Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging

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Literature review current through: Feb 2021. | **This topic last updated:** Mar 25, 2020.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common respiratory condition characterized by airflow limitation [1,2]. It affects more than 5 percent of the population and is associated with high morbidity and mortality [3,4]. It is the fourth-ranked cause of death in the United States, killing more than 120,000 individuals each year [5]. As a consequence of its high prevalence and chronicity, COPD causes high resource utilization with frequent clinician office visits, frequent hospitalizations due to acute exacerbations, and the need for chronic therapy (eg, supplemental oxygen therapy, medication) [1].

Establishing a correct diagnosis of COPD is important because appropriate management can decrease symptoms (especially dyspnea), reduce the frequency and severity of exacerbations, improve health status, improve exercise capacity, and prolong survival [6]. As current and former smokers are also at risk for a number of other medical problems for which treatment is very different, respiratory symptoms should not be attributed to COPD without appropriate evaluation and diagnosis.

The definition, clinical manifestations, diagnostic evaluation, and staging of COPD are discussed in this topic review. The risk factors, natural history, prognosis, and treatment of COPD are discussed separately. (See "Chronic obstructive pulmonary disease: Risk factors and risk reduction" and "Chronic obstructive pulmonary disease: Prognostic factors and comorbid conditions" and "Stable COPD: Initial pharmacologic management" and "COPD exacerbations: Management".)

DEFINITIONS

The definition of COPD and its subtypes (emphysema, chronic bronchitis, and chronic obstructive asthma) and the interrelationships between the closely related disorders that cause airflow limitation provide a foundation for understanding the spectrum of patient presentations.

Several features of COPD patients identify individuals with different prognoses and/or responses to treatment. Whether these features identify separate "phenotypes" of COPD or reflect disease severity remains unclear [7]. However, evaluation of these features can help guide clinical management, and their use in classification of patients is now recommended [8,9]. (See 'Staging' below.)

COPD — The Global Initiative for Chronic Obstructive Lung Disease (GOLD), a project initiated by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO), defines COPD as follows [8]:

"COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The chronic airflow limitation that characterizes COPD is caused by a mixture of small airways disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Chronic inflammation causes structural changes, small airways narrowing, and destruction of lung parenchyma. A loss of small airways may contribute to airflow limitation and mucociliary dysfunction, a characteristic feature of the disease."

Chronic bronchitis — Chronic bronchitis is defined as a chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic cough (eg, bronchiectasis) have been excluded [8]. It may precede or follow development of airflow limitation [8,10,11]. This definition has been used in many studies, despite the arbitrarily selected symptom duration. Symptoms of chronic bronchitis may develop in cigarette smokers as early as 36 years of age and have been associated with a higher frequency of exacerbation events, even in the absence of airflow obstruction [12]. Current and former smokers have increased airway mucin concentration (MUC5AC and MUC5B), compared with never smokers; those with symptoms of chronic bronchitis also have higher concentrations than those of similar GOLD stage (table 1) without symptoms [13].

Emphysema — Emphysema is a pathological term that describes some of the structural changes sometimes associated with COPD. These changes include abnormal and permanent enlargement of the airspaces distal to the terminal bronchioles that is accompanied by destruction of the airspace walls, without obvious fibrosis (ie, there is no fibrosis visible to the naked eye) [14]. Exclusion of

obvious fibrosis was intended to distinguish the alveolar destruction due to emphysema from that due to the interstitial pneumonias. However, many studies have found increased collagen in the lungs of patients with mild COPD, indicating that fibrosis can be a component of emphysema [15,16]. While emphysema can exist in individuals who do not have airflow obstruction, it is more common among patients who have moderate or severe airflow obstruction [8,17-19].

The various subtypes of emphysema (eg, proximal acinar, panacinar, distal acinar) are described below. (See 'Pathology' below.)

Asthma — The Global Initiative for Asthma (GINA) gives the following definition of asthma: "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment [20]."

Interrelationships among asthma, chronic bronchitis, and emphysema — Early definitions of COPD distinguished different types (ie, chronic bronchitis, emphysema, asthma), a distinction that is not included in the current definition [21-23]. However, individual patients present with a spectrum of manifestations of COPD and related processes, so understanding the types of COPD, as illustrated in the figure (figure 1), can be helpful diagnostically. Important points about their interrelationship include:

- Patients with asthma whose airflow obstruction is completely reversible are not considered to have COPD (subset nine in the figure).
- Patients with asthma whose airflow obstruction does not remit completely are considered to have COPD (subsets six, seven, and eight in the figure). The etiology and pathogenesis of the COPD in such patients may be different from that of patients with chronic bronchitis or emphysema.
- Chronic bronchitis and emphysema with airflow obstruction commonly occur together (subset five in the figure) [24]. Some of these patients may also have asthma (subset eight in the figure).
- Individuals with asthma may develop a chronic productive cough, either spontaneously or due to exposure (eg, cigarette smoke, allergen). Such patients are often referred to as having asthmatic bronchitis, although this terminology has not been officially endorsed in clinical practice guidelines (subset six in the figure).
- Persons with chronic bronchitis, emphysema, or both are not considered to have COPD unless they have airflow obstruction (subsets one, two, and eleven in the figure) [25,26].

- Patients with airflow obstruction due to diseases that have a known etiology or a specific pathology (eg, cystic fibrosis, bronchiectasis, obliterative bronchiolitis) are not considered to have COPD (subset 10 in the figure). However, these exclusions are loosely defined [27].

Asthma-COPD overlap — Consistent with the idea that significant overlap exists among the different types of COPD, many individuals have inflammatory features of both asthma and chronic bronchitis/emphysema [8,28-30]. Similarly, the nature of the inflammation varies widely even among individuals with a single type of COPD. In recognition of this overlap, GOLD and GINA issued a consensus statement on Asthma, COPD, and Asthma-COPD Overlap (ACO) [31], which describes the overlap as "characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. Asthma-COPD overlap is therefore identified in clinical practice by the features that it shares with both asthma and COPD."

Further study of this overlap will be needed to determine with certainty how treatment algorithms should be tailored to these patients [29,32]. As an example, a subgroup of patients with eosinophilia may experience lung function improvement with anti-interleukin-5 or anti-IL-5 receptor monoclonal antibodies that deplete blood and sputum eosinophils [33-35]. Further investigation into this medication class is ongoing. Similarly, an evolving literature suggests differential responses to inhaled glucocorticoids in patients with or without increased circulating eosinophils [36,37]. (See "Stable COPD: Follow-up pharmacologic management", section on 'Future directions'.)

PATHOLOGY

The predominant pathologic changes of COPD are found in the airways, but changes are also seen in the lung parenchyma and pulmonary vasculature. In an individual, the pattern of pathologic changes depends on the underlying disease (eg, chronic bronchitis, emphysema, alpha-1 antitrypsin deficiency), possibly individual susceptibility, and disease severity [8]. While radiographic methods do not have the resolution of histology, high resolution computed tomography can assess lung parenchyma [38], airways [39], and pulmonary vasculature [40].

- **Airways** – Airways abnormalities in COPD include chronic inflammation, increased numbers of goblet cells, mucus gland hyperplasia, fibrosis, narrowing and reduction in the number of small airways, and airway collapse due to the loss of tethering caused by alveolar wall destruction in emphysema [17]. Among patients with chronic bronchitis who have mucus hypersecretion, an increased number of goblet cells and enlarged submucosal glands are typically seen. Chronic inflammation in chronic bronchitis and emphysema is characterized by the presence of CD8+ T-lymphocytes, neutrophils, and CD68+ monocytes/macrophages (picture 1) in the airways [41-45]. In comparison, the bronchial inflammation of asthma is characterized by the presence of

CD4+ T-lymphocytes, eosinophils, and increased interleukin (IL)-4 and IL-5 [28,46,47]. While these paradigms are helpful conceptually, they are not diagnostic and overlaps exist. For example, there may be a set of asthmatic patients who progress to develop COPD.

- **Lung parenchyma** – Emphysema affects the structures distal to the terminal bronchiole, consisting of the respiratory bronchiole, alveolar ducts, alveolar sacs, and alveoli, known collectively as the acinus. These structures in combination with their associated capillaries and interstitium form the lung parenchyma. The part of the acinus that is affected by permanent dilation or destruction determines the subtype of emphysema.

  - Proximal acinar (also known as centrilobular) emphysema refers to abnormal dilation or destruction of the respiratory bronchiole, the central portion of the acinus. It is commonly associated with cigarette smoking, but can also be seen in coal workers' pneumoconiosis.

  - Panacinar emphysema refers to enlargement or destruction of all parts of the acinus. Diffuse panacinar emphysema is most commonly associated with alpha-1 antitrypsin deficiency, although it can be seen in combination with proximal emphysema in smokers. (See "Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency".)

  - In distal acinar (also known as paraseptal) emphysema, the alveolar ducts are predominantly affected. Distal acinar emphysema may occur alone or in combination with proximal acinar and panacinar emphysema. When it occurs alone, the usual association is spontaneous pneumothorax in a young adult. (See "Pneumothorax in adults: Epidemiology and etiology".)

- **Pulmonary vasculature** – Changes in the pulmonary vasculature include intimal hyperplasia and smooth muscle hypertrophy/hyperplasia thought to be due to chronic hypoxic vasoconstriction of the small pulmonary arteries [48]. Destruction of alveoli due to emphysema can lead to loss of the associated areas of the pulmonary capillary bed and pruning of the distal vasculature, which can be detected radiographically [40].

CLINICAL FEATURES

Smoking and inhalational exposure history — The most important risk factor for chronic obstructive pulmonary disease (COPD) is cigarette smoking. Other exposures including passive smoke and biomass fuel use also play roles [8,49,50].

The amount and duration of smoking contribute to disease severity [8,51-53]. Thus, a key step in the evaluation of patients with suspected COPD is to ascertain the number of pack-years smoked (packs

of cigarettes per day multiplied by the number of years), as the majority (about 80 percent) of patients with COPD in the United States have a history of cigarette smoking [51,54]. A smoking history should include the age of starting and the age of quitting, as patients may underestimate the number of years they smoked. With enough smoking, almost all smokers will develop measurably reduced lung function [6]. While studies have shown an overall "dose-response curve" for smoking and lung function, some individuals develop severe disease with fewer pack-years and others have minimal to no symptoms despite many pack-years [6].

The exact threshold for the duration/intensity of cigarette smoking that will result in COPD varies from one individual to another. In the absence of a genetic/environmental/occupational predisposition, smoking less than 10 to 15 pack-years of cigarettes is unlikely to result in COPD. In one study, the single best variable for predicting which adults will have airflow obstruction on spirometry is a history of more than 40 pack-years of smoking (positive likelihood ratio [LR], 12 [95% CI, 2.7-50]) [52,55]. However, other data suggest smoking duration may provide stronger risk estimates of COPD than the composite index of pack-years [53].

The chronologically taken environmental/occupational history may disclose other important risk factors for COPD, such as exposure to fumes or organic or inorganic dusts. These exposures help to explain the 20 percent of patients with COPD (defined by lung function alone) and the 20 percent of patients who die from COPD who never smoked [51,56,57]. A history of asthma should also be sought, as COPD is often misdiagnosed as asthma. In addition, asthma may progress to fixed airflow limitation and COPD [56]. (See "Chronic obstructive pulmonary disease: Risk factors and risk reduction" and 'Asthma-COPD overlap' above.)

Symptoms and pattern of onset — The three cardinal symptoms of COPD are dyspnea, chronic cough, and sputum production and the most common early symptom is exertional dyspnea. Less common symptoms include wheezing and chest tightness (table 2A). However, any of these symptoms may develop independently and with variable intensity.

There are three typical ways in which patients with COPD present [58]:

- Patients who have an extremely sedentary lifestyle but few complaints require careful questioning to elicit a history that is suggestive of COPD. Some patients unknowingly avoid exertional dyspnea by shifting their expectations and limiting their activity. They may be unaware of the extent of their limitations or that their limitations are due to respiratory symptoms, although they may complain of fatigue.

- Patients who present with respiratory symptoms generally complain of dyspnea and chronic cough. The dyspnea may initially be noticed only during exertion. However, it eventually becomes noticeable with progressively less exertion or even at rest. The chronic cough is

characterized by the insidious onset of sputum production, which occurs in the morning initially, but may progress to occur throughout the day. The daily volume rarely exceeds 60 mL. The sputum is usually mucoid, but becomes purulent during exacerbations.

- Patients who present with episodes of increased cough, purulent sputum, wheezing, fatigue, and dyspnea that occur intermittently, with or without fever. Diagnosis can be problematic in such patients. The combination of wheezing plus dyspnea may lead to an incorrect diagnosis of asthma. Conversely, other illnesses with similar manifestations are often incorrectly diagnosed as a COPD exacerbation (eg, heart failure, bronchiectasis, bronchiolitis) (table 3). The interval between exacerbations decreases as the severity of the COPD increases. (See "COPD exacerbations: Management".)

Approximately 62 percent of patients with moderate to severe COPD report variability in symptoms (eg, dyspnea, cough, sputum, wheezing, or chest tightness) over the course of the day or week-to-week; morning is typically the worst time of day [59].

Patients with COPD may experience weight gain (due to activity limitations), weight loss (possibly due to dyspnea while eating), limitation of activity (including sexual), cough syncope, or feelings of depression or anxiety. Weight loss generally reflects more advanced disease and is associated with a worse prognosis. However, the majority of COPD patients are overweight or obese.

Comorbid diseases that may accompany COPD include lung cancer, bronchiectasis, cardiovascular disease, osteoporosis, metabolic syndrome, skeletal muscle weakness, anxiety, depression, and cognitive dysfunction. Patients may also report a family history of COPD or other chronic respiratory illness [8,60-65].

It is also important to note that current and former smokers without spirometric evidence of airflow obstruction can have a substantial respiratory symptom and radiographic burden of disease. While such individuals are being actively investigated, the natural history of such individuals has not been fully studied and there is currently no evidence base to guide treatment in such individuals [18,19].

Physical examination — The findings on physical examination of the chest vary with the severity of the COPD (table 2A-B).

- Early in the disease, the physical examination may be normal, or may show only prolonged expiration or wheezes on forced exhalation.

- As the severity of the airway obstruction increases, physical examination may reveal hyperinflation (eg, increased resonance to percussion), decreased breath sounds, wheezes, crackles at the lung bases, and/or distant heart sounds [66]. Features of severe disease include

an increased anteroposterior diameter of the chest ("barrel-shaped" chest) and a depressed diaphragm with limited movement based on chest percussion.

- Patients with end-stage COPD may adopt positions that relieve dyspnea, such as leaning forward with arms outstretched and weight supported on the palms or elbows. This posture may be evident during the examination or may be suggested by the presence of callouses or swollen bursae on the extensor surfaces of forearms. Other physical examination findings include use of the accessory respiratory muscles of the neck and shoulder girdle, expiration through pursed lips, paradoxical retraction of the lower interspaces during inspiration (ie, Hoover's sign) [67,68], cyanosis, asterixis due to severe hypercapnia, and an enlarged, tender liver due to right heart failure. Neck vein distention may also be observed because of increased intrathoracic pressure, especially during expiration.

- Yellow stains on the fingers due to nicotine and tar from burning tobacco are a clue to ongoing and heavy cigarette smoking [69].

  Clubbing of the digits is not typical in COPD (even with associated hypoxemia) and suggests comorbidities such as lung cancer, interstitial lung disease, or bronchiectasis.

EVALUATION

Evaluation for COPD is appropriate in adults who report dyspnea, chronic cough, chronic sputum production or have had a gradual decline in level of peak activity, particularly if they have a history of exposure to risk factors for the disease (eg, cigarette smoking, indoor biomass smoke) [8,52]. All patients are evaluated with spirometry and selected patients have laboratory testing and imaging studies.

There is no evidence to support the benefit of population based screening of asymptomatic adults for COPD [70], but the Global Initiative for Chronic Obstructive Lung Disease (GOLD) does advocate active case finding among at risk individuals. (See "Chronic obstructive pulmonary disease: Risk factors and risk reduction".)

The CAPTURE questionnaire (**C**hronic obstructive pulmonary disease **A**ssessment in **P**rimary care **T**o identify **U**ndiagnosed **R**espiratory disease and **E**xacerbation risk) can help identify patients who would likely benefit from therapy for COPD and would be candidates for diagnostic evaluation (table 4)[71]. This instrument exhibits similar operating characteristics in Spanish [72].

Laboratory — No laboratory test is diagnostic for COPD, but certain tests are sometimes obtained to exclude other causes of dyspnea and comorbid diseases.

- Assessment for anemia is an important step in the evaluation of dyspnea. Measurement of plasma brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) concentrations is useful as a component of the evaluation of suspected heart failure (HF). Blood glucose, urea nitrogen, creatinine, electrolytes, calcium, phosphorus, and thyroid stimulating hormone may be appropriate depending on the degree of clinical suspicion for an alternate diagnosis. (See "Approach to the patient with dyspnea", section on 'Initial testing in chronic dyspnea'.)

- Among stable COPD patients with normal kidney function, an elevated serum bicarbonate may indirectly identify chronic hypercapnia. In the presence of chronic hypercapnia, the serum bicarbonate is typically increased due to a compensatory metabolic alkalosis (figure 2). Abnormal results must be confirmed with arterial blood gas measurement. (See "Simple and mixed acid-base disorders", section on 'Respiratory acid-base disorders'.)

- Testing for alpha-1 antitrypsin (AAT) deficiency should be obtained in all symptomatic adults with persistent airflow obstruction on spirometry, possibly excepting those from geographic areas with a low prevalence of AAT deficiency. Features that are particularly suggestive of AAT deficiency include the emphysema in a young individual (eg, age ≤45 years), emphysema in a nonsmoker or minimal smoker, emphysema characterized by predominantly basilar changes on the chest radiograph, or a family history of emphysema [73]. However, AAT deficiency may be present in a patient with otherwise "typical" COPD. A reasonable threshold for differentiating normal Pi*MM from genotypes with one or more deficient alleles is 18.4 micromol/L (100 mg/dL). Concomitant genotyping can detect the most common variants (eg, F, I, S, and Z, depending on the laboratory). (See "Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency", section on 'Evaluation and diagnosis'.)

Pulmonary function tests — Pulmonary function tests (PFTs), particularly spirometry, are the cornerstone of the diagnostic evaluation of patients with suspected COPD [74]. In addition, PFTs are used to determine the severity of the airflow limitation, assess the response to medications, and follow disease progression. (See 'Diagnosis' below and "Office spirometry".)

Spirometry — When evaluating a patient for possible COPD, spirometry is performed pre and post bronchodilator administration (eg, inhalation of albuterol 400 mcg) to determine whether airflow limitation is present and whether it is partially or fully reversible. Airflow limitation that is irreversible or only partially reversible with bronchodilator is the characteristic physiologic feature of COPD. Screening spirometry is not currently recommended. In contrast, spirometry should be performed in patients with suggestive symptoms [49]. (See "Office spirometry", section on 'Post-bronchodilator spirometry' and 'Screening' below.)

The most important values measured during spirometry are the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC). The postbronchodilator ratio of FEV_1/FVC determines whether airflow limitation is present [8]; the postbronchodilator percent predicted value for FEV_1 determines the severity of airflow limitation as shown in the table (table 1).

Lower limit of normal FEV1/FVC — GOLD guidelines support using the traditional postbronchodilator FEV_1/FVC ratio less than 0.7 as the threshold that indicates airflow limitation [8]. However, the FEV_1/FVC ratio decreases with age, so use of the fifth percentile lower limit of normal (LLN) of the FEV_1/FVC ratio, rather than the absolute value of <0.7, has been advocated by some as a dividing point for the diagnosis of COPD [75-79]. However, the distinction between the LLN and the fixed ratio as dividing points is unlikely to lead to major clinical problems because current recommendations combine physiologic assessment with assessment of symptoms and exacerbations in staging severity. Moreover, in a study of 13,847 subjects, an increased mortality was noted among those with an FEV_1/FVC <0.7, but >LLN FEV_1/FVC, when compared with those whose FEV_1/FVC was 0.7 or higher [80]. Another study that pooled data from multiple cohorts demonstrated that defining airflow obstruction as FEV_1/FVC less than 0.70 provided discrimination of COPD-related hospitalization and mortality that was not significantly different or was more accurate than other fixed thresholds and the LLN [81]. (See "Office spirometry", section on 'Ratio of FEV1/FVC'.)

Global Lung Initiative equations — As an alternative to using the LLN of FEV_1/FVC to define normal airflow on spirometry, a new approach may utilize equations developed by the Global Lung Initiative (GLI) [8,82,83]. Using GLI equations, z scores (number of standard deviations above or below mean) were calculated for FEV_1, FVC, and FEV_1/FVC and compared with fixed ratio data. The findings suggest that among adults with GLI-defined normal spirometry, the use of a fixed ratio may misclassify individuals as having respiratory impairment. These findings await additional study in other cohorts. (See "Selecting reference values for pulmonary function tests", section on 'Spirometry'.)

Forced expiratory volume in six seconds — The forced expiratory volume in six seconds (FEV_6), obtained by stopping the expiratory effort after 6 seconds rather than at cessation of airflow, is an acceptable surrogate for the FVC [84-88]. The advantages of the FEV_1/FEV_6 include less frustration by the patient and technician trying to achieve an end-of-test plateau, less chance of syncope, shorter testing time, and better repeatability, without loss of sensitivity or specificity. The appropriate LLN for FEV_1/FEV_6 from NHANES III should be used to diagnose airflow limitation. (See "Office spirometry", section on 'Forced expiratory volume in six seconds' and "Office spirometry", section on 'Ratio of FEV1/FVC'.)

Peak expiratory flow — Peak expiratory flow (PEF) is often used as a measure of airflow limitation in asthma, but may underestimate the degree of airflow limitation in COPD [8]. In addition, a

low PEF is not specific for airflow limitation and requires corroboration with spirometry. (See "Peak expiratory flow monitoring in asthma".)

Lung volumes — Lung volume measurement is not needed for all patients with suspected COPD. However, when a reduced FVC is noted on postbronchodilator spirometry, lung volume measurement by body plethysmography is used to determine whether the reduction in FVC is due to airtrapping, hyperinflation, or a concomitant restrictive ventilatory defect. Decreased inspiratory capacity (IC) and vital capacity, accompanied by an increased total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV) are indicative of hyperinflation. An increased FRC or RV with a normal TLC is indicative of air trapping without hyperinflation. (See "Overview of pulmonary function testing in adults", section on 'Lung volumes' and "Dynamic hyperinflation in patients with COPD".)

Diffusing capacity — The diffusing capacity for carbon monoxide (DLCO) is an excellent index of the degree of anatomic emphysema in smokers with airflow limitation, but is not needed for routine assessment of COPD [8]. The indications for performing a DLCO measurement include hypoxemia by pulse oximetry (eg, arterial oxygen tension [PaO_2] <92 mmHg), breathlessness out of proportion to the degree of airflow limitation, and evaluation for lung resection or lung volume reduction surgery. The DLCO decreases in proportion to the severity of emphysema; however, it cannot be used to detect mild emphysema because it is neither a sensitive nor a specific test.

Pulse oximetry and arterial blood gases — Pulse oximetry is a noninvasive, easily performed test that assesses blood oxygen saturation. It has reduced the number of patients who require arterial blood gases (ABGs), as supplemental oxygen is not needed when the pulse oxygen saturation (SpO_2) is >88 percent. However, pulse oximetry does not provide information about alveolar ventilation or hypercapnia ($PaCO_2$ >45mmHg), and assessment of oxygenation by pulse oximetry may be inaccurate in the setting of an acute exacerbation of COPD [89]. (See "Pulse oximetry" and "Arterial blood gases" and "The evaluation, diagnosis, and treatment of the adult patient with acute hypercapnic respiratory failure".)

The indications for measuring ABGs (eg, PaO_2, $PaCO_2$, and acidity [pH]), which must be considered in the clinical context, include the following:

- Low FEV_1 (eg, <50 percent predicted)
- Low oxygen saturation by pulse oximetry (eg, <92 percent)
- Depressed level of consciousness
- Acute exacerbation of COPD

- Assessment for hypercapnia in at risk patients 30 to 60 minutes after initiation of supplemental oxygen (see "The evaluation, diagnosis, and treatment of the adult patient with acute hypercapnic respiratory failure")

In patients with mild to moderate COPD, arterial blood gases usually reveal mild or moderate hypoxemia without hypercapnia. As the disease progresses, the hypoxemia becomes more severe and hypercapnia may develop. Hypercapnia becomes progressively more likely when the FEV_1 approaches or falls below one liter. Blood gas abnormalities worsen during acute exacerbations and may also worsen during exercise and sleep. The compensatory responses to acute and chronic respiratory acidosis are shown in the figure and discussed separately (figure 3). (See "Simple and mixed acid-base disorders", section on 'Response to respiratory acidosis'.)

Imaging — Chest radiography and computed tomography (CT) are typically performed in patients with COPD when the cause of dyspnea or sputum production is unclear and during acute exacerbations to exclude complicating processes (eg, pneumonia, pneumothorax, heart failure). Imaging is not required to diagnose COPD. However, in patients with severe COPD, CT scanning identifies individuals with predominantly upper lobe disease who may be candidates for lung volume reduction surgery or medical lung volume reduction with endobronchial valves. (See 'Diagnosis' below and "Lung volume reduction surgery in COPD" and "Bronchoscopic treatment of emphysema".)

Chest radiography — The main reasons to obtain a chest radiograph when evaluating a patient for COPD are to exclude alternative diagnoses, evaluate for comorbidities (eg, lung cancer with airway obstruction, bronchiectasis, pleural disease, interstitial lung disease, heart failure), or to look for complications of COPD (eg, pneumonia, pneumothorax) that might be suggested by a change in symptoms.

Plain chest radiographs have a poor sensitivity for detecting COPD. As an example, only about half of patients with COPD of moderate severity are identified as having COPD by a plain chest radiograph (ie, sensitivity of 50 percent).

Radiographic features suggestive of COPD (usually seen in advanced disease) include:

- Rapidly tapering vascular shadows, increased radiolucency of the lung, a flat diaphragm, and a long, narrow heart shadow on a frontal radiograph (image 1).
- A flat diaphragmatic contour and an increased retrosternal airspace on a lateral radiograph (image 2). These findings are due to hyperinflation.
- Bullae, defined as radiolucent areas larger than one centimeter in diameter and surrounded by arcuate hairline shadows. They are due to locally severe disease, and may or may not be

accompanied by widespread emphysema (image 3).

- When advanced COPD leads to pulmonary hypertension and cor pulmonale, prominent hilar vascular shadows and encroachment of the heart shadow on the retrosternal space may be seen [90,91]. The cardiac enlargement may become evident only by comparison with previous chest radiographs. (See "Treatment and prognosis of pulmonary arterial hypertension in adults (group 1)".)

Computed tomography — CT has greater sensitivity and specificity than standard chest radiography for the detection of emphysema. This is particularly true with high resolution CT (ie, collimation of 1 to 2 mm) [92-96]. The use of expiratory scans, particularly when used in conjunction with the inspiratory scans, can also be used to assess non-emphysematous air trapping as a surrogate measure for small airway abnormality [97] (see "High resolution computed tomography of the lungs"). However, CT scanning is not needed for the routine diagnosis of COPD. Usually, it is performed when a change in symptoms suggests a complication of COPD (eg, pneumonia, pneumothorax, giant bullae), an alternate diagnosis (eg, thromboembolic disease) is suspected, lung cancer screening is indicated, or a patient is being considered for medical lung volume reduction with endobronchial valves, lung volume reduction surgery, or lung transplantation [8]. (See "Evaluation and medical management of giant bullae", section on 'Evaluation' and "Lung volume reduction surgery in COPD", section on 'Patient selection' and "Clinical presentation, evaluation, and diagnosis of the nonpregnant adult with suspected acute pulmonary embolism" and "Bronchoscopic treatment of emphysema".)

Certain CT scan features can determine whether the emphysema is centriacinar (centrilobular), panacinar, or paraseptal, although this is usually not necessary for clinical management [95,98].

- Centriacinar emphysema occurs preferentially in the upper lobes and produces holes in the center of secondary pulmonary lobules. The walls of emphysematous spaces are usually imperceptible, but central vessels may be visible (image 4). In contrast, the walls of cysts in pulmonary Langerhans histiocytosis, another cystic lung disease of cigarette smokers, are thicker (image 5). (See 'Pathology' above.)

- Panacinar emphysema more commonly involves the lung bases and involves the entire secondary pulmonary lobule (image 6). Panacinar emphysema can cause a generalized paucity of vascular structures. Among patients with alpha-1 antitrypsin deficiency, panacinar emphysema is the more common pattern. (See "Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency", section on 'Clinical manifestations'.)

- Paraseptal (distal acinar) emphysema produces small, subpleural collections of gas located in the periphery of the secondary pulmonary lobule (image 7). It is considered to be the

precursor of bullae (image 8). (See 'Pathology' above.)

Newer CT scanners with higher resolution and new analytical methods can resolve airway dimensions, although the clinical significance of these measures is undefined [95,99,100]. Quantitative parameters based on lung density, as measured by CT scan, have been established to gauge emphysema, but are currently used primarily as research tools.

The use of low dose CT scans to screen for lung cancer is discussed separately. (See "Screening for lung cancer", section on 'Low-dose chest CT'.)

DIAGNOSIS

The presence of symptoms compatible with COPD (eg, dyspnea at rest or on exertion, cough with or without sputum production, progressive limitation of activity) are suggestive of the diagnosis, especially if there is a history of exposure to triggers of COPD (eg, tobacco smoke, occupational dust, indoor biomass smoke), a family history of chronic lung disease, or presence of associated comorbidities (table 5).

The diagnosis of COPD is confirmed by the following [8,9]:

- Spirometry demonstrating airflow limitation (ie, a forced expiratory volume in one second/forced vital capacity [FEV_1/FVC] ratio less than 0.7 or less than the lower limit of normal [LLN]) that is incompletely reversible after the administration of an inhaled bronchodilator (table 2A-B). (See 'Pulmonary function tests' above.)

- Absence of an alternative explanation for the symptoms and airflow limitation (table 3) [8]. The differential diagnosis of COPD is discussed below. (See 'Differential diagnosis' below and "Approach to the patient with dyspnea".)

- The Global Initiative for COPD (GOLD) guidelines suggest repeating spirometry on a separate occasion to demonstrate persistence of airflow limitation (FEV_1/FVC <0.7 or less than the LLN) for patients with an initial FEV_1/FVC between 0.6 and 0.8 [8,101,102].

After confirming the presence of COPD, the next step is to consider the cause. For the majority of patients, the etiology is long-term cigarette smoking. However, it is important to review with the patient whether underlying asthma, workplace exposures, indoor use of biomass fuel, a prior history of tuberculosis, or familial predisposition is contributory, because mitigation of ongoing exposures may reduce disease progression.

It is appropriate to screen all patients with COPD for alpha-1 antitrypsin (AAT) deficiency by obtaining an AAT serum level and AAT genotyping, possibly excepting areas with a low prevalence of AAT deficiency [8,103]. (See 'Laboratory' above and "Chronic obstructive pulmonary disease: Risk factors and risk reduction" and "Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency", section on 'Laboratory testing'.)

DIFFERENTIAL DIAGNOSIS

Among patients who present in mid or later life with dyspnea, cough, and sputum production, the differential diagnosis is broad (eg, heart failure, COPD, interstitial lung disease, thromboembolic disease) (table 3). Typically, the finding of persistent airflow limitation on pulmonary function testing and the absence of radiographic features of heart failure or interstitial lung disease direct the clinician to a narrower differential of COPD, chronic obstructive asthma, bronchiectasis, tuberculosis, constrictive bronchiolitis, and diffuse panbronchiolitis [8]. Importantly, these conditions can commonly occur together, for example, patients with asthma may develop COPD and patients with COPD may have concurrent bronchiectasis.

- **Chronic obstructive asthma** – In some patients with chronic asthma, a clear distinction from COPD is not possible. As an example, a patient, who has had atopic asthma since childhood and smoked cigarettes for 15 years in their twenties and thirties could present in their fifties with a combination of asthma and COPD. The importance of recognizing the coexistence of these diseases is in devising a treatment plan that is adapted to reflect both underlying disease processes. (See 'Interrelationships among asthma, chronic bronchitis, and emphysema' above and "Asthma in adolescents and adults: Evaluation and diagnosis".)

- **Chronic bronchitis with normal spirometry** – A small portion of cigarette smokers have a chronic productive cough for three months in two successive years, but do not have airflow limitation on pulmonary function tests. They are not considered to have COPD, although they may develop COPD if they continue to smoke. Some treatments for COPD may improve their cough. (See 'Interrelationships among asthma, chronic bronchitis, and emphysema' above.)

- **Central airway obstruction** – Central airway obstruction can be caused by numerous benign and malignant processes and can mimic COPD with a slowly progressive dyspnea on exertion followed by dyspnea with minimal activity (table 6). Monophonic wheezing or stridor may be present. Symptoms are minimally improved by inhaled bronchodilator, if at all. A high index of suspicion is needed as conventional chest radiographs are rarely diagnostic. Though insensitive, flow volume loops can show the characteristic changes of central airway obstruction, frequently before abnormalities in the spirometric volumes are noted (figure 4 and figure 5) [104]. A

high resolution CT scan with three-dimensional reconstruction can be helpful. The gold standard for diagnosis is direct visualization. (See "Clinical presentation, diagnostic evaluation, and management of central airway obstruction in adults", section on 'Diagnostic evaluation and initial management'.)

- **Bronchiectasis** – Bronchiectasis, a condition of abnormal widening of the bronchi that is associated with chronic or recurrent infection, shares many clinical features with COPD, including inflamed and easily collapsible airways, obstruction to airflow, and exacerbations characterized by increased dyspnea and sputum production. Bronchiectasis is suspected on the basis of prominent symptoms of cough and daily mucopurulent sputum production. The diagnosis is usually established clinically based on the characteristic cough and sputum production and the presence of bronchial wall thickening and luminal dilatation on chest computed tomographic (CT) scans. (See "Clinical manifestations and diagnosis of bronchiectasis in adults".)

- **Heart failure** – Heart failure is a common cause of dyspnea among middle-aged and older patients and some patients experience chest tightness and wheezing with fluid overload due to heart failure. Occasionally, airflow limitation is noted, although a restrictive pattern is more common. Heart failure is usually differentiated by the presence of fine basilar crackles, radiographic evidence of an increased heart size and pulmonary edema. The brain natriuretic peptide is typically increased in heart failure, but can also be increased during right heart strain from cor pulmonale. (See "Heart failure: Clinical manifestations and diagnosis in adults".)

- **Tuberculosis** – In an area endemic for tuberculosis, the overall prevalence of airflow obstruction was 31 percent among those with a past history of tuberculosis compared with 14 percent among those without. This association was unchanged after adjustment for respiratory disease in childhood, smoking, and exposure to dust and smoke [105,106]. Thus, tuberculosis is both a risk factor for COPD and a potential comorbidity [8]. (See "Clinical manifestations and complications of pulmonary tuberculosis".)

- **Constrictive bronchiolitis** – Constrictive bronchiolitis, also known as bronchiolitis obliterans, is characterized by submucosal and peribronchiolar fibrosis that causes concentric narrowing of the bronchiolar lumen. Constrictive bronchiolitis is most commonly seen following inhalation injury, transplantation (eg, bone marrow, lung), or in the context of rheumatoid lung or inflammatory bowel disease (table 7). Symptoms include progressive onset of cough and dyspnea associated with hypoxemia at rest or with exercise. Crackles may be present. Pulmonary function tests show a progressive and irreversible airflow limitation. Findings on inspiratory CT scan include centrilobular bronchial wall thickening, bronchiolar dilation, tree-in-bud pattern, and a mosaic ground-glass attenuation pattern. (See "Overview of bronchiolar disorders in adults", section on 'Bronchiolitis obliterans'.)

- **Diffuse panbronchiolitis** – Diffuse panbronchiolitis is predominantly seen in male nonsmokers of Asian descent. Almost all have chronic sinusitis. On pulmonary function testing, an obstructive defect is common, although a mixed obstructive-restrictive pattern may also be seen. Chest radiographs and high resolution CT scans show diffuse centrilobular nodular and linear opacities corresponding to thickened and dilated bronchiolar walls with intraluminal mucous plugs. (See "Diffuse panbronchiolitis", section on 'Diagnosis'.)

- **Lymphangioleiomyomatosis** – Lymphangioleiomyomatosis (LAM) is seen primarily in young women of childbearing age. Pulmonary function testing frequently reveals mild airflow obstruction, although a mixed obstructive-restrictive pattern may be seen. CT scans typically demonstrate small, thin-walled cysts that can at times be confused with emphysema. However, the airspaces in emphysema are not actually cysts but are caused by the destruction of alveolar walls and permanent enlargement of distal airspaces, so the "walls" are typically inapparent. (See 'Diagnosis' above and "Sporadic lymphangioleiomyomatosis: Epidemiology and pathogenesis".)

SCREENING

Routine screening spirometry is generally not indicated for adults who have none of the features suggestive of COPD (eg, no dyspnea, cough, sputum production or progressive decline in activity), as asymptomatic mild airflow obstruction does not require treatment [52,107]. Asymptomatic and nonsmoking subjects with mild airflow obstruction, but no history of asthma, do not have the same progressive decline in lung function that is observed among individuals who have a similar degree of airflow obstruction and are symptomatic or continue to smoke [108].

On the other hand, waiting for patients to report symptoms may miss a large number of patients who have COPD, as 20 percent of individuals with severe airway obstruction due to smoking or asthma will not report symptoms. Decrements in forced expiratory volume in one second (FEV_1), even within the normal range, are associated with increased risk of acute cardiac events independent of age, gender, and smoking history [60]. Thus, performance of spirometry seems reasonable whenever COPD is a diagnostic consideration. The diagnosis of COPD may alter management of concurrent conditions and may affect the approach to exercise. Exclusion of COPD can often contribute to clinical management as much as its diagnosis by leading to alternative diagnoses.

STAGING

The initial Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines used the forced expiratory volume in one second (FEV_1; expressed as a percentage of predicted) to stage disease severity (table 1) (see 'Spirometry' above). However, the FEV_1 only captures one component of COPD severity: two patients with the same percent predicted FEV_1 can have a substantially different exercise tolerance and prognosis. Other aspects of disease, such as the severity of symptoms, risk of exacerbations, and the presence of comorbidities, are important to the patient's experience of the disease and prognosis and are included in newer staging systems, such as the revised GOLD classification [8,109].

GOLD system — The therapeutic strategy of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy suggests using a combined assessment based on an individual's symptoms (ie, modified Medical Research Council dyspnea scale or COPD Assessment Test) and exacerbation history to guide therapy (table 1 and table 8) [8]. The multidimensional GOLD “ABCD” evaluation is discussed separately in the context of initial management of COPD. (See "Stable COPD: Initial pharmacologic management".)

While not included in the GOLD “ABCD” symptom and risk assessments, spirometry is integral to the diagnosis of COPD and severity assessment which contributes to prognosis. Follow-up spirometric assessment may also be helpful in therapeutic decision making when, for instance, there is a discrepancy between spirometry and level of symptoms or in determining the need to consider alternative diagnoses if symptoms are disproportionate to the degree of airflow obstruction. GOLD also recommends annual spirometry to track decline in FEV_1. Spirometry is also essential to decision-making for lung volume reduction and lung transplantation.

BODE index — The BODE index, which is another system for assessment of COPD severity and prognosis, is calculated based on weight (BMI), airway obstruction (FEV_1), dyspnea (mMRC dyspnea score) (table 8), and exercise capacity (six-minute walk distance) (calculator 1), has been used to assess an individual’s risk of death. This index provides better prognostic information than the FEV_1 alone and can be used to assess therapeutic response to medications, pulmonary rehabilitation therapy, and other interventions [110-113]. (See "Chronic obstructive pulmonary disease: Prognostic factors and comorbid conditions", section on 'BODE index'.)

COPD Foundation system — The COPD Foundation has introduced a staging system that includes seven severity domains, each of which has therapeutic implications (figure 6) [9,52]. These domains are based upon assessment of spirometry, regular symptoms, number of exacerbations in the past year, oxygenation, emphysema on computed tomography scan, presence of chronic bronchitis, and comorbidities. Within these domains, the COPD Foundation uses five spirometric grades:

- SG 0: Normal spirometry
- SG 1: Mild, postbronchodilator FEV_1/FVC ratio <0.7, FEV_1 ≥60 percent predicted
- SG 2: Moderate, postbronchodilator FEV_1/FVC ratio <0.7, 30 percent ≤FEV_1 <60 percent predicted
- SG 3: Severe, postbronchodilator FEV_1/FVC ratio <0.7, FEV_1 <30 percent predicted
- SG U: Undefined, postbronchodilator FEV_1/FVC ratio >0.7, FEV_1 <80 percent predicted

An advantage of this staging system is that it simplifies the interpretation of spirometry; any spirometric finding results in a classification, which is not the case in GOLD.

While FEV_1 is used to gauge severity, the FEV_1/FVC ratio is not used for this purpose because measurement of FVC becomes less reliable as the disease progresses (the long exhalations are difficult for the patients), thus making the ratio less accurate. (See "Chronic obstructive pulmonary disease: Prognostic factors and comorbid conditions", section on 'Forced expiratory volume in one second'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Chronic obstructive pulmonary disease".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Chronic obstructive pulmonary disease (COPD) (The Basics)" and "Patient education: Chronic bronchitis (The Basics)" and "Patient education:

Medicines for chronic obstructive pulmonary disease (COPD) (The Basics)")

- Beyond the Basics topics (see "Patient education: Chronic obstructive pulmonary disease (COPD) (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as follows: "Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The chronic airflow limitation that characterizes COPD is caused by a mixture of small airways disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Chronic inflammation causes structural changes, small airways narrowing and destruction of lung parenchyma. A loss of small airways may contribute to airflow limitation and mucociliary dysfunction, a characteristic feature of the disease." (See 'Definitions' above.)

- Substantial overlap exists between COPD and the other disorders that cause airflow limitation (eg, emphysema, chronic bronchitis, asthma, bronchiectasis, bronchiolitis) as illustrated in the figure (figure 1). (See 'Interrelationships among asthma, chronic bronchitis, and emphysema' above.)

- Common presentations of COPD include patients with few complaints, but an extremely sedentary lifestyle; patients with chronic, daily respiratory symptoms (eg, dyspnea on exertion, cough); and patients with recurrent acute exacerbations (eg, wheezing, cough, dyspnea, fatigue). The physical examination of the chest varies with the severity of the COPD, but is often normal in mild disease (table 2A-B). (See 'Clinical features' above.)

  The diagnosis of COPD should be considered and spirometry performed in all patients who report any combination of dyspnea, chronic cough, or chronic sputum production, especially if there is a history of exposure to triggers of COPD (eg, tobacco smoke, occupational dust, indoor biomass smoke), a family history of chronic lung disease, or presence of associated comorbidities (table 5). (See 'Pulmonary function tests' above and 'Diagnosis' above.)

- COPD is confirmed when a patient with compatible symptoms is found to have irreversible airflow limitation (ie, a post bronchodilator forced expiratory volume in one second [FEV_1]/forced vital capacity [FVC] ratio less than 0.7 [or less than the lower limit of normal]) and no alternative

explanation for the symptoms and airflow obstruction. (See 'Pulmonary function tests' above and 'Diagnosis' above.)

- In general, all symptomatic adults with fixed airflow obstruction on spirometry should be tested for AAT deficiency, preferably with an AAT serum level and genotype, with the possible exception of patients from geographic areas with a low disease prevalence. (See 'Laboratory' above and "Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency", section on 'Evaluation and diagnosis'.)

- In the evaluation of patients with COPD, chest radiography is typically performed to exclude alternative diagnoses, evaluate for comorbidities, or assess a change in symptoms that suggests a complication of COPD. Chest computed tomography is performed to evaluate abnormalities seen on the conventional chest radiograph, to exclude certain complications of COPD (eg, thromboembolic disease, lung cancer), or when a patient is being considered for lung volume reduction surgery, endobronchial valves, or lung transplantation. (See 'Imaging' above.)

- The original FEV_1-based GOLD staging system is shown in the table (table 1). Although well-recognized and commonly used, it has been criticized for underestimating the importance of the severity of symptoms, risk of exacerbations, and presence of comorbidities in predicting outcome. The revised GOLD strategy uses a combination of an individual's symptoms and history of exacerbations and hospitalizations due to exacerbations to stratify symptoms and exacerbation risk and guide therapy (table 1). Other multidimensional staging systems include the BODE index (calculator 1) and the COPD Foundation system (figure 6). (See 'Staging' above.)

- The management of COPD and strategies for smoking cessation are discussed separately. (See "Stable COPD: Initial pharmacologic management" and "Overview of smoking cessation management in adults".)

ACKNOWLEDGMENT

The editorial staff at UpToDate would like to acknowledge Stephen Rennard, MD, who contributed to an earlier version of this topic review.

Topic 1455 Version 45.0

GRAPHICS

Multidimensional assessment of COPD

GOLD "ABCD" grading: Assessment of symptoms and risk of exacerbations for initiation of COPD therapy

Assess exacerbation risk: Exacerbations/Hospitalizations	Assess symptoms	
	mMRC* 0 to 1; CAT <10 ¶	mMRC ≥2; CAT ≥10
0 or 1 exacerbations without hospitalization	A	B
≥2 exacerbations or ≥1 hospitalization	C	D

GOLD: Severity of airflow limitation (based on postbronchodilator FEV_1)

Stage	Severity	FEV_1 (percent predicted)
In patients with FEV_1/FVC <0.7: Δ		
GOLD 1	Mild	≥80
GOLD 2	Moderate	50 to 79
GOLD 3	Severe	30 to 49
GOLD 4	Very severe	<30

COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council dyspnea scale; CAT: COPD Assessment Test; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

* mMRC dyspnea scale: Refer to UpToDate graphic.

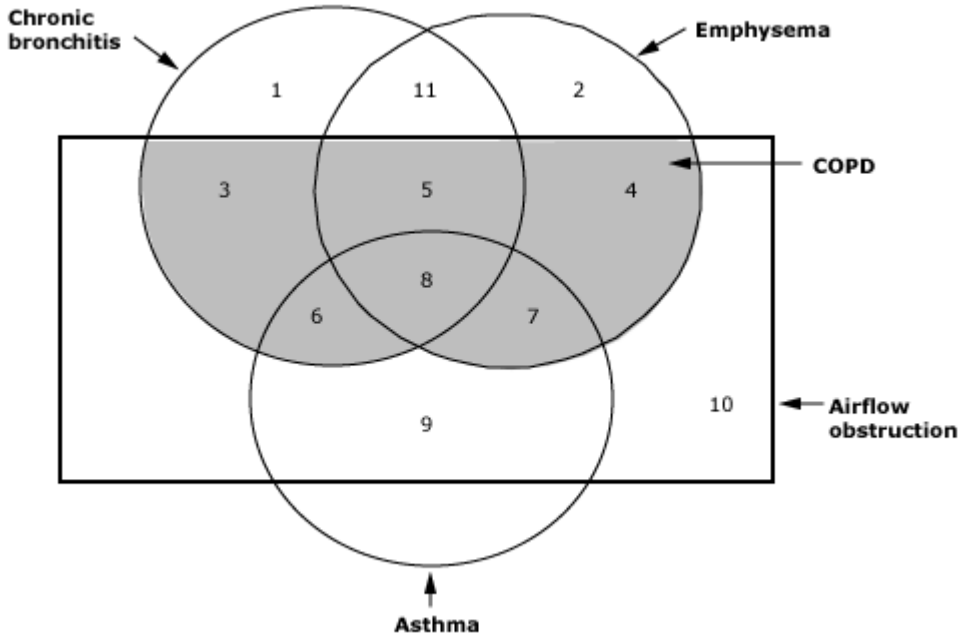
¶ http://www.catestonline.org.

Δ The GOLD guidelines (www.goldcopd.org) prefer the threshold of <0.7 to the alternative of the fifth percentile lower limit of normal (LLN) for FEV_1/FVC.

From the Global Strategy for the Diagnosis, Management and Prevention of COPD 2017, © Global Initiative for Chronic Obstructive Lung Disease (GOLD), www.goldcopd.org. Adapted with permission. The content within this table is still current as of the 2019 GOLD report.

Graphic 82690 Version 10.0

Chronic obstructive pulmonary disease

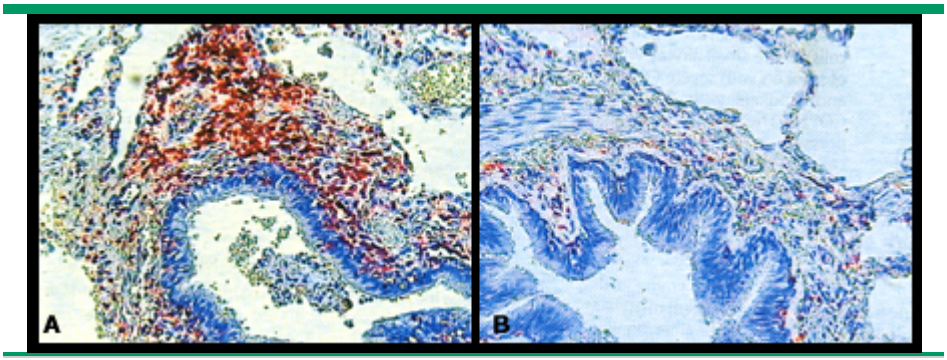


This nonproportional Venn diagram shows subsets of patients with chronic bronchitis, emphysema, and asthma (black circles). The subsets defined as COPD are shaded gray. Subset areas are not proportional to actual relative subset sizes. Asthma is, by definition, associated with reversible airflow obstruction; 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 hyperreactivity. 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. In order to emphasize that cough and sputum are abnormal, individuals with these symptoms and normal lung function were classified as GOLD Stage 0, at risk, in the original GOLD classification [1]. This stage was deleted in the 2006 revision because of uncertainties about whether it is progressive [2]. Patients with airway obstruction due to diseases with known etiology or specific pathology, such as cystic fibrosis or obliterative bronchiolitis (subset 10), are not generally included in the definition of COPD.

1. Data from: Global initiative for chronic obstructive lung disease (GOLD). Workshop report: Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: Update 2005.
2. Data from: Global initiative for chronic obstructive lung disease (GOLD). Workshop report: Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: Update 2006.

Graphic 66708 Version 1.0

Leukocyte infiltration in COPD



Photomicrograph showing leukocyte infiltration in a small airway of a smoker with severe COPD (A); and that of smoker with a mild COPD (B). Immunostaining with monoclonal antibody anti-CD45. Leukocytes are stained in red. Original magnification: X400.

Reproduced with permission from: Turato G, Zuin R Miniati M et al. Airway inflammation in severe chronic obstructive pulmonary disease: relationship with lung function and radiologic emphysema. Am J Respir Crit Care Med 2002;166:105. Copyright © 2002 American Thoracic Society.

Graphic 69029 Version 3.0

Diagnosis of chronic obstructive pulmonary disease: Clinical features

History
Risk factors
▪ Family history
▪ Smoking history
• Age at initiation
• Average amount smoked per day since initiation
• Date when stopped smoking or a current smoker
▪ Environmental history
• The chronologically taken environmental history may disclose important risk factors for COPD
▪ Asthma
Symptoms
▪ Dyspnea
• Ask about the amount of effort required to induce uncomfortable breathing. Many individuals will deny symptoms of dyspnea, but will have reduced their activity levels substantially.
▪ Cough
• Cough with or without sputum production should be an indication for spirometric testing. The presence of chronic cough and sputum has been used to define chronic bronchitis.
▪ Wheezing
• Wheezing or squeaky noises occurring during breathing indicate the presence of airflow obstruction
▪ Acute chest illnesses
• Inquire about occurrence and frequency of episodes of increased cough and sputum with wheezing, dyspnea, or fever
Physical examination
All physical findings are generally present only with severe disease
Chest
▪ The presence of emphysema (only when severe) is indicated by: overdistention of the lungs in the stable state (chest held near full inspiratory position at end of normal expiration, low diaphragmatic position), decreased intensity of breath and heart sounds, and prolonged expiratory phase
▪ Evidence of airflow obstruction: wheezes during auscultation on slow or forced breathing and prolongation of forced expiratory time
▪ Frequently observed with severe disease (characteristic, but not diagnostic): pursed-lip breathing, use of accessory respiratory muscles, retraction of lower interspaces
Other
▪ Unusual positions to relieve dyspnea at rest
▪ Digital clubbing is NOT typical in COPD (even with associated hypoxemia) and suggests other diagnoses (eg, lung cancer, bronchiectasis, pulmonary fibrosis)
▪ Mild dependent edema may be seen in the absence of right heart failure

COPD: chronic obstructive pulmonary disease.

Graphic 53303 Version 5.0

Differential diagnosis of COPD

Diagnosis	Suggestive features*
COPD	Onset in mid-life; onset in early adulthood should prompt suspicion for alpha-1 antitrypsin deficiency
	Symptoms slowly progressive
	Long smoking history, although can occur in nonsmokers
	Dyspnea during exercise
	Largely irreversible airflow limitation
Asthma	Onset early in life (often childhood)
	Symptoms vary from day to day
	Symptoms at night/early morning
	Allergy, rhinitis, and/or eczema also present
	Family history of asthma
	Largely reversible airflow limitation
Central airway obstruction (eg, bronchogenic or metastatic cancer, lymphadenopathy, scarring from endotracheal tube)	Monophonic wheeze or stridor
	Variable inspiratory or fixed slowing on flow volume loop
	Chest radiograph often normal
	Airway narrowing on three dimensional reconstruction of HRCT scan
Heart failure	Fine basilar crackles on auscultation
	Chest radiograph shows dilated heart, pulmonary edema
	Pulmonary function tests typically indicate volume restriction, but airflow limitation can sometimes be seen
Bronchiectasis	Large volumes of purulent sputum
	Commonly associated with recurrent or persistent bacterial infection
	Coarse crackles on auscultation, clubbing of digits
	Chest radiograph/HRCT shows bronchial dilation, bronchial wall thickening
Tuberculosis	Onset all ages
	Chest radiograph shows upper lung zone scarring and/or calcified granulomata
	Positive PPD or IGRA
	High local prevalence of tuberculosis
Obliterative bronchiolitis	Onset in younger age, nonsmokers
	May have history of rheumatoid arthritis or fume exposure
	HRCT on expiration shows hypodense areas, mosaic pattern
Diffuse panbronchiolitis	Most patients are male and nonsmokers
	Highest prevalence in East Asia
	Almost all have chronic sinusitis
	Chest radiograph and HRCT show diffuse small centrilobular nodular opacities and hyperinflation

HRCT: high resolution computed tomography; PPD: purified protein derivative; IGRA: interferon gamma release assay.
* These features tend to be characteristic of the respective diseases, but do not occur in every case. For example, a person who has never smoked may develop COPD (especially in the developing world, where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even elderly patients.

Adapted with permission from the Global Initiative for Chronic Obstructive Pulmonary Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Revised 2011. Global Initiative for Chronic Obstructive Lung Disease (GOLD), www.goldcopd.org (Accessed on August 10, 2012).

Graphic 51974 Version 4.0

Diagnosis of chronic obstructive pulmonary disease: PFTs

Spirometry
Spirometry is the essential test to confirm the diagnosis and establish the staging of COPD. If values are abnormal, a post-bronchodilator test may be indicated. Airflow limitation that is irreversible or only partially reversible with bronchodilator is suggestive of COPD rather than asthma. A postbronchodilator ratio of FEV1/FVC <0.7 or <LLN of FEV1/FVC is used to establish the presence of airflow limitation.
In the presence of a low FEV1/FVC, the percent of predicted FEV1 is used to determine the severity of airflow limitation. ▪ GOLD 1: Mild (FEV1 ≥80% predicted) ▪ GOLD 2: Moderate (50% predicted ≤FEV1 <80% predicted) ▪ GOLD 3: Severe (30% predicted ≤FEV1 <50% predicted) ▪ GOLD 4: Very severe (FEV1 <30% predicted)
Lung volumes
Body plethysmography to assess lung volumes is not necessary except in patients with a low FVC on spirometry (<80% predicted) or when concomitant interstitial lung disease is suspected.
Diffusing capacity for carbon monoxide
Measurement of DLCO can help establish the presence of emphysema, but is not necessary for the routine diagnosis of COPD.
Chest radiography
Only diagnostic of severe emphysema, but is frequently obtained to exclude other lung diseases.
Arterial blood gases (ABGs)
Mild and moderate airflow obstruction - ABG usually not needed.
Moderately severe airflow obstruction - ABG is optional, but oximetry should be done. ABGs are obtained if oxygen saturation is <92%.
Severe and very severe airflow obstruction - ABGs are essential to assess for hypercapnia.

PFTs: pulmonary function tests; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; LLN: lower limit of normal; GOLD: Global Initiative for Chronic Obstructive Lung Disease; DLCO: diffusing capacity for carbon monoxide; ABG: arterial blood gas.

Graphic 61983 Version 3.0

CAPTURE questionnaire for identifying patients with undiagnosed COPD

Instructions: For each question, place an X in the box with the answer that is best for you. There are no right or wrong answers, only answers which are right for you.

Please answer each question	No	Yes
1. Have you ever lived or worked in a place with dirty or polluted air, smoke, second-hand smoke, or dust?	☐	☐
2. Does your breathing change with seasons, weather, or air quality?	☐	☐
3. Does your breathing make it difficult to do things such as carry heavy loads, shovel dirt or snow, jog, play tennis, or swim?	☐	☐
4. Compared to others your age, do you tire easily?	☐	☐

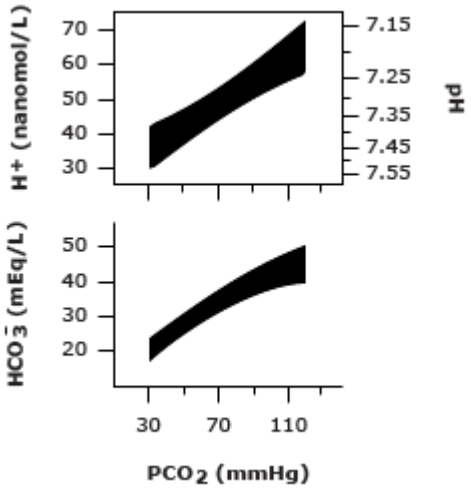
Please answer the question	0	1	2 or more
5. In the past 12 months, how many times did you miss work, school, or other activities due to a cold, bronchitis, or pneumonia?	☐	☐	☐

The final score is a summation of patient responses to each of the five items, yielding a questionnaire score ranging from 0 ("no" to all 5 questions) to 6 ("yes" to all questions and at least two respiratory events during the past year).

CAPTURE: **C**hronic obstructive pulmonary disease **A**ssessment in **P**rimary care **T**o identify **U**ndiagnosed **R**espiratory disease and **E**xacerbation risk; COPD: chronic obstructive pulmonary disease.

Graphic 121674 Version 1.0

Compensation to chronic respiratory acidosis

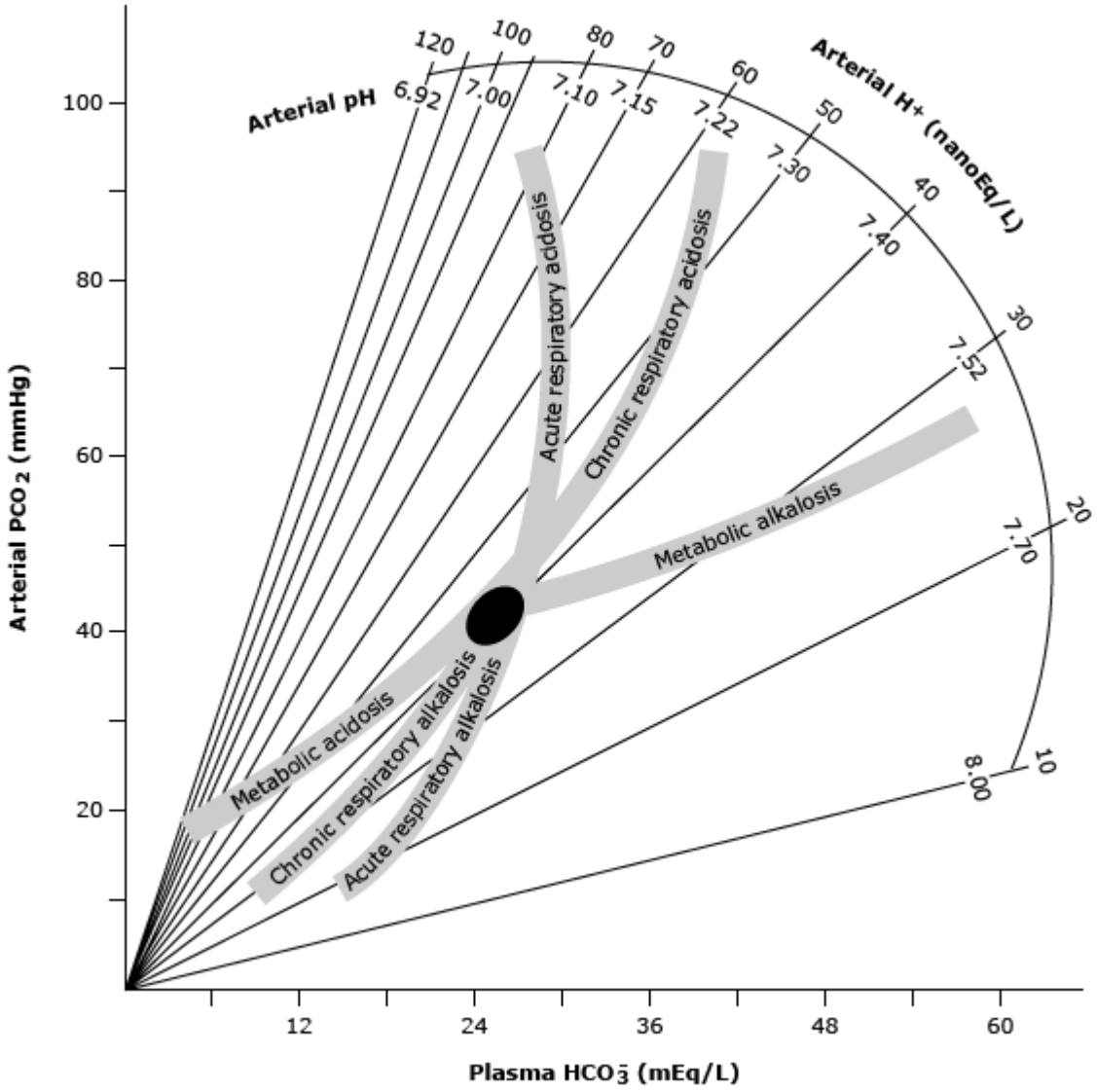


95% significance bands for plasma pH and H^+ and HCO_3^- concentrations in chronic hypercapnia. Because of the compensatory rise in the plasma HCO_3^- concentration, there is much less change in H^+ concentration and pH than in acute hypercapnia.

Schwartz WB, Brackett NC Jr, Cohen JJ. J Clin Invest 1965; 44:291. By copyright permission of the American Society for Clinical Investigation.

Graphic 63315 Version 4.0

Expected compensation ranges for simple acid-base disorders



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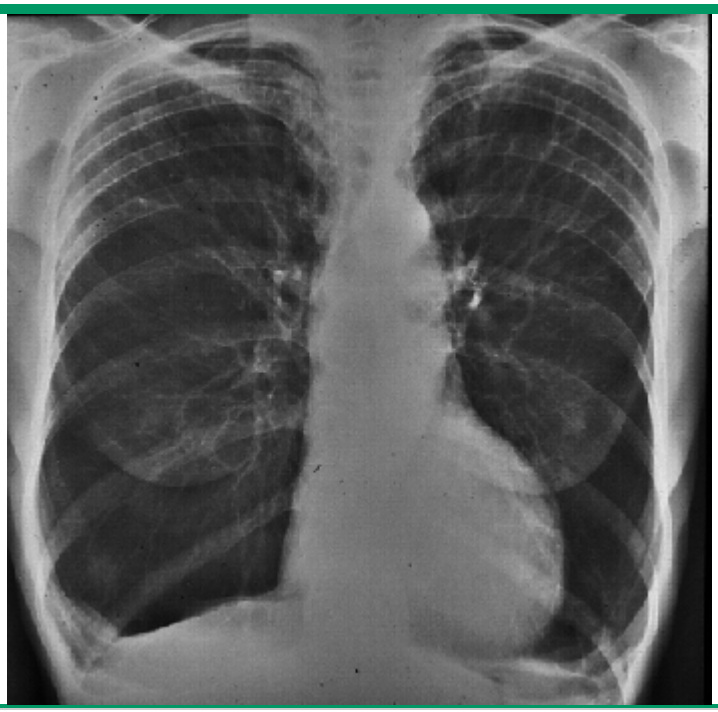
Graphic 79833 Version 9.0

Panacinar emphysema in alpha-1 antitrypsin deficiency

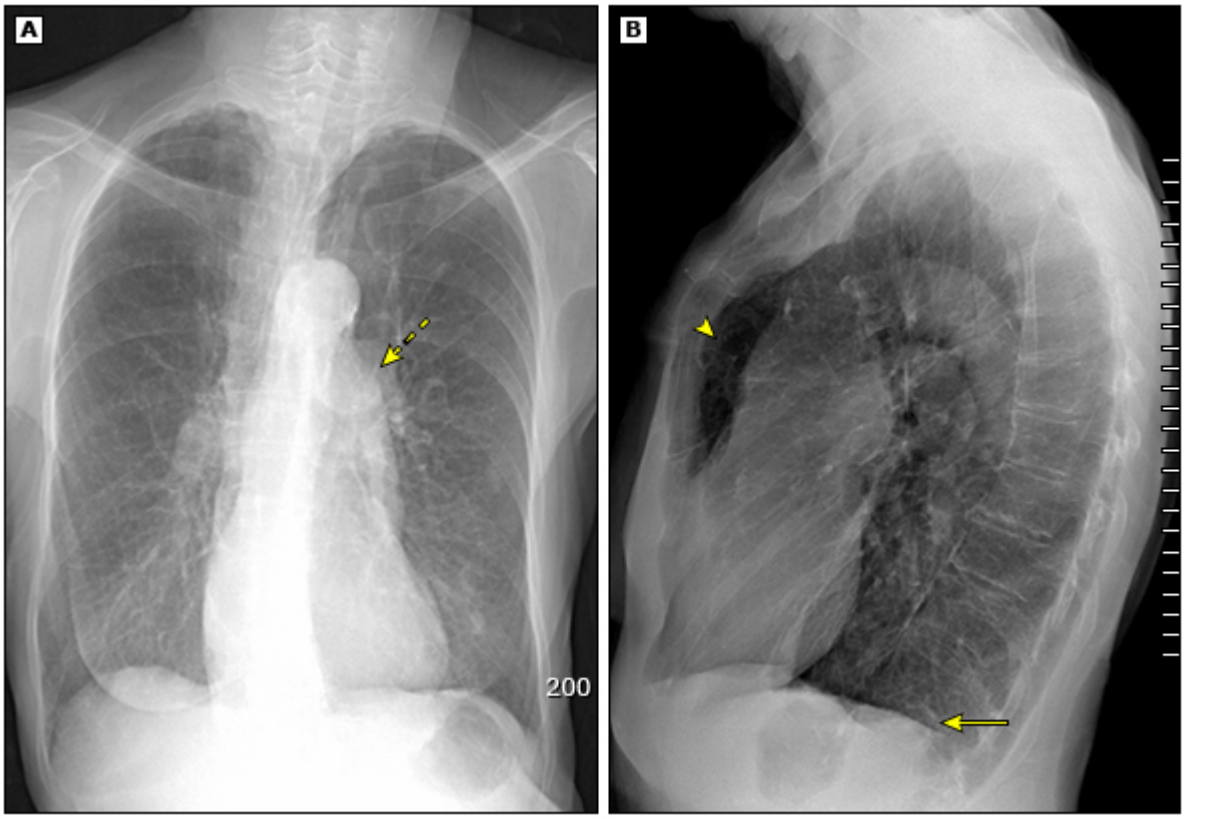


Chest radiograph shows marked hyperexpansion with paucity of vascular structures at the bases and redistribution of vascular flow to the lesser involved upper lobes. These findings are typical of severe panacinar emphysema.

Courtesy of Paul Stark, MD.

Graphic 65594 Version 4.0

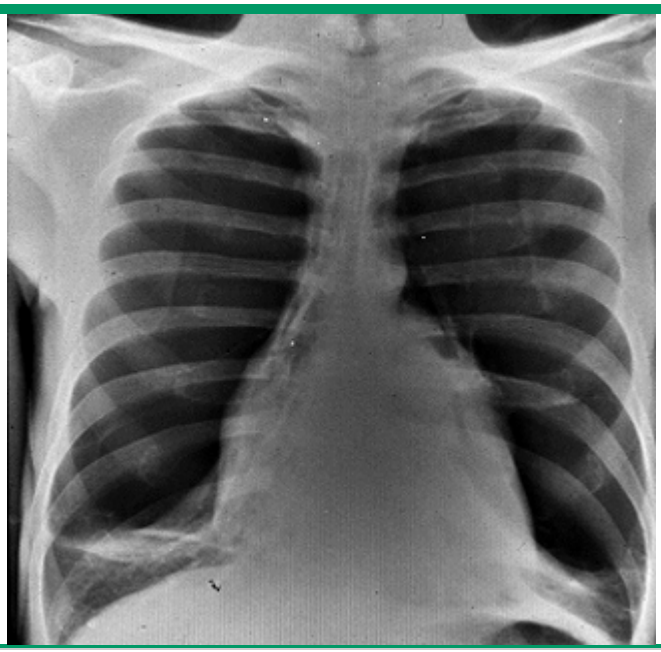
Chest x-ray emphysema



The posteroanterior (A) and lateral (B) chest x-rays of a 71-year-old female with emphysema show increased lung volumes with flattened hemidiaphragms on the lateral examination (arrow) and increase in the retrosternal space (arrowhead). The normal retrosternal airspace is less than 2.5 cm. A prominent pulmonary artery on the posteroanterior view (dashed arrow) reflects secondary pulmonary hypertension.

Graphic 87221 Version 2.0

Chest radiograph of a giant bilateral bullae in young smoker

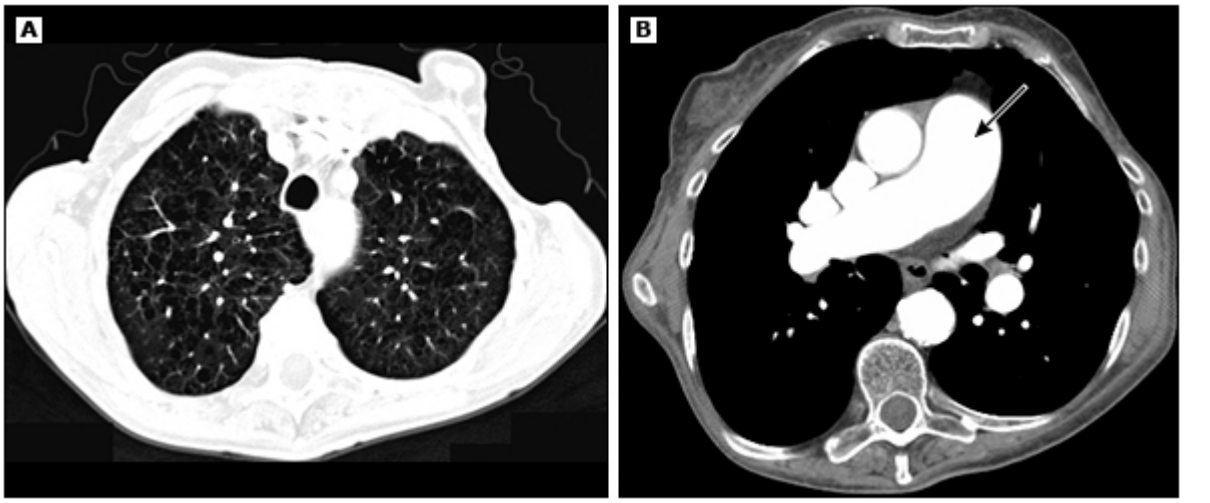


Chest radiograph shows large bilateral collections of gas devoid of any vascular structures with a sharp edge concave laterally, which is a differentiating feature from pneumothorax. The functioning lung is retracted to the bases.

Courtesy of Paul Stark, MD.

Graphic 82207 Version 4.0

Centrilobular emphysema pulmonary hypertension

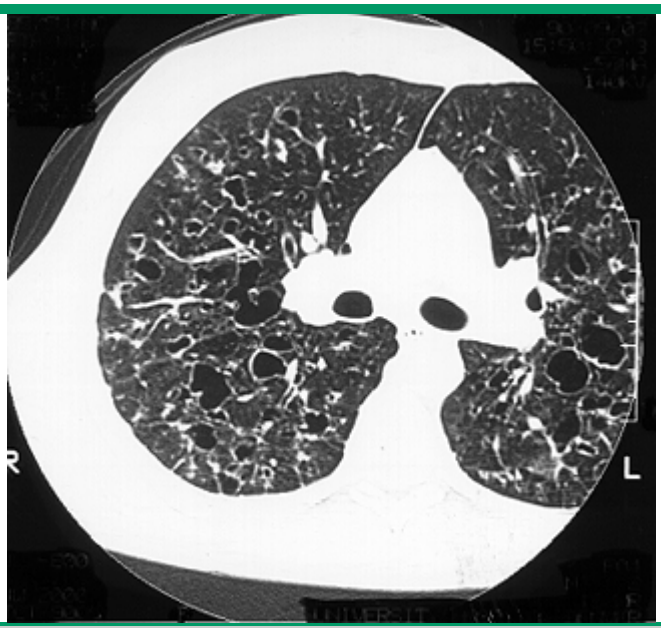


Axial CT images confirm the presence of centrilobular (centriacinar) emphysema (A) and pulmonary hypertension (B). The lung parenchyma shows lucent spaces of parenchymal destruction interspersed among normal lung tissue best appreciated in the right upper lobe (A). The main pulmonary artery (arrow) measures 3.8 cm (normal <2.9 cm). The pulmonary artery and aorta should be about the same size and in this case the main pulmonary artery is larger than the companion ascending aorta.

CT: computed tomography.

Graphic 82308 Version 3.0

Pulmonary Langerhans cell histiocytosis



High resolution CT with thin section shows the cysts in pulmonary Langerhans cell histiocytosis (PLCH), which vary markedly in size and may be larger than 10 mm. The cysts are bizarre in shape, often closely related to pulmonary arteries, and mimic bronchiectasis. Few nodules are present in this case.

CT: computed tomography.

Courtesy of Talmadge E King Jr, MD.

Graphic 72698 Version 4.0

Panlobular emphysema

HRCT shows a paucity of vascular structures in both lower lobes, most evident in the anterior-basal segment of the right lower lobe.

HRCT: high resolution computed tomography.

Courtesy of Paul Stark, MD.

Graphic 57950 Version 3.0

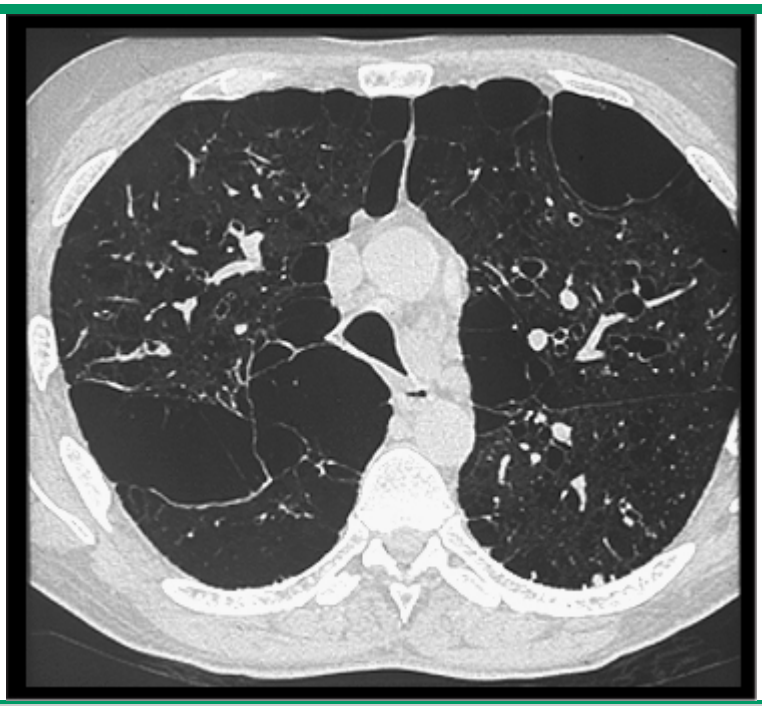
Paraseptal emphysema

Several subpleural emphysematous spaces are present in the periphery of the left upper lobe (arrows) in a patient with accompanying severe centrilobular emphysema.

Courtesy of Paul Stark, MD.

Graphic 53689 Version 2.0

Paraseptal emphysema with bullae



Paraseptal emphysema in the periphery of both upper lobes and in the left lower lobe on a background of centrilobular emphysema. Several large subpleural bullae are visible in both lungs and are the result of paraseptal emphysema.

Courtesy of Paul Stark, MD.

Graphic 60307 Version 2.0

Key indicators for considering a diagnosis of COPD

Symptoms
Dyspnea
Cough
Sputum
Risk factors
Smoking
Biomass fuel exposure
Asthma
Childhood infections
Prematurity
Family history
Comorbidities
Heart disease
Metabolic syndrome
Osteoporosis
Sleep apnea
Depression
Lung cancer
Skin wrinkling

Consider the diagnosis of COPD and perform spirometry if any of these indicators are present. These indicators are not diagnostic by themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is needed to establish a diagnosis of COPD.

Graphic 50637 Version 3.0

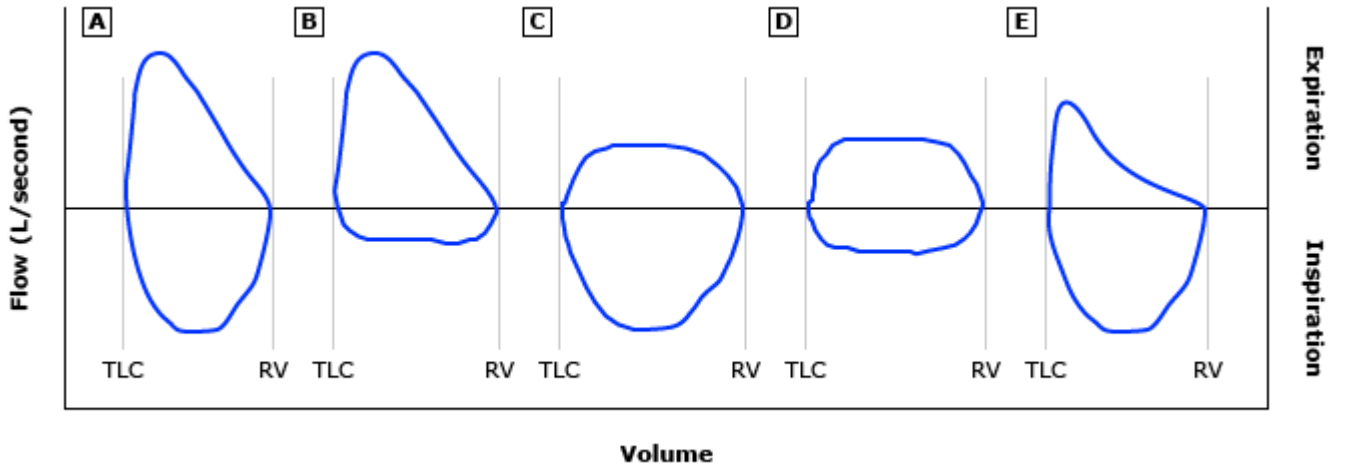
Conditions associated with central airway obstruction

Malignant	Nonmalignant
Primary endoluminal malignancy	**Benign airway tumors**
Bronchogenic	Squamous cell papilloma
Adenoid cystic	Hamartoma
Mucoepidermoid	**Lymphadenopathy**
Carcinoid	Sarcoidosis
Plasmacytoma	Infectious (ie, tuberculosis)
Metastatic carcinoma to the airway	**Vascular**
Bronchogenic	Vascular ring
Renal cell	Vascular aneurysm
Breast	**Cartilage**
Thyroid	Relapsing polychondritis
Colon	**Granulation tissue**
Sarcoma	Endotracheal tubes
Melanoma	Tracheostomy tubes
Laryngeal and nasopharyngeal carcinoma	Airway stents
Esophageal carcinoma	Foreign bodies
Mediastinal tumors	Surgical anastomosis (eg, post resection or transplant)
Thymic carcinoma	Granulomatosis with polyangiitis (Wegener's)
Thyroid carcinoma	Rhinoscleroma (klebsiella infection)
Germ cell tumors (eg, teratoma)	**Pseudotumor**
Lymphadenopathy	Endobronchial pseudotumor
Associated with any of the above malignancies	**Hyperdynamic**
Lymphoma	Tracheomalacia
	Bronchomalacia
	Webs
	Idiopathic progressive subglottic stenosis
	Tuberculosis
	Sarcoidosis
	Other
	Goiter
	Mucus plug
	Vocal cord paralysis
	Airway hematoma
	Burn/smoke injury
	Epiglottitis
	Blood clot
	Amyloid

Modified with permission from: Ernst A, Feller-Kopman D, Becker HD, Mehta AC. Central airway obstruction. Am J Respir Crit Care Med 2004; 169:1278. Copyright © 2004 American Thoracic Society.

Graphic 55320 Version 4.0

Flow-volume loops in upper airway obstruction



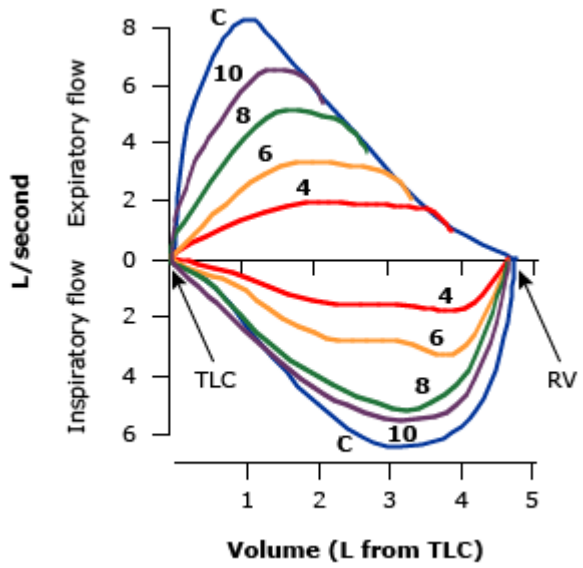
The configuration of the flow-volume loop can help distinguish the site of airway narrowing. The airways are divided into intrathoracic and extrathoracic components by the thoracic inlet.
(A) Normal flow-volume loop: the expiratory portion of the flow-volume curve is characterized by a rapid rise to the peak flow rate, followed by a nearly linear fall in flow. The inspiratory curve is a relatively symmetrical, saddle-shaped curve.
(B) Dynamic (or variable, nonfixed) extrathoracic obstruction: flow limitation and flattening are noted on the inspiratory limb of the loop.
(C) Dynamic (or variable, nonfixed) intrathoracic obstruction: flow limitation and flattening are noted on the expiratory limb of the loop.
(D) Fixed upper airway obstruction (can be intrathoracic or extrathoracic): flow limitation and flattening are noted in both the inspiratory and expiratory limbs of the flow-volume loop.
(E) Peripheral or lower airways obstruction: expiratory limb demonstrates concave upward, also called "scooped-out" or "coved" pattern.

TLC: total lung capacity; RV: residual volume.

Adapted from: Stoller JK. Spirometry: a key diagnostic test in pulmonary medicine. Cleve Clin J Med 1992; 59:75.

Graphic 76811 Version 7.0

Flow-volume loop and degree of upper airway narrowing



Volume (as liters [L] from total lung capacity [TLC]) is plotted against inspiratory and expiratory flows. The blue line (C) is the control effort; the number on each curve refers to the orifice diameter in mm. Lesions must narrow the tracheal lumen to less than 8 mm before abnormalities can be detected by spirometry.

TLC: total lung capacity; RV: residual volume.

Redrawn from Miller RD, Hyatt RE. Obstructing lesions of the larynx and trachea: clinical and physiologic characteristics. Mayo Clin Proc 1969; 44:145.

Graphic 73686 Version 4.0

Conditions associated with the histologic finding of constrictive bronchiolitis

Inhalation of dusts or toxins
Mineral dusts - asbestos, silica, iron oxide, aluminum oxide, talc, mica, and coal
Toxins - NO_2, sulfur dioxide, ammonia, chlorine, and phosgene
Drug reaction
Infection - viral, mycoplasma
Connective tissue disease, especially rheumatoid arthritis
Chronic rejection in heart-lung, lung, and bone marrow transplant recipients
Hypersensitivity reactions
Ulcerative colitis
Idiopathic

NO_2: nitrogen dioxide.

Adapted from Myers JL, Colby TV, Clin Chest Med 1993; 14:611.

Graphic 58035 Version 2.0

Modified Medical Research Council (mMRC) dyspnea scale

Grade	Description of breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

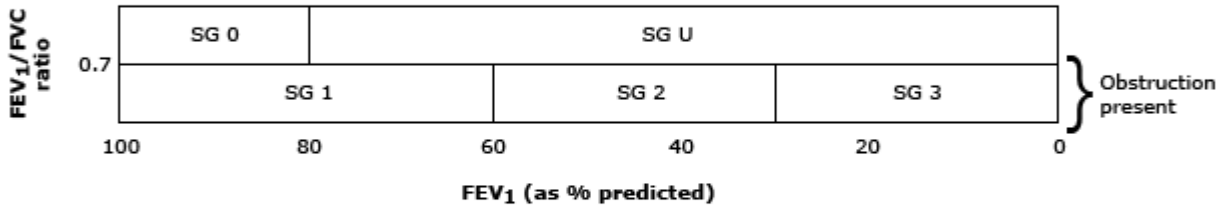
Adapted from: Fletcher CM, Elmes PC, Fairbairn MB, et al. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. British Medical Journal 1959; 2:257.

Graphic 86426 Version 2.0

COPD Foundation guide to assessment of COPD severity

Spirometry grades:

SG 0 Normal spirometry does not rule out emphysema, chronic bronchitis, asthma, or risk of developing either exacerbations or COPD.
SG 1 Mild: Post bronchodilator FEV_1/FVC ratio <0.7, FEV_1 ≥60% predicted.
SG 2 Moderate: Post bronchodilator FEV_1/FVC ratio <0.7, 30% ≤FEV_1 <60% predicted.
SG 3 Severe: Post bronchodilator FEV_1/FVC ratio <0.7, FEV_1 <30% predicted.
SG U Undefined: FEV_1/FVC ratio ≥0.7, FEV_1 <80% predicted. This is consistent with restriction, muscle weakness, and other pathologies.



Regular symptoms: Dyspnea at rest or exertion, cough, sputum.
Exacerbations: Two or more in the past year, especially if FEV_1 <50% predicted suggests high risk.
Oxygenation: Severe hypoxemia: resting O_2 sat <88% or PaO_2 <55 mmHg episodic hypoxemia: exercise or nocturnal desaturation.
Emphysema: Reduced density on CT scan, can be localized, abnormal high lung volumes, abnormal low diffusion capacity.
Chronic bronchitis: Cough, sputum most days for at least three months in at least two years.
Comorbidities: Defining and treating comorbid conditions, particularly cardiovascular, are critical components of COPD care.

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; SG: spirometry grade; PaO_2: arterial tension of oxygen; CT: computed tomography.

Graphic 95124 Version 1.0