III CHRONIC OBSTRUCTIVE DISEASES OF THE LUNG

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Chronic Bronchitis and Emphysema

DEFINITIONS

The terms chronic obstructive lung disease, chronic obstructive pulmonary disease (COPD), and chronic airflow obstruction (CAO) are synonyms used to describe permanent or minimally reversible obstruction of expiratory airflow caused by chronic bronchitis, emphysema, or both. These conditions are distinguished from asthma in that the abnormalities limiting airflow are for the most part irreversible, although irreversible airflow obstruction can develop in some patients with asthma[1] [*see 14:II Asthma*]. The inclusiveness of these terms stems from the fact that chronic bronchitis and emphysema usually occur together as the consequences of a common etiology (e.g., cigarette smoking). Chronic bronchitis and emphysema must be distinguished not only from asthma but also from bronchiectasis and obstructive bronchiolar disorders, which are covered in this chapter, and from upper airway obstruction and interstitial lung diseases that have an obstructive component (e.g., sarcoidosis, pulmonary lymphangioleiomyomatosis [*see 14:V Chronic Diffuse Infiltrative Lung Disease*]).[2]

Chronic Bronchitis

Chronic bronchitis follows prolonged exposure of the tracheobronchial tree to nonspecific irritants and is characterized by hypersecretion of mucus and structural changes in the bronchi, including inflammation, metaplasia of the epithelium, and enlargement of the mucous glands. The inflammation and hypersecretion of mucus usually cause daily cough and sputum production, which help to identify the disease clinically. For epidemiologic purposes, chronic bronchitis is defined by the presence of cough and sputum on most days for at least 3 months of the year for a minimum of 2 years in succession.

Some cigarette smokers with chronic productive cough (often called smoker's cough) do not have dyspnea, and, in fact, pulmonary function testing reveals no detectable obstruction of airflow in these patients. In other smokers, however, clinically significant narrowing of the airways develops. Because of these differing features, many physicians use the term chronic mucus hypersecretion or chronic bronchitis without airway obstruction to identify the former presentation and the term chronic obstructive bronchitis or chronic bronchitis with airway obstruction to identify the latter. The validity of such a distinction is supported by the fact that the two forms of chronic bronchitis have different natural histories.

In contrast to chronic bronchitis, acute bronchitis is a self-limited condition of the bronchi that is most often caused by viral infections in association with an upper respiratory tract illness or acute exposure to a nonspecific irritant (e.g., ammonia). Acute bronchitis, however, may also occur as a transient complication of chronic bronchitis.

Emphysema

Emphysema is a destructive process involving the lung parenchyma. It is defined in pathologic terms on the basis of findings of abnormal permanent enlargement of air spaces distal to the terminal bronchiole accompanied by the destruction of the alveolar walls without obvious fibrosis. At autopsy, some areas of emphysema are found in the lungs of most persons older than 60 years.

EPIDEMIOLOGY

Chronic bronchitis and emphysema are by far the most common causes of CAO; other causes include bronchiectasis and bronchiolitis. In the United States, an estimated 10 million adults report physician-diagnosed COPD; data suggest that 24 million adults have abnormal lung function, which points to significant underdiagnosis of COPD.[3] In 2000, CAO caused 119,054 deaths, representing a 128% increase since 1980.[3] CAO is the fourth leading cause of death in the United States. From 80% to 90% of cases of CAO can be attributed to cigarette smoking. The risk of death from chronic bronchitis or emphysema is 30 times greater for heavy smokers (i.e., those who smoke 25 or more cigarettes a day) than for nonsmokers.

In cigarette smokers, the prevalence of chronic bronchitis increases with age (and, thus, with the increase in the total cumulative amount of cigarette smoke inhaled) and the number of cigarettes smoked. More than 50% of middle-aged men who smoke at least one pack of cigarettes a day report having chronic productive cough. Cigar and pipe smokers, as well as former cigarette smokers, have a rate of chronic bronchitis higher than the general population but lower than current cigarette smokers. Although occupational dust exposure is also associated with the development of chronic bronchitis, the effect of cigarette smoking overwhelms the occupational effect.

Some degree of emphysematous changes can be found in the autopsied lungs of 65% of men and 15% of women. Severe involvement, leading to a clinical diagnosis of emphysema, occurs in slightly less than 1% of the population. However, prevalence statistics are more relevant for cigarette smokers, who constitute the major population at risk. In a series involving more than 1,800 autopsies, the prevalence of emphysema judged to be advanced to far advanced was 0% in nonsmokers, 12% in smokers of less than one pack of cigarettes a day, and 19% in those who consumed one or more packs a day.[4]

Forced expiratory volume in 1 second (FEV_1) and the ratio of FEV_1 to forced vital capacity (FEV_1/FVC) can be used to assess the prevalence of CAO. If an FEV_1 value of less than 80% of predicted and an FEV_1/FVC of less than 70% is defined as abnormal, 7.4% of men and 5.8% of women in the general adult population would be considered to have obstructive lung disease.[3] There is a normal, or bell-shaped, distribution of FEV_1 values in the nonsmoking population. In cigarette smokers, this distribution curve is shifted toward lower FEV_1 values [*see Figure 1*]. The prevalence of abnormal values increases with increasing years of cigarette smoking. For instance, after 40 to 60

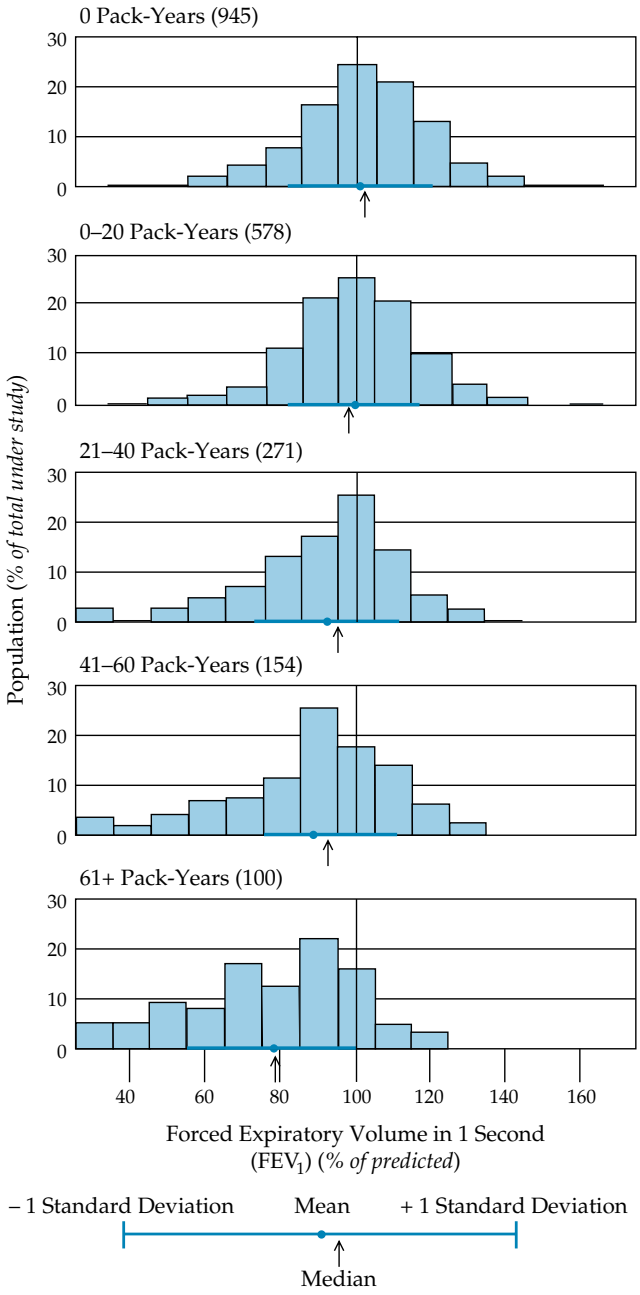


Figure 1 **There is a normal distribution of expiratory flow values, as measured by percent of the predicted forced expiratory volume in 1 second (FEV_1), among nonsmokers. Among cigarette smokers, the distribution is shifted toward lower FEV_1 values, with a larger skew at the lower range, as the number of pack-years of smoking increases.[161]**

pack-years of cigarette smoking (number of pack-years = packs of cigarettes/day × number of years the person has smoked), most smokers have slightly reduced expiratory flow, and approximately 10% manifest CAO.

ETIOLOGY

Chronic bronchitis and emphysema are usually caused by cigarette smoking of at least 10 years' duration. The specific pathogenic substances in cigarette smoke have not been identified with certainty. It is likely that particle size and gas solubility determine which of the hundreds of noxious substances found in cigarette smoke are deposited in the trachea and the large bronchi, causing bronchitis, and which are deposited in the bronchioles and the gas exchange units, causing narrowing of the small airways and emphysema.

Cigarette smoking is such a dominant factor in the pathogenesis of CAO that it has been difficult to identify any causative or contributing factors other than α_1-antitrypsin deficiency [*see* Pathogenesis, *below*]. Prolonged exposure to respirable dusts in the work environment has long been recognized as a cause of so-called industrial or occupational bronchitis in nonsmoking workers engaged in occupations such as coal or gold mining, textile manufacturing, and cement and steel making. An analysis of the accumulated data over the past 25 years suggests that these exposures are associated with the development of significant CAO, with a greater risk in gold miners than in coal miners.[5] Chronic HIV infection,[6] low body mass,[7] and low intake of dietary antioxidants may be cofactors in some cigarette smokers.[8]

In otherwise healthy adults, passive cigarette smoking (i.e., indoor exposure of nonsmokers to cigarette smoke) and outdoor air pollution may cause nonspecific respiratory symptoms such as cough and may induce subtle abnormalities in pulmonary function, but they have not been shown to lead to the development of CAO.[9] A major unknown in the etiology of CAO is why clinically significant airway obstruction develops in only 10% to 15% of smokers. Hypotheses for the unique susceptibility of some cigarette smokers to the development of severe airflow obstruction suggest the presence of host factors and exposure factors. Host factors include the presence of preexisting airway hyperresponsiveness[10]; impaired lung growth; smaller size of terminal bronchioles; and genetic determinants favoring increased elastase activity, impaired antiprotease function, or other factors.[11,12] Exposure factors include deeper and more frequent inhalation of tobacco smoke, occupational dust and chemical exposure, indoor (including possible effects of passive smoking) and outdoor air pollution, and chronic bacterial or viral infection.[13]

NATURAL HISTORY

The dominant feature of the natural history of chronic bronchitis and emphysema is the development and progression of airflow obstruction. In healthy nonsmokers, FEV_1 begins declining at about age 20 at an average rate of about 0.02 to 0.04 L/yr. In smokers with obstructive lung disease, FEV_1 decreases, on average, two to three times faster than normal [*see Figure 2*]. A person with an FEV_1 of 2.0 L (50% of normal) at age 45 who continues to smoke cigarettes heavily is apt to be breathless on light exertion at age 55; for such a smoker, the FEV_1 would be expected to have fallen to about 1.2 L, or 30% of normal, at age 55. At age 60, the expected FEV_1 would be about 0.8 L (20% of normal). The person would probably be breathless at rest or on minimal exertion and would be at risk for recurrent episodes of acute respiratory failure. At the same estimated rate of lung function loss, this person would not be expected to live past age 65.

Other factors may modify the development and progression of CAO. In addition to advanced age, variables that appear to confer a worse prognosis include hypoxemia, hypercapnia, cor pulmonale, and, possibly, increased airway responsiveness and eosinophilia (asthmatic bronchitis).[10] When smokers with mild to moderate airflow obstruction stop smoking, the rate of decline in expiratory flow reverts to that observed in nonsmokers, and there may be a slight improvement in FEV_1 during the first year.[14] Cough and phlegm production usually decrease as well.[15] Unfortunately, when obstruction is already severe, smoking ces-

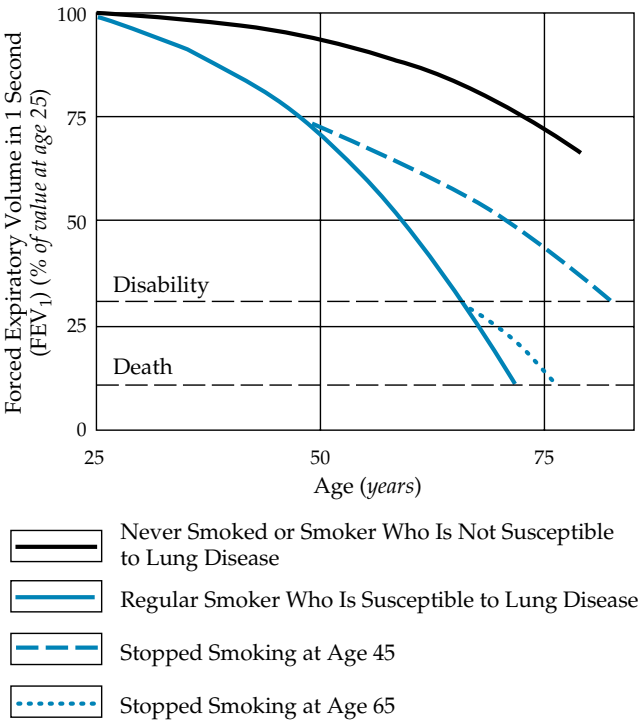


Figure 2 **Expiratory flow, as measured by FEV_1, declines up to two to three times faster in cigarette smokers who are susceptible to obstructive lung disease than in nonsmokers or in those who smoke but are not susceptible to lung disease. Smoking cessation can decrease the rate of fall in FEV_1 in susceptible cigarette smokers, delaying the onset of disability or death.[162]**

sation may not be as effective in altering future deterioration. There remains considerable variability among individuals, so that no single factor or group of factors can be used to predict the outcome in a given patient. Respiratory tract infections do not influence the overall course of the disease.

PATHOLOGY

Early Pathologic Changes

Pathologic changes are apparent in the lungs of smokers even before the appearance of CAO.[16] Breaks in the alveolar septal walls are seen, possibly representing a precursor to more generalized emphysema and inflammation of the bronchioles. The lungs of cigarette smokers, even in those as young as 25 years, can be distinguished from those of nonsmokers by the abnormal accumulation of pigmented macrophages in respiratory bronchioles, often accompanied by edema, epithelial hyperplasia, and fibrosis in adjacent bronchiolar and alveolar walls. The significance of these early findings is threefold. First, peripheral airways (bronchioles and small bronchi less than 2 mm in diameter) are an important site of airflow obstruction, both in asymptomatic cigarette smokers and in patients with advanced CAO. Second, the pathologic changes that occur in patients with the centriacinar form of emphysema [*see* Established Emphysema, *below*] initially develop in the respiratory bronchioles. Third, evidence suggests that the early abnormalities observed in cigarette smokers are for the most part reversible with cessation of smoking.

Airflow through healthy lungs is limited primarily by the resistance of the central airways (i.e., the trachea and the major bronchi) and the upper airways (i.e., the larynx and the pharynx) but also to some degree by the resistance of the small airways of the lung periphery. As CAO worsens, there is a marked increase in airflow resistance; almost all of this increase is in the peripheral airways. The degree of pathologic narrowing of the terminal bronchioles is strongly correlated with all physiologic indices of airflow obstruction, including the reduced FEV_1. The small airways either are directly narrowed by inflammatory changes or, as in emphysema, lose the tethering effect provided by the surrounding lung parenchyma, which normally limits narrowing during expiration.

Lungs of asymptomatic young smokers show clusters of macrophages in and around respiratory bronchioles. Other early pathologic lesions include squamous cell metaplasia of the epithelium, chronic inflammation of airway walls, small foci of peribronchiolar fibrosis, and muscular hypertrophy of the bronchiolar wall.[17] As CAO progresses, mural connective tissue, pigment, and muscle become more prominent. In addition, goblet cell hyperplasia develops,[18] and mucosal ulcerations appear.

Mild bronchiolitis is probably a universal finding in young smokers. The degree to which these terminal airways are narrowed by the inflammation has a strong correlation with obstruction, as measured by spirometry.[19]

Late Pathologic Changes

Established chronic bronchitis The pathologic hallmark of chronic bronchitis is enlargement of the mucous glands in the major bronchi. The diameter of the mucous glands relative to the thickness of the bronchial wall is greater in patients with chronic bronchitis.

Although excess mucus in the airways is common in patients with chronic bronchitis, it has physiologic significance only when it obstructs the lumina of small airways. The small number and irregular distribution of goblet cells among the epithelial cells lining the airways make quantification difficult. It is possible that the mucus found plugging small airways is not produced locally but originates in the central airways. Functional disorders that may contribute to mucous plugging include secretion of mucus with altered viscoelastic properties and impaired ciliary clearance mechanisms.

It has not been established whether the volume of bronchial smooth muscle is increased in patients with chronic bronchitis, as it is in those with asthma. Smooth muscle hyperplasia has been found in the main and lobar bronchi in those patients with chronic bronchitis who have intermittent attacks of wheezing.

Bronchoscopic findings include generalized erythema, edema, and friability of the tracheobronchial mucosa. Mucous gland pits, which are depressions in the mucosa approximately 1 to 2 mm in diameter that represent the orifice of one or more mucous glands, are also present. Often, the most striking finding is dynamic expiratory collapse of large central airways; however, this is the result of obstruction of small peripheral airways rather than the cause of the expiratory airflow limitation.

Established emphysema The terminology commonly used by pathologists to describe pulmonary emphysema makes reference to two distinct units of lung structure: the acinus and the lobule. The acinus is an anatomic subdivision that consists of a respiratory bronchiole together with all the alveolar ducts and alveoli extending from it [*see Figure 3*]. A lobule is defined as the smallest discrete portion of the lung surrounded

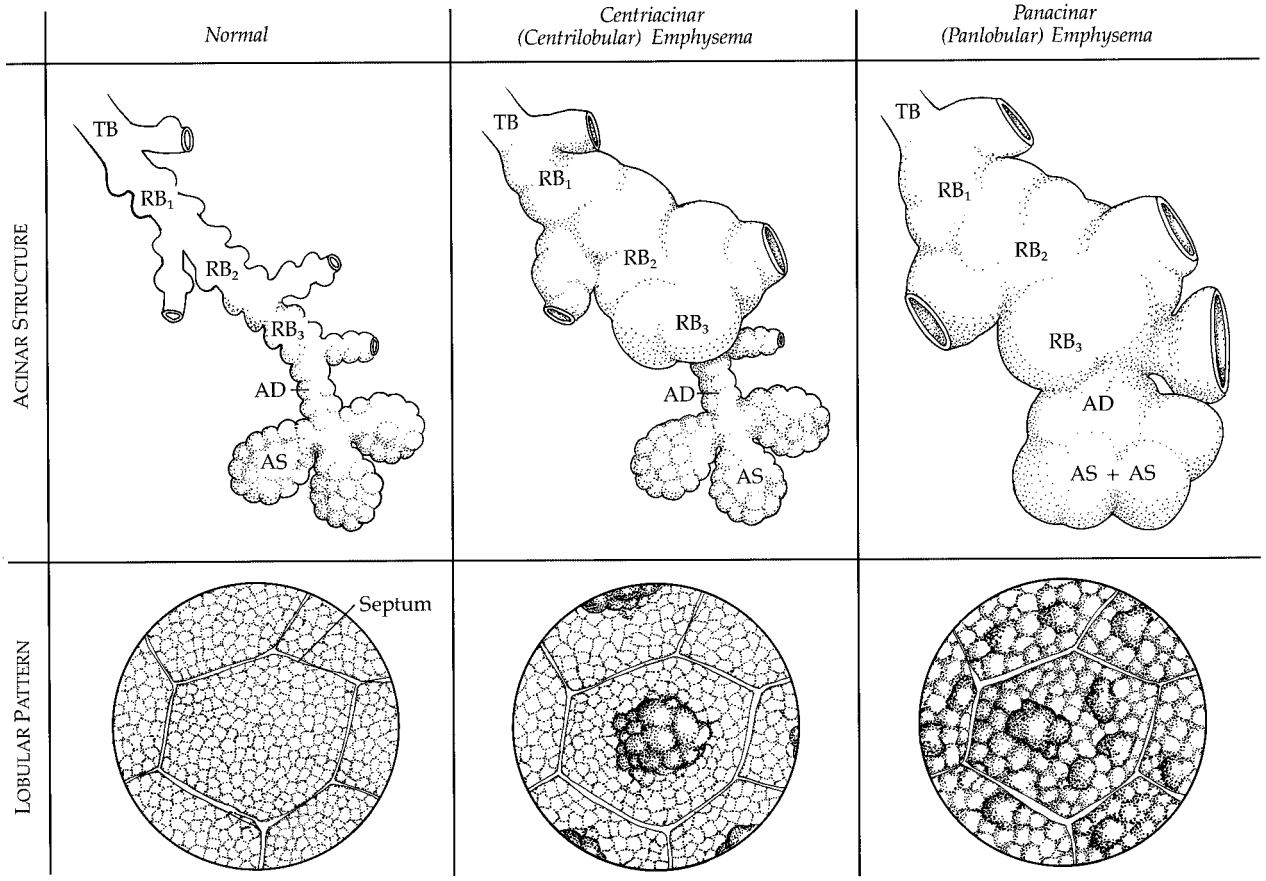


Figure 3 **In the top row, the acinar structure of normal lungs is compared with that of lungs in patients with centriacinar (centrilobular) emphysema or panacinar (panlobular) emphysema. The normal acinus has a clearly defined structure consisting of the terminal bronchiole (TB); first-, second-, and third-order respiratory bronchioles (RB_1, RB_2, and RB_3, respectively); alveolar ducts (AD); and alveolar sacs (AS). In centriacinar emphysema, there is selective enlargement and destruction predominantly of the respiratory bronchioles. In contrast, panacinar emphysema is defined by universally enlarged and destroyed air spaces throughout the acinus. Patterns of lobular destruction are depicted in the center row. The normal pulmonary lobule is a macroscopic structure, the borders of which can be identified by the presence of connective tissue septa. In centriacinar emphysema, the predominant site of overdistention is in the center of the lobule, with relative sparing toward the periphery—hence the name centrilobular emphysema. In contrast, there are uniform destructive changes throughout the lobule in panlobular emphysema.**

by connective tissue septa. Emphysema may involve the acinus and the lobule uniformly in a pattern called panacinar or panlobular emphysema. Alternatively, it may involve primarily the respiratory bronchioles; this form of the disease is termed centriacinar, centrilobular, or, perhaps most correctly, proximal acinar emphysema.

Panacinar emphysema is common in patients with α_1-antitrypsin deficiency [*see* Pathogenesis, *below*]. Pathologic examination reveals enlargement of the alveolar ducts and sacs with loss of features distinguishing them. Holes, or fenestrae, develop in the alveolar walls and progressively enlarge. The process of destruction ultimately leaves only strands of tissues containing supportive structures such as vessels, bronchi, and septa. The emphysematous spaces are spread uniformly across the lobule. Typically, the lower lobes show more involvement than the upper lobes.

Centriacinar emphysema is commonly found in cigarette smokers and is rare in nonsmokers. This form of emphysema primarily affects the respiratory bronchioles. The destroyed respiratory bronchioles enlarge and coalesce, forming emphysematous spaces surrounded by relatively normal alveolar ducts and alveoli. The emphysematous spaces are situated in the midportion of the lobule, separated from the septa by normal alveolar tissue. The small airways supplying these emphysematous spaces typically show signs of inflammation and are often narrowed. Centriacinar emphysema is usually more extensive and severe in the upper lobes.

Pure centriacinar emphysema is not a common finding at autopsy. In most cigarette smokers, a mixture of centriacinar and panacinar emphysema develops. This mixture may take the form of predominant centriacinar emphysema in the upper lung zones and panacinar emphysema in the lower zones or centriacinar emphysema that extends to the alveolar ducts and alveoli to varying degrees. Distinction between these two forms of emphysema is often difficult in advanced cases and is of no clinical significance. However, there may be subtle differences in the altered lung function between the two forms, possibly related to greater abnormalities of small airways and more fibrosis in centriacinar emphysema.[20]

Other abnormalities found at autopsy in patients with CAO include atrophy of cartilage in the walls of segmental and subsegmental bronchi, obliteration of small airways (i.e., loss of

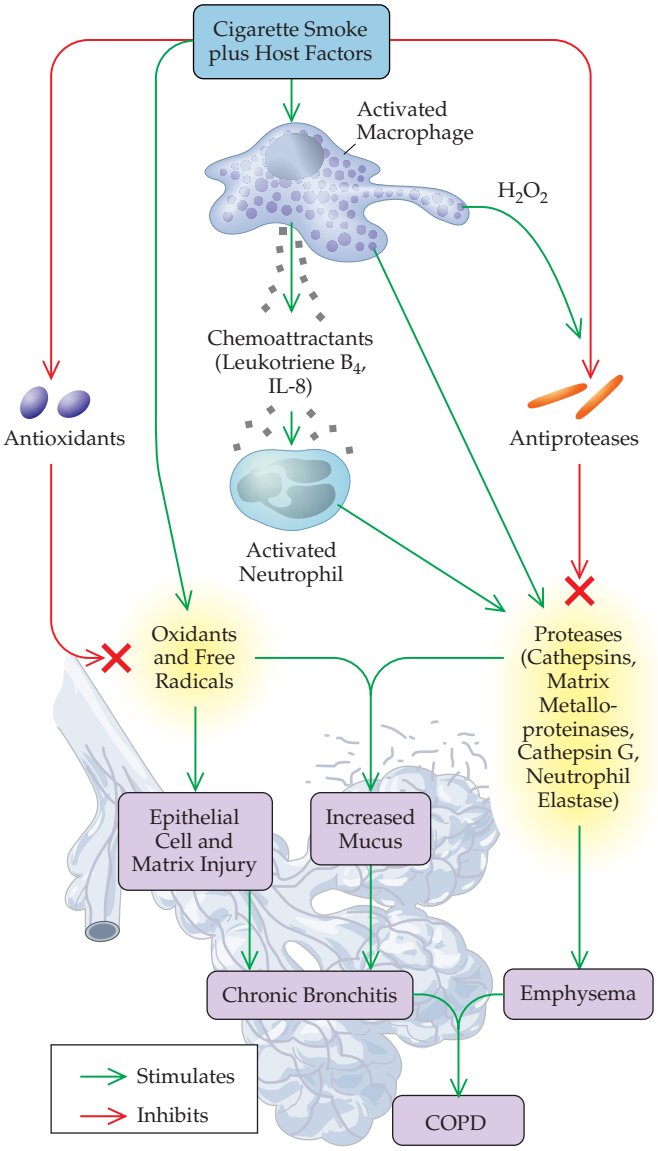


Figure 4 **Host factors play a role in the development of chronic obstructive pulmonary disease (COPD) in smokers. Cigarette smoke activates alveolar macrophages to secrete proteases (multiple cathepsins and matrix metalloproteinases). The activated macrophages release the neutrophil chemoattractants leukotriene B_4 and interleukin-8 (amplified by tumor necrosis factor–α [TNF-α]), and the chemoattractants also stimulate neutrophils to release more than the usual amount of cathepsin G and neutrophil elastase. Several oxidants that are present in cigarette smoke or are generated from products of cigarette smoke interact with hydrogen peroxide released from activated alveolar macrophages and neutrophils to oxidize and inactivate α_1-antitrypsin and other antiproteases. Cigarette smoke may inhibit the synthesis of elastin, thereby retarding repair of damaged elastin fibers. There is an increased oxidative burden from cigarette smoke and the inflammatory cells (macrophages and neutrophils), and the antioxidant system appears to be inadequate for dealing with the increased oxidants, producing an imbalance. Adverse effects of the oxidant stress include inactivation of antiproteases, membrane lipid peroxidation, DNA and matrix damage, and epithelial injury. As a consequence of the excesses of proteases and the inhibition of antiproteases, the walls of the respiratory bronchioles and the alveoli are damaged, and the altered repair mechanisms prevent remodeling and fibrosis, resulting in emphysema. The oxidative imbalance damages the walls of the airway and, along with the excess proteases, stimulates mucus hypersecretion, producing chronic bronchitis.**

bronchioles 0.4 to 0.6 mm in diameter), increased longitudinal smooth muscle in the intima of pulmonary arterioles and small arteries, and dilatation of bronchial arteries and veins.

PATHOGENESIS

Inflammatory cells are an important host factor in the development of COPD.[13,21] Activated macrophages,[22] lymphocytes with a predominance of $CD8^+$ T cells,[18,23] and neutrophils[24] are found in increased numbers in the respiratory bronchioles of smokers. These activated macrophages release the neutrophil chemotactic factors leukotriene B_4 and interleukin-8 (IL-8), which are amplified by tumor necrosis factor–α (TNF-α). Complex interactions between these cells and mediators lead to increased amounts of proteases and oxidants in the lung parenchyma and airways. Two interrelated causes—an imbalance of proteases and antiproteases and an imbalance of oxidants and antioxidants—are hypothesized to produce the chronic bronchitis and emphysema seen in cigarette smokers.[25]

Protease-Antiprotease Imbalance

One current theory of the pathogenesis of emphysema holds that the disease may develop because of an imbalance between protease and antiprotease activities in the lungs.[26] The origins of this theory date to 1963, when the Scandinavian researchers Laurell and Eriksson identified a group of patients with a deficiency in α_1-antitrypsin (also called α_1-proteinase inhibitor), a major serum antiprotease [*see also* α_1-Antitrypsin Deficiency, *below*]. Emphysema developed in a remarkably high percentage of these patients, typically at an unusually young age.

Most cigarette smokers have normal serum α_1-antitrypsin concentrations. In fact, cigarette smoking may cause a small (approximately 20%) rise in serum α_1-antitrypsin concentrations. (Increased amounts of α_1-antitrypsin often can be retrieved from the lungs of smokers by means of lavage.) Nonetheless, chronic inhalation of cigarette smoke has a number of effects that can lead to an excess of protease activity in the lung parenchyma [*see Figure 4*]. First, cigarette smoke activates alveolar macrophages to secrete proteases (multiple cathepsins and matrix metalloproteinases) and mediators that attract neutrophils; these or additional mediators also stimulate neutrophils to release more than the usual amount of cathepsin G and neutrophil elastase. Second, several oxidants that are present in cigarette smoke or are generated from products of cigarette smoke, such as the oxides of nitrogen, interact with hydrogen peroxide released from activated alveolar macrophages and neutrophils to oxidize and inactivate α_1-antitrypsin and other antiproteases.[27] Third, cigarette smoke may inhibit the synthesis of elastin, thereby retarding repair of damaged elastin fibers.

Oxidant-Antioxidant Imbalance

A number of studies have found evidence for an increased oxidative burden in cigarette smokers.[27] Sources of oxidants include cigarette smoke and the inflammatory cells (macrophages and neutrophils). In addition, the antioxidant system appears to be inadequate for dealing with the increased oxidants, producing an imbalance. Adverse effects of the oxidant stress include inactivation of antiproteases, membrane lipid peroxidation, DNA and matrix damage, epithelial injury, and stimulation of transcription of inflammatory cytokines, amplifying the inflammation.

Obviously, these two hypotheses are intertwined, suggesting a role for both in the production of COPD. As a consequence of the excesses of proteases and the inhibition of an-

Table 1 Differentiating Features in Advanced Chronic Airflow Obstruction

Features	*Type A—Pink Puffer (Predominant Emphysema)*	*Type B—Blue Bloater (Predominant Chronic Bronchitis)*
Symptoms and Signs	Dyspnea (first and predominant symptom); patients are usually thin, weight loss is common; minimal or no cough; hyperinflated lung fields; no signs of cor pulmonale	Cough and sputum production with frequent chest infections; stocky build; recurrent or persistent signs of right heart failure
Routine Laboratory Studies		
Chest radiograph	Hyperinflation; decreased vascular markings, bullae	Normal or increased markings at lung bases (so-called dirty-chest appearance)
Arterial blood gases	Mildly reduced P_aO_2; normal or decreased P_aCO_2	Marked reduction in P_aO_2; increased P_aCO_2
Total lung capacity	Increased	Normal or slightly increased
D_{LCO}	Decreased	Normal
Hematocrit	Normal	Increased
Specialized Laboratory Studies		
Inspiratory resistance	Normal	Increased
Pulmonary compliance	Increased	Normal
Ventilation-perfusion distribution	Increased V_D/V_T	Increased regions of low $\dot{V}_A/\dot{Q}$
Hemodynamics	Normal or decreased cardiac output Mild pulmonary hypertension	Normal cardiac output Marked pulmonary hypertension
Ventilatory Performance and Gas Exchange during Exercise	More wasted ventilation D_{LCO} fails to increase normally Decreased P_aO_2; small rise in P_aCO_2	Less wasted ventilation D_{LCO} increases normally P_aO_2 may increase; moderate rise in P_aCO_2
Gas Exchange during Sleep	Moderate degree of oxygen desaturation	Frequent periods of profound oxygen desaturation

D_{LCO}—diffusing capacity of lung for carbon monoxide P_aCO_2—arterial carbon dioxide tension P_aO_2—arterial oxygen tension V_D/V_T—ratio of dead space to tidal volume $\dot{V}_A/\dot{Q}$—ventilation/perfusion distribution

tiproteases, the walls of the respiratory bronchioles and the alveoli are damaged and the altered repair mechanisms prevent remodeling and fibrosis, resulting in emphysema. The oxidative imbalance damages the walls of the airway and, along with the excess proteases, stimulates mucus hypersecretion, producing chronic bronchitis.

DIAGNOSIS

Clinical Manifestations

The hallmarks of CAO are chronic productive cough and persistent, progressive exercise limitation because of breathlessness. Although these two symptoms are nonspecific, they usually point to the correct diagnosis of CAO in the context of prolonged cigarette smoking. Patients with predominant chronic bronchitis present with chronic productive cough, whereas patients with predominant emphysema complain of dyspnea [*see Table 1*]. Cough with expectoration develops 10 to 12 years after smoking begins. The symptom is often dismissed as a simple smoker's cough. However, persons with established chronic bronchitis commonly produce 2 oz or more of mucoid sputum a day. Transient periods of sputum discoloration caused by purulence commonly occur, often in association with respiratory tract infections. A small amount of hemoptysis may accompany a superimposed acute tracheobronchitis.

Wheezing is also common. It can occur transiently as mucus accumulates in airways and resolve suddenly with the expectoration of phlegm; however, some patients with chronic bronchitis experience prolonged and severe attacks of wheezing that mimic those of asthma. This combination of chronic bronchitis and reversible bronchospasm is commonly referred to as asthmatic bronchitis. These patients tend to respond more strongly to anti-inflammatory and bronchodilator drugs.

Shortness of breath, rather than cough, is more often the reason that patients in whom emphysema predominates seek medical attention. Although exertional dyspnea correlates in general with the degree of airflow obstruction, wide variability among individuals makes it impossible to predict the extent of respiratory impairment on the basis of any single value or set of values for expiratory flow. Nevertheless, as a broad guideline, only minimal limitation is imposed until the value for FEV_1 falls below 65% of normal. As airflow obstruction progresses, dyspnea develops with more moderate levels of exertion. When the FEV_1 value drops below 35% to 40% of normal, the patient may become breathless during activities of daily living such as making the bed or bathing.

Orthopnea is often present in patients with advanced airway disease, especially in cases in which increased airway secretions accompany significant airflow limitation. The orthopnea of CAO must be differentiated from the paroxysmal nocturnal dyspnea of chronic heart failure. This differentiation is based on the rapidity of onset of dyspnea with the patient lying supine: dyspnea is said to develop almost immediately in those with CAO but to be delayed for as long as a few hours in those with congestive heart failure. However, the distinction is not clear-cut, because patients with florid heart failure often refuse to lie supine even for brief periods, and patients with CAO may awaken after several hours of sleep with cough, shortness of breath, and chest congestion mimicking paroxysmal nocturnal dyspnea. Relief is obtained by coughing up secretions. To further complicate matters, the two processes most often occur together.

Physical Examination

Physical findings vary with the severity of disease and the relative contributions of chronic bronchitis and emphysema [*see Table 1*]. In the early stages, physical examination may yield en-

tirely normal results. With more advanced disease, tachypnea and a prolonged expiratory phase of the respiratory cycle are usually present. Emphysematous hyperinflation of the lungs may cause a hyperresonant percussion note and an unusually low position of the diaphragm. Breath sounds may be reduced by decreased airflow, and wheezes are heard in 40% or more of patients, especially if patients are in the supine position when examined. Rales are heard in some patients, particularly at the posterior lung bases, in the absence of heart failure. These are usually heard during the entire inspiratory phase, rather than solely at end-inspiration, which is the usual finding in interstitial lung disease (e.g., asbestosis or idiopathic pulmonary fibrosis). Clubbing of the digits is not a manifestation of CAO.

Laboratory Tests

In most patients who present with symptoms and signs described above, the order of testing should be as follows: (1) pulmonary function tests (including arterial blood gases), (2) chest radiography, and, in rare instances, (3) computed tomography of the chest.

Pulmonary function tests In the dyspneic patient, routine pulmonary function tests depict the characteristic pattern of volume-dependent airway obstruction [*see 14:I Lung Function Assessment and Thoracic Diagnostic Techniques*].[28] Spirometry reveals a reduction in the FEV_1/FVC and an even greater relative decline in the forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}). As the airflow obstruction worsens, a normal volume of gas can no longer be exhaled in the time available, and vital capacity also declines.

Measurement of lung volumes uniformly reveals an increased residual volume (RV) and a normal to increased functional residual capacity (FRC). RV may be two to four times higher than normal because of slowing of expiratory flow and trapping of gas behind prematurely closed airways. FRC increases by two mechanisms: dynamic hyperinflation and activation of inspiratory muscles during exhalation. As a result, tidal breathing may take place at lung volumes as high as 1 to 2 L above normal levels. The advantage of an increased FRC to the patient with significant airflow obstruction is enlarged airway diameter with greater radial support (which means less airway resistance) and increased driving pressure (i.e., elastic recoil) for exhalation. The cost to the patient is the greater work of breathing incurred at the higher lung volume. Total lung capacity (TLC) is normal or increased in CAO. As would be predicted, there is a correlation between the extent of emphysematous lung destruction found at postmortem examination and the TLC. However, the correlation is not close, so that only a markedly increased TLC would be used to gauge the severity of emphysema.

Pulmonary function tests are useful in patients with CAO to confirm the obstructive abnormality, to quantify the severity of the defect, to assess the reversibility of the airflow obstruction in response to therapy,[29] and to monitor the course of the disease. A low FEV_1/FVC and a decrease in expiratory flow rates prove obstruction, but the best measurement for assessing the severity of the obstruction is the FEV_1. A scheme for determining severity of COPD has been proposed [*see Table 2*]. Construction of flow-volume loops may be useful if upper airway obstruction is a diagnostic consideration.

Chest imaging Radiographic abnormalities may be minimal, even in cases of advanced CAO. In patients in whom radiographic-pathologic correlations are made, the results of chest radiography suggest a diagnosis of emphysema in fewer than half of the cases, even among those with the highest emphysema scores pathologically.

Three types of radiographic abnormalities, if paired with the appropriate clinical history, suggest the diagnosis of emphysema [*see Table 1*]. The first is arterial deficiency in the lung periphery; narrowed or absent vessels are associated with hyperlucency of the lung, usually in a symmetrical, bilateral distribution. The second abnormality relates to hyperinflation and reflects the fact that the standard posteroanterior and lateral chest radiograph is obtained at TLC; signs of hyperinflation include a low position of the diaphragm (i.e., at or below the seventh rib anteriorly), increased depth of the retrosternal air space, and a narrow, vertically oriented cardiac silhouette. Perhaps most useful in this regard is flattening of the diaphragmatic contour with loss of the normal domed appearance, especially on the lateral film. The third abnormality is bullous disease. If a bulla is present together with either of the radiographic findings above, it is virtually diagnostic of emphysema, although only a small percentage of patients afflicted with emphysema have bullae [*see* Bullous Lung Disease, *below*].

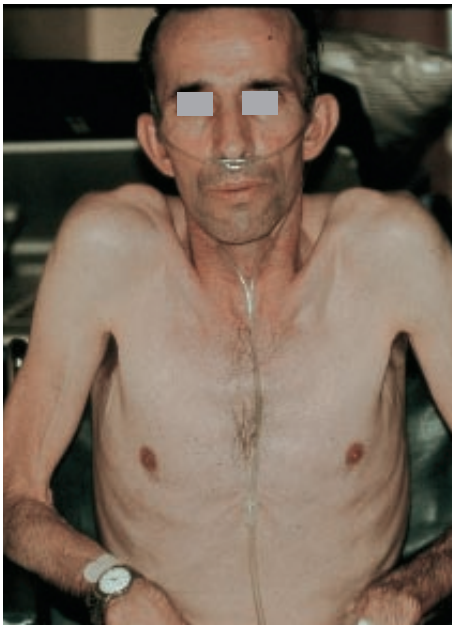
Chronic bronchitis is rarely recognized on a chest radiograph [*see Table 1*]. On occasion, the diagnosis may be suspected because of visualization of thickened bronchial walls, particularly in a parahilar bronchus viewed end-on. In other patients, bronchovascular markings at the lung bases may be accentuated, although outlines appear indistinct—a pattern that has been dubbed the dirty chest of chronic bronchitis. A similar radiographic appearance has been referred to as the increased-markings pattern of emphysema, especially when increased vascular markings are observed in the presence of pulmonary hypertension and cor pulmonale. The precise pathologic correlate of this radiographic image is unknown.

CT of the chest can be useful in the differential diagnosis of CAO.[30] Patients without abnormalities in pulmonary function may have extensive upper lobe emphysema, as demonstrated by CT.[31] Occasional smokers with normal airflow on spirometry but diminished diffusing capacity for carbon monoxide may

Table 2 Classification of Severity of COPD

Stage	*Condition*	*Characteristics*
0	At risk	Normal spirometry Chronic symptoms (cough, sputum production)
I	Mild COPD	FEV_1/FVC < 70% FEV_1 ≥ 80% predicted With or without chronic symptoms (cough, sputum production)
II	Moderate COPD	FEV_1/FVC < 70% FEV_1 ≥ 30% but < 80% predicted IIA: FEV_1 ≥ 50% but < 80% predicted IIB: FEV_1 ≥ 30% but < 50% predicted With or without chronic symptoms (cough, sputum production, dyspnea)
III	Severe COPD	FEV_1/FVC < 70% FEV_1 < 30% predicted or FEV_1 < 50% predicted plus respiratory failure or clinical signs of right heart failure

FEV_1—forced expiratory volume in 1 second FVC—forced vital capacity



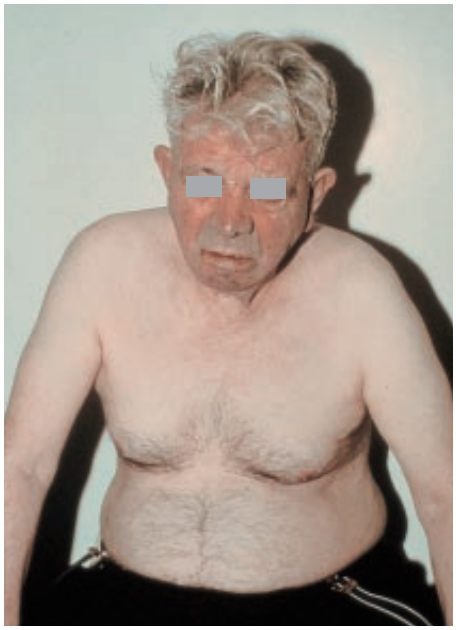


Figure 5 **In the advanced stages of chronic airflow obstruction, two distinct clinical types may emerge. Emphysema patients (so-called pink puffers, left) exhibit dyspnea without significant hypoxemia and tend to be thin, to have hyperinflated lung fields at total lung capacity, and to be free of signs of right heart failure. Chronic bronchitis patients (so-called blue bloaters, right) are characterized by marked hypoxemia with cyanosis and peripheral edema resulting from right heart failure.**

have emphysema that can be detected only by high-resolution CT scanning.[32]

Abnormalities in gas exchange It has long been recognized that the pattern of gas exchange abnormalities in CAO may differ greatly among patients with airflow obstruction of identical severity. Early in the course of disease, when expiratory flow is only slightly reduced, mild hypoxemia may be the only blood gas abnormality. However, in advanced stages of CAO, two distinct patterns emerge [*see Table 1 and Figure 5*]. Patients in one group (type A) exhibit dyspnea with only mild to moderate hypoxemia (arterial oxygen tension [P_aO_2] levels are usually > 65 mm Hg) and maintain normal or even slightly reduced arterial carbon dioxide tension (P_aCO_2) levels. These patients are sometimes referred to as pink puffers; they tend to be thin, to experience hyperinflation at total lung capacity, and to be free of signs of right heart failure. The pink puffer usually has severe emphysema. The other clinical group (type B) is characterized by marked hypoxemia and peripheral edema resulting from right heart failure. These patients, sometimes called blue bloaters, typically exhibit cough and sputum production. They have frequent respiratory tract infections, experience chronic carbon dioxide retention (P_aCO_2 > 45 mm Hg), and have recurrent episodes of cor pulmonale. The blue bloater may also have pathologic evidence of severe emphysema but, in addition, suffers from inflammation of large and small airways and possible defects in ventilatory control. These patients usually meet the criteria for chronic bronchitis.

The common denominator in the two patterns is long-term cigarette smoking. Many long-term cigarette smokers will demonstrate features of both types, giving rise to either mixed or intermediate clinical presentations.

Several explanations have been proposed for this disparate response to severe airflow obstruction, including differences in pulmonary mechanics, in the central control of ventilation, and in respiratory disturbances during sleep. Type A patients appear to have advanced emphysema with relatively little evidence of airway disease. These patients have abnormally compliant lungs, and airflow obstruction is related primarily to a loss of lung elastic recoil. In contrast, type B patients typically have intrinsic airway disease that manifests clinically as cough and sputum production (i.e., chronic bronchitis) and physiologically as increased resistance to airflow during both expiration and inspiration (airflow resistance during inspiration is not as apparent in patients with emphysema and loss of lung elastic recoil). Type B patients may compensate for the increased work of breathing imposed by this inspiratory resistive load by limiting their total amount of ventilation, causing P_aCO_2 levels to rise. Patients with both reduced elastic recoil and increased inspiratory resistance (i.e., those with a mixed type of clinical presentation) would be predicted to have chronic hypercapnia, and this is indeed the case.

It is also possible that patients with severe CAO in whom hypercapnia ultimately develops have intrinsic defects that cause relatively depressed ventilatory responses to acute rises in P_aCO_2 levels, falls in P_aO_2 levels, or both. This hypothesis is supported by the finding that the healthy first-degree relatives of patients with CAO and chronic carbon dioxide retention have blunted ventilatory responses to hypercapnia and hypoxia compared with the first-degree relatives of patients with CAO but no chronic hypercapnia.

Alternatively, arousal responses during sleep may be abnormally depressed in type B patients. Failure to arouse and resume normal ventilation may explain why, during sleep, type B patients experience more severe and prolonged decreases in P_aO_2 levels and increases in P_aCO_2 levels than normal persons or type A patients. Over time, repeated periods of hypercapnia during sleep may diminish the potency of hypercapnia as a stimulus to increased ventilation, eventually leading to fixed carbon dioxide retention.[33]

The more profound hypoxemia observed in type B patients, as compared with type A patients, is in part a result of overall alveolar hypoventilation. In addition, ventilation-perfusion mismatching in type B patients involves a greater number of alveoli receiving low levels of ventilation for the amount of blood flow delivered (low $\dot{V}_A/\dot{Q}$ units).

Regardless of the mechanisms that underlie these different patterns of gas exchange abnormalities, the two have very different consequences for the cardiovascular system in patients with advanced CAO. In the type B patient, both alveolar hypoxia and

acidosis (secondary to chronic hypercapnia) stimulate pulmonary arterial vasoconstriction, and hypoxemia stimulates erythrocytosis. Increased pulmonary vascular resistance, increased pulmonary blood volume, and, possibly, increased blood viscosity from secondary erythrocytosis all contribute to pulmonary arterial hypertension. In response to long-term pulmonary hypertension, cor pulmonale generally develops: the right ventricle becomes hypertrophic, and increases in cardiac output are achieved by means of abnormally high right ventricular filling pressures. Additional hemodynamic loads may cause the right ventricle to fail, with the consequent development of systemic venous hypertension, manifested by jugular venous distention, peripheral edema, passive hepatic congestion, and, sometimes, ascites. (Pleural effusion is not a manifestation of cor pulmonale in the absence of left heart failure.) Electrocardiographic findings of cor pulmonale correlate with increased right ventricular weight at postmortem examination [*see Table 3*].

The emphysematous lung destruction characteristic of type A patients leads to a restricted vascular bed because of the loss of pulmonary capillaries from the destroyed alveolar walls. This condition is reflected in the reduced diffusing capacity of the lung for carbon monoxide ($D_{L_{CO}}$) observed in type A (but not in type B) patients.[34] However, because P_aO_2 levels are only mildly depressed in type A patients, pulmonary vasoconstriction is minimal, and secondary erythrocytosis does not develop. Cardiac output may be slightly reduced. As a result, pulmonary hypertension in type A patients is milder than in type B patients, and cor pulmonale develops infrequently, usually only in the terminal phase of the illness.

Differences in gas exchange during exercise also distinguish the two clinical types. Type A patients have abnormally high levels of ventilation for a given workload (expressed in terms of oxygen consumption, $\dot{V}O_2$), but, nevertheless, the partial pressure of oxygen in the arterial blood falls with exercise. The $D_{L_{CO}}$ in type A patients rises minimally and remains low during exercise, reflecting inadequacies in the alveolar-capillary surface area available for gas exchange. Patients with CAO who have $D_{L_{CO}}$ levels less than 55% of normal can be expected to have oxygen desaturation with exercise. In contrast, type B patients have subnormal increases in ventilation for a given level of work (decreased ($\dot{V}_E/\dot{V}O_2$) and a greater rise in P_aCO_2 levels with exercise than type A patients, and yet, P_aO_2 levels may increase during exercise. This increase in P_aO_2 levels must reflect improved matching of ventilation to perfusion during exercise.

Table 3 ECG Findings of Right Ventricular Hypertrophy Resulting from Chronic Airflow Obstruction

Conventional Interpretation
Tall P wave (≥ 2.5 mm)
Tall R wave in lead V1 or V2 (≥ 6 mm)
Deep S wave in lead V5 or V6 (≥ 10 mm)
Right axis deviation (QRS axis +90° to +180°)
Vectorial Interpretation
Rightward P wave vector (≥ 70°)
Tall P wave in lead II, III, or aVF (≥ 2.5 mm)
Rightward initial (> 60°), terminal (> 60°), and mean (> 70°) QRS vectors
Posteriorly directed horizontal QRS vector (≥ 300°)

TREATMENT

Reviews and guidelines on the treatment of CAO have been published,[21,35-37] but the various guidelines do not agree on recommendations.[38] Suboptimal prescription of and adherence to appropriate therapies further complicate management of CAO.[39] Of the therapeutic measures available for patients with chronic bronchitis and emphysema, only smoking cessation and long-term administration of supplemental oxygen to the chronically hypoxemic patient have been definitively shown to alter the natural history of the disease favorably. Data suggest, however, that the combination of a long-acting $beta_2$ agonist and inhaled corticosteroids may also improve survival of patients with COPD.[40]

Helping a patient to quit smoking is probably the single most important intervention; effective methods include counseling by physicians and nurses, use of nicotine chewing gum or patches, behavior intervention (e.g., individual or group therapy), and several pharmacologic interventions (e.g., bupropion and nortriptyline)[41] [*see CE:III Reducing Risk of Injury and Disease*]. Smoking cessation generally causes the symptoms of chronic bronchitis to diminish or entirely remit,[15] and it eliminates the accelerated loss of lung function observed with continued cigarette smoking.[42]

Reduction in morbidity and mortality in patients with CAO can be achieved with yearly vaccinations against influenza.[43] We also favor administration of the pneumococcal vaccine, although its efficacy is less well documented in this patient population.[44] In the future, immunization with *Haemophilus influenzae* vaccine may be recommended.[45]

A variety of other therapies offer potential relief of symptoms in patients with CAO. These include the use of bronchodilators; anti-inflammatory therapy; administration of antibiotics during acute purulent exacerbations; pulmonary rehabilitation programs, including physical exercise and respiratory muscle training; and, for patients with cor pulmonale, the use of diuretics.

Bronchodilators

Chronic bronchitis and emphysema are for the most part considered to be diseases of irreversible airflow obstruction, in contradistinction to asthma. Nevertheless, most patients with chronic bronchitis and emphysema who are given a sufficiently strong bronchodilating medication will exhibit at least a 10% increase in maximal expiratory airflow.[29] Dyspneic patients should be given a trial of bronchodilators even if pulmonary function testing shows that they do not manifest significant bronchodilation, because bronchodilator responsiveness may vary over time. On the other hand, there is no evidence to suggest that daily bronchodilator therapy is beneficial in asymptomatic patients with early CAO.

The bronchodilators used to treat CAO are the same as those used in the management of asthma [*see 14:II Asthma and Table 4*], with the exception that anticholinergic therapy appears to be more effective in the treatment of chronic bronchitis and emphysema. The first line of therapy is inhaled atropine derivatives (e.g., ipratropium bromide),[46] which are approximately equipotent to inhaled $beta_2$ agonists but have a slower onset of action. A long-acting anticholinergic bronchodilator, tiotropium, is scheduled to become available in the United States late in 2003; tiotropium appears to be better than iprotropium given continuously.[47] If an inadequate response is seen with anticholinergic therapy, an inhaled $beta_2$ agonist can be substituted or added. When anticholinergic therapy and $beta_2$-agonist therapy are needed, the medications can be administered conveniently with a metered-dose inhaler containing both compounds.[48] Long-act-

Table 4 Estimated Comparative Doses of Inhaled Bronchodilators for COPD[163]

Category (Relative Efficacy)	*Drug*	*How Available*	*Maintenance Dosage*	*Exacerbation Dosage*	*Comment*
Inhaled anticholinergics (first-line therapy)	Ipratropium bromide	Nebulizer, 0.25 mg/ml	0.5 mg q. 6 hr	0.5 mg q. 2–8 hr	May mix with albuterol in same nebulizer
		MDI, 18 μg/puff	2–6 puffs q. 6 hr	3–8 puffs q. 3–4 hr	MDI as effective as nebulizer when used with spacer
Inhaled short-acting $beta_2$ agonists (second-line therapy)	Albuterol	Nebulizer, 5 mg/ml	1.25–5.0 mg q. 4–8 hr p.r.n.	5.0 mg q. 2 hr	Dilute aerosols to minimum of 4 ml at gas flow of 6–8 L/min
		MDI, 84 μg/puff	2–4 puffs q. 6 hr p.r.n.	3–8 puffs q. 2 hr	MDI as effective as nebulizer when used with spacer
		DPI, 200 μg/capsule	1–2 capsules q. 6 hr p.r.n.	Not studied in exacerbations	—
	Bitolterol	Nebulizer, 2 mg/ml	0.5–3.5 q. 4–8 hr p.r.n.	Not studied in exacerbations	—
		MDI, 370 μg/puff	2–4 puffs q. 6 hr p.r.n.	Not studied in exacerbations	—
	Pirbuterol	MDI, 200 μg/puff	2–4 puffs q. 6 hr p.r.n.	Not studied in exacerbations	—
Combined short-acting $beta_2$ agonist and anticholinergic (when both are indicated)	Albuterol + ipratropium bromide	MDI; albuterol, 90 μg/puff + ipratropium, 18 μg/puff	2–4 puffs q. 6 hr p.r.n.	3–8 puffs q. 2 hr	—
Inhaled long-acting $beta_2$ agonists (may replace anticholinergic)	Salmeterol	MDI, 21 μg/puff	2 puffs q. 12 hr	Not recommended	Slower onset of action than short-acting $beta_2$ agonists
		DPI, 50 μg/blister	1 blister q. 12 hr	Not recommended	
	Formoterol	DPI, 12 μg/capsule	1 capsule q. 12 hr	Not recommended	Faster onset of action than salmeterol

DPI—dry powder inhaler MDI—metered-dose inhaler

ing $beta_2$-agonist therapy has been shown to give a similar response to anticholinergic therapy with much longer duration of action.[49] If the patient remains symptomatic on optimized inhaled medication, a trial of theophylline is indicated.[50]

There is no evidence that nebulized bronchodilators are of greater benefit than properly administered metered-dose inhaled medications, especially when the metered-dose inhaler was used with a spacer.[51]

Corticosteroids

Given the underlying pathophysiology of emphysema, corticosteroids would be expected to provide little benefit, because tissue destruction is the basic disease mechanism. In contrast, in chronic bronchitis, and especially in asthmatic bronchitis, corticosteroids would be expected to relieve airflow obstruction by reducing airway inflammation, hypersecretion of mucus, and bronchial reactivity.

Only some patients derive significant benefit from corticosteroids. These patients may be identifiable clinically on the basis of recurrent attacks of wheezing; they are likely to exhibit a relatively significant acute response to inhaled bronchodilators (> 20% increase in FEV_1). Sputum eosinophilia may also be helpful in identifying these patients.[52] Because of the chronic nature of these illnesses and the serious adverse consequences of long-term corticosteroid administration, corticosteroids should be reserved for acute exacerbations of disease[53] or, if required on a regular basis, given in the lowest possible dose, preferably on alternate days. The addition of inhaled corticosteroids may allow reduction or elimination of the oral steroid dosage and may have significant beneficial effects on airway inflammation [*see Table 5*].[54] In published randomized trials of inhaled steroids in patients with COPD, no improvement in decline in lung function was seen, but there were reductions in respiratory symptoms, in exacerbations (worsening of symptoms), and in use of health care services.[55] Analyses of large databases have suggested that inhaled corticosteroids, especially when used with long-acting $beta_2$ agonists, may also improve survival.[40,56]

The main issue in corticosteroid therapy for CAO, as in any therapy, is how to achieve maximal benefit with minimal toxicity. If prolonged high-dose corticosteroid therapy is given to patients who do not show objective improvement in pulmonary function, the net effect will probably be negative. Complications associated with prolonged high-dose corticosteroid therapy include weight gain, osteoporosis,[57] hypertension, diabetes, cataracts, and myopathy. Serious pulmonary infections, including locally invasive aspergillosis, can ensue. Patients with CAO are at higher risk than patients with asthma, because they often have structural abnormalities in the lungs and defects in mucociliary clearance, both of which predispose to infection with organisms of low virulence.

Antibiotics

In the 1950s and 1960s, clinical trials of daily antibiotic use in patients with mild CAO demonstrated that this intervention did

not significantly alter either the degree of disability or the rate of disease progression. Only patients with very frequent purulent exacerbations (so-called chronic purulent bronchitis) derived some symptomatic benefit from regular antibiotic use.

On the other hand, intermittent antibiotic administration is indicated for acute episodes of clinical worsening marked by increased dyspnea, excessive sputum production, and sputum purulence. The duration of symptoms and the risk of serious deterioration in lung function can be reduced by a 7- to 10-day course of broad-spectrum antibiotics, presumably because a significant number of these exacerbations are caused by a superimposed bacterial tracheobronchitis.[58] Recent guidelines suggest that with advancing age, severity of disease, and the presence of comorbidity, the pathogens encountered in exacerbations tend to be more resistant, necessitating use of broader-spectrum antibiotics.[59] For patients with simple chronic bronchitis ($FEV_1 > 50\%$), in the absence of pneumonia, empirical treatment with ampicillin, tetracycline, or trimethoprim-sulfamethoxazole is satisfactory. In patients whose FEV_1 is less than 50%, many of the *H. influenzae, Moraxella (Branhamella) catarrhalis,* and *Streptococcus pneumoniae* isolates are β-lactam resistant, and other organisms, such as members of the Enterobacteriaceae family and *Pseudomonas* species, become more common.[60] In these cases, a quinolone, β-lactam–β-lactamase inhibitor combination, a second-generation oral cephalosporin, or a second-generation macrolide may be needed.

Diuretics and Vasodilators

In patients with far-advanced CAO who have cor pulmonale and right heart failure, therapies are often directed specifically at the hemodynamic consequences of the disease [*see 14:XI Pulmonary Hypertension, Cor Pulmonale, and Primary Pulmonary Vascular Diseases*].[61] Diuretics are administered for symptomatic relief of peripheral edema; they may also reduce pulmonary arterial pressure by decreasing intrapulmonary blood volume. Care must be taken to avoid chloride depletion from long-term diuretic use because the resultant hypochloremic metabolic alkalosis depresses respiratory drive and may aggravate CO_2 retention. Digoxin and aminophylline are only weak inotropic stimulants of the right ventricle. The increases in right ventricular output produced by these medications are not clinically significant.

A variety of arterial vasodilators, including hydralazine and nifedipine, have been used in an attempt to reduce pulmonary arterial hypertension secondary to severe CAO. A limited number of studies have demonstrated that long-term (6 to 12 months) vasodilator administration produces persistent reductions in pulmonary arterial pressures, but there is no evidence that such therapy produces sustained symptomatic improvement or prolongs survival.[61] A potential risk of vasodilator therapy, particularly in the patient with fixed (i.e., anatomic) pulmonary hypertension, is the development of systemic hypotension and renal hypoperfusion. In general, relief of hypoxemia with long-term supplemental oxygen administration has proved to be more effective than drug therapy in reducing pulmonary arterial resistance.

Pulmonary Rehabilitation

Physical training programs, such as treadmill walking, significantly increase the exercise capacity of patients with even far-advanced chronic bronchitis and emphysema.[62] These results have been achieved despite the fact that lung function, as reflected in such measurements as vital capacity and FEV_1, is not affected and maximal heart rate is generally not reached during the training sessions.

Much interest has focused on the possibility that resistive or endurance exercises aimed at strengthening the inspiratory muscles might increase respiratory muscle strength and endurance and thereby improve exercise capacity, at least in cases in which respiratory muscle fatigue contributes to exercise limitation. For instance, it was shown that patients with severe CAO who breathed through an inspiratory resistor (with the amount of resistive load carefully tailored to the particular patient) for 15 minutes twice daily for 1 month derived a number of benefits. Such a regimen not only increased the endurance of the inspiratory muscles but also enabled patients to walk farther during a fixed period and increased their endurance during submaximal exercise on a bicycle. However, it is not clear whether the benefit derived from respiratory muscle training exceeds that derived from general physical conditioning. As with other forms of physical training, deconditioning occurs within a few weeks of cessation of the exercise program.

Table 5 Estimated Comparative Daily Dosages of Inhaled Corticosteroids[163]

Drug	*Low Dosage*	*Medium Dosage*	*High Dosage*	*Relative Efficacy*
Beclomethasone 42 μg/puff 84 μg/puff	168–504 μg 4–12 puffs/day 2–6 puffs/day	504–840 μg 12–20 puffs/day 6–10 puffs/day	> 840 μg > 20 puffs/day > 10 puffs/day	Third-highest potency
Budesonide 200 μg/puff	200–400 μg 1–2 inhalations/day	400–600 μg 2–3 inhalations/day	>600 μg > 3 inhalations/day	Second-highest potency
Flunisolide 250 μg/puff	500–1,000 μg 2–4 puffs/day	1,000–2,000 μg 4–8 puffs/day	> 2,000 μg > 8 puffs/day	Lowest potency
Fluticasone 44 μg/puff 110 μg/puff 220 μg/puff	88–264 μg 2–4 puffs/day 2 puffs/day	264–660 μg 2–6 puffs/day 1–2 puffs/day	> 660 μg > 6 puffs/day > 3 puffs/day	Highest potency
Triamcinolone 100 μg/puff	400–1,000 μg 4–10 puffs/day	1,000–2,000 μg 10–20 puffs/day	> 2,000 μg > 20 puffs/day	Lowest potency

Intermittent application of negative pressure or noninvasive positive pressure ventilation has been used in the treatment of patients with chronic hypercapnia caused by advanced chronic bronchitis and emphysema.[63] During periods of mechanical ventilation, the respiratory muscles are rested and gas exchange improves. Results in a limited number of patients suggest that daytime symptoms, arterial blood gas levels, and exercise performance all improved when only a few hours of ventilation were applied nightly or even less frequently.

Long-term Oxygen Administration

Probably the single most important advance in recent years in the treatment of advanced CAO has been the widespread home use of supplemental oxygen.[64] Chronic hypoxemia causes secondary erythrocytosis and contributes to exercise limitation, pulmonary hypertension and right heart failure, and impaired neuropsychiatric function. Each of these consequences of chronic hypoxemia can be ameliorated or even corrected by the administration of oxygen at levels that are sufficient to maintain the arterial oxygen saturation at values exceeding approximately 90%. This target value, which corresponds to a P_aO_2 of 60 to 80 mm Hg, can usually be achieved with oxygen supplementation delivered at a rate of 2 L/min via nasal cannulas, but the rate of oxygen administration should be titrated to the individual patient's needs according to arterial blood gas measurements taken when the patient is breathing supplemental oxygen.

Supplemental oxygen administration for a minimum of 15 hr/day may suffice to ameliorate some of the adverse consequences of chronic tissue hypoxia, particularly secondary erythrocytosis and pulmonary hypertension. However, survival is significantly improved when supplemental oxygen is given for 24 hr/day.

In general, patients should receive long-term home oxygen supplementation if the P_aO_2 is 55 mm Hg or less or if the P_aO_2 is 59 mm Hg or less and one or more of the following conditions are present: peripheral edema (a sign of cor pulmonale), a hematocrit of 55% or greater, and P pulmonale on the ECG. The resting P_aO_2 should be assessed when the patient is free of an exacerbation and has received intensive bronchodilator therapy. With adequate oxygen therapy, phlebotomy for polycythemia (i.e., hematocrit > 50%) is rarely necessary.

Oxygen for home use can be stored in cylinders as compressed gas or as liquid oxygen, or it can be generated from ambient air by machines called oxygen concentrators that are the size of a bedside table. Portable tanks of oxygen, filled from a liquid oxygen reservoir tank, can provide supplemental oxygen for several hours of use outside the home. Newer methods to conserve oxygen consumption and prolong the time provided by portable oxygen tanks include devices that release oxygen only during the inspiratory phase of the respiratory cycle and direct transtracheal administration of oxygen via an indwelling tracheal catheter.[65]

Surgery

Interest in surgical therapy for diffuse emphysema has been revived because of advances in the operative technique. Emphysematous lung tissue is removed by one of several approaches and techniques.[66] The rationale is to remove overdistended, poorly functioning emphysematous regions, thereby allowing more-normal or less-affected regions to expand with a decrease in the FRC and an improvement in inspiratory muscle function.[67] The surgery produces a 13% to 96% improvement in the FEV_1 and a reduction in the RV, and many patients who previously required supplemental oxygen are able to discontinue it or reduce their use. However, results vary enormously among patients.[68] Operative mortality is 5% to 7%, patients usually stay in the hospital 7 to 10 days, and the main morbidity is prolonged air leaks.[69] Decreases in TLC, increases in elastic recoil pressures, and lengthening of inspiratory muscles have been shown to be directly related to functional improvement.[70] The surgery can be performed on many patients who are not candidates for lung transplantation, instead of lung transplantation, or as a bridge to transplantation.[71] By 5 years after surgery, only 8% of the patients continue to have a significant improvement in FEV_1.[72] In two small randomized trials, patients treated with pulmonary rehabilitation plus surgery, compared with patients treated with pulmonary rehabilitation alone, were shown to have improvement in lung function, exercise capacity, and quality of life.[73,74]

A randomized, multicenter clinical trial comparing lung volume reduction surgery with continued medical treatment in 1,218 patients with severe emphysema found that the surgery increased the chance of improved exercise capacity but did not confer a survival advantage, except in patients who had both predominantly upper lobe emphysema and low exercise capacity after rehabilitation. Patients with an FEV_1 20% or less than predicted and either homogenous emphysema on high-resolution CT scanning or a diffusion capacity 20% or less than predicted had a higher 30-day postoperative mortality than the medically treated group.[75-77] Patients with non–upper lobe emphysema and high baseline exercise capacity proved to be poor candidates because of operative mortality and negligible functional gains.

In younger patients with far-advanced CAO, lung transplantation is a therapeutic option. In patients with pure emphysema, single-lung transplantation has been performed successfully despite the concern that the remaining emphysematous lung would become further overexpanded because of the normal recoil of the transplanted lung.[78] In patients with chronic bronchitis and any evidence of concomitant bronchiectasis, bilateral lung transplantation is performed at many centers to eliminate the potential risk of persistent infection in the remaining lung. Heart-lung transplantation is not needed even in patients with cor pulmonale, because the right ventricle rapidly recovers when pulmonary vascular resistance is reduced. The median survival after lung transplantation is approximately 3.8 years.[79]

Other Conditions Associated with CAO

A1-ANTITRYPSIN DEFICIENCY

Degradation of interstitial elastin fibers by elastolysis is a central pathologic process in the development of emphysema [*see* Protease-Antiprotease Imbalance, *above*]. The main defense of normal lung tissue against this enzymatic destruction is alveolar α_1-antitrypsin, which inactivates elastase by forming a stable complex with it. α_1-Antitrypsin is synthesized predominantly in the liver and is present in the serum of normal persons at concentrations of 85 to 213 mg/dl.

The genetic model describing inheritance of α_1-antitrypsin genes invokes multiple autosomal codominant alleles at a single locus.[80] The locus on chromosome 14 has been designated Pi, which stands for protease inhibitor system. The most prevalent α_1-antitrypsin allele, found with a frequency of 0.95 in whites in the United States, is labeled Pi^M. Variant α_1-antitrypsin molecules

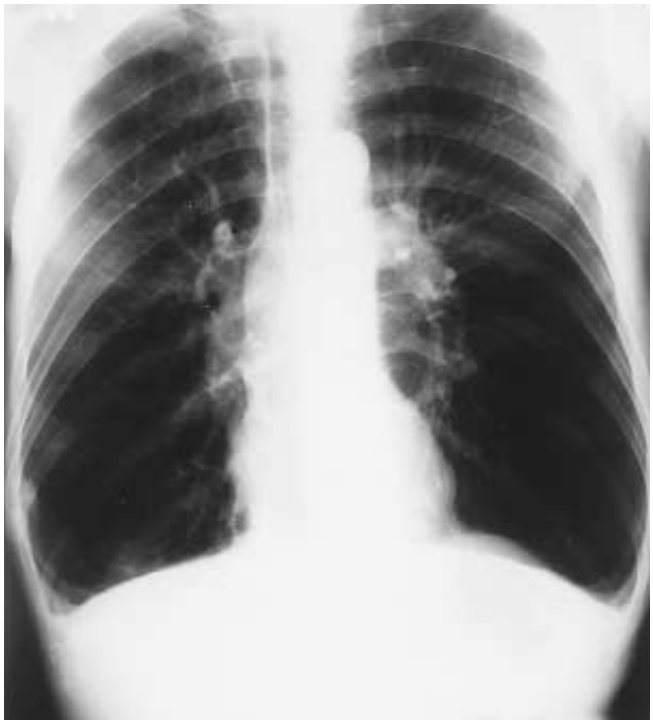


Figure 6 **This chest radiograph of a patient with homozygous α_1-antitrypsin deficiency reveals hyperinflation and hyperlucent lung fields with bilateral basilar bullae. Other findings include prominent central pulmonary arteries and rapid pruning of the pulmonary arterial branches, consistent with pulmonary arterial hypertension.**

are denoted with letters based on their electrophoretic mobility. The variant protein molecule with the lowest rate of electrophoretic mobility is Pi^Z.

Most of the various Pi phenotypes are associated with normal amounts of serum α_1-antitrypsin.[80] However, in persons homozygous for the Pi^Z allele, serum concentrations of α_1-antitrypsin are only 10% to 15% of normal. In the United States, the prevalence of α_1-antitrypsin deficiency caused by a homozygous Pi^Z genotype is one in 3,000 persons[62] but is lower in African Americans. The substitution of a single amino acid in the normal M α_1-antitrypsin protein impairs the release of the Z protein from hepatocytes into the circulation. The protein appears as granular cytoplasmic inclusions in the livers of patients heterozygous or homozygous for Pi^Z. The secreted Pi^Z α_1-antitrypsin is also a less potent inhibitor of neutrophil elastase than Pi^M.

Because of the deficient and less potent α_1-antitrypsin, endogenous proteases are not effectively inhibited, resulting in a breakdown of elastin and the development of emphysema.[80] This hypothesis is supported by studies that found evidence for uninhibited elastase activity in patients with α_1-antitrypsin deficiency.[81] Uninhibited elastase may stimulate macrophages to release IL-8 and leukotriene B_4, which is a chemoattractant for neutrophils that perpetuates the local inflammation and increased amounts of neutrophil elastase.[82]

Emphysema develops in at least 80% of patients with homozygous Pi^Z α_1-antitrypsin deficiency. The mean age at onset of dyspnea is 45 to 50 years in nonsmokers and approximately 10 years earlier in those who smoke. The typical pathologic picture is panacinar emphysema, but as many as 25% to 30% of nonsmoking patients and 60% of cigarette smokers report symptoms of chronic bronchitis as well. Many of the patients have evidence of enhanced airway reactivity.[83] High-resolution CT scanning has also detected a significant incidence of bronchiectasis.[84] Involvement of the lower lobes often predominates, perhaps because of increased neutrophil traffic and release of neutrophil elastase in the lower lung fields. The radiographic manifestation of this phenomenon is most commonly attenuation of the pulmonary vasculature to the lower lobes; in more advanced cases, basilar bullae may be seen [*see Figure 6*]. Features that would suggest α_1-antitrypsin deficiency as the cause of a particular patient's emphysema would thus include a family history of emphysema (especially among nonsmokers), the onset of symptoms at 30 to 50 years of age, the development of significant emphysema in a nonsmoker, and basilar predominance of the radiographic abnormalities. Serious liver disease, usually in the form of cirrhosis, occurs in 5% to 10% of adults with α_1-antitrypsin deficiency and may provide a clue to the underlying enzyme deficiency in some patients. Symptomatic liver disease is more common in children, who may present with neonatal hepatitis. Many infants and children recover, but 10% to 20% of those with hepatitis progress to cirrhosis and liver failure during childhood or early adulthood. It is not certain why some Pi^Z patients have symptomatic liver disease in childhood, whereas others do not and acquire emphysema later in life.

Remarkably, some nonsmoking patients with homozygous Pi^Z α_1-antitrypsin deficiency never manifest symptomatic emphysema.[85] There is no escape for smokers with this deficiency, however: all such patients have symptomatic airflow obstruction at a young age.

Persons who are heterozygous for the Z variant (Pi^{MZ}) have serum α_1-antitrypsin concentrations that are approximately 70% of normal.[86] Whether increased respiratory symptoms and airflow obstruction are greater in persons with the Pi^{MZ} phenotype than in matched Pi^M control subjects is not certain. Two long-term studies have found greater deterioration in lung function in Pi^{MZ} patients than in Pi^{MM} patients.[86,87] The uncertainty might be explained by different degrees of deficiency in antiprotease levels. It is thought that α_1-antitrypsin levels higher than 40% of normal afford protection against the development of emphysema.

For patients with homozygous Pi^Z deficiency, consideration should be given to administration of purified α_1-antitrypsin, which is commercially available for replacement therapy.[80] Weekly infusions (60 mg/kg) can elevate serum levels above the hypothetical minimum protective level (80 mg/dl) for the entire week. Alternatively, a higher dose (250 mg/kg) can be given every 4 weeks. Clinical data support this longer interval, but unlike the weekly infusion, this regimen has not been approved for the product label. Studies of both dosing regimens using bronchoalveolar lavage have shown that adequate levels of α_1-antitrypsin are achieved not only in the serum but also in the lung, where they are crucial. Preliminary data suggest reduction in the breakdown of elastin in patients on replacement therapy.[88]

There are numerous unresolved questions about antiprotease replacement therapy. The most important question is whether it will actually retard the progression of emphysema. Preliminary and uncontrolled data suggest a reduction in progression of disease with weekly replacement therapy.[89,90] For the present, individual treatment decisions have to be made without full information, with cost[91] and potential risk weighed against potential benefit. Replacement therapy probably is not indicated for patients who have normal pulmonary function; careful follow-up should be sufficient in such cases. Patients with mild to moderate airflow obstruction might benefit from replacement therapy.

Smokers with CAO who have similar degrees of obstruction do benefit at this stage of the illness if the protease burden is reduced by the cessation of smoking. Patients with very severe airflow obstruction ($FEV_1 < 1$ L) may be beyond the point at which the natural course of the disease can be favorably altered by replacement therapy, much like smokers with very severe CAO, whose clinical course may not be altered by smoking cessation if there is little lung function left to preserve. In the future, it may be feasible to use antiprotease therapy[92] or gene therapy to restore normal production of α_1-antitrypsin.[93]

For homozygous Pi^Z patients with very severe airflow obstruction, lung volume reduction surgery[94] or single-lung transplantation offers hope for improved function and prolonged survival. Survival after transplantation is similar to that in patients with CAO.[95]

BULLOUS LUNG DISEASE

A bulla is defined pathologically as an emphysematous space greater than 1 cm in diameter; it is recognized radiographically as a localized hyperlucent area of lung demarcated by a curved hairline rim. Formation of bullae may complicate either panacinar or centriacinar emphysema. As many as one third of patients with radiographic evidence of emphysema have bullae on chest radiographs, although large, clinically significant bullae develop in only a small percentage of such patients.

Bullae may also form in the presence of normal surrounding lung tissue. The pathologic picture in this circumstance is most often described as paraseptal, or periacinar, emphysema. This condition involves destructive enlargement of predominantly the acinar ducts and the alveoli and primarily affects the periphery of the lobule adjacent to the surrounding septa. These subpleural bullae may produce a so-called soap-bubble appearance along the margin of the lung or may coalesce into a single bulla or multiple large bullae, typically in the lung apices. The perimeter of a bulla is formed by a thin layer of fibrous tissue and collapsed adjacent lung parenchyma. By contrast, the wall of congenital lung cysts (i.e., bronchogenic cysts) consists of bronchial epithelium.

For the most part, bullae behave as space-occupying lesions in the lung. Although bullae are inflated with gas, they participate minimally in overall ventilation. The virtual absence of ventilation of bullae in vivo can be demonstrated by (1) the absence of a change in the size of a bulla on an expiratory chest radiograph, (2) the large discrepancy between total lung capacity as measured by body plethysmography and that measured by helium dilution techniques, and (3) diminished or absent ventilation on radionuclide lung scanning with xenon-133. Perfusion scans reveal that bullae are also underperfused or nonperfused, and angiography demonstrates that large pulmonary vessels are not present within bullae. Thus, if a bulla contributes to hypoxemia in a patient, it is usually as a result of ventilation-perfusion imbalance (low $\dot{V}/\dot{Q}$) in the surrounding atelectatic lung tissue.

Bullae that are surrounded by normal lung tissue are often asymptomatic. Until more than one third of the radiographic volume of a lung is occupied by a bulla, no clinically significant change in measured vital capacity occurs. Dyspnea may develop if the bulla is massively enlarged, or the patient may come to medical attention because of such complications as pneumothorax or infection. Although a bulla may remain stable in size for many years, the usual pattern is growth over time. Surgical resection of a large, symptomatic bulla may markedly increase vital capacity and arterial O_2 tension by allowing surrounding normal lung to expand fully.[96]

A more difficult decision regarding the management of bullous lung disease is encountered in patients who have concomitant generalized emphysema throughout their lungs. In these patients, bullae simply represent a local exaggeration of a widespread process, and lung function does not normalize after resection of a bulla. Nevertheless, some patients with mild to moderate emphysema benefit from bullectomy. Improvement may be disappointingly brief, however, because bullae tend to recur.

Tests that may be useful for assessing the severity of associated emphysema in patients with bullae include CT of the chest, radionuclide lung scans, measurement of the diffusing capacity of the lungs for carbon monoxide, expiratory chest radiographs, and static pressure-volume curves of the lungs. However, there are no established guidelines for the management of bullous lung disease in patients with emphysema, and the decision to operate on a giant bulla is ultimately based on various subjective factors.

BRONCHIECTASIS

Bronchiectasis is a chronic suppurative disease of the airways that if sufficiently widespread may cause CAO. In the preantibiotic era, it was a relatively frequent sequela of pulmonary infections in childhood, typically leading to chronic respiratory disability and death by age 40. In modern practice, bronchiectasis is far less common and carries a much less dire prognosis. Nevertheless, it continues to be an important cause of chronic productive cough with sputum purulence and accounts for a significant percentage of cases of massive hemoptysis.

Etiology

Bronchiectasis is a localized, irreversible bronchial dilatation caused by a destructive inflammatory process involving the bronchial walls. Necrotizing bacterial or mycobacterial infection is thought to be responsible for most cases of bronchiectasis. A typical history is that of a childhood respiratory infection, such as whooping cough or bacterial superinfection complicating a viral pneumonia, followed by recurrent or persistent so-called chest colds.

Adult-onset bronchiectasis may result from an untreated or inadequately treated bronchopneumonia that is caused by virulent organisms such as staphylococci or gram-negative bacilli. Mycobacterial infection frequently causes bronchiectasis, but because reactivation tuberculosis usually involves the upper lobes of the lungs, the clinical consequences differ considerably from the clinical consequences of other forms of bronchiectasis, which usually involve the right middle lobe, the lingula, or the lower lobes.

Generalized bronchiectasis may develop when systemic or pulmonary defense mechanisms are impaired in such a way as to predispose the patient to recurrent or chronic bacterial infections involving the airways. Rare congenital abnormalities of lung structure such as bronchial cartilage deficiency (Williams-Campbell syndrome) and tracheobronchomegaly (Mounier-Kuhn syndrome) may lead to generalized bronchiectasis, as may inherited deficiencies of immunoglobulins, impaired phagocytosis, complement deficiency, and α_1-antitrypsin deficiency.[97] In adults, widespread bronchiectasis occurs in association with hypogammaglobulinemia,[98] including isolated IgG subclass deficiencies[99]; cystic fibrosis (see below); primary ciliary dyskinesia (see below); and several systemic diseases,[100] including rheumatoid arthritis,[101] other connective tissue diseases, inflammatory bowel disease, sarcoidosis, yellow nail syndrome, and HIV infection.[102]

Pathogenesis

Three types of bronchiectasis have been described on the basis of bronchographic-pathologic findings: cylindrical, varicose, and cystic. Distinction between these three types of bronchiectasis is not useful clinically, however, because the manifestations and course of bronchiectasis are not correlated with the bronchographic pattern.

Bronchiectasis results from the destruction of airways. The continued progression of disease over time likely results from continued infection, often with destructive organisms such as *P. aeruginosa*,[103] and the continued presence of tissue inflammation[104] with release of cytokines that are chemotactic for neutrophils.[105] These neutrophils locally release proteolytic enzymes such as elastase and other neutrophil enzymes[106] that may be involved in further airway and parenchymal damage and also may have an enhancing effect on mucus hypersecretion.[107]

The most important consequence of bronchiectatic damage to a portion of the airways is an increased susceptibility to recurrent or persistent bacterial infections. Normal defense mechanisms against infection are breached: ciliary function is disrupted by squamous metaplasia or by ulceration of the epithelial lining cells; excess mucus is secreted and pools in dilated spaces; and cough becomes less effective in clearing mucus from dilated bronchial segments. Once bacterial superinfection is established, it is virtually impossible to eradicate, and daily expectoration of purulent sputum is the end result in advanced cases. In bronchiectasis involving the upper lobes, stasis of mucus is prevented by gravitational drainage, resulting in the dry bronchiectasis of tuberculosis, in which cough and sputum production are usually absent but hemoptysis may occur.

Diagnosis

Clinical manifestations In most cases, the clinical presentation and a plain chest radiograph suffice for a presumptive diagnosis of bronchiectasis. Factors in the history, such as chronic cough and sputum purulence originating from a serious respiratory tract infection, often in childhood, strongly suggest the diagnosis. In addition, chronic sinusitis frequently accompanies bronchiectasis, and its presence should raise the suspicion of concomitant chronic lower respiratory tract infection.

In other patients, the clinical picture is one of frequent lower respiratory tract infections limited to the same area or areas of the lungs. Symptoms, physical findings, and abnormalities on the chest radiograph may not clear completely between each episode of pneumonia. Some patients have a mucoid sputum that becomes intermittently infected, which mimics the course of chronic bronchitis with episodic infectious exacerbations. In this case, the presence of local findings on chest examination and on the chest radiograph usually points to the diagnosis of bronchiectasis.

Clubbing of the digits occurs in the majority of patients with significant bronchiectasis and is a valuable diagnostic clue, especially since clubbing of the digits is not a manifestation of CAO [*see* Chronic Bronchitis and Emphysema, Diagnosis, *above*]. Auscultation of the chest usually reveals localized findings. Typically, paninspiratory coarse crackles are heard over the involved region, and there may also be variable low-pitched wheezes if secretions are present in the airways.

Chest imaging Bronchiectasis may be seen on the plain chest radiograph in a number of different patterns. Cystic bronchiectasis is most readily recognized because of the distinctive appearance of a collection of thin-walled cystic spaces, sometimes accompanied by air-fluid levels, arranged in a segmental distribution. A localized increase in interstitial markings that follow the general orientation of the bronchovascular bundles may indicate milder degrees of ectasia. Occasionally, the thickened walls of a dilated bronchus can be visualized as the bronchus courses with its longitudinal axis perpendicular to the x-ray beam. These parallel lines are approximately 1 mm thick and are referred to as tramlines. Atelectasis often accompanies extensive bronchiectasis, in which case the radiographic appearance may mimic a postobstructive pneumonia. In approximately 7% of patients with bronchiectasis, the plain chest radiograph is entirely normal.

The current generation of CT machines provide excellent magnified images of bronchiectatic airways. CT scanning can be used to confirm a clinical suspicion of bronchiectasis, to suggest the specific cause,[108] and to evaluate the extent of disease[109] [*see Figure 7*].

Sputum examination Examination of purulent sputum produced by a patient with bronchiectasis may suggest the underlying diagnosis in two ways. First, if sputum is collected in a container for several hours until a sufficient volume is obtained, the sputum may settle into a characteristic three-layered pattern: foamy on top, purulent in the middle, and liquid at the bottom. Occasionally, the same pattern is observed in sputum from patients with chronic bronchitis or suppurative lung abscess. Second, routine bacterial culture of the sputum may grow *Pseudomonas* species. In an immunocompetent host, *Pseudomonas* species are almost never isolated from the sputum unless the host has bronchiectasis, is receiving broad-spectrum antibiotics, has a long-term tracheostomy, or is in an intensive care unit setting. *Staphylococcus aureus* and gram-negative bacilli other than *Pseudomonas* (especially *H. influenzae*) and *Mycobacterium avium* complex[110] may also infect the airways in patients with bronchiectasis. Bronchiectasis is also a feature of allergic bronchopulmonary aspergillosis [*see 14:II Asthma*].

Pulmonary function tests Pulmonary function tests may remain normal if only a small portion of the tracheobronchial tree is affected. Widespread bronchiectasis causes chronic obstruction of expiratory airflow and may also cause a restrictive deficit if there is sufficient associated atelectasis or involvement of lung parenchyma by the infectious process. However, airflow obstruction is generally the main abnormality.

Treatment

The mainstays of therapy for bronchiectasis (including cystic fibrosis and primary ciliary dyskinesia), as for any chronic suppurative disease, are administration of antibiotics and drainage.

Antibiotics The use of antibiotics in the treatment of bronchiectasis has not been subjected to careful scientific investigation, and no one method of administration has proved to be superior in clinical experience. It is reasonable to culture the sputum periodically, because in patients from whom *S. aureus* or *H. influenzae* has repeatedly been isolated, antibiotics with appropriate spectra of activity can be selected. Oral antibiotics with effective antipseudomonal activity, such as the quinolones, show promise; however, because of the potential emergence of resistant strains

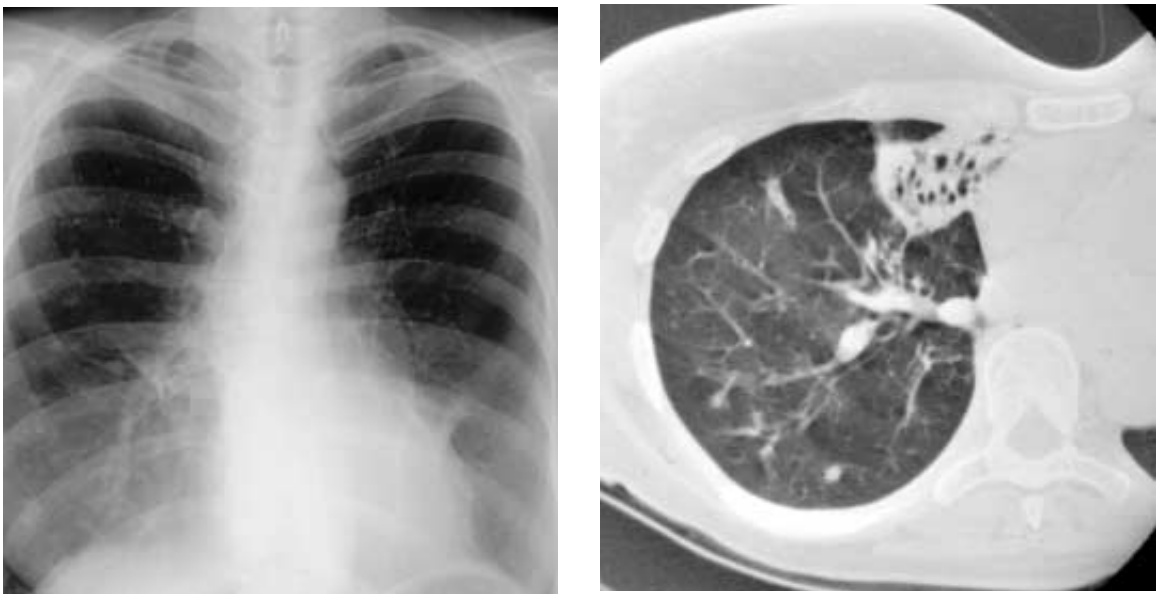


Figure 7 **In a comparison of a frontal chest radiograph with a CT scan of a patient with hemoptysis, the radiograph (left) suggests only an infiltrate in the right middle lobe; the CT scan (right) shows bronchiectasis in the right middle lobe that was the source of the bleeding.**

of *Pseudomonas,* these drugs probably should not be used as single agents for long-term suppressive therapy. Nevertheless, many patients seem to benefit from broad-spectrum oral antibiotics**,** even when *Pseudomonas* is the only pathogen in the sputum and in vitro sensitivity testing shows that the antibiotics lack activity against *Pseudomonas*. In a patient who has daily purulent sputum production and is not allergic to sulfonamides, trimethoprim-sulfamethoxazole (one double-strength tablet twice daily) can be given continuously. Alternatively, antibiotics may be given intermittently or on a schedule in which different antibiotics are rotated. Nebulized antibiotics may also be effective.[111]

If oral antibiotic therapy has failed, serious infectious complications (such as persistent fever with new areas of infiltration detected on the chest radiograph or the development of pleuritic chest pain) are generally best treated with a 10- to 14-day course of intravenous antibiotics. Two synergistic antibiotics with appropriate in vitro activities should be used for *Pseudomonas* infection.

Drainage Drainage of secretions is partially achieved by coughing and expectoration of sputum. However, because the diseased airways collapse during coughing and forced exhalation and because there is pooling of secretions distal to the areas of collapse, it is useful to include postural drainage as part of the management of bronchiectasis. Chest physiotherapy (for example, the use of chest percussion and vibration) is often used to aid bronchopulmonary drainage, although it is difficult to demonstrate that physiotherapy produces benefits beyond those that are produced by postural drainage alone. There is no role for aerosolized recombinant human deoxyribonuclease (DNase) in bronchiectasis not associated with cystic fibrosis.[112]

Bronchodilator therapy Many patients with bronchiectasis will have significant airflow obstruction, manifested clinically by wheezing and detected by pulmonary function testing. Theophylline, beta$_2$ agonists, and anticholinergic bronchodilators can be used in this setting, although the evidence for their effectiveness is limited.[113-115] Bronchodilator therapy may promote the clearance of airway secretions if the bronchodilating agents are administered before each postural drainage session.

Anti-inflammatory therapy During episodes of exacerbation, oral corticosteroids may help improve the patient's condition, although the benefit of this approach has not been established in randomized trials.[116] High-dose inhaled corticosteroids have been shown to reduce markers of airway inflammation[117] and improve lung function,[118] but the potential role of long-term therapy is uncertain.

Therapy for hemoptysis Significant hemoptysis can also usually be controlled with appropriate antibiotic therapy. Massive hemoptysis (> 200 ml of blood over a 24-hour period) that occurs as a complication of bronchiectasis was traditionally managed with surgical resection of the involved lung. Now, however, massive hemoptysis caused by bronchiectasis is often effectively treated with bronchial arterial embolization, an invasive radiologic procedure involving catheterization of the bronchial arteries. The dilated bronchial arteries that perfuse the airways in bronchiectasis are particularly suited for the application of this technique. Nevertheless, the procedure requires a skilled angiographer.

Surgery In the modern antibiotic era, the role of surgery in the management of bronchiectasis has been declining.[119] In patients with widespread bilateral disease, diseased lung tissue is better able to support gas exchange than no lung tissue at all. In patients with only limited localized disease, symptoms can usually be well controlled with the measures described above. In addition, experience indicates that after lobar resections for localized bronchiectasis have been performed, clinically evident recurrences of the disease are common in parts of the lung that had previously been thought to be uninvolved. In the rare instance in which severe symptoms or recurrent complications in a young patient lead to consideration of resection, the localized nature of

the bronchiectasis must first be demonstrated radiographically. If there is bronchiectasis distal to an obstructing bronchial lesion, surgery is indicated to remove the obstruction along with the diseased lung tissue.

CLINICAL VARIANTS OF BRONCHIECTASIS

Cystic Fibrosis

Although cystic fibrosis is an inherited disease that usually manifests itself in early childhood, a discussion of the condition in the context of general adult medicine is worthwhile for two reasons. First, increasing numbers of children with cystic fibrosis are now surviving into young adulthood: the median survival in the United States is 31.1 years in males and 28.3 years in females.[120] Second, some patients have a variant form of the disease in which symptoms first appear during adolescence or adulthood.

Pathogenesis The genetic defects responsible for cystic fibrosis have been identified. The cystic fibrosis locus is on the long arm of chromosome 7, and it codes for a 1,480 amino acid polypeptide that has been named the cystic fibrosis transmembrane regulator (CFTR).[121] In 70% of patients with cystic fibrosis, the 508th amino acid of this sequence is missing (ΔF508). The abnormal protein derived from the altered sequence is not glycosylated; it is retained in the endoplasmic reticulum and is not transferred to the cell membrane. The result is a defective membrane with decreased apical chloride conductance and increased sodium absorption.[122] Excessive dehydration of respiratory secretions may alter the character of the sol phase, in which the cilia normally beat, making it thicker and more viscous. Patients who are homozygous for the ΔF508 mutation have a more severe form of the disease than those who are heterozygous.[123] A number of other defects of the cystic fibrosis gene have also been identified, and the resultant defects in the production of CFTR can be grouped into five classes [*see Figure 8*]. Because these defects cause the CFTR to function differently, phenotypic severity differs among the classes.[124] Several of these defects are associated with mild lung disease and even normal sweat chloride concentrations.[125] As a result, patients may present at a later age, and diagnosis may be difficult. In addition, polymorphisms of other genes involved in the immune response may alter the phenotypic severity.[126,127]

It is likely that impaired tracheobronchial clearance of the abnormal secretions leads to widespread mucous plugging of airways, resulting in secondary bacterial infection, persistent inflammation, and consequent generalized bronchiectasis.[128] The bacterial flora in the airways are highly stereotyped: early in the course of the disease, *S. aureus* is found in the sputum; subsequently, mucoid strains of *P. aeruginosa* are isolated (mucoid in this context refers to a slimy substance secreted by the colony of organisms growing on a culture plate). Despite the presence of these highly virulent pathogens in the lower respiratory tract, infection remains confined to the airways. Although lung abscess and empyema are common complications of *Staphylococcus* or *Pseudomonas* pneumonia, they very rarely develop in patients with cystic fibrosis.

Diagnosis CAO is present in virtually all adult patients with cystic fibrosis and follows a relentlessly progressive course. Thus, cough, chronic purulent sputum production, and exertional dyspnea are cardinal symptoms of cystic fibrosis. Increased airway reactivity is found in approximately 20% to 25% of patients with this disease; in this subgroup, episodic wheezing may be a prominent manifestation, leading to a misdiagnosis of asthma. Nasal polyposis and chronic sinusitis are common upper respiratory tract findings in patients with cystic fibrosis and may be mistaken for signs of allergic disease. Even findings consistent with allergic bronchopulmonary aspergillosis are observed in as many as 9% of patients.[129] A small number of patients become colonized, although they are rarely infected, with atypical mycobacteria.[130] Two important complications of lower respiratory tract disease in patients with cystic fibrosis are hemoptysis and pneumothorax. Minor hemoptysis occurs intermittently in a majority of patients. In approximately 7% of adult patients, rupture of dilated bronchial arteries leads to massive, potentially fatal hemoptysis. Pneumothoraces may complicate the course of ad-

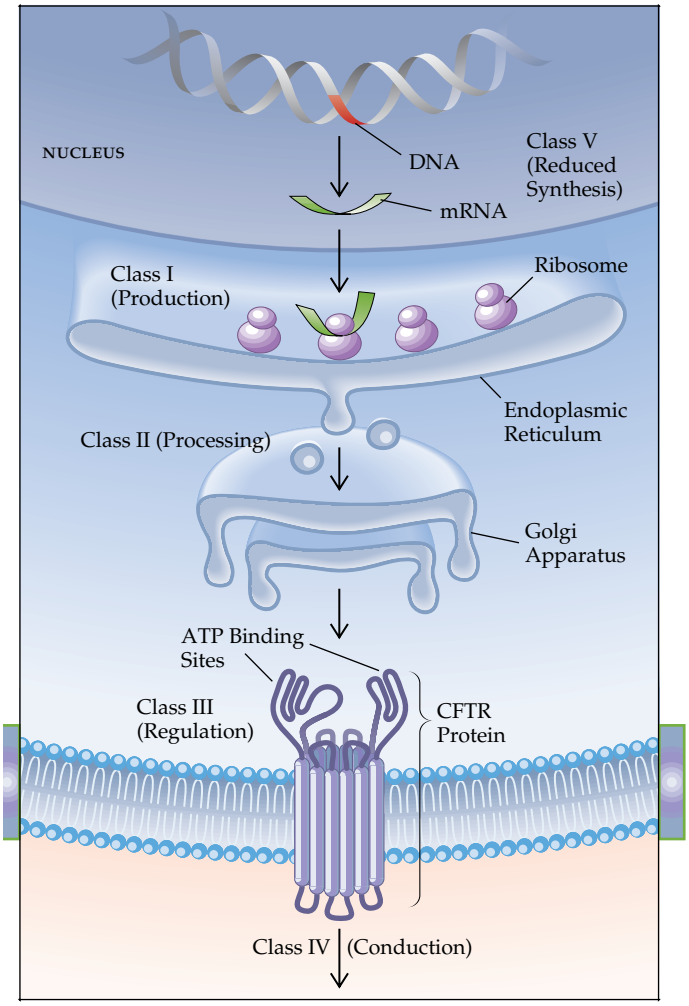


Figure 8 **Categories of cystic fibrosis transmembrane conductance regulator (CFTR) mutations. Cystic fibrosis can be produced by abnormalities at several points in the pathway from gene to functional protein on the cell surface. Class I mutants are associated with decreased transcription of the DNA or translation of the RNA. Class II mutants are attributable to abnormalities in processing of the protein in the endoplasmic reticulum, resulting in the degradation of the protein. Class III mutants are associated with abnormal regulation of the protein. Class IV mutants are associated with abnormal function of the CFTR protein on the cell surface. Class V mutants are associated with decreased synthesis of the CFTR protein. Some mutants (e.g., δF508, class II and class III) can be associated with more than one defect.**

vanced obstructive lung disease in approximately one sixth of adult patients and are frequently recurrent. Hypoxemia and hypercapnia, initially during exercise and sleep,[131] are prominent complications and can be associated with the development of pulmonary hypertension.[132] Osteoporosis producing significant kyphosis is frequent in adult patients with cystic fibrosis.[133]

The chest radiograph may strongly suggest the diagnosis of cystic fibrosis. The generalized bronchiectasis manifests itself as a diffuse increase in interstitial markings, and discrete bronchiectatic cysts are often visible; typically, involvement of the upper lobes predominates. The obstructive aspect of the disease is reflected in the typical finding of pulmonary hyperinflation. This combination of diffusely increased markings with cystic spaces, upper lobe predominance, and hyperinflation is highly characteristic of cystic fibrosis; rare alternative radiographic diagnoses include eosinophilic granuloma and lymphangiomyomatosis [*see 14:V Chronic Diffuse Infiltrative Lung Diseases*]. In the late stages of the disease, cardiomegaly and signs of pulmonary arterial hypertension appear on the chest radiograph as cor pulmonale develops.

Extrapulmonary manifestations may also suggest the diagnosis of cystic fibrosis. Prominent among these findings are pancreatic insufficiency with consequent steatorrhea, recurrent partial intestinal obstruction caused by abnormal fecal accumulation (so-called meconium ileus equivalent), heat prostration, hepatic cirrhosis, and aspermia in males.

The diagnosis of cystic fibrosis should therefore be suspected in the adolescent or young adult who has widespread bronchiectasis and *Staphylococcus* or *Pseudomonas* infection of the airways. The diagnosis should also be considered in the young patient with so-called refractory asthma, especially if the asthma symptoms are accompanied by clubbing of the digits, chronic sputum purulence, a persistently abnormal chest radiograph, or symptoms of pancreatic insufficiency. The diagnosis can be established by abnormal results on a sweat test performed in a qualified laboratory using pilocarpine iontophoresis.[134] In persons younger than 20 years, a sweat chloride level exceeding 60 mEq/L confirms the diagnosis; a value exceeding 80 mEq/L is required for diagnosis in persons 20 years of age or older.

With the identification of the gene for cystic fibrosis, genetic screening has become available. A National Institutes of Health panel suggested that genetic testing for cystic fibrosis should be offered to adults with a positive family history of the disease, to partners of people with the disease, to couples currently planning a pregnancy, and to couples seeking prenatal care, but not to the general population or newborns.[135]

Treatment Treatment of cystic fibrosis is similar to that of bronchiectasis [*see* Bronchiectasis, Treatment, *above*] and includes management of infections and the use of respiratory therapy modalities that are designed to mobilize secretions, including regular percussion and postural drainage, and to reduce airway obstruction.[136] A pneumatic bronchial drainage vest or a flutter device makes it easier to vibrate the chest so as to enhance the removal of thick secretions.[137,138] No randomized controlled trials have established the efficacy of any airway clearance regimen in cystic fibrosis, however.[139] Aerosolized antibiotics such as tobramycin may have a role in reducing the burden of infection in those who have become chronically infected with *P. aeruginosa*.[140] Treatment with intravenous antibiotics is usually required for episodes of symptomatic infection with *P. aeruginosa*.[141] Because the viscosity of the mucus in cystic fibrosis is partially caused by DNA released from cells, recombinant human DNase administered by inhalation is effective.[142] In patients with reversible airflow obstruction, treatment with bronchodilators (e.g., beta agonists), anticholinergics, and theophylline and with low-dose alternate-day oral or daily inhaled corticosteroids may be of benefit.[143-145] Strategies to reduce airway inflammation and to reduce the burden of neutrophil proteases are also being evaluated.[146,147] Attention to nutrition, physical conditioning, and emotional health must be part of an effective care plan. Bronchial artery embolization is useful in patients with significant hemoptysis.[148] Mechanical ventilatory support at night using noninvasive techniques may be useful in patients with chronic respiratory failure.[149] Lung transplantation is now being performed with good results in cystic fibrosis patients whose FEV_1 is less than 30% of predicted value.[150,151]

The discovery of a specific genetic defect raises the possibility of more specific and perhaps more effective therapy. Therapy could be either pharmacologic (aimed at altering transport through involved or uninvolved ion channels) or genetic (aimed at replenishing the CFTR). In pilot studies, inhalation of amiloride, an epithelial sodium channel blocker, led to objective improvement in sputum character. Other sodium channel blockers that are more potent and longer-acting may be available in the future. Triphosphate nucleotides (adenosine triphosphate and uridine triphosphate) have been found to be effective chloride secretagogues in vivo but have not been tested in long-term therapy.[152] Strategies aimed at correcting the genetic defect are advancing, albeit slowly.[93] An altered adenovirus (incapable of replication) has been used to introduce the cystic fibrosis gene into patients, and phase II trials of this therapy are under way.[93] Several other approaches are being taken and may be successful in the near future.[153]

Primary Ciliary Dyskinesia

In 1933, Dr. Manes Kartagener identified a group of patients with bronchiectasis who also suffered from chronic sinusitis and situs inversus. This triad of findings came to be known as Kartagener syndrome. Approximately 40 years later, it was recognized that male infertility was associated with this syndrome: men with Kartagener syndrome were found to have live sperm with absent or ineffective motility. Sperm tails and the cilia of respiratory tract epithelial cells share an ultrastructure, and in 1975, it was recognized that an inherited abnormality in that ultrastructure (i.e., an absence of the adenosine triphosphatase [ATPase]–containing dynein arms of the outer microtubular doublets) led to nonfunctioning respiratory tract cilia and immotile spermatozoa[154] [*see Figure 9*].

The consequences of congenital nonfunctioning cilia of the upper and lower respiratory tracts are chronic sinusitis, secretory otitis media, and daily productive cough dating from birth or early childhood; bronchiectasis develops during childhood in the majority of patients. With respect to situs inversus, it is speculated that the normal asymmetrical positioning of body organs is dependent on normal ciliary function on embryonic epithelium. In the absence of normal ciliary function, placement of organs to either the left or the right is random, and as expected, about one half of patients with congenitally nonfunctioning cilia manifest situs inversus. Thus, the term immotile cilia syndrome was coined to include all patients with chronic sinusitis and bronchiectasis resulting from ultrastructural abnormalities of cilia. Fertility is reduced not only in men but also in women with this syndrome, because of deficient cilia in the oviducts and fimbriae.

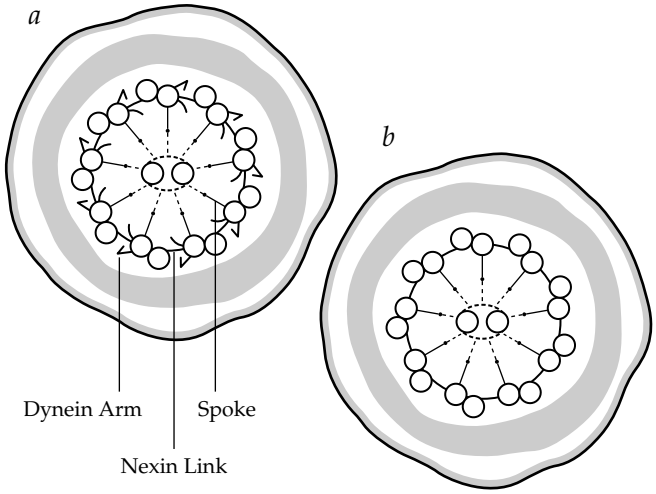


Figure 9 **A cross section (*a*) of the tail of a normal sperm reveals dynein arms. In a cross section of the tail of a sperm from a patient with Kartagener syndrome (*b*), dynein arms are missing; such a cell would be immotile. Similar changes have been noted in the cilia in the respiratory tract and paranasal sinuses in these patients.**

Primary ciliary dyskinesia highlights the importance of normal ciliary function in clearing airway mucus and the presence of other mechanisms, especially cough, in defending against disease. Ciliary dysfunction in the lower respiratory tract leads to the retention of secretions, bacterial superinfection, and bronchiectasis. Other protective mechanisms appear to prevent more serious sequelae, including acute pneumonias and progressive airflow obstruction.

Pathogenesis A variety of abnormalities in addition to absent or deficient dynein arms may impair the structure and function of cilia and sperm tails.[155] Many of these abnormalities involve derangement of the normal configuration of microtubules. In each case, in vitro microscopic studies of ciliary motility have demonstrated a pattern of decreased, uncoordinated, or ineffective beating. Because at least some movement of the cilia is observed, the term primary ciliary dyskinesia has been proposed as a more accurate description of this condition than the term immotile cilia syndrome. Inheritance is thought to be autosomal recessive. Any given ultrastructural abnormality is found consistently in the upper and lower respiratory tract cilia (as well as in sperm tails in men), and all affected members of the same family have the same defect. The clinical syndrome that results is a common expression of impaired ciliary motility independent of the specific ultrastructural defect.

Diagnosis The diagnosis of primary ciliary dyskinesia can be made clinically in all patients with Kartagener syndrome. A clinical diagnosis can also be made in patients who have a history of chronic sinusitis and productive cough since childhood and, in addition, have either live but immotile spermatozoa or a sibling with Kartagener syndrome. In patients who have had chronic sinusitis and productive cough since childhood but who have neither of the two additional conditions, three types of specialized laboratory studies can be employed to support the diagnosis of primary ciliary dyskinesia: (1) electron microscopic examination of sperm tails or of cilia from bronchial or nasal biopsy specimens, (2) in vitro light microscopic examination of the motility of cilia, and (3) measurement of mucociliary clearance in the nose or the tracheobronchial tree. An example of the last technique listed is inhalation of an aerosol of radiolabeled particles followed by external scanning over the thorax for at least 2 hours. Normal values for the ciliary structural and functional studies have been established.[156] These studies should be performed during periods of clinical stability, because acute inflammation can reversibly alter ciliary function.[157]

Differential diagnosis The respiratory disease associated with primary ciliary dyskinesia may be contrasted with that associated with cystic fibrosis. In cystic fibrosis, in the absence of acute infectious exacerbations, ciliary function is normal and mucociliary transport only modestly decreased. In primary ciliary dyskinesia, however, mucociliary transport along nasal or tracheobronchial mucosa is virtually absent. Nevertheless, disease of the lower respiratory tract is usually far milder in patients with primary ciliary dyskinesia than in those with cystic fibrosis. Bronchiectasis in primary ciliary dyskinesia usually involves the lower or the middle lung zones and is less widespread than in cystic fibrosis. Also, in primary ciliary dyskinesia, bacterial infection of the airways is more commonly caused by *Haemophilus, Neisseria,* or *Streptococcus* organisms than by *Staphylococcus* or *Pseudomonas* organisms, and acute pneumonias are relatively infrequent. Finally, airflow obstruction is usually mild in primary ciliary dyskinesia, and progression to cor pulmonale is uncommon. Patients with primary ciliary dyskinesia usually can remain fully active and may survive to old age.

Treatment Treatment with postural drainage and antibiotics for infections aids in maintaining stable lung function [*see also* Bronchiectasis, Treatment, *above*].[158]

BRONCHIOLITIS OBLITERANS

Bronchiolitis is considered a disease of childhood. One form of the disease, an acute bronchiolitis that occurs in infants, is most often the result of infection with respiratory syncytial virus. Adenovirus infection may cause a more serious necrotizing form of bronchiolitis in children, and in some of these children, the healing process is characterized by exuberant inflammation and fibrosis that obliterate the bronchiolar lumen. If only one lung is affected, the obstructive disease may appear on radiography as a unilateral hyperlucent lung because of distal alveolar overdistention (i.e., air trapping) and decreased vascularity in the affected lung. This syndrome of unilateral hyperlucent lung with bronchiolitis obliterans bears two eponyms: Swyer-James syndrome, named for the two physicians who first described the disease in children, and Macleod syndrome, named after the physician who reported the first adult case.[159]

Etiology

Bronchiolitis obliterans is a rare cause of CAO in adults. Until recently, the list of causes of bronchiolitis obliterans in adults was quite brief. An obliterative bronchiolitis as the sole or predominant pathologic lesion had been reported after viral pneumonia (e.g., pneumonia caused by measles, influenza, or adenovirus infection), after inhalation of toxic gases (e.g., chlorine and nitrogen dioxide), and as an idiopathic phenomenon. More recently, bronchiolitis obliterans has been documented as a complication of collagen vascular diseases, particularly rheumatoid arthritis, and as a sequela of stem cell transplantation in the set-

ting of graft versus host disease. A possible association with the drug penicillamine has also been suggested.

Silo-filler's disease is an example of bronchiolitis obliterans resulting from toxic gas inhalation.[159] During the first 7 to 10 days after a silo is filled, oxides of nitrogen collect in high concentrations above the fresh silage. If these gases, particularly nitrogen dioxide, are breathed even for a period as short as several minutes, they may cause severe respiratory illness.

Diagnosis

Clinical manifestations Acutely, noncardiogenic pulmonary edema may result from injury to the alveolar-capillary membrane, such as that sustained in silo-filler's disease after inhalation of nitrogen oxides. However, 2 to 4 weeks after exposure, often after an asymptomatic interval, fever, nonproductive cough, and dyspnea may develop. Chest examination typically reveals high-pitched inspiratory crackles, and wheezing may be heard.

A presumptive diagnosis of bronchiolitis obliterans is most often based on the clinical presentation. Clinical features that suggest the diagnosis are the presence of marked airflow obstruction in the absence of a history of cigarette smoking, obstruction associated with minimal or no sputum production, and little or no reversibility of obstruction in response to bronchodilators. A highly characteristic midinspiratory squeak may be heard on chest auscultation. The diagnosis is secure if the disease evolves over a period of months and is associated with a viral illness, toxic-fume exposure, rheumatoid arthritis, use of penicillamine, or graft versus host disease after bone marrow transplantation. It is likely that mild forms of the disease and cases that develop in cigarette smokers often go unrecognized.

Chest radiograph The characteristic chest radiographic finding is a pattern of diffuse, nodular densities, sometimes with a fine nodularity mimicking miliary tuberculosis.

Although these findings are typical of bronchiolitis obliterans, a spectrum of presentations is possible. Radiographically, hyperinflation and vascular attenuation mimicking emphysema may be the only findings, or there may be scattered nonhomogeneous patchy infiltrates. High-resolution CT scanning of the chest, particularly if performed on inspiration and expiration, may show nodular lesions, regions of ground-glass attenuation, bronchocentric infiltrates, and small regions of lucency, denoting obstruction and air trapping at a small airway level.[160] If associated interstitial inflammation and organizing pneumonia predominate, the chest radiograph may reveal regions of segmental or lobar consolidation. The term bronchiolitis obliterans organizing pneumonia has been used to describe this idiopathic entity.[159] Its pathophysiology is that of a restrictive lung disease and resembles the pathophysiology of other forms of interstitial pneumonitis [*see 14:V Chronic Diffuse Infiltrative Lung Disease*].

Pathology

On gross pathologic inspection, the lungs are filled with small discrete nodules, which upon microscopic examination prove to be the lesions of bronchiolitis obliterans. An organizing exudate or polypoid mass of granulation tissue occludes the bronchiolar lumen. Connective tissue proliferation may extend into alveolar ducts and alveoli, and various degrees of interstitial inflammation and organizing pneumonia may involve the lung parenchyma surrounding the involved bronchioles.

Treatment

Treatment of bronchiolitis obliterans is usually ineffective, although corticosteroids are often tried. Initially, high-dose corticosteroids (e.g., prednisone given in an oral dosage of 1 mg/kg/day) are used in an attempt to suppress the inflammatory reaction within and around the bronchioles. Although corticosteroids often benefit patients with idiopathic bronchiolitis obliterans organizing pneumonia, they are rarely effective against other forms of bronchiolitis obliterans.

Prognosis

In some patients with bronchiolitis obliterans, the disease progresses to severe airflow obstruction, respiratory failure, and death. In others, the inflammation remits, and chest x-ray and pulmonary function test results return to normal.

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Acknowledgments

Figures 1 and 2 Al Miller.

Figure 4 Dana Burns-Pizer.

Figures 8 and 9 Seward Hung.