COPD management, and spirometric testing in primary care.

Main message

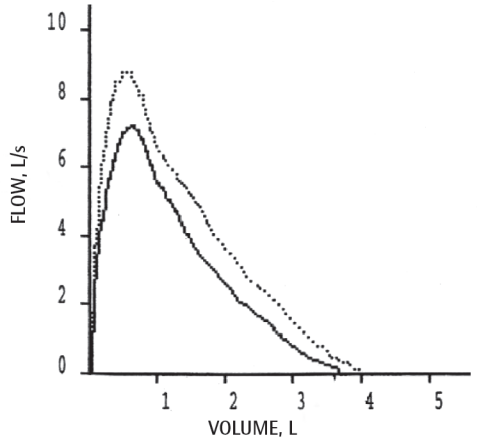
Patients with COPD, asthma, or asthma-COPD overlap (ACO) may present with similar clinical symptoms.[10,11] Furthermore, patients with non–fully reversible chronic asthma may present with spirometric overlap, making distinction between the conditions difficult since symptoms such as chronic cough or sputum production are also frequently reported in patients with COPD or ACO.[12] Once spirometric data have been obtained and considered in conjunction with other important clinical information, clinical uncertainty may be reduced and physicians may be better able to arrive at an accurate clinical diagnosis.

Definitions and diagnosis. The most recent update by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[3] defines *COPD* as a disease characterized by persistent respiratory symptoms (eg, dyspnea, cough, sputum production) and airflow limitation stemming from airway or alveolar abnormalities typically caused by substantial exposure to noxious particles or gases (eg, tobacco smoke, biomass fuel, air pollution, workplace hazards). In addition to environmental exposure, the updated definition recognizes the importance of host factors (eg, genetic abnormalities, abnormal lung development, accelerated aging) that predispose certain individuals to develop COPD.[3] Unlike asthma, which is often diagnosed earlier in life, COPD is a progressive condition of declining lung function that typically appears and is diagnosed after 40 years of age (**Table 1**).[5,6,13]

The diagnosis of COPD is established by the presence of a postbronchodilator FEV_1-FVC ratio of less than 0.70 (ie, 70%) or the lower limit of normal; in older patients the 70% cutoff value can overestimate the obstruction.[14] In COPD, airflow obstruction is determined by both irreversible (eg, alveolar destruction) and partly reversible (eg, smooth muscle bronchoconstriction) components, among others.[15] The updated GOLD strategy emphasizes the value of spirometry with bronchodilator testing at initial diagnosis.[3]

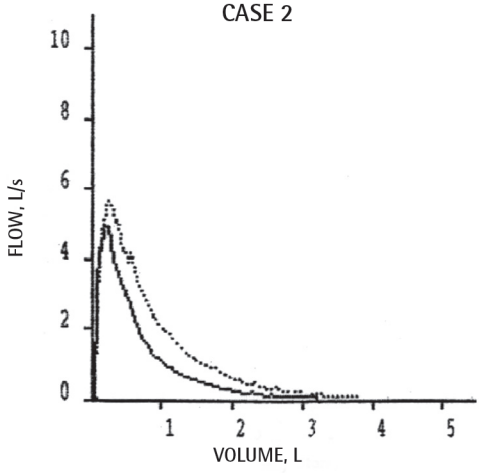
Figure 1. Spirometric data for case examples

CASE 1



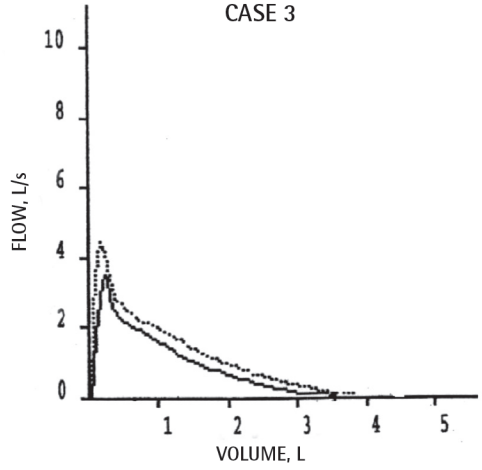
MEASUREMENT	PRE		POST		% Change*
	Best	% Pred	Best	% Pred	
FVC, L	3.68	88	3.99	95	8
FEV_1, L	2.92	86	3.29	97	13
FEV_1/FVC	79.2		82.4		

CASE 2



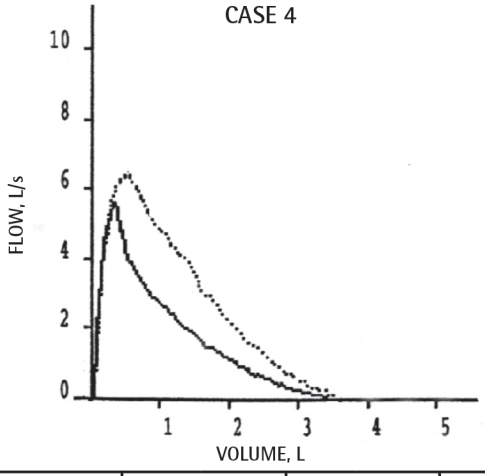
MEASUREMENT	PRE		POST		% Change*
	Best	% Pred	Best	% Pred	
FVC, L	3.18	69	3.74	82	18
FEV_1, L	1.52	44	1.88	54	24
FEV_1/FVC	47.8		50.3		

CASE 3



MEASUREMENT	PRE		POST		% Change*
	Best	% Pred	Best	% Pred	
FVC, L	3.54	89	3.86	97	9
FEV_1, L	1.65	50	1.94	59	18
FEV_1/FVC	46.7		50.3		

CASE 4



MEASUREMENT	PRE		POST		% Change*
	Best	% Pred	Best	% Pred	
FVC, L	3.39	98	3.52	101	4
FEV_1, L	2.17	73	2.74	92	26
FEV_1/FVC	63.9		77.8		

FEV_1—maximal volume of air exhaled after a maximal inhalation in the first second of a forced exhalation, FVC—maximal volume of air exhaled after inhalation during forced exhalation, % Pred—percent of predicted normal value, Pre—prebronchodilator value, Post—postbronchodilator value.

*Percent change = $\frac{(FEV_1 \text{ Post-}FEV_1 \text{ Pre})}{FEV_1 \text{ Pre}}$.

Reproduced from D'Urzo et al.[9]

Table 1. Usual features of asthma and COPD

FEATURES OF ASTHMA	FEATURES OF COPD
Onset before 20 y of age	Onset after 40 y of age
Variation in symptoms over minutes, hours, or days	Persistent symptoms despite treatment
Symptoms worse during the night or early morning	Good and bad days but always daily symptoms and exertional dyspnea
Symptoms triggered by exercise, emotions, or dust or allergen exposure	Chronic cough and sputum precede dyspnea, unrelated to triggers
Variable airflow limitation	Persistent airflow limitation
Lung function normal between symptoms	Lung function abnormal between symptoms
Family history of asthma and other allergic conditions	Heavy exposure to tobacco smoke or biomass fuels
Symptoms do not worsen over time; symptoms vary seasonally	Symptoms slowly worsen over time
Immediate response to bronchodilator therapy	Limited relief provided by bronchodilator therapy
Normal lungs	Severe hyperinflation of lungs

COPD—chronic obstructive pulmonary disease.

It is important to note that in COPD there are no restrictions on the magnitude of FEV_1 reversibility as long as the FEV_1-FVC ratio remains reduced (**Figure 1**, case 3).[9]

The Global Initiative for Asthma (GINA)[4] defines *asthma* as a heterogeneous disease that is typically characterized by chronic airway inflammation. This condition is demarcated by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness, and cough, which can vary in intensity and over time.[4] In addition, asthma is characterized by variable (usually largely reversible) expiratory airflow limitation. Objective evidence of asthma may include excessive variability in lung function (eg, an increase in lung function postbronchodilator up to the normal range is frequent but not always possible; or changes in function between visits); a decrease in lung function after exercise or during a bronchial provocation test; and variation in lung function beyond the normal range with repeated measurement.[4] In adults with respiratory symptoms suggestive of asthma, an increase in FEV_1 of more than 12% and of more than 200 mL from baseline is usually accepted as fulfilling the reversibility criteria consistent with asthma (**Figure 1**, case 1).[4,9] However, as noted above, it is important to recognize that many patients with COPD may also fulfil this criteria as long as the FEV_1-FVC ratio remains below 70% or the lower limit of normal (**Figure 1**, case 2),[9,16-18] resulting in a scenario of lung function overlap where disease misclassification may result if solely FEV_1 reversibility is used to distinguish between these 2 conditions. However, an important exception is that a postbronchodilator increase of FEV_1-FVC ratio into the normal range excludes the diagnosis of COPD (**Figure 1**, case 4).[9]

There are, however, patients with clinical or spirometric features of both asthma and COPD. Recently, GINA and GOLD have jointly recommended that the term *asthma–COPD overlap syndrome* be abandoned because it has been used to represent a single disease state or phenotype; the term *asthma–COPD overlap* includes patients presenting with objective features of both asthma and COPD (**Figure 1**, cases 2 and 3).[4,9] Furthermore, acknowledging that both asthma and COPD are highly heterogeneous diseases, Reddel reinforced that ACO similarly encompasses different phenotypes caused by a variety of underlying mechanisms.[19]

Pathogenesis and pathophysiology. Both asthma and COPD are associated with some degree of inflammation of the respiratory tract, mediated by the increased expression of inflammatory proteins such as cytokines, chemokines, adhesion molecules, and inflammatory enzymes and receptors. However, there are clear differences between asthma and COPD in the pattern of inflammation that occurs in the lungs. These differences are due to the involvement of different inflammatory cells and mediators and, importantly, to the underlying triggers of inflammation, eg, chronic exposure to smoke and noxious particles for COPD as opposed to allergens and infections for asthma (**Table 1**).[20] There is also systemic inflammation in patients with COPD that is thought to contribute to comorbidities such as cardiovascular disease, diabetes, and osteoporosis.[21] The distinction between asthma and COPD inflammatory profiles may become blurred in individuals with severe asthma; in asthma patients who smoke and have a neutrophilic pattern of inflammation; and during acute exacerbations of both asthma and COPD, which have similar (mixed) inflammatory features.[20]

Chronic airway inflammation is a prominent feature of asthma and it is well known that controlling the inflammation will help reduce symptoms and exacerbations, and also likely limit the extent of airway remodeling, ie, structural changes over the course of the disease.[22] As such, anti-inflammatory agents like corticosteroids

remain first-line and cornerstone treatment for asthma (although not all asthma patients respond to inhaled corticosteroids [ICS]).

In COPD, it is thought to be chronic exposure to noxious particles that, by insulting the bronchial tree and distal airways, causes inflammation that culminates in obstruction of predominantly small airways and destruction and distension of the alveolar walls (ie, bronchitis or emphysema).[23] As such, smoking cessation is the only disease-modifying approach, while bronchodilators, which improve airflow and reduce hyperinflation (air trapping), are the cornerstone of COPD management. In contrast to asthma, benefits from anti-inflammatory ICS are restricted to patients with frequent exacerbations and some patients with elevated eosinophil levels.[3]

Differential diagnosis. In certain cases, distinguishing between asthma and COPD is straightforward; for example, asthma would be diagnosed in an atopic individual who is younger than 50 years of age, is a non-smoker, has a history of childhood wheeze, has a family history of asthma, presents with wheezing, and has substantial or full bronchodilator reversibility at the time of clinical evaluation (**Figure 1**, case 1).[9]

Diagnostic confusion between COPD and asthma is most likely to arise in older patients with respiratory concerns, particularly against a background of cigarette smoke or workplace exposure.

In light of the considerable overlap between features of asthma and COPD (**Figure 1**, cases 2 and 3),[9] differential disease characteristics of asthma, COPD, and ACO have been summarized in the collaborative report by GOLD and GINA,[24] focusing on the features that are most helpful in identifying and distinguishing typical asthma or COPD; this report also recommends that a diagnosis of ACO should be considered if a similar number of features of both asthma and COPD are present.[24] In addition to asthma and ACO, other potential differential diagnoses for COPD include congestive heart failure, bronchiectasis, tuberculosis, obliterative bronchiolitis, diffuse panbronchiolitis (in patients with Asian heritage), and sarcoidosis, although these are usually easier to distinguish from COPD.[3]

It is also recommended that targeted testing be carried out for α_1-antitrypsin deficiency (AATD)[3] in all newly diagnosed patients with COPD since AATD is a predisposing genetic cause of pulmonary emphysema.[6] Adults diagnosed with presumed asthma that is not completely reversible after bronchodilator treatment are also candidates for AATD testing.[25,26] Fewer than 10% of individuals with symptomatic AATD in primary care are appropriately diagnosed, which may be owing to COPD being underdiagnosed and the lack of awareness of AATD.[25] The lack of awareness of AATD is similar in the context of patients with asthma or asthmalike symptoms.[26]

Finally, it should be highlighted that patient history and clinical evaluation should be taken into account during the differential diagnosis investigations; for example, many patients with ACO who are 40 years and older have a long-standing history of atopy or wheezing starting before the age of 40 years[27] but they come to the attention of their physicians much later (ie, when 50 to 70 years of age).[7,28]

If ACO is the working diagnosis, then treatment must include ICS plus long-acting bronchodilators to maximize lung function, symptom control, and other important clinical outcomes. It is safe to say that unlike asthma, where symptoms are variable over time, including at times within a given day, COPD progresses in an insidious fashion such that patients may report few symptoms as a result of lifestyle adjustments designed to minimize the effects of pulmonary impairment on the sensation of breathlessness.

Role of spirometry in differential diagnosis. Both asthma and COPD are clinical diagnoses based on patient history, symptoms, physical examination findings, and objective measures of lung function. Postbronchodilator spirometry is always needed to confirm a new diagnosis of COPD and should also be performed prebronchodilator for the diagnosis of asthma. In many cases, the interpretation of spirometry results is not straightforward for the following reasons:

- A spirometric distinction between COPD and asthma is only seen if the flow limitation postbronchodilator completely resolves, which is a finding consistent only with asthma (**Figure 1**, case 4).[9]
- In cases of normal spirometry findings (normal FEV_1, FVC, FEV_1-FVC ratio) but classical clinical data for symptoms and history of asthma the diagnosis of asthma is still probable,[29] and some patients may show improvements at an FEV_1 of more than 200 mL and more than 12% after bronchodilator challenge (**Figure 1**, case 1).[9]
- In permanent flow limitation, the higher the extent of postbronchodilator FEV_1 reversibility (>400 mL) the more likely an asthma diagnosis is, but this is not a validated assumption.
- In permanent flow limitation, FEV_1 reversibility (>12% and >200 mL) may be compatible with both asthma and COPD (**Figure 1**, cases 2 and 3).[9] In these cases, clinical and historical factors and follow-up visits are needed to establish a clinical diagnosis.

While a thorough description of the performance of a correct maximal breathing maneuver is beyond the scope of this article, selection of the most appropriate test results and correct interpretation of the data are essential.[30] A recent systematic scoping review suggests that in primary care COPD misdiagnosis is attributable to factors related to spirometric testing.[31]

Spirometric overlap between asthma and COPD is highlighted in an analysis examining acute bronchodilator responsiveness (using 3 criteria) in a large

cohort with moderate to very severe COPD.[32] The UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) trial found that 53.9% of patients had 12% or greater and 200 mL or greater improvement in FEV_1 over baseline, 65.6% had 15% or greater improvement in FEV_1 over baseline, and 38.6% had 10% or greater absolute increase in FEV_1 percentage of predicted value.[32] This study demonstrated substantial acute bronchodilator reversibility in COPD patients who had no other features of asthma, regardless of the criteria used to define reversibility.[32] In the most recent reports, the prevalence of bronchodilator reversibility, expressed as increase in FEV_1 of 12% or greater and 200 mL or greater, was 17.3% and 18.4% among participants with asthma and COPD, respectively,[33,34] underscoring that FEV_1 reversibility is of limited value for distinguishing asthma from COPD.

In asthma, spirometry results at a single visit do not always confirm a diagnosis; results must be considered in the context of the clinical presentation and whether treatment has been started (see Box 5-3 in the 2021 GINA report).[4]

The spirometric overlap between asthma and COPD was also recently highlighted in the Effect of Indacaterol/Glycopyronium versus Fluticasone/Salmeterol on COPD Exacerbations (FLAME) study,[34] which compared the effectiveness of the long-acting β_2-agonist (LABA) indacaterol plus the long-acting antimuscarinic glycopyrronium once daily with the LABA-ICS combination of salmeterol–fluticasone propionate twice daily for preventing exacerbations in patients with COPD. The mean reversibility of the FLAME study population met the FEV_1 reversibility required for asthma. The FLAME protocol nevertheless applied stringent asthma exclusion criteria (excluding all COPD patients with a history of concomitant allergic rhinitis, asthma, or very pronounced blood eosinophils [>600 cells/µL]) and lung function reversibility was performed using methods adopted in most bronchodilator studies in COPD. The FLAME study importantly demonstrated COPD patients with a history of exacerbations benefited more from an ICS-free dual bronchodilation with indacaterol-glycopyrronium than from a LABA-ICS combination for the prevention of further exacerbations, a finding that would not be expected in an asthma-rich population.[34]

Conclusion

The clinical and spirometric overlap between asthma and COPD presents important challenges for primary care physicians who are often faced with considerable time constraints in day-to-day clinical practice. Understanding the nature and extent of this overlap is critical for tailoring a therapeutic strategy that is based on factors that include medical and family history, signs and symptoms, and a clear interpretation of spirometry data. This information will be leveraged differently for individual patients to determine the correct clinical diagnosis and the appropriate therapy.

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Contributors

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Competing interests

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