Chapter 45: Chronic Obstructive Pulmonary Disease

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 80, Chronic Obstructive Pulmonary Disease.

KEY CONCEPTS

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1. Chronic obstructive pulmonary disease (COPD) is a treatable and preventable disease characterized by progressive airflow limitation that is not fully reversible and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

2. Mortality from COPD has increased steadily over the past three decades; it is the fourth leading cause of death in the United States.

3. The primary cause of COPD is cigarette smoking, implicated in 75% of diagnosed cases in the United States. Other risks include genetic predisposition, environmental exposures (including occupational dust and chemicals), and air pollution.

4. In patients with COPD, staging of airflow limitation (GOLD 1-4) is classified by spirometry measurements. Disease severity (Category A-D) is classified using a combined assessment of symptom score, as measured by a validated questionnaire, and risk for future exacerbations.

5. Smoking cessation and avoidance of other known toxins are the only management strategies proven to slow COPD progression.

6. Oxygen therapy can reduce mortality in selected patients with COPD. Oxygen therapy is indicated for patients with a resting PaO_2 of less than 55 mm Hg (7.3 kPa) or a PaO_2 of less than 60 mm Hg (8.0 kPa) and evidence of right-sided heart failure, polycythemia, or impaired neurologic function.

7. Inhaled bronchodilators are the mainstay of drug therapy for COPD and are used to relieve patient symptoms and improve exercise tolerance and quality of life. Guidelines recommend short-acting bronchodilators as initial therapy for patients with occasional symptoms and all patients as rescue therapy to relieve symptoms.

8. For patients experiencing persistent symptoms, either a long-acting β_2-agonist (LABA) or long-acting anticholinergic (LAMA) offers significant benefits, and both are of comparable efficacy. If a patient has continued symptoms, combining long-acting bronchodilator agents (LABA plus LAMA) is recommended.

9. For patients at high risk for future exacerbations, either a long-acting β_2-agonist (LABA) or long-acting anticholinergic (LAMA) is effective at reducing exacerbation frequency. Anticholinergic agents are more effective at reducing exacerbation frequency and should be considered first-line. If a patient has continued exacerbations or has more severe disease, combining long-acting bronchodilator agents (LABA plus LAMA) is recommended.

10. The role of inhaled corticosteroid (ICS) therapy in COPD is controversial. Patients with frequent and severe exacerbations may benefit from ICS therapy, although the risk of pneumonia is increased.

11. Acute exacerbations of COPD (AECOPD) 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.

12. Antimicrobial therapy should generally be used during AECOPD if the patient exhibits at least two of the following: increased dyspnea, increased sputum volume, and increased sputum purulence. A C-reactive protein (CRP) test may be helpful to guide the decision to treat a COPD exacerbation with antibiotics.

BEYOND THE BOOK

BEYOND THE BOOK

Watch the video entitled "Pathophysiology of Large and Small Airway Disease in COPD" in AccessPharmacy by Scott Stern, MD. This 5-minute video provides a visual explanation of pathophysiologic changes occurring in lungs of patients with COPD. This video assists with comprehension of physiologic changes and correlation with clinical presentation in COPD.

Watch the video "Gasping for Air: Life with COPD" (*The New York Times*, July 31, 2008). This 6-minute video provides the perspective of a patient diagnosed with COPD. This video helps remind clinicians of patient experiences with the disease, how physiologic changes are correlated with symptoms, and challenges to optimal diagnosis and treatment.

INTRODUCTION

1 Chronic obstructive pulmonary disease (COPD) is a common lung disease characterized by airflow limitation that is not fully reversible, in contrast to the reversibility of airflow limitation in asthma. COPD is both chronic and progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[1] COPD is preventable and treatable and causes significant extrapulmonary effects that contribute to disease severity in a subset of patients.

To standardize the care of patients with COPD and present evidence-based recommendations, the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) launched the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2001. The GOLD expert panel revises their recommendations annually, typically in December.[1] The goals of the GOLD organization are to increase awareness of COPD and reduce morbidity and mortality associated with the disease. In addition to GOLD, other international organizations have developed consensus guidelines focusing on preventing and managing acute exacerbations associated with COPD. The American College of Chest Physicians (ACCP) and the Canadian Thoracic Society collaborated on guidelines for the prevention of COPD exacerbations which were published in 2015.[2] In 2017, the American Thoracic Society (ATS) and European Respiratory Society (ERS) jointly published guidelines for both the prevention and management of acute exacerbations of COPD (AECOPD).[3,4]

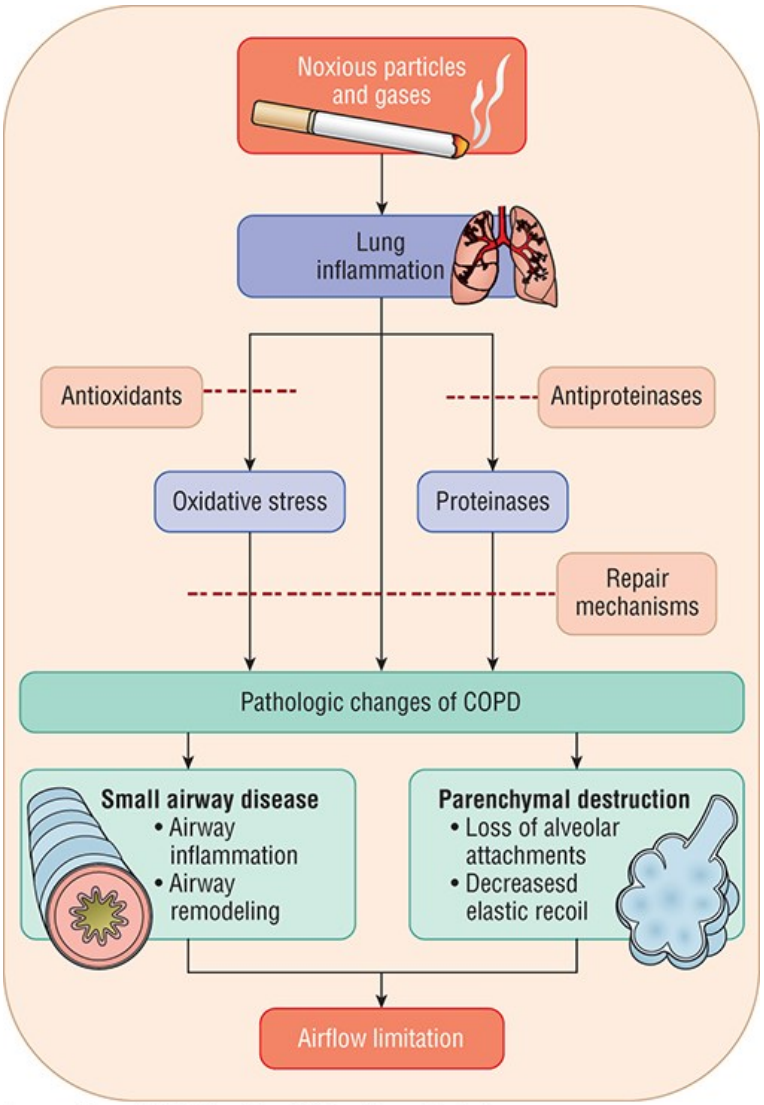
International guidelines emphasize the terms *preventable* and *treatable* to support a positive approach to managing the patient with COPD. Support is also reflected in advocacy and availability of research funding to improve understanding about this disease and its management. Examples include the creation of the Division of Lung Diseases of the NHLBI to promote and fund multidisciplinary research and collaboration as well as the Centers for Disease Control and Prevention's COPD National Action Plan, which outlines strategic goals for empowering patients and caregivers, preventing and managing disease, supporting research initiatives, and developing educational and public health policies related to COPD.[5,6]

COPD has historically described a group of pulmonary diseases with a fixed airflow limitation. The two principal conditions are chronic bronchitis and emphysema, which are phenotypes. Chronic bronchitis is associated with chronic or recurrent episodes of excessive mucus secretion into the bronchial tree with a cough 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.[1] While chronic bronchitis is defined in clinical terms, emphysema is defined in terms of anatomic pathology. Historically, emphysema was diagnosed based on histologic findings at autopsy. Given that this histologic definition has 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 without obvious fibrosis.[1]

Differentiating COPD as either chronic bronchitis or emphysema as distinct subsets of COPD is no longer considered relevant because both are caused by a common risk factor (cigarette smoking), and most patients exhibit features of both. Emphasis is placed on the pathophysiologic features of small airways disease and parenchymal destruction as contributors to chronic airflow limitation. Chronic inflammation affects the integrity of the airways, causes damage, and promotes the destruction of the parenchymal structures. The underlying problem is persistent exposure to noxious particles or gases that sustain the inflammatory response. The airways of both the lung and the parenchyma are susceptible to inflammation, and the result is the chronic airflow limitation that characterizes COPD (Fig. 45-1).

FIGURE 45-1

Pathogenesis of COPD.



EPIDEMIOLOGY

In the United States, approximately 16 million Americans are estimated to have COPD, although the true prevalence of people with chronic airflow obstruction as measured by spirometry may exceed 28 million.[7] Despite a decline in the rate of cigarette smoking among adults in the United States, the prevalence of airflow obstruction and COPD is not expected to significantly decrease in the future. Approximately 14% of the population in the United States currently smoke cigarettes. While cessation of cigarette smoking has steadily decreased over the last 10 years, the use of e-cigarettes and smokeless tobacco products has increased.[8] Historically considered a disease primarily affecting White men, women in the United States are now more likely to have a diagnosis of COPD than men. The prevalence of COPD diagnosis also varies among ethnic and racial groups and by state or region of the country. Among ethnic and racial groups, American Indians/Alaskan Natives are more affected than others, and the prevalence is higher in some southeastern states.[9,10]

Chronic obstructive pulmonary disease is the fourth leading cause of death in the United States, exceeded only by cancer, heart disease, and

unintentional injuries. Over 150,000 deaths are attributed to COPD annually.[9,10] In contrast to other leading causes of death, which have declining mortality rates, the mortality rate attributable to COPD has increased over the last 40 years. The trend of increasing COPD mortality likely reflects the long latency period between smoking exposure and complications associated with COPD. Between 1969 and 1985, the mortality rate due to COPD increased for men and then plateaued between 1985 and 1999.[11] From 1999 to 2014, the mortality rate due to COPD decreased among men but remained unchanged among women.[11,12] The magnitude difference is likely reflective of changes in smoking status among women in the first decades of the 20th century, although other gender-based differences may also contribute.[13]

While the mortality associated with COPD is significant, morbidity and costs associated with the disease also have a significant impact on patients, their families, and the healthcare system. Annually, patients with COPD account for over 15 million physician office visits and 700,000 hospitalizations. Surveys indicate that individuals with COPD are more likely to report physical activity limitations and be unable to work compared to individuals without COPD.[14] In the United States, an estimated $32 billion was spent on services related to COPD care in 2010 and increasing to $49 billion in the year 2020.[6] Costs associated with the disease are directly related to the severity of COPD and frequency of exacerbations.

ETIOLOGY

3 Cigarette smoking is the most common risk factor and accounts for approximately 75% of cases of COPD in the United States.[1,10] Although the remaining 25% of patients who develop COPD do not have a history of smoking, these patients may have exposure to environmental tobacco smoke or secondhand smoke through their occupation or family. Components of tobacco smoke activate inflammatory cells, which produce and release the inflammatory mediators characteristic of COPD. Smokers are 12 to 13 times more likely to die from COPD than nonsmokers.[15] 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.

Chronic obstructive pulmonary disease is attributed to a combination of risk factors that results in lung injury and tissue destruction, as evidenced by the fact that less than 50% of all smokers develop COPD, but not all smokers who have equivalent smoking histories develop the same degree of pulmonary impairment.[16] Risk factors can be divided into host factors and environmental factors (Table 45-1), and the interaction between these risks leads to the 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.

TABLE 45-1

Risk Factors for Development of Chronic Obstructive Pulmonary Disease (COPD)

Exposures	Host Factors
Environmental tobacco smoke	Genetic predisposition (AAT deficiency)
Occupational dust and chemicals	Airway hyperresponsiveness
Air pollution	Impaired lung growth

Environmental factors, such as tobacco smoke, 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, which result in inflammation and cell injury. Exposure to multiple environmental toxins increases the risk of COPD. Thus, the total burden of inhaled particles (eg, cigarette smoke as well as occupational and environmental particles and pollutants) plays a significant role in the development of COPD. 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.

In nonindustrialized countries, occupational exposures may be a more common risk 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 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.

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. Specific genes, such as matrix metalloproteinase 12 (MMP12), α_1-antitrypsin, and other genetic markers, have been implicated with the decline of lung function and potential risk of developing COPD.[1] However, only hereditary deficiency of α_1-antitrypsin (AAT) has been definitively shown to correlate with the development of emphysema and pulmonary dysfunction.[17] AAT-associated emphysema is an example of a purely genetic disorder inherited in an autosomal recessive pattern. A primary role of AAT, a plasma protein synthesized in hepatocytes, is to protect cells, especially those in the lung, from destruction by elastase released by neutrophils. Deficiency of AAT results in a protease–antiprotease imbalance and accelerated decline in lung function. Several types of AAT deficiency have been identified and are due to mutations in the AAT gene. True AAT deficiency accounts for less than 1% of COPD cases.[1]

Patients with AAT deficiency develop COPD at an early age (20-50 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 AAT gene 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.[17] Patients developing COPD at an early age or those with a strong family history of COPD should be screened for AAT deficiency.

Additional host factors that may influence the risk of developing COPD include airway hyperresponsiveness and lung growth. Individuals with airway hyperresponsiveness, such as asthma, 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

Chronic obstructive pulmonary disease is characterized by chronic inflammatory changes that lead to destructive tissue changes and chronic airflow limitation. The inflammatory process is widespread and involves airways, pulmonary vasculature, and lung parenchyma. Exposure to noxious gas and particles activate inflammatory cells to release a variety of chemical mediators. While both asthma and COPD result from inflammatory responses, it is helpful to contrast the types of inflammatory cells and mediators involved because the response to anti-inflammatory therapy differs between the two diseases. The inflammation seen in COPD is often referred to as *neutrophilic* in nature, but macrophages and CD8+ lymphocytes also play major roles.[1,18] In a small subset of patients with COPD, there may be inflammation common to both COPD and asthma, and such patients may be classified as having “asthma-COPD overlap syndrome.”[19] Characteristics of inflammation for the two diseases are summarized in Table 45-2.

TABLE 45-2

Features of Inflammation in COPD Compared with Asthma

	COPD	Asthma
Cells	Neutrophils Large increase in macrophages Increase in CD8+ T lymphocytes	Eosinophils Small increase in macrophages Increase in CD4+ Th2 lymphocytes Activation of mast cells
Mediators	LTB4 IL-8 TNF-α	LTD4 IL-4, IL-5 (Plus many others)
Consequences	Squamous metaplasia of the epithelium Parenchymal destruction Mucus metaplasia Glandular enlargement	Fragile epithelium Thickening of basement membrane Mucus metaplasia Glandular enlargement
Response to treatment	Glucocorticosteroids have a variable effect	Glucocorticosteroids inhibit inflammation

Other processes proposed to play a major role in the pathogenesis of COPD include increased oxidative stress and imbalance between destructive and protective defense systems in the lungs (proteases and antiproteases).[1,20] Altered interaction between airway oxidants and antioxidants is responsible for the increased oxidative stress present in COPD. Increases in oxidant markers (eg, hydrogen peroxide and nitric oxide) are seen in the epithelial lining fluid and are generated by cigarette smoke or noxious particles.[1]

Oxidants 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.[20] These processes may be the result of ongoing inflammation or occur because of environmental pressures and exposures (Fig. 45-1).

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. Mucous 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. Airflow obstruction is attributed to airway inflammation, while the blood gas abnormalities result from impaired gas transfer due to parenchymal damage and loss of alveolar-capillary networks.

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 resulting airflow obstruction and chronic airflow limitation may be reversible or irreversible. The various causes of airflow obstruction are summarized in Table 45-3.

TABLE 45-3

Etiology of Airflow Limitation in COPD

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

Parenchymal changes affect the gas-exchanging units of the lungs, including the alveoli and pulmonary capillaries. As the disease progresses, abnormalities in gas exchange lead to hypoxemia and/or hypercapnia, although there is not a strong correlation between pulmonary function and arterial blood gas (ABG). Significant changes in ABGs usually are not present until airflow limitation is very severe.[1] In such patients, hypoxemia, or low arterial oxygen tension (pressure exerted by oxygen gas in arterial blood [PaO_2] = 45-60 mm Hg [6.0-8.0 kPa]), and hypercapnia, or elevated arterial carbon dioxide tension (pressure exerted by carbon dioxide gas in arterial blood [$PaCO_2$] = 50-60 mm Hg [6.7-8.0 kPa]), can become chronic problems. Initially, when present, hypoxemia is associated with exertion. As the disease progresses, hypoxemia develops at rest. Hypoxemia is attributed to hypoventilation (V) of lung tissue relative to perfusion (Q) of the area. This low (V/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 hypoxemia.

As COPD progresses and gas exchange worsens, patients may exhibit chronic hypercapnia and are referred to as carbon dioxide retainers. In such patients, central respiratory response to chronically increased $PaCO_2$ is blunted. These changes in PaO_2 and $PaCO_2$ are subtle and progress over a period of many years. As a result, serum pH usually is near normal because the kidneys compensate by retaining bicarbonate. If acute respiratory distress develops, such as seen with significant pneumonia or COPD exacerbation with respiratory failure, $PaCO_2$ may rise sharply, and the patient presents with a worsening respiratory acidosis.

The vascular changes of COPD include loss of pulmonary capillary beds, thickening of pulmonary vessels, and vasoconstriction of pulmonary arteries in response to hypoxemia.[1,21] Chronic hypoxemia and permanent changes in pulmonary vasculature lead to increases in pulmonary pressures, especially during exercise. When elevated pulmonary pressures are sustained, right-sided heart failure, or cor pulmonale, develops and is characterized by right ventricle hypertrophy in response to increased pulmonary vascular resistance. Pulmonary hypertension is the most common cardiovascular complication of COPD and can result in significant morbidity.

Thoracic over-inflation is a relevant feature in the pathophysiology of COPD because it is a central factor in causing dyspnea. Chronic airflow obstruction leads to air trapping, resulting in thoracic hyperinflation that can be detected on chest radiograph. Hyperinflation results in several dynamic changes in the chest, including flattening of diaphragmatic muscles. Under normal circumstances, diaphragms are dome-shaped muscles tethered at the lung bases. When diaphragms contract, the muscles become shorter and flatter, creating the negative inspiratory force through which air flows into lungs during inspiration. With thoracic hyperinflation, diaphragmatic muscles are placed at a disadvantage and are less efficient muscles of ventilation. Increased work required by diaphragmatic contractions predisposes patients to muscle fatigue, especially during periods of exacerbations.

Another consequence of thoracic hyperinflation is the change in lung volumes. For patients with COPD exhibiting thoracic hyperinflation, there is an increase in functional residual capacity (FRC), which is the amount of air left in the lung after exhalation at rest. Therefore, these patients are breathing at higher lung volumes that perturb gas exchange. Increased FRC limits the inspiratory reserve capacity, which is the amount of air that the patient can inhale to fill the lungs. Increased FRC limits the duration of inhalation time and has been associated with increased complaints of dyspnea by patients.[1]

Pharmacotherapy for COPD, especially bronchodilators, can reduce thoracic hyperinflation by reducing airflow obstruction and air trapping. This explains symptom improvement reported by patients with COPD despite minimal improvements in expiratory lung function.

Another important systemic consequence of COPD is loss of skeletal muscle mass and a general decline in the overall health status. These changes are partially attributed to systemic inflammation and can have devastating effects on overall health status and comorbidities. Systemic effects include cardiovascular events associated with ischemia, cachexia, weight loss, osteoporosis, anemia, and muscle wasting.[1] There has been interest in measuring C-reactive protein as a marker to assess systemic inflammation and its correlation with disease severity; however, it is premature to recommend its use in practice for chronic management.[22] Instead, C-reactive protein may have a role in identifying patients with acute exacerbation of COPD who should receive treatment with antibiotics.

CLINICAL PRESENTATION: Chronic Obstructive Pulmonary Disease

Symptoms

- Chronic cough—may be intermittent; may be unproductive
- Chronic sputum production
- Dyspnea—worse with exercise; progressive over time
  - Decreased exercise tolerance or decline in physical activity
  - Chest tightness or wheezing

Risk Factors

- Tobacco smoke exposure
- Indoor air pollution (eg, burning wood and biofuel for cooking or heating)
- Occupational and environmental hazards (eg, organic and inorganic dusts, chemical fumes)
- α_1-Antitrypsin deficiency

Physical Examination

- Shallow breathing
- Increased resting respiratory rate
- Pursed lips during exhalation
- Use of accessory respiratory muscles
- Cyanosis of mucosal membranes (seen in later stages of disease)

Diagnostic Tests

- Spirometry with postbronchodilator testing
- Radiograph of chest (to rule out other diagnoses)
- Arterial blood gas (not routinely obtained in chronic management; has utility in acute decompensation). Lab abnormalities may include pH <7.35, PaO_2 <80 mm Hg (10.6 kPa), $PaCO_2$ >50 mm Hg (6.7 kPa), and bicarbonate >26 mEq/L (mmol/L)

The diagnosis of COPD is made based on the patient's symptoms, history of exposure to risk factors, and confirmed by pulmonary function testing, such as spirometry. Patients may experience cough for several years before dyspnea develops and often will not seek medical attention until dyspnea is significant. A diagnosis of COPD should be considered for any patient, age 40 years or older, with persistent or progressive dyspnea, with chronic cough productive of sputum, and who exhibits an unusual or abnormal decline in activity, especially in the presence of exposure to environmental tobacco smoke. In addition, the presence of genetic factors, including AAT deficiency, and occupational exposures should be evaluated as approximately 15% of patients with COPD do not have a history of cigarette smoking. Current preventative guidelines do not endorse routine screening tests for asymptomatic patients with risk factors for COPD, although some medical societies advocate proactively identifying patients early in the stages of the disease.[23]

Spirometry combined with physical examination improves the diagnostic accuracy of COPD.[1] Spirometry represents a comprehensive assessment of lung volumes and capacities. Patients with all levels of severity of COPD exhibit the hallmark finding of airflow obstruction; specifically, a reduction in FEV_1/FVC ratio to less than 70% (0.70). FVC is the total volume of air exhaled after maximal inhalation and FEV_1 is the total volume of air exhaled in 1 second. A fixed ratio of less than 70% (0.70) may be problematic because normal aging may affect this result; however, it continues to be the current standard. Previous criteria for the diagnosis of COPD included measuring the degree of airflow limitation before and after inhaled bronchodilator challenge. It is no longer recommended to obtain prebronchodilator values or to calculate the degree of reversibility to diagnose COPD (Table 45-4).[1] Postbronchodilator spirometry results should be used in assessing lung function in patients with COPD.

TABLE 45-4

Procedures for Postbronchodilator Testing

Preparation Tests should be performed when patients are clinically stable and free from a respiratory infection. Patient must be able to participate with maximal effort during the test
Spirometry Bronchodilators can be given by either a metered-dose inhaler or nebulization Usual doses are 400 mcg of β-agonist, 160 mcg of anticholinergic, or the two combined FEV_1 should be measured 10-15 minutes after a short-acting β-agonist or 30-45 minutes after a short-acting anticholinergic or combination
Results Airflow limitation is confirmed by a postbronchodilator FEV_1/FVC <0.70

Data from Reference 1.

Spirometry is useful to confirm the presence of airflow limitation and to determine the severity of obstruction.[24] GOLD consensus guidelines suggest a four-grade classification of airflow limitation (Table 45-5). The use of peak expiratory flow measurements as a diagnostic tool or to classify severity is not adequate for COPD due to low specificity and the high degree of effort dependence; however, a low peak expiratory flow is consistent with the clinical presentation of COPD. A comprehensive discussion about spirometry and interpretation can be found in Chapter e43, "Evaluation of Respiratory Function."

TABLE 45-5

Spirometric Grades: Classification of Severity of Airflow Obstruction (Based on Postbronchodilator FEV_1)

GOLD 1: mild $FEV_1/FVC < 70\%$ (0.70) $FEV_1 \geq 80\%$ With or without symptoms
GOLD 2: moderate $FEV_1/FVC < 70\%$ (0.70) $50\% \leq FEV_1 < 80\%$ With or without symptoms
GOLD 3: severe $FEV_1/FVC < 70\%$ (0.70) $30\% \leq FEV_1 < 50\%$ With or without symptoms
GOLD 4: very severe $FEV_1/FVC < 70\%$ (0.70) $FEV_1 < 30\%$

Data from Reference 1.

Dyspnea is typically the most troublesome complaint for patients with COPD and often is the stimulus for seeking medical attention. It 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.[1] As a subjective symptom, dyspnea is often difficult for the clinician to assess. Various tools are available to evaluate the severity of dyspnea. The modified Medical Research Council (mMRC) scale is commonly employed and categorizes dyspnea grades from 0 to 4.[1] Patients with COPD may experience a variety of symptoms, not limited only to dyspnea. Therefore, the impact of COPD on other measures of health status has been recognized and newer patient assessment tools, such as COPD assessment Test (CAT) and COPD Control Questionnaire (CCQ), include items related to overall symptoms and activities. Other patient assessment questionnaires, such as the Chronic Respiratory Questionnaire (CRQ) and St. George's Respiratory Questionnaire (SGRQ), are comprehensive measures of disease impact on health status and are used frequently in clinical trials; however, use in clinical practice is limited by their length and complexity. There are three patient assessment questionnaires amenable to use in routine clinical practice and recommended by international guidelines (Table 45-6).[1]

TABLE 45-6

Comparison of Patient Assessment Questionnaires Used in COPD

Name	Description of Scoring System	Link to Assessment Tool
COPD Assessment Test (CAT)	• Includes 8 items related to health status and impact of COPD on daily activities • Each item scored 0-5 with a maximum total score of 40 • Score of <10 means less symptoms • Score of ≥10 means more symptoms	http://catestonline.org
Modified Medical Research Council Dyspnea Questionnaire (mMRC)	• Includes 5 descriptive statements related to dyspnea only • Patient chooses the most appropriate statement • Each statement corresponds to a score of 0-4 • Score of <2 means less symptoms • Score of ≥2 means more symptoms	http://www.goldcopd.org
COPD Control Questionnaire (CCQ)	• Includes 10 items in 3 domains related to symptoms, functional state, mental state • Assesses clinical control of disease in the past week • Score weighted for each domain • Score <1 means less symptoms[a] • Score ≥1 means more symptoms[a]	http://www.ccq.nl

[a]Exact cut point values have not yet been established for this assessment questionnaire.

Classification Based on Severity

Previously, therapy guidelines have defined disease severity solely by spirometry. Observations that patients with similar spirometric parameters exhibit variations in symptom severity and risk of adverse health events, such as exacerbations, led to a revision in severity classification. The GOLD consensus guidelines recommend using multiple factors to determine disease severity, and that spirometric severity (ie, GOLD spirometric grade 1-4, see Table 45-5) be evaluated separately from symptom and exacerbation risk. A combined "ABCD" classification system is now used and the classification is based on the patient's symptom severity and risk of future exacerbation (Table 45-7). This classification system acknowledges that symptom management and prevention of exacerbations should be used to guide therapy. Classification of airflow limitation severity and spirometric grade predicts disease outcomes such as mortality and exacerbations and is useful when considering therapies such as lung reduction surgery or transplantation.

TABLE 45-7

Combined Assessment of COPD Severity

Patient Group	Description	Exacerbations in Last Year[a]	CAT	mMRC
A	Less symptoms; low risk	0-1	<10	0-1
B	More symptoms; low risk	0-1	≥10	≥2
C	Less symptoms; high risk	≥2	<10	0-1
D	More symptoms; high risk	≥2	≥10	≥2

[a]greater than 1 exacerbation, or one requiring hospitalization equals high risk (eg, Patient Group C or D)

Data from Reference 1.

Symptom assessment should be measured at baseline and then during routine visits using CAT or mMRC. Defined cut points for patients exhibiting "more symptoms" and "less symptoms" have been established for CAT and mMRC but are not as well defined for CCQ. The frequency of exacerbations can be assessed by a review of exacerbation history for the past 12 months. Patients with at least two exacerbations in the last 12 months, or one exacerbation requiring hospitalization, are considered high risk for future exacerbations (category C or D). Patients are then assigned to an ABCD category based on these two assessments. Classifying patients according to ABCD categories helps inform treatment decisions as guideline-recommended initial and escalation therapy is based on ABCD category classification.

Prognosis

Patients with COPD are a heterogeneous group and multiple factors, such as airflow limitation, age, frequency and severity of exacerbations, and comorbidities, have been implicated in the rate of disease progression and prognosis. The rate of COPD progression is variable and not easily predicted for individual patients. Several prognostic indices have been shown to be useful in predicting survival among populations of patients with COPD (Table 45-8).[25,26] Based on prognostic indices, mortality for patients with COPD increases with worsening airflow limitation (lower FEV_1 percent of predicted), greater age, lower body mass index (BMI), higher dyspnea score (mMRC), shorter 6-minute walk distance, continued smoking, frequent and severe exacerbations, and presence of selected comorbidities. The primary causes of death of patients with COPD include respiratory failure, cardiovascular events or diseases, and lung cancer.[1] Advanced directives, palliative care coordination and end-of-life care are appropriate options to consider for patients with significant progression and comorbidities.

TABLE 45-8

Selected Prognostic Indices Used in COPD

Name	Description of Tool
BMI, Obstruction, Dyspnea, Exercise (BODE) Index	• Composite score of body mass index, measured FEV_1, mMRC score, and 6MWT distance • Score provides an estimate of 4-year survival • Well-known and validated tool
Age, Dyspnea, Obstruction (ADO) Index	• Composite score of age, mMRC score, and measured FEV_1 • Score provides an estimate for 3-year survival • Maybe more helpful in primary care if 6MWT cannot be measured
COPD Specific Comorbidity Test (COTE) Index	• Includes 12 comorbidities observed to contribute to mortality in COPD patients • Better predictive power if combined with ADO or BODE index

FEV_1, forced expiratory volume in one second; mMRC, modified Medical Research Council scale; 6MWT, six-minute walk test.

Complications of Progressive COPD

Pulmonary Hypertension

Pulmonary hypertension associated with COPD (PH-COPD) may occur in up to 30% of patients and is associated with increased mortality.[27] Given the management complexity of patients with pulmonary hypertension, referral to expert centers specializing in PH is recommended. Investigations of pharmacologic therapy typically used in the treatment of pulmonary arterial hypertension (ie, endothelin receptor antagonists, phosphodiesterase type 5 [PDE5] inhibitors, prostacyclin analogs) for patients with PH-COPD are limited and provide conflicting results. Due to concerns of worsening gas exchange in patients with COPD, pulmonary vasodilators are not recommended outside of clinical trials or specialized pulmonary hypertension centers.

Cor Pulmonale

Cor pulmonale is right-sided heart failure secondary to pulmonary hypertension. Long-term oxygen therapy and diuretics are mainstays of therapy for cor pulmonale. Increasing PaO_2 above 60 mm Hg (8.0 kPa) with supplemental oxygen therapy decreases pulmonary hypertension and resistance against which the right ventricle must work. While diuretics may help decrease fluid overload, caution should be used because patients with significant right-sided heart failure are highly dependent on preload for cardiac output. Digitalis glycosides have no role in the treatment of cor pulmonale.

Beta-blocker therapy is indicated to treat systolic heart failure including patients who have experienced a myocardial infarction. Beta-blocker therapy can present unique challenges for patients with airway disease but are generally well tolerated by patients with COPD who do not exhibit bronchial hyperreactivity. Patients with COPD should generally be treated with β_1-selective agents, although there is some evidence the non-selective agents can be tolerated. Use of beta-blocker therapy for patients with COPD and cardiac disease has been associated with improved overall survival.[28]

Polycythemia

Polycythemia secondary to chronic hypoxemia in COPD patients can be improved by either continuous oxygen therapy (COT) or periodic phlebotomy if oxygen therapy alone is not sufficient. Acute phlebotomy is indicated if the hematocrit is above 55% to 60% (0.55-0.60) and the patient is experiencing CNS effects suggestive of sludging from high blood viscosity. Long-term oxygen then can be used to maintain a lower hematocrit.

TREATMENT

Chronic Obstructive Pulmonary Disease

Desired Outcome

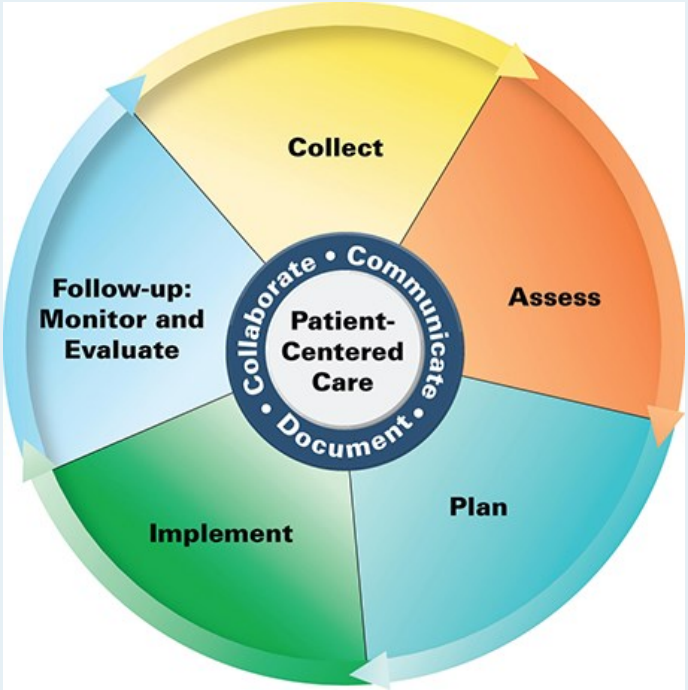
Given the significant clinical and economic impact of COPD, a major focus in healthcare should be on its prevention in patients at risk of the disease. Limiting or eliminating exposure to tobacco smoke and other environmental irritants should be the goal of prevention efforts. For patients already with a diagnosis of COPD, the primary goal is to prevent or slow disease progression. Specific goals are listed in Table 45-9. Optimally, these goals can be accomplished with minimal risks or adverse effects. Therapy of the patient with COPD is multifaceted and includes pharmacologic and nonpharmacologic strategies.

TABLE 45-9

Goals of COPD Management

1. Prevent disease progression
2. Relieve symptoms
3. Improve exercise tolerance
4. Improve overall health status
5. Prevent and treat exacerbations
6. Prevent and treat complications
7. Reduce morbidity and mortality

Patient Care Process for the Management of Chronic Obstructive Pulmonary Disease (COPD)



Collect

- Patient characteristics (eg, age, gender)
- History of present illness including a history of COPD exacerbations in last 12 months and management (eg, home, Primary Care Provider visit, Emergency Department visit, or hospitalization)
- Patient history (past medical, family, social-environmental exposures, tobacco use, exercise tolerance, and capacity)
- Current medications including immunizations (eg, influenza, pneumococcus, tetanus/diphtheria/pertussis) and any prior pulmonary medication use
- Objective data (see Tables 45-5 to 45-7)
    - Symptom scores using validated questionnaire (eg, CAT, mMRC)
    - Current and previous spirometry/pulmonary function tests (eg, FEV_1)

Assess

- Severity of symptoms (eg, “more symptoms” or “less symptoms” based on questionnaires, Table 45-6)
- Risk of future exacerbation (eg, high risk or low risk)
- Degree of airflow limitation (eg, GOLD spirometry group, Table 45-5)
- Patient category based on GOLD Combined Assessment (eg, Category ABCD, Table 45-7)
- Readiness to quit, if current tobacco use (see Tables 45-10 to 45-12)
- Appropriateness and effectiveness of current pulmonary medication regimen
- Ability to administer/participate with inhaled therapies (eg, dexterity, vision, coordination)
- Ability to pay for medications (eg, insurance, formulary considerations, self-pay)

Plan

- Patient-specific goals of therapy (see Tables 45-13 and 45-19)
- Preventative health measures (eg, immunizations, smoking cessation)
- Drug therapy regimen including specific medication, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Tables 45-13 and 45-14)
- Oxygen therapy if severe airflow limitation
- Monitoring parameters including efficacy (eg, symptoms, exacerbations), safety (medication-specific adverse effects), and time frame
- Patient education (eg, purpose of medications, administration technique, recognition of exacerbations)
- Referrals to other providers when appropriate (eg, physician, pulmonary rehabilitation)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Determine goal attainment (eg, symptoms, exacerbations, complications)
- Presence of treatment-related adverse effects
- Patient adherence to treatment plan using multiple sources of information

**Collaborate with patient, caregivers, and other healthcare professionals.*

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 as well as reduce the risk of COPD exacerbations and duration of hospitalization. While earlier studies of COPD therapies focused primarily on relief of symptoms and improvements in pulmonary function measurements such as FEV_1, more recent studies also measure disease-specific quality-of-life and the frequency and severity of exacerbations. A reduction in exacerbation frequency is an important outcome to consider when evaluating the role and benefit of chronic therapies used in COPD management.

General Approach to Treatment

To be effective, clinicians should address four major components of management: assess and monitor the condition, avoid or reduce exposure to risk factors, manage stable disease, and treat exacerbations.[1] These components are addressed through a variety of nonpharmacologic and pharmacologic approaches.

Nonpharmacologic Therapy and Health Maintenance Strategies

Patients with COPD should receive education about their disease, treatment plans, and strategies to slow progression and prevent complications. For those patients who smoke and who are exposed to environmental smoke, advising and counseling patients about smoking cessation are essential for patients in all stages of the disease. Because the natural course of the disease leads to respiratory failure, clinicians should address end-of-life decisions and advanced directives prospectively with the patient and family. Increasingly, palliative care services, which include both end-of-life and hospice care for patients with all types of life-threatening acute and chronic illnesses, have been utilized for patients with severe COPD.[29]

Smoking Cessation

5 Smoking cessation represents the single most important intervention in preventing the development, as well as progression, of COPD. A primary component of COPD management is avoidance of or reduced exposure to risk factors. 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. As confirmed by the Lung Health Study, smoking cessation is the only intervention proven to affect long-term decline in FEV_1 and slow the progression of COPD.[30] 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 follow-up, the rate of decline in FEV_1 among subjects who continued to smoke was more than twice the rate in sustained quitters.[31] 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.

Tobacco cessation has mortality benefits beyond those related to COPD. A follow-up 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 with usual care.[32] Intervention patients had lower death rates due to cardiovascular diseases (the leading cause of mortality) and lung cancer.

Every clinician has a responsibility to advise smokers regarding smoking cessation and should take an active role in assisting patients with tobacco dependence to reduce the burden on the individual, their family, and the healthcare system. Counseling that is provided by clinicians is associated with greater success rates than self-initiated efforts. The major findings from recent clinical practice guidelines for treating tobacco dependence are summarized in Table 45-10. Since 2004, reports from the Surgeon General on the health consequences of smoking have emphasized the detrimental

effects of cigarette smoking on the general health of smokers and individuals exposed to secondhand smoke. Over 20 million Americans have died prematurely from exposure to cigarette smoking since 1964.

TABLE 45-10

Key Guideline Recommendations Regarding Tobacco Use and Dependence

- Tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit. Effective treatments are available that can significantly improve rates of long-term abstinence
- Clinicians and healthcare delivery systems should systemically identify tobacco use and dependence and treat every patient who uses tobacco
- Tobacco-dependence treatments are effective over a broad range of populations. Clinicians should encourage every patient willing to quit to use counseling and medications recommended in the guideline
- Brief tobacco-dependence treatments are effective. Clinicians should offer every patient who uses tobacco at least these brief treatments
- Individual, group, and telephone counseling are effective, and their effectiveness increases with treatment intensity. Practical counseling (problem-solving and/or skills training) and social support are very effective and should be part of treatment
- There are numerous effective medications for tobacco dependence, and clinicians should encourage their use by patients during a quit attempt, except when medically contraindicated or with populations in which the evidence of effectiveness is insufficient (pregnancy). Seven first-line medications (five nicotine and two non-nicotine) consistently increase long-term abstinence rates. Clinicians should also consider the use of combinations as identified in the guideline
- Counseling and medication are effective when used by themselves for treating tobacco dependence. The combination of the two is more effective than either alone. Patients should be encouraged to use both counseling and medication
- Telephone quitline counseling is effective for diverse populations and offers the advantage of broad reach. Clinicians should ensure patient access to quitlines and promote quitline use
- For a patient with tobacco dependence who is currently unwilling to make a quit attempt, clinicians should use motivational treatments that have been shown to be effective in increasing future quit attempts
- Tobacco-dependence treatments are both clinically effective and highly cost-effective relative to interventions for other clinical disorders. Providing coverage for these treatments increases quit rates. Insurers and purchasers should ensure that all insurance plans include the counseling and medications identified as effective in the guideline as covered benefits

Data from References 33 and 34.

Evidence from long-term trials shows that tobacco cessation, either sustained or intermittent, is of benefit at any point. For patients with COPD, maximum benefit is seen with early and sustained cessation; however, incremental benefit is seen at all time points. Given that approximately 40% of patients with COPD continue to smoke, patients and clinicians should understand it is never too late to quit, and repeated attempts at cessation may be necessary. Approximately 70% of smokers want to quit, and over half have made a cessation attempt in the last year. Yet complete and sustained tobacco cessation is difficult.[33,34] Understanding that tobacco dependence is a chronic disease, the focus should be on congratulating and encouraging patients for any behavior changes that result in reduced exposure to tobacco smoke rather than admonishing patients for unsuccessful attempts, relapses, or incomplete cessation.

The guidelines recommend that clinicians take a comprehensive approach to smoking cessation assessment. All patients should be routinely assessed for tobacco use and advice 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 motivational efforts to determine the patient's readiness and support cessation attempts. Even brief interventions (3 minutes) of counseling have been shown to be effective. There are several stages that influence patient decision making. Based on this, a five-step intervention program is proposed (Table 45-11).

TABLE 45-11

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

Ask	Use a systematic approach to identify all patients who use tobacco at every visit
Advise	Strongly urge all patients who use tobacco to quit
Assess	Determine willingness and motivation to make a cessation attempt
Assist	Provide support for the patient to quit smoking
Arrange	Schedule follow-up and monitor for continued abstinence

There is strong evidence to support the use of pharmacotherapy to assist in smoking cessation, and therapy should be offered to most patients as part of a cessation attempt. In general, available pharmacotherapies will double the effectiveness of a cessation effort when combined with behavioral counseling. Agents considered first line are listed in Table 45-12. 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 for patients with recent (less than 2 weeks) myocardial infarction or stroke. Varenicline, a nicotine acetylcholine receptor partial agonist, relieves physical withdrawal symptoms and reduces the rewarding properties of nicotine. Nausea and headache are the most frequent complaints associated with varenicline. Second-line agents are less effective or associated with greater adverse effects; however, they may be useful in selected clinical situations. These therapies include clonidine and nortriptyline, a tricyclic antidepressant. Given the significant increase in the use of e-cigarettes and other electronic nicotine delivery systems (ENDS), there is interest in the potential role of these nicotine delivery systems as smoking cessation strategies. It is not clear if substituting ENDS for traditional cessation therapy produces similar or greater tobacco cessation rates, and long-term safety outcomes of these systems have not been determined.[1,34] ENDS should not be recommended as part of a smoking cessation strategy until additional evidence is available. A comprehensive discussion of tobacco cessation can be found in Chapter 86, "Substance Use Disorders II: Alcohol Nicotine and Caffeine."

TABLE 45-12

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 or lozenge	2-4 mg prn, up to 24 pieces daily	12 weeks	Sore mouth, dyspepsia
Nicotine inhaler	6-16 cartridges daily	Up to 6 months	Sore mouth and throat
Nicotine nasal spray	8-40 doses daily	3-6 months	Nasal irritation
Nicotine patches	Various, 7-21 mg every 24 hr	Up to 8 weeks	Skin reaction, insomnia
Varenicline	0.5 mg daily orally for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily	12 weeks	Nausea, sleep disturbances

Other Environmental Triggers

Although cigarette smoke is by far the most common risk for developing COPD in most patients, exposure to other environmental toxins also confers risks.[1] Exposure to occupational dust and fumes has been implicated as a cause of COPD in 19% of smokers and 31% of nonsmokers with COPD in the United States. In the case of known environmental hazards, primary prevention is appropriate. Policies to limit airborne exposures in the workplace and outdoors, as well as education efforts of workers and policymakers, are recommended.

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. Pulmonary rehabilitation has no direct effect on lung function or gas exchange. Instead, it optimizes other body systems so that the impact of poor lung function is minimized. Exercise training reduces the CNS response to dyspnea, ameliorates anxiety and depression, reduces thoracic hyperinflation, and improves skeletal muscle function.[35]

High-intensity training (70% maximal workload) is possible even in advanced COPD patients, and 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 for patients with moderate-to-severe COPD.[36] Improvements in dyspnea do not always result in improvements in spirometry. While rehabilitation programs vary in length as well as exercise frequency and intensity, optimal benefits result from programs of 6 to 8 weeks in duration and including at least twice a week supervised sessions with targeted feedback.[1]

Surgical Intervention

Various surgical options have been employed in the management of COPD.[1] These include bullectomy, lung volume reduction surgery (LVRS), and lung transplantation. 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. Lung volume reduction surgery removes sections of lung to reduce hyperinflation and may improve survival in selected patients. Lung transplantation, either single or double, may improve exercise capacity and health status but median survival is only 5.5 years after transplant.[1]

Long-Term Oxygen Therapy

6 The use of supplemental oxygen therapy increases survival in COPD patients with chronic hypoxemia at rest. Patients receiving oxygen therapy for at least part of the day have lower rates of mortality than those not receiving oxygen. Long-term oxygen therapy provides more benefit in terms of survival after at least 5 years of use and improves the quality of life for patients by increasing walking distance, improving neuropsychological condition, and reducing time spent in the hospital.[1] Before patients are considered for long-term oxygen therapy, they should be stabilized in the outpatient setting, and pharmacotherapy should be optimized. Once optimized, long-term oxygen therapy should be instituted if either of the following conditions is observed and documented twice in a 3-week period:

1. A resting PaO_2 of less than 55 mm Hg (7.3 kPa) or SaO_2 less than 88% (0.88) with or without hypercapnia.
2. A resting PaO_2 between 55 and 60 mm Hg (7.3 and 8.0 kPa) or SaO_2 less than 88% (0.88) with evidence of right-sided heart failure, polycythemia, or pulmonary hypertension.

The most practical means of administering long-term oxygen is with a nasal cannula, at 1 to 2 L/min, providing 24% to 28% (0.24 to 0.28) fraction of inspired oxygen (FiO_2) with a goal to raise PaO_2 above 60 mm Hg (8.0 kPa). 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, devices are bulky and subject to failure. Patient education about flow rates and avoidance of flames (ie,

smoking) is of the utmost importance.

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] The role of nutritional support for patients with COPD is controversial. Several studies have shown associations of malnutrition, low BMI, and impaired pulmonary status among patients with COPD. However, results from multiple studies suggest that the effect of nutritional support on physical and functional outcomes in COPD is small and may be most beneficial for malnourished patients.[37]

Vaccinations

The GOLD guidelines include specific recommendations about vaccines.[1] The CDC also provides advice about vaccines for COPD patients in the United States and these are updated periodically based on new evidence and as new vaccines become available. Recommended vaccines can reduce the likelihood of respiratory infections that lead to COPD exacerbations. Influenza is a common complication in COPD that can lead to exacerbations and respiratory failure. Therefore, annual vaccination with the inactivated intramuscular influenza vaccine is recommended.[1,38] Immunization against influenza can reduce exacerbations, hospitalization, all-cause death, and respiratory death in COPD patients.[39] Influenza vaccine should be administered annually during each influenza season. Vaccination against influenza can begin as early as August, with most patients being vaccinated during regular medical visits or at vaccination clinics in October and November. The oral antiviral agent, oseltamivir, can be considered for non-immunized patients with COPD during an outbreak; however, this therapy is less effective and causes more adverse effects.

Vaccination against pneumococcal infection is recommended for all adults with COPD. For individuals who have not previously received a pneumococcal conjugate vaccine (PCV), either PCV20 or PCV15 followed by a pneumococcal polysaccharide vaccine (PPSV23) at least 1 year later is recommended.[38] If the patient has previously received PPSV23, either PCV15 or PCV20 should be administered at least 1 year later. Individuals with COPD who have not received the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine, the CDC and GOLD guidelines recommend Tdap and then subsequent tetanus and diphtheria boosters, with or without acellular pertussis, every 10 years.[1,40] Herpes zoster vaccine is recommended for adults with COPD at age 50 or older.[1]

After the global outbreak of novel coronavirus SARS-Co-V-2, the CDC recommend all individuals over the age of 5 years receive a viral vector or mRNA vaccine to prevent severe illness and death associated with coronavirus infection and disease (COVID-19).

Pharmacologic Therapy

In contrast to survival benefit conferred by supplemental oxygen therapy and tobacco cessation, there is no medication available for the treatment of COPD that has been conclusively shown to modify lung function decline or prolong survival.[1] There is some evidence that chronic treatment with pharmacotherapy may reduce the rate of lung function decline in a subset of patients, although more definitive studies are needed to confirm these observations. The primary goal of pharmacotherapy is to improve patient symptoms, reduce the frequency and severity of exacerbations, and improve the patient's exercise tolerance.

Currently available therapies for COPD are summarized in Tables 45-13 to 45-15. International guidelines recommend a stepwise approach to the use of pharmacotherapy based on disease severity determined by an assessment of symptom burden and exacerbation risk.[1] The impact of recurrent exacerbations on accelerating disease progression is increasingly recognized as an important factor to be considered. There is inadequate evidence to support the routine use of more aggressive pharmacotherapy early in the course of the disease because of the lack of a disease-modifying benefit. Due to the progressive nature of COPD, pharmacotherapy tends to be chronic and cumulative. Step-down approaches in stable patients may be considered if adverse effects outweigh therapeutic benefits or if patients do not demonstrate a sufficient response. Patients exhibit varied responses to available therapies and the treatment approach must be individualized.

TABLE 45-13

Recommended Initial Pharmacologic Therapy for Stable COPD and Evaluation of Therapeutic Outcomes

Patient Group	Initial Therapy	Assessment
A (less symptoms, less risk)	Offer bronchodilator, either short- or long-acting depending on symptoms	Assess symptomatic benefit of therapy after initiation (ie, mMRC or CAT score) Assess exacerbation history Assess inhaler technique regularly Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal)
B (more symptoms, less risk)	Start either LAMA or LABA for symptom control	Assess symptomatic benefit of therapy after initiation (ie, mMRC or CAT score) Assess exacerbation history Assess inhaler technique regularly Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal)
C (less symptoms, more risk)	• Start long-acting bronchodilator for exacerbation prevention • LAMA is preferred over LABA for initial monotherapy	Assess symptomatic benefit of therapy after initiation (ie, mMRC or CAT score) Assess exacerbation history Assess inhaler technique regularly Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal)
D (more symptoms, more risk)	• LAMA is preferred over LABA for initial monotherapy • For severe breathlessness, may start with dual LAMA/LABA. If less symptoms, may start only LAMA monotherapy and add LABA at a later time • If blood eosinophils ≥300 cells/microliter (0.3×10^9/L), start ICS/LABA as initial dual therapy	Assess symptomatic benefit of therapy after initiation (ie, mMRC or CAT score) Assess exacerbation history Assess inhaler technique regularly Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal)

CAT, COPD assessment test; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonists; mMRC, modified Medical Respiratory Council questionnaire; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic antagonists.

TABLE 45-14

Recommended Escalation Pharmacologic Therapy for Stable COPD and Evaluation of Therapeutic Outcomes

Target Symptom	Current Therapy	Assessment	Escalation Therapy
Dyspnea	LABA or LAMA monotherapy	Assess symptomatic benefit of therapy after initiation (ie, mMRC or CAT score) Assess exacerbation history Assess inhaler technique regularly Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal) Assess other causes of dyspnea	Add additional long-acting bronchodilator if persistent symptoms on monotherapy. New regimen = LAMA + LABA If dual bronchodilators do not improve symptoms, consider changing device or active ingredient and/or stepping back to monotherapy If a patient becomes high risk for future exacerbations, choose escalation therapy based on the target symptom of “Exacerbations”
Dyspnea	LABA + ICS	Assess symptomatic benefit of therapy after initiation (ie, mMRC or CAT score) Assess exacerbation history Assess inhaler technique regularly Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal)	Add additional long-acting bronchodilator if persistent symptoms on dual therapy. New regimen = LAMA + LABA + ICS If pneumonia, inappropriate indication or lack of response to ICS, consider de-escalation back to LABA + LAMA only
Exacerbations	LABA or LAMA monotherapy	Assess symptomatic benefit of therapy after initiation (ie, mMRC or CAT score) Assess exacerbation history Assess inhaler technique regularly Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal)	Add long-acting bronchodilator if persistent exacerbations on monotherapy. New regimen = LABA + LAMA If current therapy is LABA and blood eosinophils ≥300, consider adding ICS to LABA. New regimen = LABA + ICS If current therapy is LABA and blood eosinophils ≥100 AND ≥2 moderate exacerbations/1 hospitalization, consider adding ICS to LABA. New regimen = LABA + ICS

Exacerbations	LABA + ICS	Assess symptomatic benefit of therapy after initiation (ie, mMRC or CAT score) Assess exacerbation history Assess inhaler technique regularly Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal)	Add long-acting bronchodilator if persistent exacerbations on dual therapy. New regimen = LAMA + LABA + ICS If pneumonia, inappropriate indication or lack of response to ICS, consider de-escalation back to LABA + LAMA only
Exacerbations	LABA + LAMA + ICS	Assess symptomatic benefit of therapy after initiation (ie, mMRC or CAT score) Assess exacerbation history Assess inhaler technique regularly Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal)	If FEV_1 <50% and presence of chronic bronchitis, consider adding roflumilast If a former or never smoker, consider adding azithromycin daily or three times a week for 12 months If pneumonia, inappropriate indication or lack of response to ICS, consider de-escalation and withdrawal of ICS

CAT, COPD assessment test; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonists; mMRC, modified Medical Respiratory Council questionnaire; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic antagonists.

TABLE 45-15

COPD Medication Chart

	Active Ingredient	Dosage Form; Route	Usual Frequency	Proprietary Name	Device Type
Short-Acting Bronchodilators					
Short-acting beta-agonist (SABA)	Albuterol sulfate	Aerosol, metered; inhalation	Four to six times a day as needed	Proventil-HFA; Ventolin-HFA; Proair HFA	MDI
	Albuterol sulfate	Solution; inhalation	Four to six times a day as needed	Accuneb; generic	Nebulization
	Levalbuterol hydrochloride	Solution; inhalation	Three to four times a day as needed	Xopenex; generic	Nebulization

	Levalbuterol tartrate	Aerosol, metered; inhalation	Three to four times a day as needed	Xopenex HFA	MDI
Short-acting anticholinergics (SAMA)	Ipratropium bromide	Aerosol, metered; inhalation	Four times a day as needed	Atrovent HFA	MDI
	Ipratropium bromide	Solution; inhalation	Four times a day as needed	generic	Nebulization
Long-Acting Bronchodilators					
Long-acting beta-agonist (LABA)	Arformoterol tartrate	Solution; inhalation	Twice daily	Brovana	Nebulization
	Formoterol fumarate	Solution; inhalation	Twice daily	Perforomist	Nebulization
	Olodaterol hydrochloride	Spray metered; inhalation	Once daily	Striverdi Respimat	SMI
	Salmeterol xinafoate	Powder; inhalation	Twice daily	Serevent Diskus	DPI
Long-acting anticholinergics (LAMA)	Aclidinium bromide	Powder; inhalation	Twice daily	Tudorza Pressair	DPI
	Tiotropium bromide	Spray metered; inhalation	Once daily	Spiriva Respimat	SMI
	Tiotropium bromide	Powder; inhalation	Once daily	Spiriva Handihaler	DPI
	Glycopyrrolate	Solution; inhalation	Twice daily	Lonhala Magnair	Nebulization
	Glycopyrrolate	Powder; inhalation	Twice daily	Seebri Neohaler	DPI
	Umeclidinium bromide	Powder; inhalation	Once daily	Incruse Ellipta	DPI
	Revefenacin	Solution; inhalation	Once daily	Yupelri	Nebulization
Inhaled Corticosteroids					
Inhaled Corticosteroids (ICS)	Beclomethasone dipropionate	Aerosol, metered;	Twice daily	Qvar Redihaler	MDI

		inhalation			
	Budesonide	Powder; inhalation	Twice daily	Pulmicort Flexhaler	DPI
	Budesonide	Suspension; inhalation	Once or twice daily	Pulmicort Respules; generic	Nebulization
	Fluticasone propionate	Aerosol, metered; inhalation	Twice daily	Flovent HFA	MDI
	Fluticasone furoate	Powder; inhalation	Twice daily	Arnuity Ellipta	DPI
	Mometasone furoate	Powder; inhalation	Twice daily	Asmanex Twisthaler	DPI
	Mometasone furoate	Aerosol; metered; inhalation	Twice daily	Asmanex HFA	MDI
Combination Inhalers					
Dual combination (SABA/SAMA)	Albuterol sulfate; ipratropium bromide	Solution; inhalation	Four to six times a day as needed	Duoneb; generic	Nebulization
	Albuterol sulfate; ipratropium bromide	Spray metered; inhalation	Four to six times a day as needed	Combivent Respimat	SMI
Dual combination (LAMA/LABA)	Umeclidium bromide; vilanterol trifenatate	Powder; inhalation	Once daily	Anoro Ellipta	DPI
	Tiotropium bromide; olodaterol hydrochloride	Spray metered; inhalation	Once daily	Stiolto Respimat	SMI
	Glycopyrrolate; formoterol fumarate	Aerosol, metered; inhalation	Twice daily	Bevespi Aerosphere	MDI
	Aclidinium; formoterol fumarate	Powder; metered; inhalation	Twice daily	Duaklir Pressair	DPI
Dual combination (ICS/LABA)	Budesonide; formoterol fumarate dihydrate	Aerosol, metered; inhalation	Twice daily	Symbicort	MDI
	Fluticasone furoate; vilanterol trifenatate	Powder; inhalation	Once daily	Breo Ellipta	DPI

	Fluticasone propionate; salmeterol xinafoate	Powder; inhalation	Twice daily	Advair Diskus; Airduo Respiclick; Airduo Digihaler	DPI
	Fluticasone propionate; salmeterol xinafoate	Aerosol, metered; inhalation	Twice daily	Advair HFA	MDI
	Mometasone furoate; formoterol fumarate	Aerosol, metered; inhalation	Twice daily	Dulera	MDI
Triple combination (ICS/LAMA/LABA)	Fluticasone furoate; umeclidinium bromide; vilanterol trifenatate	Powder; inhalation	Once daily	Trelegy Ellipta	DPI
	Budesonide; formoterol fumarate; glycopyrrolate	Aerosol; metered; inhalation	Twice daily	Breztri Aerosphere	DPI
Oral Medications					
	Roflumilast	Tablet; oral	Once daily	Daliresp	Oral
	Theophylline	Tablet; capsule; oral	Once or twice daily (extended-release)	Theo-24; generic	Oral

Pharmacotherapy for COPD involves the use of inhaled medications that require patient knowledge and skill using various inhalation devices. Several delivery devices are available (ie, metered-dose inhalers [MDIs], dry powder inhalers [DPIs], soft-mist inhalers [SMIs], nebulizers, and ancillary devices such as holding chambers), and instructions about proper use vary (see Chapter 44, "Asthma" for information about inhalation devices). There is no clear advantage of one delivery system over another, and all devices are associated with administration errors.[41] Comorbidities common for patients with COPD, including physical and cognitive impairments, can have a significant effect on the patient's ability to use devices, and it is recommended that patient-specific factors and preferences be considered.[1] Periodic and frequent reinforcement and observation by clinicians are required to assess optimal use and determine if alternative devices or therapy are needed.

Treatment regimens with multiple inhalation devices add complexity and may adversely impact adherence and disease management. In one cohort study, patients prescribed multiple types of inhalation devices had worse outcomes (increased exacerbations and rescue therapy use) compared to patients using devices of a similar type or administration technique.[42] For patients requiring therapy with multiple inhaled medications, clinicians should prescribe devices with a similar administration technique or containing combinations of medications. Formulary restrictions and healthcare payer reimbursement issues often make this recommendation difficult to apply in practice.

Bronchodilators

Bronchodilators represent the mainstay of drug therapy for COPD and are used to relieve patient symptoms, improve exercise tolerance, and quality of life. For patients with COPD, clinical benefits of bronchodilators include increased exercise capacity, decreased air trapping in lungs, and relief of symptoms such as dyspnea. However, the use of bronchodilators does not produce significant improvements in pulmonary function measurements of expiratory airflow such as FEV_1. Bronchodilator classes available for the treatment of COPD include short- and long-acting β_2-agonists, short- and long-acting anticholinergics, and methylxanthines. 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. In general, adverse 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 adverse effects and drug interactions is higher compared with patients with asthma.

Short-Acting Bronchodilators

The initial recommended therapy for COPD patients who experience occasional symptoms (category A) is a bronchodilator, either long- or short-acting (Tables 45-13 and 45-14). Short-acting bronchodilators are also recommended for all patients for use as rescue or as-needed therapy to manage symptoms (category A, B, C, D). Among short-acting bronchodilators, choices include short-acting β_2-agonist or short-acting anticholinergic agents. Both classes of agents have a relatively rapid onset of action, relieve symptoms, and improve exercise tolerance and lung function. Of note, short-acting bronchodilators do not reduce the frequency or severity of exacerbations in COPD. Both classes are equally effective for symptom management. When a patient does not achieve adequate management of symptoms with one agent, a combination of a short-acting β_2-agonist and short-acting anticholinergic is reasonable.

Short-Acting Sympathomimetics (β_2-Agonists)

β_2-agonists cause bronchodilation by stimulating adenyl cyclase to increase the formation of cyclic adenosine monophosphate (cAMP), which is responsible for mediating the relaxation of bronchial smooth muscle. In addition, β_2-agonists may improve mucociliary clearance within the airways. In COPD patients, short-acting β_2-agonists exert a rapid onset of effect, although 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.

Choices for short-acting, selective β_2-agonists are albuterol and levalbuterol. Racemic epinephrine is available as an over-the-counter product but is not appropriate for chronic treatment. Albuterol is the most frequently used short-acting β_2-agonist and is a racemic mixture of (*R*)-albuterol, which is responsible for the bronchodilator effect, and (*S*)-albuterol, which 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. Despite years of clinical use, there is no compelling evidence to suggest that levalbuterol offers a clear advantage in terms of clinical effectiveness or safety over albuterol, and it is more expensive.[1]

The preferred route of administration for short-acting, selective β_2-agonists is inhalation. The use of oral and parenteral β-agonists in COPD is discouraged because they are no more effective than properly used inhalation devices, and the incidence of systemic adverse effects such as tachycardia and hand tremor is greater. Administration of β_2-agonists in outpatient and emergency room settings via inhalers (MDIs or DPIs) is at least as effective as nebulization therapy and is usually favored for reasons of cost and convenience.[1,4] Chapter 44 includes information about the devices used for delivering aerosolized medication and a comparison of β_2-agonist therapies.

Inhaled β_2-agonists are generally well tolerated. They can cause sinus tachycardia and rhythm disturbances in predisposed patients, but these are rarely reported. Skeletal muscle tremors can occur initially but generally subside as tolerance develops. Older patients may be more sensitive and may experience palpitations, skeletal muscle tremors, and “jittery” feelings after β_2-agonist use.

Short-Acting Anticholinergics

When given by inhalation, anticholinergics, also referred to as antimuscarinics, produce bronchodilation by competitively inhibiting muscarinic receptors, subtypes M_1, M_2, and M_3, in bronchial smooth muscle and mucus glands. This activity blocks acetylcholine, with the net effect being a reduction in cyclic guanosine monophosphate (cGMP), which normally acts to constrict bronchial smooth muscle and decreased mucus secretion.

Ipratropium is the most prescribed short-acting anticholinergic agent for COPD in the United States. Studies comparing ipratropium with inhaled β_2-agonists have generally reported similar improvements in pulmonary function, although ipratropium has a slower onset of action and a more prolonged bronchodilator effect. Because of the slower onset of effect (15-20 minutes compared with 5 minutes for albuterol), ipratropium may be less suitable for as-needed use; however, it is often prescribed in that manner. In contrast to albuterol, ipratropium exhibits a dose-response effect with increasing dose rather than increasing frequency. Patients may experience additional symptom improvement with a higher number of inhalations (ie, 6 puffs Q6 hours, maximum 24 puffs/day), whereas no additional improvement is seen with increasing the frequency (ie, more frequent than Q6

hours).[1]

Lack of systemic absorption of ipratropium greatly diminishes anticholinergic adverse effects such as blurred vision, constipation, urinary retention, nausea, and tachycardia associated with the prototype anticholinergic, atropine. The most frequent patient complaints with ipratropium are dry mouth, nausea, and an occasional metallic taste. In rare instances, inhaled anticholinergics may precipitate narrow-angle glaucoma symptoms. Compared to albuterol, ipratropium has a lower incidence of skeletal muscle tremor and tachycardia.

Long-Acting Bronchodilators

8 9 For patients with COPD who experience persistent symptoms, or in whom short-acting therapies do not provide adequate relief, long-acting bronchodilator therapies are recommended (Tables 45-13 and 45-14). Long-acting agents are also recommended as initial therapy for patients at high risk for exacerbation (category C and D). Long-acting inhaled bronchodilator therapy can be administered as an inhaled β_2-agonist (LABA) or an anticholinergic (LAMA). Compared with short-acting agents, long-acting inhaled bronchodilator therapy is more convenient for patients with persistent symptoms and has shown superior outcomes in improving lung function, relieving symptoms, reducing exacerbation frequency, and improving quality of life. For symptom management, both LABAs and LAMAs are equally effective. However, LAMAs appear to be slightly more effective at preventing exacerbations. Treatment selection should consider the individual patient's response, tolerability, adherence, and economic factors.

Long-Acting Inhaled β_2-Agonists

Multiple LABAs are currently available in the United States (Table 45-15) and differ primarily by dosing frequency (twice daily vs once daily) and device type (SMI, DPI, nebulizer). One LABA, vilanterol, is currently available in the United States only in combination with an inhaled corticosteroid (fluticasone) or long-acting anticholinergic (umeclidinium). Arformoterol, formoterol, indacaterol, and olodaterol have an onset of action similar to albuterol (less than 5 minutes), whereas salmeterol has a slower onset (15-20 minutes). However, none of these agents are recommended for acute relief of symptoms in COPD. There is no dose titration for any of these agents; the starting dose is the effective and recommended dose for all patients.

Clinical benefits of LABAs compared with short-acting bronchodilators include similar or superior improvements in lung function and symptoms, as well as reduced exacerbation rates and need for hospitalization.[1] The use of the long-acting agents should be considered for patients with frequent and persistent symptoms and those at higher risk for exacerbation (see Tables 45-13 and 45-14). When patients require short-acting β_2-agonists on a scheduled basis, LABAs are more convenient based on dosing frequency but may be more expensive. In contrast to their use in asthma, LABA monotherapy for COPD is not associated with increased mortality and is recommended as part of international guidelines.

Long-acting β_2-agonists are similar with regard to the impact on disease outcomes. Salmeterol and formoterol improve lung function, symptoms, exacerbation frequency, and associated hospitalizations.[1] Indacaterol improves symptoms, health status, and frequency of exacerbations.[1] Olodaterol also decreases symptoms and improves lung function, but evidence for exacerbation outcomes is limited. Effect of olodaterol on exacerbation frequency has not been evaluated when used as monotherapy; however, when used with tiotropium, it moderately reduces exacerbations requiring systemic corticosteroids compared to tiotropium monotherapy alone.[43]

Long-Acting Anticholinergics

Several LAMAs are currently available in the United States (Table 45-15) and differ in terms of dosing frequency (twice daily vs once daily) and device type (SMI, DPI, nebulizer). Long-acting anticholinergic agents are more selective than ipratropium at blocking important muscarinic receptors. They dissociate slowly from M_3 receptors, resulting in prolonged bronchodilation with once or twice a day dosing.[44] Aclidinium, glycopyrrolate, and umeclidinium have a faster onset of action (5-15 minutes) compared to tiotropium (80 minutes); however, none of these agents are recommended for acute relief of symptoms. There is no dose titration for any of these agents; the starting dose is the effective and recommended dose for all patients.

Clinical benefits of LAMAs compared with placebo or short-acting bronchodilators include superior improvements in lung function and symptoms, as well as reduced exacerbation rates and hospitalization.[44,45] Available in the United States since 2004, tiotropium is the most extensively studied LAMA with regard to comparative outcomes. In clinical trials, aclidinium and glycopyrrolate have been shown to have similar improvements in lung function and symptoms compared to tiotropium and also reduce the frequency of exacerbations.[46-48] Clinical benefits of umeclidinium have primarily been

evaluated as part of combination bronchodilator regimens.

[8] [9] Long-acting anticholinergics provide similar improvements ins symptoms and health status when compared to long-acting β_2-agonists. Either class is an appropriate choice for patients with persistent symptoms or those needing a step-up from short-acting agents. When evaluating exacerbation outcomes, LAMAs (primarily tiotropium) provide a greater reduction in exacerbation frequency compared to LABAs and should be considered as first-line monotherapy for patients at high risk for exacerbation (Tables 45-13 and 45-14).

Long-acting anticholinergics have been evaluated in clinical trials to determine the potential impact of bronchodilator therapy on the progression of lung function decline. In the landmark clinical trial understanding potential long-term impacts on function with tiotropium (UPLIFT), patients were randomized to therapy with either placebo or inhaled tiotropium, and lung function decline was followed for 4 years.[49] Tiotropium was not shown to have significant effect on lung function decline over time but was effective for reducing symptoms and frequency of exacerbations. Patients in this trial were in more advanced stages of COPD as reflected by the mean postbronchodilator FEV_1 of 1.32 L, corresponding to 48% of predicted FEV_1 or GOLD spirometric stage 3. More recently, tiotropium has again been evaluated for its effect on lung function, but this time in patients in earlier stages of the disease. In the Tie-COPD trial, patients with an $FEV_1 > 50\%$ of predicted (GOLD spirometric grade 1 or 2) were randomized to placebo or tiotropium, and lung function decline followed for 2 years.[50] At the end of the trial, patients in the tiotropium group had a higher measured FEV_1 and slower annual decline compared to patients in the placebo group. Application of these results to clinical practice may be difficult given that current goals for inhaled therapy are targeted at patients with symptoms or those at high risk of future exacerbation. Slowing lung function has not yet been a therapeutic target with inhaled therapy. If used in early-stage disease, it would require patients who do not yet have symptoms or experienced an exacerbation to commit to long-term maintenance therapy. Future studies are needed to determine optimal timing and length of bronchodilator therapy.

Previously, retrospective analyses have reported an increased risk of cardiovascular events associated with ipratropium and tiotropium use.[51] However, the UPLIFT study, which was a prospective trial over 4 years, did not report an increased cardiovascular risk associated with tiotropium use.[49] Additionally, a prospective, noninferiority trial (TIOSPIR) has been published which compared the effects of tiotropium delivered via Handihaler or Respimat devices among 17,000 patients with COPD over a median 2.3-year period.[52] Primary outcomes in this trial were risk of death and risk of first COPD exacerbation. Secondary outcomes included cardiovascular safety. No significant differences were seen in any of the primary or secondary outcomes when comparing tiotropium delivery devices. Further studies are needed to evaluate the cardiovascular safety of ipratropium.

Combination Anticholinergics and β-Agonists (Dual Bronchodilators)

Combination regimens of bronchodilators are often used in the treatment of COPD as 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] Short-acting bronchodilators may be combined for patients experiencing persistent symptoms, although step-up to long-acting bronchodilator monotherapy is usually preferred (Tables 45-13 and 45-14).

Current clinical practice guidelines recommend combining long-acting bronchodilators for patients who have persistent symptoms or recurrent exacerbations on bronchodilator monotherapy (Tables 45-13 and 45-14). Combination of long-acting bronchodilators (LAMA/LABA) provides significant improvement in lung function, symptoms, and quality-of-life measures compared with LABA or LAMA monotherapy.[1,53] In addition, dual long-acting bronchodilator therapy has been shown to decrease the frequency of moderate-to-severe exacerbations compared to either LAMA or LABA monotherapy.

Methylxanthines

Methylxanthines, including theophylline and aminophylline, may produce bronchodilation through numerous mechanisms, including (a) inhibition of phosphodiesterase, thereby increasing cAMP 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.[1] Chronic theophylline use for patients with COPD may offer improvements in lung function and gas exchange. Subjectively, theophylline has been shown to reduce dyspnea, increase exercise tolerance, and improve respiratory drive in COPD patients.[1]

Methylxanthines 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 LABAs and LAMAs, the role of methylxanthine therapy has become more limited. Because of the risk for drug interactions and significant intrapatient and interpatient variability in dosage requirements, theophylline therapy generally is considered for patients who are intolerant or unable to use an inhaled bronchodilator. Theophylline is considered an alternative to commonly used inhaled therapies for bronchodilation and improving symptoms.[1] However, the evidence does not support the use of theophylline to prevent exacerbations.[54]

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 advantage of improving medication adherence 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 is considerable variability in their sustained-release characteristics.

Therapy can be initiated at 200 mg twice daily and titrated upward every 3 to 5 days to the target dose. Most patients require daily doses of 400 to 900 mg. Dosage adjustments generally should be made based on serum concentration results. Traditionally, the therapeutic range of theophylline has been 10 to 20 mcg/mL (mg/L; 55-111 µmol/L); however, because of the frequency of dose-related adverse effects and a lack of a clear benefit when used in higher concentrations, a more conservative therapeutic range of 8 to 15 mcg/mL (mg/L; 44-83 µmol/L) is now targeted, especially in the elderly. When concentrations are measured, trough measurements should be obtained.

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. Adverse effects are dose-related; however, there is an overlap between therapeutic and toxic ranges. Minor adverse effects include dyspepsia, nausea, vomiting, diarrhea, headache, dizziness, and tachycardia. More serious toxicities, which typically do not occur until concentrations exceed 20 mcg/mL (mg/L; 111 µmol/L), 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.

Theophylline is a challenging medication to dose, monitor, and manage due to the significant intrapatient and interpatient variability in pharmacokinetics and the potential for drug interactions and toxicities. Consequently, inhaled bronchodilator therapy is currently preferred based on superior efficacy and safety, as well as ease of use. Current guidelines recommend theophylline only when inhaled bronchodilators are unavailable or unaffordable.[1]

Corticosteroids

Anti-inflammatory 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. The benefits of chronic systemic corticosteroid therapy in the chronic management of COPD are not clear, and the risk of toxicity is significant. 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. Therefore, chronic therapy with oral steroids should be avoided in COPD patients.[1] While a small number of COPD patients are responders to oral steroids, many of these patients may have an asthmatic, or reversible, component to their disease. Asthma-COPD overlap syndrome (ACOS) is now a recognized condition affecting both asthma and COPD patients, and patients exhibiting this syndrome may benefit from therapies traditionally considered for asthma alone.[19] Inhaled corticosteroids may be considered in patients with chronic stable COPD who are at high risk of exacerbation (category C or D) and used short-term as systemic therapy for acute exacerbations (Tables 45-13, 45-14, and 45-22).

10 It has been postulated that inhaled corticosteroid therapy might be beneficial in COPD to slow disease progression. Unfortunately, the results of major clinical trials have failed to demonstrate any clear benefit from chronic treatment with ICS in modifying long-term decline in lung function.[1] ICS have been associated with improvements in clinical endpoints related to exacerbations, including a decrease in exacerbation frequency and time to first exacerbation.[1,55] Clinical benefits of ICS therapy in COPD have been observed with combination therapy, primarily as an addition to LABA monotherapy. Given the lack of supporting evidence and in contrast to evidence in patients with asthma, ICS monotherapy for patients with COPD is not recommended.

Although a dose-response relationship for ICS has not been demonstrated in COPD, initial clinical trials employed moderate-to-high doses for chronic

treatment. At these doses, adverse effects must be considered with long-term therapy. Recent trials have reported an increased risk of pneumonia and mycobacterial pulmonary infections in patients with COPD who receive inhaled corticosteroids, and there is increasing recognition for utilizing lower doses of ICS and withdrawing therapy in selected patients.[55-57] Risk factors for developing pneumonia include age >55 years, body mass index (BMI) less than 25 kg/m^2, current smoker, history of exacerbation or pneumonia (last 12 months), or severe airflow limitation.[1] Other adverse effects associated with inhaled corticosteroids include hoarseness, sore throat, oral candidiasis, and skin bruising. Severe adverse 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 inhaled therapy.

There has been conflicting evidence supporting a dose relationship between ICS use and risk of fractures among patients with COPD. A recent nested, case-control analysis of over 200,000 patients observed an increased risk of fracture with higher daily doses of ICS and long-term use (>4 years).[58] Given this evidence, it appears prudent to treat patients with the lowest effective dose of ICS to minimize the risk of fracture. Clinicians should also recommend adequate intake of calcium and vitamin D and consider periodic bone mineral density testing for patients at risk of osteopenia.

ICS therapy is recommended for initial treatment in patients at high risk of exacerbation and with a blood eosinophil count greater than 300 cells per microliter (category D).[1] For escalation therapy, inhaled corticosteroids may be considered for patients who have recurrent exacerbations despite optimal therapy with inhaled bronchodilators (Table 45-14). Given the risks associated with long-term ICS therapy, clinicians should appropriately identify patients who will receive the best benefit, and patient-specific factors should be considered when making the decision to initiate ICS therapy (Table 45-16). Evaluations of current practice have shown that many patients with COPD may be inappropriately prescribed an ICS (ie, not high risk for exacerbations nor elevated blood eosinophil count), exposing them to unnecessary adverse effects.[59,60]

TABLE 45-16

Considerations for Initiating Inhaled Corticosteroid Therapy in COPD

Recommend ICS Initiation	Consider ICS Initiation	Recommend Against ICS Initiation
History of hospitalization(s) for acute exacerbation of COPD despite appropriate long-acting bronchodilator therapy Two or more moderate exacerbations of COPD per year despite appropriate long-acting bronchodilator therapy Blood eosinophils greater than 300 cells/μL(0.3×10^9/L) History of or concomitant asthma	One moderate exacerbation of COPD per year despite appropriate long-acting bronchodilator therapy Blood eosinophils between 100 and 300 cells/μL(0.1×10^9/L – 0.3×10^9/L)	Repeated pneumonia events Blood eosinophils less than 100 cells/μL(0.1×10^9/L) History of mycobacterial infection

ICS, inhaled corticosteroid.

Given concern for increased pulmonary infections among patients treated with ICS and growing evidence for benefit of dual bronchodilator therapy, clinicians have advocated for withdrawing ICS therapy in selected patients (Table 45-17). Recent trials have reported that ICS can be safely withdrawn from combination ICS/LABA therapy in patients with no initial indication for ICS (ie, FEV_1 > 50% and low risk of exacerbation), without an increase in exacerbation frequency.[60] For patients with more severe disease or at high risk of exacerbation, ICS may also be safely withdrawn from combination ICS/LABA/LAMA therapy in selected situations. These situations may include patients experiencing adverse effects, such as recurrent pneumonia, or those who do not appear to benefit from ICS therapy. For patients with blood eosinophil counts greater than 300 cells/μL (0.3×10^9/L), the benefit of continuing ICS therapy may outweigh the risk of adverse effects.

TABLE 45-17

Considerations for Withdrawing Inhaled Corticosteroid Therapy in COPD

Recommend ICS Withdrawal	Consider ICS Withdrawal	Recommend Against ICS Withdrawal
Patients initiated on ICS therapy with no clear guideline-based indication Patients experiencing adverse effects with ICS therapy and limited therapeutic benefit Patients experiencing no perceived therapeutic benefit with ICS Blood eosinophils less than 100 cells/μL(0.1×10^9/L)	Patients experiencing adverse effects with ICS therapy and some therapeutic benefit Blood eosinophils between 100 and 300 cells/μL(0.1×10^9/L – 0.3×10^9/L)	Blood eosinophils greater than 300 cells/μL(0.3×10^9/L) History of concomitant asthma

ICS, inhaled corticosteroid.

Combination Therapy: Dual Therapy (LAMA/LABA or ICS/LABA)

For most patients with recurrent exacerbations despite optimal long-acting bronchodilator monotherapy, combination therapy with dual long-acting bronchodilators (LAMA/LABA) is preferred over combination therapy with ICS/LABA (Table 45-14).[1,61] This recommendation is based on results of the FLAME trial which reported superior efficacy with regard to exacerbation prevention with LAMA/LABA (glycopyrrolate/indacaterol) therapy compared to ICS/LABA (fluticasone/salmeterol) and a lower rate of pneumonia (3.2% for LAMA/LABA vs 4.8% for ICS/LABA).[6,62] Subgroup analyses of several trials have indicated that patients with elevated sputum and blood eosinophil counts and those with concomitant asthma have greater therapeutic benefit with ICS therapy compared to other patients.[63] Consequently, guidelines recommend combination therapy with ICS/LABA instead of LAMA/LABA for patients with blood eosinophil ≥300 cells/μL (0.3×10^9/L) or ≥100 cells/μL (0.1×10^9/L) and ≥ two moderate exacerbations or one exacerbation requiring hospitalization in the last year (high risk).[1]

A more recent study appears to contradict the superiority of LAMA/LABA over ICS/LABA for exacerbation prevention. In the IMPACT trial, which was a three-arm study designed to evaluate the benefit of escalation to triple therapy (LAMA/LABA/ICS) versus dual therapy with ICS/LABA or LAMA/LABA, exacerbation prevention was greater in the ICS/LABA group compared to the LAMA/LABA group.[64] While these results are in contrast to the outcomes of the FLAME trial, 70% of patients enrolled in the IMPACT trial were already receiving ICS prior to randomization and the run-in period after randomization was only 2 weeks. Thus, patients on ICS and randomized to the LAMA/LABA group effectively discontinued ICS therapy without tapering and may account for the higher number of exacerbations seen initially after randomization. Additionally, patients with asthma were not excluded from this study, which may account for the lower exacerbation rate observed in the ICS/LABA group compared to the LAMA/LABA group.

Combination Therapy: Triple Therapy (LAMA/LABA/ICS)

For patients with persistent symptoms and recurrent exacerbations on dual inhaled therapy, triple therapy with LAMA/LABA/ICS is recommended as initial escalation therapy for patients with blood eosinophil counts greater than 100 cells/μL (0.1×10^9/L) (Table 45-14). Evidence for the benefit of triple therapy has emerged from recent studies evaluating combination therapy within a single device, and there is also limited evidence supporting triple therapy given by multiple devices.[64-67] Compared to dual therapy with either LAMA/LABA or ICS/LABA, triple therapy with LAMA/LABA/ICS provides additional benefit in reducing the frequency of moderate-to-severe exacerbations in patients with COPD. Given the risk of adverse effects with ICS, clinicians may consider bypassing triple inhalation therapy (LAMA/LABA/ICS) for those patients with persistent exacerbations and lower blood eosinophil count (<100 cells/μL [0.1×10^9/L]) in favor of oral alternatives such as roflumilast or azithromycin.[1]

Post-hoc analyses from two recent trials have reported a potential association between triple therapy with LAMA/LABA/ICS and reduction in mortality.[68,69] Early information suggests that the addition of ICS may provide a survival benefit when compared to combination therapy with LAMA/LABA alone in some patients. Definitive causation and conclusions cannot yet be determined until more prospective studies are conducted. As has been seen with therapeutic outcomes from ICS treatment in COPD patients, it is likely that any potential survival benefit may vary based on patient-specific factors and considerations.

Phosphodiesterase Inhibitors

Phosphodiesterase 4 (PDE4) is the major phosphodiesterase found in airway smooth muscle cells and inflammatory cells and is responsible for degrading intracellular cAMP. Inhibition of PDE4 results in relaxation of airway smooth muscle cells and diminished inflammatory mediators such as TNF-α and IL-8. Roflumilast, an oral PDE4 inhibitor available in the United States, is recommended for patients with recurrent exacerbations despite treatment with triple inhalation therapy (LAMA/LABA/ICS) (Table 45-14).[1] It may also be considered as escalation therapy for patients with recurrent exacerbations on dual long-acting bronchodilators (LAMA/LABA) who are not candidates for ICS, such as those with low blood eosinophil count (<100 cells/μL [0.1×10^9/L]) or who are at higher risk of adverse effects associated with ICS. Given both theophylline and roflumilast have similar mechanisms of action through inhibition of phosphodiesterases, both should not be used together for the management of COPD.

Roflumilast has bothersome adverse effects that may limit therapy in some patients.[70] Major effects include diarrhea, nausea, decreased appetite, weight loss, headache, and neuropsychiatric effects such as suicidal thoughts, insomnia, anxiety, and new or worsened depression. Most symptoms such as diarrhea, nausea, and headache occur early after initiation and usually resolve over time. The starting dose should be 250 mcg orally for 4 weeks and then increase to a maintenance dose of 500 mcg orally once a day to avoid adverse effects that may lead to early discontinuation of therapy. Weight loss (average of 2 kg) may be of concern in patients with low BMI, and discontinuation may be necessary if significant weight loss is observed. The use of roflumilast is cautioned in patients with a history of depression or suicidality. Both patients and family members should be counseled regarding the potential for mood and behavior changes and to alert healthcare providers if they occur.

Roflumilast is metabolized by CYP3A4 and 1A2, and coadministration with strong inducers of cytochrome P450 is not recommended due to the potential for subtherapeutic plasma concentrations. Although there are no recommended dose adjustments, caution should also be used when administering roflumilast with strong inhibitors of cytochrome P450 due to the potential for adverse effects.

Azithromycin

In certain pulmonary conditions such as cystic fibrosis and bronchiectasis, chronic therapy with macrolide antibiotics, specifically azithromycin, has proven clinical benefit due to their anti-inflammatory and antimicrobial properties. Studies evaluating chronic azithromycin therapy (either 250 mg orally daily or 500 mg orally three times a week for 12 months) in patients with COPD have reported lower rates of exacerbations among treated patients.[71,72] In a subgroup analysis, patients who continued to smoke did not have a reduction in exacerbation frequency with azithromycin. Therapy with azithromycin was associated with a higher rate of colonization with macrolide-resistant bacteria and hearing deficits. In 2012, a retrospective, observational study reported an increase in cardiac events with short courses of azithromycin.[73] The Food and Drug Administration (FDA) has since updated product labeling to include a precaution about QT prolongation.

Given limited evidence supporting the use of long-term treatment with azithromycin, it would be prudent to wait for more safety data before routinely recommending this therapy for more than 12 months in patients with COPD who are at high risk for exacerbations. Current guidelines recommend considering the addition of chronic azithromycin for patients with recurrent exacerbations despite optimal therapy and who are not active smokers (Table 45-14). Clinicians may choose to consider azithromycin for individual patients at high risk for exacerbations but must carefully weigh the risks and benefits of therapy.

α_1-Antitrypsin Replacement Therapy

For patients with inherited AAT deficiency (AATD)–associated emphysema, treatment focuses on the 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, augmentation therapy is intended to maintain serum concentrations above the protective threshold throughout the dosing interval.[1,17] Augmentation therapy consists of weekly infusions of pooled human AAT to maintain AAT

plasma levels over 10 µmol/L (0.54 g/L). Much of the data supporting the use of AAT replacement are based on evidence of biochemical efficacy (eg, 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 follow-up required, and the expense of conducting such a trial. A systematic review of available trials found an association between intravenous augmentation therapy and reduction in disease progression, as measured by computed tomography (CT) density, and decrease in exacerbation frequency.[74] Augmentation therapy with AAT remains the mainstay of treatment for patients with AATD-associated lung disease.

The recommended dosing regimen for replacement AAT is 60 mg/kg administered IV once a week at a rate of 0.08 mL/kg/min, adjusted to patient tolerance. Augmentation therapy can cost over $50,000 annually. In the absence of alternative treatments, it is difficult to assess the cost-effectiveness using conventional criteria. Based on the high cost and limited availability of therapy in some countries, consensus guidelines have suggested that therapy be considered for patients with an FEV_1 35% to 60% predicted. AAT replacement therapy is derived from pooled blood donors. There have been repeated problems with the supply of this product due to production and contamination issues. There are several products available, which should minimize interruption in product supply in the future. Development of recombinant products and AAT replacement via inhalation continues.

Other Pharmacologic Considerations

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

Expectorants, Mucolytics, and Antioxidants

Adequate water intake generally is sufficient to maintain hydration and assist in the removal of airway sections. Mucolytics and expectorants such as N-acetylcysteine and guaifenesin have been evaluated as adjunctive therapy for patients with COPD. In one trial, patients with moderate-to-severe COPD were randomized to either placebo or oral N-acetylcysteine 600 mg twice daily for 1 year. Patients were not required to be on ICS prior to randomization. N-acetylcysteine was associated with a significant decrease in exacerbation rate among patients with moderate disease only.[75] Strong evidence of clinical benefit is lacking for the routine use of mucolytics in the treatment of COPD.[76]

In 2011, FDA removed unapproved cough and cold preparations, including several containing guaifenesin, from the market due to safety and efficacy concerns. Several extended-release tablet formulations are currently approved by the FDA. Other approved formulations of guaifenesin contain dextromethorphan or pseudoephedrine and should not be used for COPD maintenance therapy.

Opioids

Systemic (oral and parenteral) opioids, especially morphine, can relieve dyspnea for patients with end-stage COPD. Nebulized therapy is sometimes used in clinical practice, although data about clinical benefit are lacking. Opioids should be used carefully, if at all, to avoid reducing ventilatory drive.

Emerging Therapies

Based on knowledge about the importance of neutrophilic inflammation in COPD and potential therapeutic benefit of inhibition of neutrophil activity, several anti-inflammatory compounds have been explored. Many studies of these strategies have been disappointing or report inconsistent results. Therapy with mepolizumab, an anti-interleukin 5 antibody, and benralizumab, an anti-interleukin 5 receptor-alpha antibody, has been shown to decrease exacerbations among COPD patients and may be associated with a greater effect among patients with elevated blood eosinophils.[1] Other current areas of investigation immunoglobulin E, inhibitors of interleukin 5, interleukin 4, interleukin 13, and tyrosine kinases.[77]

The role of HMG-CoA reductase inhibitors for patients with COPD has garnered interest due to known pleiotropic effects statins and the role of systemic inflammation in COPD. Retrospective and observational trials have reported previous associations with simvastatin therapy and reduction in exacerbation frequency, although this effect was not confirmed in a prospective, randomized trial.[78]

In a meta-analysis of trials, vitamin D supplementation for patients with COPD and low baseline levels of 25-hydroxyvitamin D (less than 25 nmol/L [10 ng/mL]) significantly reduced the rate of moderate and severe exacerbations but was not associated with a reduction in exacerbations in patients with levels of 25-hydroxyvitamin D greater than 25 nmol/L (10 ng/mL).[79] Given the low cost and multiple benefits of vitamin D supplementation, it is recommended to check 25-hydroxyvitamin D concentrations for patients hospitalized with AECOPD and supplement if below 25 nmol/L (10 ng/mL).[1]

Acute Exacerbation of COPD

Pathophysiology

The natural history of COPD is characterized by recurrent acute 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] Exacerbations have a significant impact on the natural course of COPD and occur more frequently in patients with advanced age, significant airflow limitation, and comorbid conditions. Because many patients experience chronic symptoms, diagnosis of an exacerbation is based, in part, on subjective measures and clinical judgment; thus, it can be considered a syndrome. Exacerbations are significant events associated with significant morbidity, including worsening health status, increased risk for acute cardiovascular events, impairment of daily activities, and acceleration of lung function decline. Additionally, exacerbations, especially those requiring hospitalization, are associated with increased mortality risk. Acute exacerbations have a significant impact on the economics of treating COPD, estimated at 35% to 45% of the total costs of the disease in some settings.[2-4]

There is limited data about the pathophysiology of COPD exacerbation due to the chronic nature of the disease and the poor health of patients. Inflammatory mediators, including neutrophils and eosinophils, may be increased in sputum during an exacerbation. Airflow limitation may not change remarkably during an exacerbation compared to chronic baseline limitation.[1] Lung hyperinflation, if present, is worsened during an exacerbation, which contributes to increasing dyspnea and poor gas exchange.

The primary physiologic change is often a worsening of ABG values due to poor gas exchange and increased muscle fatigue. For a patient experiencing a severe exacerbation, profound hypoxemia and hypercapnia can be accompanied by respiratory acidosis and respiratory failure.

Criteria used to define acute exacerbation of COPD (AECOPD) among clinicians vary 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 purulence (Table 45-18). With an exacerbation, patients using rapid-acting bronchodilators may report an increase in the frequency of use and may seek additional medical care. Acute exacerbations can range from mild to severe and are classified based on the level of treatment and intervention required (Table 45-19).

TABLE 45-18

Staging Acute Exacerbations of COPD[a]

Mild (type 1)	One cardinal symptom[a] plus at least one of the following: URTI[b] 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]

[a]Cardinal symptoms include worsening of dyspnea, increase in sputum volume, and increase in sputum purulence.

[b]URTI, upper respiratory tract infection.

TABLE 45-19

Classification of Acute Exacerbation of COPD

Severity	Definition
Mild	Treated with short-acting bronchodilators only No treatment with antibiotics or systemic corticosteroids required
Moderate	Treated with short-acting bronchodilators Treatment with antibiotics and/or systemic corticosteroids required
Severe	Treated with short-acting bronchodilators Treatment with antibiotics and/or systemic corticosteroids required Treatment requires hospitalization or a visit to an emergency department May be associated with acute respiratory failure

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 based on an acute change in the ABGs. Defining acute respiratory failure as a PaO_2 of less than 50 mm Hg (6.7 kPa) or a $PaCO_2$ of greater than 50 mm Hg (6.7 kPa) 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 (1.3-2.0 kPa) 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.

Clinical Presentation

CLINICAL PRESENTATION: COPD Exacerbations

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

AECOPD 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 with the highest rates among those admitted to the intensive care unit. COPD exacerbations contribute to in-hospital mortality, deaths after discharge, and the decline of lung function. Many patients experiencing an exacerbation do not return to their baseline clinical status for several weeks, significantly affecting their quality of life.

As many as 50% of patients hospitalized for an exacerbation are readmitted within 6 months.[2-4] Risk factors for relapse and potential readmission include FEV_1 less than 50% of predicted, the severity of exacerbation, previous exacerbation frequency, presence of comorbidities, and inadequate antibiotic therapy.[80] As part of the 2010 Affordable Care Act, the Hospital Readmission Reduction Program was established by the Centers for Medicare & Medicaid Services (CMS) that incentivize healthcare organizations to reduce readmission rates for selected conditions, including COPD. The most important predictor for a future exacerbation is past exacerbation history; thus, prevention of AECOPD is a major therapeutic goal for patients with a history of frequent exacerbations (ie, high risk).

TREATMENT

COPD Exacerbations

Desired Outcomes

11 The goals of therapy for patients experiencing AECOPD are to minimize the negative consequences of the acute exacerbation (ie, reduce symptoms, prevent hospitalization, shorten hospital stay, prevent acute respiratory failure or death), and prevent future exacerbations.[1] Factors that

influence severity, and subsequently the level of care required, include the severity of airflow limitation, presence of comorbidities, and history of previous exacerbations. Table 45-20 includes factors that warrant treatment in the hospital, and Table 45-21 describes the assessment of hospitalized patients for the presence of acute respiratory failure.

TABLE 45-20

Factors Favoring Hospitalization for Treatment of COPD Exacerbation

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

TABLE 45-21

Assessment of Patients Hospitalized for Acute Exacerbations of COPD

Assessment	Presentation
No respiratory failure	Respiratory rate 20-30 bpm No use of accessory muscles No changes in mental status Hypoxemia improved with supplemental oxygen No increase in $PaCO_2$
Acute respiratory failure—not life-threatening	Respiratory rate >30 bpm Using accessory muscles No changes in mental status Hypoxemia improved with supplemental oxygen Increase in $PaCO_2$ compared to baseline or 50-60 mm Hg (6.7-8.0 kPa)
Acute respiratory failure—life-threatening	Respiratory rate >30 bpm Using accessory muscles Acute changes in mental status Hypoxemia not improved with supplemental oxygen or need for FIO_2 > 40% (0.40) Increase in $PaCO_2$ compared to baseline or >60 mm Hg (8.0 kPa) or acidosis (pH <7.25)

bpm, beats per minute.

Various therapeutic options for exacerbation management are summarized in Table 45-22. Pharmacotherapy consists of intensification of bronchodilator therapy and a short course of systemic corticosteroids. Antimicrobial therapy is indicated in the presence of selected symptoms. Since 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 45-22

Therapeutic Options for Acute Exacerbations of COPD

Therapy	Comments
Antibiotics	Recommended if all three of the following cardinal symptoms are present: ○ Increased dyspnea ○ Increased sputum production ○ Increased sputum purulence Recommended if at least two of the following cardinal symptoms are present as long as one of the symptoms is increased sputum purulence: ○ Increased dyspnea ○ Increased sputum production ○ Increased sputum purulence Recommended for patients requiring mechanical ventilation (either noninvasive or invasive) regardless of symptoms present Recommended treatment duration is 5-7 days
Corticosteroids	Oral or IV therapy may be used for a total duration of 5-7 days. If IV is used, it should be changed to oral after improvement in pulmonary status. Longer courses of therapy are associated with increased risk of pneumonia and adverse effects
Bronchodilators	MDIs and DPIs equal in efficacy to nebulization β-Agonists also may increase mucociliary clearance Long-acting β-agonists or long-acting antimuscarinics 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% [0.90]) Monitor arterial blood gas for the 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

Nonpharmacologic Therapy

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. There have been numerous trials reporting the benefits of NPPV for patients with acute respiratory failure due to COPD exacerbations. NPPV has been associated with lower mortality, lower intubation rates, and shorter hospital stays for COPD exacerbations. A recent analysis regarding NPPV in patients with respiratory failure, in general, included a subset of patients with COPD and reported that the risk of hospital-based mortality and long-term mortality was reduced by 56%.[81] 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 who fail a trial of NPPV or those considered poor candidates should be considered for intubation and mechanical ventilation if appropriate based on the patient's goals of care.

Pharmacologic Therapy

Bronchodilators

During exacerbations, intensification of bronchodilator regimens is used commonly. Short-acting β_2-agonists are preferred due to their rapid onset of action. The doses and frequency of bronchodilator administration can be increased to provide symptomatic relief. Anticholinergic agents may be added if symptoms persist despite increased doses of β_2-agonists. Combinations of these agents are often employed, although data are lacking about their benefit versus using higher doses of a single agent. Bronchodilators may be administered via MDIs or nebulization with equal efficacy.[1] Nebulization may be considered for patients with severe dyspnea who cannot hold their breath after the actuation of an MDI. Evidence supporting the use of theophylline during exacerbations is lacking, and thus theophylline generally should be avoided due to concern for adverse effects.

Corticosteroids

Treatment with systemic corticosteroids in AECOPD has been shown to improve oxygenation, recovery time, shorten hospitalization, and reduce the risk of relapse.[4,82] Studies have varied with regards to the severity of exacerbation (ie, moderate or severe), clinical setting (ie, outpatient management or hospitalization), and dosing regimen (ie, dose, route, frequency, and duration). Several trials enrolling hospitalized patients have used high initial doses (often intravenous) before tapering to a lower oral dose to complete the duration of therapy. Adverse effects such as hyperglycemia, insomnia, and hallucinations may occur at higher doses. Depending on the patient's clinical status, treatment may be initiated at a lower dose or tapered more quickly if these effects occur.

The optimal corticosteroid dosing regimen for each presentation of AECOPD is unknown. However, a regimen of prednisone 40 mg orally daily (or equivalent) for 5 days can be effective for most patients. The REDUCE trial evaluated a 5-day course of prednisone 40 mg versus 14 days in a noninferiority study.[83] Shorter treatment duration was noninferior to longer treatment duration for the primary outcome of time to next exacerbation and resulted in less systemic corticosteroid exposure. Longer courses of systemic steroids have been associated with increased risk of pneumonia, hospitalization, and all-cause mortality, and shorter courses (5-7 days) are preferred to avoid adverse effects.[84] Areas of emerging evidence in the treatment of AECOPD include using nebulized corticosteroid (budesonide) rather than systemic administration and correlation of blood eosinophil counts and benefits of therapy.[1]

Antimicrobial Therapy

12 Viral or bacterial infections cause most AECOPD. However, as many as 30% of exacerbations are caused by unknown factors.[1] Data supporting the use of antibiotics for COPD exacerbations are remarkably sparse. To limit unnecessary use, antibiotics should be initiated in any of these clinical situations: (1) patients presenting with three cardinal symptoms of AECOPD, (2) patients presenting with two cardinal symptoms as long as one is increased sputum purulence, and (3) patients requiring mechanical ventilation (noninvasive or invasive) regardless of symptoms (Table 45-22).[1] Utility of sputum Gram stain and culture is questionable, as some patients have chronic bacterial colonization of the bronchial tree between exacerbations.

C-reactive protein (CRP) has been evaluated as a potential biomarker to assist with decisions regarding the use of antimicrobial therapy for COPD exacerbations. An open-label randomized controlled trial evaluated the use of CRP measurement versus no CRP measurement when deciding whether to use antibiotics for AECOPD. The primary outcome was the percentage of antibiotic prescriptions issued within 4 weeks of initial exacerbation. Antibiotic prescriptions were issued less frequently when CRP levels were used to guide decisions compared to usual care. Moreover, patients in the CRP-guided group had improved COPD health status scores. The risk of hospitalization was similar in both groups. These results support the use of CRP measurements to guide antimicrobial decisions for AECOPD, and it supports antimicrobial stewardship efforts.[85]

The emergence of drug-resistant organisms has mandated that antibiotic regimens be chosen judiciously. The selection of empirical antimicrobial therapy should be based on the most likely organism(s) thought to be responsible for the infection based on the patient's presentation and site-specific sensitivities. The most common organisms for acute exacerbation of COPD are *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Haemophilus parainfluenzae*. More virulent bacteria may be present for patients with more complicated AECOPD, including drug-resistant pneumococci, β-lactamase–producing *H. influenzae* and *M. catarrhalis*, and enteric gram-negative organisms, including *Pseudomonas aeruginosa*. Table 45-23 summarizes recommended antimicrobial therapy for exacerbations of COPD and the most common organisms based on patient presentation. Therapy with antibiotics generally should be continued for at least 5 to 7 days. 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.

TABLE 45-23

Recommended Antimicrobial Therapy in Acute Exacerbations of COPD

Patient Characteristics	Likely Pathogens	Recommended Therapy
Uncomplicated exacerbations <4 exacerbations per year No comorbid illness	*S. pneumoniae* *H. influenzae* *M. catarrhalis* *H. 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 and >4 exacerbations per year Presence of comorbid illness	As above plus drug-resistant pneumococci, β-lactamase–producing *H. influenzae,* and *M. catarrhalis*	Amoxicillin/clavulanate Fluoroquinolone with enhanced pneumococcal activity (levofloxacin, gemifloxacin, and moxifloxacin)
Presence of risk factors for colonization and infection with multidrug-resistant pathogens Need for chronic corticosteroid therapy Recent hospitalization (90 days) Recent antibiotic treatment (90 days) Resident of long-term care facility	Some enteric gram-negatives As above plus *P. aeruginosa*	Fluoroquinolone with enhanced pneumococcal and *P. aeruginosa* activity (levofloxacin) IV therapy if required: β-lactamase–resistant penicillin with antipseudomonal activity third- or fourth-generation cephalosporin with antipseudomonal activity

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

Controlled Oxygen Therapy

Oxygen therapy should be provided for patients with significant hypoxemia during an exacerbation (eg, oxygen saturation less than 90% [0.90]). Caution must be used, however, because many patients with COPD rely on mild hypoxemia to trigger their drive to breathe. In healthy individuals, drive to breathe is triggered by carbon dioxide accumulation. For patients with COPD who retain carbon dioxide due to disease progression, hypoxemia rather than hypercapnia becomes the main trigger for the 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 (8.0 kPa) or oxygen saturation of greater than 90% (0.90). An ABG should be obtained after oxygen initiation to monitor carbon dioxide retention resulting from hypoventilation.

Discharge Planning and Follow-up

Patients hospitalized for AECOPD are at high risk for relapse and readmission to the hospital; therefore, appropriate planning should take place prior to discharge to ensure therapy issues, and post-discharge care coordination are clearly addressed. Patients should be initiated or restarted on appropriate maintenance therapy (such as long-acting bronchodilators) before discharge. Patient assessment and education regarding new or continuing therapy should also occur before discharge and be reinforced during post-discharge follow-up. Some patients may require supplemental oxygen during their exacerbation and for a period of time after discharge. The continued need for long-term oxygen therapy should be assessed as part of post-discharge follow-up (Table 45-24). Other critical elements of discharge planning and follow-up include medication reconciliation, self-management plans, when to seek medical attention, assessment of symptoms and activities of daily living, and status of other comorbid conditions. Early follow-up after discharge (within 1-4 weeks) is associated with a reduction in readmission due to exacerbations of COPD, and lack of post-discharge follow-up is associated with an increase in 90-mortality.[1]

TABLE 45-24

Discharge Planning and Post-Discharge Follow-up in Acute Exacerbations of COPD

Timeline	Assessment	Plans
Prior to discharge	Assess maintenance therapy and optimize per therapeutic goals and patient factors Assess inhaler technique Assess technique and adherence before modifying therapy Assess understanding of AECOPD medications (steroids and/or antibiotics) and when to stop taking after discharge Assess the need for vitamin D supplementation to prevent future exacerbations Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal) Assess need for oxygen therapy after discharge Assess needed follow-up for comorbid conditions	Ensure patient will be able to obtain and afford prescriptions for therapy Utilize motivational interviewing and teach-back for education and counseling Ensure understanding of medications to continue and/or stop (ie, antibiotics, systemic corticosteroids) Coordinate referral to outpatient tobacco cessation services, if indicated Provide immunizations while hospitalized Coordinate outpatient services for supplemental oxygen, if indicated Ensure follow-up care plans are communicated and appointments scheduled (ie, within 1-4 weeks post-discharge)
1-4 weeks post-discharge	Assess symptoms (ie, mMRC or CAT score) Assess patient ability to cope in their usual environment Assess physical activity and ability to do activities of daily living (ADLs) Assess inhaler technique Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal) Assess continued need for oxygen therapy, if continued after discharge Assess the status of comorbidities	Ensure patient completes mMRC or CAT before or during a visit Coordinate home care services for assistance with ADLs, if indicated Ensure patient will be able to obtain and afford prescriptions for therapy Utilize motivational interviewing and teach-back for education and counseling Ensure understanding of medications Coordinate referral to outpatient tobacco cessation services, if indicated Provide immunizations, if appropriate Coordinate outpatient services for supplemental oxygen, if indicated Ensure follow-up care plans are communicated and appointments scheduled
12-16 weeks	Assess symptoms (ie, mMRC or CAT score)	Ensure patient completes mMRC or CAT before or during a

post-discharge	Assess patient ability to cope in their usual environment Assess physical activity and ability to do activities of daily living Assess airflow limitation via spirometry Assess inhaler technique Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal) Assess continued need for oxygen therapy, if continued after discharge Assess the status of comorbidities	visit Coordinate home care services for assistance with ADLs, if indicated Refer the patient for spirometry testing Ensure patient will be able to obtain and afford prescriptions for therapy Utilize motivational interviewing and teach-back for education and counseling Ensure understanding of medications Coordinate referral to outpatient tobacco cessation services, if indicated Provide immunizations, if appropriate Coordinate outpatient services for supplemental oxygen, if indicated Ensure follow-up care plans are communicated and appointments scheduled

It is important to assess medication understanding and potential barriers to adherence, inhaler technique, optimal pharmacotherapy, tobacco cessation readiness, and immunization status before discharge. In acute care or ambulatory care settings, clinical pharmacists are often called on to educate patients, recommend appropriate therapy changes, assist patients with formulary and insurance barriers, and complete prior authorization requests. The focus of COPD exacerbation management and prevention has shifted from only clinician-delivered education to patient-clinician collaboration that integrates motivation, engagement, and support to develop self-management interventions and target behaviors.[1,86] Key elements that should be addressed in self-management programs include risk factor management, inhaler technique, management of breathlessness, and a written action plan for acute exacerbations.[1] Incorporating an action plan for AECOPD within a self-management program has been shown to decrease respiratory-related hospital admissions and increase health-related quality of life indicators.[87] Dedicated programs targeting recently discharged patients have shown improvements in health outcomes, such as readmissions, when combined with clinical pharmacy services.[88-90]

PALLIATIVE CARE, END-OF-LIFE CARE, AND HOSPICE

Based on the natural course of COPD, characterized by a progressive decline in lung function and the development of complications, it is important to periodically reconsider the goals of care, end-of-life decisions, and advanced directives.[1] Involvement of palliative care services is recommended once symptoms become significantly limiting or disabling or if repeated hospitalizations occur. An effective strategy to discuss end-of-life care involves the patient's participation in identifying advanced directives and goals of care. Clinicians reassure patients that their symptoms, including pain, will be managed, and their dignity will be preserved. Specific issues that are addressed include the location and provider for terminal care, desire to use or withhold mechanical ventilation, and involvement of other family members in decisions on behalf of the patient.

EVALUATION OF THERAPEUTIC OUTCOMES

To evaluate therapeutic outcomes of COPD, the practitioner must first delineate between chronic stable COPD and acute exacerbations. In chronic stable COPD, pulmonary function tests should be annually assessed as recommended by guidelines and following any treatment additions or discontinuations. The average rate of decline of FEV_1 is a useful objective measure to assess the course of COPD over time. However, patients with similar FEV_1 values may differ in the frequency and severity of symptoms and exacerbation history, thus emphasizing the need for a combined assessment for all patients. The average rate of decline in FEV_1 for healthy, nonsmoking patients attributable to age alone is 25 to 30 mL/year. The rate of decline in smokers is steeper, especially for heavy smokers compared with light smokers. The decline in pulmonary function is a curvilinear path. The more severely diminished the FEV_1 at diagnosis, the steeper the rate of decline. Greater numbers of years of smoking and the number of cigarettes smoked correlate with a steeper decline in pulmonary function.[1]

Objective improvements in PFTs often are minimal—therefore, subjective assessments are important. These include symptom scores and quality-of-life assessments. In addition, exacerbation rates, visits to the emergency department, and hospitalizations should be quantified and evaluated. During AECOPD, the patient's white blood cell count, vital signs, chest x-ray, and changes in dyspnea, sputum volume, and sputum purulence should be assessed at presentation and periodically throughout the treatment of an exacerbation. In severe exacerbations, ABGs and oxygen saturation also should be monitored. As with any drug therapy, adherence, adverse effects, and potential drug interactions should also be evaluated.

To date, there is limited evidence that any available pharmacotherapies for COPD impact disease progression. Removal of the primary causative factor for COPD (eg, cessation of cigarette smoking) does improve survival, as does supplemental oxygen therapy in a subset of patients. The most pertinent clinical outcomes that have emerged from clinical trials over the past decade are symptom improvement and reductions in exacerbation frequency. While it is important to continue to explore strategies to improve survival, consideration should be given to these two relevant and important outcome measures when initiating, continuing, and monitoring therapy.

ABBREVIATIONS

AAT	α_1-antitrypsin
AATD	α_1-antitrypsin deficiency
ABG	arterial blood gas
ACCP	American College of Chest Physicians
ACIP	Advisory Committee on Immunization Practices
ACOS	asthma and COPD overlap syndrome
AECOPD	acute exacerbations of COPD
ATS	American Thoracic Society
BMI	body mass index
cAMP	cyclic adenosine monophosphate
CAT	COPD Assessment Test
CCQ	Clinical COPD Questionnaire
CDC	Centers for Disease Control and Prevention
cGMP	cyclic guanosine monophosphate
COPD	chronic obstructive pulmonary disease
COT	continuous oxygen therapy
COVID-19	coronavirus disease 2019
CRQ	Chronic Respiratory Questionnaire

CT	computed tomography
DPI	dry powder inhaler
ENDS	electronic nicotine delivery systems
ERS	European Respiratory Society
FEV_1	forced expiratory volume in 1 second
FRC	functional residual capacity
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HPA	hypothalamic–pituitary–adrenal
ICS	inhaled corticosteroid
IL	interleukin
LABA	long-acting inhaled β_2-agonist
LTB_4	leukotriene B_4
LVRS	lung volume reduction surgery
MDI	metered-dose inhaler
MMP12	matrix metalloproteinase 12
mMRC	modified Medical Research Council
NETT	National Emphysema Treatment Trial
NHLBI	National Heart, Lung, and Blood Institute
NOT	nocturnal oxygen therapy
NPPV	noninvasive positive-pressure ventilation
$PaCO_2$	pressure exerted by carbon dioxide gas in arterial blood
PaO_2	pressure exerted by oxygen gas in arterial blood
PDE4	phosphodiesterase 4
PDE5	phosphodiesterase type 5
PHS	Public Health Service

PH-COPD	pulmonary hypertension associated with COPD
SARS-CoV-2	severe acute respiratory syndrome coronavirus
SCCOPE	Systemic Corticosteroids in Chronic Obstructive Pulmonary Disease Exacerbations
SGRQ	St. George's Respiratory Questionnaire
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
TNF-α	tumor necrosis factor-α
TORCH	Towards a Revolution in COPD Health
UPLIFT	understanding potential long-term impacts on function with tiotropium
VC	vital capacity
WHO	World Health Organization

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD). 2021. Available at: http://www.goldcopd.

2. Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest*. 2015;147(4):894–942. doi: 10.1378/chest.14-1676.

3. Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of COPD exacerbations: A European Respiratory Society/American Thoracic Society guideline. *Eur Respir J.* 2017;50:1602265. http://www.thoracic.org/statements/copd.php. [PubMed: 28889106]

4. Papi A, Rabe KF, Rigau D, et al. Management of COPD exacerbations: A European Respiratory Society/American Thoracic Society guideline. *Eur Respir J.* 2017;49:1600791. http://www.thoracic.org/statements/copd.php. [PubMed: 28298398]

5. Mannino DM. Fifty years of progress in the epidemiology of chronic obstructive pulmonary disease: A review of National Heart, Lung, and Blood Institute-sponsored studies. *Chronic Obstr Pulm Dis.* 2019;6(4):350–358. 10.15326/jcopdf.6.4.2019.0145. PMID: 31647857; PMCID: PMC7006703.

6. U.S. Department of Health and Human Services. COPD National Action Plan. National Heart, Lung, and Blood Institute. Bethesda, MD. Publication NO. 17-HL-8031. Available at: http://copd.nih.gov.

7. Ford ES, Mannino DM, Wheaton AG, Giles WH, Presley-Cantrell LR, Croft JB. Trends in the prevalence of obstructive and restrictive lung function among adults in the United States: Findings from the National Health and Nutrition Examination Survey from 1988-1994 to 2007-2010. *Chest*. 2013;143(5):1395–1406. [PubMed: 23715520]

8. Creamer MR, Wang TW, Babb S, et al. Tobacco product use and cessation indicators among adults—United States, 2018. *MMWR Morb Mortal Wkly Rep.* 2019;68:1013–1019. doi: http://dx.doi.org/10.15585/mmwr.mm6845a2.

9. Sullivan J, Pravosud V, Mannino DM, Siegel K, Choate R, Sullivan T. National and state estimates of COPD morbidity and mortality—United States, 2014–2015. *Chronic Obstr Pulm Dis.* 2018;5(4):324–333. 10.15326/jcopdf.5.4.2018.0157. PMID: 30723788; PMCID: PMC6361472.

10. Wheaton AG, Liu Y, Croft JB, VanFrank B, et al. Chronic obstructive pulmonary disease and smoking status—United States, 2017. *MMWR.* 2019;68(24):553–538.

11. Ma J, Ward EM, Siegel RL, Jemal A. Temporal trends in mortality in the United States, 1969–2013. *JAMA.* 2015;314:1731–1739. [PubMed: 26505597]

12. COPD Death Rates in the United States, 1999–2014. National Vital Statistics System. Available at: https://www.cdc.gov/copd. Accessed May 2, 2021.

13. Jenkins CR, Chapman KR, Donohue JF, Roche N, Tsiligianni I, Han MK. Improving the management of COPD in women. *Chest* 2017;151(3):686–696. 10.1016/j.chest.2016.10.031. Epub 2016 Nov 2. PMID: 27816445.

14. Wheaton AG, Cunningham TJ, Ford ES, Croft JB. Employment and activity limitations among adults with chronic obstructive pulmonary disease—United States, 2013. *MMWR.* 2015:64(11):290–295.

15. U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

16. Rennard SI, Vestbo J. COPD: The dangerous underestimate of 15%. *Lancet*. 2006;367(9518):1216–1219. doi: 10.1016/S0140-6736(06)68516-4.

17. Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. *Chronic Obstr Pulm Dis.* 2016;3(3):668–682. 10.15326/jcopdf.3.3.2015.0182. PMID: 28848891; PMCID: PMC5556762.

18. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol.* 2016;138:16–27. [PubMed: 27373322]

19. Global Initiative for Asthma. Asthma, COPD and Asthma-COPD Overlap. 2017. Available at: http://www.ginasthma.org.

20. Domej W, Oettl K, Renner W. Oxidative stress and free radicals in COPD—Implications and relevance for treatment. *Int J Chron Obstruct Pulmon Dis.* 2014;9:1207–1224. [PubMed: 25378921]

21. Sakao S, Voelkel, NF, Tatsumi K. The vascular bed in COPD: Pulmonary hypertension and pulmonary vascular alterations. *Eur Respir Rev.* 2014;23:350–355. [PubMed: 25176971]

22. Patel N, Belcher J, Thorpe G, Forsyth NR, Spiteri MA. Measurement of C-reactive protein, procalcitonin and neutrophil elastase in saliva of COPD patients and healthy controls: Correlation to self-reported well-being parameters. *Respir Res.* 2015;16:62–69. [PubMed: 26018813]

23. Guirguis-Blake JM, Senger CA, Webber EM, Mularski RA, Whitlock EP. Screening for chronic obstructive pulmonary disease: Evidence report and systematic review for the US Preventive Services Task Force. *JAMA.* 2016;315:1378–1393. [PubMed: 27046366]

24. Dempsey TM, Scanlon PD. Pulmonary function tests for the generalist: A brief review. *Mayo Clin Proc.* 2018;93:763–771. [PubMed: 29866281]

25. de Torres JP, Casanova C, Marín JM, et al. Prognostic evaluation of COPD patients: GOLD 2011 versus BODE and the COPD comorbidity index COTE. *Thorax*. 2014;69:799–804. [PubMed: 24969641]

26. Morales DR, Flynn R, Zhang J, Trucco E, Quint JK, Zutis K. External validation of ADO, DOSE, COTE and CODEX at predicting death in primary care patients with COPD using standard and machine learning approaches. *Respir Med.* 2018;138:150–155. [PubMed: 29724388]

27. Grimminger J, Ghofrani HA, Weissmann N, Klose H, Grimminger F. COPD-associated pulmonary hypertension: Clinical implications and current methods for treatment. *Expert Rev Respir Med.* 2016;10:755–766. [PubMed: 27212458]

28. Rezaei SS, Rinner C, Ratajczak P, Grossmann W, Gall W, Wolzt M. Use of beta-blocker is associated with lower mortality in patients with coronary artery disease with or without COPD. *Clin Respir J.* 2018;12(12):2627–2634. 10.1111/crj.12968. Epub 2018 November 4. PMID: 30276967.

29. Vermylen JH, Szmuilowicz E, Kalhan R. Palliative care in COPD: An unmet area for quality improvement. *Int J Chron Obstruct Pulmon Dis.* 2015;10:1543–1551. [PubMed: 26345486]

30. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline in FEV1: The Lung Health Study. *JAMA.* 1994;272:1497–1505. [PubMed: 7966841]

31. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med.* 2002;166:675–679. [PubMed: 12204864]

32. Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality: A randomized clinical trial. *Ann Intern Med.* 2005;142:233. [PubMed: 15710956]

33. Leone FT, Zhang Y, Evers-Casey S, et al. Initiating pharmacologic treatment in tobacco-dependent adults. An official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2020;202(2):e5–e31. 10.1164/rccm.202005-1982ST. PMID: 32663106; PMCID: PMC7365361.

34. Krist AH, Davidson KW, Mangione CM, et al., US Preventive Services Task Force. Interventions for tobacco smoking cessation in adults, including pregnant persons: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2021;325(3):265–279. 10.1001/jama.2020.25019. PMID: 33464343.

35. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2015;2:CD003793.

36. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med.* 2013;188(8):e13–e64. [PubMed: 24127811]

37. van Beers M, Rutten-van Mölken MPMH, van de Bool C, et al. Clinical outcome and cost-effectiveness of a 1-year nutritional intervention programme in COPD patients with low muscle mass: The randomized controlled NUTRAIN trial. *Clin Nutr.* 2020;39(2):405–413. 10.1016/j.clnu.2019.03.001. Epub 2019 March 18. PMID: 30954363.

38. Centers for Disease Control and Prevention (CDC). Adult Immunization Schedule by Vaccine and Age Group. Available at: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html. Accessed May 9, 2021.

39. Bekkat-Berkani R, Wilkinson T, Buchy P, et al. Seasonal influenza vaccination in patients with COPD: A systematic literature review. *BMC Pulmonary Medicine.* 2017;17(1):79. [PubMed: 28468650]

40. Centers for Disease Control and Prevention Mortality and Morbidity Weekly Report. Use of Tetanus Toxoid, Reduced Diptheria Toxoid, and Acellular Pertussis Vaccines: Updated Recommendations of the Advisotry Committee on Immunization Practices – United States, 2019. Available at: https://www.cdc.gov/mmwr/volumes/69/wr/mm690a5.html. Accessed May 9, 2021.

41. Chrystyn H, van der Palen J, Sharma R, et al. Device errors in asthma and COPD: Systematic literature review and meta-analysis. *NPJ Primary Care Respiratory Medicine*. 2017;27:1–10. [PubMed: 28077854]

42. Bosnic-Anticevich S, Chrystyn H, Costello R, et al. The use of multiple respiratory inhalers requiring different inhalation techniques has an adverse effect on COPD outcomes. *Int J Chron Obstruct Pulmon Dis.* 2016;12:59–71. [PubMed: 28053517]

43. Calverley PMA, Anzueto AR, Carter K, et al. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): A double-blind, randomised, parallel-group, active-controlled trial. *Lancet Respir Med.* 2018;6:337–344. doi: 10.1001/jama.2018.14432.

44. Melani AS. Long-acting muscarinic antagonists. *Expert Rev Clin Pharmacol.* 2015;8(4):479–501. doi: 10.1001/jama.2018.14432.

45. Cheyne L, Irvin-Sellers MJ, White J. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2015;9:CD009552.

46. Wedzicha JA, Agusti A, Donaldson G, Chuecos F, Lamarca R, Garcia Gil E. Effect of aclidinium bromide on exacerbations in patients with moderate-to-severe COPD: A pooled analysis of five phase III, randomized, placebo-controlled studies. *COPD: J Chron Obstruct Pulmon Dis.* 2016;13:669–676.

47. Tashkin DP, Gross NJ. Inhaled glycopyrrolate for the treatment of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2018;13:1873–1888. [PubMed: 29928118]

48. Chen W, Huang C, Sheu C, et al. Long-acting beta2-agonists versus long-acting muscarinic antagonists in patients with stable COPD: A systematic review and meta-analysis of randomized controlled trials. *Respirology*. 2017;22:1313–1319. [PubMed: 28654201]

49. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease (UPLIFT). *N Engl J Med.* 2008;359:1543–1554. [PubMed: 18836213]

50. Zhou Y, Zhong N, Li X, et al. Tiotropium in early-stage chronic obstructive pulmonary disease. *N Eng J Med.* 2017;377:923–935.

51. Celli B, Decramer M, Leimer I, Vogel U, Kesten S, Tashkin DP. Cardiovascular safety of tiotropium in patients with COPD. *Chest*. 2010;137:2–30.

52. Wise RA, Anzueto A, Cotton D, et al.; TIOSPIR Investigators. Tiotripium Respimat inhaler and the risk of death in COPD. *N Engl J Med.* 2013;369(16):1491–1501. [PubMed: 23992515]

53. Oba Y, Sarva ST, Dias S. Efficacy and safety of long-acting β-agonist/long-acting muscarinic antagonist combinations in COPD: A network meta-analysis. *Thorax*. 2016;71:15. [PubMed: 26490732]

54. Devereux G, Cotton S, Fielding S, et al. Effect of theophylline as adjunct to inhaled corticosteroids on exacerbations in patients with COPD: A randomized clinical trial. *JAMA.* 2018;320(15):1548–1559. 10.1001/jama.2018.14432.

55. Tashkin DP, Strange C. Inhaled corticosteroids for chronic obstructive pulmonary disease: What is their role in therapy? *Int J Chron Obstruct Pulmon Dis.* 2018;13:2587–2601. doi: 10.2147/COPD.S172240. PMID: 30214177; PMCID: PMC6118265.

56. Izquierdo JL, Cosio BG. The dose of inhaled corticosteroids in patients with COPD: When less is better. *Int J Chron Obstruct Pulmon Dis.* 2018;13:3539–3547. doi: 10.2147/COPD.S175047. PMID: 30498343; PMCID: PMC6207269.

57. Castellana G, Castellana M, Castellana C, et al. Inhaled corticosteroids and risk of tuberculosis in patients with obstructive lung diseases: A systematic review and meta-analysis of non-randomized studies. *Int J Chron Obstruct Pulmon Dis.* 2019;14:2219–2227. 10.2147/COPD.S209273. PMID: 31576118; PMCID: PMC6769028.

58. Gonzalez AV, Coulombe J, Ernst P, Suissa S. Long-term use of inhaled corticosteroids in COPD and the risk of fracture. *Chest*. 2018;153:321–328. [PubMed: 28716642]

59. Chalmers JD, Tebboth A, Galyle A, et al. Determinants of initial inhaled corticosteroid use in patients with GOLD A/B COPD: A retrospective study of UK general practice. *NPJ Prim Care Respir Med.* 2017;27(1):43. [PubMed: 28663549]

60. Avdeev S, Aisanov Z, Arkhipov V, et al. Withdrawal of inhaled corticosteroids in COPD patients: Rationale and algorithms. *Int J Chron Obstruct Pulmon Dis.* 2019;14:1267–1280. 10.2147/COPD.S207775. PMID: 31354256; PMCID: PMC6572750.

61. Beeh KM, Burgel P, Franssen FME, et al. How do dual long-acting bronchodilators prevent exacerbations of chronic obstructive pulmonary

disease? *Am J Respir Crit Care Med.* 2017;196:139–149. [PubMed: 27922741]

62. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD (FLAME). *N Eng J Med.* 2016;374:2222–2234.

63. Cheng SL. Blood eosinophils and inhaled corticosteroids in patients with COPD: Systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2018;13:2775–2784. doi: 10.2147/COPD.S175017. PMID: 30233168; PMCID: PMC6132232.

64. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD (IMPACT). *N Eng J Med.* 2018;378:1671–1680.

65. Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): A double-blind, parallel group, randomised controlled trial. *Lancet*. 2018;391:1076–1084. [PubMed: 29429593]

66. Vestbo J, Papi A, Corradi M, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): A double-blind, parallel group, randomised controlled trial. *Lancet*. 2017;389:1919–1929. [PubMed: 28385353]

67. Siler TM, Kerwin E, Sousa AR, Donald A, Ali R, Church A. Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: Results of two randomized studies. *Respir Med.* 2015;109(9):1155–1163. [PubMed: 26117292]

68. Vestbo J, Fabbri L, Papi A, et al. Inhaled corticosteroid containing combinations and mortality in COPD. *Eur Respir J.* 2018;52(6):1801230. 10.1183/13993003.01230-2018. PMID: 30209195.

69. Lipson DA, Crim C, Criner GJ, et al. Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2020;201(12):1508–1516. 10.1164/rccm.201911-2207OC. PMID: 32162970; PMCID: PMC7301738.

70. Wedzicha JA, Calverley PM, Rabe KF. Roflumilast: A review of its use in the treatment of COPD. *Int J Chron Obstruct Pulmon Dis.* 2016;11:81–90. [PubMed: 26792988]

71. Albert RK, Connett J, Bailey WD, et al. Azithromycin for prevention of exacerbation in COPD. *N Engl J Med.* 2011;365:689–698. [PubMed: 21864166]

72. Uzun S, Djamin RS, Kluytmans JA, et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): A randomised, double-blind, placebo-controlled trial. *Lancet Respir Med.* 2014;2(5):361–368. 10.1016/S2213-2600(14)70019-0. Epub 2014 April 15. PMID: 24746000.

73. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med.* 2012;366:1881–1890. [PubMed: 22591294]

74. Edgar RG, Patel M, Bayliss S, Crossley D, Sapey E, Turner AM. Treatment of lung disease in alpha-1 antitrypsin deficiency: A systematic review. *Int J Chron Obstruct Pulmon Dis.* 2017;12:1295–1308. doi: 10.2147/COPD.S130440. PMID: 28496314; PMCID: PMC5422329.

75. Zheng JP, Wen FQ, Bai CX, et al.; PANTHEON study group. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): A randomised, double-blind placebo-controlled trial. *Lancet Respir Med.* 2014;2(3):187–194. [PubMed: 24621680]

76. Poole P, Sathananthan K, Fortescue R. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2019;5(5):CD001287. doi: 10.1002/14651858.CD001287.pub6. PMID: 31107966; PMCID: PMC6527426.

77. Wechsler ME. Current and emerging biologic therapies for asthma and COPD. *Respir Care*. 2018;63(6):699–707. 10.4187/respcare.06322. PMID: 29794205.

78. Criner GJ, Connett JE, Voelker H. Simvastatin in moderate-to-severe COPD. *N Eng J Med.* 2014;371:970.

79. Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D to prevent exacerbations of COPD: Systematic review and meta-analysis of individual participant data from randomised controlled trials. *Thorax*. 2019;74(4):337–345. 10.1136/thoraxjnl-2018-212092. Epub 2019 January 10. PMID: 30630893.

80. Mantero M, Rogliani P, DiPasquale M, et al. Acute exacerbations of COPD: Risk factors for failure and relapse. *Int J COPD*. 2017;12:2687–2693.

81. Cabrini L, Landoni G, Oriani A, et al. Noninvasive ventilation and survival in acute care settings: A comprehensive systematic review and meta-analysis of randomized controlled trials. *Crit Care Med.* 2014;43(4):880–888.

82. Hernandez JM, Edmonds M. Do systemic corticosteroids improve outcomes in chronic obstructive pulmonary disease exacerbations? *Ann Emerg Med.* 2016;67(2):258–259. doi: 10.1016/j.annemergmed.2015.07.009.

83. Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: The REDUCE clinical trial. *JAMA.* 2013;309(21):2223–2231. [PubMed: 23695200]

84. Sivapalan P, Ingebrigtsen TS, Rasmussen DB, et al. COPD exacerbations: The impact of long versus short courses of oral corticosteroids on mortality and pneumonia: Nationwide data on 67 000 patients with COPD followed for 12 months. *BMJ Open Respir Res.* 2019;6(1):e000407. 10.1136/bmjresp-2019-000407. PMID: 31179005; PMCID: PMC6530506.

85. Butler CC, Gillespie, D, White P, et al. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. *N Engl J Med.* 2019;381(2):111–120. doi: 10.1056/NEJMoa1803185.

86. Effing TW, Vercoulen JH, Bourbeau J, et al. Definition of a COPD self-management intervention: International Expert Group consensus. *Eur Respir J.* 2016;48(1):46–54. 10.1183/13993003.00025-2016. Epub 2016 April 13. PMID: 27076595.

87. Lenferink A, Brusse-Keizer M, van der Valk PD, et al. Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2017;8(8):CD011682. 10.1002/14651858.CD011682.pub2. PMID: 28777450; PMCID: PMC6483374.

88. Fathima M, Bawa Z, Mitchell B, Foster J, Armour C, Saini B. COPD management in community pharmacy results in improved inhaler use, immunization rate, COPD action plan ownership, COPD knowledge, and reductions in exacerbation rates. *Int J Chron Obstruct Pulmon Dis.* 2021;16:519–533. 10.2147/COPD.S288792. PMID: 33688177; PMCID: PMC7936701.

89. Cavanaugh JJ, Lindsey KN, Shilliday BB, Ratner SP. Pharmacist-coordinated multidisciplinary hospital follow-up visits improve patient outcomes. *J Manag Care Spec Pharm.* 2015;21:256–260. [PubMed: 25726034]

90. Sanchez GM, Douglass MA, Mancuso MA. Revisiting project re-engineered discharge (RED): The impact of a pharmacist telephone intervention on hospital readmission rates. *Pharmacotherapy*. 2015;35:805–812. [PubMed: 26406772]

SELF-ASSESSMENT QUESTIONS

1. Which of the following estimates of cigarette smoking as a cause of COPD is most accurate?

   A. 12%

   B. 30%

   C. 55%

   D. 75%

2. Which of the following is a risk associated with inhaled corticosteroid use for the treatment of COPD?

   A. Increased mortality

   B. Leukopenia

   C. Osteoporosis

   D. Pneumonia

3. Which of the following medication classes is utilized in the treatment of an acute exacerbation of COPD?

   A. Short-acting beta-agonists

   B. Long-acting beta-agonists

   C. Inhaled corticosteroids

   D. Long-acting muscarinic antagonists

4. Which of the following is an achievable outcome of pharmacotherapy for chronic management of COPD?

   A. Reduced mortality

   B. Normalization of spirometry

   C. Reduced exacerbations

   D. Prevention of accelerated loss of lung function

5. Which of the following pneumococcal vaccination strategies is recommended for a 59-year-old patient with COPD?

   A. PPSV 23 only (pneumococcal polysaccharide)

   B. PCV 13 only (pneumococcal conjugate)

   C. PPSV 23 (pneumococcal polysaccharide) now, and PCV 13 (pneumococcal conjugate) in 8 weeks

   D. PCV 13 (pneumococcal conjugate) now, and PPSV 23 (pneumococcal polysaccharide) in one year

6. Which of the following is a goal of supplemental oxygen therapy for chronic management of COPD?

   A. Maintain pO_2 at normal levels

   B. Reserve pCO_2 elevations

   C. Prevent detrimental end-organ effects from hypoxemia

   D. Increased hemoglobin concentrations

7. Which of the following counseling points is recommended for patients switching inhaled drug therapy from a metered-dose inhaler (MDI) to a dry powder inhaler (DPI)?

   A. Continue to use an ancillary holding chamber with the new inhaler

   B. There is no need to exhale before using the new inhaler

   C. Use a rapid, forceful inhalation effort to aerosolize the dose of the new inhaler

D. Rinse the new inhaler in warm water daily to ensure consistent dose delivery

8. Which of the following genetic factors is a risk for developing COPD?

A. Poor metabolizer status for cytochrome 3A4

B. G6PD enzyme deficiency

C. Atopic phenotype

D. Alpha-1 antitrypsin deficiency

9. Which of the following best describes the impact of smoking cessation on the natural course of COPD?

A. Cessation allows recovery of most of the excess loss of lung function.

B. Following cessation, the rate of loss of lung function decreases to that of a nonsmoker.

C. Significant increases in spirometry are evident within one year.

D. The risk for lung cancer is similar to life-long nonsmokers following cessation.

10. Which of the following pharmacotherapy strategies is recommended for a patient newly diagnosed with Gold stage 1, category A COPD?

A. Start an inhaled corticosteroid

B. Start an inhaled bronchodilator

C. Start an oral leukotriene modifier

D. Start supplemental oxygen

11. Which of the following strategies is recommended for a COPD patient who currently smokes but is reluctant to attempt a cessation attempt because of the everyday stress in his life?

A. Recommend bupropion therapy

B. Recommend varenicline

C. Recommend a nicotine replacement therapy and an anxiolytic agent

D. Counsel about the relevance and rewards of smoking cessation

12. Which of the following therapies is appropriate to reduce the risk for exacerbations from COPD?

A. Oral corticosteroids

B. Long-acting muscarinic antagonists

C. Antimicrobial agents

D. Inhaled corticosteroids

13. Which of the following counseling points should be discussed with a patient who is starting roflumilast therapy?

A. Do not use this medication with inhaled corticosteroids.

B. This therapy should only be taken during periods of increased symptoms of exacerbation.

C. A common side effect of this medication is gastrointestinal, including nausea.

D. Take in divided doses at least twice daily.

14. Which of the following management strategies has been shown to reduce the progressive decline in lung function associated with COPD?

A. Smoking cessation

B. Inhaled corticosteroids

C. Long-acting beta-agonists

D. Supplemental oxygen therapy

15. Which of the following is recommended for a patient who continues to experience symptoms of COPD despite treatment with a single long-acting bronchodilator therapy?

A. Add a scheduled short-acting bronchodilator agent

B. Add an inhaled corticosteroid

C. Add another long-acting bronchodilator

D. Add a chronic anti-inflammatory such as azithromycin

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Cigarette smoking is implicated in approximately 75% of cases of COPD. However, less than 50% of smokers develop COPD. For more information, see the "Etiology" section.

2. **D.** There is good evidence regarding the association of inhaled corticosteroid use and an increased risk of pneumonia in patients with COPD. For more information, see subsection "Corticosteroids" under section "Pharmacologic Therapy."

3. **A.** When treating an acute exacerbation of COPD, intensification of short-acting bronchodilators and initiation of systemic corticosteroids and antimicrobials are primary strategies. For more information, see the "Exacerbation Management" section.

4. **C.** One of the most important goals of chronic COPD management is to prevent exacerbations that hasten disease progression. For more information, see subsection "Desired Outcomes" under section "Treatment."

5. **A.** PPSV 23 is recommended for patients under 65 years of age with COPD. For more information, see the "Immunizations" section.

6. **C.** A primary goal of supplemental oxygen is to maintain adequate oxygen concentrations in the blood to prevent detrimental effects on other organs. For more information, see the "Long-Term Oxygen Therapy" section.

7. **C.** When switching from an MDI to a DPI, the patient should be advised that the inhalation effort is different. A DPI requires a rapid, forceful inhalation effort. For more information, see section "Pharmacologic Therapy" as well as Chapter 44, "Asthma."

8. **D.** A deficiency of alpha-1 antitrypsin enzyme is associated with developing COPD (emphysema) at an early age. This enzyme usually has a protective role in lung tissue. For more information, see the "Etiology" section.

9. **B.** Upon cessation of smoking, the annual rate of FEV_1 loss is reduced to that of a nonsmoker. This provides potential years before the patient develops chronic symptoms associated with airflow limitation. For more information, see subsection "Smoking Cessation" under section "Nonpharmacologic Therapy and Health Maintenance Strategies."

10. **B.** The current GOLD guidelines recommend initial therapy with an inhaled bronchodilator for Group A patients without indicating any preference

among agents. For more information, see subsection "Bronchodilators" under section "Pharmacologic Therapy," as well as Table 45-13.

11. **D.** In counseling individuals regarding tobacco cessation, it is essential to ensure readiness to quit before recommending pharmacotherapy. If the patient is not ready, ongoing counseling and encouragement are warranted. For more information, see subsection "Smoking Cessation" under section "Nonpharmacologic Therapy and Health Maintenance Strategies."

12. **B.** Long-acting bronchodilators (LAMA or LABA), either alone or in combination with each other, or ICS are the primary therapies shown to reduce exacerbation risks. For more information, see subsection "Bronchodilators" under section "Pharmacologic Therapy."

13. **C.** The most common side effects associated with roflumilast therapy are related to the gastrointestinal tract and include nausea. For more information, see subsection "Phosphodiesterase Inhibitors" under section "Pharmacologic Therapy."

14. **A.** Smoking cessation can impact the natural course of COPD and the progressive loss of lung function. To date, no pharmacotherapy has been shown to slow the loss of lung function. For more information, see subsection "Smoking Cessation" under section "Nonpharmacologic Therapy and Health Maintenance Strategies."

15. **C.** The central focus of COPD management is on bronchodilator therapy. If a patient is not adequately controlled with one agent, then combination bronchodilator therapy is recommended. Long-acting bronchodilators offer convenience as well as reducing exacerbation risks. For more information, see section "Pharmacologic Therapy."