Chapter

133

Is It Asthma or COPD?

AMALKUMAR BHATTACHARYA

Different conditions, which involve a variety of anatomic airway locations, can produce obstruction and expiratory or inspiratory wheezing (Table 1). Asthma is not the most common cause of wheezing. Post-nasal drip syndrome was the most common cause of wheeze in patients referred to a pulmonary out-patient clinic (Fig. 1).

Differentiation of COPD from asthma is not difficult on clinical grounds in the majority of cases. The ultimate test is supposed to be a reversibility testing of FEV_1. But the current line of thinking is that clinical assessment and follow-up should suffice to differentiate these two conditions and reversibility testing has its problems too:

- Repeated FEV_1 measurements can show small spontaneous fluctuations.
- The results of a reversibility test performed on the same patients on different occasions can be inconsistent and not reproducible.

Table 1: Use of the history in the diagnosis of asthma

1. Does the patient have compatible symptoms?
   - Cough
   - Wheeze
   - Dyspnea
   - Chest discomfort
   - Phlegm production
   - Hyperventilation syndrome
   - Combinations of the above
2. Are the symptoms episodic?
3. Do the symptoms respond favorably to specific asthma therapy?
4. If not, are they due to a disease that can mimic asthma?

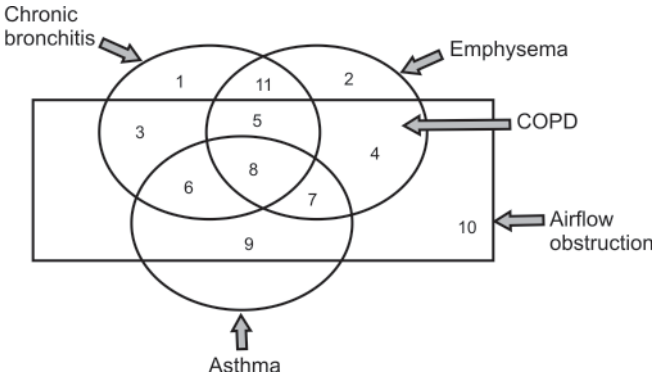

Fig. 1: Chronic obstructive pulmonary disease. This non-proportional Venn diagram shows subsets of patients with chronic bronchitis, emphysema, and asthma (black circles). The subsets defined as COPD are shaded gray. Subset areas are not proportional to actual relative subset sizes. Asthma is, by definition, associated with reversible airflow obstruction; in variant asthma special maneuvers may be necessary to make the obstruction evident. Patients with asthma whose airflow obstruction is completely reversible (subset 9) are not considered to have COPD. In many cases it is virtually impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema who have partially reversible airflow obstruction with airway hyper-reactivity. Thus, patients with unremitting asthma are classified as having COPD (subsets 6, 7 and 8). Chronic bronchitis and emphysema with airflow obstruction usually occur together (subset 5), and some patients may have asthma associated with these two disorders (subset 8). Individuals with asthma exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough, a feature of chronic bronchitis (subset 6). Such patients are often referred to in the United States as having asthmatic bronchitis or the asthmatic form of COPD. Persons with chronic bronchitis or emphysema without airflow obstruction (subsets 1, 2 and 11) are not classified as having COPD. Patients with airway obstruction due to diseases with known etiology or specific pathology, such as cystic fibrosis or obliterative bronchitis (subset 10), are not included in this definition

- Over-reliance on a single reversibility test may be misleading unless the change in FEV_1 Is very large (> 400 ml).
- The definition of what constitutes the magnitude of a significant change is purely arbitrary.
- Response to long-term therapy in COPD is not predicted by acute reversibility testing.

DEFINITION, DIAGNOSTIC CRITERIA, AND PREVALENCE OF ASTHMA

Definition

Asthma has defied a precise definition acceptable to all disciplines involved in its study, even though clinicians recognize the constellation of signs and symptoms of intermittent dyspnea, cough, and wheezing. Part of the problem relates to the lack of specificity of these "classic" symptoms of asthma. There may, for example, be difficulty in differentiating asthmatic subjects from those with chronic obstructive pulmonary disease by symptoms alone, particularly in adults. Newer criteria have allowed better definition for use in studies of the prevalence of the disease.

Clinical Definition and Criteria for Diagnosis

Definition of asthma is updated and refined as aspects of its pathophysiology become recognized.

"A chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils, and T lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli."

Diagnosis of Asthma

History and Physical Examination

The classic triad of symptoms associated with asthma consists of cough, shortness of breath, and wheezing occurring simultaneously (Table 1). However, it is not unusual for one or more of these complaints to be absent or for asthmatics to present with other symptoms. In addition, similar symptoms can occur in other conditions. As an example, prospective studies have shown that the COPD or post-nasal drip syndrome, from a variety of upper respiratory tract disorders, can lead to symptoms that include cough, wheezing, dyspnea, and/or expectoration of phlegm[1-2].

The classic triad of symptoms – Since patients sometimes present with only single elements of the classic triad, several studies have evaluated the diagnostic specificity of these symptoms in the diagnosis of asthma. The percentages of patients presenting with persistent wheeze, chronic cough, and chronic dyspnea who were eventually given the diagnosis of asthma were (Fig. 1):

Persistent wheeze: 35%; Chronic dyspnea: 29%; Chronic cough: 24%.

Diagnostic accuracy increased when more than one symptom was present.

Other presentations – In addition to the classic triad, asthma can present solely with one of the following symptoms:

Cough with or without expectoration of excessive mucus (bronchorrhea), chest pain or tightness, hyperventilation syndrome, hemoptysis (as part of the syndromes of Churg-Strauss vasculitis and allergic bronchopulmonary aspergillosis).

Since all of the above symptoms also can occur in a variety of other diseases, their presence, singly or in combination, is too non-specific to be used to diagnose asthma. Some authorities believe that a history of intermittent, seasonal waxing and waning of symptoms; nocturnal episodes; exacerbation of symptoms on exposure to stimuli such as exercise, cold air, aeroallergens, air pollutants, upper respiratory tract infections, or strong odors argues for the diagnosis of asthma. These features, however, have not been prospectively studied and have been found in patients with a variety of upper respiratory tract disorders, left ventricular failure, bronchiectasis, and chronic obstructive pulmonary disease (COPD).

Age, gender, family history, and race have little specificity for the diagnosis of asthma. Asthma can occur for the first time at any age and its cumulative prevalence rate is similar in women and men[3]. Although there is a parental history of asthma in approximately 50% of children with asthma[4,5], the predictive value of this history is unknown. Race does not appear to be diagnostically useful with the exception of Eskimos, in whom asthma is rare[6,7].

Physical examination – Widespread, high-pitched, musical wheezes are characteristic of asthma although they are not specific. Asthmatic wheezing usually presents as sounds with multiple different pitches, starting and stopping at various points in the respiratory

cycle and varying in tone and timing over time. It is to be distinguished from the monophasic wheezing of a local bronchial narrowing (e.g. due to an aspirated foreign body or bronchogenic cancer), which has single pitch and repeatedly begins and ends at the same point in each respiratory cycle. Transmission of expiratory wheezing from the upper airway (e.g. larynx) can mimic asthma on auscultation of the chest. However, this type of wheezing typically is loudest over the neck and is unusually diminished during auscultation of the lower thorax.

The presence or absence of wheezing on physical examination is a poor predictor of the severity of airflow obstruction in asthma. Wheezing may be heard in patients with mild, moderate, or severe airway narrowing; significant airway narrowing also may be found in individuals without wheezing. The presence of wheezing alerts one to the likely presence of some degree of airway narrowing; measurement of lung function (e.g. with spirometry or peak flow measurement) is needed to quantify its severity.

Physical findings that suggest severe airflow obstruction in asthma, including use of the accessory (e.g. sternocleidomastoid) muscles of breathing during inspiration and a pulsus paradoxus (greater than 10 mmHg fall in systolic pressure during inspiration), usually are found only during acute asthmatic attacks. However, these signs are insensitive manifestations of severe airflow obstruction, even during asthmatic attacks.

Other physical findings in patients with asthma, such as hives, eczema, and allergic rhinitis, may suggest associated allergic diseases. Nasal polyps also can be found, with or without the associated history of aspirin sensitivity. In contrast, clubbing is not a feature of asthma; its presence should raise the possibility of alternative diagnoses such as interstitial lung disease and cystic fibrosis.

Pulmonary Function Test

Pulmonary function tests are key to the diagnosis and management of asthma. Peak expiratory flow rate and spirometry are the two pulmonary function tests most often diagnostic of asthma.

Peak expiratory flow rate – The peak expiratory flow rate (PEFR) is measured during a maximal exhalation that has immediately followed a maximal inhalation. Simple inexpensive equipment is used to measure the PEFR; the patient can be taught to measure his or her performance with the PEFR monitor routinely at home. The resulting measurements are highly dependent upon the patient's technique. Thus, it is important that the physician assesses the patient's use of the monitor and corrects any mistakes.

The patient should be taught to establish a baseline measure with which to compare future readings. Each patient must establish his or her own personal best PEFR value by recording measurements at least twice daily for at least two weeks, because values in an individual patient will often be higher or lower than average predicted norms. The baseline values should ideally be obtained in the absence of symptoms.

The patient should perform the PEFR maneuver three or more times and record the best value in a diary. The personal best is generally the highest PEFR measurement achieved on the evening measurement after a period of maximum therapy. This measure is used to determine a normal PEFR range, which is between 80 and 100% of the patient's personal best. Readings below this normal range indicate airway narrowing, a change that often occurs before the onset of symptoms.

Most clinicians currently use a zone scheme for categorizing results of PEFR measurements:

- Red is defined as less than 50% of the predicted or personal best values.
- Yellow is defined as 50 to 80% of the predicted or personal best values.
- Green is defined as greater than 80% of the predicted or personal best values.

The utility of PEFR to detect the presence of airflow limitation is not particularly good, since the variability of PEFR among individuals is very large (± 30%). However, PEFR is a useful method of monitoring changes or trends in the patient's lung function.

There are several situations in which PEFR can be misleading:

- PEFR can fall during a steroid burst as the respiratory muscles weaken.
- PEFR may not adequately reflect airflow limitation in some patients. Much like using a blood gas to "calibrate" the pulse oximeter, it is important initially to correlate PEFR values with a more definitive measure of airflow limitation, e.g. spirometry and flow-volume loops.

Spirometry: Spirometry, which includes measurement of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), is a readily available and useful pulmonary function test.

FEV_1 is the most important spirometric variable for assessment of airflow obstruction. The FEV_1 reflects the average flow rate during the first second of the forced vital capacity (FVC) maneuver. It declines in direct and linear proportion with clinical worsening of airways obstruction, and it increases with successful treatment of airways obstruction.

Degrees of obstruction are defined according to the percentage of predicted FEV_1 achieved by the patient:

- > 80% – borderline obstruction
- 60 to 80% – mild obstruction
- 40 to 60% – moderate obstruction
- < 40% – severe obstruction

FEV_1 can be used for determining the degree of obstruction (mild, moderate, or severe) and for serial comparisons when following patients with asthma, although PEFR measurements are adequate in most patients.

Administration of a bronchodilator (e.g. albuterol) by metered-dose inhaler (MDI) is indicated during an initial work-up if baseline spirometry demonstrates airway obstruction or if one suspects asthma. There is no absolute contraindication to the administration of a bronchodilator in an ambulatory patient. However, if the patient is known to have angina or episodes of cardiac arrhythmias, it may be safer to use a beta-2 selective drug such as albuterol. Spirometry should be repeated 15 minutes after albuterol. The technique for using the MDI is important to avoid false negative results.

In a patient with mild to moderate obstruction, an increase in FEV_1 of more than 12% and greater than 0.2 L suggests acute bronchodilator responsiveness. However, the lack of an acute bronchodilator response should not preclude a six to eight week therapeutic trial of bronchodilators and/or corticosteroids, with reassessment of clinical status and change in FEV_1 at the end of that time.

Serial measurements of lung function over time: Some patients suspected of having asthma on the basis of historical information will have a normal chest examination and normal lung function at the time of their office visit. Two approaches to establishing the diagnosis of asthma can be used in this setting: serial measurements of lung function over time; and bronchoprovocative testing.

Patients experiencing asthmatic symptoms can be expected to have significant airflow obstruction and a decrease in their peak expiratory flow compared with when they feel entirely well. On the other hand, individuals without asthma experience little variability (less than 20%) in their PEFR, even during upper respiratory tract infections. One useful strategy to diagnose asthma in patients with normal lung function at their medical visit is to provide them with a portable peak flow meter for home use. Patients are asked to keep a diary of their peak flow recordings. A reliable series of recordings that documents more than 20% variability in PEFR over time (especially when PEFR reductions are associated with asthmatic symptoms) confirms the diagnosis of asthma. Similar data collection can take place in the clinician's office by recording PEFR at each patient visit; this method is less dependent upon patient cooperation but requires more time to elapse.

This approach to diagnosing asthma lends itself well to combination with a "therapeutic trial" using a bronchodilator. Significant decreases in PEFR that reverse within minutes of use of an inhaled beta-adrenergic agonist typify asthma. In normal individuals, the increase in PEFR following bronchodilator would be expected to be less than 20%. Other obstructive lung diseases, including COPD, diffuse bronchiectasis, and constrictive bronchiolitis, might also manifest variable airflow obstruction over time and airflow obstruction that improves significantly after bronchodilator administration; however, normal baseline lung function would not be expected in these diseases.

Bronchoprovocation testing: Another strategy for diagnosing asthma in patients with normal lung function is to attempt to provoke airflow obstruction using a stimulus known to elicit airway narrowing. It can be thought of being similar to exercise stress testing in a patient suspected of having angina who has a normal resting electrocardiogram. The provocative stimulus most widely used to evaluate for asthma is inhaled methacholine, although exercise, hyperventilation of cold (dry) air, or inhaled histamine are common alternatives.

A common indication for bronchoprovocation testing is in the evaluation of atypical symptoms of asthma, especially cough. Asthma is one of the most frequent causes of unexplained chronic cough. Bronchoprovocation testing also can be used in patients with an established diagnosis of asthma when further evaluation of the role of a suspected precipitating factor is needed. An example would be an athlete with exercise-induced respiratory symptoms not effectively controlled despite administration of appropriate antiasthmatic medications prior to exercise.

Bronchoprovocation tests are usually reported as the dose of the provocative agent needed for a 20% fall in the FEV_1. A positive test result (indicating bronchial hyperresponsiveness) is not entirely specific for asthma. "Positive" tests occasionally are found in asymptomatic patients, which may be a variant of normal. Up to 7% of the normal population shows more than a 20% decrease in FEV_1 to high concentrations of methacholine; as many as 20 to 25% of individuals with allergic rhinitis but free of asthma also will have positive results. On the other hand, false negative results are uncommon (<5%). Thus, a negative methacholine challenge argues strongly against the diagnosis of asthma.

Other Laboratory Tests

Occasionally used: CXR, blood tests, and tests for allergy.

Chest radiograph – The chest radiograph is almost always normal in patients with asthma. Its potential value is to detect rare complications (e.g. allergic bronchopulmonary aspergillosis, eosinophilic pneumonia, or atelectasis due to mucus plugging), and to exclude alternative or comorbid diagnoses. Is certainly indicated in patients with presenting features atypical for asthma, such as fever, hemoptysis, weight loss, clubbing, inspiratory rales, significant hypoxemia, or airflow obstruction that does not reverse with bronchodilators.

Blood tests – No blood tests are available to assess the presence or absence of asthma or to gauge its severity. However, in some patients it may be of value to investigate the allergic basis of their disease. The eosinophil count and serum immunoglobulin E (IgE) concentration, if elevated, may indicate the presence of an allergic tendency (or "atopy"). A complete blood count (CBC) with differential white blood cell analysis suffices to screen for eosinophilia.

Markedly elevated eosinophil percentages (>15%) should be prompt consideration of alternative diagnoses, including parasitic infections, drug reactions, and syndromes of pulmonary infiltrates with eosinophilia. Similarly, very high IgE levels (>1000 ng/ml) suggest asthma as well as the associated conditions of eczema or allergic bronchopulmonary aspergillosis.

Tests for allergy – Two methods are available to test for allergic sensitivity to specific allergens in the environment: allergy skin tests and blood radioallergosorbent tests (RAST). The allergens most commonly causing asthma, and those for which testing is most accurate, are aeroallergens (e.g. house dust mite antigen, cat and dog danders, cockroach antigen, pollens, and molds spores) rather than foods. Assessing for allergic sensitivity to inhaled allergens begins with history taking. If a patient reports that exposure to typical allergens causes him or her to have asthmatic symptoms, clinical suspicion is raised and a positive allergy test will have a greater positive predictive value.

A positive skin test combined with a compelling history of sensitivity predicts that inhalation of the same allergen would cause an asthmatic reaction with more than 80 to 90% accuracy

Assessment of allergic sensitivities can be useful in managing patients with asthma, especially those who remain symptomatic despite regular use of a preventative or controller medication. In addition, patients often request this information. One goal of therapy is to identify allergens in the environment for which modifications can reduce patient exposure, e.g. dust mite antigen avoidance in the home is a useful therapeutic strategy in asthma, but only in patients with dust mite sensitivity.

Differential Diagnosis

The diagnosis of asthma ultimately is made when a history of respiratory symptoms consistent with the diagnosis is combined with a determination of variable expiratory flow. Differential diagnostic considerations depend in part upon the age of the patient.

- In children: foreign body aspiration, cystic fibrosis, and viral bronchiolitis.
- In young and middle-aged adults: bronchiectasis, pulmonary embolism, gastroesophageal reflux disease (GERD), and sarcoidosis.
- In older-aged patients, especially cigarette smokers: COPD and heart failure.

DIAGNOSIS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Introduction

Chronic obstructive pulmonary disease (COPD) is the most important lung disease encountered in the world, for the following reasons:[1]

- Volume of patients with this disorder.
- The high frequency of physician encounters in both outpatient and inpatient settings.
- The substantial debility, physical impairment, and reduced quality of life caused by disease.
- The need for continued outpatient management.

- The associated medical morbidity and need for hospital care during acute exacerbations.
- The high utilization of medical resources associated with hospital care for exacerbations as well as with chronic treatment, e.g., long-term oxygen therapy.
- The disease is the fourth-ranked cause of death.

Definition

"A disease state characterized by airflow limitation that is not fully reversible. Airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Symptoms, functional abnormalities, and complications of COPD can all be explained on the basis on this underlying inflammation and the resulting pathology."

Airflow obstruction is the result of both small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). The relative contributions of each vary from person to person, and can be accompanied by partially reversible airways hyperreactivity[2-4].

Earlier definitions have also focused on the terms emphysema, chronic bronchitis, and asthma, which are not included in the definition provided above[3,5,6].

- Chronic bronchitis is a clinical diagnosis defined by the presence of chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic cough have been excluded[7].
- Emphysema is a pathological term describing the abnormal permanent enlargement of airspaces distal to the terminal bronchioles, accompanied by destruction of their walls without obvious fibrosis. Emphysema may be noted in patients with COPD[2].

Disease interrelationships – Although neither chronic bronchitis nor emphysema is a required element in the definition of COPD, there is substantial overlap among all of the entities described above. Fig. 1 is a nonproportional Venn diagram showing the relationship of chronic bronchitis, emphysema, asthma, and airflow obstruction; the shaded area delineates COPD (Fig. 1). Specific issues related to some of the subsets on this diagram include:

- Patients with asthma (subset 9) whose airflow obstruction is completely reversible are not considered to have COPD.
- It is virtually impossible in many cases to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with COPD who have partially reversible airflow obstruction and airway hyperreactivity[8]. Because of this difficulty, patients with nonremitting asthma are classified as having COPD (subsets 6 to 8).
- Chronic bronchitis and emphysema with airflow obstruction usually occur together (subset 5)[9]. Some patients may have asthma associated with these two disorders (subset 8).
- Persons with asthma who are exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough, a feature of chronic bronchitis (subset 6). In the United States, such patients are often referred to as having asthmatic bronchitis or the asthmatic form of COPD.
- Persons with chronic bronchitis[10] or emphysema[11] without airflow obstruction are not classified as COPD (subsets 1, 2, and 11).
- Patients with airways obstruction due to diseases with known etiology or specific pathology, such as cystic fibrosis or obliterative bronchiolitis (subset 10), are not included in the definition of COPD.

Evidence suggests that the bronchial inflammation of COPD is pathophysiologically different from that of asthma, thus adding justification for separating asthma from COPD when possible[9-10]. In COPD, CD-8+ lymphocytes, neutrophils and CD-68+ monocytes/ macrophages predominate[11-12]. In asthma, CD4+ (helper) T-lymphocytes and eosinophils predominate. There is increased production and release of interleukin (IL)-4 and IL-5, which is referred to as a Th2-type response. There is no IL-4 or IL-5 response in COPD (Fig. 2).

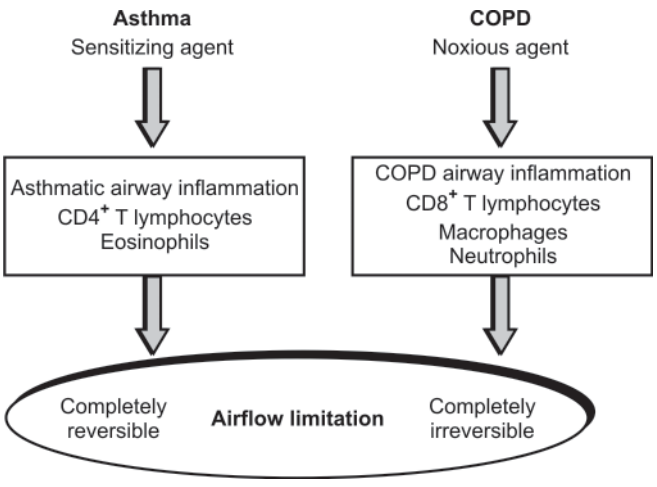

Fig. 2: Asthma and COPD

In addition, asthma affects all ages and has a low mortality-to-prevalence ratio. COPD is predominantly a disease of the sixth decade of life and later and has a high ratio of mortality to prevalence.

A number of animal models of induction of emphysema by cigarette smoking have been reported[18,19]. Why then should we not define COPD in terms of cigarette smoking as its main etiology? The reason is that there are other harmful inhalants that contribute to the pathogenesis of COPD. Furthermore, only about 15 to 20% of smokers develop COPD suggesting that host factors (most likely genetic) also contribute to pathogenesis of the disease.

Alpha-1 antitrypsin deficiency – The only established genetic abnormality that predisposes to lung disease clinically and pathologically similar to COPD is alpha-1 antitrypsin (AAT) deficiency. For convenience, this lung disease will be referred to as AAT-COPD.

Severe AAT deficiency has a frequency of about 1 in 3,000 live births. About 95% of severely deficient persons have Pi*ZZ alleles rather than the normal Pi*MM. These individuals may have liver disease in infancy or in old age, or they may develop AAT-COPD in their thirties or forties, especially if they smoke. However, as many as 2% of patients with COPD or sustained asthma may have severe AAT deficiency. For these reasons, those persons with known COPD, or asthma with non-remittent airflow obstruction, be screened for AAT deficiency.

Clinical Features

Patients with COPD have usually been smoking at least 20 cigarettes per day for 20 or more years before symptoms develop. Chronic productive cough, sometimes with wheezing, often begins when patients are in their forties, although the patients are frequently less aware of these symptoms than the persons they live with (Table 1).

An acute chest illness, generally when patients are in their fifties, may prompt a visit to the doctor. Dyspnea on effort does not usually begin until the mid sixties or early seventies. Sputum production is insidious, initially occurring only in the morning; the daily volume rarely exceeds 60 mL. Sputum is usually mucoid but becomes purulent with an exacerbation.

Acute chest illnesses may occur intermittently, and are characterized by increased cough, purulent sputum, wheezing, dyspnea, and occasionally fever. The history of wheezing and dyspnea may lead to the erroneous diagnosis of asthma. Conversely, other diseases with respiratory symptoms are commonly mistaken for COPD, especially in patients who also smoke cigarettes.

With disease progression, the intervals between acute exacerbations shorten. Late in the course of the illness, an exacerbation may give rise to hypoxemia with cyanosis; the latter is accentuated by erythrocytes. Associated findings also include:

Weight loss, hypercapnia with more severe hypoxemia in the setting of end-stage disease, Morning headache, which suggests hypercapnia, Cor pulmonale with right heart failure and edema. These abnormalities can develop in patients with hypoxemia and hypercapnia.

A staging system for COPD, in which the need for diagnostic evaluation and therapy is stratified by stage, has also been proposed although not yet validated[2]. One trial examined the value of the GOLD Stage 0 designation in predicting future development of COPD. Individuals in this group (symptomatic smokers with normal spirometry) did not demonstrate an accelerated decline in lung function compared with a control group of asymptomatic smokers[13].

Subsequently, a novel staging system, based on the body-mass index (B), the degree of airflow obstruction (O) dyspnea (D), and exercise capacity (E, measured by the six-minute walk test), has been proposed[14]. These variables are used to construct the BODE index, a multidimensional 10-point scale in which higher scores indicate a higher risk of death. The hazard ratio for death from any cause per one-point increase in the BODE score was 1.34 (95% CI, 1.26 to 1.42; $P<0.001$), and the hazard ratio for death from respiratory causes was 1.62 (95% CI, 1.48 to 1.77; $P<0.001$). The BODE index was better than the FEV1 at predicting the risk of death from any cause and from respiratory causes among patients with COPD.

Since bronchogenic carcinoma occurs with increased frequency in smokers with COPD, an episode of hemoptysis raises the possibility that carcinoma has developed. However, most episodes of hemoptysis are due to bronchial mucosal erosion.

Physical examination – Physical examination of the chest early in the disease may show only prolonged expiration and wheezes on forced exhalation. As obstruction progresses, hyperinflation becomes evident, and the anteroposterior diameter of the chest increases. The diaphragm is depressed and limited in its motion. Breath sounds are decreased and heart sounds often become distant. Coarse crackles may be heard at the lung bases. Wheezes are frequently heard, and permit the diagnosis of airflow obstruction.

Although airflow obstruction can be caused by many conditions, if the history and chest X-ray are compatible, a clinical diagnosis of COPD may be made. However, a forced expiratory spirogram before and after bronchodilator is always necessary for confirmation and quantification of the airflow obstruction.

Patients with end-stage COPD may adopt positions which relieve dyspnea, such as leaning forward with arms outstretched and weight supported on the palms. Other signs in a patient with end-stage disease may include:

- The full use of the accessory respiratory muscles of the neck and shoulder girdle.
- Expiration through pursed lips.
- Paradoxical retraction of the lower interspaces during inspiration (Hoover's sign)[15].
- Cyanosis.
- An enlarged, tender liver secondary to right heart failure. Neck vein distention, especially during expiration, may be observed in the absence of heart failure because of increased intrathoracic pressure.
- Asterixis due to severe hypercapnia.

Plain chest radiography – Since emphysema is defined in anatomical terms, radiographic images of the lungs provide the clearest evidence of its presence. Overdistention of the lungs is indicated on frontal chest radiographs by a low, flat diaphragm and a long, narrow heart shadow. Flattening of the diaphragmatic contour and an increased retrosternal airspace are observed on the lateral projection. Rapid tapering of the vascular shadows accompanied by hypertransradiancy of the lungs is a sign of emphysema.

Bullae, presenting as radiolucent areas larger than one centimeter in diameter and surrounded by arcuate hairline shadows, are proof of the presence of emphysema. However, bullae reflect only locally severe disease and are not necessarily indicative of widespread emphysema.

Studies correlating lung structure and the chest radiograph show that emphysema is consistently diagnosed when the disease is severe, is not diagnosed when the disease is mild, and is diagnosed in about half the instances when the disease is of moderate severity.

Pulmonary hypertension and right ventricular hypertrophy are indicated by prominent hilar vascular shadows and encroachment of the heart shadow on the retrosternal space as the right ventricle enlarges anteriorly. The cardiac enlargement may become evident only on comparison with previous chest radiographs.

Computed tomography – Computed tomography (CT), especially high resolution CT (collimation of 1 to 2 mm), has much greater sensitivity and specificity than standard chest radiography for the diagnosis of emphysema. CT may also identify the specific anatomic type of emphysema, i.e. panacinar or centriacinar.

- Centriacinar emphysema occurs preferentially in the upper lobes and produces holes in the center of the secondary pulmonary lobules.
- Panacinar emphysema more commonly involves the lung bases, resulting in a generalized paucity of vascular structures; it also affects the entire secondary pulmonary lobule.

Pulmonary function tests – Pulmonary function measurements are necessary for diagnosing and assessing the severity of airflow obstruction, and are helpful in following its progress. Airflow obstruction is an important indicator of impairment and the likelihood of blood gas abnormalities. The FEV_1 is easily measurable and has less variability than other measurements of airways dynamics, and its normal value is predictable from age, gender, and height.

The FVC is also readily measured, although it is dependent on the expiratory time in severe COPD. In the mildest degree of airflow obstruction, the FEV1/FVC ratio falls below 0.70 and the FEV_1 percent predicted is normal. The FEV_1 and the FEV_1/FVC ratio fall progressively as the severity of COPD increases. As noted earlier, up to 30% of patients have an increase of 15% or more in their FEV_1 following inhalation of a beta-agonist aerosol. However, the absence of a bronchodilator response during a single test never justifies withholding bronchodilator therapy. No tests of airflow obstruction can distinguish between chronic bronchitis and emphysema.

Lung volume measurements reveal an increase in total lung capacity, functional residual capacity, and residual volume, and often a decrease in the vital capacity. The single breath carbon monoxide diffusing capacity is decreased in proportion to the severity of emphysema because of the loss of alveolar-capillary bed. The test is not specific, nor can it detect mild emphysema.

Arterial blood gases reveal mild or moderate hypoxemia without hypercapnia in the early stages. As the disease progresses, hypoxemia becomes more severe and hypercapnia supervenes. Hypercapnia is observed with increasing frequency as the FEV_1 falls below one liter. Blood gas abnormalities worsen during acute exacerbations and may worsen during exercise and sleep.

Erythrocytosis is infrequently observed in patients living at sea level who have arterial PO_2 levels above 55 mmHg; the frequency of erythrocytosis increases as arterial PO_2 falls below 55 mmHg. The response of the bone marrow to hypoxemia is complex, resulting in a variable relation between blood oxygen level and red cell mass in COPD.

Sputum examination – In stable chronic bronchitis, sputum is mucoid and the predominant cell is the macrophage. During an exacerbation, sputum usually becomes purulent with an influx of neutrophils. The Gram stain usually shows a mixture of organisms. The most frequent pathogens cultured from the sputum are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Other oropharyngeal flora such as Moraxella catarrhalis have been shown to cause exacerbations. However, cultures and even Gram stains are rarely necessary before instituting antimicrobial therapy in the outpatient setting.

REFERENCES

1. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet 1998;351:1225.
2. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variations in the prevalence of asthma symptoms: The International Study of Asthma and Allergies in Childhood (ISAAC). Eur Respir J 1998; 12:315.
3. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECHRS). Eur Respir J 1996; 9:687.
4. Dubois P, Degrave E, Vandenplas O. Asthma and airway hyperresponsiveness among Belgian conscripts 1978-1991. Thorax 1998;53:101.
5. Kemp T, Pearce N. The decline in asthma hospitalizations in persons aged 0-34 years in New Zealand. Aust NZ J Med 1997; 27:578.
6. CDC. Asthma mortality and hospitalization among children and young adults - United States, 1980-1993. MMWR Morb Mortal Wkly Rep 1996;45:350.
7. CDC. Asthma mortality - Illinois, 1979-1994. MMWR Morb Mortal Wkly Rep 1997;46:877.
8. Snider GL. Nosology for our day: its application to chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003;167:678.
9. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet 2004;364:709.
10. Hogg JC, Chu, F, Utokaparch, S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 2004;350:2645.
11. Baraldo S, Turato G, Badin C, et al. Neutrophilic infiltration within the airway smooth muscle in patients with COPD. Thorax 2004;59:308.
12. Sutherland ER, Martin RJ. Airway inflammation in chronic obstructive pulmonary disease: comparisons with asthma. J Allergy Clin Immunol 2003;112:819.
13. Vestbo J, Lange P. Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease?. Am J Respir Crit Care Med 2002;166:329.
14. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004; 350:1005.
15. Garcia-Pachon E. Paradoxical movement of the lateral rib margin (Hoover sign) for detecting obstructive airway disease. Chest 2002; 122:651.