CHAPTER 29

Chronic Obstructive Pulmonary Disease

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KEY CONCEPTS

1. Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airflow limitation that is not fully reversible and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.
2. COPD is historically described as either *chronic bronchitis* or *emphysema.* Chronic bronchitis is defined in clinical terms, whereas emphysema is defined in terms of anatomic pathology. Because most patients exhibit some features of each disease, the appropriate emphasis of COPD pathophysiology is on small airway disease and parenchymal damage that contributes to chronic airflow limitation.
3. Mortality from COPD has increased steadily over the past three decades; it currently is the fourth leading cause of death in the United States.
4. The primary cause of COPD is cigarette smoking. Other risks include a genetic predisposition, environmental exposures (including occupational dusts and chemicals), and air pollution.
5. Smoking cessation is the only management strategy proven to slow progression of COPD.
6. Oxygen therapy has been shown to reduce mortality in selected patients with COPD. Oxygen therapy is indicated for patients with a resting Pa_{O_2} (partial pressure alveolar oxygen) of less than 55 mm Hg or a Pa_{O_2} of less than 60 mm Hg and evidence of right-sided heart failure, polycythemia, or impaired neurologic function.
7. Bronchodilators represent the mainstay of drug therapy for COPD. Pharmacotherapy is used to relieve patient symptoms and improve quality of life. Guidelines recommend short-acting bronchodilators as initial therapy for patients with mild or intermittent symptoms
8. For the patient who experiences chronic symptoms, long-acting bronchodilators are appropriate. Either a β_2-agonist or an anticholinergic offers significant benefits. Combining long-acting bronchodilators is recommended if necessary despite limited data.
9. The role of inhaled corticosteroid therapy in COPD is controversial. International guidelines suggest that patients with severe COPD and frequent exacerbations may benefit from inhaled corticosteroids.
10. Acute exacerbations of COPD have a significant impact on disease progression and mortality. Treatment of acute exacerbations includes intensification of bronchodilator therapy and a short course of systemic corticosteroids.
11. Antimicrobial therapy should be used during acute exacerbations of COPD if the patient exhibits at least two of the following: increased dyspnea, increased sputum volume, and increased sputum purulence.

Learning objectives, review questions, and other resources can be found at **www.pharmacotherapyonline.com.**

Chronic obstructive pulmonary disease (COPD) is a common chronic disease of the airways characterized by the gradual and progressive loss of lung function. The prevalence and mortality of COPD have increased substantially over the past two decades. Currently, COPD is the fourth leading cause of death in the United States.

Although national guidelines for COPD management have been available for nearly two decades, questions were raised concerning their quality and supporting evidence. To standardize the care of patients with COPD and present evidence-based recommendations, the National Heart, Lung, and Blood Institute and the World Health Organization launched the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2001.[1] This report was updated most recently in 2006. The goals of the GOLD organization are to increase awareness of COPD and reduce morbidity and mortality associated with the disease. International guidelines have also been developed through a collaborative effort of the American Thoracic Society and the European Respiratory Society and are widely available.[2] These two guidelines are generally concordant in their recommendations.

1 A consensus definition recognizes COPD as a disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[2] Although COPD primarily affects the lungs, it also is associated with significant consequences. Finally, COPD is preventable and treatable.

For many years, clinicians and researchers have exhibited a nihilistic attitude toward the value of treatments for COPD. This was based on the paucity of effective therapies, the destructive nature of the condition, and the fact that the common etiology is cigarette smoking, a modifiable health risk. Currently, there is renewed interest in evaluating the value of treatments and prevention based on the availability of new therapeutic options for pharmacotherapy and guidelines based on evidence.[3] Support for renewed optimism is also reflected in the availability of research funding to improve understanding about this disease and its management. This includes National Heart, Lung, and Blood Institute funding of Specialized Centers of Clinically Oriented Research programs in COPD, whose objective is to promote multidisciplinary research on clinically rele-

vant questions enabling basic science findings to be more rapidly applied to clinical problems.[4]

2 The most common conditions comprising COPD are chronic bronchitis and emphysema. Chronic bronchitis is associated with chronic or recurrent excessive mucus secretion into the bronchial tree with cough that is present on most days for at least 3 months of the year for at least 2 consecutive years in a patient in whom other causes of chronic cough have been excluded.[2] Although chronic bronchitis is defined in clinical terms, emphysema is defined in terms of anatomic pathology. Emphysema historically was defined on histologic examination at autopsy. Because this histologic definition is of limited clinical value, emphysema also has been defined as abnormal permanent enlargement of the airspaces distal to the terminal bronchioles accompanied by destruction of their walls yet without obvious fibrosis.[2]

Current guidelines have moved away from chronic bronchitis and emphysema as descriptive subsets of COPD. This is based on the observation that the majority of COPD is caused by a common risk factor (cigarette smoking), and most patients exhibit features of both chronic bronchitis and emphysema. Therefore, emphasis is currently placed on the pathophysiologic features of small airways disease and parenchymal destruction as contributors to chronic airflow limitation. Most patients with COPD demonstrate features of both problems. Chronic inflammation affects the integrity of the airways and causes damage and destruction of the parenchymal structures. The underlying problem is persistent exposure to noxious particles or gases that sustain the inflammatory response. The airways of the lung and the parenchyma are both susceptible to inflammation and the result is chronic airflow limitation that characterizes COPD (Fig. 29–1).

EPIDEMIOLOGY

The true prevalence of COPD is likely underreported. Data from the National Health Interview Survey in 2001 indicate that 12.1 million people older than age 25 years in the United States have COPD.[5] More than 9 million of these individuals have chronic bronchitis; the remainder have emphysema or a combination of both diseases. According to national surveys, the true prevalence of people with symptoms of chronic airflow obstruction may exceed 24 million.[6] The burden may be even greater because more than one-third of adults in the United States reported respiratory complaints compatible with symptomatic COPD in some surveys.[7]

3 COPD is the fourth leading cause of death in the United States, exceeded only by cancer, heart disease, and cerebrovascular accidents. In 2004, COPD accounted for 123,884 deaths in the United States.[8] It is the only leading cause of death to increase over the last 30 years and is projected to be the third leading cause by 2020.[9] Overall, the mortality rate is higher in males; however, the female death rate has doubled over the last 25 years, and the number of female deaths has exceeded male deaths since 2000. The mortality rate is higher in whites than in blacks.[9]

Cigarette smoking is the primary cause of COPD and although the prevalence of cigarette smoking has declined compared with 1965, approximately 25% of individuals in the United States currently smoke. The trend of increasing COPD mortality likely reflects the long latency period between smoking exposure and complications associated with COPD.

Although the mortality of COPD is significant, morbidity associated with the disease also has a significant impact on patients, their families, and the healthcare system. COPD represents the second leading cause of disability in the United States. In the last 20 years, COPD has been responsible for nearly 50 million hospital visits nationwide.[10] In recent years, a diagnosis of COPD accounts for more than 15 million physician office visits, 1.5 million emergency room visits, and 700,000 hospitalizations annually. A survey by the American Lung Association revealed that among COPD patients, 51% reported that their condition limits their ability to work, 70% were limited in normal physical activity, 56% were limited in performing household chores, and 50% reported that sleep was affected adversely.[11]

The economic impact of COPD continues to increase as well. It was estimated at $23 billion in 2000 and rose to $37.2 billion in 2004, including $20.9 billion in direct costs and $16.3 billion in indirect morbidity and mortality costs.[9,12] By 2020, COPD will be the fifth most burdensome disease, as measured by disability-adjusted life years lost as a consequence of illness.

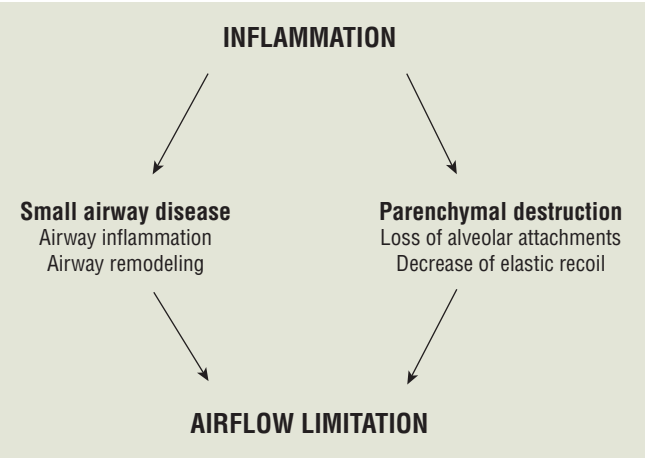

FIGURE 29-1. Mechanisms for developing chronic airflow limitation in chronic obstructive pulmonary disease. *(From reference 1.)*

ETIOLOGY

4 Although cigarette smoking is the primary modifiable risk factor for the development of COPD, the disease can be attributed to a combination of risk factors that results in lung injury and tissue destruction. Smokers are 12 to 13 times more likely to die from COPD than nonsmokers.[13] Risk factors can be divided into host factors and environmental factors (Table 29–1), and commonly, the interaction between these risks leads to expression of the disease. Host factors, such as genetic predisposition, may not be modifiable but are important for identifying patients at high risk of developing the disease.

Environmental factors, such as tobacco smoke and occupational dust and chemicals, are modifiable factors that, if avoided, may reduce the risk of disease development. Environmental exposures associated with COPD are particles that are inhaled by the individual and result in inflammation and cell injury. Exposure to multiple environmental toxins increases the risk of COPD. Thus, the total burden of inhaled particles (e.g., cigarette smoke as well as occupational and environmental particles and pollutants) can play a significant role in the development of COPD. In such cases, it is helpful to assess an individual's total burden of inhaled particles. For example, an individual who smokes and works in a textile factory has a higher total burden of inhaled particles than an individual who smokes and has no occupational exposure.

TABLE 29-1 Risk Factors for Development of Chronic Obstructive Pulmonary Disease

Exposures	Host Factors
Environmental tobacco smoke	Genetic predisposition (α_1-antitrypsin)
Occupational dusts and chemicals	Airway hyperresponsiveness
Air pollution	Impaired lung growth

Cigarette smoking is the most common risk factor and accounts for 85% to 90% of cases of COPD.[1] Components of tobacco smoke activate inflammatory cells, which produce and release the inflammatory mediators characteristic of COPD. Although the risk is lower in pipe and cigar smokers, it is still higher than in nonsmokers. Age of starting, total pack-years, and current smoking status are predictive of COPD mortality.

However, only 15% to 20% of all smokers go on to develop COPD, and not all smokers who have equivalent smoking histories develop the same degree of pulmonary impairment, suggesting that other host and environmental factors contribute to the degree of lung dysfunction. Nevertheless, the rate of loss of lung function is determined primarily by smoking status and history.[2] Children and spouses of smokers are also at increased risk of developing significant pulmonary dysfunction by passive smoking, also known as *environmental tobacco smoke* or *secondhand smoke*.

Occupational exposures are also important risk factors for COPD and, in nonindustrialized countries, may be more common than cigarette smoking. These exposures include dust and chemicals such as vapors, irritants, and fumes. Reduced lung function and deaths from COPD are higher for individuals who work in gold and coal mining, in the glass or ceramic industries with exposure to silica dust, and in jobs that expose them to cotton dust or grain dust, toluene diisocyanate, or asbestos. Other occupational risk factors include chronic exposure to open cooking or heating fires.

It is unclear whether or not air pollution alone is a significant risk factor for the development of COPD in smokers and nonsmokers with normal lung function. However, in individuals with existing pulmonary dysfunction, significant air pollution worsens symptoms. As evidence for this, emergency department visits are increased during higher-intensity periods of air pollution.

Individuals exposed to the same environmental risk factors do not have the same chance of developing COPD, suggesting that host factors play an important role in pathogenesis.[1,2] While many not yet identified genes may influence the risk of developing COPD, the best documented genetic factor is a hereditary deficiency of α_1-antitrypsin (AAT). AAT-associated emphysema is an example of a pure genetic disorder inherited in an autosomal recessive pattern. Some researchers sometimes describe inheritance as autosomal codominant because heterozygotes can also have decreased concentrations of AAT enzyme.[14] The consequences of AAT deficiency are discussed in Pathophysiology below as protease-antiprotease imbalance. True AAT deficiency accounts for less than 1% of COPD cases.[2]

AAT is a 42-kDa plasma protein that is synthesized in hepatocytes. A primary role of AAT is to protect cells, especially those in the lung, from destruction by elastase released by neutrophils. In fact, AAT may be responsible for 90% of the inhibition of this destructive enzyme.[15] In individuals with the most common allele (M), plasma levels of AAT are approximately 20 to 50 micromolars (100 to 350 mg/dL). The protective effect of AAT in the lungs is significantly diminished when plasma levels are less than 11 micromolars (80 mg/dL).[15] AAT is an acute-phase reactant, and the serum concentration can be quite variable.

Several types of AAT deficiency have been identified and are caused by mutations in the AAT gene. Two main gene variants, S and Z, have been identified. In patients who are homozygous with the S variant, AAT levels are at least 60% of those of normal individuals. These patients usually do not have an increased risk of COPD compared with normal individuals. Patients with homozygous Z deficiency (ZZ), represent 95% of clinical cases of AAT-associated emphysema[14] and have AAT levels that are 10% of those of normal individuals, whereas patients with heterozygous Z variant (SZ) have levels closer to 40% of those of normal individuals. Homozygous Z patients have a higher risk of developing COPD than do heterozygous Z patients. A history of cigarette smoking increases this risk. A small number of patients have a null, null phenotype and are at high risk for developing emphysema because they produce virtually no AAT.

Patients with AAT deficiency develop COPD at an early age (20 to 50 years) primarily owing to an accelerated decline in lung function. Compared with an average annual decline in forced expiratory volume in 1 second (FEV_1) of 25 mL/year in healthy nonsmokers, patients with homozygous Z deficiency have been reported to have declines of 54 mL/year for nonsmokers and 108 mL/year for current smokers. Effective diagnosis is dependent on clinical suspicion, diagnostic testing of serum concentrations, and genotype confirmation.[14] Patients developing COPD at an early age or those with a strong family history of COPD should be screened for AAT deficiency. If the concentration is low, genotype testing (DNA) should be performed.

Two additional host factors that may influence the risk of COPD include airway hyperresponsiveness and lung growth. Individuals with airway hyperresponsiveness to various inhaled particles may have an accelerated decline in lung function compared with those without airway hyperresponsiveness. Additionally, individuals who do not attain maximal lung growth owing to low birth weight, prematurity at birth, or childhood illnesses may be at risk for COPD in the future.[1]

PATHOPHYSIOLOGY

COPD is characterized by chronic inflammatory changes that lead to destructive changes and the development of chronic airflow limitation. The inflammatory process is widespread and involves not only the airways but also extends to the pulmonary vasculature and lung parenchyma. The inflammation of COPD is often referred to as neutrophilic in nature, but macrophages and CD8+ lymphocytes also play major roles.[16–18] The inflammatory cells release a variety of chemical mediators, of which tumor necrosis factor-α, interleukin (IL-8), and leukotriene (LT) B_4 play major roles.[1,19] The actions of these cells and mediators are complementary and redundant, leading to the widespread destructive changes. The stimulus for activation of inflammatory cells and mediators is an exposure to noxious particles and gas through inhalation. The most common etiologic factor is exposure to environmental tobacco smoke, although other chronic inhalational exposures can lead to similar inflammatory changes.

Other processes that have been proposed to play a major role in the pathogenesis of COPD include oxidative stress and an imbalance between aggressive and protective defense systems in the lungs (proteases and antiproteases).[16] These processes may be the result of ongoing inflammation or occur as a result of environmental pressures and exposures (Fig. 29–2).

An altered interaction between oxidants and antioxidants present in the airways is responsible for the increased oxidative stress present in COPD. Increases in markers (e.g., hydrogen peroxide and nitric oxide) of oxidants are seen in the epithelial lining fluid.[1] The increased oxidants generated by cigarette smoke react with and damage various proteins and lipids, leading to cell and tissue damage. Oxidants also promote inflammation directly and exacerbate the protease-antiprotease imbalance by inhibiting antiprotease activity.

The consequences of an imbalance between proteases and antiproteases in the lungs was described over 40 years ago when the hereditary deficiency of the protective antiprotease AAT was discovered to result in an increased risk of developing emphysema prematurely. This enzyme (AAT) is responsible for inhibiting several protease enzymes, including neutrophil elastase. In the presence of unopposed activity, elastase attacks elastin, a major component of alveolar walls.[1]

In the inherited form of emphysema, there is an absolute deficiency of AAT. In cigarette smoking-associated emphysema, the

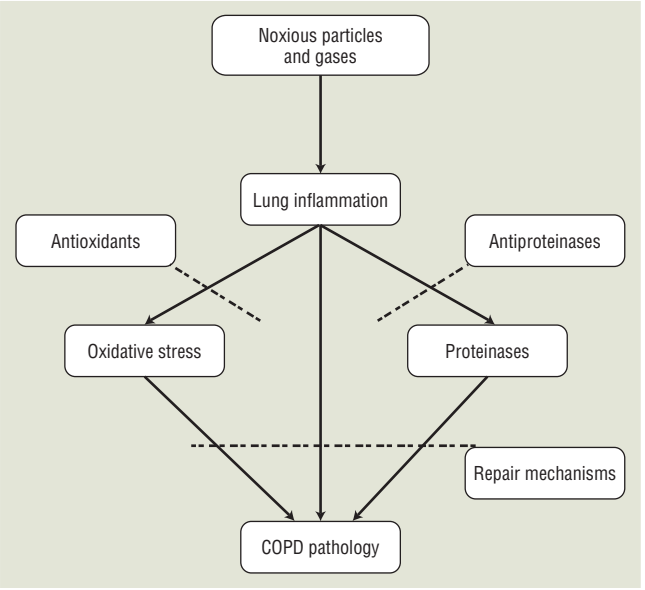

FIGURE 29-2. Pathogenesis of chronic obstructive pulmonary disease (COPD). *(From reference 1.)*

imbalance is likely associated with increased protease activity or reduced activity of antiproteases. Activated inflammatory cells release several proteases other than AAT, including cathepsins and metalloproteinases. In addition, oxidative stress reduces antiprotease (or protective) activity.

It is helpful to differentiate inflammation occurring in COPD from that present in asthma because the response to antiinflammatory therapy differs. The inflammatory cells that predominate differ between the two conditions, with neutrophils playing a major role in COPD and eosinophils and mast cells in asthma. Mediators of inflammation also differ with LTB_4, IL-8, and tumor necrosis factor-α predominating in COPD, compared with LTD_4, IL-4, and IL-5 among the numerous mediators modulating inflammation in asthma.[1] Table 29–2 summarizes the characteristics of inflammation for the two diseases.

Pathologic changes of COPD are widespread, affecting large and small airways, lung parenchyma, and the pulmonary vasculature.[1] An inflammatory exudate is often present that leads to an increase in the number and size of goblet cells and mucus glands. Mucus secretion is increased, and ciliary motility is impaired. There is also a thickening of smooth muscle and connective tissue in the airways. Inflammation is present in central and peripheral airways. The chronic inflammation results in a repeated injury and repair process that leads to scarring and fibrosis. Diffuse airway narrowing is present and is more prominent in smaller peripheral airways. The decrease in FEV_1 is attributed to the presence of inflammation in the airways while the blood gas abnormalities result from impaired gas transfer due to parenchymal damage.

Parenchymal changes affect the gas-exchanging units of the lungs, including the alveoli and pulmonary capillaries. The distribution of destructive changes varies depending on the etiology. Most commonly, smoking-related disease results in centrilobular emphysema that primarily affects respiratory bronchioles. Panlobular emphysema is seen in AAT deficiency and extends to the alveolar ducts and sacs.

The vascular changes of COPD include a thickening of pulmonary vessels and often are present early in the disease. Increased pulmonary pressures early in the disease are caused by hypoxic vasoconstriction of pulmonary arteries. If persistent, the presence of chronic inflammation may lead to endothelial dysfunction of the pulmonary arteries. Later, structural changes lead to an increase in pulmonary pressures, especially during exercise. In severe COPD, secondary pulmonary hypertension leads to the development of right-sided heart failure.

Mucus hypersecretion is present early in the course of the disease and is associated with an increased number and size of mucus-producing cells. The presence of chronic inflammation perpetuates the process, although the resulting airflow obstruction and chronic airflow limitation may be reversible or irreversible. Table 29–3 summarizes the various causes of airflow obstruction.

Recently, there has been interest in the role of thoracic overinflation as it relates to the pathophysiology of COPD. Chronic airflow obstruction leads to air trapping which results in thoracic hyperinflation that can be detected on chest radiograph. This problem results in several dynamic changes in the chest, including flattening of diaphragmatic muscles. Under normal circumstances, the diaphragms are dome-shaped muscles tethered at the base of the lungs. When the diaphragm contracts, the muscle becomes shorter and flatter, which creates the negative inspiratory force through which air flows into the lung during inspiration. In the presence of thoracic hyperinflation, the diaphragmatic muscle is placed at a disadvantage and is a less-efficient muscle of ventilation. The increased work required by diaphragmatic contractions predisposes the patient to muscle fatigue especially during periods of exacerbations.

The other consequence of thoracic hyperinflation is a change in lung volumes. In patients with COPD who exhibit thoracic hyperinflation there is an increase in the functional residual capacity which is the amount of air left in the lung after exhalation at rest. Therefore, these patients are breathing at higher lung volumes which perturbs gas exchange. In addition, the increased functional residual capacity limits the inspiratory reserve capacity which is the amount of air that

TABLE 29-2 Features of Inflammation in Chronic Obstructive Pulmonary Disease (COPD) Compared with Asthma

	COPD	Asthma
Cells	Neutrophils	Eosinophils
	Large increase in macrophages	Small increase in macrophages
	Increase in CD8+ T lymphocytes	Increase in CD4+ TH_2 lymphocytes
		Activation of mast cells
Mediators	LTB_4	LTD_4
	IL-8	IL-4, IL-5
	TNF-α	(Plus many others)
Consequences	Squamous metaplasia of epithelium	Fragile epithelium
	Parenchymal destruction	Thickening of basement membrane
	Mucus metaplasia	Mucus metaplasia
	Glandular enlargement	Glandular enlargement
Response to treatment	Glucocorticosteroids have variable effect	Glucocorticosteroids inhibit inflammation

IL, interleukin; LT, leukotriene; TH, T-helper; TNF, tumor necrosis factor.
From reference 1.

TABLE 29-3 Etiology of Airflow Limitation in Chronic Obstructive Pulmonary Disease

Reversible
Presence of mucus and inflammatory cells and mediators in bronchial secretions
Bronchial smooth muscle contraction in peripheral and central airways
Dynamic hyperinflation during exercise
Irreversible
Fibrosis and narrowing of airways
Reduced elastic recoil with loss of alveolar surface area
Destruction of alveolar support with reduced patency of small airways

the patient can inhale to fill the lungs. The increased functional residual capacity also limits the duration of inhalation time and this has been associated with an increase in dyspnea complaints by patients.[20] Drug therapy for COPD, especially bronchodilators, can reduce thoracic hyperinflation by reducing airflow obstruction. This may partially explain the improvement in symptoms reported by patients with COPD despite minimal improvements in lung function with drug therapy.

Airflow limitation is assessed through spirometry, which represents the "gold standard" for diagnosing and monitoring COPD. The hallmark of COPD is a reduction in the ratio of FEV_1 to forced vital capacity (FVC) to less than 70%.[1,2] The FEV_1 generally is reduced, except in very mild disease, and the rate of FEV_1 decline is greater in COPD patients compared with normal subjects.

The impact of the numerous pathologic changes in the lung perturbs the normal gas-exchange and protective functions of the lung. Ultimately, these are exhibited through the common symptoms of COPD, including dyspnea and a chronic cough productive of sputum. As the disease progresses, abnormalities in gas exchange lead to hypoxemia and/or hypercapnia; although there often is not a strong relationship between pulmonary function and arterial blood gas results.

Significant changes in arterial blood gases usually are not present until the FEV_1 is less than 1 L.[1] In these patients, hypoxemia and hypercapnia can become chronic problems. Initially, when hypoxemia is present, it usually is associated with exercise. However, as the disease progresses, hypoxemia at rest develops. Patients with severe COPD can have a low arterial oxygen tension (PaO_2 = 45 to 60 mm Hg) and an elevated arterial carbon dioxide tension ($PaCO_2$ = 50 to 60 mm Hg). The hypoxemia is attributed to hypoventilation ($\dot{V}$) of lung tissue relative to perfusion ($\dot{Q}$) of the area. This low $\dot{V}/\dot{Q}$ ratio will progress over a period of several years, resulting in a consistent decline in the PaO_2. Some COPD patients lose the ability to increase the rate or depth of respiration in response to persistent hypercapnia. Although this is not completely understood, the decreased ventilatory drive may be a result of abnormal peripheral or central respiratory receptors responses. This relative hypoventilation subsequently leads to hypercapnia. In this case, the central respiratory response to a chronically increased $PaCO_2$ can be blunted. These changes in PaO_2 and $PaCO_2$ are subtle and progress over a period of many years; as a result, the pH usually is nearly normal because the kidneys compensate by retaining bicarbonate. If acute respiratory distress develops, such as might be seen in pneumonia or a COPD exacerbation with impending respiratory failure, the $PaCO_2$ may rise sharply, and the patient presents with an uncompensated respiratory acidosis.

The consequences of long-standing COPD and chronic hypoxemia include the development of secondary pulmonary hypertension that progresses slowly if appropriate treatment of COPD is not initiated. Pulmonary hypertension is the most common cardiovascular complication of COPD and can result in cor pulmonale, or right-sided heart failure.[21]

The elevated pulmonary artery pressures are attributed to vasoconstriction (in response to chronic hypoxemia), vascular remodeling, and loss of pulmonary capillary beds. If elevated pulmonary pressures are sustained, cor pulmonale can develop, characterized by hypertrophy of the right ventricle in response to increases in pulmonary vascular resistance.

The risks of cor pulmonale include venous stasis with the potential for thrombosis and pulmonary embolism. Another important systemic consequence of COPD is a loss of skeletal muscle mass and general decline in the overall health status.

Although airway inflammation is prominent in patients with COPD, there is also evidence of systemic inflammation.[22] The systemic manifestations can have devastating effects on overall health status and comorbidities. These include cardiovascular events associated with ischemia, cachexia, and muscle wasting. There is some interest in the role of measuring C-reactive protein as a parameter to assess systemic inflammation and its impact on COPD severity; however, it is premature to recommend this strategy currently.[23]

PATHOPHYSIOLOGY OF EXACERBATION

The natural history of COPD is characterized by recurrent exacerbations associated with increased symptoms and a decline in overall health status. An exacerbation is defined as a change in the patient's baseline symptoms (dyspnea, cough, or sputum production) beyond day-to-day variability sufficient to warrant a change in management.[1,2] Exacerbations have a significant impact on the natural course of COPD and occur more frequently in patients with more severe chronic disease. Because many patients experience chronic symptoms, the diagnosis of an exacerbation is based, in part, on subjective measures and clinical judgment. Repeated exacerbations, especially those requiring hospitalization, are associated with an increased mortality risk.

There are limited data about pathology during exacerbations owing to the nature of the disease and the condition of patients; however, inflammatory mediators including neutrophils and eosinophils are increased in the sputum. Chronic airflow limitation is a feature of COPD and may not change remarkably even during an exacerbation.[1] The lung hyperinflation present chronic COPD is worsened during an exacerbation which contributes to worsening dyspnea and poor gas exchange.

The primary physiologic change is often a worsening of arterial blood gas results owing to poor gas exchange and increased muscle fatigue. In a patient experiencing a severe exacerbation, profound hypoxemia and hypercapnia can be accompanied by respiratory acidosis and respiratory failure.

CLINICAL PRESENTATION

The diagnosis of COPD is made based on the patient's symptoms, including cough, sputum production, and dyspnea, and a history of exposure to risk factors such as tobacco smoke and occupational exposures. Patients may have these symptoms for several years before dyspnea develops and often will not seek medical attention until dyspnea is significant. A diagnosis of COPD should be considered in any patient who presents with chronic cough, sputum production, or dyspnea and who has risk factors for the disease.

The presence of airflow limitation should be confirmed with spirometry. Spirometry represents a comprehensive assessment of lung volumes and capacities. The hallmark of COPD is an FEV_1:FVC ratio of less than 70%, which indicates airway obstruction, and a postbronchodilator FEV_1 of less than 80% of predicted confirms the presence of airflow limitation that is not fully reversible.[1] An improvement in FEV_1 of less than 12% following inhalation of a rapid-acting bronchodilator is considered to be evidence of irreversible airflow obstruction. Reversibility of airflow limitation is measured by a bronchodilator challenge, which is described in Table 29–4. Although a low peak expiratory flow is consistent with COPD, the use of peak expiratory flow measurements is inadequate for the diagnosis of COPD owing to low specificity and the high degree of effort dependence. Chapter 27 has a comprehensive discussion of spirometry.

Spirometry combined with a physical examination improves the diagnostic accuracy of COPD.[7] Spirometry is also used to determine the severity of the disease, along with an assessment of symptoms and the presence of complications. A primary benefit of spirometry is to identify individuals who might benefit from pharmacotherapy to reduce exacerbations. Currently, the GOLD consensus guidelines suggest a four-stage classification system (Table 29–5).

TABLE 29-4 Procedures for Reversibility Testing

Preparation
Tests should be performed when patients are clinically stable and free from respiratory infection.
Patients should not have taken inhaled short-acting bronchodilators in the previous 6 hours, long-acting β-agonists in the previous 12 hours, or sustained-release theophylline in the previous 24 hours.
Spirometry
FEV_1 should be measured before bronchodilator is given.
Bronchodilators can be given by either metered-dose inhaler or nebulization.
Usual doses are 400 mcg of β-agonist, up to 160 mcg of anticholinergic, or the two combined.
FEV1 should be measured 10–15 minutes after the β-agonist or 30–45 minutes after combination is given.
Results
An increase in FEV_1 that is both greater than 200 mL and 12% above the prebronchodilator FEV_1 is considered significant.

FEV_1, forced expiratory volume in the first second of expiration.
From reference 1.

The 2006 GOLD guidelines were modified to remove the stage 0 category for COPD classification. Patients at risk (stage 0) have normal spirometry but experience chronic symptoms of cough or sputum production and a history of exposure to risk factors. This change was made because of inadequate evidence to identify patients who might progress to stage 1 disease. Patients in the remaining four stages of classification all exhibit the hallmark finding of airflow obstruction, that is, a reduction in the FEV_1:FVC ratio to less than 70%. FVC is the total amount of air exhaled after a maximal inhalation. The extent of reduction in FEV_1 further defines the patient with mild, moderate, severe, or very severe disease.[1]

Spirometry is the primary tool in classifying COPD according to severity. However, two other factors that influence disease severity, survival, and health-related quality are life are body mass index (BMI) and dyspnea.[2] A low BMI is a systemic consequence of chronic COPD and a BMI of less than 21 kg/m^2 is associated with increased mortality.[24]

Dyspnea is often the most troublesome complaint for the patient with COPD. Dyspnea can impair exercise performance and functional capacity and is frequently associated with depression and anxiety. Together, these have a significant effect on health related quality of life.[20] As a subjective symptom, dyspnea is often difficult for the clinician to assess. Various tools are available to evaluate the severity of dyspnea. A version of the Medical Research Council scale, modified by the American Thoracic Society, is commonly employed and categorizes dyspnea grades from 0 to 4 (Table 29–6).[25]

TABLE 29-5 Classification of Chronic Obstructive Pulmonary Disease Severity

Stage I: mild
$FEV_1/FVC < 70\%$
$FEV_1 \geq 80\%$
With or without symptoms
Stage II: moderate
$FEV_1/FVC < 70\%$
$50\% < FEV_1 < 80\%$
With or without symptoms
Stage III: severe
$FEV_1/FVC < 70\%$
$30\% < FEV_1 < 50\%$
With or without symptoms
Stage IV: very severe
$FEV_1/FVC < 70\%$
$FEV_1 < 30\%$ or $< 50\%$ with presence of chronic respiratory failure or right heart failure

FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity.
From reference 1.

TABLE 29-6 Modified Medical Research Council (MRC) Dyspnea Scale

Grade 0	No dyspnea	Not troubled by breathlessness except with strenuous exercise
Grade 1	Slight dyspnea	Troubled by shortness of breath when hurrying on a level surface or walking up a slight hill
Grade 2	Moderate dyspnea	Walks slower than normal based on age on a level surface due to breathlessness or has to stop for breath when walking on level surface at own pace
Grade 3	Severe dyspnea	Stops for breath after walking 100 yards or after a few minutes on a level surface
Grade 4	Very severe dyspnea	Too breathless to leave the house or becomes breathless while dressing or undressing

From reference 2.

Although a physical examination is appropriate in the diagnosis and assessment of COPD, most patients who present in the milder stages of COPD will have a normal physical examination. In later stages of the disease, when airflow limitation is severe, patients may have cyanosis of mucosal membranes, development of "barrel chest" because of hyperinflation of the lungs, an increased respiratory rate and shallow breathing, and changes in breathing mechanics such as pursing of the lips to help with expiration or use of accessory respiratory muscles.

CLINICAL PRESENTATION

Symptoms

- Chronic cough
- Sputum production
- Dyspnea

Exposure to Risk Factors

- Tobacco smoke
- α_1-Antitrypsin deficiency
- Occupational hazards

Physical Examination

- Cyanosis of mucosal membranes
- Barrel chest
- Increased resting respiratory rate
- Shallow breathing
- Pursed lips during expiration
- Use of accessory respiratory muscles

Diagnostic Tests

- Spirometry with reversibility testing
- Radiograph of chest
- Arterial blood gas (not routine)

FEATURES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION

Symptoms

- Increased sputum volume
- Acutely worsening dyspnea
- Chest tightness
- Presence of purulent sputum
- Increased need for bronchodilators
- Malaise, fatigue
- Decreased exercise tolerance

Physical Examination

- Fever
- Wheezing, decreased breath sounds

Diagnostic Tests

- Sputum sample for Gram stain and culture
- Chest radiograph to evaluate for new infiltrates

PROGNOSIS

For the patient with COPD, the combination of impaired lung function and recurrent exacerbations promote a clinical scenario characterized by dyspnea, reduced exercise tolerance and physical activity, and deconditioning. These factors lead to disease progression, poor quality of life, possible disability, and premature mortality.[26] COPD is ultimately a fatal disease if it progresses and advanced directives and end-of-life care options are appropriate to consider.

The FEV_1 is the most important prognostic indicator in a patient with COPD. The average rate of decline of FEV_1 is the most useful objective measure to assess the course of COPD. The average rate of decline in FEV_1 for healthy, nonsmoking patients owing to age alone is 25 to 30 mL/year. The rate of decline for smokers is steeper, especially for heavy smokers compared with light smokers. The decline in pulmonary function is a steady curvilinear path. The more severely diminished the FEV_1 at diagnosis; the steeper is the rate of decline. Greater numbers of years of smoking and number of cigarettes smoked also correlate with a steeper decline in pulmonary function.[27] Conversely, the rate of decline of blood gases has not been shown to be a useful parameter to assess progression of the disease. Patients with COPD should have spirometry performed at least annually to assess disease progression.

The survival rate of patients with COPD is highly correlated to the initial level of impairment in the FEV_1 and to age. Other, less-important factors include degree of reversibility with bronchodilators, resting pulse, perceived physical disability, diffusing capacity of lung for carbon monoxide (D_{LCO}), cor pulmonale, and blood gas abnormalities. A rapid decline in pulmonary function tests indicates a poor prognosis. Median survival is approximately 10 years when the FEV_1 is 1.4 L, 4 years when the FEV_1 is 1.0 L, and about 2 years when the FEV_1 is 0.5 L.

Although arterial blood gas (ABG) measurements are important, they do not carry the prognostic value of pulmonary function tests. Measurement of ABGs is more useful in patients with severe disease and is recommended for all patients with an FEV_1 of less than 40% of predicted or those with signs of respiratory failure or right-sided heart failure.[1]

It is important to recognize that patients with COPD die from a variety of causes, not only respiratory failure. Cardiovascular complications, as well as lung cancer, are the leading causes of death in patients with COPD.[28,29]

CLINICAL PRESENTATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION

Because of the subjective nature of defining an exacerbation of COPD, the criteria used among clinicians varies widely; however, most rely on a change in one or more of the following clinical findings: worsening symptoms of dyspnea, increase in sputum volume, or increase in sputum purulence. Acute exacerbations have a significant impact of the economics of treating COPD as well, estimated at 35% to 45% of the total costs of the disease in some settings.[30]

With an exacerbation, patients using rapid-acting bronchodilators may report an increase in the frequency of use. Exacerbations are commonly staged as mild, moderate, or severe according to the criteria summarized in Table 29–7.[31]

TABLE 29-7 Staging Acute Exacerbations of Chronic Obstructive Pulmonary Disease[a]

Mild (type 1)	One cardinal symptom[a] plus at least one of the following: URTI within 5 days, fever without other explanation, increased wheezing, increased cough, increase in respiratory or heart rate >20% above baseline
Moderate (type 2)	Two cardinal symptoms[a]
Severe (type 3)	Three cardinal symptoms[a]

URTI, upper respiratory tract infection.
[a]Cardinal symptoms include worsening of dyspnea, increase in sputum volume, and increase in sputum purulence.

An important complication of a severe exacerbation is acute respiratory failure. In the emergency department or hospital, an ABG usually is obtained to assess the severity of an exacerbation. The diagnosis of acute respiratory failure in COPD is made on the basis of an acute change in the ABGs. Defining acute respiratory failure as a PaO_2 of less than 50 mm Hg or a $PaCO_2$ of greater than 50 mm Hg often may be incorrect and inadequate because these values may not represent a significant change from a patient's baseline values. A more precise definition is an acute drop in PaO_2 of 10 to 15 mm Hg or any acute increase in $PaCO_2$ that decreases the serum pH to 7.3 or less. Additional acute clinical manifestations of respiratory failure include restlessness, confusion, tachycardia, diaphoresis, cyanosis, hypotension, irregular breathing, miosis, and unconsciousness.

PROGNOSIS

COPD exacerbations are associated with significant morbidity and mortality. While mild exacerbations may be managed at home, mortality rates are higher for patients admitted to the hospital. In one study of patients hospitalized with COPD exacerbations, in-hospital mortality was 6% to 8%.[32] Many patients experiencing an exacerbation do not have a return to their baseline clinical status for several weeks, significantly affecting their quality of life. Additionally, as many as half the patients originally hospitalized for an exacerbation are readmitted within 6 months.[33]

It is now evident that acute exacerbations of COPD have a tremendous impact on disease progression and ultimate mortality. For exacerbations requiring hospitalizations, mortality rates range from 22% to 43% after 1 year, and 36 to 49% in 2 years.[32,34,35]

TREATMENT

Chronic Obstructive Pulmonary Disease

DESIRED OUTCOMES

Given the nature of COPD, a major focus in healthcare should be on prevention. However, in patients with a diagnosis of COPD, the primary goal is to prevent or minimize progression. Table 29–8 lists specific management goals. The primary goal of pharmacotherapy has been relief of symptoms, including dyspnea. More recently, however, there has been increased interest in the value of therapeutic interventions that reduce exacerbation frequency and severity, as well as reduce mortality.

Optimally, these goals can be accomplished with minimal risks or side effects. The therapy of the patient with COPD is multifaceted and includes pharmacologic and nonpharmacologic strategies. Appropriate measures of effectiveness of the management plan include continued smoking cessation, symptom improvement, reduction in FEV_1

TABLE 29-8 Goals of Chronic Obstructive Pulmonary Disease Management

Prevent disease progression
Relieve symptoms
Improve exercise tolerance
Improve overall health status
Prevent and treat exacerbations
Prevent and treat complications
Reduce morbidity and mortality

decline, reduction in the number of exacerbations, improvements in physical and psychological well-being, and reduction in mortality, hospitalizations, and days lost from work.

Unfortunately, most treatments for COPD have not been shown to improve survival or to slow the progressive decline in lung function. However, many therapies do improve pulmonary function and quality of life and reduce exacerbations and duration of hospitalization. Several disease-specific quality-of-life measures are available to assess the overall efficacies of therapies for COPD, including the Chronic Respiratory Questionnaire and the St. George's Respiratory Questionnaire. These questionnaires measure the impact of various therapies on such disease variables as severity of dyspnea and level of activity; they do not measure impact of therapies on survival. Whereas early studies of COPD therapies focused primarily on improvements in pulmonary function measurements such as FEV_1, there is a trend toward greater use of these disease-specific quality-of-life measures to evaluate the benefits of therapy on larger clinical outcomes.

GENERAL APPROACH TO TREATMENT

To be effective, the clinician should address four primary components of management: assess and monitor the condition; avoidance of or reduced exposure to risk factors; manage stable disease; and treat exacerbations. These components are addressed through a variety of nonpharmacologic and pharmacologic approaches.

NONPHARMACOLOGIC THERAPY

Patients with COPD should receive education about their disease, treatment plans, and strategies to slow progression and prevent complications.[1] Advice and counseling about smoking cessation are essential, if applicable. Because the natural course of the disease leads to respiratory failure, the clinician should address end-of-life decisions and advanced directives prospectively with the patient and family.[36]

Smoking Cessation

5 A primary component of COPD management is avoidance of or reduced exposure to risk factors. Exposure to environmental tobacco smoke is a major risk factor, and smoking cessation is the most effective strategy to reduce the risk of developing COPD and to slow or stop disease progression. The cost-effectiveness of smoking-cessation interventions compares favorably with interventions made for other major chronic diseases.[37] The importance of smoking cessation cannot be overemphasized. Smoking cessation leads to decreased symptomatology and slows the rate of decline of pulmonary function even after significant abnormalities in pulmonary function tests have been detected (FEV_1:FVC <60%).[27] As confirmed by the Lung Health Study, smoking cessation is the only intervention proven at this time to affect long-term decline in FEV_1 and slow the progression of COPD.[28] In this 5-year prospective trial, smokers with early COPD were randomly assigned to one of three groups: smoking-cessation intervention plus inhaled ipratropium three times a day, smoking-cessation intervention alone, or no intervention. During an 11-year followup, the rate of decline in FEV_1 among subjects who continued to smoke was more than twice the rate in sustained quitters. Smokers who underwent smoking-cessation intervention had fewer respiratory symptoms and a smaller annual decline in FEV_1 compared with smokers who had no intervention. However, this study also demonstrated the difficulty in achieving and sustaining successful smoking cessation.

Tobacco cessation has mortality benefits beyond those related to COPD. A followup analysis of the Lung Health Study data conducted more than 14 years later demonstrated an 18% reduction in all-cause mortality in patients who received the intervention compared to usual care.[29] Intervention patients had lower death rates as a consequence of coronary artery disease (the leading cause of mortality), cardiovascular diseases, and lung cancer, although no category reached clinical significance.

Every clinician has a responsibility to assist smokers in smoking-cessation efforts. A clinical practice guideline for treating tobacco dependence from the U.S. Public Health Service was updated in 2000.[38] Table 29–9 summarizes the major findings and recommendations of that report. In 2004, a report from the Surgeon General on the health consequences of smoking broadened the scope of the detrimental effects of cigarette smoking, indicating that "Smoking harms nearly every organ of the body, causing many diseases and reducing the health of smokers in general."[13]

All clinicians should take an active role in assisting patients with tobacco dependence in order to reduce the burden on the individual, the individual's family, and the healthcare system. It is estimated that more than 75% of smokers want to quit and that one-third have made a serious effort. Yet complete and permanent tobacco cessation is difficult.[28] Counseling that is provided by clinicians is associated with greater success rates than self-initiated efforts.[38]

The U.S. Public Health Service guidelines recommend that clinicians take a comprehensive approach to smoking-cessation counseling. Advice should be given to smokers even if they have no symptoms of smoking-related disease or if they are receiving care for reasons unrelated to smoking. Clinicians should be persistent in their efforts because relapse is common among smokers owing to the chronic nature of dependence. Brief interventions (3 minutes) of counseling are proven effective. However, it must be recognized that the patient must be ready to stop smoking because there are several stages of decision making. Based on this, a five-step intervention program is proposed (Table 29–10).

TABLE 29-9 Treating Tobacco Use and Dependence: Public Health Service Report (2000) Major Findings and Recommendations

Tobacco dependence should be recognized as a chronic condition requiring repeated treatment until permanent abstinence is achieved.
Effective treatments for tobacco dependence are available and should be offered to all tobacco users.
Clinicians and healthcare systems should ensure mechanisms to identify, document, and treat all tobacco users in the system.
Brief treatment interventions for tobacco dependence should be offered to all tobacco users at a minimum.
There is a strong dose–response relationship between the intensity of tobacco dependence counseling and its effectiveness.
The most effective types of counseling and behavioral therapies are (a) practical counseling employing problem-solving and skills training, (b) social support as part of treatment, and (c) social support outside of treatment.
Numerous pharmacotherapies are effective for smoking cessation and should be offered in the absence of contraindications. These include sustained-release bupropion, nicotine gum, nicotine inhaler, nicotine nasal spray, nicotine patch, and varenicline.
Tobacco dependence treatments are effective and cost-effective compared with other medical and disease-prevention measures.

TABLE 29-10 Five-Step Strategy for Smoking-Cessation Program (5 A's)

Ask	Use systematic approach to identify all tobacco users.
Advise	Urge all tobacco users to quit.
Assess	Determine willingness to make a cessation attempt.
Assist	Provide support for the patient to quit smoking.
Arrange	Schedule followup and monitor for continued abstinence.

There is strong evidence to support the use of pharmacotherapy to assist in smoking cessation. In fact, it should be offered to most patients as part of a cessation attempt. In general, available therapies will double the effectiveness of a cessation effort. Table 29–11 lists first-line agents. The usual duration of therapy is 8 to 12 weeks, although some individuals may require longer courses of treatment. Precautions to consider before using bupropion include a history of seizures or an eating disorder. Nicotine-replacement therapies are contraindicated in patients with unstable coronary artery disease, active peptic ulcers, or recent myocardial infarction or stroke. Nicotine patch, bupropion, and the combination of bupropion and the nicotine patch were compared with placebo in a controlled trial.[39] The treatment groups that received bupropion had higher rates of smoking cessation than the groups that received placebo or the nicotine patch. The addition of the nicotine patch to bupropion slightly improved the smoking-cessation rate compared with bupropion monotherapy. Recently, a new agent became available to assist in tobacco cessation attempts. Varenicline is a nicotine acetylcholine receptor partial agonist that has shown benefit in tobacco cessation.[40] Varenicline relieves physical withdrawal symptoms and reduces the rewarding properties of nicotine. Nausea and headache are the most frequent complaints associated with varenicline. Currently, varenicline has not been studied in combination with other tobacco cessation therapies. Second-line agents, such as clonidine and nortriptyline, a tricyclic antidepressant, are less effective or associated with greater side effects; however, they may be useful in selected clinical situations.

Behavioral modification techniques or other forms of psychotherapy also may be helpful in assisting in smoking cessation. Programs that address the many issues associated with smoking (i.e., learned behaviors, environmental influences, and chemical dependence) using a team approach are more likely to be successful. The role of alternative medicine therapies in smoking cessation is controversial. Hypnosis may aid in improving abstinence rates when added to a smoking-cessation program but appears to give little benefit when used alone. Acupuncture has not been shown to contribute to smoking cessation and is not recommended.[2]

Pulmonary Rehabilitation

Exercise training is beneficial in the treatment of COPD to improve exercise tolerance and to reduce symptoms of dyspnea and fatigue.[1] Pulmonary rehabilitation programs are an integral component in the management of COPD and should include exercise training along with smoking cessation, breathing exercises, optimal medical treatment, psychosocial support, and health education. High-intensity training (70% maximal workload) is possible even in advanced COPD patients, and the level of intensity improves peripheral muscle and ventilatory function. Studies have demonstrated that pulmonary rehabilitation with exercise three to seven times per week can produce long-term improvement in activities of daily living, quality of life, exercise tolerance, and dyspnea in patients with moderate to severe COPD.[41] Improvements in dyspnea can be achieved without concomitant improvements in spirometry. Programs using less-intensive exercise regimens (two times per week) are not beneficial.[42]

Immunizations

Vaccines can be considered as pharmacologic agents; however, their role is described here in reducing risk factors for COPD exacerbations. Because influenza is a common complication in COPD that can lead to exacerbations and respiratory failure, an annual vaccination with the inactivated intramuscular influenza vaccine is recommended. Immunization against influenza can reduce serious illness and death by 50% in COPD patients.[43] Influenza vaccine should be administered in the fall of each year (October and November) during regular medical visits or at vaccination clinics. There are few contraindications to influenza vaccine except for a patient with a serious allergy to eggs. An oral antiinfluenza agents (oseltamivir) can be considered for patients with COPD during an outbreak for patients who have not been immunized; however, this therapy is less effective and causes more side effects.[44]

The polyvalent pneumococcal vaccine, administered one time, is widely recommended for people from 2 to 64 years of age who have chronic lung disease and for all people older than age 65 years. Thus COPD patients at any age are candidates for vaccination. Although evidence for the benefit of the pneumococcal vaccine in COPD is not strong, the argument for continued use is that the current vaccine provides coverage for 85% of pneumococcal strains causing invasive disease and the increasing rate of resistance of pneumococcus to selected antibiotics. Currently, administering the vaccine remains the standard of practice and is recommended by the Centers for Disease Control and Prevention and the American Lung Association. Repeated vaccination with the 23-valent product is not recommended for patients ages 2 to 64 years with chronic lung disease; however, revaccination is recommended for patients older than 65 years of age if the first vaccination was more than 5 years earlier and the patient was younger than age 65 years. The GOLD guidelines recommend pneumococcal vaccine for all COPD patients age 65 years and older and for patients younger than age 65 years only if the FEV_1 is less than 40% of predicted.[45,46]

Long-Term Oxygen Therapy

6 The use of supplemental oxygen therapy increases survival in COPD patients with chronic hypoxemia. Although long-term oxygen has been used for many years in patients with advanced COPD, it was not until 1980 that data became available documenting its benefits. At that time, the Nocturnal Oxygen Therapy Trial Group published its data comparing nocturnal oxygen therapy (12 h/day) with continuous oxygen therapy (average of 20 h/day).[47] Among patients who were followed for at least 12 months, the results revealed a mortality rate in the nocturnal oxygen therapy group that

TABLE 29-11 First-Line Pharmacotherapies for Smoking Cessation

Agent	Usual Dose	Duration	Common Complaints
Bupropion SR	150 mg orally daily for 3 days, then twice daily	12 weeks, up to 6 months	Insomnia, dry mouth
Nicotine gum	2–4 mg gum prn, up to 24 pieces daily	12 weeks	Sore mouth, dyspepsias
Nicotine inhaler	6–16 cartridges daily	Up to 6 months	Sore mouth and throat
Nicotine nasal spray	8–40 doses daily	3 to 6 months	Nasal irritation
Nicotine patches	Various, 7–21 mg every 24 hours	Up to 8 weeks	Skin reaction, insomnia
Varenicline	0.5 mg daily for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily	12 weeks	Nausea, sleep disturbances

was nearly double that of the continuous oxygen therapy group (51% versus 26%). Statistical estimates of the continuous oxygen therapy group suggest that continuous oxygen therapy may have added 3.25 years to a COPD patient's life. Additional data from the Nocturnal Oxygen Therapy Trial Group revealed that continuous oxygen therapy patients had fewer (but statistically insignificant) hospitalizations, improved quality of life and neuropsychological function, reduced hematocrit, and decreased pulmonary vascular resistance.[47]

The decline in mortality with oxygen therapy was further substantiated in 1981 in a study by the British Medical Research Council that compared 15 h/day of oxygen versus no supplemental oxygen in COPD patients.[48] Patients receiving oxygen therapy for at least part of the day had lower rates of mortality than those not receiving oxygen. Long-term oxygen therapy provides even more benefit in terms of survival after at least 5 years of use, and it improves the quality of life of these patients by increasing walking distance and neuropsychological condition and reducing time spent in the hospital.[49] Before patients are considered for long-term oxygen therapy, they should be stabilized in the outpatient setting, and pharmacotherapy should be optimized. Once this is accomplished, long-term oxygen therapy should be instituted if either of two conditions exists: (a) a resting Pa_{O_2} of less than 55 mm Hg or (b) evidence of right-sided heart failure, polycythemia, or impaired neuropsychiatric function with a Pa_{O_2} of less than 60 mm Hg.

The most practical means of administering long-term oxygen is with the nasal cannula, at 1 to 2 L/min which provides 24% to 28% oxygen. The goal is to raise the Pa_{O_2} above 60 mm Hg. Patient education about flow rates and avoidance of flames (i.e., smoking) is of the utmost importance.

There are three different ways to deliver oxygen, including (a) in liquid reservoirs, (b) compressed into a cylinder, and (c) via an oxygen concentrator. Although conventional liquid oxygen and compressed oxygen are quite bulky, smaller, portable tanks are available to permit greater patient mobility. Oxygen concentrator devices separate nitrogen from room air and concentrate oxygen. These are the most convenient and the least-expensive method of oxygen delivery. Oxygen-conservation devices are available that allow oxygen to flow only during inspiration, making the supply last longer. These may be particularly useful to prolong the oxygen supply for mobile patients using portable cylinders. However, the devices are bulky and subject to failure.

Adjunctive Therapies

In addition to supplemental oxygen, adjunctive therapies to consider as part of a pulmonary rehabilitation program are psychoeducational care and nutritional support. Psychoeducational care (such as relaxation) has been associated with improvement in the functioning and well-being of adults with COPD.[1,2] The role of nutritional support in patients with COPD is controversial. Several studies have shown an association between malnutrition, low BMI, and impaired pulmonary status among patients with COPD. However, a meta-analysis suggests that the effect of nutritional support on outcomes in COPD is small and not associated with improved anthropometric measures, lung function, or functional exercise capacity.[50]

PHARMACOLOGIC THERAPY

In contrast to the survival benefit conferred by supplemental oxygen therapy, there is no medication available for the treatment of COPD that has been shown to modify the progressive decline in lung function or prolong survival.[1] Thus a primary goal of pharmacotherapy is to control patient symptoms and reduce complications, including the frequency and severity of exacerbations and improving the overall the health status and exercise tolerance of the patient.

International guidelines recommend a stepwise approach to the use of pharmacotherapy based on disease severity,[1,2] which is determined by the extent of airflow limitation and degree of symptoms. The impact of recurrent exacerbations on disease progression is increasingly recognized as an important factor and should be considered. The primary goals of pharmacotherapy are to control symptoms (including dyspnea), reduce exacerbations, and improve exercise tolerance and health status. Currently, there is inadequate evidence to support the use of more aggressive pharmacotherapy early in the course of disease, although data from ongoing trials may provide answers.

7 Pharmacotherapy focuses on the use of bronchodilators to control symptoms. There are several classes of bronchodilators to choose from, and no single class has been proven to provide superior benefit over other available agents. The initial and subsequent choice of medications should be based on the specific clinical situation and patient characteristics. Medications can be used as needed or on a scheduled basis depending on the clinical situation, and additional therapies should be added in a stepwise manner depending on the response and severity of disease. Considerations should be given to individual patient response, tolerability, adherence, and economic factors. A stepwise approach to the management of COPD has been proposed based on the stage of disease severity (Fig. 29–3).

8 According to the guidelines, patients with intermittent symptoms should be treated with short-acting bronchodilators. When symptoms become more persistent, long-acting bronchodilators should be initiated. For patients with an FEV_1 less than 50% and who experience frequent exacerbations, inhaled corticosteroids should be considered. Short-acting bronchodilators relieve symptoms and increase exercise tolerance. Long-acting bronchodilators relieve symptoms, reduce exacerbation frequency, and improve quality of life and health status. Patients have a variety of choices in using inhalational therapies, including metered dose inhalers (MDIs), dry powder inhalers (DPIs), or nebulizers. There is not a clear advantage of one delivery method over another and it is recommended that patient-specific factors and preferences should be considered in selecting the device.[51]

Bronchodilators

Bronchodilator classes available for the treatment of COPD include β_2-agonists, anticholinergics, and methylxanthines. There is no clear benefit to one agent or class over others, although inhaled therapy generally is preferred. In general, it can be more difficult for patients with COPD to use inhalation devices effectively compared with other populations owing to advanced age and the presence of other comorbidities. Clinicians should advise, counsel, and observe patient technique with the devices frequently and consistently.

Bronchodilators generally work by reducing the tone of airway smooth muscle (relaxation), thus minimizing airflow limitation. In patients with COPD, the clinical benefits of bronchodilators include increased exercise capacity, decreased air trapping in the lungs, and relief of symptoms such as dyspnea. However, use of bronchodilators may not be associated with significant improvements in pulmonary function measurements such as FEV_1. In general, side effects of bronchodilator medications are related to their pharmacologic effects and are dose-dependent. Because COPD patients are older and more likely to have comorbid conditions, the risk for side effects and drug interactions is higher compared with patients with asthma.

Short-Acting Bronchodilators The initial therapy for COPD patients who experience symptoms intermittently are short-acting bronchodilators. Among these agents, the choices are a short-acting β_2-agonist or an anticholinergic. Either class of agents has a relatively rapid onset on action, relieves symptoms, and improves exercise tolerance and lung function. In general, both classes are equally effective.

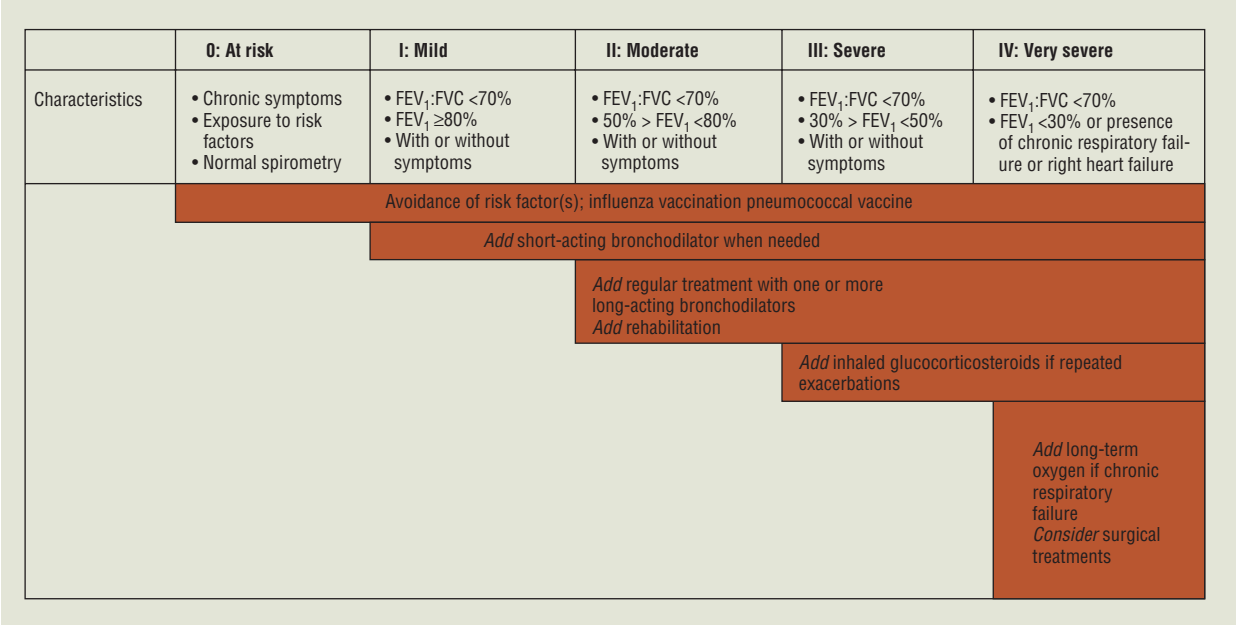

FIGURE 29-3. Recommended therapy of stable chronic obstructive pulmonary disease. (FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity.) *(From reference 1.)*

Short-Acting Sympathomimetics (β_2-Agonists) A number of sympathomimetic agents are available in the United States. They vary in selectivity, route of administration, and duration of action. In COPD management, sympathomimetic agents with β_2-selectivity, or β_2-agonists, should be used as bronchodilators. β_2-Agonists cause bronchodilation by stimulating the enzyme adenyl cyclase to increase the formation of cyclic adenosine monophosphate. Cyclic adenosine monophosphate is responsible for mediating relaxation of bronchial smooth muscle, leading to bronchodilation. In addition, it may improve mucociliary clearance. Although shorter-acting and less-selective β-agonists are still used widely (e.g., metaproterenol, isoetharine, isoproterenol, and epinephrine), they should not be used owing to their shorter duration of action and increased cardiostimulatory effects. Short-acting, selective β_2-agonists such as albuterol, levalbuterol, and pirbuterol, are preferred for therapy.

Sympathomimetics are available in inhaled, oral, and parenteral dosage forms. The preferred route of administration is by inhalation. The use of oral and parenteral β-agonists in COPD is discouraged because they are no more effective than a properly used MDI or DPI, and the incidence of systemic adverse effects such as tachycardia and hand tremor is greater. Administration of β_2-agonists in the outpatient and emergency room settings via inhalers (MDIs or DPIs) is at least as effective as nebulization therapy and usually favored for reasons of cost and convenience.[51] Chapter 28 includes a complete description of the devices used for delivering aerosolized medication and a comparison β_2-agonist therapies.

Albuterol is the most frequently used β_2-agonist. It is available as an oral and inhaled preparation. Albuterol is a racemic mixture of (*R*)-albuterol that is responsible for the bronchodilator effect and (*S*)-albuterol that has no therapeutic effect. (*S*)-Albuterol is considered by some clinicians to be inert, whereas others believe that it may be implicated in worsening airway inflammation and antagonizing the response to (*R*)-albuterol. Levalbuterol is a single-isomer formulation of (*R*)-albuterol. A retrospective evaluation of levalbuterol versus albuterol use in patients with asthma and COPD concluded that levalbuterol offered significant advantages over albuterol for hospitalized patients.[52] Other clinicians feel that there are no significant differences between the products and that the use of levalbuterol is not justified owing to its higher acquisition cost.[53] The effects of a single dose of levalbuterol have been compared with those of albuterol and ipratropium plus albuterol in patients with COPD. No significant differences in pulmonary function improvements or adverse effects were noted.[54]

In COPD patients, β_2-agonists exert a rapid onset of effect, although the response generally is less than that seen in asthma. Short-acting inhaled β_2-agonists cause only a small improvement in FEV_1 acutely but may improve respiratory symptoms and exercise tolerance despite the small improvement in spirometric measurements.[55] Patients with COPD can use quick-onset β_2-agonists as needed for relief of symptoms or on a scheduled basis to prevent or reduce symptoms. The duration of action of short-acting β_2-agonists is 4 to 6 hours.

Short-Acting Anticholinergics When given by inhalation, anticholinergics such as ipratropium or atropine produce bronchodilation by competitively inhibiting cholinergic receptors in bronchial smooth muscle. This activity blocks acetylcholine, with the net effect being a reduction in cyclic guanosine monophosphate, which normally acts to constrict bronchial smooth muscle. Muscarinic receptors on airway smooth muscle include M_1, M_2, and M_3 subtypes. Activation of M_1 and M_3 receptors by acetylcholine results in bronchoconstriction; however, activation of M_2 receptors inhibits further acetylcholine release.

Ipratropium is the primary short-acting anticholinergic agent used for COPD in the United States. Atropine has a tertiary structure and is absorbed readily across the oral and respiratory mucosa, whereas ipratropium has a quaternary structure that is absorbed poorly. The lack of systemic absorption of ipratropium greatly diminishes the anticholinergic side effects such as blurred vision, urinary retention, nausea, and tachycardia associated with atropine. Ipratropium bromide is available as a MDI and a solution for inhalation. The MDI was recently reformulated with an hydrofluoroalkane propellant and delivers 17 mcg per puff. Ipratropium is also available as a MDI in combination with albuterol and as a solution for nebulization at 200 mcg/mL. It provides a peak effect in 1.5 to 2 hours and has a duration of effect of 4 to 6 hours. Ipratropium has a slower onset of action and a more prolonged bronchodilator effect compared with standard β_2-agonists. Because of the slower onset of effect (15 to 20 minutes

compared with 5 minutes for albuterol), it may be less suitable for as-needed use; however, it is often prescribed in that manner. Although the role of inhaled anticholinergics in COPD is well established,[56–58] results from the Lung Health Study showed that treatment with ipratropium did not affect the progressive decline in lung function.[28] Studies comparing ipratropium with inhaled β_2-agonists have generally reported similar improvements in pulmonary function. Others report a modest benefit with ipratropium, including a lower incidence of side effects such as tachycardia.[56,57]

Although the recommended dose of ipratropium is 2 puffs four times a day, there is evidence for a dose–response, so the dose can be titrated upward, often to 24 puffs a day. Ipratropium has been shown to increase maximum exercise performance in stable COPD patients with doses of 8 to 12 puffs prior to exercise but not with doses of 4 puffs or fewer.[58,59] During sleep, ipratropium also has been shown to improve arterial oxygen saturation and sleep quality.[60] Ipratropium is well tolerated. The most frequent patient complaints are dry mouth, nausea, and an occasional metallic taste.

Clinicians differ about preference in choosing the initial short-acting bronchodilator therapy for the patient with COPD. Both a short-acting β_2-agonist and ipratropium represent reasonable choices for initial therapy.

Long-Acting Bronchodilators For patients with moderate to severe COPD who experience symptoms on a regular and consistent basis, or in whom short-acting therapies do not provide adequate relief, long-acting bronchodilator therapies are the recommended treatment. Long-acting, inhaled bronchodilator therapy can be administered as a β_2-agonist or an anticholinergic. Long-acting bronchodilators provide similar benefits to short-acting agents. In addition, they reduce exacerbation frequency and improve quality of life.

Long-Acting, Inhaled β_2-Agonists Long-acting, inhaled β_2-agonists offer the convenience and benefit of a long duration of action for patients with persistent symptoms. Both salmeterol and formoterol are dosed every 12 hours and provide sustained bronchodilation. Formoterol has an onset of action similar to albuterol (less than 5 minutes), whereas salmeterol has a slower onset (15 to 20 minutes); however, neither agent is recommended for acute relief of symptoms. The clinical benefits of long-acting inhaled β_2-agonists compared to short-acting therapies include similar or superior improvements in lung function and symptoms, as well as reduced exacerbation rates.[61–63] The use of the long-acting agents should be considered for patients with frequent and persistent symptoms. When patients require short-acting β_2-agonists on a scheduled basis, long-acting agents, such as formoterol and salmeterol, are more convenient based on dosing frequency, but are also more expensive.

Long-acting β-agonists are also useful to reduce nocturnal symptoms and improve quality of life. When compared to short-acting bronchodilators or theophylline, both salmeterol and formoterol improve lung function, symptoms, exacerbation frequency and quality of life.[64] These benefits are apparent even in patients with poorly reversible lung function and are related to improvements in inspiratory capacity.[65] Both salmeterol and formoterol have been compared to ipratropium. In separate studies, each agent improved FEV_1 compared to ipratropium and, in addition, the long-acting bronchodilator was more effective for other selected outcomes (e.g., prolonged time to exacerbation for salmeterol while formoterol reduced symptoms and rescue inhaler use).[66,67]

In 2007, two new long-acting, inhaled β-agonists became available in the United States. Formoterol and arformoterol are unique in that they are the first long-acting β-agonists available as nebulized solutions. When arformoterol was compared to salmeterol (administered by MDI) in a 12-week study, both treatments increased the trough FEV_1.[68] Arfomoterol also improved peak flows and reduced short-acting bronchodilator use. These two new products are the first long-acting bronchodilator therapies available for use by nebulization. They offer an important option for patients with COPD in whom nebulization therapy is warranted.

Long-Acting Anticholinergics Tiotropium bromide, a long-acting quaternary anticholinergic agent, has been available in the United States since 2004. This agent blocks the effects of acetylcholine by binding to muscarinic receptors in airway smooth muscle and mucus glands, blocking the cholinergic effects of bronchoconstriction and mucus secretion. Tiotropium is more selective than ipratropium at blocking important muscarinic receptors. Tiotropium dissociates slowly from M_1 and M_3 receptors, allowing prolonged bronchodilation. The dissociation from M_2 receptors is much faster, allowing inhibition of acetylcholine release. Binding studies of tiotropium in the human lung show that it is approximately 10-fold more potent than ipratropium and protects against cholinergic bronchoconstriction for greater than 24 hours.[69]

When inhaled, tiotropium is minimally absorbed into the systemic circulation and results in bronchodilation within 30 minutes, with a peak effect in 3 hours. Bronchodilation persists for at least 24 hours, allowing for a once-daily dosing. In the United States, it is delivered via the HandiHaler, a single-load, dry-powder, breath-actuated device. Because it acts locally, tiotropium is well tolerated, with the most common complaint being a dry mouth. Other anticholinergic side effects that are reported include constipation, urinary retention, tachycardia, blurred vision, and precipitation of narrow-angle glaucoma symptoms.

The benefits of tiotropium have been evaluated in numerous trials of patients with COPD. Similar to long-acting β-agonists, tiotropium improves lung function and, dyspnea, exacerbation frequency, and health-related quality of life.[70] The tolerance that is demonstrated with chronic use of β-agonists does not occur with tiotropium therapy, as improvements in lung function are sustained with long-term therapy.[71]

There is a large body of evidence supporting the use of tiotropium as a long-acting bronchodilator for COPD patients. Benefits have been demonstrated compared to placebo[72] and to ipratropium.[73] Equivalent or superior effects have been proven compared to long-acting β-agonist therapy.[72] Tiotropium therapy is associated with a decreased risk of exacerbations compared to placebo or ipratropium, and equal or superior efficacy compared to long-acting β-agonists.[74]

Tiotropium was evaluated as an addition to standard COPD medications in a 1-year, placebo-controlled, double-blind study involving more than 900 subjects. Tiotropium 18 mcg/day improved the FEV_1 response an average of 12% (trough) to 22% (peak) when added to standard therapy.[70]

The efficacy and safety of tiotropium administered via a DPI was compared with ipratropium administered four times daily by MDI in a multicenter, double-blind study that followed patients for 1 year.[73] Patients who received once-daily tiotropium demonstrated significantly greater improvements in lung function and selected quality-of-life scores, decreased dyspnea, and fewer exacerbations compared with patients who received ipratropium. There were no differences in side effects between the two agents.

As a long-acting bronchodilator, tiotropium is an option to consider in addition to long-acting inhaled β_2-agonists for COPD management. Once-daily tiotropium has been compared with twice-daily salmeterol in two placebo-controlled trials of 6 months' duration. Tiotropium reduced asthma exacerbations and hospital admissions and improved quality of life, whereas both active treatments improved lung function and reduced dyspnea.[72] In another 6-month randomized, controlled trial of patients with COPD, patients were randomized to receive either tiotropium once daily by DPI, salmeterol twice daily by MDI, or placebo.[75] Patients receiving

tiotropium had greater improvements in trough FEV_1 and dyspnea scores than those receiving salmeterol. Patients also were more likely to have improvements in quality-of-life indicators with tiotropium than with salmeterol. However, no differences in frequency of exacerbations were noted among the three groups.

These data offer some promise about the long term benefit of tiotropium on slowing the progressive decline in lung function, although this claim is premature. A major clinical trial evaluating the benefit of long-term treatment is currently ongoing. This trial is evaluating the long-term benefits of tiotropium in the treatment of COPD, including the effects on FEV_1 decline, exacerbation frequency, and overall mortality. The results of the UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium) trial are anticipated in 2008.[76]

The potential benefit of tiotropium therapy in augmenting pulmonary rehabilitation has been evaluated. The basis for this combination is that tiotropium can improve ventilatory mechanics and allow greater participation in exercise and muscle training. Tiotropium therapy combined with pulmonary rehabilitation improved exercise endurance and health status, and reduced dyspnea compared to pulmonary rehabilitation alone.[77] The effects were sustained for three months after the pulmonary rehabilitation program was complete.

Combination Anticholinergics and β-Agonists Combination regimens of bronchodilators are used often in the treatment of COPD, especially as the disease progresses and symptoms worsen over time. Combining bronchodilators with different mechanisms of action allows the lowest possible effective doses to be used and reduces potential adverse effects from individual agents.[1] Combinations of both short- and long-acting β_2-agonists with ipratropium have been shown to provide added symptomatic relief and improvements in pulmonary function.[78–80]

A combination of albuterol and ipratropium (Combivent) is available as a MDI in the United States for chronic maintenance therapy of COPD. This product offers the obvious convenience of two classes of bronchodilators in a single inhaler.

Although clinical practice guidelines recommend that combinations of long-acting bronchodilators are appropriate in patients who do not receive adequate benefit from a single agent, data to support the use of these combinations have been lacking. These approaches have been the focus of more recent research. Future combination inhalation products may contain long-acting β_2-agonists with tiotropium to reduce the need for frequent dosing. In a preliminary single-dose study, the combination of tiotropium and formoterol resulted in a faster and greater improvement in FEV_1 compared with either treatment alone.[81] In another trial, 95 subjects received either tiotropium 18 mcg or tiotropium plus formoterol 12 mcg, either once or twice daily. All patients received each therapy for 2 weeks each in an open-label crossover design. Both combination regimens improved lung function and reduced rescue therapy use compared to tiotropium alone.[82]

Methylxanthines Methylxanthines, including theophylline and aminophylline, have been available for the treatment of COPD for at least five decades and at one time were considered first-line therapy. However, with the availability of long-acting inhaled β_2-agonists and inhaled anticholinergics, the role of methylxanthine therapy is significantly limited. Inhaled bronchodilator therapy is preferred for COPD. Because of the risk for drug interactions and the significant intrapatient and interpatient variability in dosage requirements, theophylline therapy generally is considered in patients who are intolerant or unable to use an inhaled bronchodilator. Theophylline is still an alternative to commonly used inhaled therapies partially because of the potential for multiple mechanisms (bronchodilation and antiinflammatory) and the possible benefit that systemic administration may exert on peripheral airways.[83]

The methylxanthines may produce bronchodilation through numerous mechanisms, including (a) inhibition of phosphodiesterase, thereby increasing cyclic adenosine monophosphate levels, (b) inhibition of calcium ion influx into smooth muscle, (c) prostaglandin antagonism, (d) stimulation of endogenous catecholamines, (e) adenosine receptor antagonism, and (f) inhibition of release of mediators from mast cells and leukocytes.[84]

Chronic theophylline use in patients with COPD has been shown to exert improvements in lung function, including vital capacity, FEV_1, minute ventilation, and gas exchange.[83] Subjectively, theophylline has been shown to reduce dyspnea, increase exercise tolerance, and improve respiratory drive in COPD patients.[83,84] Other nonpulmonary effects of theophylline that may contribute to improved overall functional capacity in patients with COPD include improved cardiac function and decreased pulmonary artery pressure.

Although theophylline is available in a variety of oral dosage forms, sustained-release preparations are most appropriate for the long-term management of COPD. These products have the advantages of improving patient compliance and achieving more consistent serum concentrations over rapid-release theophylline and aminophylline preparations. However, caution must be used in switching from one sustained-release preparation to another because there are considerable variations in sustained-release characteristics.[84] Aside from intravenous aminophylline, there is no need to use any of the various salts forms of theophylline.

Regular use of methylxanthines has not been shown to have either a beneficial or a detrimental effect on the progression of COPD. However, methylxanthines may be added to the treatment plan of patients who have not achieved an optimal clinical response to ipratropium and an inhaled β_2-agonist. Studies suggest that adding theophylline to a combination of albuterol and ipratropium provides added benefit for stable COPD patients, supporting the hypothesis that there is a synergistic bronchodilator effect.[85–87] The efficacy of combination therapy with salmeterol and theophylline for patients with COPD was reported to improve pulmonary function and reduce dyspnea better than either treatment alone.[88] Combination treatment also was associated with a reduced number of exacerbations only when compared with the theophylline group, suggesting that the salmeterol component was responsible for this beneficial effect.

As is the case with other bronchodilator therapy, parameters other than objective measurements, such as FEV_1, should be monitored to assess efficacy of theophylline in COPD. Subjective parameters, such as perceived improvements in symptoms of dyspnea, and exercise tolerance, become increasingly important in assessing the acceptability of methylxanthines for COPD patients. Although objective improvement may be minimal, patients may experience an improvement in clinical symptoms, and thus benefit to the individual may be meaningful.

Theophylline's role in COPD is as maintenance therapy in the nonacutely ill patient. Therapy can be initiated at 200 mg twice daily and titrated upward every 3 to 5 days to the target dose. Most patients required daily doses of 400 to 900 mg. Dosage adjustments generally should be made based on serum concentration results. Traditionally, the therapeutic range of theophylline was identified as 10 to 20 mcg/mL; however, because of the frequency of dose-related side effects and the relatively minor benefit of higher concentrations, a more conservative therapeutic range of 8 to 15 mcg/mL often is targeted. This is especially preferable in the elderly. When concentrations are measured, trough measurements are most appropriate.

Once a dose is established, serum concentrations should be monitored once or twice a year unless the patient's disease worsens, medications that interfere with theophylline metabolism are added to therapy, or toxicity is suspected. The most common side effects of theophylline therapy are related to the gastrointestinal system, the cardiovascular system, and the central nervous system. Side effects are dose-related; however, there is overlap in side effects

between the therapeutic and toxic ranges. Minor side effects include dyspepsia, nausea, vomiting, diarrhea, headache, dizziness, and tachycardia. More serious toxicities, especially at toxic concentrations, include arrhythmias and seizures.

Factors that decrease theophylline clearance and lead to reduced maintenance-dose requirements include advanced age, bacterial or viral pneumonia, left or right ventricular failure, liver dysfunction, hypoxemia from acute decompensation, and use of drugs such as cimetidine, macrolides, and fluoroquinolone antibiotics. Factors that may enhance theophylline clearance and result in the need for higher maintenance doses include tobacco and marijuana smoking, hyperthyroidism, and the use of such drugs as phenytoin, phenobarbital, and rifampin.

In summary, there are decades of experience with theophylline and other methylxanthine products in the management of patients with COPD. However, inhalation therapy is currently preferred based on superior efficacy and safety, as well as ease of use by the clinician. Theophylline is a challenging medication to dose, monitor, and manage because of the significant intrapatient and interpatient variability in pharmacokinetics and the potential for drug interactions and toxicities.

Corticosteroids

9 Corticosteroid therapy has been studied and debated in COPD therapy for half a century; however, owing to the poor risk-to-benefit ratio, chronic systemic corticosteroid therapy should be avoided if possible.[1] Because of the potential role of inflammation in the pathogenesis of the disease, clinicians hoped that corticosteroids would be promising agents in COPD management. However, their use continues to be debated, especially in the management of stable COPD.

The antiinflammatory mechanisms whereby corticosteroids exert their beneficial effect in COPD include (a) reduction in capillary permeability to decrease mucus, (b) inhibition of release of proteolytic enzymes from leukocytes, and (c) inhibition of prostaglandins. Unfortunately, the clinical benefits of systemic corticosteroid therapy in the chronic management of COPD are often not evident, and the risk of toxicity is extensive and far-reaching. Currently, the appropriate situations to consider corticosteroids in COPD include (a) short-term systemic use for acute exacerbations and (b) inhalation therapy for chronic stable COPD.

The role of oral steroid use in chronic stable COPD patients was evaluated in a meta-analysis over a decade ago.[89] Investigators concluded that only a small fraction (10%) of COPD patients treated with steroids showed clinically significant improvement in baseline FEV_1 (increase of 20%) compared with those treated with placebo. While a small number of COPD patients are considered responders to oral steroids, many of these patients actually may have an asthmatic, or reversible, component to their disease. The best predictors for response to oral steroids is the presence of eosinophils on sputum examination (≥3%) and a significant response on pulmonary function tests to sympathomimetics.[90] Both the presence of eosinophils in sputum and the responsiveness to sympathomimetics suggest an asthmatic component to the disease process and thus may explain the clinical benefit seen with steroids.

Long-term adverse effects associated with systemic corticosteroid therapy include osteoporosis, muscular atrophy, thinning of the skin, development of cataracts, and adrenal suppression and insufficiency. The risks associated with long-term steroid therapy are much greater than the clinical benefits. If a decision to treat with long-term systemic corticosteroids is made, the lowest possible effective dose should be given once per day in the morning to minimize the risk of adrenal suppression. If therapy with oral agents is required, an alternate-day schedule should be used.

Previously, a common clinical practice was to administer a short course (2 weeks) of oral corticosteroids as a trial to predict which patients would benefit from chronic oral or inhaled corticosteroids. There is now sufficient evidence suggesting that this practice is not effective in predicting a long-term response to inhaled corticosteroid and should not be recommended.[91]

The use of chronic inhaled corticosteroid therapy has been of interest for the past decade. Their use has been common despite the lack of firm evidence about significant clinical benefit until recently. Inhaled corticosteroids have an improved risk-to-benefit ratio compared with systemic corticosteroid therapy. Using the model for asthma, it was hoped that the inhalation of potent corticosteroid would result in high local efficacy and limited systemic exposure and toxicity. In the latter part of the 1990s, several large international trials were initiated to evaluate the effect on inhaled corticosteroids in COPD. Unfortunately, the results of these major clinical trials failed to demonstrate any benefit from chronic treatment with inhaled corticosteroids in modifying long-term decline in lung function that is characteristic of COPD. Therefore, the role of inhaled corticosteroids in COPD continues to be debated in the literature, unlike asthma, where their use is clearly advocated. Much of the debate centers on the appropriate outcome measures in this population of patients.

During the last decade, several studies of inhaled corticosteroids in COPD were designed to detect a benefit on slowing the progressive loss of lung function, but the results were disappointing.[92–98] None of the large national or international trials were able to demonstrate a benefit of high-dose inhaled corticosteroid therapy on this primary outcome. However, inhaled corticosteroids are associated with other important benefits in some patients, including a decrease in exacerbation frequency and improvements in overall health status.[94,98,99] Clinicians continue to debate the most appropriate and relevant outcome measure to evaluate in COPD studies. Based on the results of clinical trials, consensus guidelines suggest that inhaled corticosteroid therapy should be considered for symptomatic patients with stage III or IV disease (FEV_1 <50%) who experience repeated exacerbations.[1,2] These are the patients who demonstrated benefit in clinical trials and in whom a trial of inhaled corticosteroid therapy is warranted. There are also data from epidemiologic studies that suggest that chronic treatment with inhaled corticosteroids is associated with a lower risk of rehospitalization for a broader group of patients with COPD. Thus the debate about the appropriate role for this antiinflammatory therapy continues.

A meta-analysis evaluating randomized clinical trials involving inhaled corticosteroids in patients COPD indicated that treatment was associated with a relative risk reduction in exacerbation frequency of 33%. The report indicated that 12 patients would require treatment for 20.8 months to prevent one exacerbation episode. The benefit was evident for patients with moderate to severe COPD.[100] This meta-analysis did not detect a mortality benefit.

Other investigators have reported a reduction in mortality in patients with COPD who were treated with inhaled corticosteroids. In an epidemiologic study of a Canadian database, patient mortality 3 months to 1 year following a hospitalization for a COPD exacerbation was evaluated in patients who received inhaled corticosteroids in the first 3 months compared to those who did not. For patients older than 65 years of age, inhaled corticosteroid therapy reduced mortality by 25%. Much of the mortality reduction was reflected in deaths from cardiovascular causes. Conversely, patients who received only bronchodilator therapy trended toward higher mortality rates, although not significant.[101] A pooled analysis of seven large trials also concluded that inhaled corticosteroids reduced all-cause mortality in COPD patients.[102]

Currently, the recommended role of inhaled corticosteroid therapy is for COPD patients with moderate to severe airflow obstruction

(FEV_1 <50% predicted), and who experience frequent exacerbations despite bronchodilator therapy. The initial hope that treatment with inhaled corticosteroids would prevent or slow the progressive decline in FEV_1 remains unproven; however, it is often argued that additional important outcomes in patients with COPD include relief of symptoms, fewer and less-severe exacerbations, and improved quality of life.[103] The role of inhaled corticosteroids in prolonging survival of patients with COPD has been widely debated in recent years. Investigators have reported mixed success and studies are confounded by small sample size and differences in study design.[104]

Although a dose–response relationship for inhaled corticosteroids has not been demonstrated in COPD, the major clinical trials employed moderate to high doses for treatment. Side effects of inhaled corticosteroids are relatively mild compared with the toxicity from systemic therapy. Hoarseness, sore throat, oral candidiasis, and skin bruising have been reported in the clinical trials. Severe side effects, such as adrenal suppression, osteoporosis, and cataract formation, have been reported less frequently than with systemic corticosteroids, but clinicians should monitor patients who are receiving high-dose chronic therapy.[105,106]

There is evidence supporting a dose relationship between inhaled corticosteroid use and the risk of fractures. In a cohort of more than 1,600 subjects with a diagnosis of asthma or COPD (mean age: 80 years), the risk of a fracture was 2.53 times higher (confidence interval: 1.65 to 3.89) in those receiving a mean daily dose of inhaled corticosteroid of 601 mcg or greater.[107] However, the data are conflicting about this issue. A meta-analysis found no evidence supporting an increased risk of fractures or decreased bone mineral density with chronic inhaled corticosteroid use.[108] It appears prudent to suggest that, to minimize the risk of fracture, patients should be treated with the lowest effective dose of inhaled corticosteroids.[109] It may also be helpful to recommend adequate intake of calcium and vitamin D, and possibly periodic bone mineral density testing.

Combination Therapy: Bronchodilators and Inhaled Corticosteroids

Following the disappointing results of chronic inhaled corticosteroid studies and the progressive decline in lung function, investigators became interested in the combination of potent antiinflammatory therapies and long-acting bronchodilators. Subsequently, several studies have shown an additive benefit with long-acting bronchodilators.[110–113] In various studies, combination therapy with salmeterol plus fluticasone or formoterol plus budesonide was associated with greater improvements in clinical outcomes such as FEV_1, health status, and frequency of exacerbations compared with inhaled corticosteroids or long-acting bronchodilators alone. The availability of combination inhalers (e.g., salmeterol plus fluticasone) makes administration of both inhaled corticosteroids and long-acting bronchodilators more convenient for patients and decreases the total number of inhalations needed daily. Therefore, there is growing evidence that inhaled corticosteroid and long-acting β-agonist combinations improve lung function, as well as reduce symptoms of dyspnea and exacerbation frequency.[112–114]

The combination of a long-acting β-agonist and inhaled corticosteroid has been compared to the long-acting β-agonist therapy alone. In a study involving nearly 1,000 patients with severe but stable COPD, subjects received either salmeterol 50 mcg/fluticasone 500 mcg twice daily or salmeterol 50 mcg twice daily for 44 weeks. Exacerbation frequency was significantly lower in the combination group (334 versus 464 episodes) which corresponded to a 35% reduction in the annualized rate. The time to the first exacerbation was also delayed with the combination therapy.[115] One finding of concern reported in this trial was the increased number of pneumonia cases in patients receiving combination therapy compared to salmeterol alone. There were 23 cases reported, compared with 7 in the salmeterol group.[115] An increase in the risk for pneumonia was also reported in the Towards a Revolution in COPD Health (TORCH) study.[116] This finding requires further investigation.

The largest prospective study to date is referred to as the TORCH study.[116] This trial consisted of 6,112 patients who received one of four treatments for 3 years. Treatment groups were placebo, salmeterol 50 mcg twice daily, fluticasone 500 mcg twice daily, or the combination of salmeterol and fluticasone in a single inhaler. The primary outcome was death from any cause and secondary outcomes were exacerbation rates, lung function, and health status. None of the active treatments differed significantly from placebo, although the combination of salmeterol and fluticasone trended toward fewer deaths ($p = 0.052$). The combination also reduced exacerbation rates, and improved lung function and health status compared to the other treatments. Exacerbation rates were also significantly reduced with combination therapy compared to either single agent alone. Both treatment groups that included fluticasone had higher rates of pneumonia. Although this study did not reflect a mortality benefit, the authors indicated the risk of death was reduced by 17.5% with the combination and that the number needed to treat for 1 year to provide a benefit was 4.

Combinations of Long-Acting Bronchodilators Compared to Long-Acting Bronchodilators Plus Inhaled Corticosteroids The combination of salmeterol and tiotropium has also been evaluated in a short-term crossover study involving only 22 subjects who received either salmeterol (50 mcg twice daily) plus fluticasone (500 mcg twice daily), fluticasone plus tiotropium (18 mcg once daily), or fluticasone, salmeterol, and tiotropium for 1 week. The triple combination provided a significant benefit of improved lung function compared to either of the dual treatments in subjects with moderate to severe COPD.[117] The benefit of triple therapy was evaluated in a 1-year randomized, double-blind, placebo control study involving 449 subjects with moderate to severe COPD. Treatment consisted of either tiotropium, tiotropium plus salmeterol, or tiotropium, salmeterol and fluticasone.[118] There was no difference between treatments for the primary outcome of percentage of patients experiencing an exacerbation requiring systemic corticosteroids or antibiotics. The triple-drug regimen improved lung function, quality of life, and reduced hospitalization compared to tiotropium alone, whereas two-drug therapy did not offer any benefit in lung function improvement or hospitalization rates compared to the single agent. Another small study evaluated the addition of tiotropium for 1 month to a regimen of an inhaled corticosteroid and a long-acting β-agonist.[119] The addition of tiotropium improved lung function and quality-of-life scores, apparently by improving dynamics of lung capacity (inspiratory capacity). These effects were reversed when tiotropium therapy was discontinued. These data involving combinations of long acting bronchodilators are limited and preliminary. More research is required and should include other outcome parameters including relief of symptoms, exacerbation rates and quality of life. Larger sample sizes and longer durations will provide insight into the value of combinations.

α_1-Antitrypsin Replacement Therapy

In patients with inherited AAT deficiency-associated emphysema, treatment focuses on reduction of risk factors such as smoking, symptomatic treatment with bronchodilators, and augmentation therapy with replacement AAT. Based on knowledge about the relationship between serum concentrations of AAT and the risk of developing emphysema, the rationale for augmentation therapy is to maintain serum concentrations above the protective threshold throughout the dosing interval.[120] Indirect evidence of AAT activity in the interstitium of the lung has been demonstrated by measuring

concentrations of the enzyme in epithelial lining fluid obtained during bronchoalveolar lavage. Augmentation therapy consists of weekly infusions of pooled human AAT to maintain AAT plasma levels greater than 10 micromolars. Much of the data supporting the use of AAT replacement is based on evidence of biochemical efficacy (e.g., administering the product and demonstrating protective serum concentrations of AAT).

Clinical evidence for slowing lung function decline or improving outcomes with augmentation therapy is sparse. Stated challenges to performing randomized clinical trials include the large sample size and long duration of followup required, and the expense of conducting such a trial. One observational study followed patients in the National Registry of Severe AAT Deficiency over a period of several years and documented clinical outcomes. In this study, patients who received weekly augmentation therapy with purified AAT had slower declines in FEV_1 and decreased mortality compared with patients who never received augmentation therapy.[121] However, this was an observational study of patients, not a randomized, placebo-controlled trial, and so direct cause-and-effect relationships cannot be concluded. One randomized, placebo-controlled study of patients with severe AAT deficiency (ZZ phenotype) did show a significant reduction in lung tissue loss and destruction as measured by computed tomographic scan in patients receiving augmentation therapy.[122] Other measures of lung function and mortality were not recorded.

The recommended dosing regimen for replacement AAT is 60 mg/kg administered intravenously once a week at a rate of 0.08 mL/kg per minute, adjusted to patient tolerance. It has been estimated that this form of augmentation therapy will cost more than $54,000 annually.[123] In the absence of alternative treatments, it is difficult to assess cost-effectiveness using conventional criteria. There have been repeated problems with supply of this biologic replacement therapy (derived from pooled blood donors) related to production difficulty and contamination issues. Currently, there are three products available (Prolastin [Bayer], Aralast [Baxter], and Zemaira [ZLB Behring]), which should minimize this problem in the future. Drug development research continues in the area of recombinant products and inhalational therapy.

The safety of AAT replacement therapy has been recently evaluated in two large observational studies. In the most recent study, 174 patients (n = 747) reported 720 adverse events, classified as severe in 8.8% of cases and moderate in 72.4% of cases.[124] Common complaints included headache, dizziness, nausea, dyspnea, and fever. The overall rate of adverse events was low (i.e., two events over 5 years).

TREATMENT

Chronic Obstructive Pulmonary Disease Exacerbation

■ DESIRED OUTCOMES

10 The goals of therapy for patients experiencing exacerbations of COPD are (a) prevention of hospitalization or reduction in hospital stay, (b) prevention of acute respiratory failure and death, and (c) resolution of exacerbation symptoms and a return to baseline clinical status and quality of life. Acute exacerbations can range from mild to severe. Factors that influence the severity, and subsequently the level of care required, include the severity of airflow limitation, presence of comorbidities and the history of previous exacerbations. Table 29–12 includes factors that warrant treatment in the hospital.

Table 29–13 summarizes the various therapeutic options for exacerbation management. Pharmacotherapy consists of intensification of bronchodilator therapy and a short course of systemic corticosteroids. Antimicrobial therapy is indicated in the presence of selected symptoms. As the frequency and severity of exacerbations are closely related to each patient's overall health status, all patients should receive optimal chronic treatment, including smoking cessation, appropriate pharmacologic therapy, and preventative therapy such as vaccinations.

TABLE 29-12 Factors Favoring Hospitalization for Treatment of Chronic Obstructive Pulmonary Disease Exacerbation

Presence of high risk comorbidity (e.g., pneumonia, arrhythmia, congestive heart failure, diabetes, renal or hepatic failure)
Suboptimal response to outpatient management
Marked worsening of dyspnea
Inability to eat or sleep because of symptoms
Worsening hypoxemia or hypercapnia
Mental status changes
Lack of home support for care
Uncertain diagnosis

Modified from the American Thoracic Society.
Adapted from reference 2.

■ NONPHARMACOLOGIC THERAPY

Controlled Oxygen Therapy

Oxygen therapy should be considered for any patient with hypoxemia during an exacerbation. Caution must be used, however, because many patients with COPD rely on mild hypoxemia to trigger their drive to breathe. In normal, healthy individuals, the drive to breathe is triggered by carbon dioxide accumulation. In patients with COPD who retain carbon dioxide as a result of their disease progression, hypoxemia rather than hypercapnia becomes the main trigger for their respiratory drive. Overly aggressive administration of oxygen to patients with chronic hypercapnia may result in respiratory depression and respiratory failure. Oxygen therapy should be used to achieve a PaO_2 of greater than 60 mm Hg or oxygen saturation of greater than 90%. However, an ABG should be obtained after oxygen initiation to monitor carbon dioxide retention owing to hypoventilation.

Noninvasive Mechanical Ventilation

Noninvasive positive-pressure ventilation (NPPV) provides ventilatory support with oxygen and pressurized airflow using a face or nasal mask with a tight seal but without endotracheal intubation. Numerous

TABLE 29-13 Therapeutic Options for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Therapy	Comments
Antibiotics	Recommended if two or more of the following are present: Increased dyspnea Increased sputum production Increased sputum purulence
Corticosteroids	Oral or intravenous therapy may be used. If intravenous is used, it should be changed to oral after improvement in pulmonary status. If continued longer than 14 days, then the dose should be tapered to avoid hypothalamic–pituitary–adrenal axis suppression.
Bronchodilators	Metered-dose inhalers and dry-powder inhalers equal in efficacy to nebulization. β-Agonists also may increase mucociliary clearance. Long-acting β-agonists should not be used for quick relief of symptoms or on an as-needed basis.
Controlled oxygen therapy	Titrate oxygen to desired oxygen saturation (>90%). Monitor arterial blood gas for development of hypercapnia.
Noninvasive mechanical ventilation	Consider for patients with acute respiratory failure. Not appropriate for patients with altered mental status, severe acidosis, respiratory arrest, or cardiovascular instability.

trials have reported the benefits of NPPV in patients with acute respiratory failure caused by COPD exacerbations. In one meta-analysis of eight studies, NPPV was associated with lower mortality, lower intubation rates, shorter hospital stays, and greater improvements in serum pH in 1 hour when compared with treatment with usual care alone.[125] The benefits seen with NPPV generally can be attributed to a reduction in the complications that often arise with invasive mechanical ventilation. Not all patients with COPD exacerbations are appropriate candidates for NPPV. Patients with altered mental status may not be able to protect their airway and thus may be at increased risk for aspiration. Patients with severe acidosis (pH <7.25), respiratory arrest, or cardiovascular instability should not be considered for NPPV. Patients failing a trial of NPPV or those considered poor candidates may be considered for intubation and mechanical ventilation.

■ PHARMACOLOGIC THERAPY

Bronchodilators

During exacerbations, intensification of bronchodilator regimens is used commonly. The doses and frequency of bronchodilators are increased to provide symptomatic relief. Short-acting β_2-agonists are preferred owing to rapid onset of action. Anticholinergic agents may be added if symptoms persist despite increased doses of β_2-agonists. In fact, combinations of these agents are employed often, although data are lacking about the benefit versus higher doses of one agent. Bronchodilators may be administered via MDIs or nebulization with equal efficacy. Nebulization may be considered for patients with severe dyspnea who are unable to hold their breath after actuation of an MDI. Clinical evidence supporting the use of theophylline during exacerbations is lacking, and thus theophylline generally should be avoided. However, addition of one of these agents may be considered for patients not responding to other therapies. The risk of adverse effects such as cardiac arrhythmias should be considered and serum levels monitored closely.

Corticosteroids

Until recently, the literature supporting the use of corticosteroids in acute exacerbations of COPD was sparse. However, since 1996, five studies have been performed that document the value of systemic corticosteroids in exacerbations of COPD.[126–130] The Systemic Corticosteroids in Chronic Obstructive Pulmonary Disease Exacerbations (SCCOPE) trial evaluated three groups of patients hospitalized for exacerbations of COPD.[126] The first group received an 8-week course of corticosteroids given as methylprednisolone 125 mg intravenously every 6 hours for 72 hours, followed by once-daily oral prednisone (60 mg on days 4 through 7; 40 mg on days 8 through 11; 20 mg on days 12 through 43; 10 mg on days 44 through 50; and 5 mg on days 51 through 57). The second group received a 2-week course given as methylprednisolone 125 mg intravenously every 6 hours for 72 hours, followed by oral prednisone (60 mg on days 5 through 7; 40 mg on days 8 through 11; and 20 mg on days 12 through 15) and placebo on days 16 through 57. The third group received placebo for all 57 days of study. Rates of treatment failure and hospital stay were significantly higher in the placebo group than in either treatment group at 30 and 90 days. Groups randomized to corticosteroid treatment also had a significantly shorter length of hospital stay than did the placebo group. The 8-week regimen was not found to be superior to the 2-week regimen. Significant treatment benefits were no longer evident at 6 months.

Davies et al.[127] evaluated the oral use of corticosteroids in hospitalized patients with acute exacerbations of COPD. Patients received either 30 mg/day oral prednisolone or placebo for 14 days. Patients who were treated with corticosteroids had a significantly more rapid improvement in FEV_1 and a shorter hospital stay than did patients who received placebo. There was no significant difference between groups at 6-week followup.

In total, results from these trials suggest that patients with acute exacerbations of COPD should receive a short course of intravenous or oral corticosteroids. However, because of the large variability in dosage ranges, the optimal dose and duration of corticosteroid treatment are not known. It appears that short courses (9 to 14 days) are as effective as longer courses and have a lower risk of associated adverse effects owing to less time of exposure. Several trials used high initial doses of steroids before tapering to a lower maintenance dose. Adverse effects such as hyperglycemia, insomnia, and hallucinations may occur at higher doses. Depending on the clinical status of the patient, treatment may be initiated at a lower dose or tapered more quickly if these effects occur. It appears that a regimen of prednisone 40 mg orally daily (or equivalent) for 10 to 14 days can be effective for most patients.[131] If steroid treatment is continued for longer than 2 weeks, a tapering oral schedule should be employed to avoid signs of hypothalamic–pituitary–adrenal axis suppression.

Antimicrobial Therapy

⓫ Most acute exacerbations of COPD are thought to be caused by viral or bacterial infections. However, as many as 30% of exacerbations are caused by unknown factors.[1] A meta-analysis of nine studies evaluating the effectiveness of antibiotics in treating exacerbations of COPD determined that patients receiving antibiotics had a greater improvement in peak expiratory flow rate than those who did not.[132]

This meta-analysis concluded that antibiotics are of most benefit and should be initiated if at least two of the following three symptoms are present: increased dyspnea, increased sputum volume, and increased sputum purulence. The utility of sputum Gram stain and culture is questionable because some patients have chronic bacterial colonization of the bronchial tree between exacerbations.

The emergence of drug-resistant organisms has mandated that antibiotic regimens be chosen judiciously. Selection of empirical antimicrobial therapy should be based on the most likely organism(s) thought to be responsible for the infection based on the individual patient profile. The most common organisms for any acute exacerbation of COPD are *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae,* and *Haemophilus parainfluenzae.* More virulent bacteria may be present in patients with more complicated acute exacerbations of COPD, including drug-resistant pneumococci, β-lactamase–producing *H. influenzae* and *M. catarrhalis,* and enteric gram-negative organisms, including *Pseudomonas aeruginosa.* Table 29–14 summarizes recommended antimicrobial therapy for exacerbations of COPD and the most common organisms based on patient presentation.[133]

Therapy with antibiotics generally should be continued for at least 7 to 10 days. Studies evaluating shorter treatment courses (usually 5 days) with the fluoroquinolones, second- and third-generation cephalosporins, and macrolide antimicrobials have demonstrated comparable efficacy with the longer treatment regimens.[134] If the patient deteriorates or does not improve as anticipated, hospitalization may be necessary, and more aggressive attempts should be made to identify potential pathogens responsible for the exacerbation.

■ COMPLICATIONS

Cor Pulmonale

Cor pulmonale is right-sided heart failure secondary to pulmonary hypertension. Long-term oxygen therapy and diuretics have been the mainstays of therapy for cor pulmonale. Increasing the PaO_2 above 60 mm Hg with supplemental oxygen therapy decreases pulmonary hypertension and thus decreases the force against which the right ventricle has to work. Although diuretics may help decrease fluid overload, caution should be used because patients with significant

TABLE 29-14 Recommended Antimicrobial Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Patient Characteristics	Likely Pathogens	Recommended Therapy
Uncomplicated exacerbations <4 exacerbations per year No comorbid illness FEV_1 >50% of predicted	*Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis* *Haemophilus parainfluenzae* Resistance uncommon	Macrolide (azithromycin, clarithromycin) Second- or third-generation cephalosporin Doxycycline Therapies not recommended[a]: TMP-SMX, amoxicillin, first-generation cephalosporins, and erythromycin
Complicated exacerbations Age ≥65 years >4 exacerbations per year FEV_1 <50% but >35% of predicted	As above plus drug-resistant pneumococci, β-lactamase–producing *H. influenzae* and *M. catarrhalis*	Amoxicillin/clavulanate Fluoroquinolone with enhanced pneumococcal activity (levofloxacin, gemifloxacin, moxifloxacin)
Complicated exacerbations with risk of *Pseudomonas aeruginosa*	Some enteric gram-negatives	Fluoroquinolone with enhanced pneumococcal and *P. aeruginosa* activity (levofloxacin)
Chronic bronchial sepsis[b] Need for chronic corticosteroid therapy Resident of nursing home >4 exacerbations per year FEV_1 >35% of predicted	As above plus *P. aeruginosa*	IV therapy if required: β-lactamase–resistant penicillin with antipseudomonal activity Third- or fourth-generation cephalosporin with antipseudomonal activity

FEV_1, forced expiratory volume in the first second of expiration; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] TMP-SMX should not be used because of increasing pneumococcal resistance; amoxicillin and first-generation cephalosporins are not recommended because of β-lactamase susceptibility; and erythromycin is not recommended because of insufficient activity against *H. influenzae*.

[b] In sepsis, double antipseudomonal coverage should be considered (e.g., addition of aminoglycoside).

Modified and updated from reference 1.

right-sided heart failure are highly dependent on preload for cardiac output. Consequently, the decision to use diuretics must be based on a risk-to-benefit ratio. Digitalis glycosides have no role in the treatment of cor pulmonale.

Other pharmacologic agents that have been investigated to treat cor pulmonale include hydralazine, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II antagonists. However, there is insufficient evidence to offer guidelines for the role of these agents in COPD patients with cor pulmonale.

Polycythemia

Polycythemia secondary to chronic hypoxemia in COPD patients can be improved by either oxygen therapy or periodic phlebotomy if oxygen therapy alone is not sufficient. Continuous oxygen therapy was shown by the Nocturnal Oxygen Therapy Trial Group to reduce hematocrit values in treated patients.[31] Acute phlebotomy is indicated if the hematocrit is above 55% to 60% and the patient is experiencing central nervous system effects suggestive of sludging from high blood viscosity. Long-term oxygen then can be used to maintain a lower hematocrit.

OTHER PHARMACOLOGIC CONSIDERATIONS

A number of other treatments have been explored over the years. Among these therapies, there is either insufficient evidence to warrant recommending their use, or they have been proven to not be beneficial in the management of COPD. A brief summary is provided because the clinician likely will encounter patients who are receiving or inquire about these treatments.

Suppressive Antimicrobial Agents

Because COPD patients often are colonized with bacteria and experience recurrent exacerbations of their condition, a common practice employed in the past has been the use of low-dose antimicrobial therapy as preventative or prophylaxis against these acute exacerbations. However, clinical studies over the past 40 years have failed to demonstrate any benefit from this practice.[1] The role of antimicrobial therapy is limited to acute exacerbations of COPD meeting specific criteria.

Expectorants and Mucolytics

Adequate water intake generally is acceptable to maintain hydration and assist in the removal of airway sections. Beyond this, the regular use of mucolytics or expectorants for COPD patients has no proven benefit.[135] This includes the use of saturated solutions of potassium iodide, ammonium chloride, acetylcysteine, and guaifenesin. In 2007, the FDA announced its intention to take action against several companies marketing unapproved timed-released formulations of guaifenesin. Two formulations are approved by the FDA (Humibid and Mucinex); however, data are lacking on their benefit.

Narcotics

Systemic (oral and parenteral) opioids, especially morphine, can relieve dyspnea in patients with endstage COPD. Nebulized therapy is sometimes used in clinical practice although data about clinical benefit are lacking.[136] Opioids should be used carefully, if at all, to avoid adverse effects on ventilatory drive.

Respiratory Stimulants

There is no role for respiratory stimulants in the long-term management of COPD.[1] Agents that have shown some usefulness in the acute setting include almitrine and doxapram. However, amiltrine is available only in Europe, and its usefulness is limited by neurotoxicity. Doxapram is available for intravenous use only and may be no better than intermittent NPPV.

SURGICAL INTERVENTION

Various surgical options have been employed in the management of COPD. These include bullectomy, lung volume reduction surgery (LVRS), and lung transplantation. Bullectomy has been performed for many years and may be useful when large bullae (>1 cm) are noted on computed tomographic scan. The presence of bullae may contribute to complaints of dyspnea and their removal can improve lung function and reduce symptoms, although there is no evidence of a mortality benefit. Because of the prevalence of COPD, it is the most frequent indication for lung transplantation. Intervention is considered when predicted survival is less than 2 years, FEV_1 is <25% predicted, and hypoxemia, hypercapnia, and pulmonary hypertension exists despite medical management.[2] Experience to

date shows 2-year survival of 65% to 90%, and 5-year survival of 41% to 53%.

Recent trials have evaluated the effect of bilateral LVRS for management of severe COPD. Short-term trials comparing the effects of pulmonary rehabilitation plus LVRS with pulmonary rehabilitation alone reported that the combination of treatments resulted in greater improvements in lung function, gas exchange, and quality of life at 3 months. Only recently have data evaluating the long-term effect of LVRS compared with pulmonary rehabilitation been published. The National Emphysema Treatment Trial, a prospective, randomized trial evaluating the long-term effects of LVRS plus pulmonary rehabilitation compared with pulmonary rehabilitation alone, followed 1,218 patients for 3 years.[137] The primary end points for the study were mortality and maximal exercise capacity 2 years after randomization. Secondary end points included pulmonary function, distance walked in 6 minutes, and quality-of-life measurements. At an interim analysis, patients with an FEV_1 of less than 20% of predicted or a carbon monoxide diffusing capacity of less than 20% of predicted were noted to be at high risk of death after surgery and subsequently were excluded from the study. Results of the study showed no mortality benefit with LVRS compared with pulmonary rehabilitation alone. Patients undergoing surgery had improved exercise capacity, lung function, and quality of life at 2 years, but these patients also had a higher risk of short-term morbidity and mortality associated with the surgery. A subgroup analysis of the study noted that patients with predominately upper-lobe emphysema and low exercise capacity undergoing surgery had lower mortality rates at 2 years compared with patients treated with medical therapy alone. Because of the costs and risks associated with LVRS, more studies are needed to better determine the ideal surgical candidates and identify subgroups of patients who would benefit most from surgery.

DIETARY SUPPLEMENTS

There is increasing interest in the role of antioxidants, including vitamins E and C and β-carotene, in reducing the frequency of exacerbations. It is postulated that they may be beneficial in COPD as a result of an imbalance between oxidants and antioxidants that has been considered in the pathogenesis of smoking-induced lung disease. However, there is no good evidence that antioxidant therapies improve COPD symptoms or slow disease progression.

INVESTIGATIONAL THERAPIES

Based on the knowledge about the importance of neutrophilic inflammation in COPD and potential therapeutic benefit of inhibition of neutrophil activity, a number of antiinflammatory compounds are being explored. Specifically, agents inhibiting leukotriene B_4, neutrophil elastase, and phosphodiesterases currently are being evaluated. To date, studies evaluating leukotriene-modifying therapies have been disappointing. Further studies are needed to evaluate the clinical benefit of such inhibitors in patients with COPD.

Phosphodiesterase-4 is the major phosphodiesterase found in airway smooth muscle cells and inflammatory cells and is responsible for degrading cyclic adenosine monophosphate. Inhibition of phosphodiesterase-4 results in relaxation of airway smooth muscle cells and decreased activity of inflammatory cells and mediators such as tumor necrosis factor-α and interleukin-8. Two phosphodiesterase-4 inhibitors have reached clinical trials—cilomilast and roflumilast. Cilomilast has been evaluated in several human trials and has been shown to improve expiratory airflow as measured by FEV_1 in patients with COPD when given at a dose of 15 mg twice daily for 6 weeks. To date, the results of clinical trials investigating these agents have been modest. Future studies of these agents should evaluate effects on other clinical outcomes such as health status, exacerbation frequency, and progression of disease.

Neutrophil elastase is implicated in the induction of bronchial disease, causing structural changes in lungs, impairment of mucociliary clearance, and impairment of host defenses. Protease inhibitors, namely, inhibitors of neutrophil elastase, are being investigated currently for the treatment of COPD.

Results have been disappointing in evaluating the benefit of infliximab, a tumor necrosis factor-α blocker, in treating COPD. A total of 234 patients with moderate to severe COPD received either infliximab 3 mg/kg or 5 mg/kg, or placebo at baseline, 2, 6, 12, 18, and 24 weeks. Subjects completed a quality-of-life questionnaire (Chronic Respiratory Questionnaire) during treatment and out to 44 weeks. There were no differences on the Chronic Respiratory Questionnaire, or on any secondary end points, including lung function, exercise capacity, or exacerbation rates. The discontinuation rate as a consequence of adverse events was high (20% to 27%) in the active-treatment group.[138]

PHARMACOECONOMIC CONSIDERATIONS

The overall cost of therapy is an important consideration in contemporary medical practice. Meaningful cost analysis goes beyond the cost of the medication itself and incorporates the impact of a given therapeutic agent on overall healthcare cost. Because of the relative lack of benefit among objective outcome measures in COPD clinical trials, pharmacoeconomic studies can be useful in decision making about pharmacotherapy options. Pharmacoeconomic analyses in COPD, although limited, are available regarding antibiotic use in acute exacerbations and some therapies for management of chronic stable COPD.

The costs of managing an acute exacerbation of COPD in the ambulatory setting was evaluated in more than 2,400 patients. Subjects were followed for 1 month following the diagnosis of the exacerbation. The overall relapse rate was 21%, with 31% and 16% of subjects requiring care in the emergency department and hospital, respectively. The overall costs for exacerbation treatment averaged $159, with 58% attributed to hospitalization.[139] These authors concluded that a significant cost savings would result from improving the successful ambulatory management of acute exacerbations.

Grossman et al. conducted a trial investigating the use of aggressive antimicrobial therapy (ciprofloxacin), comparing it with usual antibiotic therapy (defined as any nonquinolone) in the treatment of acute exacerbations of COPD.[140] Overall, the results indicated no preference for either treatment arm. However, in patients who were categorized as high risk (severe underlying lung disease, more than four exacerbations per year, duration of bronchitis longer than 10 years, elderly, significant comorbid illness), the use of aggressive antibiotic therapy was associated with improved clinical outcome, higher quality of life, and fewer costs. The results of this study are consistent with Table 29–14, which suggests that higher-risk patients are likely to have more resistant strains of organisms and thus require more aggressive antimicrobial treatment.

Friedman et al. conducted a post hoc pharmacoeconomic evaluation of two multicenter, randomized trials comparing the combination of ipratropium and albuterol with both drugs used as monotherapy.[141] Patients who received a combination of ipratropium and albuterol had lower rates of exacerbations, lower overall treatment costs, and improved cost-effectiveness compared with either drug used alone. With the introduction of new bronchodilator therapies, and with no clearly consistent advantage of one class of agents over another, pharmacoeconomic analyses may be useful for clinicians in determining the most appropriate therapy for their patients.

CLINICAL CONTROVERSIES

Albuterol is one of the most commonly prescribed medications in the United States. Albuterol is a 50/50 racemic mixture of (*R*)-albuterol and (*S*)-albuterol, with the (*R*)-isomer responsible for all the therapeutic effect. A single-isomer product, levalbuterol, claims clinical superiority based on the absence of the (*S*)-isomer, which may have detrimental effects in the airway and antagonistic effects on the active isomer. However, the acquisition cost of levalbuterol is significantly higher than that of generic albuterol. The advantages of using the single-isomer product in clinical practice are not clear and require further investigation.

A combination product of a long-acting inhaled β-agonist (salmeterol) and an inhaled corticosteroid agent (fluticasone) is one of the most commonly prescribed medications for lung disease, including COPD. However, in expert guidelines, inhaled corticosteroids are indicated only for patients with more severe disease who experience frequent exacerbations. Many patients now receiving therapy with the combination inhaler may be candidates for bronchodilator therapy alone, although the benefit of inhaled corticosteroids continues to be a focus of clinical research, including the potential for a mortality benefit.

The role of systemic corticosteroids for acute exacerbations of COPD has been clarified in recent years. However, the appropriate dosage regimen is not well established. Regimens range from initial high doses (methylprednisolone 125 mg every 6 hours) to more conservative dosing (prednisone 40 to 60 mg/day). Consensus guidelines indicate that bronchodilator therapy is the focus of pharmacotherapy for COPD. However, there is no clear choice for the initial agent. For patients with daily but not persistent symptoms, either ipratropium or albuterol offers advantages as initial therapy. Both also have limitations if chosen as the initial therapy.

International guidelines recommend long-acting bronchodilator therapy in patients with moderate to very severe disease, or who when symptoms are not adequately managed with short-acting agents or as needed therapy. When response to a single long-acting bronchodilator is not optimal, guidelines recommend the use of combinations. However, data are lacking presently about the therapeutic benefit of combinations of long-acting bronchodilators and this approach is associated with substantial costs.

EVALUATION OF THERAPEUTIC OUTCOMES

To evaluate therapeutic outcomes of COPD effectively, the practitioner must first delineate between chronic stable COPD and acute exacerbations. In chronic stable COPD, pulmonary function tests should be assessed periodically and with any therapy addition, change in dose, or deletion of therapy. Because objective improvements often are minimal, subjective assessments are important. Other outcome parameters are commonly evaluated, including dyspnea score, quality-of-life assessments, and exacerbation rates, including visits to the emergency department or hospitalization. In acute exacerbations of COPD, white blood cell count, vital signs, chest radiography, and changes in frequency of dyspnea, sputum volume, and sputum purulence should be assessed at the onset and throughout treatment of an exacerbation. In more severe exacerbations, ABGs and oxygen saturation also should be monitored. As with any drug therapy, patient adherence to therapeutic regimens, side effects, potential drug interactions, and subjective measures of quality of life also must be evaluated.

END-OF-LIFE CARE

Based on the natural course of COPD, characterized by the progressive decline in lung function, and development of complications, consideration should be given to end-of-life decisions and advanced directives.[142] Factors associated with expected mortality within 1 year have been identified and include older age, diagnosis of depression, declining overall health status, hypercapnia, an FEV_1 of less than 30% predicted, ability to walk only a few steps without resting, more than one emergent hospitalization in the past year, and the presence of comorbidities, including congestive heart failure. An effective strategy to discuss end-of-life care involves the patient's participation in identifying advanced directives. Patients should be assured that symptoms, including pain, will be managed, and their dignity will be preserved. Specific issues that should be addressed include location and provider for terminal care, desires to use or withhold mechanical ventilation, and involvement of other family members in decisions on behalf of the patient.

ABBREVIATIONS

AAT: α_1-antitrypsin

BMI: body mass index

COPD: chronic obstructive pulmonary disease

DPI: dry-powder inhaler

FEV_1: forced expiratory volume in the first second of expiration

FVC: forced vital capacity

GOLD: Global Initiative for Chronic Obstructive Lung Disease

LVRS: lung volume reduction surgery

MDI: metered-dose inhaler

NPPV: noninvasive positive-pressure ventilation

PaO_2: pressure exerted by oxygen gas in arterial blood

$PaCO_2$: pressure exerted by carbon dioxide gas in arterial blood

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