American Thoracic Society
MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE ATS BOARD OF DIRECTORS, MARCH 1995

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Definitions, Epidemiology, Pathophysiology, Diagnosis, and Staging --

DEFINITIONS

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.

In the past, asthma-viewed as a condition in which increased responsiveness of the tracheobronchial tree was the most prominent feature-was generally subsumed under COPD. Now, inflammation with participation of complex cellular and chemical mediators is considered the salient characteristic of asthma. It therefore seems prudent and practical to separate these conditions. That has been done in this statement, bearing in mind that the obstruction in many patients with COPD may include a significant reversible component and that some patients with asthma may go on to develop irreversible airflow obstruction indistinguishable from COPD.

Chronic bronchitis is defined as the presence of chronic productive cough for 3 mo in each of two successive years in a patient in whom other causes of chronic **cough** have been excluded (1).

Emphysema is defined as abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis. ***Destruction*** is defined as lack of uniformity in the pattern of respiratory airspace enlargement; the orderly appearance of the acinus and its components is disturbed and may be lost (2).

Note that chronic bronchitis is defined in clinical terms and emphysema in terms of anatomic pathology (see Figure 1, a nonproportional Venn diagram showing the relationships among chronic bronchitis, emphysema, asthma, and airflow obstruction).

EPIDEMIOLOGY OF COPD

Knowledge of the prevalence of COPD is incomplete. It is estimated that approximately 14 million persons in the United States suffer from COPD — about 12.5 million from chronic bronchitis and about 1.65 million from emphysema. The estimated number of those with COPD has increased 41.5% since 1982. Estimates of diagnosed emphysema or chronic airflow obstruction in population-based studies in the United States range from 4 to 6% of adult white males and from 1 to 3% of adult white females (3).

Age-adjusted prevalence rates for men rose only slightly over the period from 1979-1985, with a prevalence of 110 per 1,000 in 1985. Among women, however, prevalence rates increased by over 30% during that period, with a prevalence of 119 per 1,000 in 1985 (4).

Mortality

In 1991, there were 85,544 deaths due to COPD and allied conditions, a death rate of 18.6 per 100,000 persons; this category ranked as the fourth leading cause of death. The mortality rate rose nearly 32.9% between 1979 and 1991. In 1985, COPD was the underlying cause for 3.6% of all deaths and was a contributory factor in an additional 4.3% of deaths. Men and women have similar COPD mortality rates before the age of 55, but the rate for men rises thereafter; at age 70, the rate for men is more than double that for women, and at 85 and older, the COPD death rate for males is more than 3.5 times that for females (4).

The age-adjusted death rate for COPD rose 71% between 1966 and 1986; over those same two decades, the death rate from all causes declined by 22%, and the rates for heart and cerebral vascular disease declined by 45 and 58%, respectively (3). Observed increases in mortality and morbidity appear to be related to past trends in cigarette smoking. Part of the rise in morbidity and mortality may also be due to increasing numbers of people living longer; the increases in morbidity and mortality are particularly striking among older people who continue to smoke. Since smoking frequency has fallen over the past 30 yr, there should be a decrease in COPD mortality in coming decades (5).

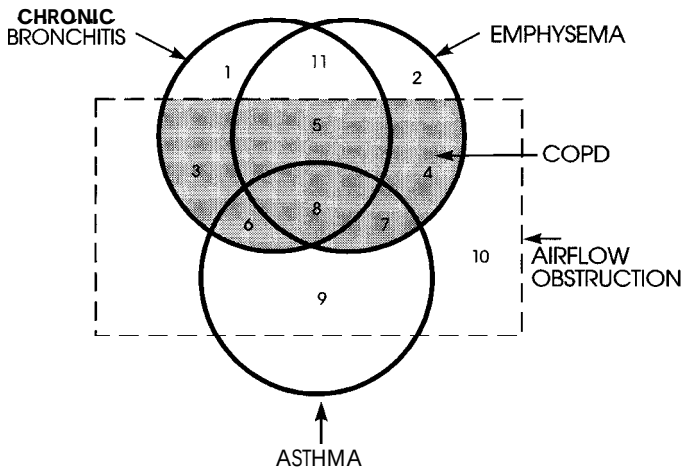


Figure 1. Schema of chronic obstructive pulmonary disease. This nonproportional Venn diagram shows subsets of patients with chronic bronchitis, emphysema, and asthma. The subsets comprising COPD are shaded. Subset areas are not proportional to actual relative subset sizes. Asthma is by definition associated with reversible airflow obstruction, although in variant asthma special maneuvers may be necessary to make the obstruction evident. Patients with asthma whose airflow obstruction is completely reversible (subset 9) are not considered to have COPD. Because in many cases it is virtually impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema who have partially reversible airflow obstruction with airway hyperreactivity (55), patients with unremitting asthma are classified as having COPD (subsets 6, 7, and 8). Chronic bronchitis and emphysema with airflow obstruction usually occur together (26) (subset 5), and some patients may have asthma associated with these two disorders (subset 8). Individuals with asthma exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough, a feature of chronic bronchitis (subset 6). Such patients are often referred to in the United States as having *asthmatic* bronchitis or the *asthmatic form of COPD*. Persons with chronic bronchitis (56) and/or emphysema (57) without airflow obstruction (subsets 1, 2, and 11) are not classified as having COPD. Patients with airway obstruction due to diseases with known etiology or specific pathology, such as cystic fibrosis or obliterative bronchiolitis (subset IO), are not included in this definition.

RISK FACTORS FOR COPD

The primary cause of COPD is without question exposure to tobacco smoke.

Cigarette Smoking

The major risk factor is cigarette smoking. Smokers have higher death rates for chronic bronchitis and emphysema; they also have a higher prevalence of lung-function abnormalities, respiratory symptoms, and all forms of chronic obstructive airway disease. Cigarette smokers also have a greater annual rate of decline in FEV,. Differences between cigarette smokers and nonsmokers increase in direct proportion to quantity of smoking. (Pipe and cigar smokers have higher morbidity and mortality rates for COPD than nonsmokers, although their rates are lower than those for cigarette smokers.) Age of starting, total pack-years, and current smoking status are predictive of COPD mortality. For unknown reasons, presumably related to constitutional differences, only about 15% of cigarette smokers develop clinically significant COPD (3, 6, 7).

Overall, tobacco smoking accounts for an estimated 80 to 90% of the risk of developing COPD (6). The smoking-attributable fraction of COPD mortality in the United States during the 1980s was 0.850 for men and 0.694 for women (8). The only other risk factor of comparable importance for the individual is homozygous alpha,-antitrypsin (AAT) deficiency, but that heritable condition accounts for less than 1% of COPD cases (see further comment below).

Passive Smoking

Also known as environmental tobacco smoke (ETS) or "secondhand smoke," passive smoking is the exposure of nonsmokers to cigarette smoke. Children whose parents smoke have a higher prevalence of respiratory symptoms and respiratory disease and appear to have small but measurable deficiencies in tests of pulmonary function when compared with children of nonsmokers. These deficiencies may presage airway hyperreactivity and less than maximal attainment of lung function in adult life, although the significance of these findings in relation to the future development of COPD is unclear. Despite these uncertainties, children should be protected from exposure to tobacco smoke (9).

Ambient Air Pollution

High levels of urban air pollution are demonstrably harmful to persons with heart or lung disease, but the role of environmental air pollution in the etiology of COPD in this country is unclear; its role appears to be small when compared with that of cigarette smoking. Reported respiratory symptoms, but not lung function deficiencies, have been associated with indoor nitrogen dioxide levels and damp housing. The use of various solid fuels for cooking and heating without adequate ventilation, however, may result in high levels of indoor air pollution and account for the development of COPD (9).

Hyperresponsive Airways

Asthma, atopy, and nonspecific airway hyperresponsiveness may possibly play a role in COPD. In 1960, Orie and colleagues (10) from the Netherlands proposed than an "asthmatic constitution" (a predisposition to atopic disease, airway hyperresponsiveness, and eosinophilia) underlay the development of chronic airflow obstruction; smoking, they suggested, was only one extrinsic factor that, superimposed on this constitutional susceptibility, could lead to chronic airflow obstruction.

Many studies have since focused on "the Dutch hypothesis." It has become evident that skin test reactivity to allergens, elevated serum IgE, and eosinophilia, while all markers of atopy, are apparently not interchangeable and have different relations to clinical manifestations such as asthma and hay fever. In contrast to asthma, neither the diagnoses of chronic bronchitis or emphysema nor the presence of ventilatory impairment in the absence of asthma is related to age-sex standardized serum IgE levels. Smokers tend, in fact, to be less atopic than nonsmokers but to have higher serum levels of IgE (11).

The possibility that nonspecific airway hyperreactivity might be a risk factor for COPD was first raised as a part of the Dutch hypothesis. Such hyperreactivity is inversely related to FEV,, and evidence is steadily accumulating that it is predictive of an accelerated rate of decline of lung function in smokers. But its possible role as a risk factor that may predispose to the development of COPD in smokers or others is unclear. Nonspecific hyperreactivity might also stem from the airway inflammation typically seen with the development of smoking-related chronic airflow obstruction (12-14). In the Lung Health Study, nonspecific airway hyperreactivity was noted in a significantly higher percentage of women (85.1%) than men (58.9%). Moreover, nearly twice as many women as men responded to ≤ 5 'm/ml of methacholine (46.6 and 23.9%, respectively). In both sexes, degree of airflow obstruction was highly correlated with severity of airflow obstruction but not with age (15).

Sex, Race, and Socioeconomic Status

Even controlling for smoking, there is a higher prevalence of respiratory symptoms in men (7). Mortality rates for COPD are higher in whites than in nonwhites, but the difference is decreasing in males (3). Morbidity and mortality rates are inversely related to socioeconomic status and are higher in blue-collar than white-collar workers (3, 6, 7, 16). Apart from homozygous alpha,-antitrypsin deficiency, COPD may aggregate in families (17).

Occupational Factors

Occupational factors give rise to increased prevalence of chronic airflow obstruction, increased rates of FEV, decline, and higher COPD mortality. Interaction between cigarette smoking and job exposure to hazardous airborne substances results in higher rates of COPD. However, smoking effects greatly exceed occupational effects (18).

Alpha$_1$-antitrypsin Deficiency

Alpha$_1$-antitrypsin (AAT) is the only known genetic abnormality that leads to COPD; AAT deficiency accounts for less than 1% of COPD in the United States. Also known as alpha$_1$-protease inhibitor, AAT is a serum protein produced by the liver and normally found in the lungs; its main role is the inhibition of neutrophil elastase (19). It is a glycoprotein, coded for by a single gene on chromosome 14. The serum protease inhibitor phenotype (Pi type) is determined by the independent expression of the two parental alleles. The AAT gene is highly pleomorphic.

Some 75 alleles are known, and the states they produce have been classified as: *normal,* associated with normal serum levels of normally functioning AAT; *deficient,* associated with serum AAT levels lower than normal; *null,* associated with undetectable serum AAT; and *dysfunctional,* in which AAT is present at normal levels but does not function normally (20). The variants of AAT occur because of point mutations that result in a single amino acid substitution. The normal M alleles occur in about 90% of persons of European descent with normal serum AAT levels; their phenotype is designated Pi MM. Normal values of serum AAT are 150 to 350 mg/dl (commercial standard) or 20 to 48 μM (true laboratory standard).

More than 95% of persons in the severely deficient category are homozygous for the Z allele, designated Pi ZZ, and have serum AAT levels of 2.5 to 7 μM (mean, 16% of normal). Most of these persons are Caucasians of northern European descent, because the Z allele is rare in Orientals and blacks. Rarely observed phenotypes that are associated with low levels of serum AAT include Pi SZ and persons with nonexpressing alleles, Pi-null. The latter occur in homozygous form, Pi null-null, or in

heterozygous form with a deficient allele, Pi ZZ-null. Persons with phenotype Pi SS have AAT values ranging from 15 to 33 μM (mean, 52% of normal). The threshold protective level of 11 μM or 80 mg/dl (35% of normal) is based on the knowledge that Pi SZ heterozygotes, with serum AAT values of 8 to 19 μM (mean, 37% of normal), rarely develop emphysema.

Severe AAT deficiency leads to premature emphysema, often with chronic bronchitis and occasionally with bronchiectasis. The onset of pulmonary disease is accelerated by smoking: dyspnea begins at a median age of 40 yr in smokers, and a median age of 53 yr in nonsmokers. Panacinar emphysema usually begins at the bases. The severity of lung disease varies markedly. Persons classified as nonindex cases (those discovered in population surveys) tend to have better lung function, whether they smoke or not, than patients classified as index cases (those discovered because they have lung disease). People identified as nonindex cases may live into their eighth or ninth decade. Airflow obstruction occurs more frequently in men; asthma, recurrent respiratory infections, and familial factors are also concomitant risk factors for airflow obstruction (21).

The diagnosis of AAT deficiency is made by measuring the serum AAT level, followed by Pi typing for confirmation. The circumstances in which the tests should be ordered are listed in Table 1.

Pi MZ heterozygotes have serum AAT levels that are intermediate between Pi MM normals and Pi ZZ homozygotes (12 to 35 μM; mean, 57% of normal). In population studies, they do not appear to be at increased risk for COPD; in family studies and in surveys of some populations of COPD patients, however, there has been an increased frequency of heterozygotes (22). There is some evidence that MS heterozygotes may have an increased frequency of nonspecific airway hyperreactivity (23).

THE NATURAL HISTORY OF COPD

The FEV, in nonsmokers without respiratory disease declines by 25 to 30 ml per year beginning at about age 35 (see Figure 2). The rate of decline of FEV, is steeper for smokers than for nonsmokers, and the heavier the smoking the steeper the rate. The decline in function occurs along a slowly accelerating curvilinear path. In most persons, the loss occurs uniformly; in some, it develops in stages, with relatively steep declines. There is a direct relationship between initial FEV, level and the slope of FEV, decline (24). There is also a somewhat stronger association between a low FEV_1/FVC and subsequent decline in FEV, in men but not in women (25). Age, which cannot be separated from the number of years of cigarette smoking, is clearly a risk factor for more rapid decline of lung function; so are lifetime smoking history and the number of cigarettes currently smoked (26).

Individuals with COPD have more frequently acute chest illnesses, which generally decrease lung function for about 90 d (24). The role of mucus hypersecretion is unclear. Earlier studies showed that it was not associated with mortality from COPD (27), but recent studies have shown a weak correlation (28, 29).

The small airways, those less than 2 mm in diameter, are important sites of airflow obstruction. The relative contribution of peripheral airway disease and loss of elastic recoil from emphysema may vary. Indices such as the closing capacity and the slope of the alveolar plateau derived from a single-breath nitrogen test are unable to identify individuals susceptible to chronic airway obstruction with cigarette smoke exposure (30). Tests reflecting emphysema (single-breath diffusing capacity, FRC, total lung capacity) predict survival in a relatively minor way (31).

After cessation of smoking, a small amount of lung function is regained. In the Lung Health Study placebo group, for example, the 35% of subjects who had stopped smoking at the first annual visit showed an increase in mean postbronchodilator FEV, of 57 ml, while placebo participants who had not stopped smoking showed a mean decline in postbronchodilator FEV, of 38 ml (32).

Thereafter, the rate of lung function decline slows to approximate that seen in never-smokers of the same age (33, 34). Data from several studies suggest that the susceptible subgroup of smokers having more rapid decline of lung function can be defined by their greater loss of FEV, or FEV_1/FVC ratio (25, 35). Smoking cessation improves prognosis regardless of age (36).

TABLE 1

SCREENING FOR $ALPHA_1$-ANTITRYPSIN DEFICIENCY: INDICATIONS

- Chronic bronchitis with airflow obstruction in a never-smoker
- Bronchiectasis, especially in the absence of clear risk factors for the disease
- Premature onset of COPD, with moderate or severe impairment, by or before age 50
- A predominance of basilar emphysema
- Development of unremitting asthma, especially in a person under age 50 (screening is indicated even in the presence of atopy)
- A family history of $alpha_1$-antitrypsin deficiency or of COPD onset before age 50
- Cirrhosis without apparent risk factors

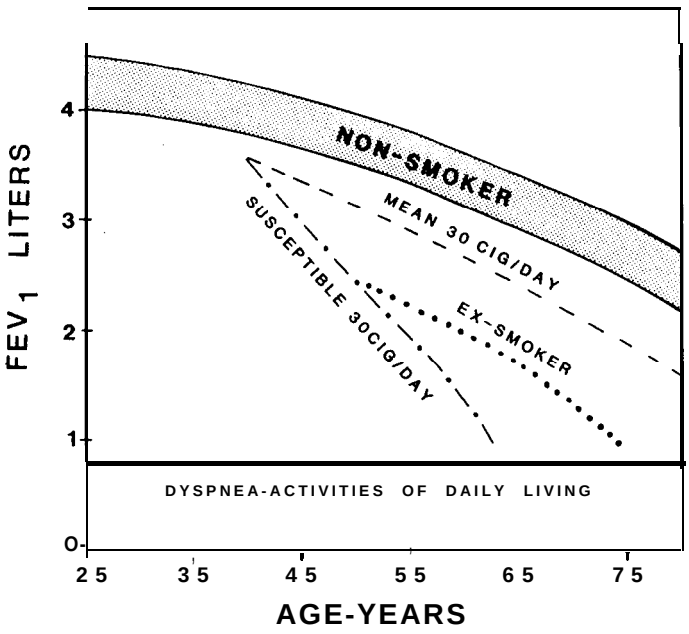


Figure 2. Relationship of FEV_1, age, and smoking. Nonsmokers lose FEV_1 at an accelerating rate with age; the average loss is about 30 ml/yr. Smokers of 30 cigarettes per day average a slightly greater rate of decline and have FEV_1 values slightly below average when first studied at age 40yr. A small proportion of susceptible smokers (about 15%) lose function much more rapidly, approximately 150 ml/yr, with FEV_1 of 0.8 L by age 65, a level so low that they experience dyspnea in the course of ordinary daily living. Susceptible smokers who stop smoking at age 50 do not regain lost function or regain only a little, but they subsequently lose function at the same rate as never-smokers; dyspnea with ordinary activity will not develop until the mid-70s. Reprinted with permission from Snider, G. L., L. J. Faling, and S. I. Rennard. 1994. Chronic bronchitis and emphysema. *In* J. F. Murray and J. A. Nadel, editors. Textbook of Respiratory Medicine. W. B. Saunders, Philadelphia. 1342.

PATHOLOGY AND STRUCTURAL EFFECTS

In COPD, there is enlargement of bronchial mucous glands, with dilation of gland ducts. Goblet cell frequency is increased. Focal squamous metaplasia and hypertrophy of airway smooth muscle may be present. The mucous gland enlargement of chronic bronchitis is nonspecific; similar changes occur in other diseases, such as cystic fibrosis (37).

The respiratory bronchioles display a predominantly mononuclear inflammatory process (38). Membranous bronchioles less than 2 mm in diameter show varying degrees of plugging with mucus, goblet-cell metaplasia, inflammation, increased smooth muscle, and distortion due to fibrosis. These changes and the loss of alveolar attachments from the destructive process of emphysema cause loss of cross-sectional area (39, 40).

Three types of emphysema can be distinguished (41). The first type, ***centriacinar emphysema,*** begins in the respiratory bronchioles and spreads peripherally. ***Centrilobular emphysema*** is the form of centriacinar emphysema associated with longstanding cigarette smoking. This form predominantly involves the upper half of the lungs. ***Focal emphysema*** is the form of centriacinar emphysema that occurs in coal workers' pneumoconiosis.

The second type is ***panacinar emphysema,*** which involves the entire alveolus uniformly and predominates in the lower half of the lungs; this is the type of emphysema generally seen with homozygous AAT deficiency. Focal panacinar emphysema at the lung bases may accompany centrilobular emphysema in smokers (42).

The third type, ***distal acinar emphysema,*** also known as *paraseptal emphysema,* preferentially involves distal airway structures, alveolar ducts, and sacs. The process is localized adjacent to fibrous septa or to the pleura. Apical bullae may cause spontaneous pneumothorax; occasionally, giant bullae cause severe compression of relatively uninvolved lung. With this form of emphysema, airflow is frequently well preserved.

Airspace enlargement with pulmonary fibrosis is commonly seen as an inconsequential lesion adjacent to scars, but it may sometimes be severe with extensive fibrosing disease, such as sarcoidosis or tuberculosis. The underlying fibrosis is usually evident radiographically, with extensive linear or nodular shadows accompanying increased transradiancy or bullae.

The structural basis of airflow obstruction in COPD (43-45) may be summarized as follows: alterations in the glands of the central airways have little effect on spirometry. Alteration of the small airways is a major cause of airflow obstruction. Mononuclear cell inflammation in the respiratory bronchioles is the earliest lesion in young smokers. Inflammation, fibrosis, goblet cell metaplasia, and smooth muscle hypertrophy in terminal bronchioles are important causes of airflow obstruction; loss of alveolar attachments to bronchioles due to the destructive changes in emphysema is also a major cause.

Airflow obstruction in COPD cannot be explained entirely on a structural basis; bronchoconstriction is another mechanism. A significant increase in FEV, after an inhaled beta-adrenergic agonist has been observed in up to one third of COPD patients during single testing sessions and in up to two thirds during serial testing (46). The response varies greatly between tests and correlates only weakly with patient features such as demographics, smoking history, symptoms, or measurements of lung function.

In summary, airflow obstruction in COPD is primarily irreversible and is caused by disease of the small airways, which is due in part to the effects of inflammation in those airways and in part to the loss of alveolar septal tethering of small airways that accompanies the destructive changes of emphysema. Bronchoconstriction due to inflammation accounts for a limited amount of reversible airflow obstruction.

CLINICAL FEATURES OF COPD

History

Patients with COPD have usually been smoking at least 20 cigarettes per day for 20 or more years before symptoms develop. They commonly present in the fifth decade with productive cough or an acute chest illness. Dyspnea on effort usually does not occur until the sixth or seventh decade.

Sputum production is insidious, initially occurring only in the morning; the daily volume rarely exceeds 60 ml. Sputum is usually mucoid but becomes purulent with an exacerbation. Acute chest illnesses characterized by increased cough, purulent sputum, wheezing, dyspnea, and occasionally fever may occur intermittently. The history of wheezing and dyspnea may lead to an erroneous diagnosis of asthma.

With disease progression, the intervals between acute exacerbations grow shorter. Late in the course of the disease, an exacerbation may give rise to hypoxemia with cyanosis, the latter accentuated by erythrocytosis. Morning headache suggests hypercapnia; hypercapnia, with more severe hypoxemia, is often present in end-stage disease. Weight loss occurs in some patients. Cor pulmonale with right heart failure and edema may develop in patients with hypoxemia and hypercapnia.

Since bronchogenic carcinoma occurs with increased frequency in smokers with COPD, an episode of hemoptysis raises the possibility that carcinoma has developed. Most episodes of hemoptysis, however, are due to mucosal erosion and not to carcinoma.

Physical Examination

Early on, examination of the chest may reveal only slowed expiration and wheezing on forced expiration. As obstruction progresses, hyperinflation becomes evident, and the anteroposterior diameter of the chest increases. The diaphragm becomes limited in its motion. Breath sounds are decreased, expiration is prolonged, and heart sounds often become distant. Coarse crackles may be heard at the lung bases. Wheezes are frequently heard, especially on forced expiration.

Patients with end-stage COPD may adopt positions that relieve dyspnea, such as leaning forward with arms outstretched and weight supported on the palms. The accessory respiratory muscles of the neck and shoulder girdle are in full use. Expiration often takes place through pursed lips. Paradoxical indrawing of the lower interspaces is often evident. Cyanosis may be present. An enlarged, tender liver indicates heart failure; neck vein distention, especially during expiration, may be observed in the absence of heart failure, due to increased intrathoracic pressure. Asterixis may be seen with severe hypercapnia.

LABORATORY FINDINGS AND DIAGNOSTIC TESTS

Chest Radiography

Because emphysema is defined in anatomical terms, radiographic images of the lungs provide the clearest evidence of its presence. In frontal and lateral chest radiographs, distention of the lungs is indicated by a low, flat diaphragm, an increased retrosternal airspace, and a long, narrow heart shadow. Rapid tapering of the vascular shadows, accompanied by hypertransradiancy of the lungs, is a sign of emphysema; bullae, presenting as radiolucent areas larger than 1 cm in diameter and surrounded by arcuate hairline shadows, are proof of its presence. Bullae, however, reflect only locally severe disease and are not necessarily indicative of widespread emphysema. With complicating pulmonary hypertension and right ventricular hypertrophy, the hilar vascular shadows are prominent, and the heart shadow encroaches on the retrosternal space as the right ventricle enlarges anteriorly

(47). The enlargement may become evident only on comparison with previous chest radiographs.

Studies correlating lung structure and the chest radiograph show that emphysema is consistently diagnosed when the disease is severe, is not diagnosed when the disease is mild, and is diagnosed in about half the instances of moderate disease (47).

Computed Tomography

Computed tomography (CT), especially high resolution CT (collimation of l-2 mm), has much greater sensitivity and specificity than standard chest radiography (48). It may even identify the specific anatomic type of emphysema. Because this information rarely alters therapy, CT has no place in the routine care of patients with COPD. It is, however, the main imaging tool to predict the benefit of pulmonary resection for giant bullous disease and for diagnosing complicating bronchiectasis.

Pulmonary Function Measurements

These measurements are necessary for diagnosis and assessment of the severity of disease and are helpful in following its progress (49). Airflow obstruction is an important indicator of impairment of the whole person and of the likelihood of blood gas abnormalities. The FEV, is easily measurable, has less variability than other measurements of airway dynamics, and is more accurately predictable from age, sex, and height. Roughly comparable information can be obtained from the peak flow measurement or from the forced expiratory flow-volume curve. None of these tests can distinguish between chronic bronchitis and emphysema.

Lung volume measurements show an increase in total lung capacity, functional residual capacity, and residual volume. The vital capacity may be decreased. The single-breath carbon monoxide diffusing capacity is decreased in proportion to the severity of emphysema because of the loss of alveolar capillary bed. The test is not specific, nor can it detect mild emphysema. Arterial blood gases reveal mild or moderate hypoxemia without hypercapnia in the early stages. As the disease progresses, hypoxemia becomes more severe and hypercapnia supervenes. Hypercapnia is observed with increasing frequency as the FEV, falls below 1 L. Blood gas abnormalities worsen during acute exacerbations and may also worsen during exercise and sleep.

As noted earlier, up to 30% of patients have an increase in 15% or more in FEV, after inhalation of a beta-agonist aerosol. The absence of a bronchodilator response during a single test never justifies withholding bronchodilator therapy.

Erythrocytosis is infrequently observed in patients living at sea level who have Pa_{O_2} levels of > 55 mm Hg; the frequency of erythrocytosis increases as Pa_{O_2} levels fall below 55 mm Hg.

Sputum Examination

In stable chronic bronchitis, sputum is mucoid, and the predominant cell is the macrophage. With an exacerbation, sputum usually becomes purulent, with an influx of neutrophils. Gram's stain usually shows a mixture of organisms. The most frequent pathogens cultured from the sputum are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Other oropharyngeal flora, such as *Moraxella catarrhalis*, have been shown to cause exacerbations. In the outpatient setting, however, cultures or even Gram's stains are rarely necessary before instituting antimicrobial therapy (50). The approach to diagnosis of COPD is summarized in Table 2.

TABLE 2

DIAGNOSIS OF COPD

History
- Smoking: age at initiation, quantity smoked per day, whether or not still smoker (if not, date of cessation)
- Environmental (chronological): may disclose important risk factors
- Cough (chronic, productive): frequency and duration, whether or not productive (especially on awakening), presence or absence of blood
- Wheezing
- Acute chest illnesses: frequency, productive cough, wheezing, dyspnea, fever
- Dyspnea

Physical Examination
- Chest
  - Airflow obstruction evidenced by
    - -Wheezes during auscultation on slow or forced breathing
    - -Prolongation of forced expiratory time
  - Severe emphysema indicated by
    - —Overdistention of lungs in stable state, low diaphragmatic position
    - -Decreased intensity of breath and heart sounds
  - Severe disease suggested by (characteristic, not diagnostic)
    - -Pursed-lip breathing
    - -Use of accessory respiratory muscles
    - —Indrawing of lower interspaces
- Other: unusual positions to relieve dyspnea at rest, digital clubbing (suggests possibility of lung cancer or bronchiectasis), mild dependent edema (may be seen in absence of right heart failure)

Laboratory
- Chest radiography: diagnostic only of severe emphysema but essential to exclude other lung diseases
- Spirometry (pre- and post-bronchodilator): essential to confirm presence and reversibility of airflow obstruction and to quantify maximum level of ventilatory function
- Lung volumes: measurement of more than forced vital capacity not necessary except in special instances (e.g., presence of giant bullae)
- Carbon monoxide diffusing capacity: not necessary except in special instances (e.g., dyspnea out of proportion to severity of airflow limitation)
- Arterial blood gases: not needed in stage I airflow obstruction ($FEV_1 \geq$ 50% predicted) essential in stages II and III airflow obstruction ($FEV_1 <$ 50% predicted); in very severe airflow obstruction, major monitoring tool

PROGNOSIS

Predictors of mortality in patients with COPD are advancing age, severity of airflow obstruction, as indicated by FEV,, severity of hypoxemia, and the presence of hypercapnia. In persons with moderate airway obstruction, but with an FEV, > 1.0 L, there is a slight excess mortality at 10 yr in comparison with an age- and gender-matched population. Recent data suggest that marked reversibility of airway obstruction is a favorable prognostic factor (26).

In persons with FEV, values < 0.75 L, the approximate mortality rate at 1 yr is 30% and at 10 yr 95% (51). However, longitudinal studies have shown that some patients with severe airway obstruction may survive for many years beyond the average, some for as long as 15 yr. The reason appears to be that death in COPD generally occurs as a result of a medical complication, such as acute respiratory failure, severe pneumonia, pneumothorax, cardiac arrhythmia, or pulmonary embolism.

STAGING: PROSPECTS AND PROPOSAL

The approach to COPD would be greatly facilitated by a staging system, which would allow standardized categorization of the heterogeneous population of patients with this common disorder. Such a system would be useful for epidemiologic and clinical studies, health resource planning, prognostication, and the application of clinical recommendations such as those in this document.

Ideally, a staging system would offer a composite picture of disease severity based on the interrelationship of the sensation of breathlessness, impairment in airflow, and derangement in gas exchange (52, 53). These factors and their magnitude are interactive but not necessarily additive. At present, there are no

data defining their interrelationship in a quantitative manner; the best correlate with mortality and morbidity is decrease in FEV,. Consequently, COPD severity may be staged on the basis of the degree of airflow obstruction, using the criteria of the ATS statement on interpretation of lung function (54): stage I is $FEV_1 \geq 50\%$ predicted; stage II is FEV, 35 to 49% predicted; and stage III is FEV, < 35% predicted. Patients with FEV, $\geq 50\%$ do not usually have severe hypoxemia, and arterial blood gas measurements are not required. Patients in stages II and III should have arterial blood gas measurements breathing air, and the oxygen and carbon dioxide tensions should be stated.

Stage I COPD comprises the great majority of patients. In these patients, COPD has minimal impact on health-related quality of life and results in only modest per capita health care expenditure. Patients in stage I will usually be cared for on a continuing basis by a generalist. The presence of severe dyspnea in a patient with stage I COPD warrants additional studies and evaluation by a respiratory specialist.

Stage II COPD includes a minority of patients. In these patients, COPD has significant impact on health-related quality of life and results in large per capita health care expenditure. Patients with stage II COPD usually merit evaluation by a respiratory specialist and may receive continuing care by such a specialist.

Stage III COPD also includes a minority of patients. In these patients, COPD has profound impact on health-related quality of life and results in large per capita health care expenditure. Patients with stage III COPD will usually be under the care of a respiratory specialist.

Comprehensive Outpatient Management of COPD

Once the diagnosis of COPD is established, the patient should be educated about the disease and should be encouraged to participate actively in therapy and, especially, in preventive care (e.g., immunizations, including pneumococcal and annual influenza vaccines) and maintenance of an active lifestyle. Above all, a patient who still smokes must be encouraged and supported in an effort to quit.

An overall algorithmic approach to management is illustrated in Figure 3, which forms a framework for the detailed guidelines in this section.

SMOKING CESSATION

Reported data are not encouraging. Continuous abstinence, even in pulmonary patients after counseling, may be as low as 27% in follow-up periods ranging from 6 mo to 7 yr (58). Factors fostering smoking continuation, which may vary among patients, include the additive potential of nicotine, conditioned response to smoking-associated stimuli (e.g., work and social situations), and psychosocial problems, such as depression, poor education, low income, and forceful promotional campaigns by the tobacco industry.

Just as the causes of smoking initiation and continuation are multifactorial, successful solutions most often involve multiple interventions (59-62). Elements of successful smoking cessation programs, which are summarized in Table 3, are discussed in detail in the following paragraphs.

Physician Intervention

The clinician should always express strong and continued interest in smoking cessation for the patient with COPD. Physician counseling frequently makes the difference between successful and unsuccessful efforts to quit. As a first step, the physician and patient should identify the patient's stage of readiness for smoking cessation.

There are five stages of change or transition from smoking to nonsmoking status (63). These stages are precontemplation, contemplation, preparation, action, and maintenance. The clinician's role is to help the patient move through these stages and ensure that interventions are tailored to the patient's stage.

A strong social support system is associated with cessation and long-term abstinence. Support may come from professionals as well as from family and friends. The intended quitter should take positive steps to recruit support and cooperation, including insistence on other smokers in the home environment absenting themselves from the premises when they insist on smoking. The smoker should also devote thought to other ways to avoid circumstances likely to prompt relapse, including coping with personal and interpersonal stresses.

Setting a "quit date" may be helpful. For most, though not all, patients, quitting "cold turkey" is more likely to be successful than gradual withdrawal. It is helpful for the physician and other health care providers to participate in setting the target date. Encouraging telephone calls to the patient on that date and at follow-up intervals thereafter may be helpful.

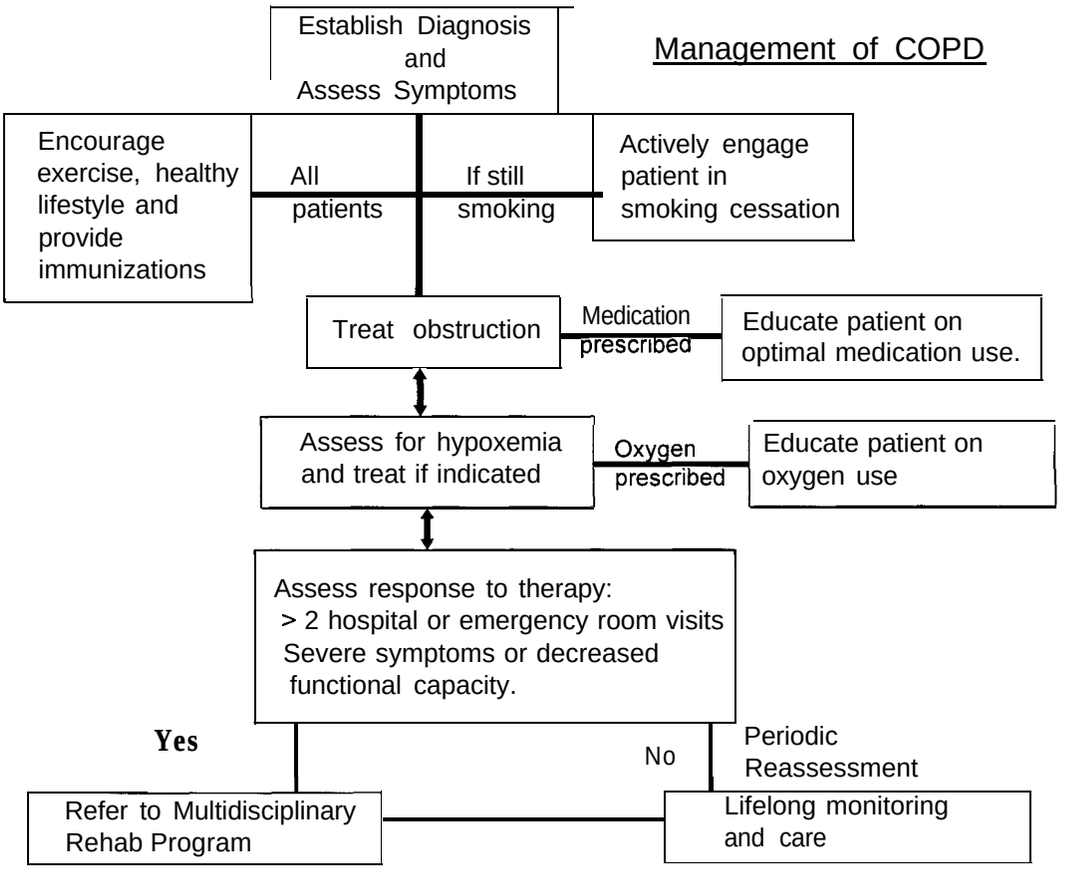


Figure 3. **Management of COPD (adapted from reference 194). Used with permission from Barry Make, M.D. and National Jewish Center for Immunology and Respiratory Medicine, 1995.**

TABLE 3

PROTOCOL FOR SMOKING CESSATION

1. Initiation
   Physician or health care worker should initiate quitting, explaining risks of cigarette smoking for the individual and including strong admonition. Encourage establishment of a definite quit date. Offer referral for self-help or group program.
2. Early follow-up
   Telephone patient on or within 3 to 5 d after quit date. Review progress and counsel regarding recruitment of support person. Call again 1 to 2 wk after quit date. Repeat as needed.
3. Continuing reinforcement
   Further follow-up should be arranged by physician or health care worker. Next regular visit should be less than 2 mo after initiating cessation program; assess progress with CO and expired air and/or cotinine in urine, blood, or saliva. If abstinent, review and reward success and reinforce prior warnings. May follow by phone monthly until next visit; continue follow-up at increasing intervals for 12 mo after quit date.
4. Failure or recidivism
   If patient fails to achieve abstinence or does so but relapses, physician or health care worker should review program with patient, emphasizing elements of success and identifying circumstances of failure; explore alternatives. Nicotine replacement may be offered to control withdrawal symptoms; Infrequently, other pharmacologic therapy, such as clonidine or buspirone, may be discussed. Hypnosis may be considered but is of little value when as a single-session recourse. Acupuncture is not recommended.

Group smoking cessation clinics are offered by many hospitals and in many work sites as well as by voluntary agencies (the American Lung Association's Freedom from Smoking clinics, for example). Such programs may play an important support role for patients who are attempting to quit smoking, as well as for recent quitters. They are especially important when the physician or other primary caregiver is insufficiently skilled in smoking cessation techniques. They may also effectively integrate behavioral therapy, additional counseling, adjunctive pharmacologic treatment, and relapse prevention.

Pharmacologic Intervention

Nicotine is the ingredient in cigarettes primarily responsible for the addiction of smoking (61). With each cigarette smoked, between 1 and 2 mg of nicotine is delivered to the lungs. Because of rapid absorption into the bloodstream and a half-life of 2 hr, regular daytime smoking can cause nicotine accumulation over an entire 24-h period.

Nicotine is metabolized chiefly by the liver. Cotinine, a primary metabolite of nicotine, has a longer half-life, can be detected in the urine, and can confirm smoking continuation as well as exposure to secondhand smoke.

Withdrawal from cigarettes causes unpleasant side effects in many, perhaps most, quitters. Among those reported have been anxiety, irritability, difficulty concentrating, anger, fatigue, drowsiness, depression, and sleep disruption; these reactions are most likely to occur during the first week following cessation.

Nicotine replacement after smoking cessation reduces withdrawal symptoms for those who are addicted and enhances abstinence in a dose-dependent manner. Highly dependent smokers can be identified as those who smoke over one pack of cigarettes per day, require their first cigarette within 30 min of arising, and find it difficult to refrain from smoking in places where it is forbidden. Physical dependence can also be assessed by a form such as the Fagerstrom tolerance questionnaire (64).

Nicotine polacrilex is available in the form of chewing gum, providing 2 mg of nicotine per piece. Its effectiveness compared with placebo has been demonstrated, especially in highly addicted, self-referred smokers. A recently approved dosage of 4 mg per piece is even more efficacious in those who are highly addicted to nicotine (62).

Transdermal nicotine patches are also readily available for replacement therapy (65). Short-term success rates have varied widely between 18 and 77%, but in general, rates have been about twice those reported for placebo patch users. Long-term (6 mo or more) success rates are considerably lower (22-42%) but are still consistently better than those for placebo trials (2-26%). Nicotine patches are well tolerated; mild erythema or other local skin reaction may be seen in up to 50% of patients but can be minimized by rotating the patch among different skin sites and trying different brands.

Nicotine replacement regimens combined with adjuvant programs such as individual counseling or group therapy produce higher success rates than nicotine replacement alone. It has also been shown that smoking behavior early in a nicotine-patch program can often predict the outcome (66); abstinence during the first 2 wk suggests probable success. Smoking during the second week of treatment is a consistently powerful predictor of failure at the end of a 6-mo trial. Patients who fail during the first 2 wk of therapy should be offered more intense pharmacologic or adjuvant therapy. The ideal duration of therapy for each nicotine replacement dosage has not been established, although it has been suggested that nicotine patch therapy beyond 6 to 8 wk may not be necessary (66, 67).

Clonidine, an alpha$_2$-adrenergic agonist, may enhance abstinence in the short term, but enduring effects have not been documented. The anxiolytic buspirone has been shown to reduce withdrawal symptoms and may enhance abstinence.

Other Techniques

Hypnosis may be an effective adjunct to a basic smoking cessation program. It is of little or no value, however, as a single-session "cure." Acupuncture is not recommended, as there is little evidence that it contributes to smoking cessation beyond its placebo or demand characteristics (68).

PHARMACOLOGIC THERAPY

Outpatient pharmacotherapy should be organized according to the severity of disease and the patient's tolerance for specific drugs. The therapy goals are to induce bronchodilation, decrease the inflammatory reaction, and facilitate expectoration. In general, a stepwise approach should be considered (69, 70). Guidelines for use of currently employed drugs in relation to signs and symptoms, disease severity, and other variables are outlined in Table 4.

Bronchodilators

The pharmacotherapy of COPD is similar to that of asthma, but important differences are recognized. Beta,-agonists produce less bronchodilatation in COPD than in asthma; in some patients, spirometric changes may be insignificant despite symptomatic benefit. COPD patients, as an older group, may exhibit less tolerance for sympathomimetic-induced tremor, nervousness, and cardiac side effects.

Beta,-agonists. There is no evidence that early, regular use of pharmacotherapy can alter the progress of COPD. Thus, in a patient with intermittent symptoms it is reasonable to initiate metered-dose inhaler therapy of a beta,-selective bronchodilator only when needed for relief of symptoms. Albuterol, pirbuterol, metaproterenol, terbutaline, or isoetharine-each of which is preferable to less selective drugs, such as epinephrine, isoproterenol, and ephedrine- should be used up to a maximum of three or four times a day or as prophylaxis before exercise. A spacer should be used, if indicated, to improve aerosol delivery and reduce side effects.

TABLE 4

STEP-BY-STEP PHARMACOLOGIC THERAPY FOR COPD

1. For mild, variable symptoms:
   - Selective β_2-agonist metered dose inhaler (MDI) aerosol, 1-2 puffs every 2-6 h as needed not to exceed 8-12 puffs per 24 h
2. For mild to moderate continuing symptoms:
   - Ipratropium MDI aerosol, 2-6 puffs every 6-8 h; not to be used more frequently

   plus
   - Selective β-agonist MDI aerosol, l-4 puffs as required four times daily for rapid relief, when needed, or as regular supplement
3. If response to step 2 is unsatisfactory, or there is a mild to moderate increase in symptoms:
   - Add sustained release theophylline, 200-400 mg twice daily or 400-800 mg at bedtime for nocturnal bronchospasm

   and/or
   - Consider use of sustained release albuterol, 4-8 mg twice daily, or at night only

   and/or
   - Consider use of mucokinetic agent
4. If control of symptoms is suboptimal:
   - Consider course of oral steroids (e.g., prednisone), up to 40 mg/d for 10–14 d
     - -If improvement occurs, wean to low daily or alternate-day dose, e.g., 7.5 mg
     - -If no improvement occurs, stop abruptly
     - -If steroid appears to help, consider possible use of aerosol MDI, particularly if patient has evidence of bronchial hyperreactivity
5. For severe exacerbation:
   - Increase β_2-agonist dosage, e.g., MDI with spacer 6-8 puffs every ½–2 h or inhalant solution, unit dose every ½–2 h or subcutaneous administration of epinephrine or terbutaline, 0.1-0.5 ml

   and/or
   - increase ipratropium dosage, e.g., MDI with spacer 6-8 puffs every 3-4 h or inhalant solution of ipratropium 0.5 mg every 4-8 h

   and
   - Provide theophylline dosage intravenously with calculated amount to bring serum level to 10–12 μg/ml

   and
   - Provide methylprednisolone dosage intravenously giving SO-100 mg immediately, then every 6-8 h; taper as soon as possible

   and add:
   - An antibiotic, if indicated
   - A mucokinetic agent if sputum is very viscous

The rapid onset of action of beta-agonist aerosols may lead dyspneic patients to favor them for regular use. At present, there is little evidence to suggest that their regular use is harmful in COPD, although some studies suggest that it results in a slow decline in FEV, (71, 72) (as has been reported for asthma). There is no evidence to suggest that regular use of beta-agonists significantly curtails survival of patients with COPD. The potential for arrhythmias necessitates careful dosing in patients with probable or known cardiac disease, although serious cardiac complications are rare with conventional doses.

In more advanced disease, it may be reasonable to use slow-release oral albuterol, but the value and acceptability of such formulations have not been established. Similarly, the role of the new, long-lasting aerosol salmeterol in COPD needs to be determined, but it has been shown to prevent nocturnal bronchospasm. Both of these agents improve compliance, but further studies are required to establish their place in management of bronchospastic diseases in older patients.

Anticholinergic agents. Topical administration of an anticholinergic aerosol may be more effective than a topical beta-agonist in COPD, and the side effects tend to be less troublesome; currently, ipratropium is the only metered product. Once the patient suffers from daily symptoms, regular use of ipratropium via a metered dose inhaler is recommended. The drug has a slower onset and longer action than such beta,-agonists as albuterol and thus is less suitable for use on an "as needed" basis. Appropriate dosage is two to four puffs three or four times a day, but some patients require and tolerate larger doses, e.g., six to eight puffs three times a day.

Inhaled anticholinergic bronchodilators do not appear to influence the long-term decline of FEV, (32). However, there is no substantial evidence to suggest that regular use of anticholinergic therapy, with or without a beta,-agonist, leads to a worsening of spirometry or to exacerbations or premature death in COPD. It is thus appropriate at this time to use ipratropium therapy and add a beta$_2$-agonist as often as needed, up to four times a day. The use of a combination of albuterol and ipratropium in the same metered dose inhaler will help simplify therapy.

Theophylline. During the decade following the introduction of sustained-release theophylline, the agent was greatly favored for the management of both asthma and COPD, particularly in cases involving nocturnal bronchospasm. Theophylline's potential for toxicity led to a decline in its popularity, but it still retains an important role in COPD (73). It is of particular value for less compliant or less capable patients who cannot use aerosol therapy optimally because they can readily take long-acting theophylline once or twice a day.

The ability of theophylline to improve respiratory muscle function, stimulate the respiratory center, and enhance activities of daily living can be important to patients who are severely limited by COPD. Theophylline can also improve cardiac output, reduce pulmonary vascular resistance, and improve the perfusion of ischemic myocardial muscle. Thus, there are several advantages to theophylline therapy in patients with COPD who also have cardiac disease or cor pulmonale (74).

Theophylline has been shown to have some anti-inflammatory effects (75). Regular use of theophylline has not been shown to have either a progressively beneficial or a detrimental effect on the course of COPD. Recent information suggests that adding theophylline to the combination of albuterol and ipratropium can result in maximum benefit in stable COPD (76). Careful dosing is needed, particularly in the presence of other disease or other interacting drugs in the therapeutic regimen (Table 5). Precautions that should be taken when using beta agonists, ipratropium, and theophylline are shown in Table 6.

Anti-inflammatory Therapy

In contrast to their value in asthma management, the role of anti-inflammatory drugs in the routine treatment of COPD is less clear. Cromolyn and nedocromil have not been established as useful agents, although they could possibly be helpful if the patient has associated respiratory tract allergy. Corticosteroids may merit more careful evaluation in individual patients on adequate bronchodilator therapy who fail to improve sufficiently or whose disease undergoes exacerbation.

Corticosteroids. At present, there is no evidence to suggest that patients with COPD who are being treated with regular bronchodilator therapy require the "protective" effects of added steroid therapy as used in asthma. In outpatients, exacerbations may necessitate a course of oral steroids, but it is important to wean patients quickly, since the older COPD population is susceptible to complications such as skin damage, cataracts, diabetes, osteoporosis, and secondary infection. These risks do not accompany standard doses of steroid aerosols, which may cause thrush but pose a negligible risk for causing pulmonary infection.

Most studies suggest that only 20 to 30% of patients with COPD improve if given chronic oral steroid therapy (74). The dangers of steroids require that careful documentation of the effectiveness of such therapy be recorded before a patient is put on prolonged daily or alternate-day dosing; the latter regimen may be safer, but its effectiveness has not been evaluated in COPD. It is possible that steroids can slow the deterioration rate in COPD, but this suggestion has not been adequately evaluated

TABLE 5

FACTORS THAT MIGHT AFFECT THEOPHYLLINE DOSAGE REQUIREMENTS

	Larger Theophylline Dosage Required*	Smaller Theophylline Dosage Required
Major change (26–50%)	Cigarette smoking	Hepatic insufficiency
	Phenytoin	Heart failure
	Rifampin	Cor pulmonale
	Isoproterenol I.V.	Viral pneumonia
	Phenobarbital	Cimetidine
	Carbamazepine	Mexiletine
	Aminoglutethimide	Ciprofloxacin, other quinolones
		Allopurinol
		Erythromycin
		Influenza vaccination
		Triacetyloleandomycin (TAO)
		Propranolol
		Oral contraceptives
Lesser change (10–25%)†	Low carbohydrate, high protein diet	Verapamil
		Nifedipine
	Charcoaled food	Tetracycline
	Isoniazid	Hydrocortisone
	Ketoconazole	Aluminum hydroxide
		Magnesium hydroxide
		Thiabendarole

* When increasing dosage, serum levels must be used for guidance.
† Data supporting these changes are less well-documented.

(71, 72). It is possible, too, that aerosol steroids could be used in place of low-dose oral steroids, but again there is insufficient documentation to support such therapy; several multicenter studies are evaluating the course of COPD treated with aerosol steroids. Adding an inhaled steroid to a regimen that includes regular aerosol therapy with ipratropium and a beta-agonist results in the probability of noncompliance being increased. If patients are placed on long-term oral corticosteroids, supplemental calcium may help to prevent osteoporosis. Precautions required with steroid therapy are noted in Table 6.

Drugs Affecting Mucus

The only controlled study in the United States suggesting a value for a *mucokinetic agent* in the management of chronic bronchitis was a multicenter evaluation of organic iodide (77). This study did demonstrate symptomatic benefits, but objective evidence of benefit was deemed insufficient, and the FDA required that marketing of the drug be discontinued. The values of other agents, including water, have not been clearly demonstrated, although some established drugs, such as oral acetylcysteine, are favored in Europe for their anti-oxidant effects in addition to their mucokinetic properties. Genetically engineered DNAse has been proved to be useful in cystic fibrosis. The efficacy of DNAse in the treatment of COPD is under investigation.

Antibiotics are not of proven value in the prevention or treatment of COPD exacerbations unless there is evidence of infection, such as fever, leukocytosis, or a change in the chest radiograph (78-80). In cases of recurrent infection, particularly in winter, prolonged courses of antibiotics, whether continuous or intermittent, may be useful.

When an acute bacterial infection of sputum is believed to be present, antibiotic therapy may be justified. The decision is usually made clinically because sputum culture is not cost-effective. The major bacteria to be considered are *Streptococcus pneumoniae, Hemophilus influenzae,* and *Moraxella catarrhalis.* Antibiotic choice will depend on local experience, supported by sputum culture and sensitivities in those cases where the patient is moderately ill or needs to be admitted to the hospital. In general, fiscal concerns should be taken into account, and older, less costly agents-tetracycline, doxycycline, amoxicillin, erythromycin, trimethoprim-sulfamethoxazole, cefaclor, etc. -are often as effective as newer, more expensive ones.

Other Pharmacologic Agents

Alpha$_1$-antitrypsin augmentation therapy is appropriate in nonsmoking, younger patients with severe alpha$_1$-antitrypsin (AAT) deficiency and associated emphysema (see the earlier discussion of this subject); such therapy is not indicated in the common form of COPD.

Respiratory stimulants, used in some other countries, are not currently recommended in the United States.

Psychoactive agents are often sought by older patients with COPD to treat depression, anxiety, insomnia, or pain. These agents can be helpful with appropriate care and with particular awareness of potential depressant effects on the respiratory center (81). Benzodiazepines do not have a marked effect on respiration in mild or moderate COPD but can be suppressive in severe disease, especially during sleep. The safer hypnotics for use in insomnia include sedating antihistamines and chloral hydrate; antidepressants may also have the advantage of improving sleep.

Cardiovascular therapy may be needed in severe COPD and cor pulmonale; agents may include diuretics, angiotensin-converting enzyme (ACE) inhibitors, or calcium channel blockers. Digoxin is occasionally useful, while beta-adrenergic blockers are generally contraindicated. All such drugs must be used cautiously to avoid precipitating electrolyte imbalance, dehydration, hypotension, myocardial ischemia, and arrhythmias. Because most patients requiring such therapy are elderly or have impaired drug clearance, alertness to potential side effects is vital; if they occur, the drug regimen must be promptly modified.

Immunization with pneumococcal and influenza vaccines is recommended to prevent infectious complications involving the respiratory tract. Although the available vaccines are not totally effective, there is evidence that COPD patients are likely to benefit from their use.

Adjustment of Therapy

The relationship between patient and physician must be dynamic

TABLE 6

PRECAUTIONS IN DRUG USE

Precautions when using beta-agonists
- Watch for nonimprovement or paradoxical deterioration with aerosol use
- Use spacers to improve compliance and reduce systemic side effects
- Avoid overuse; check number of metered dose inhalers (MDIs) used per month against number of puffs per MDI (200 to 300+ depending on brand).
- Instruct patient on maximum number of puffs per day (usually 8-12) and on number allowed during an exacerbation (e.g., 12-24 over 3-4 h) before additional intervention is required
- If a long-acting agent is used, caution patient that frequent use must be avoided
- Home updraft nebulizers with inhalant solutions that provide large dosages are rarely needed

Precautions when using theophylline
- Initiate treatment with a low dose (e.g., 400 mg/d) and adjust after a few days
- Reduce dosage if drug clearance is likely to be impaired because of illness, liver malfunction, or concomitant drugs.
- Do not allow any additional theophylline preparation to be taken
- Drug must be taken at the same time each day with respect to meals
- When symptoms change, acute illness develops, new drugs are added, or symptoms suggestive of toxicity develop, check serum level of theophylline
- Aim for a serum level of 8-12 μg/ml; adjust dosage and follow serum level when indicated

Precautions when using ipratropium
- Patients should generally use a spacer and should avoid spraying into eyes
- Be prepared to increase dose if necessary from 2-3 puffs 3-4 times a day to 6-8 puffs 3-4 times a day, if tolerated
- Caution patient that onset of effect is relatively slow; additional doses should not be taken for acute symptom relief
- Monitor for side effects, e.g., tachycardia, dry mouth, glaucoma, prostatism, or bladder neck obstruction

Precautions when using oral steroids
- Reduce dosage to lowest effective daily dose or to alternate-day dosing as quickly as symptoms allow
- Monitor for hypertension, diabetes, weight gain, mental changes, infections, central polar cataracts, skin thinning, purpura, osteoporosis, and osteonecrosis
- Distinguish psychological benefit from true pulmonary benefit by following FEV_1 for 2 wk after initiating therapy
- Administer prophylactic calcium therapy to women; treat osteoporosis appropriately
- Steroid-dependent patients require steroid coverage during any crisis for many months after stopping steroids
- Repeatedly evaluate patient to determine if steroid therapy can be discontinued

Precautions when using aerosol steroids
- Seek objective evidence of the value of this therapy because its use may decrease compliance with other aerosol usage
- Standard dosing (2-4 puffs 2-4 times a day) should not be exceeded
- Use a spacer; monitor for oral thrush and laryngeal dysfunction
- Be aware that aerosol steroid side effects may occur in skin, bone, etc.
- When introducing aerosol steroids in a patient on an oral steroid, wean slowly off the oral druq

and participative. Since there are a number of therapeutic choices available, patients must become educated and take part in their own care. This dynamic interaction, known as *collaborative self-management,* allows patients to modify therapy according to disease severity and variations in symptoms. Patients may, for example, add regular doses of ipratropium when the persistence of symptoms lessens the usefulness or safety of beta-agonists. Similarly, courses of antibiotics or corticosteroids could be initiated by self-managed patients who are knowledgeable about their disease and the need to introduce specific types of treatment.

Further investigation is needed in a number of areas. Optimal dosages of $beta_2$-agonist bronchodilators, including new long-acting aerosols and oral preparations, and the value of their combination with ipratropium or other anticholinergic agents, need to be determined. Some studies that suggest regular use of these agents on a daily basis may lead to more rapid deterioration of COPD point to the need for further study. The value of current theophylline preparations and new derivatives, either alone or in combined regimens, has to be evaluated. The most important area for research is to define clinical criteria for the use of oral or aerosol steroids in COPD and determine if their use can retard the rate of deterioration.

Additionally, the possible value of cromolyn, nedocromil, and other yet-to-be marketed anti-inflammatory drugs needs to be determined for various types of COPD and associated chronic cough. Mucus therapy and antioxidant therapy are strongly favored in Europe, but definitive studies are still required for both old and newer drugs. It is important to determine whether or not appropriate muco-active drug therapy will reduce the liability of patients to pulmonary infections and their consequences because antibiotic therapy is of limited benefit in the typical, less severe exacerbation. Respiratory stimulants may prove to be beneficial, but the value of European drugs such as almitrine is uncertain. Genetically engineered agents such as alfa-dornase may have an important role in future therapy, and this avenue should continue to be explored.

LONG-TERM OXYGEN THERAPY

COPD is commonly associated with progressive hypoxemia. Hypoxemia can rapidly lead to damaging cellular hypoxia, and the administration of oxygen can be life preserving. Thus, the correction or prevention of hypoxemia assumes high priority. In preserving cellular oxygenation, the clinician must also address other oxygen transport variables, including adequate hemoglobin, cardiac output, and tissue perfusion.

Oxygen Therapy, Survival, and Quality of Life

Long-term oxygen therapy will reverse secondary polycythemia, increase body weight, alleviate right heart failure due to cor pulmonale, strengthen cardiac function, enhance neuropsychological function, and improve exercise performance and activities of daily living (82, 83).

Two-studies have shown that long-term oxygen therapy improves survival in hypoxemic patients with COPD. The British Medical Research Council (MRC) study, which compared hypoxemic patients receiving oxygen for 15 h/d, including the hours of sleep, with patients receiving none, showed a significant reduction in mortality (84). The National Heart, Lung, and Blood Institute's Nocturnal Oxygen Therapy Trial (NOTT), comparing continuous oxygen therapy (average 19 h/d) versus 12 h/d, including the hours of sleep, showed a further reduction in mortality using continuous oxygen (85).

The mechanism for improved survival has yet to be completely delineated; however, it appears likely that pulmonary hemodynamics may be involved (86). Chronically hypoxemic patients tend to have increased pulmonary artery pressures; when they receive oxygen, they experience a fall in those pressures. While such correction in pulmonary artery pressure is not complete, lowering it will reduce cardiac work and improve tissue oxygen delivery.

The overriding concern is to prevent tissue hypoxia. Simply correcting hypoxemia may not be sufficient to treat or prevent tissue hypoxia. The clinician must be concerned about the full scope of oxygen transport and delivery to the tissues. Accordingly, lung function ought to be maximized, including correction of bronchospasm, control of bronchopulmonary infection, and resolution of congestive heart failure. The transport vari-

ables, including hemoglobin and cardiac output, must also be addressed.

There has been overemphasis on the fear that oxygen therapy might lead to respiratory drive depression, hypercapnia, and respiratory acidosis. As a consequence, clinicians may be overly timid about prescribing oxygen. It is now understood that, while CO, retention does occur (87, 88), it is often caused by ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatching rather than by respiratory center depression (89). Therapeutic preference must be given to correcting the hypoxemia.

When oxygen is delivered via nasal cannula, a relatively low flow of 100% oxygen is mixed into a much higher inspiratory flow of room air (20.9% oxygen). The net effect is to increase the Pa_{O_2} by an amount dependent on gas exchange variables, respiratory pattern, and arteriovenous shunting. Unless the shunt fraction approaches 50%, low-flow oxygen is very effective in correcting hypoxemia. On the negative side, oxygen therapy itself may be associated with such adverse effects as absorptive atelectasis and reduction of hypoxic vasoconstriction that might extend $\dot{V}/\dot{Q}$ mismatch. In general, however, the net effect of oxygen therapy is to reverse hypoxemia.

Measurement of arterial blood gases (ABG) is the usual means of assessing gas exchange status. The methodology for arterial sampling has been standardized, it is safe, and complications are uncommon and relatively minor. With frequent requirement for ABG assessment, an arterial line may be considered. Sources of error in ABG measurements include improper sample site (vein), inadequate blood handling techniques, high white blood cell count (decreases the Pa_{O_2}), and instrumentation error.

The arterial blood gas analyzer measures Pa_{O_2}, Pa_{CO_2}, and pH. Bicarbonate and Sa_{O_2} are calculated using standard algorithms. Sa_{O_2} can also be measured directly, using a co-oximeter, which also measures carboxyhemoglobin and hemoglobin.

Noninvasivepulse oximetry measures the transmission of two wavelengths of light through the skin, typically of the finger or earlobe. The red band represents oxygenated hemoglobin, while the infrared band represents unbound hemoglobin. Pulse oximetry generally correlates well with co-oximetry measured from arterial blood, with 1 to 2% error. Inaccuracies are created by high levels of methemoglobin, carboxyhemoglobin, bilirubin, dark skin pigment, inadequate tissue perfusion, and movement artifact. In spite of these error sources, pulse oximetry is a good method for following oxygen saturation and can be used for titrating the oxygen flow setting. Oximetry is *not* considered sufficiently accurate to replace ABG in an initial assessment and cannot be used to determine acid base status. A blood gas Sa_{O_2} can be used to corroborate the oximetry Sao,.

Transcutaneous Po, measures local oxygen level across the dermal surface. It allows continuous assessment and, in contrast to oximetry, measurement of hyperoxia. In the neonatal patient, this measurement is accurate and strongly correlates with Pa_{O_2}. In the adult, however, the skin surface is uneven, thicker, and subject to changes in local blood flow. Transcutaneous Po_2 has not been widely used because there is little agreement on its accuracy or interpretation in adults. Additionally, it requires a heated electrode that can occasionally cause burns and heat blisters.

In summary, arterial blood gas measurement is recommended for initiation of oxygen therapy as well as to determine Pco_2 and acid-base status. ABG may also be used initially to confirm the accuracy of pulse oximetry in adjusting the oxygen flow setting. Noninvasive pulse oximetry is useful for assessing Sa_{O_2} and adjusting oxygen flow settings; it is less reliable in exercise studies than at rest, and ABG at the beginning and end of an exercise session may provide confirmatory data. Transcutaneous measurements of Po_2 are inaccurate and are therefore not recommended in adults.

Oxygen Therapy during Sleep

Patients who are hypoxemic while awake are likely to be hypoxemic during sleep as well. If the patient does not have sleep-disordered breathing due to other causes, the administration of nocturnal oxygen therapy will correct nocturnal hypoxemia. It is often recommended that 1 L/min of continuous flow oxygen be added to the daytime resting prescription to allow for additional hypoventilation and gas exchange abnormalities during sleep, but continuous oximetry monitoring during sleep will support a more accurate prescription.

Oxygen Therapy for Exercise-induced Hypoxemia

COPD patients are encouraged to remain active. Due to the underlying lung disease and inefficient gas exchange, continuation of an active lifestyle becomes increasingly difficult. Many patients with COPD who are hypoxemic at rest worsen during exertion, while others develop hypoxemia only during exertion. Home supplemental oxygen is commonly prescribed for the latter group, even though studies designed to determine the long-term benefit of oxygen solely for exercise have yet to be conducted.

Some short-term studies have shown that supplemental oxygen during exercise can prevent transient increases in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) (90). The immediate benefits of oxygen during exercise are reduction in dyspnea and improvement in exercise tolerance at submaximal workloads (91). There are data suggesting that oxygen can also increase peak exercise level via a reduction in minute ventilation at submaximal workloads (92).

In determining the exercise flow setting for home oxygen, arterial blood gases may be measured while the patient is carrying on a level of exertion equal to or slightly greater than that normally experienced during daily activities. Repeated exercise tests may be necessary to titrate oxygen administration to increase Sa_{O_2} to greater than 90% during usual exertion. There will be cases in which this goal is not achievable; hence, clinical decisions will be required to determine optimal oxygen flow, delivery method, and acceptable Sa_{O_2}. Patients should be evaluated using the same delivery devices that they expect to use at home, e.g., nasal cannula or oxygen-conserving device. Exercise testing is best carried out using muscle groups where dyspnea is most pronounced (legs versus arms, for example).

While ABG measurement remains the gold standard for determining arterial oxygenation, Sa_{O_2} may be measured via noninvasive pulse oximetry. Unfortunately, absolute values may not be accurate during exercise, particularly in patients with poor peripheral perfusion. Verification of oximetry accuracy can be accomplished by obtaining ABG before and after exercise. The advantages of pulse oximetry are that it is noninvasive and provides continuous read-out of Sa_{O_2}, which allows for Sa_{O_2} tracking. Following Sa_{O_2} during exercise testing helps to determine the speed and extent of the desaturation response.

Optimal Medical Regimen

One of the goals of any medical regimen is to optimize $\dot{V}/\dot{Q}$ matching as a means of correcting hypoxemia. This is particularly important during and after an acute exacerbation. If there is evidence of congestive heart failure due to cor pulmonale, diuretic therapy may be advisable. The adequacy of oxygen delivery to the tissues may be improved by correcting anemia or polycythemia. An exercise program may improve oxygen transport to working muscles. If the patient nevertheless remains hypoxemic, long-term oxygen therapy is continued, probably for the life of the patient.

One aspect of good medical management is the oxygen therapy itself. Recent reports suggest that oxygen may have a reparative effect by reducing pulmonary artery vasoconstriction and

improving $\dot{V}/\dot{Q}$ matching (86, 93). If this is the case, withdrawal of oxygen because of improved Pao, may be distinctly detrimental.

Hazards of Oxygen

Oxygen therapy is generally safe. Hazards the clinician must recognize include oxygen toxicity, CO, retention, and the possibility of accidents during the storage and handling of oxygen.

Oxygen *toxicity* is related to *free radicals.* The major end product of normal oxygen metabolism is water. Some oxygen molecules, however, are converted into highly reactive species called radicals, which include superoxide anions, perhydroxy radicals, hydroxyl radicals, and hydrogen peroxide; they are toxic to alveolar and tracheobronchial cells.

Normally, antioxidant enzymes, including metaloproteins (superoxide desmutase), catalase, and glutathione peroxidase, protect cells by scavenging the O_2 radicals. But in the face of prolonged exposure to high concentrations of oxygen, the antioxidant system becomes overwhelmed, permitting oxidative destruction of lung tissue. Acute changes may be manifested as tracheobronchial irritation, impaired mucociliary clearance, and diminished vital capacity secondary to edema and reabsorption atelectasis. As exposure continues, leaky capillaries, alveolar hemorrhage, surfactant dysfunction, and alveolar edema will develop. Adult respiratory distress syndrome may follow, with pulmonary infiltrates and fibrosis or death (94).

Pathophysiologic changes include decreased lung compliance, reduced inspiratory airflow, decreased diffusing capacity, and small airway dysfunction. While these changes are well-recognized in the acute care setting of mechanically ventilated patients receiving F_{IO_2} in excess of 50%, little is known about the long-term effect of low flow (24 to 28%) oxygen. In one uncontrolled autopsy series, patients with chronic obstructive lung disease who had been treated with chronic low-flow oxygen therapy showed exudative and proliferative changes consistent with oxygen toxicity (95); there was no indication that these changes had impaired survival. Animal studies have demonstrated that long-term exposure to 80% F_{IO_2} may induce tolerance, perhaps in the form of greater levels of protective antioxidant enzymes. It is widely accepted that the increased survival and quality-of-life benefits of long-term oxygen therapy outweigh the possible risks.

CO, *retention* may pose a threat in patients with impaired CO, ventilatory drive. Depression of hypoxic drive by supplemental oxygen may induce worsening hypercarbia, respiratory acidosis, and CO, narcosis. While this complication is not common in low-flow oxygen therapy, it is best avoided by titration of oxygen delivery to maintain Pao, between 60 and 65 mm Hg. When hypercarbia is present, initial oxygen delivery settings should be titrated using serial ABG assessments rather than relying solely on oximetry.

Some CO, retention is tolerable; patients with an intact renal system are capable of reabsorbing enough bicarbonate to compensate for the extra CO, and maintain the acid-base balance. The ability of patients to tolerate CO, retention may be an adaptive mechanism that lessens the work of breathing, since an increased alveolar P_{CO_2} results in increased CO_2 excretion with each breath.

The major physical hazards of oxygen therapy are fires or explosions. Most fires have been caused by patients lighting cigarettes as oxygen is flowing into their noses (96). While the cannula is constructed of fire-retardant plastic, both the patient's nose and the cannula will burn vigorously in the presence of oxygen in high concentrations. *Patients, family, and other caregivers must be warned not to smoke.* Oxygen containers should not be stored near water heaters, furnaces, or other sources of heat or flame. Serious freeze burns can occur if the patient does not take proper precautions while transfilling liquid oxygen. Finally, a compressed oxygen cylinder can be accidentally knocked over, causing explosive disconnection of the regulator and rendering the cylinder a dangerous missile. In general, major accidents associated with oxygen therapy are rare and can be avoided by good patient and family training and common sense.

Oxygen Systems

Oxygen comes packaged in three types of systems: compressed gas, liquid, and oxygen concentrators. The trade-offs include size and weight of the device, storage capacity, cost, and transfillability. The features of the systems are compared in Table 7.

Oxygen Delivery Methods

The continuous flow dual-prong nasal cannula is the standard means of oxygen delivery for the stable hypoxemic patient. It is simple, reliable, and generally well-tolerated. In some patients with advanced disease and severe hypoxemia, however, a face mask may be required to increase the fraction of inspired oxygen (F_{IO_2}).

The nasal cannula delivers a low flow of pure oxygen entrained in a much larger volume of atmospheric air (20.9% oxygen). Each liter per minute of oxygen flow adds about 3 to 4% to the F_{IO_2}.

TABLE 7

COMPARISON OF GAS, LIQUID, AND CONCENTRATOR OXYGEN SYSTEMS

Type	Gas	Liquid	concentrator
Availability	Common	Limited	Common
Reliability	Generally good; Bourdon gauges may become inaccurate	Possible inaccurate setting, freezing of connector	Good, but needs regular service
Cost	Moderate	High	
Weight + use time 2 L/m			
Stationary	H cylinder: 200 lb., 2.5 d	Reservoir: 120 lb., 8.9 d	Stationary 35-lb.unit; no storage capability
Portable	E cylinder: 20 lb., 5 h	Portable: 6 lb., 4 h	
Portable + OCD (O_2-conserving device)	Fiber/alum: 4.5 lb., 12 h	OCD system: 5.5 lb., 8 h	
Transfill	Limited	Excellent	N/A
Power	None	None	110 volts AC
Ambulatory use	Good with conserver	Good alone and with conserve,	Portable, but not suitable for ambulatory use

A rough approximation is that 1 L/min increases the Fro, to 24%, 2 L/min to 28%, and 3 L/min to 32%. These small increases are usually sufficient to increase the arterial oxygen content to acceptable clinical levels. The actual F_{IO_2} for any particular patient is variable, depending on the anatomy and patency of the nares and moment-to-moment variation in respiratory rate and pattern, as well as the underlying pathophysiologic process. The F_{IO_2} is inversely related to the inspiratory rate; a more rapid inspiratory rate dilutes the oxygen flowing into the nares with more room air, thereby reducing the F_{IO_2}.

Some studies indicate that mouth breathing impairs oxygen delivery, while others show no such reduction (97, 98). It appears that some nasal oxygen flows over the top of the lip into the mouth. And most mouth breathers have some nasal airflow as well. Since only a small nasal inspiratory flow is necessary, nasal oxygen delivery is still beneficial to these patients.

Oxygen-conserving devices function by delivering all of the oxygen during early inhalation. These devices were developed in an effort to improve the portability of oxygen therapy by reducing the size and weight of the oxygen system. Other advantages include a reduction of overall costs of home oxygen therapy and the ability to more effectively treat refractory hypoxemia. There are three distinct devices; their characteristics are summarized in Table 8.

Reservoir cannulas operate by storing oxygen in a small chamber during exhalation for subsequent delivery during early-phase inhalation; they are driven by the patient's nasal inspiratory and expiratory pressures. They are available in two configurations, oxymizer and pendant (99, 100). The delivery efficacies of the two are roughly equivalent. Compared with continuous flow oxygen, reservoir cannulas are two to four times as efficacious. They reduce oxygen usage by lowering oxygen flow setting to 25 to 50% of that required for continuous flow oxygen to achieve equivalent Sa_{O_2}. The advantages of reservoir cannulas lie in their simplicity, reliability, and low cost. Their disadvantage is that they are larger and more noticeable than demand devices.

Demand pulsing oxygen delivery devices deliver a small bolus of approximately 100% oxygen at the onset of inhalation (101). Interposed between patient and oxygen source, they serve as sensor switches, permitting a bolus of oxygen to flow immediately after sensing the inspiratory effort pressure signal through either a standard or modified nasal cannula. Because oxygen delivered during early inhalation reaches the alveoli, small oxygen pulses are very effective in oxygenating the patient. The devices vary in their design features, including delivery strategy, missing breath alarms, and battery life. Pulse demand devices have also been combined with a transtracheal oxygen catheter, which further improves the delivery efficacy of transtracheal therapy (102); the overall delivery efficacy of this combination is about equivalent to the most efficacious pulsed demand nasal delivery.

Transtracheal oxygen (TTO) delivery involves insertion of a catheter percutaneously between the second and third tracheal interspaces. Oxygen enters the trachea via this catheter. Patients have been reported to use 37 to 58% less oxygen during TTO delivery compared with continuous flow nasal oxygen (103-105).

Although TTO is considered in the category of oxgyen-conserving devices, it is considerably different from the mechanical types discussed earlier. TTO is invasive and requires special training by the physician. The procedure has risks as well as medical benefits and is of limited applicability. In addition to the medical indications and contraindications noted below, TTO is of distinct benefit to patients who will not accept the intrusive nature of the nasal cannula and mechanical oxygen-conserving devices in the context of social interaction.

Not all patients are suitable candidates for TTO. The ideal candidate for TTO has a strong desire to remain active; is willing to follow the care protocol; is not experiencing frequent exacerbations; has a caregiver who is willing to assist with problem solving and details of care; and lives within 2 h of the institution or has equivalent follow-up in the home community. It is important to note the TTO is instituted in phases and requires active participation by the patient; not every patient is able and willing to learn the required care.

Relative contraindications include high-dose steroids (> 30 mg/d) and conditions that predispose to delayed healing, e.g., diabetes mellitus, connective tissue disease, or severe obesity. *Absolute contraindications* include subglottic stenosis or vocal cord paralysis, herniation of the pleura into the insertion site, severe coagulopathy, uncompensated respiratory acidosis, and inability to practice self-care.

TTO reduces inspired minute ventilation (106). High flow via a transtracheal catheter reduces total dead space volumes in an amount proportional to the increase in flow rate. Pleural pressure-time index and tension-time index for the diaphragm decrease, changing the respiratory pattern of the diaphragm to a less demanding one (106), which may account for the decrease in dyspnea and increase in exercise tolerance seen in these patients. TTO delivery has also led to a decrease in hematocrit, prob-

TABLE 8

CHARACTERISTICS OF OXYGEN-CONSERVING DEVICES

Method	Reservoir	Demand Pulse	Transtracheal
Mechanism of conservation	Store during exhalation	Early inspiratory delivery	Store at end exhalation; bypass dead space
Savings	2:1 to 4:1	3:1 to 7:1	2:1 to 3:1
Cosmetics	Obtrusive	Adequate	Best
Comfort	Adequate	Adequate	Good
Reliability	Good; simple	Mechanical	Mucus plug possible
cost	LOW	Significant	Significant
Specific advantages	Inexpensive, easily initiated, reliable,	Highest savings, programmable delivery possible with alarms	Cosmetics, lack of nasal/ear irritation, good compliance, may reduce minute ventilation
Specific disadvantages	Bulky on face	Mechanically complicated, failure possible	Special care and training, surgical complications

ably due to increased use of oxygen because of improved compliance and less tendency to disconnect the delivery system (107).

Complications of TTO are infrequent and generally mild. They include catheter displacement, bacterial cellulitis, subcutaneous emphysema, hemoptysis, severed catheter, and mucus balls. Mucus balls can develop on the catheter due to the drying effect of the oxygen, increased sputum production, and poor adherence to cleaning schedules; they may cause coughing, catheter blockage, and tracheal obstruction, with serious consequences. Although daily cleaning prevents mucus ball formation in most patients, tracheal obstruction has also been reported in patients who meticulously followed cleaning routines. After 2 mo, the catheter can be removed for cleaning, and risk of mucus ball formation is markedly decreased.

If a patient using TTO requires endotracheal intubation, the catheter may be capped and left in place in the tract. Irrigation is not necessary, since mucus does not form on the catheter when oxygen is not flowing through it. Because of the physiologic effects of catheter flow, TTO delivery may be used to facilitate the weaning of patients from mechanical ventilation.

The overall goal of oxygen-conserving devices is to improve portability, mobility, and comfort. These devices can reduce the overall cost of oxygen therapy in the home-not by reducing the cost of oxygen itself, which is relatively inexpensive- but by reducing the number of deliveries per month to the home. The cost of the devices themselves ought to be factored in. The pulsing devices are expensive, but the same device may be used for more than one patient over several years. Thus, the most expensive system might be the most cost-effective, after the initial investment is made.

Humidification

There is no evidence that humidification is necessary when oxygen is given by nasal cannula at flows ≤ 5 L/min (108). There are no differences in subjective complaints or in severity of symptoms over time. These findings are explained by the low water vapor output of bubble humidifiers and small contribution of oxygen flow to the patient's inspired minute ventilation, since most of the patient's tidal volume consists of atmospheric gas. Moreover, oxygen flowing through the bubble humidifier is at room temperature; when it is raised to body temperature, the relative humidity falls.

This does not apply to patients receiving oxygen by tracheostomy or TTO therapy, in whom the upper airway has been bypassed by the catheter; for these patients, humidification of inspired gas is essential even at low flow rates (1 L/min). TTO patients at high risk for mucus ball formation, including those with oxygen flows ≥ 5 L/min, large amounts of mucus, or weak cough, may benefit from a servocontrolled heated humidifier because this device more efficiently humidifies inspired gas.

Clinical Guidelines for Long-term Oxygen Therapy

Patients whose disease is stable on a full medical regimen, with $Pa_{O_2} \leq 55$ mm Hg (corresponding to an $Sa_{O_2} \leq 88\%$), should receive long-term oxygen therapy (LTOT). A patient whose Pa_{O_2} is between 55 and 59 mm Hg (Sa_{O_2}, 89%) and who exhibits signs of tissue hypoxia, such as cor pulmonale, erythrocytosis, edema from right heart failure, or impaired mental status, should also receive LTOT. Desaturation only during exercise or sleep suggests consideration of oxygen therapy specifically under those conditions. These guidelines are generally accepted and have been adopted by Medicare as reimbursement criteria. Some gray areas remain, such as patients with adequate Pa_{O_2} who have severe dyspnea relieved by low-flow oxygen, or patients who are limited in their exertional capacity but improve their exercise performance with supplemental oxygen. The generally and officially recognized indications for LTOT (109) are summarized in Table 9.

Prescribing Home Oxygen Therapy

It is recommended that measurement of resting Pa_{O_2} after 30 min of air breathing, not pulse oximetry (Sa_{O_2}), be the clinical standard for initiating LTOT. Oximetry may be used to adjust oxygen flow settings over time. If hypercapnia or acidosis are suspected, ABG analysis must be performed.

The standard of care for patients with COPD is for them to be as active and mobile as possible. It is therefore recommended that the oxygen system be stationary with a portable component, unless the patient is incapable or unwilling to be mobile. If the patient is immobile and will not move beyond a radius of 50 ft, an oxygen concentrator with 50 ft of tubing is suitable.

LTOT is the only therapy for advanced COPD that has been shown to decrease mortality (84, 85). For patients who are hypoxemic at rest, the more continuously oxygen is administered, the greater the benefit. It is recommended that patients be provided oxygen continuously, 24 h/d, with an ambulatory capacity to include oxygen during exertion.

Settings should be adjusted for rest, exertion, and sleep to meet the individual patient's needs. Ideally, the resting flow rate can be adjusted by monitoring oximetry to $Sa_{O_2} \geq 90\%$. Twenty minutes or more may be required for full equilibration to occur. ABG should then be used to establish initial Pa_{O_2} with corroborating oximetry Sa_{O_2}; the oxygen flow should be titrated to a level that maintains a $Pa_{O_2} \geq 60$ mm Hg during rest.

In the Nocturnal Oxygen Therapy Trial (NOTT) (85), oxygen flow rates were arbitrarily increased 1 L/min above the resting rate for exercise and sleep. Exercise flow rates determined in this manner may be excessive for some patients and inadequate for others. If the patient is using an oxygen-conserving system, Pa_{O_2} should be measured using the patient's oxygen delivery system. This is particularly true during exercise conditions. Exercise testing can be accomplished via a timed walk, treadmill or bicycle ergometry, or a free walk at the patient's normal pace. If dyspnea is especially prevalent during arm exertion, the patient may also be tested while performing arm tasks. It is recognized that pulse oximetry measurements become less accurate during exercise, but they do provide useful comparative information. The goal is to maintain $Pa_{O_2} > 60$ mm Hg or $Sa_{O_2} > 90\%$.

When the clinician has adjusted the oxygen delivery setting to achieve > 90% Sa_{O_2} during seated rest, the delivery setting for sleep may be turned up 1 L/min greater than the resting setting for possible sleep desaturation. If there are signs of cor pulmonale despite adequate daytime oxygenation, the patient may be monitored with oximetry during sleep to determine the best sleep oxygen setting.

TABLE 9

INDICATIONS FOR LONG-TERM OXYGEN THERAPY

Absolute
- $Pa_{O_2} \leq 55$ mm Hg or $Sa_{O_2} \leq 88\%$

In presence of cor pulmonale:
- Pa_{O_2} 55-59 mm Hg or $Sa_{O_2} \geq 89\%$
- EKG evidence of "P" pulmonale, hematocrit > 55%, congestive heart failure

Only in specific situations:
- $Pa_{O_2} \geq 60$ mm Hg or $Sa_{O_2} \geq 90\%$
- With lung disease and other clinical needs, such as sleep apnea with nocturnal desaturation not corrected by CPAP

If the patient meets criteria at rest, O_2 should also be prescribed during sleep and exercise, appropriately titrated.

If the patient is normoxemic at rest but desaturates during exercise or sleep ($Pa_{O_2} \leq 55$ mm Hg), O_2 should be prescribed for these indications. Also consider nasal CPAP or BiPAP.

Definition of abbreviations: CPAP = continuous positive airway pressure; EKG = electrocardiogram; BiPAP = bilevel positive airway pressure.

Determination of Continued Need

Standards for continuing oxygen therapy differ depending on whether-it is prescribed for the first time during an acute exacerbation or at a time when the patient is relatively stable and receiving optimal therapy (93). Some patients with COPD who were not hypoxemic before an exacerbation will eventually reach a point when they no longer need oxygen. For such patients, the need for long-term oxygen should be reassessed in 30 to 90 d, when the patient is clinically stable and receiving adequate medical management. If the patient does not meet blood gas criteria at that time, oxygen therapy can be discontinued.

The majority of patients who are clinically stable will continue to meet prescribing criteria for LTOT. Some patients, however, experience an improvement in Pa_{O_2} and, as a consequence, may no longer meet criteria for such therapy. This can occur in stable patients receiving optimal therapy who have been on oxygen for months or years (86, 93).

Improved oxygenation in patients with stable COPD is believed to result from the "reparative" effects of oxygen, including reversal of hypoxic pulmonary vasoconstriction, and it should not be used to justify discontinuation of therapy (93). Once the need for LTOT has been established in a stable patient on optimal therapy, LTOT most likely represents a lifetime commitment. Measurements of oxygen saturations > 90% should not be used as a rationale for discontinuing the therapy.

Reimbursement Criteria and Documentation (HCFA Criteria)

Oxygen is prescribed by the physician based on physiologic findings and clinical judgment. In the United States, reimbursement will not be approved unless patients meet established physiologic criteria. It is therefore essential for the physician to provide appropriate documentation that oxygen is medically necessary and meets physiological criteria as shown in Table 9. Most private insurance carriers and the Department of Veterans Affairs follow Medicare guidelines for reimbursement.

For a prescription of LTOT, a certificate of medical necessity (Health Care Financing Administration, HCFA form 484) must be completed. The document evolved in an attempt to be certain that the physician, not a home medical equipment supplier, is responsible for decisions concerning therapy. HCFA requires the physician or an employee of the physician, rather than the supplier, to complete form 484; guidelines for completing the form have recently been summarized (109).

Patient education and monitoring of compliance are essential to assure the success of LTOT. Many patients harbor fears regarding the therapy. Some, for example, associate a need for long-term oxygen with profound deterioration rather than prolongation of life and enhancement of quality of life; they may therefore experience anger or denial. Some may believe oxygen is an addictive substance and may therefore avoid its use as much as possible. These and other concerns need to be explored and discussed so that the patient is reassured of the helpful nature of the therapy.

Future technological advances in oxygen extraction from the atmosphere should lead to the development of practical portable concentrators. Another probability is that oxygen storage containers will become lighter, smaller, and more easily transfillable, not only from liquid but from gas and concentrators as well. Oxygen delivery and conserving devices will be rendered more efficient, less costly, and more accessible to all who need them.

PULMONARY REHABILITATION

The three major goals in the management of COPD are: (I) to lessen airflow limitation; (2) to prevent and treat secondary medical complications, such as hypoxemia and infections; and (3) to decrease respiratory symptoms and improve quality of life. Many patients may be unable to enjoy life to the fullest because of shortness of breath, physical limitations and inactivity imposed by that fear-provoking symptom, and mechanical impairment of their respiratory system. Pulmonary rehabilitation (110, 111) comprises a constellation of therapeutic modalities in an ongoing, multidimensional continuum of services designed to provide a framework for quality-of-life improvement.

Recent comprehensive review articles and texts provide extensive references delineating the components of pulmonary rehabilitation and expected results (112-115). In evaluating the benefits of pulmonary rehabilitation, it is difficult to distinguish the relative contributions of specific therapies because they are integrally related. Almost any treatment (e.g., education, exercise) given by well-trained personnel will inevitably provide elements of psychosocial support and motivation for chronically ill and disabled patients. As a result of rehabilitation, improvements have been demonstrated in objective measures of quality of life (116), well-being (117), and health status (118), including reduction in respiratory symptoms, increase in exercise tolerance and functional activities such as walking, increased independence, enhanced ability to perform activities of daily living, improved psychological function with less anxiety and depression, and increased feelings of hope, control, and self-esteem.

Health Care Utilization

Pulmonary rehabilitation also results in substantial savings in health-care costs. Several studies have analyzed COPD patients' hospital and medical resource utilization before and after rehabilitation (119, 120). Lertzman and Cherniack (120) reported an average decrease of 20 hospital days in the year after pulmonary rehabilitation, resulting in an estimated savings of $2,000 per patient. In a randomized controlled study, Jensen (121) found that pulmonary rehabilitation led to significantly fewer hospitalizations over a 6-mo follow-up of patients with COPD who have "high-risk" markers for psychosocial problems.

Several reports have followed patients for more than 1 yr after rehabilitation. Hudson and coworkers (122) surveyed hospitalizations for pulmonary disease over 4 yr after a pulmonary rehabilitation program for patients with COPD. For the 44 patients still alive at the end of that period, hospital days were reduced from 529 d in the year preceding the program to 145,270, 278, and 207 d in the 4 yr after rehabilitation. This benefit was most striking in the 14 patients hospitalized in the year before the program; hospital days in this group decreased from an average of 38 d per patient in the prerehabilitation year to 10 d in the year after rehabilitation.

Survival studies of patients with COPD after pulmonary rehabilitation have shown variable results (123-125). There have been no prospective randomized controlled studies that provide conclusive evidence regarding survival; reported increased survival may relate to the use of historical controls.

Application, Resources, and Organization

An algorithm for the outpatient management of COPD is shown in Figure 3, including pulmonary rehabilitation in the therapeutic schema. After the diagnosis of COPD and assessment of the patient's symptoms, the physician should actively encourage a healthy lifestyle, including regular exercise, weight control, and smoking cessation. Immunizations against pneumococci and influenza should be routinely administered. Assessment of the patient's perception of his or her quality of life should follow the institution and evaluation of response to the traditional aspects of medical therapy.

Referral to a comprehensive pulmonary rehabilitation program is indicated in COPD patients who have been placed on

optimal medical therapy and who: (1) continue to display severe respiratory symptoms, including dyspnea; (2) have had several emergency room or hospital admissions per year; (3) exhibit limited functional status, restricting activities of daily living; or (4) experience impairment in quality of life.

Pulmonary rehabilitation and its therapeutic modalities are usually employed on an outpatient basis, and comprehensive pulmonary rehabilitation programs vary in their frequency and duration. A national survey of 150 programs showed wide variation in program delivery (126). The optimal frequency and length of such programs have not been determined.

Although inpatient pulmonary rehabilitation programs have been described, precise indications for them have not been elucidated. Experience suggests, however, that some patients are extremely incapacitated and have such limited ability to perform even very low-level activities of daily living and functional tasks that simply traveling from home to an outpatient program is prohibitively taxing; such patients cannot derive benefits from outpatient programs.

The individual components of pulmonary rehabilitation should be provided by health professionals who are knowledgeable and experienced in the management of patients with COPD and in the therapeutic modalities to be employed. Team members may include a physician, a dietitian, a respiratory care practitioner, a nurse, a physical therapist, a cardiorespiratory technician, an occupational therapist, a recreational therapist, a pharmacist, a cleric, an exercise physiologist, and psychosocial professionals (psychologists, social workers, psychiatrists). The specific members of the team will vary from one program to another depending on the availability and interest of individuals in a given locale; in smaller programs, one health professional may perform several functions.

A rehabilitation program may include a number of components and should be tailored to the needs of the individual patient. The various therapeutic modalities may be employed singly or in combination, based on the physician's assessment of the patient in the physician's office, in other outpatient settings, in the hospital, and/or in the home.

Because the goal of pulmonary rehabilitation is to improve the patient's function in the home and community setting, the benefits accrue not only to the patient but also to family members, particularly those living in the home (111). Ideally, all patients who complete a pulmonary rehabilitation program should be given written as well as oral guidelines for home continuation of the program. Ongoing care is generally the responsibility of the referring physician. Periodic retesting and reassessment may be extremely beneficial to the patient and may also provide motivation for regular chest physiotherapy, practice of breathing techniques, and exercise training. Support groups may be useful for educational, psychosocial, and maintenance purposes.

Because most patients with COPD are older and have a history of cigarette smoking, they are at risk for heart disease. Before any patient with COPD enters a rehabilitation program, cardiac and pulmonary stress testing should be routinely performed to exclude silent cardiac disease and assure safety during exercise training.

Education is important for every patient with COPD who has been placed on a therapeutic regimen, particularly when medications and/or oxygen have been prescribed. Educational efforts should be focused on achieving behavioral change (127) and enhancing patient adherence to the prescribed therapy. Although the physician's office is the most common setting for education and the physician is the most frequent provider of patient education, nurses, respiratory therapists, physical therapists, and other health professionals may also provide education in outpatient, hospital, or home settings.

Education is a key component of comprehensive pulmonary rehabilitation (110, 112, 128). Patients with COPD understand their disease better after education (129), and similar effects have been repeatedly demonstrated in patients with asthma. Research on the efficacy of education as part of pulmonary rehabilitation programs has been limited.

One group of investigators (117) evaluated exercise and quality-of-life outcomes in 76 patients with moderate-to-severe COPD randomized to one of five groups: behavior modification, cognitive modification, cognitive-behavior modification, attention control, and no-treatment control. Patients met with a health professional seven times over a period of 3 mo; the first and last sessions took place at the health care facility, with the remainder in the patient's home. Behavior modification therapy included a contract signed by the patient outlining specific times for walking exercise, muscle relaxation training, and breathing retraining. Cognitive therapy included training to replace negative feelings, thoughts, and behaviors with more positive attitudes. After 3 mo, the three treatment groups increased their treadmill exercise tolerance more than the two control groups. Similar improvements were demonstrated in the Quality of Well-Being Health Status Index and were correlated with exercise compliance and self-efficacy.

Another study found that, after a pulmonary rehabilitation program incorporating principles of adult education, patients demonstrated an increased ability to recognize and treat symptoms, including the use of breathing and relaxation exercises (125). An educational program provided without pulmonary rehabilitation appeared to offer little benefit (130). The educational component of pulmonary rehabilitation prepares patients and significant others to be actively involved in providing care, improves their understanding of the disease process, and teaches practical ways of coping with disabling symptoms; this reliance on the patient and supportive others to assume charge of care is known as *collaborative self-management (129).*

Recognizing diversity of learning styles, the educational component of a rehabilitation program should be custom-tailored for the individual patient. Group discussions and didactic presentations are generally most effective when they include visual information in the form of videos, slides, or overheads; adjunctive printed materials are also helpful, perhaps included in a manual to be referenced at home. Learning does not take place only in the formal classroom setting. Every interaction between health professional and patient should incorporate educational elements, and education should be part of the care of every patient with COPD. This approach need not await the results of the further research needed to confirm and define the specific benefits of education in the comprehensive pulmonary rehabilitation program.

Exercise Training

There is considerable evidence documenting favorable responses to general aerobic exercise training in patients with chronic lung disease (119). Benefits are both physiologic and psychological. In fact, patients experience increased capacity and endurance for exercise and physical activity after rehabilitation, even though lung function may remain unchanged. Exercise training also provides an ideal opportunity for patients to learn their capacity for physical work and to practice and use methods for controlling dyspnea (e.g., breathing retraining techniques taught at the same time).

Many studies have reported benefits of exercise conditioning in patients with COPD. Casaburi (119) reviewed 37 published studies of such training, incorporating a variety of regimens in more than 900 patients. Nearly unanimously, these studies demonstrated improvement in exercise endurance and/or maximum

exercise tolerance. These conclusions are supported by several controlled trials documenting the beneficial effects of exercise training in patients with chronic lung disease (114, 120, 131). Significantly more patients in the exercise groups noted improvement in sense of well-being and decreased breathlessness, cough, and sputum. Significant increases in exercise performance have also been seen on both 12-min walk challenges and maximum cycle ergometer tests in trained patients compared with control subjects.

The basic elements of the exercise prescription are mode, frequency, intensity, and duration. In general, the guidelines for exercise prescription in patients with COPD are adapted from those established for healthy individuals. The program should incorporate activities that involve large-muscle groups and closely relate to daily activities, e.g., walking and cycling. Exercise sessions should take place 3 to 5 d/wk. Intensity and duration are interrelated. Various regimens have been recommended, based on experience in healthy individuals and published studies of patients with COPD. Experience generally indicates that a range of exercise intensities can be selected based on the patient's motivation, tolerable levels of dyspnea and discomfort, and whether the sessions are supervised. Widely differing regimens have been shown to be beneficial; further studies to establish optimal guidelines for patients with COPD would be welcome.

Exercise training is a mandatory component of pulmonary rehabilitation. Patients with COPD should regularly perform aerobic lower-extremity endurance exercises to enhance performance of daily activities and reduce dyspnea. Resistance training is particularly important when weakness of specific muscle groups has been demonstrated.

Upper extremity training. Many patients with COPD report disabling dyspnea associated with daily activities involving the upper extremities, e.g., lifting or grooming, at work levels much lower than for the legs. This is because upper extremity exercise is accompanied by a higher ventilatory demand for a given level of work than lower extremity exercise. Since exercise benefits are generally specific to the muscles and tasks involved in training, basic training primarily involving the lower extremities may not alleviate upper extremity difficulties. Special upper extremity exercises may be important in addressing this problem.

Arm exercise endurance is significantly less than endurance for leg exercise in many patients with severe COPD and may be limited by dyspnea accompanied by dysynchronous thoracoabdominal breathing (115). Simply raising the arms creates increased metabolic demand (increased oxygen consumption, minute ventilation, and diaphragm work). Metabolic and ventilatory requirements for arm exercise decrease after comprehensive pulmonary rehabilitation including arm exercise (132). However, no significant changes on tests of ventilatory muscle performance or simulated activities of daily living have been shown after arm exercise (133).

Upper extremity exercise training should be considered a part of pulmonary rehabilitation. The reduction in oxygen consumption during arm activity that results from such training might be expected to improve dyspnea and allow increased activities of daily living requiring use of the upper extremities; further investigations are needed to confirm these benefits.

Inspiratory muscle training: The potential role of ventilatory muscle weakness and possible fatigue as a cause of ventilatory limitation and respiratory failure in patients with COPD has stimulated attempts to train the ventilatory muscles. Various inspiratory muscle training techniques have been shown to improve the function of these muscles (134). Improvement in general exercise performance after training of only the ventilatory muscles, however, has not been consistently demonstrated — perhaps due to lack of an appropriate training stimulus in many studies.

Selected trials establishing a resistive intensity and/or controlling breathing strategy during training have demonstrated both physiologic and symptomatic improvement (134). Decreased dyspnea has been demonstrated after ventilatory muscle training in patients with COPD compared with untreated control subjects (135). One group of investigators has shown improved symptoms, decreased dyspnea, and improved ability to perform daily activities when inspiratory resistive loading training was added to the pulmonary rehabilitation regimen (136).

At present, there is no simple way to select patients most likely to benefit from inspiratory muscle training. Moreover, there has been no benefit demonstrated from such training compared with aerobic lower extremity exercise conditioning. Thus, although such training may result in improved ventilatory muscle function and/or alleviation of symptoms for some patients, it is not yet clear that this modality is appropriate for routine use in rehabilitation. Additional research is needed to guide selection of patients who would be expected to benefit and to define the association of improved ventilatory muscle performance with improvement in exercise tolerance, daily activities, and other quality-of-life areas.

Psychosocial Support

Many patients experience anxiety, depression, fatigue, coping difficulties, and somatic preoccupation (123), symptoms that may be related to the dyspnea associated with COPD. Inability to work and decreased capacity to participate in social, recreational, and sexual activities are common and often lead to depression. Neuropsychological deficits related to chronic hypoxemia may occur. Patients with chronic hypoxemia also have decreased ability to acquire and retain new information, form new concepts, think flexibly, perform complex perceptual-motor maneuvers, and engage in perceptual discrimination.

Psychosocial intervention and support are considered important components of pulmonary rehabilitation. Since patients with COPD are frequently depressed, a careful evaluation of the patient's psychological status should be performed and the use of antidepressant medications considered in patients with severe depression. In addition to the informal or formal support that patients may receive from others with similar conditions, social support is facilitated by psychosocial sessions with a focus on stress management techniques, including relaxation strategies and cognitive approaches to coping with emotional changes. Group sessions incorporating spouses and other family members may be beneficial.

Psychosocial interventions may also be directed toward modeling appropriate methods for the patient to enlist the help of family and friends, while helping the patient to maintain realistic short-term and long-term goals, especially in the context of family and social relationships. Issues involving sex and sexuality should be explored and discussed (137). Sexual counseling may be recommended when indicated, using the PLISSIT stepwise model, which includes permission-giving (P), limited information (LI), specific suggestions (SS), and intensive therapy (IT).

Breathing Retraining

Diminishing of dyspnea has been a consistent benefit of pulmonary rehabilitation, possibly due in part to the breathing retraining frequently included in rehabilitation programs. The goal is helping the patient to relieve and control breathlessness and to counteract such physiologic abnormalities as hyperinflation related to chronic airflow obstruction.

Retraining techniques include diaphragmatic and pursed-lips breathing to improve the ventilatory pattern (i.e, slow respiratory rate and increase tidal volume), prevent dynamic airway corn-

pression, improve respiratory synchrony of abdominal and thoracic musculature, and improve gas exchange. Review of clinical studies evaluating the effects of such techniques indicates that improvement in clinical symptoms is a more consistent finding than any measurable impact on physiologic parameters. The most consistent physiologic change observed has been an increase in tidal volume and a decrease in respiratory rate; improved oxygenation may also occur.

Although many patients with COPD "discover" pursed-lips breathing on their own, specific instructions can be given to decrease dyspnea, as follows: breathe in slowly and deeply through the nose; purse the lips lightly, as if to whistle; then breathe out slowly through the pursed lips, taking twice as long to exhale as to inhale. Leaning forward, with arms resting on the patient's thighs or on a table or other hard surface, may also help some patients in relieving breathlessness. Diaphragmatic breathing is often taught along with pursed-lips breathing; the patient learns to coordinate expansion of the abdominal wall with inspiration. The value of diaphragmatic breathing has been questioned by studies documenting worsened thoracoabdominal dyssynchrony with this breathing pattern (138).

Elective Ventilatory Assistance

In patients with severe COPD, the standard medical therapy often does not reverse hypercapnia or alleviate the severe dyspnea, diminished stamina, and limited quality of life experienced by these patients. They have an increased mortality rate and are at risk for hospitalization with respiratory acidosis, potentially necessitating mechanical ventilation to reduce Pa_{CO_2}.

Although there have been numerous studies evaluating the efficacy of elective mechanical ventilation in patients with COPD, the results have been variable and the conclusions controversial (139). Decreased respiratory muscle activity has been demonstrated with use of a cuirass, pneumowrap, and ventilation delivered per nasal mask. Thus, it appears that mechanical ventilation can reduce respiratory muscle activity. In addition, short-term use of mechanical ventilation (1 to 7 d) has been shown to reduce Pa_{CO_2} in patients with chronic hypercapnia due to severe COPD. There is no relationship, however, between the degree of respiratory muscle rest achieved with mechanical ventilation and the reduction in Pa_{CO_2}.

Respiratory muscle strength has improved in some studies after elective mechanical ventilation but not in others, and respiratory muscle endurance may also improve. But improved respiratory muscle function may not be the mechanism responsible for reduction in Pa_{CO_2}; it seems more likely that the reduction is related to the increased ventilatory response to inhaled CO, that occurs with mechanical ventilation (140).

Despite the observation of physiologic benefits, it has not been demonstrated that this therapy has any impact on patient symptoms. Shapiro and colleagues (141) randomly assigned 184 patients with COPD to receive active or sham negative pressure ventilation at home for 12 wk. These investigators did not report any diminution in dyspnea or improvement in exercise capacity as measured by a 6-min walk test, even in patients with more severe hypercapnia. But only 29% of the patients had a 50% reduction in diaphragm electromyogram activity, and patients used the ventilator for very limited periods of time during the day.

Routine elective use of ventilatory support in ambulatory patients with COPD with hypercapnia cannot be recommended at this time. Additional investigations are necessary to determine the potential role of this therapy in COPD. Such studies should use less cumbersome methods of ventilation, such as a nasal mask; should define which patients, if any, might benefit from elective ventilation; and should evaluate potential benefits on dyspnea, exercise capacity, and quality of life as well as physiologic measures.

Nonelective Mechanical Ventilation

Patients with COPD who require emergency institution of mechanical ventilation for acute exacerbation may require more than short-term ventilatory assistance. Such patients may not be easily weaned from support because of the severity of the underlying disease and associated altered respiratory mechanics. In such cases, a tracheostomy may be required to assure long-term airway access. There is no simple, reliable way to predict inability to wean from the ventilator, nor is there a precise definition of chronic ventilator-dependency. In most cases, failure to achieve sufficient 24-h ventilation without ventilatory support is a conclusion that can be reached only after multiple weaning trials in a critical care unit. Thus, chronic ventilator dependency in a patient with COPD might be defined as the inability to achieve spontaneous ventilation 24 h a day after repeated unsuccessful attempts to remove the patient from the ventilator. For the best chance of weaning success, attempts should take place when the patient is in optimal medical condition.

Long-term management of patients who require chronic mechanical ventilation raises several health care issues, including high costs, location of appropriate sites for continued care, availability of resources and personnel for that care, and prospects for improving quality of life. The cost of chronic care for a ventilator-assisted patient with COPD in a critical care unit is very high, in terms of both possible use of expensive and limited resources for a relatively stable patient (albeit a patient dependent on high technology) and financial cost to patient and insurer.

Potential sites for continued care of ventilator-assisted individuals include short-term care in specialized but nonintensive care units in acute hospitals and in general hospital medical–surgical areas. Long-term care may be available in chronic hospitals, skilled nursing facilities, group living facilities, and the patient's own home. However, there appear to be inadequate numbers of long-term beds in medical facilities with appropriate resources to care for these individuals. The most appropriate site for long-term care should be carefully chosen for each patient and depends on the patient's respiratory and personal care requirements (e.g., oxygen, suctioning, ventilation, toileting, bathing) and available resources (e.g., family members, skilled nursing, respiratory therapy, electrical power and outlets, insurance and financial resources) to meet those needs (142).

Home Care

COPD is the third most frequent medical diagnosis (after congestive heart failure and stroke) for patients receiving home care. Home care for ventilator-assisted individuals with COPD is effective in selected patients (143), and they may be relatively independent in the home. The life expectancy of patients with COPD in the home is about 50% at 3 yr, and these patients may require rehospitalization for either respiratory or other problems.

The cost-effectiveness of home care for these patients was documented in a recent study (144). Seventeen patients with severe COPD received care from a multi-disciplinary team in a hospital-based home care program. Use of health care resources before and for at least 6 mo after entry into the program showed significant savings of $328 per patient per month due to decreased hospitalizations and emergency room visits.

These findings contrast with results of a randomized controlled study of 300 patients with COPD assigned to receive care for 1 yr using respiratory home care nurses, standard home care, or office care (145). Average annual health care costs for the two home care groups were higher than those for the office care group.

Patients for the study demonstrating reduced health care costs were selected because of their high risk, based on prior hospitalizations (144). This was not a criterion for patient selection in the prospective randomized study that did not demonstrate reduced care costs. Thus, further research is needed.

Inpatient Management of COPD

Although an acute exacerbation of COPD is difficult to define and its pathogenesis is poorly understood, impaired lung function can lead to respiratory failure requiring intubation and mechanical ventilation. Accurate diagnosis in a patient experiencing rapid deterioration of respiratory function may be confounded by underlying myocardial ischemia, congestive heart failure, thromboemboli, or recurrent aspiration, which can simulate an exacerbation of airway disease.

EMERGENCY EVALUATION

The acute exacerbation frequently prompts patient evaluation and initiation of treatment regimens in an office or emergency department. The key components of the history, physical examination, and laboratory evaluation that should be obtained during a moderate-to-severe acute exacerbation to assist the formulation of therapy and the decision for hospital admission are listed in Table 10.

Although acute exacerbations of COPD represent a major cause of hospital admissions in the United States, indications for hospitalization and the purpose of the hospital stay have received little attention. Traditionally, the decision to admit derives from subjective interpretation of clinical features, such as the severity of dyspnea, determination of respiratory failure, short-term response to emergency therapeutic efforts, degree of cor pulmonale, and the presence of complicating features, such as severe bronchitis, pneumonia, or other co-morbid conditions. This approach to decision-making is less than ideal, since up to 28% of patients with an acute exacerbation of COPD who are discharged from an emergency room (ER) have recurrent symptoms within 14 d (146). Additionally, 17% of patients discharged after ER management of COPD will relapse and require hospitalization (147).

Data are also lacking regarding the potential overuse of hospitalization in patients with acute exacerbations of COPD who might have responded to more aggressive outpatient therapy. Furthermore, there is no accepted standard for deciding which surgical or diagnostic procedures in stable patients with COPD require hospitalization and which could be performed on an outpatient basis.

In short, there are presently no guidelines for clinicians in selecting patients for hospital admission on the basis of medical need. The Diagnosis-Related Group (DRG) system uses an analysis of historic experience of similar patients rather than patient-specific prognosis-modifying features. To determine the necessity for admission, Medicare patient review practices of the Health Services Advisory Group, Inc., use criteria that have not been prospectively validated.

Relatively few clinical studies have investigated patient-specific, objective clinical and laboratory features identifying patients with COPD who require hospitalization. General consensus supports the need for hospitalization in patients with severe, acute hypoxemia or acute hypercarbia; however, less extreme arterial blood gas abnormalities do not assist in the decision process (148). Most studies using spirometric values (FEV,, FEV, as a percentage of baseline, FEV, as a percentage of predicted, or change in FEV, after emergency treatment) find a poor correlation with success of ER discharge (146, 147, 149).

Murata and coworkers (149) recently validated in male patients at the Veterans Health Administration Medical Center a multivariate model that identified patients with decompensated COPD who had high and low risks of relapsing after ER management. Factors identifying high-risk patients included a previous emergency visit within 1 wk, the number of doses of nebulized bronchodilators required in the ER, use of home oxygen, previous relapse rate, administration of aminophylline, and use of corticosteroids and antibiotics at the time of ER discharge (149). This study requires validation in women as well as men cared for in other institutions. In addition, the low numbers of study patients in this and other published investigations do not allow subgroup analysis to determine whether hospitalization indications differ for patients with chronic bronchitis and those with emphysema. It is possible that the heterogeneity of COPD and the variety of confounding coexisting conditions may limit the value of hospitalization prediction indices in individual patients.

Prediction of the required duration of hospitalization is further complicated by the numerous conditions that can compound respiratory dysfunction. They include bronchospasm, pulmonary infection, level of airway secretions, inspiratory muscle fatigue, malnutrition, hypoxemia, systemic acidosis, pulmonary embolism, heart failure, and metabolic derangements. It is not surprising, therefore, that no correlation exists between the lengths of hospital stay that were medically required and expected lengths of stay per the assigned DRG in patients with acute COPD exacerbations (150). The actual median length of stay required in patient series to produce maximum benefit is 6 d, with a range of 1 to 57 d (150), which is longer than allowed by the DRG financial incentives to attain shorter hospitalization.

TABLE 10

EMERGENCY ROOM EVALUATION OF PATIENT WITH ACUTE EXACERBATION OF COPD: KEY COMPONENTS

History:
- Baseline respiratory status
- Sputum volume and characteristics
- Duration and progression of symptoms
- Dyspnea severity
- Exercise limitations
- Sleep and eating difficulties
- Home care resources
- Home therapeutic regimen
- Symptoms of co-morbid acute or chronic conditions

Physical examination, evidence of:
- Cor pulmonale
- Bronchospasm
- Pneumonia
- Hemodynamic instability
- Altered mentation
- Paradoxical abdominal retractions
- Use of accessory respiratory muscles
- Acute co-morbid conditions

Laboratory, usually includes:
- ABC
- Chest radiograph (yearly, lateral)
- EKG
- Theophylline level, if outpatient theophylline used

and may include:
- Pulse oximetry monitoring
- EKG monitoring
- Additional studies as indicated (e.g., lung scan, leg venous thrombosis studies)

HOSPITALIZATION CRITERIA

The purpose of hospitalization is to manage the patient's acute decompensation and co-morbid conditions to prevent further deterioration and readmission, which occurs in 7% of patients within 2 wk of hospitalization (149). Additionally, patients require education as to the nature of their disease, correct use of medications, activity modifications, and awareness of appropriate

action in case of future emergency. Plans for clinical reassessment of drug regimens, use of home oxygen, or potential benefits from pulmonary rehabilitation programs should be prepared. Longer hospital stays are required in patients with worse baseline lung function and co-morbid conditions (150). Although based on limited data, emerging patient profiles may allow prediction of duration of hospitalization when confirmed in larger studies.

Duration of hospitalization in COPD depends at least partially on the presence of a multidisciplinary team directing respiratory management. Because of the complex management issues in caring for patients who have COPD with impending or frank respiratory failure, physician specialists with extensive experience in and knowledge of COPD should participate in the care of hospitalized patients who present with underlying stage II or III disease, require mechanical ventilation, develop hypoxemia unresponsive to F_{IO_2} of 0.50 or new-onset hypercarbia, require steroids for more than 48 h to maintain adequate respiratory function, undergo thoracoabdominal surgery, or require specialized techniques to manage copious airway secretions. The length of hospitalization may be shortened with early discharge planning and development of alternate sites of care when patients are being observed during the final stages of pulmonary improvement. A patient care coordinator can direct modifications of the care plan and organize a system of home evaluation to prevent the need for early rehospitalization.

Guidelines

Expert consensus identifies indications for hospital admission that consider the severity of the underlying respiratory dysfunction, progression of symptoms, response to outpatient therapies, existence of co-morbid conditions, necessity of surgical interventions that may affect pulmonary function, and the availability of adequate home care. That consensus is reflected in Table 11. The severity of respiratory dysfunction dictates the further need for admission to an intermediate care unit (ICU) (Table 12). Depending on the resources available within an institution, admission of patients with severe COPD exacerbations to intermediate or special respiratory care units may be appropriate if personnel, skills, and equipment exist to identify and manage acute respiratory failure successfully.

Insufficient clinical data exist to establish the duration of hospitalization in individual patients to achieve maximal benefit. Consensus and limited data support the discharge criteria listed in Table 13. Emerging data suggest that prolonged hospitalization can be avoided and good clinical outcome assured, even in patients with severe disease, when effective discharge planning is combined with coordination of multidisciplinary care and temporary alternative placement, if needed. The complexity of management issues requires that certain patients with moderate-to-severe acute exacerbations be evaluated by a specialist trained in the evaluation and care of patients with COPD.

Because existing guidelines lack adequate research support, additional studies are required to determine precisely which patients with COPD are likely to benefit from admission, as well as the ideal duration of hospitalization.

PHARMACOTHERAPY OF COPD EXACERBATIONS

Inpatient management usually begins in the emergency room. Drug therapy will be tailored to the following variables: (I) the degree of reversible bronchospasm; (2) prior therapy of the patient when stable; (3) recent drug usage and evidence of potential toxicity; (4) the ability of the patient to cooperate in taking inhaled medications; (5) the presence of contraindications to any drug or class of drugs; (6) specific causes or complications related to the exacerbation.

TABLE 11

INDICATIONS FOR HOSPITALIZATION OF PATIENTS WITH COPD

1. Patient has acute exacerbation characterized by increased dyspnea, cough, or sputum production, plus one or more of the following:
   - Inadequate response of symptoms to outpatient management
   - Inability to walk between rooms (patient previously mobile)
   - Inability to eat or sleep due to dyspnea
   - Conclusion by family and/or physician that patient cannot manage at home, with supplementary home care resources not immediately available
   - High-risk co-morbid condition, pulmonary (e.g., pneumonia) or non-pulmonary
   - Prolonged, progressive symptoms before emergency visit
   - Altered mentation
   - Worsening hypoxemia
   - New or worsening hypercarbia
2. Patient has new or worsening corpulmonale unresponsive to outpatient management
3. Planned invasive surgical or diagnostic procedure requires analgesics or sedatives that may worsen pulmonary function
4. Co-morbid condition, e.g., severe steroid myopathy or acute vertebral compression fractures, has worsened pulmonary function

Other indications for hospitalization may apply to patients undergoing pulmonary rehabilitation (see Pulmonary Rehabilitation).

Condition and Considerations

Exacerbations may be provoked by inhalation of environmental irritants, gastroesophageal reflux or aspiration, viral and bacterial infections, intercurrent illnesses leading to debility or weakness, or cardiopulmonary events, such as heart failure, arrhythmias, or pulmonary emboli. Increased work of breathing, ineffective cough, mucostasis, progressive hypoxemia/hypercarbia, confusion, and fatigue may be associated with impaired use of drug therapy and resulting overmedication or undermedication. In an exacerbation, underlying general problems, such as nausea and progressive weakness, as well as specific abnormalities, such as pneumonia or fluid and electrolyte imbalance, must be addressed.

Exacerbations in COPD may cause nonspecific complaints, such as malaise, insomnia or sleepiness, fatigue, and depression, or more specific difficulties, such as increased dyspnea, productive cough with altered sputum, fever, leg edema, or obtundation. Management is facilitated if the patient's history, findings, and drug regimen are known; lack of this information may justify more vigorous intervention, including early enddtracheal intubation and ventilatory support. The physician needs to determine the recent pattern of drug use and the possible overuse or misuse of drugs such as theophylline, antibiotics, or sedatives. Individual judgment is needed to determine if the patient should be admitted to the hospital or to the ICU. Inability of the patient to cooperate in taking aerosol medications and the finding of marked impairment in vital signs are clear indications for ICU management. Initial choices in drugs may have to be empiric, but it is usually advisable to follow a step-care plan in the first few hours of therapy (151, 152).

TABLE 12

INDICATIONS FOR ICU ADMISSION OF PATIENTS WITH ACUTE COPD EXACERBATION

1. Severe dyspnea that responds inadequately to initial emergency therapy
2. Confusion, lethargy, or respiratory muscle fatigue (the last characterized by paradoxical diaphragmatic motion)
3. Persistent or worsening hypoxemia despite supplemental oxygen or severe/worsening respiratory acidosis (pH < 7.30)
4. Assisted mechanical ventilation is required, whether by means of endotracheal tube or noninvasive technique

TABLE 13

DISCHARGE CRITERIA FOR PATIENTS WITH ACUTE EXACERBATIONS OF COPD

- Inhaled beta-agonist therapy is required no more frequently than every 4 h
- Patient, if previously ambulatory, is able to walk across room
- Patient is able to eat and sleep without frequent awakening by dyspnea
- Reactive airway disease, if present, is under stable control
- Patient has been clinically stable, off parenteral therapy, for 12-24 h
- ABC has been stable for 12-24 h
- Patient (or home caregiver) fully understands correct use of medications
- Follow-up and home care arrangements have been completed (e.g., visiting nurse, oxygen delivery, meal provisions)
- Patient, family, and physician are confident patient can manage successfully

A patient who does not fully meet criteria for home discharge may be considered for discharge to a nonacute care facility for observation during the final resolution of symptoms.

Most patients with COPD exacerbations respond to anticholinergic aerosols and beta-agonists, and adequate dosages of these drugs are essential components of inpatient care. Theophylline may be given as a primary drug or in addition to other bronchodilators; dosage must be carefully calculated and excessive dosing avoided. Combination bronchodilator therapy can be beneficial in severe disease. Systemic corticosteriods may be added to the regimen if the patient is very ill, shows an inadequate response to bronchodilators, or has previously responded to steroids. A change in sputum color or consistency during an exacerbation of COPD is a standard indication for antibiotic therapy; mucokinetic drugs may also be given, although their value has not been firmly established in COPD. Oxygen is generally needed when the Pa_{O_2} is less than 60 mm Hg, particularly if there is cardiac irritability. Any additional problem, such as heart failure or renal failure, must be taken into account, and treatment must be modified appropriately.

Clinical Guidelines

Stepwise therapy is recommended, with initial emphasis on drugs that can be expected to produce a rapid response.

1. Identify cause of exacerbation, e.g., infection or sedative drug narcosis, and direct specific therapy accordingly.

2. A beta$_2$-agonist aerosol is usually given as the first step in management of acute, severe COPD. Patients can be treated with an inhalant solution given by nebulization, or a metered dose inhaler (MDI) with a spacer can be used. These drugs have a reduced functional half-life in exacerbations of COPD and therefore they may be given every 30 to 60 min if tolerated. The safety and value of continuous nebulization have not been established in COPD (153, 154). Long-acting aerosols are currently not approved for use in exacerbations of COPD. Subcutaneous dosing of favorable agents is recommended only if aerosol delivery is not feasible; intravenous administration is not acceptable practice at present, although it is favored in some countries when aerosol therapy is not possible in a life-threatening situation. Dosages of sympathomimetic bronchodilators are summarized in Table 14.

3. Anticholinergic aerosols have not been adequately assessed as a first step in COPD, although they are often favored when the history indicates poor responsiveness to beta-agonists. The chosen agent is given using an MDI with a spacer or as an inhalant solution by nebulization. Ipratropium is usually employed; although an upper dosage limit has not been established, the drug is generally well-tolerated, and higher dosages than usual can be given to a poorly responsive patient (155). The prolonged half-life, however, means that repeat doses need not usually be given more often than every 4 to 8 h.

4. Combination therapy with a beta$_2$-agonist and ipratropium can be employed (156, 157), although their combined use has not been clearly demonstrated to be more effective than larger doses of each. There is evidence to suggest that they may act synergistically, however, and there is no increase in adverse effects with combined usage. After the patient has improved, lower dosages of ipratropium and the selected beta-agonist may be given less frequently. Any synergistic effect may not be noted after the patient stabilizes (158), and one of the two drugs may be discontinued, particularly if side effects are a problem (159).

5. Theophylline can be added if aerosol therapy cannot be given or proves inadequate. The drug can be given as intravenous aminophylline in a severe exacerbation; suggested dosages are noted in Table 15. Use serum levels as a guide to avoid haz-

TABLE 14

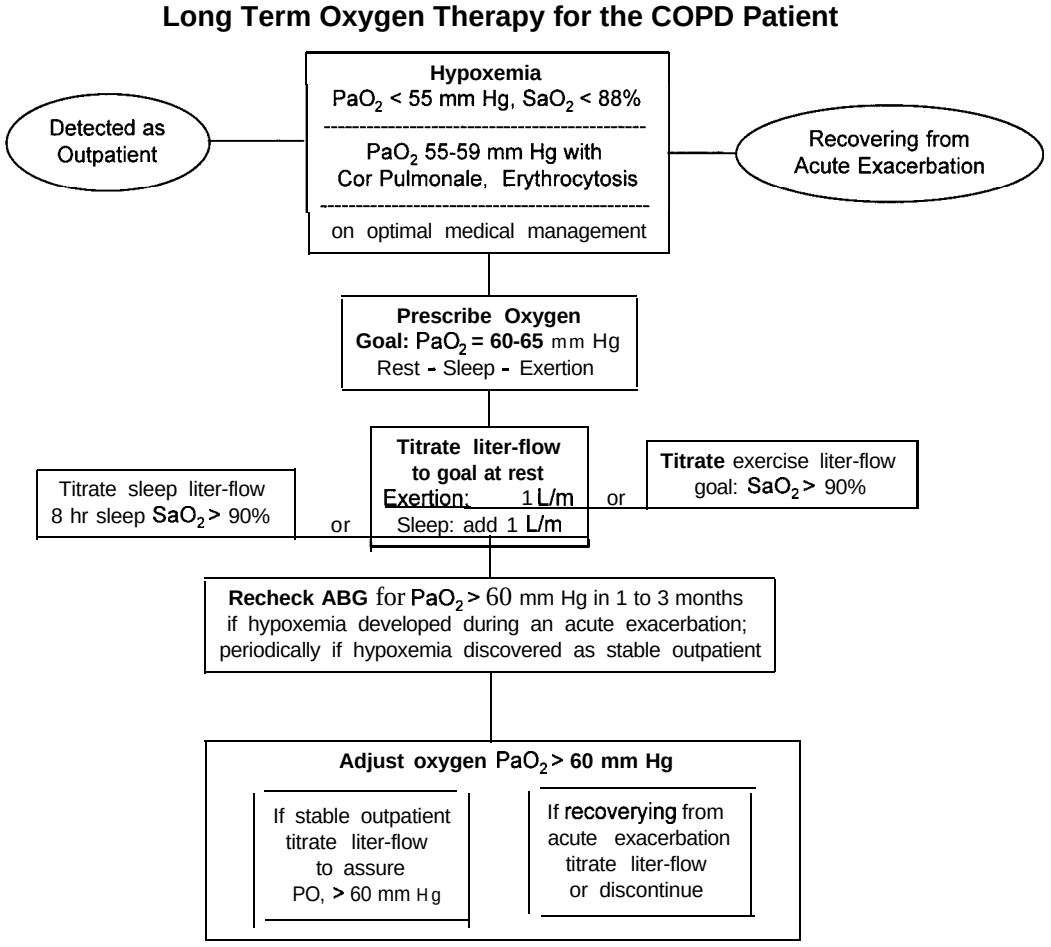
SYMPATHOMIMETIC BRONCHODILATOR DOSAGES

	MDI Dose	MDI Puffs	Standard Doses of Inhalant Solutions*	Equivalent MDI Puffs from Inhalant Dose*
Epinephrine (Adrenalin, Primatene, *et al.*)	0.16-0.15 mg	2-4 every 4-6 h	0.25–0.5 ml (1.25-l 1 mg)	5–70
Isoproterenol (Isuprel, Medihaler-Iso)	0.08-0.13 mg	2-4 every 4-6 h	0.25-0.5 ml (1.25–2.5 mg)	10-30
Isoetharine (Bronkometer, Bronkosol, Arm-a-Med, *et al.*)	0.34 mg	l-2 every 4 h	0.25-l ml (2.5-10 mg)† or 1.25-S ml (2.5-S mg)†	7-30
Metaproterenol (Alupent, Metaprel)	0.65 mg	1-2 every 3-4 h	0.2-0.3 ml (10–15 mg)† or 2-5 ml (10 mg)† or 2-5 ml (15 mg)†	15-23
Terbutaline (Brethaire, Brethine)‡	0.20 mg	2 every 4-6 h	0.25–0.5 ml (0.25–0.5 mg)	–
Albuterol (Proventil, Ventolin)	0.09 mg	1-2 every 4-6 h	0.5 ml (2.5 mg)† or 3.0 ml (2.5 mg)†	27
Pirbuterol (Maxair)	0.20 mg	l-2 every 4-6 h	–	–
Bitolterol (Tornalate)	0.37 mg	2 every 4-8 h	0.25-l ml (0.5-2 mg)	1-5
Salmeterol (Serevent)	0.02 mg	2 every 12 h	–	–

*Unit dose is standard dose recommended for adults. Amount is usually available in 0.25-2.5 ml, and percentage delivered to lungs depends on both nebulizer and breathing technique used.

† Dosage depends on brand.

‡ Marketed for subcutaneous use.



ardous overdosing. In most patients, a theophylline level of 8 to 12 μg/ml is appropriate; occasionally patients benefit from higher levels, up to 18 to 20 μg/ml. When the patient improves, oral long-acting theophylline can be substituted, using 80% of the daily dose of aminophylline. When the change is to be made, the appropriate dose of theophylline should be given at the appropriate time of day (e.g., 8:00 A.M. or 8:00 P.M.), and the intravenous administration should then be discontinued. Theophylline has been shown to be of value in exacerbations of COPD, but overdosage and toxicity are avoided (160, 161).

6. Corticosteroids can be useful if there is an asthmatic component in a patient who demonstrates responsiveness to beta-agonist therapy, although there is limited information supporting the use of intravenous or oral steroids in the management of COPD exacerbations (162). It is vital to avoid prolonged high-dose steroid therapy in those patients who show little improvement, because such severe complications as avascular necrosis of the ends of long bones can follow after a few weeks of therapy. Careful observation and spirometric evaluation are needed to prove the continuing benefit of steroids after a course of 1 to 2 wk; rapid weaning must be accomplished if possible, and the drug must be stopped if there is no clear objective evidence of improvement. For continuing therapy in a responder, steroids are usually given orally, since intramuscular or aerosol administration have not been proved to be of value in COPD (163).

TABLE 15

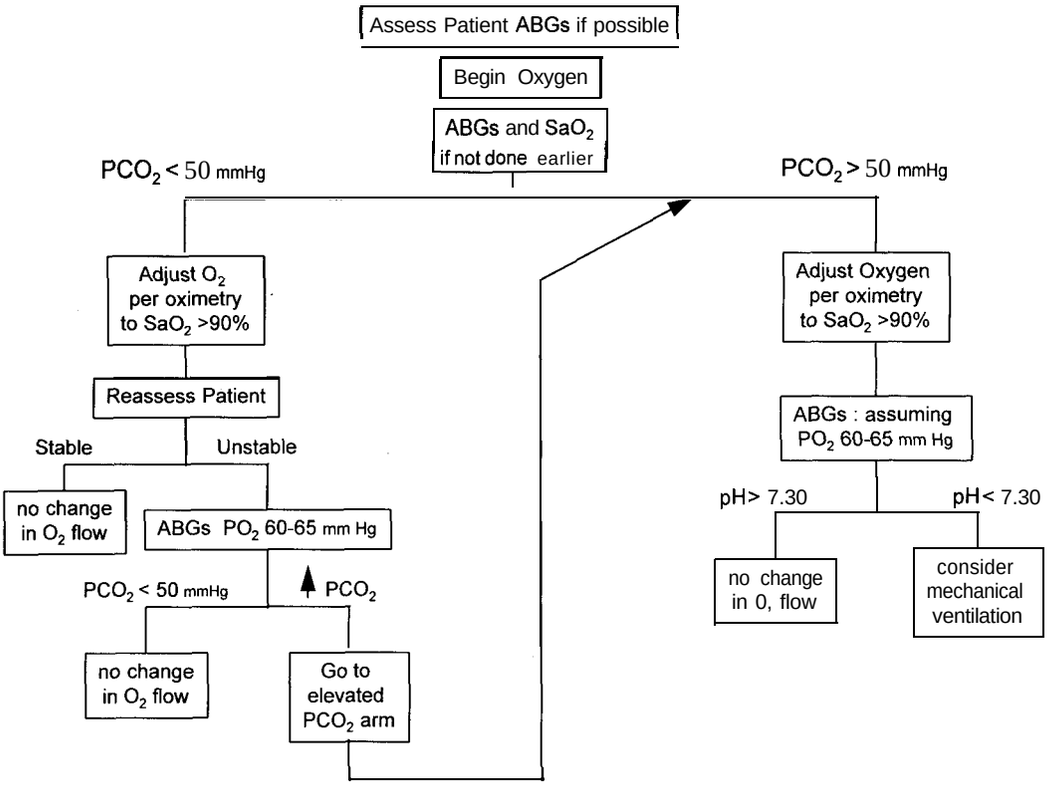
SUGGESTED **AMINOPHYLLINE** DOSAGES

1. Initial dose: 2.5-5 mg/kg (loading); give Over course of 30 min
2. After 30 min: 3 mg/kg (second loading), if needed; give slowly
3. Subsequently: maintenance, e.g., 0.5 mg/kg per hour; modify as needed, based on symptoms or serum levels

7. Abnormal mucus usually provides a rationale for a course of antibiotic therapy; amoxicillin, trimethoprim-sulfamethoxazole, doxycycline, or erythromycin may be chosen. It has been shown that such agents may be of some help in resolving an exacerbation, but they have more value in decreasing the risk of further deterioration (164). In severe exacerbations, a broad-spectrum penicillin preparation or a cephalosporin may be preferred to provide coverage of resistant organisms. Sputum culture can help direct therapy in such cases, particularly if prior antibiotic therapy has recently been given or the patient has lived in a nursing home. Mucokinetic agents, such as acetylcysteine or iodides, have not been shown to be effective in exacerbations of COPD. Preliminary evidence suggests that DNAse may be of value. Failure to improve mucociliary clearance is an important factor leading to endotracheal intubation and mechanical ventilation.

8. Sedation and pain management must be provided to many seriously ill patients with respiratory depression, including those with COPD. Fortunately, tolerance to the effects of narcotics and sedatives in depressing the respiratory center usually occurs more quickly than does tolerance to the desired beneficial effect (165). Thus, these drugs can be used in patients with COPD and the dosage slowly increased over several days to achieve the desired effect. Renal insufficiency may occur as part of the aging process and can markedly prolong the effect of drugs; its presence dictates the choice of an agent with a shorter half-life. If an overdose is inadvertently given, the patient may require respiratory support and a pharmacologic antagonist. In contrast, marked

Algorithm for Correcting Hypoxemia in the Acutely Ill COPD Patient



sedation may be required in agitated ventilated patients, and in some cases, pharmacologic paralysis will be needed (166). Haloperidol is of value for agitated or confused patients, because it has little if any respiratory depressant effect.

Because it is important to ensure the comfort and safety of the patient, undertreatment can be as harmful as overtreatment. In terminal management, appropriate use of narcosis or sedation must be attempted when severe distress necessitates such treatment. Dyspnea, a major symptom, may be helped by benzodiazepines or narcotics; these drugs need not be withheld when indicated to relieve severe, persisting discomfort, even though there is a risk of shortening the patient's life (167).

Much research remains to be carried out in this area. More information is needed regarding appropriate minimal and maximal dosages for established bronchodilator drugs, as well as the value of drug combinations. Dosage changes and optimal delivery methods need to be investigated in endotracheally intubated patients receiving ventilator support. The possible value of mucokinetics, surfactants, and lung lavage to correct mucostasis has not been adequately addressed in ventilated patients with COPD. Although COPD is associated with airway inflammation, criteria for the use of steroids and other anti-inflammatory drugs have not been established. The possible roles of other agents, such as respiratory-center stimulants, sedatives, hypnotics, and euphoriants, need to be further evaluated. The use of pharmacologic relief for distressing terminal symptoms deserves more attention.

MOBILIZATION OF SECRETIONS

Mucus hypersecretion and impaired tracheobronchial clearance are frequent in patients with COPD. Although increased airway secretions may correlate weakly with airflow obstruction, chronic mucus hypersecretion does correlate with hospital admissions for acute exacerbations of COPD (168) and may contribute to the risk of death in patients with severe ventilatory impairment (169).

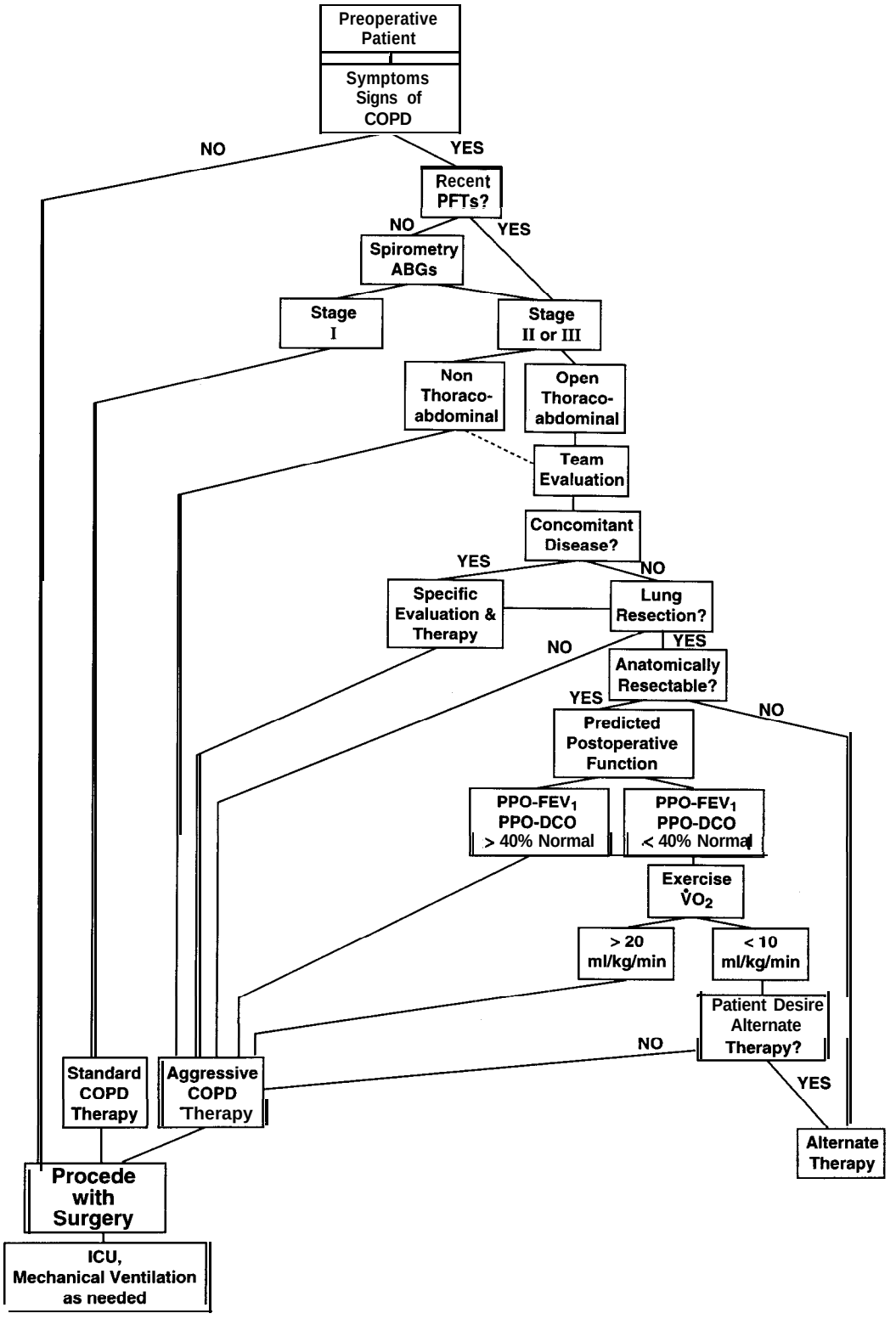
During acute COPD exacerbations, many factors, such as viral and bacterial airway infections, stimulate increased mucus production, alter mucus viscoelastic properties, and impair airway mucociliary clearance mechanisms. Treatment is commonly directed toward enhancing airway secretion clearance. The efficacy of these techniques in patients with chronic bronchitis and emphysema has often been inferred from investigations of patients with cystic fibrosis and bronchiectasis. Scant scientific evidence supports their application in hospitalized patients with acute exacerbations of COPD uncomplicated by bronchiectasis.

Directed Coughing

During acute exacerbations of COPD, nonintubated patients may cough repeatedly in an ineffective manner. Patients can be coached to use a controlled cough or a forced expiratory technique (known as "huff coughing"). Controlled coughing consists of a slow, maximal inspiration and breath-holding for several seconds, followed by two or three coughs. The forced expiratory technique consists of one or two forced exhalations ("huffs") from mid to low lung volumes, with the glottis open. "Huff coughing" avoids the dynamic airway collapse, bronchoconstriction, and patient fatigue associated with undirected forkful coughing. Although beneficial in patients with cystic fibrosis and applied without supporting data in patients with stable COPD, these techniques are difficult to use with dyspneic patients during acute COPD exacerbations and provide unproven benefits in this clinical setting.

Physical Methods

Although *chest physiotherapy with postural drainage,* with or without chest percussion and/or vibration, has been considered a standard approach to patients with emphysema and chronic bronchitis, bronchiectasis, and cystic fibrosis, its value in hospitalized patients with acute exacerbations of COPD has not been documented. Trials of postural drainage in patients acutely ill



with COPD have failed to show a positive effect on sputum volume, gas exchange, or spirometric measurements (170). Chest wall percussion and vibration used with postural drainage similarly lack scientific support. Furthermore, in patients acutely ill with COPD, chest percussion and vibration can cause a transient decrease in FEV_1 and an increase in FRC as a result of acute bronchoconstriction (171). As shown in patients with cystic fibrosis or pneumonia, no clear evidence supports the superiority of manual versus mechanical methods.

In patients with cystic fibrosis, the benefits of postural drainage are limited to patients who expectorate at least 25 ml of sputum per day (172). Extrapolating from these observations, it is recommended that postural drainage, with or without chest percussion or vibration, should be limited to hospitalized patients with COPD whose sputum production also exceeds 25 ml/d. Firmer data from patients without COPD support the role of chest physiotherapy in patients whose course is complicated by mucus plugging with lobar atelectasis (173).

Intermittentpositivepressure breathing (IPPB) has been abandoned in the care of patients with COPD, because no scientific evidence supports its use as an aid either in promoting clearance of airway secretions or in delivering aerosolized medications.

Positive expiratory pressure (PEP) techniques have recently been prescribed to facilitate secretion clearance by simulating the effects of continuous positive airway pressure face mask systems. With these techniques, patients exhale against a fixed-orifice resistor, generating pressures that range from 10 to 20 cm H_2O (174). Although some, but not all, reports indicate improved airway clearance with PEP in patients with cystic fibrosis, its value in stable patients with chronic bronchitis remains unclear (175).

No objective evidence confirms benefits from *inhalation of aerosolized water or saline* via mask or mouthpiece. Because only a small portion of aerosolized water droplets reaches the lower airways, sufficient volumes of water or saline cannot be administered by jet nebulization alone to liquefy airway secretions. Furthermore, bland aerosols are potentially dangerous, they may produce airway irritation that can increase bronchospasm and present a risk of nosocomial pneumonia. One study (176) observed marginally enhanced sputum production when 5 min of aerosolized saline preceded chest physiotherapy, but the sample size was small, and other variables may have contributed to improved mucociliary clearance. However, bland aerosols provide benefit in patients with artificial airways who have COPD to prevent inspissation of airway secretions.

Although there have been suggestions for systemically overhydrating patients with acute exacerbations of COPD, this practice cannot be supported with data (177).

Nasotrachealsuctioning in the nonintubated patient with respiratory distress is seldom indicated. It is a traumatic and uncomfortable procedure that may impair ventilatory function and exhaust patients with borderline ventilatory reserve. Its very short-term or infrequent use should be limited to patients who may be able to avoid endotracheal intubation and mechanical ventilation if relieved of excessive airway secretions.

For patients hospitalized with COPD who require frequent nasotracheal suctioning, some centers advocate a percutaneous temporary "mini-tracheotomy," which provides airway access for repeated nontraumatic suctioning with a 10 Fr suction catheter (178). Catheter misplacement and airway hemorrhage are important potential complications of the procedure. There have been no studies examining clinical outcome compared with noninvasive suctioning techniques or late airway complications in patients treated with mini-tracheotomy.

Clinical Guidelines

Controlled coughing and "huff coughing" techniques are of possible benefit to hospitalized patients with COPD with ineffective coughing. Although postural drainage, chest percussion, and chest vibration have not been shown to benefit patients with COPD, these maneuvers may be used- with careful monitoring — after pretreatment with inhaled bronchodilators in patients with more than 25 ml of expectorated sputum a day.

IPPB is no longer indicated in most patients with COPD. PEP techniques may possibly enhance airway clearance but require further investigation. Bland aerosol therapy and systemic hydration beyond euvolemia do not enhance liquefaction of airway secretions in nonintubated patients.

Nasotracheal suctioning of nonintubated patients should be generally avoided or limited to short-term use. Some centers advocate mini-tracheotomy to provide temporary access for airway suctioning in selected patients.

A summary of possible measures and their present status is found in Table 16. Most of these measures lack adequate investigative support and are used because of demonstrated benefit in patients with cystic fibrosis or bronchiectasis. Research efforts should be focused on methods that are both effective and inexpensive, including patient education and techniques such as PEP, which can be self-administered using low-cost equipment.

TABLE 16

MEASURES TO MOBILIZE AIRWAY SECRETIONS IN HOSPITALIZED PATIENTS WITH COPD

- Directed coughing, "huff coughing." Benefit extrapolated from experience in cystic fibrosis
- Chest physiotherapy: manual or mechanical chest percussion and postural drainage. Benefit extrapolated from experience in cystic fibrosis. Can cause transient fall in FEV_1. Assumed role limited to patients with > 25 ml sputum per day or lobar atelectasis from mucus plugging
- Intermittent positive pressure breathing (IPPB). Not indicated; no proven benefit in COPD
- Positive expiratory pressure (PEP). Benefit extrapolated from experience in cystic fibrosis. No reported experience in acute exacerbations of COPD
- Bland aerosol therapy. No demonstrated benefit in COPD unless artificial airway is in place. May cause bronchospasm in nonintubated patients.
- Systemic hydration. No demonstrated benefit beyond repletion of intravascular volume to euvolemia.
- Nasotracheal suctioning. Limited benefit; tolerated only for short periods
- Mini-tracheotomy. Possible temporary benefit in patients with persistent airway secretions causing respiratory deterioration

ASSISTED VENTILATION

Progressive airflow obstruction may impair oxygenation and/or ventilation to the degree that assisted ventilation will be required. The goals of assisted ventilation in this clinical context are to support the patient over the short term, during the course of acute respiratory failure, and to enhance gas exchange and functional status in patients with chronically impaired ventilation.

Although no objective guidelines exist for determining the ideal time to initiate ventilatory support, that support will benefit two classes of patients: (I) those who have experienced progressive worsening of respiratory acidosis and/or altered mental status, despite aggressive pharmacologic and nonventilatory support; and (2) those with clinically significant hypoxemia, which has developed despite the provision of supplemental oxygen by usual techniques. In deciding to initiate assisted ventilation, the clinician must select from an array of ventilatory modes and appliances, including endotracheal tube, oral or nasal mask ventilation, and negative pressure ventilation.

Airway Access

Translaryngeal intubation provides a secure airway for positive pressure ventilation as well as a route for tracheobronchial suctioning in patients with excessive airway secretions. The decision to intubate through an oral or nasal route depends on the skills of the person in charge of the procedure and patient-specific features that may obviate one route or the other (e.g., micrognathia, nasal polyps, and bleeding diathesis with epistaxis).

Intubated patients with COPD may benefit from tracheotomy at some time during the course of respiratory failure (179). Because no study confirms that duration of translaryngeal intubation correlates with the incidence of laryngotracheal complications, no arbitrary limits to translaryngeal intubation based on safety issues exist to guide the timing of tracheotomy (180). Available clinical data clearly dictate neither special efforts to avoid tracheotomy based on unacceptable complications, nor are early applications of the procedure justified by definite benefits.

Patients with COPD should be selected for tracheotomy when weaning from mechanical ventilation appears distant and antic-

ipated benefits of the procedure appear to outweigh its immediate surgical and long-term risks. However, it is rarely justifiable in patients with COPD to prolong translaryngeal intubation beyond 14 d, because the likelihood of rapid weaning markedly diminishes after that time. Potential benefits of tracheotomy include increased patient comfort and mobility, promotion of transfer to an ICU, expanded ability to eat, enhanced verbal communication, avoidance of direct laryngeal injury, and improved removal of secretions. In short, there are no clear, valid guidelines. The decision to perform a tracheotomy requires careful clinical judgment.

Mechanical Ventilation

Assisted ventilation should be considered for patients with acute exacerbations of COPD when pharmacologic and other nonventilatory treatments fail to reverse clinically significant respiratory failure. Indications for initiating assisted ventilation during acute COPD exacerbations include signs of respiratory muscle fatigue, worsening respiratory acidosis, and/or deteriorating mental status. Although several investigators have reported success with negative pressure ventilation, most studies advocate positive pressure inflation for acute exacerbations of COPD (181). Additionally, negative pressure ventilation may cause upper airway obstruction and arterial oxygen desaturation (when upper airway muscle activation is asynchronous with negative pressure breaths). Its role in managing patients with COPD has therefore been questioned (181, 182).

The main goals of assisted positive pressure ventilation in acute respiratory failure complicating COPD are the resting of ventilatory muscles and the restoration of gas exchange to a stable baseline. At the same time, the clinician must aim to avoid complications associated with mechanical ventilation and should initiate weaning and discontinuation of mechanical ventilation as soon as possible.

Major risks associated with assisted positive pressure ventilation include ventilator-associated pneumonia, pulmonary barotrauma, and laryngotracheal complications associated with intubation and/or tracheotomy. In addition to these general hazards, there are three specific pitfalls in ventilating patients with COPD. One is overventilation, resulting in acute respiratory alkalemia, especially in patients with chronic hypercapnia. A second is initiation of complex pulmonary and cardiovascular interactions that may result in systemic hypotension. The third is creation of intrinsic positive end-expiratory pressure (PEEP), or "auto-PEEP," especially if expiratory time is inadequate or if dynamic airflow obstruction exists (183).

Auto-PEEP has been reported to occur in up to 39% of mechanically ventilated patients (184). Because COPD predisposes to the development of auto-PEEP, and auto-PEEP can have the same adverse consequences as applied PEEP (e.g., decreased venous return, the promotion of barotrauma, and impaired inspiratory effort due to expiratory pressure that must be overcome before inspiration begins) recognizing and minimizing auto-PEEP is important. Maneuvers to diminish auto-PEEP include: (1) treating airflow obstruction; (2) increasing expiration time, e.g., by decreasing respiratory rate, increasing inspiratory flow rates to avoid a disadvantageous inspiratory:expiratory (I:E) ratio, and employing a large-caliber endotracheal tube; and (3) reducing compressible volume in the ventilator circuit (185).

The three ventilatory modes most widely used for managing patients with COPD are assist-control ventilation (ACV), intermittent mandatory ventilation (IMV), and pressure support ventilation (PSV). Because some, though not all, clinical reports indicate that PSV provides increased patient comfort (186), promotes patient synchrony with the ventilator, and may accelerate weaning (187), it may be a particularly valuable mode of ventilatory support for stabilized patients with COPD and acute respiratory failure who maintain adequate ventilatory drive. No direct evidence exists, however, that patient outcome is improved with the use of PSV compared with volume-cycled modes of mechanical ventilation.

Noninvasive Ventilation

Translaryngeal intubation presents risks of nosocomial pneumonia, laryngotracheal injury, and bacterial sinusitis; it also interferes with the patient's capacity for verbal communication (188). The advent of noninvasive assisted ventilation may offer an alternative to intubation in some patients with COPD and acute respiratory failure. The weight of available evidence suggests that positive pressure noninvasive techniques unload respiratory muscles (182) and avoid upper airway obstruction more effectively than negative pressure techniques.

Noninvasive positive pressure ventilation for acute exacerbation of COPD has been examined in several studies, using both facial and nasal masks in conjunction with volume-cycled ventilation, bilevel positive airway pressure (BiPAP), and pressure support modes (189, 190). Although available studies suggest a pooled success rate of 76% in patients with acute respiratory failure complicating COPD, the reported experience is based on small patient numbers, and failure rates up to 40% have been reported in individual studies (181). Comparison studies with intubation and mechanical ventilation have not demonstrated an improved clinical outcome in terms of patient survival. The maximal duration of successful ventilatory support using noninvasive positive pressure ventilation has been brief, usually 7 d or less.

Primary use of noninvasive techniques for respiratory failure in patients with COPD should be reserved for centers with adequate expertise and patient supervision to allow safe implementation. Patient features that should discourage considering noninvasive ventilation for acute COPD exacerbations include hemodynamic instability, copious secretions, inability to defend the airway, poor cooperation with the technique, or impaired mental status.

The following are necessary to ensure the success and safety of noninvasive positive pressure techniques: (I) institutional experience and extensive preparedness for noninvasive ventilation by physicians, nurses, and respiratory care practitioners; (2) adequate unit staffing to manage the techniques, which require close patient monitoring, frequent bedside skilled care, and preparedness for emergent intubation; and (3) the patient's mental alertness, tolerance of noninvasive appliances (i.e., without agitation), hemodynamic stability, capability to control the airway and to clear secretions, and absence of copious airway secretions.

In the absence of these safeguards of success, intubation with positive pressure ventilation remains the therapy of choice for acute respiratory failure. Patients managed with noninvasive assisted positive pressure ventilation require close supervision to assess response to therapy and the ability to proceed promptly with intubation should noninvasive support fail (181, 191).

Weaning from Mechanical Ventilation

Many patients with COPD who undergo mechanical ventilation for acute bronchospasm, fluid overload, oversedation, or inadvertent hyperoxygenation may experience successful extubation without going through a period of weaning. However, some patients with COPD intubated for respiratory failure require gradual weaning. The most important factors that determine the ability of patients to wean from prolonged mechanical ventilation are neuromuscular reserve capacity relative to respiratory load, cardiovascular performance, oxygenation, and psychological factors. The relative contribution of each of these factors in wean-

ing varies among patients. Although some clinicians believe that impaired neuromuscular capacity, in the form of respiratory muscle fatigue, plays a major role in determining the success or failure of the weaning process, no studies have confirmed this impression. Nor are there reliable techniques to detect and quantify respiratory muscle fatigue and endurance in ventilator-dependent patients.

A variety of objective physiological indices (maximal inspiratory pressure, vital capacity, respiratory frequency/tidal volume, P0.1) are designed to evaluate patients for extubation. When measured values are better than anticipated from the bedside observation of a patient's status, these indices may identify which patients with COPD can undergo discontinuance of ventilator support earlier than otherwise thought possible. Conversely, severely deranged indices may obviate futile weaning efforts that have no chance of being well-tolerated. Aside from these situations, however, no clear physiologic indices assist the selection of patients for weaning, determination of the rapidity of weaning, or identification of the ideal weaning method.

Available techniques for weaning patients with COPD from mechanical ventilation include assist-control ventilation with T-piece trials, IMV, and PSV. IMV and PSV offer theoretical advantages: they provide partial support when the patient is connected to the ventilator, and they present less opportunity for barotrauma. There is insufficient evidence, however, to establish that weaning is accelerated or outcomes improved with any particular weaning technique now known.

General Clinical Guidelines

Translaryngeal intubation through the nose or mouth with positive pressure ventilation remains the primary approach to assisted ventilation in patients with acute exacerbations of COPD. There is no ideal time to convert patients from translaryngeal intubation to a tracheotomy when prolonged airway access is required. Consensus indicates that the need for tracheotomy should be anticipated and the procedure performed when the advantages of tracheotomy appear to outweigh its risks. Prolongation of translaryngeal intubation beyond 14 d is justifiable only infrequently.

The mode of mechanical ventilation should be determined on the basis of institutional experience and perceived patient benefit. Although PSV has theoretical benefits and some emerging clinical investigative support, further experience is needed to determine the relative value of the available modes of ventilatory support. Regardless of the mode selected, special effort should be expended to minimize auto-PEEP, normalize pH, avoid alkalemia, maintain Pa_{CO_2} values equivalent to those achievable by the patient when weaning is initiated, and direct aggressive respiratory, general medical, psychological, and physical therapy support to promote successful weaning.

No physiological indices reliably identify patients who can tolerate weaning or establish an ideal weaning technique. Some theoretical benefits and limited clinical data support the possible advantages of PSV for weaning patients with COPD; consensus indicates, however, that T-piece trials, IMV, and variable combinations of these three techniques, when expertly applied, are equivalent in weaning patients from mechanical ventilation.

The use of noninvasive modes of positive pressure ventilation should be reserved for centers with extensive experience with these techniques and should be discouraged in patients with hemodynamic instability, poor airway control, excessive secretions, altered mentation, or an inability to cooperate. Present experience does not support the role of negative pressure ventilatory techniques for patients with COPD and acute respiratory failure.

Needed Research

Greater understanding of the risks and benefits of tracheotomy specifically related to patients with COPD is required to determine its role in ventilatory support and accelerating weaning from mechanical ventilation. Comparative trials of PSV and other new ventilatory modes relative to standard positive pressure techniques are required to identify an ideal ventilatory approach to patients with COPD and acute respiratory failure. These trials should include considerations of patient comfort and cost effectiveness. Although the initial clinical trials of noninvasive positive pressure support have created enthusiasm for these techniques, additional comparative trials with standard approaches are required to establish their role in management and to identify patient-specific features that improve their success.

Continued effort is required to discover new techniques to accelerate weaning from mechanical ventilation and to identify patients who can undergo weaning and discontinuance of mechanical ventilation with a high likelihood of success. Greater understanding is also needed of the relationship between ventilatory load and ventilatory muscle performance, in addition to the other factors that limit spontaneous ventilation and an ability to wean. Continued efforts to develop consensus among experts on mechanical ventilation and to disseminate information (192) promise to improve the care of patients with COPD and respiratory failure.

INPATIENT OXYGEN THERAPY

The most important consequence of hypoxemia is tissue hypoxia. Hence, the first responsibility of the physician is to correct or prevent life-threatening hypoxemia. Ideally, an arterial blood gas might be obtained before starting oxygen, but this is not always possible. Moreover, in preserving cellular oxygenation, the clinician must also consider the other oxygen transport variables, including adequate hemoglobin, cardiac output, and the distribution of tissue perfusion.

Oxygen Delivery Methods

The most common oxygen delivery method in the hospital setting is the ***standard dual-prong nasal cannula.*** It is inexpensive, relatively comfortable, and accepted by most patients. The F_{IO_2}, using the nasal cannula, is affected by the geometry of the nose, mouth breathing, ventilatory rate, tidal volume, respiratory pattern, and oxygen flow setting. The F_{IO_2} thus varies from moment to moment but can be approximately stated as follows: F_{IO_2} = 20% + (4 x oxygen liter flow).

As noted, ventilatory rate and pattern affect the F_{IO_2}. This is because the slower inspiratory flow of room air causes less dilution of the constant (fixed) flow of oxygen. Additionally, a high dead space-to-tidal-volume ratio (Vd/Vt) will reduce the efficacy of nasal oxygen delivery.

The ***simple face mask,*** with a mask volume of 100 to 300 ml, will deliver an F_{IO_2} of 35 to 55% at 6 to 10 L/min. Supply flows greater than 5 L/min are recommended to wash out CO_2. The mask is similar to the nasal cannula in its dependence on ventilatory rate and respiratory pattern to achieve its desired F_{IO_2}. The mask is useful in patients who are strictly mouth breathers, as well as some patients with extreme nasal irritation or epistaxis. On the negative side, face masks are obtrusive, uncomfortable, and confining, they muffle communication, and they obstruct eating. Not all mouth breathers require a mask. Most mouth breathers have some nasal airflow; hence, the standard nasal cannula can provide adequate oxygenation in many of these patients.

If an accurate and constant F_{IO_2} is required, perhaps due to concern about CO_2 retention, a ***Venturi mask*** can be effective. The Venturi mask, supplied by high oxygen flows, maintains a fixed ratio of oxygen to room air, thus maintaining a constant F_{IO_2}. Typical F_{IO_2} settings include 24, 28, 31, 35, and 40%.

If higher than 40% F_{IO_2} is required, the patient can be ad-

TABLE 17

RECOMMENDED INITIAL OXYGEN SETTINGS TO ACHIEVE AMBIENT AIR $Pa_{O_2} > 60$ mm Hg

Pa_{O_2} Breathing Ambient Air (mm Hg)	FI_{O_2} (%)	Nasal Cannula Setting to Achieve Approximate FI_{O_2} (L/min)
50	24	1
45	28	2
40	32	3
35	35	4

ministered oxygen via a ***non-rebreathing mask with reservoir and one-way valve.*** Oxygen flows into the reservoir at 8 to 10 L/min, so that the patient inhales a high concentration of oxygen. Hence, these systems can deliver FI_{O_2} up to 90% when the mask has a tight seal on the face. On the negative side, a tightly sealed mask can be very uncomfortable and thus poorly tolerated. The higher oxygen concentration also creates a greater risk of CO, retention.

Some patients who are difficult to oxygenate using the standard nasal cannula can be oxygenated using a reservoir cannula or transtracheal catheter because of their higher delivery efficacy. (Oxygen-conserving devices were discussed previously in detail in Long-term Oxygen Therapy.)

In general, the choice of device will depend on its effectiveness, reliability, and ease of therapeutic application as well as the patient's ability to tolerate it. Whenever there is a change in the delivery device, the patient will require an ABG or oximetry. Continued monitoring is highly advisable in the unstable patient.

Setting and Adjusting Oxygen Flow

The goal of oxygen therapy is correction of hypoxemia to a $Pa_{O_2} > 60$ mm Hg or $Sa_{O_2} > 90\%$. These values correspond to an arterial oxygen concentration (Cao,) of about 18 vol %. Because of the shape of the oxyhemoglobin dissociation curve, increasing the Pao, to values much greater than 60 mm Hg confers little added benefit (1 to 2 vol %) and may, in rare cases, increase the risk of CO_2 retention. It is therefore recommended that the initial flow setting be adjusted to bring the Pao, to just above 60 mm Hg. Recommended initial settings are summarized in Table 17 (adapted from Mithoefer and colleagues [193]).

It is recommended that Pco_2 and pH be monitored while initially titrating the oxygen flow setting. In general, patients receiving oxygen sufficient to raise Pa_{O_2} to 60 mm Hg will not experience CO, retention or acute respiratory acidosis. If CO, retention does occur, it is often minor and not accompanied by significant acidosis. If the patient is a chronic CO_2 retainer, a reasonable goal is to adjust the oxygen setting to correct the hypoxemia to a Pao, of 60 mm Hg and maintain the CO, at a stable, albeit elevated, level. Again, the pH should be monitored. If adequate oxygenation is unachievable without progressive respiratory acidosis, then mechanical ventilation may be required.

In titrating the oxygen flow setting, the clinician must remember that it can take 20 to 30 min to achieve a steady state after a change in FI_{O_2} in a patient with COPD. Therefore, ABG sampling at closer intervals may be misleading.

Following the initial setting, adjust oxygen flow via ABG to bring $Po_2 > 60$ mm Hg or Sao, > 90%. If CO, retention occurs, observe the pH: if it is nonacidemic, accept the high CO, as it is chronic. If the pH is acidemic, consider a Venturi mask to closely control the FI_{O_2} or mechanical ventilation. All other medical treatments should be optimized. This includes bronchodilators, bronchial toilet, treatment of infection, and congestive heart failure. As the patient becomes ambulatory, a walking oximetry can be used to determine an exercise flow setting.

These recommendations are summarized in Table 18 and the algorithm shown in Figure 3 (adapted from Carter [194]).

Patients are often started on oxygen for the first time during an acute exacerbation. As the lingering effects of the exacerbation take time to resolve, the patient may have to be discharged from the hospital on oxygen. After 3 to 4 wk, oxygen may no longer be required; the determination may be made by a blood gas measurement performed at that time.

Future research should focus on maximizing oxygen transport and use at all levels. Since patients become hypoxemic due to $\dot{V}/\dot{Q}$ mismatching, oxygen delivery and pharmacological approaches might maximize ventilation in well-perfused lung units. Hemoglobin and other oxygen transport vehicles may be improved to increase the blood oxygen content. Tighter control of oxygen delivery might be achieved through the use of closed-loop systems in which oxygen delivery would be tied directly to oxygen saturation; such methodology might become a viable alternative to Venturi masks. Techniques to direct blood flow and oxygen uptake into specific target tissues may also be developed.

TABLE 18

ADJUSTMENT OF OXYGEN SETTINGS BASED ON ARTERIAL BLOOD GASES

Pa_{O_2} (mm Hg)	Pa_{CO_2}	pH	Therapeutic Decision
> 60	Normal	Normal	No change in O_2 flow
> 60	Mild rise	Normal	No change in O_2 flow; monitor ABC
> 60	High	Normal	No change in O_2 flow; monitor ABC
> 60	Large rise	Low	Consider Venturi/mechanical ventilation
< 60	No rise	Normal	Raise O_2; monitor ABG
< 60	Mild rise	Normal	Raise O_2; monitor ABC
< 60	Large rise	Low	Consider Venturi/mechanical ventilation

When Pa_{O_2} is much greater than 60 mm Hg, flow settings may be reduced to maintain values near 60 mm Hg.

Surgery and the COPD Patient

Patients with COPD are susceptible to all the diseases that may require surgical therapy. They are also more likely to develop some diseases due to age, COPD itself, and prior tobacco use (e.g., atherosclerotic vascular disease and cancer). Surgery in the patient with COPD can therefore be associated with increased risk of morbidity and mortality. But recent enhancements in perioperative monitoring, pain control, and surgical techniques may allow for surgery in patients with such severe obstructive lung disease that their risk was formerly regarded as prohibitive.

PREOPERATIVE EVALUATION

Evaluation of the patient with COPD must identify the goal of surgery and determine whether the risk-benefit ratio makes potential attainment of the goal worthwhile (195-198). This process will depend on the indications for the surgery, surgery site, experience of the surgical team, type of anesthesia, and degree of respiratory impairment (195–200). The risk factors are identified by history, physical examination, chest X-ray, and a battery of pulmonary and cardiovascular screening tests. With that information, the type of surgical approach, anesthesia, and perioperative therapy can be determined.

The incidence of postoperative pulmonary complications (PPC) varies in the medical literature, depending on the definition of the term. Investigators often perform routine postoperative chest radiographs or blood gases to detect abnormalities that may be prevented or treated with various forms of therapy. The finding of a decrease in Pa_{O_2} or the appearance of a basilar infiltrate may thus be defined as a PPC. In asymptomatic patients, however, these occurrences may not increase morbidity, hospital stay, costs of care, or mortality. True complications capable of producing these untoward outcomes are purulent bronchitis, atelectasis requiring bronchoscopy or respiratory therapy, pneumonia, pulmonary embolism, myocardial infarction, pulmonary edema, and cardiorespiratory failure.

Careful attention to perioperative respiratory management of patients with COPD can improve both outcomes and resource utilization (201-204). This precaution applies specifically to patients with severe disease (stage II or III); patient with mild-to-moderate COPD (stage I) have operative risks similar to the general population and need no special approach (195).

The health care provider is challenged to assess risk, project benefit, and provide perioperative management. Education is crucial to the success of this endeavor. Both patient and family must not only be counseled concerning the possibility of permanent disability or death (e.g., after lung resection), but they must also be reassured that the need for short-term postoperative mechanical ventilation does not necessarily constitute morbidity but may be a useful postoperative care technique.

Multispecialty Consultation

Because the expertise required for optimal management of patients with stage II or III COPD spans several specialties, a multidisciplinary team of consultants should be assembled to advise the patient's surgeon. A respiratory physician may serve as primary patient advocate, coordinating all preoperative input. The consulting team might include the patient's primary care physician, an anesthesiologist, a respiratory therapist, and a respiratory nurse specialist. Because many patients with COPD have other illnesses associated with tobacco abuse, input from a cardiologist, vascular surgeon, and otorhinolaryngologist is often helpful. Scheduling preoperative visits well in advance of elective surgical procedures assures that all opinions are obtained and necessary preoperative therapy is started in time to have a beneficial effect.

Preoperative specialist consultation for patients with stage II or III COPD impairment is especially crucial when cardiothoracic or upper abdominal surgery is contemplated (196-200). Treatment of perioperative pain with intercostal nerve blockade or epidural anesthesia in patients with severe respiratory impairment often requires the expertise of an anesthesiologist/anesthetist or other pain specialists. The primary care physician should initiate therapies to reduce respiratory risk factors, including smoking cessation and treatment of airflow obstruction (201-204).

The respiratory specialist should participate as part of the team and help advise the anesthesiologist/anesthetist and surgeon regarding the type of physiologic dysfunction present and the likely response to the type of procedure planned. Patients with stage II or III COPD should be admitted to the hospital at least 24 h in advance of the procedure and should have their lung disease aggressively treated (201). If an upper abdominal procedure can be performed laparoscopically, every attempt should be made to do so, because this appears to significantly reduce PPC (205).

Allied health care professionals are instrumental in teaching the patient with stage II and III COPD maneuvers, such as breathing exercises and coughing techniques, to reduce postoperative risk factors (206). Aids to lung expansion, such as incentive spirometry and continuous positive airway pressure (CPAP), may be of use in extremely high-risk patients. Perioperative teaching and deep-breathing exercises have been shown to be equally effective with other physical measures, including incentive spirometry and intermittent positive-pressure breathing (IPPB).

Assessment

In addition to routine history and physical examination, when the nature and severity of a patient's lung disease is unclear, physiologic testing should be considered. Lung resection patients should have pulmonary function studies, such as spirometry and diffusing capacity, routinely performed. While there is no definitive study supporting the routine use of preoperative spirometry in upper abdominal surgery, this simple test can be useful in the preoperative evaluation of patients with symptoms of COPD, especially if the test has not previously been performed (195-199). Preoperative arterial blood gas analysis in all patients with severe COPD is recommended if a recent test is not available; knowledge of preoperative blood gases may be helpful in determining appropriate postoperative ventilator settings. An elevated arterial Pco_2 has traditionally been deemed a contraindication to major surgery; more data are needed, however, since successful lung resection has now been reported in hypercapnic patients. A preoperative chest X-ray in patients for noncardiothoracic surgery is sensible, because patients with COPD are at increased risk of pulmonary neoplasm. Quantitative lung scintigraphy and exercise testing may be helpful in determining risk of postoperative complications, particularly in patients undergoing lung resection. In addition, exercise testing may reveal previously unexpected cardiovascular dysfunction.

RISK OF SURGICAL PROCEDURES IN COPD PATIENTS

Nonthoracic Procedures

In patients with reduced airflow (stage II or III), the complication rate varies with the surgical site; the farther the procedure from the diaphragm, the lower the risk (195, 198, 199). Common nonthoracoabdominal procedures in patients with COPD, because of their age, include ophthalmologic, otorhinolaryngologic, and orthopedic procedures.

Ophthalmologic procedures carry a low mortality rate, under 1% (207). Factors that might increase this risk in patients

with COPD include use of sedatives, narcotics, and general anesthesia. Many of these patients have a cough, which may be of concern to the ophthalmologist because of transmitted ocular pressure; however, excessive cough suppression may lead to retained secretions, atelectasis, pneumonitis, or gas exchange problems. Narcotics may also decrease minute ventilation. Beta-blockers such as timolol, which may be used to reduce intraocular pressure, may precipitate bronchospasm and cardiorespiratory failure even when employed topically. Anticholinergics may decrease mucociliary clearance when given systemically, but this risk should be negligible if the agents are administered in eye-drop form. Pulmonary embolism is possible in ophthalmologic patients when bed rest is unduly prolonged (207).

Head-and-neck procedures involving the airway may present a risk to patients with COPD. Sleep-disordered hypoxemia is common in COPD, for example, and nasal packing with sedation could worsen it. Aspiration and direct inflammation, compression, or compromise of the airway after nasopharyngeal, laryngeal, or thyroidal procedures could also occur. Secretion management in the laryngectomy patient may, early on, require administration of humidity and agents such as beta-agonists to enhance mucociliary function.

Orthopedic procedures pose a risk of venous thromboembolism (208). Deep venous thrombosis is present in the calf veins of 40 to 60% of normal patients not given prophylaxis with heparin. Propagation of the thrombus to the iliofemoral veins, with subsequent pulmonary embolization, will lead to death in 2 to 4% of all cases; the figures could be higher in patients with COPD.

Urologic, gynecologic, and colorectal procedures in patients with stage II or III COPD that are likely to be short and/or unlikely to involve intraoperative complications should be performed under local or epidural anesthesia whenever possible (198). This recommendation also applies to retroperitoneal surgery, including renal surgery. Lengthy abdominal and pelvic procedures involving general anesthesia may be associated with an increased risk in these patients. If the risk of surgery in patients with impaired lung function is greater than the potential benefit, the surgery should not be undertaken. Patients with FEV_1 of less than 1 L are at an increased risk for complications and may require perioperative mechanical ventilation (195, 196, 199). However, there are no absolute contraindications to lower abdominal surgery, especially if the risk/benefit ratio is low, e.g., a vaginal hysterectomy for a curable malignancy.

Upper abdominal surgery poses a risk of PPC for all patients (196, 198, 199,206). Complications are particularly likely in persons with predisposing factors, such as morbid obesity, cigarette smoking, chronic airway obstruction, heart disease, and old age. In these patients, morbidity may approach 80%, and the mortality rate is approximately 3 to 5%. Upper abdominal surgery shifts the respiratory pump from the diaphragm to the accessory muscles, due to a non-pain-related reflex (198). Intraoperative physiological changes result from both the anesthesia and the surgical procedure itself (198, 200). Other pathophysiological changes include mucus hypersecretion with airway closure and lung or chest wall restriction.

Nonimperative upper abdominal surgery, such as cholecystectomy for asymptomatic cholelithiasis, should be avoided in patients with stage II or III COPD. If surgery is necessary, attempts should be made to provide careful anesthesia (198,203). Another potential way to decrease operative risk may be to perform the procedure laparoscopically (205).

Cardiovascular Surgery

This category includes both cardiac procedures and abdominal vascular surgery.

Cardiac procedures. COPD is the most common cause of preoperative pulmonary dysfunction in patients undergoing cardiac surgery (195). Cessation of smoking should precede surgery by a minimum of 8 wk (204). Postoperative management of patients with COPD after cardiac surgery should include treatment with inhaled $beta_2$-adrenergic or anticholingeric bronchodilators (209, 210).

If the patient has been treated with theophylline preoperatively, it can be continued postoperatively if the patient's pulmonary dysfunction is not satisfactorily improved with inhaled beta-adrenergic agonists alone, and the patient's cardiac status permits. Monitoring of theophylline levels in the perioperative period seems prudent. If there is postoperative bronchospasm unrelieved by the above treatment, corticosteriods should be considered. Experimental studies of the effects of corticosteroids on wound healing indicate that the administration of glucocorticoids after the third postoperative day should not delay the wound healing process.

Postoperative mechanical ventilation is routine after many cardiac surgical procedures. Ventilation should maintain arterial carbon dioxide tension at the preoperative level with a normal pH. Weaning may require an extended time and should not be attempted until the patient's postoperative pulmonary status is stable. In the patient with severe COPD, gradual weaning may permit the patient's cardiovascular status to become sufficiently stable to tolerate assumption of the full work of breathing. If the patient continues to fail weaning from mechanical ventilation, and the spontaneous tidal volumes are less than 5 to 6 ml/kg, there may be diaphragm dysfunction secondary to phrenic nerve injury. This problem can be diagnosed with ultrasound and in most cases will improve within 6 to 12 wk of surgery.

Major abdominal vascular surgery poses a high statistical risk of postoperative respiratory failure, because patients who have undergone these procedures have had very high incidence of moderate-to-severe COPD. A recent prospective study found that 24% of patients who had such procedures required mechanical ventilation for 24 h or more after surgery (211). Three factors were associated with the need for prolonged mechanical ventilation: a history of heavy cigarette smoking, preoperative arterial hypoxemia, and major intraoperative blood loss. Whether reversing these factors would change the outcome remains to be studied.

Lung Surgery

Lung surgery may encompass both diagnostic and therapeutic procedures.

Bronchoscopy in the patient with COPD carries slightly increased risk only if pulmonary dysfunction is severe. After bronchoscopy, acute respiratory failure is very rare, but it can be encountered if sedation is excessive or airway reactivity increased. Hypoxemia during bronchoscopy is almost routine, and thus, administration of supplemental oxygen under pulse oximetry monitoring has become routine as well, although its benefits are not well-documented.

Thoracoscopy is currently used for evaluation of refractory pleural effusion, performance of pleurodesis, and mini-lung resections to remove superficial nodules or perform biopsies. Data in patients without COPD suggest that this procedure is less invasive and better tolerated than open thoracotomy (212).

Thoracotomy is performed primarily for the resection of lung masses diagnosed or suspected of malignancy. Approximately 80 to 90% of patients with lung cancer have concomitant COPD, and 20 to 30% have severe pulmonary dysfunction (213). Thoracotomy alone will have a transient adverse effect, lasting several months, on lung function; there may be as much as a 30% decrease in vital capacity. Pneumonectomy may permanently reduce all lung function by 40 to 50%, which could prove devastat-

ing to patients with COPD. Surgeons have therefore sought to resect the smallest lung volume possible via wedge resection (0 to 10% permanent lung function decrease), segmentectomy (5 to 10% permanent loss), and lobectomy (10 to 20% loss). If the region resected has no function, then no loss other than the temporary decrement attributable to the thoracotomy should result. This principle forms the basis of the regional physiological assessment of lung function via ventilation or perfusion scintigraphy (213).

It is in the area of lung resectional surgery that preoperative pulmonary function studies have a well-documented role (197). Lung function studies consisting of spirometry and possibly diffusing capacity should be routinely performed preoperatively (197,213, 214). However, the results of these tests should not be used to categorically reject a patient with an anatomically resectable lung cancer from a potentially life-saving procedure.

Whereas the risk of postoperative respiratory insufficiency or death is greater in adult male patients undergoing a pneumonectomy with a preoperative FEV, < 2 L in an adult man or 50% of predicted, a maximal voluntary ventilation (MVV) < 50% predicted or carbon monoxide diffusion in the lung (D_{LCO}) < 60% predicted, these tests are too nonpredictive to be exclusionary. They should be used, however, to indicate which patients can have resection without further testing ($FEV_1 > 2$ L or > 60% predicted, MVV > 50% predicted, and/or $D_{LCO} > 60\%$ predicted). Those patients failing to meet these criteria should have quantitative lung scintigraphy using ventilation or perfusion radionuclide imaging to determine which lung has the better function. Another approach is to count the number of bronchopulmonary segments to be resected and establish a proportion (215). A simple formula can be applied to predict the FEV, after pneumonectomy (213-216): Post-op FEV, = Pre-op FEV, x% function of contralateral lung.

Pneumonectomy is generally chosen for this assessment, because it is the largest resection likely to occur as a result of the intraoperative staging of the extent of tumor involvement. A modification of the above equation can be used to assess the impact of lesser resection (215, 216).

If the calculated FEV, after resection is greater than 40% of normal for the patient's age, sex, and height, resection can be carried out with relative safety (216). It has been shown, however, that preoperative measurement of oxygen uptake ($\dot{V}o_2$) during exercise may also be predictive of postoperative problems. The exercise test is generally performed by symptom-limited maximum incremental cycle ergometry. If the patient's Vo_2 on exercise is below 10 to 15 ml/kg/min, complication rates are increased; if it is below 10 ml/kg/min, death is more likely (217). Lung scintigraphy assesses regional lung function, while exercise testing evaluates systemic cardiopulmonary oxygen transport; thus, they may be complementary.

Perioperative Management

General guidelines, as noted earlier in the discussion of preoperative planning, include smoking cessation at least 8 wk preoperatively (204) and aggressive treatment of lung dysfunction, using inhaled bronchodilators, theophylline, corticosteroids, and antibiotics as indicated. Patients with stage II or III COPD may be admitted to the hospital before surgery for multidisciplinary evaluation, patient education, and aggressive therapy (201).

Intraoperative considerations. The effects of analgesics and regional and general anesthetic agents have been reviewed (200). In general, the patient with COPD may have increased sensitivity to the ventilatory depressant effects of these agents. But since mechanical ventilation with oxygen is generally provided during general anesthesia, and monitoring with pulse oximetry and end-tidal CO, sampling are common, the intraoperative period appears not to pose major problems.

The postoperative period. In the immediate postoperative recovery period, a number of potential threats are present, including respiratory muscle dysfunction, acidemia, hypoxemia, and hypoventilation. It is in this delicate period that close monitoring and, if necessary, mechanical ventilatory support become crucial to the patient with COPD (198, 199, 218).

The inability to overcome the previously mentioned diaphragmatic dysfunction probably explains the failure of deep breathing, intermittent positive pressure breathing, or incentive spirometry to completely eliminate postoperative complications after upper abdominal surgery. A controlled study has shown that postoperative complications can be reduced from 58% (control) to approximately 20 to 25% (202). Incentive spirometry was found to be the only modality reducing length of hospital stay. This finding has not been uniformly supported, however (203). Incentive spirometry has not been tested extensively in the postoperative management of nonabdominal surgery.

The obvious characteristic of all maneuvers to enhance lung expansion is that they are applied intermittently. Perhaps more continuous intervention is required; this premise has yet to be tested. In addition, none of these interventions can sustain an increase in FRC, because increased expiratory activity quickly decreases FRC at the cessation of the maneuver. Indications for postoperative mechanical ventilation are higher risk cardiothoracic procedures, respiratory acidosis, severe hypoxemia, retained secretions, atelectasis, and pneumonia (198, 199). Continuation of the preoperatively prescribed antibiotics, aerosol bronchodilators, corticosteroids, and theophylline is standard therapy.

Surgical Procedures to Improve Quality of Life

The following procedures may be contemplated for the patient with COPD, with the goal of either symptomatic relief or definitive correction.

Symptom relief. Resection of the carotid body or glomectomy is a procedure designed to blunt the symptoms of dyspnea by removing the primary source of hypoxic drive. However, initial claims of success were followed by problems in patients who developed ventilatory failure because of insensitivity to their hypoxic state (219). This procedure has now been abandoned. Procedures designed to change the chest wall's response to the hyperinflation of COPD, e.g., costochondrectomy, thoracoplasty, and pleurectomy, have also been abandoned.

Surgery to improve lung function. Resection of large bullae compressing more normal lung tissue can be helpful in relieving severe dysfunction and dyspnea. The significant challenge is to differentiate noncompressive destructive emphysema from bullae. This differentiation is generally possible with computed tomography.

Resection of bullae occupying more than one third of a hemithorax produces the best result. Pulmonary function studies showing primarily a restrictive defect without severe obstruction tend to reflect the suspected space-occupying nature of the bullae. Severe airflow obstruction should increase concern over a possibly useless resection of an area of generalized emphysema. However, several studies have suggested that even with very low FEV_1, removal of compressive bullae is indicated (220). Treatment of compressive bullae and recurrent pneumothoraces with the application of laser or other sclerosing agents via thoracoscopy has been reported, but there have been no controlled studies to clarify their indications.

Preliminary reports of the use of lung pneumectomy in patients (lung volume reduction) with nonuniform emphysema have been encouraging (221). In select patients, the improvements in symptoms, FEV,, FVC, and arterial blood gases have been significant. Studies are under way to evaluate the role of this procedure in patients with COPD. Preliminary studies are under way to reevaluate surgical therapy for more generalized emphysema.

Localized expiratory collapse of the major airways due to a cartilaginous abnormality can be disabling. Surgical resection of the problem area or bronchoscopic placement of a stent may improve ventilation and lessen symptoms (222).

Dyspnea may be relieved by the control of a large, often malignant, pleural effusion in the patient with COPD. Pleurodesis for this purpose or to prevent the recurrence of spontaneous pneumothoraces may be performed operatively or by needle placement of a sclerosing agent.

Lung transplantation. The definitive procedure to "cure" COPD would be double lung transplantation. This subject has been thoroughly discussed elsewhere (223), but recent experience suggests that single lung transplantation can be life saving (224). The procedure is costly, is hampered by lack of donor availability, and requires lifelong immunosuppression.

SUMMARY OF APPROACH

The approach to surgery in the patient with COPD is summarized below.

Surgery Definitely indicated

Lung resection. Pulmonary function studies should be performed before lung resection. Simple spirometry has the greatest utility in documenting physiologic operability. FEV, > 2 L in an adult man or > 60% of predicted is acceptable for pneumonectomy. Values below this suggest that further studies, such as split function assessment by quantitative lung scintigraphy and exercise testing, are warranted.

FEV, predicted after lung resection to be less than 40 to 50% of normal for the patient's sex, age, and height suggests higher morbidity and mortality. An exercise $\dot{V}O_2$ of less than 10 to 15 ml/min per kg of body weight is associated with higher morbidity and mortality after lung resection.

All elective surgery Prophylaxis against deep venous thrombosis should be given before most procedures that will require postoperative bed rest or significantly reduce mobility. Heparin in low doses seems well accepted for most procedures. External pneumatic compression of the lower legs can be used when anticoagulants are contraindicated.

Surgery Possibly Indicated

In patients with COPD, a preoperative multidisciplinary evaluation that includes the primary care physician, consultant pulmonologist/intensivist, anesthesiologist/anesthetist, and operating surgeon is warranted. Consensus as to preoperative physiologic status, therapeutic preparation, and postoperative management is essential.

Lung function studies such as simple spirometry, including an arterial blood gas analysis, should be performed before upper abdominal surgery in patients exhibiting symptoms and signs of obstructive airway disease, if not previously obtained. There are no values that preclude a life-enhancing operation. Stage II or III impairment suggests the need for intensive postoperative respiratory therapy, which may include mechanical ventilation.

Smoking cessation should begin at least 8 wk preoperatively.

Preoperative therapy for elective surgery with antibiotics for sputum purulence, $beta_2$-agonist, or anticholinergic bronchodilator aerosols (theophylline optional), plus education concerning cough and lung expansion techniques, should begin at least 24 to 48 h preoperatively.

Therapy begun preoperatively should continue for 3 to 5 d into the postoperative period. Incentive spirometry is noninvasive and relatively inexpensive and may reduce the incidence of atelectasis and shorten the hospital stay. Incentive spirometry has not been documented to be effective after thoracotomy and probably plays no role in the postoperative care of peripheral procedures.

Postoperative pain control with regional (epidural) anesthetic injection should be performed after thoracotomy. Its value after upper abdominal surgery is less well documented.

Laparoscopic approaches to upper abdominal surgery may be attempted. Postoperative morbidity and hospital stay appear lessened in patients without COPD. The effect on the patient with COPD of CO, absorbed from the peritoneal cavity during the procedure is unknown.

Thoracoscopic approaches to small volume (e.g., biopsy) lung resection should be considered.

COPD should not be contraindication to life-enhancing cardiac or abdominal vascular surgery, which may be successfully performed even in the presence of severe disease. Respiratory care after coronary artery bypass grafting often includes mechanical ventilatory support. Antibiotic therapy, incentive spirometry, and pain control therapies, as discussed previously, are also warranted.

Resection of bullae occupying greater than one third of a hemithorax and compressing more normal lung tissue may produce improvement in dyspnea and physiologic function.

Recurrent pneumothoraces may be treated by surgical pleurodesis or other forms of sclerosis.

Lung transplantation may be considered for COPD in those patients who meet established criteria.

Surgical resection of noncompressive emphysema aimed to reduce hyperinflation may be effective; further studies are under way.

Unproven indications

Elective tracheostomy performed in the stable outpatient to reduce dead space and enhance secretion removal has been abandoned. Incentive spirometry performed for procedures peripheral to the thoracoabdominal cavity has no demonstrated role.

Contraindications

Glomectomy is contraindicated for relief of dyspnea in COPD.

THE FUTURE OF SURGERY FOR COPD PATIENTS

More data are needed on the comparison of quantitative lung scintigraphy versus exercise testing for prediction of physiologic operability for lung resection. More data are needed on how reduced exercise oxygen delivery is associated with increased morbidity and mortality after thoracotomy. We need to improve our understanding of the pathophysiology of diaphragmatic dysfunction after upper abdominal surgery and of therapy to reverse it. More data are needed on the physiological impact of laparoscopic and thoracoscopic procedures in COPD and on the role of regional anesthesia after thoracoabdominal surgery. Studies are under way on surgical approaches to emphysema, but more investigations are needed. More data are needed on the role of preoperative preparation techniques, including their efficacy and comparison of their effectiveness with that of postoperative maneuvers.

Additional Considerations

SLEEP AND THE COPD PATIENT

Patients with COPD seem to have a higher prevalence of insomnia, excessive daytime sleepiness, and nightmares than the general population (225).

Although theophylline or beta-agonists could be implicated in the insomnia, studies with these agents have failed to demonstrate any adverse effects on sleep staging or sleep efficiency. Maximization of drug therapy to prevent coughing and shortness of breath from disrupting sleep at night may help in coping with insomnia. If the patient is severely desaturating in rapid eye movement (REM) sleep, supplemental oxygen may help as well. The use of hypnotics is controversial. One recent study on the use of low doses of short-acting hypnotics has shown that such agents can be safely tolerated without significant worsening of oxygen saturation (226). These agents should be used with caution, however, especially in patients with CO, retention.

Daytime sleepiness may stem from disrupted sleep due to pulmonary symptoms, but coexistent obstructive sleep apnea (OSA) should also be considered. One night of sleep deprivation has been shown to lead to small but statistically significant falls in both FVC and FEV, (227).

Oxygen Desaturation during Sleep

Oxygen desaturation during sleep, especially REM sleep, has been long recognized in patients with COPD. Clinical parameters that have been associated with the presence of nocturnal desaturation include daytime hypoxemia, blunted chemosensitivity while awake, severe dysfunction on pulmonary function testing, and chronic CO, retention. None of these characteristics has been useful in predicting individual REM desaturators; in fact, patients have been observed to desaturate with a daytime Po_2 above 60 mm Hg (228). One mechanism leading to hypoxemia is reduced ventilation in sleep, especially in REM sleep. It has also been postulated that the hypoxemia may be related to ventilation perfusion imbalance, although this has been difficult to prove.

Hemodynamics and Long-term Effects

REM-associated drops in Sa_{O_2} are associated with increases in pulmonary artery pressures. It is not clear if isolated increases in pulmonary artery pressures during sleep can lead to sustained pulmonary hypertension. However, recent studies of patients with COPD with nocturnal desaturation and daytime Po_2 levels over 60 mm Hg have demonstrated higher daytime resulting (229) and exercise-induced (230) pulmonary artery pressures in these patients than in a similar group of patients who did not desaturate at night.

Patients with COPD have increased premature ventricular contractions during sleep, which may decrease in frequency when these patients are given supplemental oxygen (231).

The effect of nocturnal oxygen saturation on survival in 97 patients with COPD has recently been reported (232). Both the mean nocturnal Sa_{O_2} and the Sa_{O_2} nadir during sleep were significantly related to survival. However, neither measure improved the prediction of survival over measurements of vital capacity or awake Sao,. Measurement of nocturnal Sa_{O_2} during sleep therefore cannot be recommended in the routine clinical management of patients with COPD. Other groups found that survival was reduced in patients with COPD with $Pa_{O_2} > 60$ mm Hg but < 80 mm Hg, suggesting that there is a subgroup of patients with COPD in whom it may be worthwhile to determine the extent of nocturnal oxygen desaturation (233). However, this group could not demonstrate a reduction in mortality with nocturnal oxygen supplementation.

The role of sleep studies is controversial. The major sequelae of nocturnal oxygen desaturation, including pulmonary hypertension and an increase in mortality, can usually be predicted from the measurement of daytime gas exchange and pulmonary function. At the same time, it is difficult to recommend routine measurement of nocturnal Sa_{O_2} in patients with COPD with daytime Po, over 60 mm Hg.

Relation of COPD to Obstructive Sleep Apnea

Several studies have demonstrated that COPD and OSA can coexist, but there is no evidence that this coexistence is more common than would be expected from the relative frequencies of the two conditions (230). The significance of the association seems to be that patients with both disorders seem more likely to develop pulmonary hypertension and right-sided heart failure than do patients who have either condition alone. However, full polysomnography would be beneficial in those patients with COPD with symptoms suggestive of coexistent OSA.

Research should be undertaken to determine if treatment with supplemental oxygen of isolated falls in nocturnal Sa_{O_2}, in the absence of severe daytime hypoxemia, prevents morbidity and mortality in patients with COPD. If it does, guidelines need to be established to help identify those patients with daytime Po_2 over 60 mm Hg who should undergo nocturnal Sa_{O_2} monitoring.

Guidelines

Nocturnal oxygen should be used in patients who have been demonstrated to have significant ($\leq$ 88%) desaturation during sleep. This can generally be predicted from daytime hypoxia (Pa_{O_2} < 55 mm Hg). Measurement of nocturnal oxygen saturation in patients with COPD with daytime $Pa_{O_2} > 60$ mm Hg is not recommended, except in patients with unexplained polycythemia or cor pulmonale.

Full polysomnography should be performed in those patients with COPD symptoms suggestive of coexistent obstructive sleep apnea.

THE ROLE OF NUTRITION

As many as 25% of outpatients with COPD may be malnourished; almost 50% of patients with COPD admitted to the hospital have evidence of malnutrition (234, 235). Sixty percent of patients critically ill with COPD and acute respiratory failure are malnourished (236). The incidence of malnutrition also varies with the degree of pulmonary function and gas exchange abnormalities. In patients with chronic hypoxemia as well as in normoxemic patients with very severe airflow obstruction (FEV_1 < 35%), malnutrition occurs in 50% -but it is also present in 25% of patients with only moderate airflow obstruction (237).

Malnutrition is associated with wasting of respiratory muscles, resulting in respiratory muscle weakness (238). In patients with myopathy, hypercapnia occurs when inspiratory pressures are less than one third of the maximal inspiratory pressure ($P_{I_{max}}$) (239). But hypercapnia is found in a majority of patients with COPD when inspiratory pressures are less than *half* of normal (240). Thus, hypercapnia occurs with much less respiratory muscle weakness in COPD than other conditions.

Nutritional Assessment

Nutritional assessment of patients with COPD includes several possible techniques (241). Loss of body weight provides a read-

ily accessible parameter of altered nutrition status; weight loss in excess of 10% of ideal body weight suggests malnutrition. Edema, of course, limits the utility of body weight measurement in assessment of malnutrition.

Hepatic secretory proteins, such as albumin, transferrin, retinol binding protein, and prealbumin, are markers of visceral protein stores and have been proposed as methods of nutritional assessment; unfortunately, all are influenced by numerous factors in addition to the nutritional state. Anthropometry involves application of simple measurements of skin folds and circumferences to assess the body's proportions of fat, muscle tissue, and skeletal mass; while techniques of measurement are standardized, interpretations of results remain controversial. Immunoincompetence is a common accompaniment of malnutrition and may be tested by cellular immunity or delayed cutaneous hypersensitivity; depression of cellular immunity is consistently associated with malnutrition, and nutritional repletion is associated with improved immunocompetence. The utility of skin testing is limited by multiple factors, including technical application and interpretation of such tests.

Tests of muscle function are also used as markers of nutritional status. Changes in twitch characteristics of the abductor pollicus muscle occur with stimulation of the ulnar nerve in malnourished patients; lack of technical expertise and equipment limits widespread clinical application. Respiratory muscle strength can be assessed by maximal mouth or transdiaphragmatic pressures, while endurance is assessed by maximal voluntary ventilation; both are reduced in malnourished patients. Limitations of these techniques are multiple and include the need for alert, awake patients. Other potential limitations include metabolic factors, such as hypercapnia or hypoxia, as well as medications and intrinsic muscle disease.

In summary, multiple tests are available to assess nutritional status. No simple recommendation can be given regarding the "best" test for nutritional assessment. Use of any of these methods can be appropriate, providing the limitations are clearly understood.

Data in hospitalized patients generally (not COPD patients specifically) suggest that weight loss and physical findings of weight loss are likely to indicate malnutrition as reliably as more complex tests of nutritional status. And when assessed by body weight gain, nutritional support that reverses protein-calorie malnutrition may result in small improvements in respiratory muscle strength in both outpatient and hospitalized patients with COPD (242).

Patients with COPD have increased resting energy requirements, approximately 15% above values predicted by Harris-Benedict equations. This "relative hypermetabolism" is explained by the increased energy needs of the ventilatory muscles (243). The energy cost of respiratory muscles can be approximated from the severity of lung hyperinflation.

Nutritional Support

Nutritional support in COPD has been administered orally with supplements when spontaneous oral intake is insufficient as well as enterally with continuous or nocturnal feedings. Aggressive oral nutritional supplementation of patients with COPD does result in improvement of respiratory strength, but it is laborious and time-intensive; often, it cannot be maintained by the patient (244). The optimal level of caloric support for patients with COPD has not been determined; it depends on both the degree of malnutrition and the severity of the illness.

Establishment of the most appropriate substrate mixture, i.e., carbohydrates versus fats, for malnourished patients with COPD is also complicated. The respiratory quotient (RQ) is dependent on the substrate used. Provision of total calories that exceed metabolic demand leads to net lipogenesis, resulting in a raised RQ from increased carbon dioxide production. Hypercapnia resulting from increased carbon dioxide production (Vco,) is normally avoided by a compensatory increase in ventilation, but individuals with compromised ventilatory status, such as patients with COPD are unable to increase ventilation appropriately. Clinical sequelae of overfeeding may include precipitation of hypercapnic respiratory failure and delayed weaning from mechanical ventilation (245).

It has been suggested that patients with COPD might benefit from a high-lipid, low-carbohydrate diet, owing to the reduced RQ. However, the clinical benefits of altering fat-to-carbohydrate ratios in patients with COPD when calories supplied are appropriate have not been demonstrated (246). In addition, the increase in ventilatory demand attributed to carbohydrate administration has been noted only when total calories administered were far in excess of estimated demands (247). There are thus few data to support the use of diets with altered fat-to-carbohydrate ratios in patients with COPD. Instead, overfeeding-calories in excess of metabolic demands-should be avoided. Evaluation of overfeeding can be determined by metabolic rate and carbon dioxide production.

Protein requirements in patients with COPD are generally unchanged from routine recommendations. Protein, however, has been shown to increase minute ventilation, oxygen consumption, and ventilatory response to hypoxia and hypercapnia. In patients with acute respiratory failure, high levels of protein may cause further fatigue, and protein administration may need to be temporally reduced. No data exist suggesting which patients with COPD in the ICU setting are at risk for this potential complication. If a patient is protein-malnourished, an attempt should be made to correct that status.

Electrolytes and Microelements

Electrolyte disturbances are common in patients with COPD and have potential for significant adverse outcomes. Hypophosphatemia, hyperkalemia, hypocalcemia, and hypomagnesemia are associated with diminished diaphragmatic function, while repletion of these elements results in improved function (248). While these complications apply to all patients receiving nutritional support, patients with COPD may be at increased risk, because of decreased respiratory muscle function secondary to the primary lung disease. Monitoring electrolyte levels and providing supplemental electrolytes, especially phosphorus, in malnourished patients should be routine in patients with COPD and respiratory failure.

General Guidelines

Patients with COPD should be instructed on good dietary habits. Their weight should approximate ideal body weight. If they are malnourished, attempts should be made to restore nutritional balance. Several smaller meals a day may help maintain caloric needs but avoid undue dyspnea. Forced nutrition or special diets are not recommended at the present time.

COPD AND AIR TRAVEL

Commercial airline travel exposes passengers to hypobaric hypoxia, since aircraft cabins are not routinely pressurized to sea level (249). In patients who have compensated COPD at sea level, lowering the partial pressure of oxygen in the aircraft cabin can produce severe hypoxemia (250). The appearance of dyspnea, wheezing, chest pain, cyanosis, and right heart failure can lead to urgent requests for oxygen during flights (251). Physical exertion during a flight can increase the risk of exacerbation of symptoms (250). Death due to purely respiratory causes rarely occurs

during flight, but the frequency of less morbid events, including worsening symptoms that present or persist after leaving the plane, may be underreported by patients. The proportion of patients suffering cardiac events during air travel who have COPD as a co-morbid condition is not known.

Cabin Pressures

The cabin pressure limit for a passenger aircraft is 10,000 ft (3,048 m). Newer aircraft are usually pressurized to between 5,000 and 7,000 ft (1,524 to 2,134 m). For the preflight evaluation of most patients, clinicians should consider 8,000 feet (2,438 m) of altitude above sea level as a realistic "worst case scenario." Many factors influence the cabin altitude for a particular flight. These include the type of aircraft, the flight altitude and flight plan, weather conditions, and the operation of the aircraft. In one report, half the flights of B-767 aircraft produced cabin conditions equivalent to 7,412 ft or more above sea level (252). Short flights usually reach lower cabin altitudes, but exceptions do occur. Helicopters and small aircraft, including commuter planes, often do not have pressurized cabins. Consequently, travel by these aircraft can also entail significant exposure to altitude conditions. Whenever specific information concerning the cabin altitude can be ascertained by the clinician, it should be integrated into decision making.

Preflight Assessment

Patients with COPD should have a preflight assessment that includes estimation of the expected degree of hypoxemia at altitude, identification of co-morbid disease conditions, and provision of an oxygen prescription if necessary. Documentation of recent clinical condition and laboratory tests, particularly if the patient is traveling abroad, and counseling are also desirable elements of preflight care.

Estimation of the degree of hypoxia at altitude is accomplished via hypoxia inhalation testing (253, 254) and the use of regression formulae (249, 253). The hypoxia inhalation test (HIT) assesses the effects of hypoxemia on the patient with COPD. The subject is exposed to a hypoxic gas mixture equivalent to 8,000 ft of altitude (an oxygen fraction of 15.1% at sea level) for a minimum of 15 min (255). During the test, the patient is assessed for clinical and electrocardiographic changes and arterial blood gases. While the HIT has the advantage of assessing the acute clinical effects of hypoxia, one study of patients with COPD comparing the test with actual hypobaric exposures of 5,413 ft (1,650 m) found variability of up to 11 mm Hg in Pa_{O_2} values. The HIT is not performed in many clinical laboratories in the United States and is not recommended for routine use.

Patients with COPD who may be considered candidates for the HIT include: (I) those with coexisting conditions that may be affected by hypoxemia, e.g., coronary artery disease; (2) those who have manifested symptoms during previous air travel; (3) those recovering from acute exacerbations; (4) those who develop hypoventilation with oxygen administration; and (5) those who require additional reassurance before undertaking air travel.

Regression equations offer the opportunity to compare a patient with a group of patients with similar clinical characteristics who have been previously studied during exposure to hypoxia (249,253). While regression equations may provide a more physiologic basis for the effects of high altitude than the HIT (249), the regression approach does not assess the individual's susceptibility to the development of symptoms or electrocardiographic changes during hypoxia. The alveolo-arterial oxygen tension (A-a O_2) gradient and a-A O_2 ratio generally have no advantages over regression equations (249, 253).

Oxygen Supplementation

It is currently recommended that the Pa_{O_2} during air travel should be maintained above 50 mm Hg (254). While 2 to 3 L of oxygen by nasal cannula will replace the inspired oxygen partial pressure lost at 8,000 ft compared with sea level (256), lesser increments of oxygen will maintain the Pa_{O_2} above 50 mm Hg in many patients.

Patients with COPD receiving continuous oxygen at home will require supplementation during flight. Such patients should receive greater oxygen supplementation during the flight than at sea level. Increments equivalent to 1 or 2 L of oxygen by nasal cannula during flight should suffice for most patients. Patients will also require additional oxygen supplementation if the elevation at the destination is significantly greater than at home.

The Federal Aviation Administration requires a physician's statement of oxygen need for a patient to receive continuous oxygen during flight. There is no uniform airline request form; the airline must be contacted by the patient to determine what is required. As the airlines do not provide oxygen for ground use in terminals, patients who require continuous oxygen should be advised to make plans for such locations. The American Lung Association provides patient education material for individuals who travel with oxygen ("Airline Travel with Oxygen"); it includes requirements for each commercial carrier as well as the costs of oxygen during flight, data helpful to both physicians and patients.

Many ambulatory patients with COPD not receiving oxygen at home can tolerate PO_2 values below 50 mm Hg for brief periods of time without serious consequences. Patients with COPD but without co-morbid disease who have previously traveled without incident and who are currently clinically stable compared with their previous air travel may be permitted to travel by air with little risk.

Airline travel is safe for most patients with COPD. Hypoxemic patients should be evaluated clinically, and a decision should be made regarding O_2 requirements. The use of regression formulae helps to assess those needs. Those patients already on oxygen should be instructed to increase their O_2 by 1 or 2 L/min while in flight.

Additional data are desirable. Investigators should explore the physiologic consequences of allowing Pa_{O_2} values continuously below 50 mm Hg for 4 to 12 h in patients with uncomplicated COPD, as well as the effects of acute hypoxia on patients with COPD who are hypercapnic or have co-morbid disease states. It is also helpful to determine the frequency of adverse clinical events occurring in patients with COPD who engage in air travel.

Ethical Issues in COPD

Because COPD affects patients at more advanced ages, frequently progresses, and may require highly expensive and prolonged life-preserving medical technology, management and care frequently present ethical dilemmas. Although fundamental principles of health care ethics have been commonly adopted and widely disseminated through professional medical societies during the last decade, the decision to withhold, limit, or withdraw care in patients with COPD remains complex and difficult. Deliberations concerning individual patients require careful analysis involving COPD survival statistics, quality of life, community health care resources, and economic aspects of care.

The chief ethical concern in COPD focuses on the institution and withdrawal of mechanical ventilation, particularly in the hospital setting.

Prediction and Prognosis

The onset of respiratory failure is a major event in the life of a patient with COPD. The complex decision to intubate and mechanically ventilate such patients requires efforts to balance the immediate life-saving benefits of ventilatory support with the poor long-term prognosis of severe COPD and the discomforts, potential risks, expense, and resource utilization of prolonged mechanical ventilation.

Clinicians commonly attempt to determine the value of mechanical ventilation in individual patients by subjectively evaluating clinical features of the acute respiratory failure and estimating the likelihood of survival after intubation. Unfortunately, physicians using subjective bedside judgment cannot accurately predict the likelihood of survival in these circumstances. There is *no* correlation between predictive accuracy and physicians' experience or level of training (257).

Furthermore. no studies have established that objective markers of the severity or specific clinical features of the respiratory failure can predict the probability of survival after mechanical ventilation. No correlation exists, for instance, between short-term survival and admission arterial blood gas results, admission spirometric values, hematocrit, patient age, or number of previous admissions for exacerbations of COPD (258,259). Multivariate analysis techniques may improve predictive accuracy for long-term survival in intubated patients, but they still misclassify up to 23% of patients. Scoring systems such as the Simplified Acute Physiology Score are weak predictors of short-term outcome in patients with COPD and respiratory failure (260).

Clinical data do indicate, however, that outcome following an episode of respiratory failure correlates with the severity of the underlying COPD and patient activity levels when the patient is well or during stable periods of the disease (259). If non-pulmonary co-morbid conditions, such as gastrointestinal hemorrhage, pulmonary embolism, or coronary heart disease, are also present at the onset of respiratory decompensation, that factor contributes to poor patient outcome (257,259). Housebound patients with severe, end-stage lung disease and co-morbid conditions have a worse short-term prognosis than more active patients with less severe underlying pulmonary impairment, given similarly severe episodes of respiratory failure.

Analysis of the typical clinical outcome of patients with COPD who present with acute respiratory failure can assist decision making for intubation and mechanical ventilation. Between 75 and 90% of such patients who are mechanically ventilated survive to hospital discharge (258, 259, 261). Two-year survival for patients followed from the onset of an episode of acute respiratory failure has ranges between 28 and 70% (260, 262). Indeed, among patients presenting with acute respiratory failure due to a variety of causes, patients with COPD have the highest survival rate (263).

Overall, the long-term prognosis of patients surviving mechanical ventilation is similar to that of patients with the same degree of underlying respiratory impairment who have not required mechanical ventilation (260). Thus, it appears that patients with COPD whose course is complicated by acute respiratory failure requiring life-support measures do *not* have a generally grim prognosis. Consequently, there is *no fundamental ethical dilemma* in considering all patients with COPD for intubation and mechanical ventilation.

Nevertheless, patients who have poor baseline function, marginal nutritional status, severely restricted activity, and inexorable deterioration of late-stage pulmonary dysfunction may elect to forgo intubation if, in the judgment of both patient and physician, it will only temporarily interrupt the terminal phase of the disease.

Advance Directives

Physicians have a solemn obligation to assist their patients with COPD in formulating directives in advance of respiratory decompensation. In counseling patients regarding the value of mechanical ventilation and the implications of declining life-support measures, physicians have the responsibility, as outlined in the ATS statement on *Withholding and Withdrawing Life-Sustaining Therapy (264)* and by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (265), to ensure that:

> "(I) the patient has decision-making capacity; (2) the patient has been informed regarding his or her diagnosis, prognosis, the risks, benefits, and consequences for the full range of available medical interventions including the option of no therapy; (3) the patient has received from the physician professional recommendations regarding the medical choices available, including the use of life-sustaining therapy, based on knowledge of both the medical situation and the values and goals of the patient" (263).

As observed earlier, survival after respiratory failure is closely linked to baseline function and the presence of co-morbid conditions. Decisions regarding limitations of care are best made during stable periods before respiratory failure or any other life-threatening condition has occurred. Patients who choose to forgo life-support measures should be encouraged to outline their wishes in as much detail as possible in a written instrument such as a "living will." Patients with COPD should specify their health care preferences for the several clinical situations likely to be encountered by those with pulmonary impairment, including intubation, mechanical ventilation, cardiopulmonary resuscitation, tracheotomy, and long-term life support with difficult weaning. Assistance and open discussion should be offered by the physician during the formulation of the advance directive to prevent misinterpretation and enhance proper implementation of the patient's wishes. The patient should also be encouraged to share these preferences with a trusted family member, friend, or other individual who can be designated as a surrogate decision maker for health care matters through a durable power of attorney (263).

When advance directives have been properly established or the wishes of an informed patient with decision-making capacity made known, respect for patient autonomy requires physicians caring for the patient to honor the patient's right to forgo medical intervention (263). Honoring such requests is considered neither participation in assisted suicide nor active euthanasia.

However, a physician faced with a critically ill patient should determine that requests to forgo care are reasonable under the clinical circumstances and derive from deep-seated values and appropriate responses to the severity of underlying disease rather than from endogenous depression or from temporary conditions of pain, fear, depression, or anxiety during episodes of acute respiratory failure. A physician who has personal ethical or religious values that do not permit compliance with a patient's well-conceived request to forgo life support should transfer the patient's care to another physician who can honor the patient's directives.

It should be recognized that there is no ethical difference between withholding and withdrawing life-support measures in patients with acute respiratory failure. Ethical principles underlying the decision to withhold intubation and mechanical ventilation apply equally when patients or proxies request discontinuance of care for patients with terminal disease or a progressive degenerative condition who have no hope for an acceptable and meaningful recovery. Patients electing to have ventilatory support withdrawn may request and receive adequate sedation and analgesia to extinguish all pain and suffering during the dying process even if such treatment accelerates their imminent death.

Basic Guidelines

Because patients who have COPD with acute respiratory failure have a favorable short-term prognosis after intubation and mechanical ventilation, no fundamental ethical dilemma exists in considering all such patients for critical care support. No clinical features of the respiratory failure should be used to select patients for intubation, because these features do not correlate with outcome. However, the severity of the patient's underlying COPD and the presence of co-morbid conditions do correlate to a degree with clinical outcome and allow physicians to assist patients with advance directives when patients are well or in stable condition. Although not absolute, the principle of autonomy directs physicians to honor requests of patients with severe disease to forgo life-support measures, even when that decision will cause a patient's death. Physicians cannot honor such requests without further patient evaluation, however, if the requests appear inappropriate in the clinical circumstances or appear to be derived from endogenous depression or acute pain, fear, or anxiety in patients without terminal disease.

Future Research

During the last decade, there have been major advances in arriving at consensus regarding ethical principles of life support. These principles have been disseminated through professional societies and frank exchanges among physicians, patients, and others, with the aim of ensuring respect for patient autonomy. Still, the majority of patients with COPD have not formulated advance directives and have not discussed these matters with their physicians.

Future investigative efforts should focus on the behavioral influences that keep patients and physicians from exploring these questions in a timely fashion. Greater insights are needed not only to promote these discussions among patients, families, and physicians but also to develop ways to address such intangibles as quality of life, cost of life-years saved, and impact on mortality in connection with these decisions.

FUTURE DIRECTIONS

Knowledge is constantly evolving. This is particularly true of disease entities, such as COPD, that afflict and will continue to plague many individuals. With passage of time, many of the concepts expressed here will change. Periodically, this statement will be modified to include those changes that will stand critical scientific scrutiny.

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GLOSSARY

AAT abbreviation for alpha,-antitrypsin.
ABG abbreviation for arterial blood gases.
acidemia increased hydrogen ion concentration (decreased pH) of the blood.
acinus in the lung, a primary respiratory lobule, consisting of a bronchiole and its branches; also used synonymously with ***alveolus.***
ACV abbreviation for assist-control ventilation.
alkalemia decreased hydrogen ion concentration (increased pH) of the blood.
alpha,-antitrypsin a serum glycoprotein coded for by a single gene on chromosome 14, produced by the liver and normally found in the lungs; it is the major inhibitor of proteolytic enzymes, and its deficiency is associated with the development of emphysema.
anticholinergic a parasympathetic nerve blocker.
apical bullae vesicles found at the upper border of the emphysematous lung.
apnea absence or cessation of respiration; "sleep apnea" denotes transient attacks occurring during sleep.
asterixis a motor disturbance, known also as "flapping tremor" or "liver flap," characterized by involuntary jerking movements on assuming a particular fixed posture.
atelectasis pulmonary collapse, nonexpansion, or incomplete expansion.
barotrauma pressure injury, generally involving the eustachian tube, the eardrum, or the paranasal sinuses.
beta,-agonists a subclass of agents (beta-blockers or beta-adrenergic blocking agents) that inhibit responses to sympathetic adrenergic nerve activity and to epinephrine and other adrenergic amines.
bronchiectasis chronic dilation of the bronchi.
centriacinar emphysema emphysema that begins in the respiratory bronchioles and spreads peripherally.
centrilobular emphysema the form of centriacinar emphysema associated with longstanding cigarette smoking, predominantly involving the upper half of the lungs.
CO, **narcosis CNS** depression, typically marked by stupor, associated with carbon dioxide retention due to depression of hypoxic drive.
cor pulmonale heart disease stemming from pulmonary hypertension due to lung disease; it is characterized by right ventricular hypertrophy and, acutely or ultimately, right heart failure.
cotinine a metabolic nicotine derivative which, detected in body fluids such as urine, provides evidence of exposure to tobacco smoke, whether primary or secondary.
distal acinar emphysema emphysema preferentially involving distal airway structures, alveolar ducts and sacs; also known as paraseptal emphysema.
dyspnea difficult or labored breathing.
emphysema a chronic condition characterized by abnormally enlarged air spaces distal to the terminal bronchioles, with dilation of the alveoli and destruction of the alveolar walls.
FEV, abbreviation for forced expiratory volume in one second; the maximum that can be expired, starting from maximum inspiration.
fibrosis any abnormal formation of fibrous tissue; in the pulmonary context, a chronic, progressive condition involving the alveolar walls, associated with chronic inflammation, and causing steadily increasing respiratory dysfunction.
focal emphysema the form of centriacinar emphysema that occurs in coal workers' pneumoconiosis.
FRC abbreviation for functional residual capacity, the gas volume remaining in the lungs at the end of a normal expiration.
FVC abbreviation for forced vital capacity, FEV measured without regard to time and with the subject exhaling as rapidly as possible.
goblet cell a type of epithelial cell, functioning as a mucous gland, found in various mucous membranes, including those of the respiratory passages.
hemoptysis the expectoration of blood.
hilar of or pertaining to the hilus (or hilum) of the lung, a depressed area on the mediastinal surface marking the entry point of the bronchus, nerves, and blood vessels.
hypercapnia an abnormal increase in blood carbon dioxide.
hypercarbia hypercapnia.
hyperoxia a condition of excessive oxygen in tissues and organs, as from exposure to greater than atmospheric pressures.
hypoventilation reduced alveolar ventilation, especially relative to carbon dioxide production.
hypoxemia abnormally low oxygenation of the blood.
IMV abbreviation for intermittent mandatory ventilation.
mucostasis a halt in the secretion of mucus.
oximetry measurement of the oxygen saturation of arterial blood.
panacinar emphysema emphysema involving the entire alveolus uniformly and predominating in the lower half of the lungs, the type generally seen with homozygous AAT deficiency; focal panacinar emphysema at the lung bases may accompany centrilobular emphysema in smokers.
PAP abbreviation for positive airway pressure ***or*** for pulmonary artery pressure.
paraseptal emphysema distal acinar emphysema (see above).
PEEP abbreviation for positive end-expiratory pressure, a mechanical ventilation technique in which pressure is maintained in order to increase the volume remaining in the lungs at the end of expiration.
pleurodesis the surgical creation of adhesions between the visceral and parietal layers of the pleura, it may be used in treatment of recurrent pneumothorax.
pneumothorax air or gas in the pleural cavity.
polycythemia an abnormal increase in the number of red blood cells.
protease any proteolytic enzyme.
PSV abbreviation for pressure support ventilation.
PVR abbreviation for pulmonary vascular resistance.
respiratory acidosis a state of abnormally high carbon dioxide retention, also called hypercapnic acidosis or carbon dioxide acidosis, due to inadequate pulmonary ventilation.
sarcoidosis a lung disease of unknown etiology marked by the presence of granulomatous lesions on the walls of the alveoli and/or bronchioles, with loss of lung volume and elasticity.
spirometry the measurement of lung capacity.
surfactant a locally produced fluid essential to expansion and contraction of the alveoli; it consists of phospholipids, chiefly lecithin and sphingomyelin.
tidal volume the quantity of air inspired and expired in one respiratory cycle during regular breathing.