Chronic obstructive pulmonary disease (COPD) is a poorly reversible disease of the lungs that is one of the major causes of morbidity and mortality worldwide. In the United States, it is the fourth leading cause of death after heart disease, cancer, and cerebrovascular disease. By 2020, it is projected to become the third leading cause of death worldwide. Contrary to the trends for other major chronic diseases in the United States, the prevalence of and mortality from COPD have continued to rise; the death rates doubled between 1970 and 2002, and for the first time in 2000, mortality figures for women surpassed those for men. In the United States, 12 million patients are currently diagnosed with COPD, but there is believed to be at least an equal number of individuals with impaired lung function suggestive of COPD who are undiagnosed. Given that the majority of COPD cases are caused by smoking, it is primarily a preventable disease.

Most patients with COPD are middle-aged or elderly. In 2000, 16 million office visits were attributed to COPD-related conditions, with the caseload expected to increase with the aging of the population. There is no cure for COPD. True breakthroughs in treatment, particularly disease-modifying agents, have been elusive. The only strategy known to reduce the incidence of the disease is smoking cessation. Healthcare costs associated with COPD are approaching $18 billion and $14 billion in direct and indirect costs, respectively. Hospitalizations, which often result from acute exacerbations, account for approximately 40% of direct costs; prescription drugs account for 20%. Emergency department visits for COPD totaled 1.5 million in 2000. Inpatient mortality from acute exacerbation is 10% by some estimates, and nearly 60% at 1 year for patients older than 65 years of age.

Despite these disturbing figures, COPD remains largely unrecognized as a public health problem. To increase awareness of COPD, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was launched in 1997, as a collaboration of the National Heart, Lung, and Blood Institute, the National Institutes of Health, and the World Health Organization, to disseminate information on causes of COPD and issue management guidelines. Further multidisciplinary efforts involving government, healthcare workers, and public health officials are needed to reduce the disease burden of COPD, which comprises not only economic and healthcare system costs but also losses to patients and families from progressive disability and impaired quality of life.

**Definitions**

COPD comprises a diverse group of clinical syndromes that share the common feature of limitation of
expiratory airflow. The American Thoracic Society defines COPD in terms of chronic bronchitis and emphysema. Chronic bronchitis is characterized by the clinical symptoms of excessive cough and sputum production; emphysema refers to chronic dyspnea, resulting from enlarged air spaces and destruction of lung tissue. The GOLD initiative defines COPD as “a disease state 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.” Asthma is also characterized by airflow obstruction and inflammation, but in addition it involves hyperresponsiveness of the airways to stimulus; therefore, the reversibility of functional deficits in asthma differentiates it from COPD.

### Risk Factors
Cigarette smoking is the principal risk factor for COPD. However, approximately 1 of 6 Americans with COPD has never smoked. Occupational and environmental exposures to chemical fumes, dusts, and other lung irritants account for 10% to 20% of cases. Individuals with a history of severe lung infections in childhood are more likely to develop COPD. Alpha-1 antitrypsin deficiency is a rare cause of COPD but should be suspected in persons in whom emphysema develops before the age of 40 or those who lack the common risk factors.

### Clinical Course
COPD is a slowly progressing disease with a long asymptomatic phase, during which lung function continues to decline. Persistent cough, particularly with mucus production, is a common symptom. Dyspnea, especially with exercise, wheezing, and chest tightness may also be present. Patients often present with the first acute exacerbation of COPD at an advanced stage. Symptoms do not usually occur until forced expiratory volume in 1 second (FEV1) is approximately 50% of the predicted normal value. As the disease progresses, exacerbations may become more frequent and life-threatening complications may develop. End-stage COPD is characterized by severe airflow limitation, severely limited performance, and systemic complications. Patients often succumb to respiratory failure or pulmonary infection. Extrapulmonary effects associated with COPD include weight loss, nutritional abnormalities, and muscle atrophy. Various phenotypes of COPD, with specific prognostic implications, have been identified.

### Pathogenesis
Cigarette smoking or exposure to noxious agents induces an inflammatory process in the lungs and airways of the bronchial tree that leads to small airway disease and parenchymal destruction. Loss of elasticity of the alveolar attachments, or their destruction, is a hallmark of emphysema. The inability of the lungs to empty results in air trapping and hyperinflation, manifested as dyspnea on exertion. Over time, this can cause the diaphragm to flatten and the rib cage to enlarge. In the late stages of COPD, hypoxemia develops. Pulmonary hypertension is a consequence of thickening of the intima and vascular smooth muscle and indicates a poor prognosis.

COPD is a slowly progressing disease with a long asymptomatic phase, during which lung function continues to decline. The net result of the pathophysiologic processes of COPD is increased resistance to airflow and decreased expiratory flow rate. Removing the inflammatory stimulus (eg, stopping smoking) does not diminish the inflammatory process. The inflammatory process in asthma is markedly different from that in COPD, but since approximately 10% of COPD patients also have asthma, some of the pathologic features may overlap.
Comorbid Conditions

Clinicians need to be aware of comorbidities in patients with COPD, which can adversely affect health status and complicate management. COPD is associated not only with other respiratory diseases (eg, pneumonia) but also with diseases affecting organ systems, such as the musculoskeletal system (eg, osteoporosis) and the cardiovascular system (eg, angina). A study of comorbidities in COPD shows the following relative risk of COPD patients for pneumonia (16.00), osteoporosis (3.14), respiratory infection (2.24), myocardial infarction (1.75), angina (1.67), fractures (1.58), and glaucoma (1.29).22 The disease has also been associated with depression.23,24

Diagnosis

Early symptom detection and evaluation allows for earlier treatment, designed to preserve lung function and slow disease progression. The diagnosis is primarily clinical,21 and most patients are diagnosed by primary care physicians. Suggestive symptoms include chronic cough, excessive sputum production, and dyspnea, especially when any of these symptoms are accompanied by a history of cigarette smoking or regular exposure to occupational or environmental pollutants or toxins. Close attention is needed to identify patients who have these findings and consider further evaluation earlier than we have in the past.

Screening for the history of smoking, cough, sputum, dyspnea, and exposures should be a routine part of the review of systems, and when present, suggests the need for further evaluation. Spirometry is used to confirm the diagnosis of COPD in suspected cases. However, evidence does not support the use of spirometry for screening purposes in adults who have no respiratory symptoms.26 A high index of suspicion is essential for early diagnosis. Patients whose FEV1/FEV1 <0.70, whose ratio of FEV1 to forced vital capacity (FVC) is <0.70 after inhalation of a short-acting bronchodilator are considered to have restricted airflow, indicative of COPD. The FEV1/FVC ratio should be compared with age-related norms before the diagnosis is confirmed, since that ratio normally declines with aging. Spirometry is useful in establishing the need for inhaled treatment in adults with COPD symptoms and whose FEV1 is <60% of predicted value.26 Spirometric measurements can be used to classify the severity of COPD, as established by GOLD (Table 1).27

Asthma should be ruled out in the differential diagnosis. Unlike COPD, asthma onset is generally early in life and its symptoms vary from day to day, tending to worsen at night or in the early morning. Asthma is often associated with allergy, rhinitis, or eczema and tends to be present in the family history.27 The degree of reversibility of airflow limitation also differentiates the 2 conditions.28

Treatment of COPD

Smoking Cessation

The single most important intervention in modifying the course of COPD in patients who smoke is smoking cessation. The Lung Health Study reported a progressive decline in postbronchodilator FEV1 in men and women who continued to smoke over an 11-year period.29 At 11 years, 38% of continuing smokers had an FEV1 <60% of the predicted normal value compared with 10% of sustained quitters.29 Most patients will make several attempts before they succeed in giving up the use of tobacco, but even a 3-minute counseling session has been shown to result in quitting rates of 5% to 10%.30 A number of drugs are effective in promoting smoking cessation, including nicotine replacement products (eg, nicotine gum, patch, inhaler), the anti-

| Table 1 Staging of COPD |
|---|---|---|
| Stage | Description | Findings (postbronchodilator FEV1) |
| 0 | At risk | Risk factors, chronic symptoms, but normal spirometry |
| 1 | Mild | FEV1/FVC ratio <70% FEV1 at least 80% of predicted value May have symptoms |
| 2 | Moderate | FEV1/FVC ratio <70% FEV1 50% to <80% of predicted value May have chronic symptoms |
| 3 | Severe | FEV1/FVC ratio <70% FEV1 30% to <50% of predicted value May have chronic symptoms |
| 4 | Very severe | FEV1/FVC ratio <70% FEV1 <30% of predicted value OR FEV1 <50% of predicted value plus severe chronic symptoms |

COPD indicates chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.
### Table 2 Medications Available for the Treatment of COPD

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Brand (generic)</th>
<th>Inhaler (µg/use)</th>
<th>Solution for NEB (mg/mL)</th>
<th>Maintenance dose</th>
<th>Indications</th>
<th>Side effects (&gt;10%, unless otherwise noted)</th>
<th>Cost of 30-day supply</th>
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<tbody>
<tr>
<td><strong>Beta2-agonist</strong></td>
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<td><strong>Anticholinergics</strong></td>
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<td><strong>Inhaled corticosteroids</strong></td>
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<td><strong>Combination short-acting beta2-agonist + anticholinergic in 1 inhaler</strong></td>
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<td><strong>Combination long-acting beta2-agonist + corticosteroid in 1 inhaler</strong></td>
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<td><strong>Methylxanthines Oral tablets/capsules</strong></td>
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COPD indicates chronic obstructive pulmonary disease; DPI, dry-powder inhaler; EIA, exercise-induced asthma; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; NEB, nebulizer; URTI, upper respiratory tract infection.

* Generic available. † Pending approval.

depressant bupropion (Zyban), the drug varenicline (Chantix), in addition to counseling. Most smokers should be treated with varenicline as a first-line agent. Smoking-cessation rates are highest when medical management is combined with counseling. Relapse is common, and patients need to be coached and realize that multiple attempts at quitting are often required before quitting permanently.

Acupuncture and hypnosis are often advertised as smoking cures; however, a meta-analysis of 22 studies comparing acupuncture with sham acupuncture or with other methods of smoking cessation found no differences in outcome.

### Employers as Motivators

Employers are in a unique position to educate, counsel, and assist employees who use tobacco. Some are viewing it as an opportunity to keep their employees healthier and reduce healthcare costs. Evangelical Community Hospital in Lewisburg, Pennsylvania, is an example of an organization that has been very proactive with smoking-cessation efforts. Through the respiratory therapy department, they developed a program that offers free nicotine replacement to employees, along with counseling. The program has a good success rate and offers ongoing encouragement to those who do not quit. More employees quit smoking when the hospital became tobacco free in November 2007.

Varenicline and nicotine replacement patches were offered to employees and their spouses at no cost since June 2007; 55 employees and 24 spouses have participated so far. This program is an example of the impact an employer can have on the health of employees.

### Pharmacotherapy

None of the medications currently available for COPD has been shown to alter the progressive deterioration of lung function that characterizes the disease. Therefore, the goals of treatment are to relieve symptoms, prevent or minimize exacerbations and complications, improve exercise performance, and decrease mortality.

Regular use of inhaled bronchodilators, either alone or in combination, to prevent and relieve symptoms is the mainstay of COPD management. Although short-acting inhaled agents are often used when needed to provide immediate symptom relief, especially in mild COPD, long-acting inhaled bronchodilators are more effective and offer greater convenience. Use of 2 bronchodilators with different durations and mechanisms of action may produce greater bronchodilation than use of a single agent, as well as reduce the potential for adverse effects from increasing the dose of a single agent. The bronchodilators most often prescribed are beta-agonists, anticholinergics, and methylxanthines (Table 2). Selecting the right agent mainly depends on the patient’s response.

On May 30, 2008, the US Food and Drug Administration (FDA) issued a public health advisory alerting patients and physicians on the transition from inhalers containing chlorofluorocarbons (CFCs) to ozone-friendly hydrofluoroalkane (HFA) inhalers by December 31, 2008. These inhalers are being phased out “because they are harmful to the environment,” the FDA says. The 3 HFA albuterol inhalers approved by the FDA are ProAir, Proventil, and Ventolin. The fourth HFA inhaler, Xopenex, contains the active medication levodilbuterol. These 4 inhalers are safe and effective replacements for the CFC inhalers, but they may feel and taste different from the CFC inhalers.

Review of published randomized controlled trials involving different types of aerosol devices (eg, metered-dose inhalers, dry-powder inhalers, nebulizers) for outpatient management of COPD did not reveal...
any differences in pulmonary function responses between the various delivery devices. Thus, cost, convenience, and the patient’s ability to use the device properly are important considerations in choosing the mode of delivery.35 In patients who have difficulty adequately using inhalers, nebulized medication may result in more reliable drug delivery.

In addition to bronchodilators, inhaled glucocorticosteroids are recommended for the treatment of severe to very severe COPD in patients who have repeated exacerbations.27 The combination of a long-acting beta,-agonist (salmeterol) and an inhaled glucocorticosteroid (fluticasone propionate) was shown in the Towards a Revolution in COPD Health (TORCH) trial to be significantly more effective than either agent alone or placebo in reducing the number of moderate or severe exacerbations and in improving health status over the 3-year study.36 However, the combination regimen did not significantly decrease the rate of death compared with placebo. The investigators say the probable reason was that the study was not sufficiently powered to detect an effect on mortality.36

Table 3 lists the types of pharmacotherapy appropriate at each stage of COPD.33 Choosing a specific medication within the class of short- or long-acting beta,-agonists, inhaled steroids, methylxanthines, or combination agents is a decision that is based on provider preference, local standards of care, and formulary availability. Several novel therapies are being investigated; many of them target inflammatory-signaling pathways.37

Although bacterial lung infections should be treated with appropriate antibiotics, long-term prophylaxis with antibiotics has not been shown to be effective in preventing bacterial infections or COPD exacerbations.31

Managing Exacerbations

Exacerbation of COPD is generally defined as an acute increase in symptoms beyond normal day-to-day variation.22 Symptoms of an exacerbation range from increased breathlessness accompanied by cough and sputum production in mild COPD to life-threatening respiratory failure in severe COPD. The frequency and severity of exacerbations correspond to the severity of the patient’s underlying disease.33 Infection, particularly bacterial infection, is frequently implicated in exacerbations. Air pollution can also trigger exacerbations; however, the cause cannot be determined in about one third of severe cases.34

COPD exacerbations can often be managed at home. Strategies include developing a plan and educating patients on its implementation during an acute exacerbation. The patient-initiated plan may include increasing the dose and/or frequency of the short-acting bronchodilator (administered by nebulizer, if necessary) and adding an anticholinergic agent. If the patient’s FEV1 is <50% of predicted value, a systemic glucocorticosteroid should also be considered to restore lung function and shorten recovery time.31,35 Antibiotic therapy should be started if infection is suspected,31 such as in the case of fever and/or purulent sputum.

Many primary care practices have acute care visits, offering same-day appointments for patients with acute exacerbations of chronic illness. If a same-day appointment with the patient’s primary provider is not offered, urgent care centers may be utilized. For home-bound patients, home health agencies can play a crucial role for expediting appropriate treatment services.

When symptoms are severe, emergency department evaluation is necessary. High-risk patients with comorbid conditions, including pneumonia, arrhythmias, heart failure, diabetes, chronic kidney disease, or liver failure, often require inpatient care. Patients who have worsening hypoxemia or hypercapnea, changes in mental status, or those who have a poor response to initial treatment are among those frequently admitted. Patients who cannot eat, sleep, or care for themselves because of worsening condition often cannot be managed at home.38 For patients who require hospitalization, oxygen therapy is the foundation of treatment. The use of supplemental oxygen should achieve a goal of a hemoglobin saturation of 90% (PaO2 of 60-65 mm Hg).37 Noninvasive intermittent ventilation is preferable in certain presentations of exacerbations. Invasive mechanical ventilation may be necessary if the patient has life-threatening hypoxemia, is in respiratory arrest, or has cardiovascular complications. Drug therapy in the hospital is similar to that for home management of an exacerbation. In addition, a methylxanthine such as theophylline may be warranted when the patient’s response to a short-acting bronchodilator is inadequate.38

Symptoms of an exacerbation range from increased breathlessness accompanied by cough and sputum production in mild COPD to life-threatening respiratory failure in severe COPD.
Nonpharmacologic Interventions

The foundation of most rehabilitation programs for patients with COPD is endurance exercise to increase work and exercise capacity.\textsuperscript{26} Meta-analysis of the results of 6 small randomized controlled trials showed that compared with usual care, exercise training reduced the number of unplanned hospital admissions as well as significantly improved the patients' health-related quality of life and capacity for exercise.\textsuperscript{19} The 6 trials all compared the efficacy of a respiratory rehabilitation program (including physical exercise) with standard care in the management of patients after an acute exacerbation of COPD. Baseline FEV\textsubscript{1} was ≤40% of predicted value for all patients included in these trials.

On the basis of clinical evidence, the American College of Physicians recommends that physicians prescribe oxygen therapy for patients with COPD and resting hypoxemia, which is defined as a PaO\textsubscript{2} ≤55 mm Hg. Supplemental oxygen for at least 15 hours daily has been shown to help increase survival in patients with severe airway obstruction (FEV\textsubscript{1} <30% of predicted value) and resting hypoxemia.\textsuperscript{26}

All patients with COPD should receive pneumococcal vaccination. An annual influenza vaccination is advised for all older patients who have COPD.\textsuperscript{27} Vaccination of persons aged 65 or older can reduce rates of hospitalization and death.\textsuperscript{28}

Surgical Modalities

Lung volume reduction surgery (LVRS) has been shown—but only among a small, very selective population of patients—to be superior to medical therapy in increasing survival, exercise capacity, and quality of life in patients who have upper-lobe emphysema and low exercise capacity.\textsuperscript{41} However, because LVRS is an expensive, palliative procedure, it should be undertaken only in carefully selected patients.\textsuperscript{27}

The multidimensional BODE index was developed to assess the risk of death from COPD in an individual patient.\textsuperscript{42} The index includes 4 variables:

- Body mass index (weight)
- Airway Obstruction (FEV\textsubscript{1})
- Dyspnea
- Exercise capacity (6-minute walk distance).

The BODE index can be useful in predicting survival after LVRS. A reduced BODE score index postoperatively has been associated with reduced mortality.\textsuperscript{43}

Lung transplantation to improve quality of life and pulmonary function is sometimes performed in appropriately chosen patients with very advanced COPD. The potential benefits of surgery in patients with COPD need to be weighed against its risks, including postoperative complications, such as lung infections and increased airflow obstruction.\textsuperscript{27}

Conclusions

COPD will remain a significant healthcare problem for years to come. Early identification of the disease through primary care screening for the common symptoms in smokers or those exposed to air pollutants or toxins will lead to earlier diagnosis and treatment. Focusing on smoking cessation will have a great impact on the progression of disease. Advancements in treatment will require translation of a more fundamental understanding of the pathophysiologic pathways involved into disease-modifying interventions. At present, management efforts are directed toward improving patients' symptoms and functional limitations through carefully selected treatment modalities.

References


Chronic Obstructive Pulmonary Disease

Stakeholder Perspective

Cost and Quality Issues in COPD Management

**PATIENTS:** Chronic obstructive pulmonary disease (COPD) is a progressive disease of adults that in many cases leads to the total debilitation of patients as they age. This is particularly significant when the patient does not take precautions to reduce the impact of active personal factors, such as smoking or obesity, which could lead to worsening of symptoms. In addition, COPD is a difficult disease for patients and physicians to manage because many environmental issues can exacerbate COPD episodes, which can lead to deterioration in quality of life over time.

The most effective way for patients with COPD to keep symptoms at a minimum and maintain a high quality of life is to actively manage their prescribed medical and pharmaceutical regimens. Cost can be a significant difficulty for patients if they do not have a prescription insurance benefit, since some of the newer medications are relatively expensive. Another
Cost issue has arisen as a result of the recent US Food and Drug Administration decision to phase out chlorofluorocarbon propellants for inhalers used to treat COPD. These inhalers, some of which have very inexpensive generics available, are being replaced with significantly more expensive new formulations with other propellants. These issues add difficulties for physicians and payers in addition to patients.

**Physicians:** Physicians have to manage patients without the benefit of a long-available medication, becoming familiar with the effectiveness of newer formulations, and fully understanding the additional cost burdens to their patients. The best way to ensure good care for these patients is to manage COPD in all of their patients according to best practice treatment guidelines, considering the cost burden when a patient has no insurance benefit or understanding the formulary issues for the insurance payers of their patients, and most important, knowing how to get exceptions when medically necessary.

**Payers:** Payers have a unique set of issues as well, since the newer inhaler formulations can significantly drive up the monthly cost of COPD treatment for patients. Payers have the unique problem of trying to balance good medical care (quality) with the value of the medications they choose for their formulary (cost-effectiveness).

Payers need to drive value-based care by adhering to best practice guidelines, educating physician panels about their guidelines, ensuring that patients that need it have access to additional services—such as educational programs, disease management programs, counselors, and, as appropriate, programs for smoking cessation, obesity, or exercise management—to deliver the highest quality of life to patients. All of this can lead to high and unnecessary costs if not well coordinated with patients and physicians. Care that is not coordinated well can also lead to poor patient compliance, patient and physician satisfaction issues, and less-than-optimal disease management for the patient.

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