Chronic Obstructive Pulmonary Disease (COPD)

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

John M. Leonard, MD, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his postgraduate clinical training at the Yale and Vanderbilt University Medical Centers before joining the Vanderbilt faculty in 1974. He is a clinician-educator and for many years served as director of residency training and student educational programs for the Vanderbilt University Department of Medicine. Over a career span of 40 years, Dr. Leonard conducted an active practice of general internal medicine and an inpatient consulting practice of infectious diseases.

Faculty Disclosure

Contributing faculty, John M. Leonard, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, primary care providers, nurses, respiratory therapists, and medical assistants involved in the care of patients with COPD.

Accreditations & Approvals

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A complete Works Cited list begins on page 52.

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NetCE designates this continuing education activity for 10 ANCC contact hours.

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This activity was planned by and for the healthcare team, and learners will receive 10 Interprofessional Continuing Education (IPCE) credits for learning and change.

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Special Approvals

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About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

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Course Objective

The purpose of this course is to provide healthcare professionals a current review of pathogenesis, diagnosis, assessment, and treatment of chronic obstructive pulmonary disease (COPD), emphasizing strategies for prevention and best practice clinical guidelines for managing the stable patient and COPD exacerbations.

Learning Objectives

Upon completion of this course, you should be able to:

1. Define chronic obstructive pulmonary disease (COPD) and associated conditions.
2. Identify risk factors and discuss the role of cigarette use, infection, and chronic inflammation in the pathogenesis and progression of COPD.
3. Correlate pathologic changes in the lung with the clinical features of COPD.
4. Describe the pathophysiology of airflow limitation and air trapping.
5. Recognize and evaluate the clinical signs and symptoms of COPD.
6. Analyze the various criteria and tests used in the diagnosis of COPD.
7. Discuss the investigations used to assess the severity and to stage COPD.
8. Identify interventions that may reduce the risk of developing COPD, including smoking cessation.
9. Outline pharmacologic and nonpharmacologic options for the management of stable COPD.
10. Use your knowledge of pathophysiology and options for therapy to devise a strategy for managing COPD exacerbations in the ambulatory setting or in the hospital.
11. Describe the appropriate monitoring and assessment of COPD disease progression, as well as associated comorbidities.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a diffuse inflammatory disorder of the pulmonary airways and lung parenchyma caused by the chronic inhalation of noxious gases and particles, resulting in fixed airflow limitation and the insidious onset and progression of breathlessness, cough, and fatigue. COPD is a major cause of chronic morbidity and premature death, ranking fourth among causes of death worldwide [1]. In many parts of the world, the prevalence of COPD is increasing because of the widespread habit of smoking cigarettes and because of the extensive use of indoor biomass fuels for heating and cooking [2]. The disorder is preventable and, once established, is amenable to therapeutic interventions that slow progression. The degree of airflow obstruction and the pace of clinical change can easily be measured and monitored by simple pulmonary function tests [3].

The World Health Organization estimates that the global prevalence of COPD is about 10% (251 million cases) and that the disease is responsible for more than 3 million deaths annually [1]. Unless managed appropriately, COPD is expected to become the third leading cause of death worldwide by 2030. In recent decades, the mortality rate for COPD has not declined as it has for other chronic diseases such as heart disease, cancer, and stroke.

COPD is a leading cause of morbidity and mortality in the United States. Major risk factors include smoking tobacco, occupational and environmental exposures, respiratory infections, and genetic predisposition. A 2018 data analysis by the Centers for Disease Control and Prevention (CDC) showed that 16.4 million adults in the United States have been diagnosed with COPD [4]. The age-adjusted prevalence of COPD, of Medicare hospitalizations, and of deaths caused by COPD were found to be significantly higher among residents living in rural areas than among those living in metropolitan areas, perhaps because of higher rates of smoking and limited access to effective management. The prevalence of COPD varies considerably by state, from less than 4.5% of the population in Hawaii, Colorado, and Utah to more than 10% in Alabama, Tennessee, Kentucky, and West Virginia [4]. In 2018, COPD was the fourth leading cause of death in the United States, with an age-adjusted mortality rate of 39.1 deaths per 100,000 persons [4].

Although traditionally considered a disease of men, the prevalence of COPD in some countries is now higher among women. In the United States, death rates for COPD declined among men from 1999 (57.4 per 100,000) to 2018 (42.9 per 100,000), but death rates have not changed significantly among women (35.3 per 100,000 in 1999 and 35.8 per 100,000 in 2018). As of 2019, more women than men are living with COPD in the United States [4].

The public health cost burden of COPD is considerable. In 2016, COPD accounted for 652,000 hospitalizations and nearly 2.1 million emergency department visits [4]. Annually, the total direct medical costs attributable to COPD and its sequelae are estimated at $29.5 billion, and the indirect (absenteeism) costs are more than $8 billion [4].

DEFINITIONS

The Global Initiative for Chronic Obstructive Lung Disease (GOLD), a project of the WHO, has defined COPD as a common, preventable, and treatable disease characterized by airflow limitation and persistent respiratory symptoms that are due to airway and/or alveolar abnormalities, usually caused by exposure to inhaled noxious particles or gases [199]. The principal diagnostic requirement is spirometric confirmation of airflow limitation, measured as a reduction in the expected forced expiratory volume in 1 second (FEV1). In recognition of the complexity and heterogeneity of COPD and the limitations of FEV1 as a marker of early disease, an alternate clinical definition has been proposed: COPD is a syndrome characterized by chronic respiratory symptoms, structural pulmonary abnormalities (i.e., airway disease, emphysema, or both), lung-function impairment (e.g., airflow limitation that is poorly reversible), or any combination of these [10; 228]. Exacerbations and comorbidities contribute to the overall severity in individual patients.

Clinically and pathologically, COPD is comprised of two overlapping disease processes: chronic bronchitis and emphysema. Chronic bronchitis is defined as a cough with sputum production on most days for at least three months of a year for two consecutive years [40]. Patients with chronic bronchitis have a characteristic hyperplasia and hypertrophy of the goblet cells and mucous glands of the airway, leading to excessive mucus secretion narrowing the airways, which results in repeated cough with sputum. The airway walls are infiltrated with inflammatory cells, and persistent inflammation results in thickening of the wall and airway narrowing. Progression of chronic bronchitis results in fibrosis and squamous metaplasia, which limits airflow [42]. Chronic bronchitis is a recurrent and irreversible condition, which differentiates it from acute bronchitis. Acute bronchitis is an inflammation of the large bronchi in the lungs typically caused by viruses or bacteria that may last several days or weeks [43].

Emphysema is an enlargement of the air spaces (alveoli) distal to the terminal bronchioles, with destruction of their walls [40]. The destruction of air space walls reduces elastic recoil and the surface area available for the exchange of oxygen and carbon dioxide during breathing. These airways can collapse, leading to further limitation in airflow. Emphysema can be classified by location as panacinar/panlobular and centriacinar/centrilobular [41].

Panacinar emphysema results in enlargement of respiratory bronchiole to alveoli and includes entire respiratory acini. It usually involves all lung fields, particularly the bases and anterior margins of the lungs. This type of emphysema is common in individuals with alpha-1 antitrypsin deficiency.

Centriacinar emphysema predominantly occurs in the upper lobes, resulting in enlargement of the respiratory bronchiole (i.e., the proximal and central part of the acinus); however, the distal acinus and alveoli are unaffected. This type of emphysema is common in smokers. Emphysema can also be classified as distal acinar emphysema, irregular emphysema, or congenital lobar emphysema (CLE). Distal acinar emphysema preferentially involves the distal airway structures, alveolar ducts, and alveolar sacs. CLE is a rare congenital disorder characterized by hyperinflation of one or more of the pulmonary lobes. Irregular emphysema is a fibrotic form of the disease that shows no consistent relationship to any portion of the acinus. Scarring is very common in patients with irregular emphysema.

RISK FACTORS FOR COPD
Genetic predisposition
Exposure to particles (e.g., tobacco smoke, organic and inorganic occupational dusts, outdoor air pollution, indoor air pollution from heating and cooking with biomass in poorly vented dwellings)
Poor lung growth and development
Oxidative stress
Female sex
Older age
Respiratory infections
Lower socioeconomic status
Poor nutrition
Comorbidities
Source: Compiled by Author *Table 1*

PATHOGENESIS

In susceptible individuals, COPD develops gradually over years as the result of chronic inflammation induced by sustained inhalational exposure to cigarette smoke and other noxious (causative) agents, augmented by intercurrent infection of the bronchial tree and lower airways. Although cigarette smoking is the most common initiating factor, there are multiple other risk factors, often acting in concert, including genetic predisposition, occupational exposures, air pollution, and infection (***Table 1***).

TOBACCO SMOKE AND OTHER INHALATIONAL EXPOSURE

Cigarette smoking is the predominant and primary risk factor for COPD, and approximately 15% of all persons who smoke will develop clinically apparent COPD. Smokers of more than 40 pack-years exposure have a much higher likelihood of developing COPD than nonsmokers. The combined exposure to tobacco smoke and certain occupational dusts and chemicals magnifies the risk for COPD [6; 7; 8; 9; 10; 11]. In developing countries, COPD has been attributed to chronic exposure to smoke from burning biomass fuels for indoor cooking and heating purposes. The COPD caused by smoking is associated with more rapid disease progression and more severe emphysema than COPD from biomass exposure, which is characterized primarily by airway-wall thickening and improved lung function in response to the use of bronchodilators [11]. Smokers with pre-existing airway reactivity also have a greater susceptibility to developing COPD.

The mode of tobacco use appears to affect risk. The morbidity and mortality rates from COPD are higher for persons who smoke cigarettes than for those who smoke a pipe or cigars [6]. The level of risk in smokers is related to dose, age at initiation of smoking, total pack-years smoked, and current smoking status [6; 7].

OCCUPATIONAL DUSTS AND CHEMICALS

Occupational exposures to dusts, fumes, and chemicals also predispose to COPD [12]. The American Thoracic Society has concluded that occupational exposures account for 10% to 20% of symptoms or functional impairment consistent with COPD [13].

INDOOR AIR POLLUTION

Biomass in the form of wood, animal dung, crop residues, or coal, each of which is typically burned in open fires or poorly functioning stoves, can result in significant indoor air pollution. Worldwide, approximately 40% of people use biomass and coal for cooking and heating, which increases their risk for developing COPD. This risk factor is responsible for the high prevalence of COPD among nonsmoking rural women in developing countries [14; 15]. It is estimated that every year, 2 million women and children die due to indoor air pollution caused by from the burning of wood and other biomass fuels [16].

OUTDOOR AIR POLLUTION

The role of outdoor air pollution in the development of COPD is still unclear, but it is considered to be of minor significance compared with that of cigarette smoking [75]. High levels of urban outdoor air pollution are known to be detrimental to the health of patients with pre-existing heart or lung disease. Studies on this point have demonstrated that decreases in pulmonary function measures can be directly related to increases in urban air pollution from fossil fuel combustion [17].

INFECTION

The airways of normal lungs are sterile, and pulmonary defense mechanisms (e.g., mucociliary clearance, alveolar macrophage phagocytosis) work in concert to maintain this sterility. Smoking cigarettes eventually leads to bronchial inflammation and disrupts host defense mechanisms to such an extent that "colonization" of the airways by microbial pathogens is established early in the course of many persons with COPD [23]. The pathogens most commonly implicated are adenovirus, *Chlamydia*, *Haemophilus influenzae*, *Moraxella*, and *Streptococcus pneumoniae* [23; 24]. Bacterial colonization in this setting represents low-grade chronic infection, which, in combination with clinical exacerbations, augments airway inflammation and contributes to pathogenesis and disease progression. The airway inflammation associated with bacterial colonization is neutrophilic in character and mediated by interleukin-8 and other chemokines [25].

A study among older (mean age: 70 years) adults in Devonshire, England, found that men with a history of pneumonia in early childhood had a significantly greater prevalence of COPD in late life [26]. This association was not found in women, perhaps because men in that time and place were more likely to have had this predisposition unmasked by cigarette use and occupational exposures.

LUNG GROWTH AND DEVELOPMENT

Individuals with poor lung growth are susceptible to developing COPD as they age. Some studies have confirmed a positive association between low birth weight and decreased forced expiratory volume (FEV1) in adulthood [18].

OXIDATIVE STRESS

A higher risk for developing COPD has been attributed to conditions of imbalance between oxidants and antioxidants [19]. Antioxidant capacity in COPD is substantially reduced as a result of cigarette smoking and exacerbations, with oxidative stress persisting long after the cessation of cigarette smoking or exacerbation due to the continued production of reactive oxygen species from endogenous sources [187].

GENDER AND GENETIC FACTORS

The role of an individual's biologic sex in determining COPD risk remains unclear [20]. Some studies have indicated that women are more susceptible than men to the effects of tobacco smoke and other harmful substances and more likely to have an advanced stage of disease at diagnosis[1; 20; 21; 22]. There is evidence that air pollution and indoor biomass fuel used during cooking and heating account for the relatively high prevalence of COPD among women in developing countries.

It is believed that a variety of genes play an important role in COPD pathogenesis. A genetic disorder that causes alpha-1 antitrypsin deficiency is an important cause of emphysema in nonsmokers and increases susceptibility to disease in smokers. People with severe hereditary deficiency of alpha-1 antitrypsin are genetically predisposed to developing COPD. Alpha-1 antitrypsin deficiency stimulates neutrophil elastase activity, which leads to parenchymal destruction in the lungs and causes emphysema.

PATHOLOGIC CHANGES IN COPD		
Area	**Inflammatory Changes**	**Structural Changes**
Proximal airways (trachea, bronchi >2 mm internal diameter)	Increase in number of macrophages and CD8+ (cytotoxic) T-lymphocytes Few neutrophils or eosinophils	Increase in goblet cells Enlarged submucosal glands Squamous metaplasia of epithelium
Peripheral airways (bronchioles <2 mm in diameter)	Increase in number of macrophages, T-lymphocytes (CD8+ > CD4+), B-lymphocytes, lymphoid follicles, and fibroblasts Few neutrophils or eosinophils	Thickening of airway wall Luminal inflammatory exudate Peribronchial fibrosis Airway narrowing Increased inflammatory response and exudate correlated with disease severity
Lung parenchyma (respiratory bronchioles and alveoli)	Increase in number of macrophages and CD8+ T-lymphocytes	Destruction of alveolar wall Apoptosis of epithelial and endothelial cells In centrilobular emphysema: Destruction and dilatation of respiratory bronchioles (frequently seen in smokers) In panacinar emphysema: Destruction of alveolar sacs as well as respiratory bronchioles (frequently seen in alpha-1 antitrypsin deficiency)
Pulmonary vasculature	Increase in number of macrophages and T-lymphocytes	Thickening of intima Endothelial cell dysfunction Smooth muscle pulmonary hypertension

Source: [33; 34; 35] *Table 2*

NUTRITION

Experimental studies in animals have demonstrated a strong direct correlation between starvation and anabolic/catabolic status and the development of emphysema [30]. A study conducted in chronically malnourished women showed an increased propensity for emphysema-like changes in the lungs [31].

SOCIOECONOMIC STATUS

Studies have demonstrated that the risk of developing COPD increases in people of low socioeconomic status [27]. However, it is unclear to what extent this is related to excessive exposure to cigarette smoke, other pollutants, and harmful pathogens or to the prevalence of other risk factors, such as poor nutrition and infrequent healthcare contact [28; 29].

ASTHMA

Asthma may contribute to the development of COPD, although the available evidence is inconclusive. Some studies have shown that asthmatics have a higher risk for developing COPD over time compared to non-asthmatics, but more research is necessary before a definitive correlation can be established [32].

PATHOLOGY

Although the defining pathologic changes of COPD are found in the lower airways of the tracheobronchial tree, the disease process also extends to the lung parenchyma and pulmonary vasculature (***Table 2***) [33; 34; 35].

INFLAMMATORY CELLS IN COPD	
Cell Type	**Characteristic Changes**
Neutrophils	Elevated levels of neutrophils in sputum of normal smokers, with greater levels in those with COPD related to disease severity. Few neutrophils are seen in tissue. They may be important in mucus hypersecretion and the release of proteases.
Macrophages	Greatly increased numbers of macrophages are seen in airway lumen, lung parenchyma, and bronchoalveolar lavage fluid. Derived from blood monocytes that differentiate within lung tissue, these cells produce increased inflammatory mediators and proteases in patients with COPD in response to cigarette smoke and may show defective phagocytosis.
T-lymphocytes (T-cells)	Both CD4+ and CD8+ cells are increased in the airway wall and lung parenchyma, with an increased CD8+:CD4+ ratio. Greater numbers of CD8+ T-cells (Tc1) and T helper 1 (Th1) cells, which secrete interferon-γ and express the chemokine receptor CXCR39. CD8+ cells may be cytotoxic to alveolar cells, contributing to their destruction.
B-lymphocytes (B-cells)	Elevated levels in peripheral airways and within lymphoid follicles, possibly as a response to chronic colonization and infection of the airways.
Eosinophils	Elevated levels of eosinophil proteins in sputum and increased eosinophils in airway wall during exacerbations.
Epithelial cells	May be activated by cigarette smoke to produce inflammatory mediators.
Source: Reprinted with permission from Alldredge BK, Corelli RL, Ernst ME, et al. (eds). Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs. Philadelphia, PA: Lippincott Williams & Wilkins; 2012. *Table 3*	

AIRFLOW LIMITATION AND CHRONIC INFLAMMATION

COPD is characterized by a chronic, fixed limitation to airflow during the normal respiratory cycle and is caused by the combined effects of chronic inflammation, bronchial glandular hypertrophy, excess mucus production, and obstructive bronchiolitis. Airway inflammation plays the central role in pathogenesis and disease progression. Affected patients demonstrate an amplified inflammatory response within the airways to inhaled cigarette smoke, other noxious particles, and viral and bacterial infection. Chronic inflammation leads to structural changes, narrowing of the small airways, and loss of alveolar attachments to the small airways and impaired lung elasticity within the lung parenchyma. This in turn compromises the ability of lungs to remain open during expiration, further impeding airflow, trapping air, and diminishing gas exchange. Diagnosis is made by demonstrating the presence of airflow limitation, which can be done easily, accurately, and reliably by spirometry.

Inflammatory Cells

The chronic inflammatory process of COPD is mediated by a proliferation of inflammatory cells such as neutrophils, macrophages, B-cells, and CD8+ T-cells, particularly in the small airways (***Table 3***) [33; 195]. The degree of inflammation mirrors the severity of disease.

It is suggested that neutrophils play a primary role in the generation of mucous metaplasia in chronic bronchitis and the destruction of lung tissue in emphysema. The neutrophilic inflammatory response appears to account for the excessive mucus secretion observed in response to an acute secretagogue and for augmentation of the bronchial mucus-producing apparatus observed in these patients [34; 35]. There is a strong correlation between peripheral airway dysfunction in COPD and sputum neutrophil counts [36].

Macrophages are the predominant inflammatory cells present in lavage fluid in patients with COPD [37]. Numerous studies have demonstrated a direct correlation between the number of alveolar macrophage in the lung tissue and the severity of lung destruction [38].

INFLAMMATORY MEDIATORS INVOLVED IN COPD	
Cell Type	**Action**
Lipid mediators (e.g., leukotriene B4)	Attract neutrophils and T-lymphocytes
Chemokines (e.g., interleukin-8)	Attract neutrophils and monocytes
Proinflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-1ß, and interleukin-6)	Amplify the inflammatory process and may contribute to some of the systemic effects of COPD
Growth factors (e.g., transforming growth factor-ß)	May induce fibrosis in small airways

Source: Reprinted with permission from Alldredge BK, Corelli RL, Ernst ME, et al. (eds). Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs. Philadelphia, PA: Lippincott Williams & Wilkins; 2012. *Table 4*

In COPD, the total T-cell count is elevated. CD8+ cells are the predominant subtype [39].

Inflammatory Mediators

A number of inflammatory mediators are increased in patients with COPD (***Table 4***) [195]. These mediators function to attract inflammatory cells from the circulation (chemotactic factors), amplify the inflammatory process (proinflammatory cytokines), and induce structural changes (growth factors).

OXIDATIVE STRESS

Oxidative stress plays an important role in both inflammation and emphysematous response to cigarette smoke exposure, and it also promotes mucus secretion and plasma exudation. Biomarkers of oxidative stress (e.g., hydrogen peroxide, 8-isoprostane) are elevated in patients with COPD. It is suspected that oxidative stress plays a key role in activating inflammatory genes and inactivating antiproteases.

PROTEASE-ANTIPROTEASE IMBALANCE

The protease-antiprotease imbalance is suspected to be the culprit in the development of emphysema in smokers with severe alpha-1 antitrypsin deficiency because of a deficient antiprotease protection against neutrophil elastase release in the lung. In addition, smoke exposure can inactivate endogenous antiproteases, contributing to this imbalance [191].

PATHOPHYSIOLOGY

Research has resulted in a better understanding of the pathophysiology of the underlying disease process that results in the characteristic abnormalities and symptoms of COPD.

AIRFLOW LIMITATION AND AIR TRAPPING

There is a direct correlation between degree of inflammation, fibrosis, and luminal exudates in small airways and the reduction in FEV1 and FEV1/forced vital capacity (FVC) ratio. The effect on airflow is pronounced in the smaller (<2 mm in diameter) conducting airways. The resultant peripheral airway obstruction produces alveolar hyperinflation and air trapping during expiration. Hyperinflation diminishes inspiratory capacity and increases functional residual capacity, which causes dyspnea and limitation of exercise capacity.

GAS EXCHANGE ABNORMALITIES

Inefficient and impaired gas exchange results in arterial oxygen deficiency (hypoxemia) and carbon dioxide (CO_2) retention (hypercapnia). Gas exchange abnormalities worsen as the disease progresses. There is a strong relationship between the severity of emphysematous change and the degree of arterial oxygen deficit coupled with ventilation-perfusion (VA/Q) imbalance.

Patients with COPD often have respiratory muscle weakness and reduced respiratory muscle endurance. This further confounds the problem of ventilation and can result in serious hypercapnia during intercurrent illness, inadvertent sedation, and episodes of infectious bronchitis. The alveolar ventilation impairment and pulmonary vascular bed shrinkage leads to further deterioration of the VA/Q mismatch.

MUCUS HYPERSECRETION

Excessive mucus secretion causes chronic productive cough in patients with chronic bronchitis. Ordinarily, this plays a minor role in airflow limitation but may become significant during episodes of infectious bronchitis. However, symptomatic mucus hypersecretion is not present in all patients with COPD. Many mediators and proteases can stimulate mucus hypersecretion by activating the epidermal growth factor receptor (EGFR).

PULMONARY HYPERTENSION

Pulmonary hypertension develops late in the course of COPD, typically after the patient develops severe gas exchange impairments. Pulmonary hypertension supervenes in COPD because of vasoconstriction of small pulmonary arteries, endothelial cell dysfunction, and loss of the pulmonary capillary bed. This combination of events leads to progressive pulmonary hypertension, which causes right ventricular hypertrophy and ultimately cor pulmonale (right-side cardiac failure).

SYSTEMIC EFFECTS

COPD is associated with systemic inflammation and skeletal muscle loss, especially in patients with a severe course. These systemic effects can lead to poor exercise capacity, cachexia, chronic anemia, osteoporosis, and depression. Inflammatory markers are typically elevated in COPD, and there is a direct correlation between elevated C-reactive protein (CRP) and risk of cardiovascular diseases [82].

CLINICAL FEATURES

The cardinal signs and symptoms of COPD are chronic cough, sputum production, breathlessness (shortness of breath and dyspnea), and limited exercise tolerance. Other common signs that may be present in COPD include:

- Tachypnea
- Pursed lips breathing
- Prolonged expiration phase of breathing (compared with inspiration)
- Active use of neck muscles during breathing
- Increased resonance of the chest (by percussion) caused by hyperaeration and emphysematous change
- Increased anteroposterior (A-P) diameter of the chest ("barrel chest")

In established and late-stage disease, systemic complications can develop, including skeletal muscle wasting and weakness, poor exercise capacity, weight loss, depression and anxiety, osteoporosis, cor pulmonale, and polycythemia.

COUGH

Symptomatic COPD usually begins insidiously with a chronic cough, often intermittent and nonproductive, gradually becoming more frequent and productive of sputum as disease progresses. This productive cough may be more pronounced on arising in the morning, but eventually recurs throughout the day in advanced stages. In cases in which emphysema is the predominant form of COPD, patients may experience little or no cough despite progression to severe airflow limitation.

The prevalence of cough in patients with COPD increases with disease progression, age, and smoking status. Of 2,950 individuals with COPD who participated in a clinical survey, 55% reported chronic cough and 20% rated the cough as severe or extreme [83]. The high prevalence of cough may be related to increased mucus production, inefficient mucus clearing, and increased mucus retention. The number and severity of COPD exacerbations varies directly with the chronicity and severity of productive cough. Moreover, pervasive cough is fatiguing, interrupts sleep, and adversely affects overall health status and quality of life.

INCREASED SPUTUM PRODUCTION

Sputum is a mucous substance produced from the lungs, usually expelled by coughing or clearing of the throat. Copious amounts of sputum can be associated with inflammation or infection of the respiratory tract and may be indicative of COPD. The color and consistency of sputum may be related to the type of COPD. Purulent sputum indicates an increase in inflammatory mediators such as interleukin (IL)-8, myeloperoxidase (MPO), and leukotriene B4 (LTB4) [44]. Presence of this type of sputum may signify the onset of an exacerbation [45].

DYSPNEA

Dyspnea, or severe and distressing shortness of breath, is the most common and characteristic symptom of COPD. Patients typically describe their dyspnea as air hunger, heaviness, difficulty breathing, or gasping. Dyspnea is usually first noticed during vigorous physical activity; however, as COPD progresses, dyspnea worsens and is felt even during a light physical activity. Eventually, it becomes constant even while resting.

FATIGUE

Fatigue is the second most frequent symptom experienced by individuals with COPD. It is often poorly understood and frequently under-reported. Fatigue gradually impacts functional capabilities of patients with COPD, diminishing quality of life. Dyspnea and fatigue are the most predominant disabling symptoms in COPD.

WHEEZING AND CHEST TIGHTNESS

Wheezing is caused by obstruction of the airways and is associated with labored breathing, while chest tightness is caused by an increased amount of mucus in the lungs and subsequent obstruction of the airways. Chest tightness can cause short, shallow respiration and is often present in patients with COPD. Severity of wheezing and chest tightness can fluctuate daily and over the course of a single day. These nonspecific symptoms may be present in early stages of COPD but are more characteristic of asthma or later stage COPD. Audible wheezes, or stridor, may be heard when retained sputum is present at the bronchial or laryngeal level. Bilateral, widespread inspiratory or expiratory wheezes can usually be heard on auscultation of the chest.

HEMOPTYSIS

Hemoptysis is common in patients with COPD during periods of acute bronchitis or pneumonia. Though not a hallmark of the disease, hemoptysis may be present, and patients with more severe airflow obstruction tend to have more severe bleeding [193]. In some cases, angiographic embolization may be necessary.

CLUBBING OF THE FINGERS

Clubbing of the fingers may be present in patients with COPD, in part caused by chronic oxygen deprivation. However, it is relatively uncommon. Clubbing is more likely indicative of other chronic diseases such as congenital heart defect, bronchiectasis, infectious endocarditis, or cirrhosis of the liver.

DIAGNOSIS AND CLINICAL ASSESSMENT

A clinical diagnosis of COPD should be considered in the patient who presents with shortness of breath or dyspnea, chronic productive cough, and easy fatigue, especially if combined with a history of risk factor exposure (e.g., long-term exposure to tobacco or dust and chemicals, age, genetics). The diagnosis should then be confirmed by spirometry. The presence of a Tiffeneau index or postbronchodilator FEV1/FVC less than 0.70 and FEV1 less than 80% predicted confirms the presence of airflow limitation that is not fully reversible [199].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Physicians (ACP), the American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) recommend that spirometry should be obtained to diagnose airflow obstruction in patients with respiratory symptoms. Spirometry should not be used to screen for airflow obstruction in individuals without respiratory symptoms.

(https://www.thoracic.org/statements/resources/copd/179full.pdf. Last accessed October 25, 2022.)

Strength of Recommendation: Strong (Benefits clearly outweigh risks and burden)

The possibility of COPD should be assessed in any individual older than 35 years of age who presents with any of the following key indicators [199]:

- Breathlessness that is persistent, progressive, and worsens with exertion. (It may be described by the patient as increased effort of breathing, heaviness, air hunger, or gasping.)
- Chronic cough (may be intermittent and unproductive)
- Chronic sputum production
- Family history of COPD
- History of exposure to risk factors, particularly tobacco smoke, smoke from home cooking and heating fuels, and/or occupational dusts and chemicals

Spirometry, which is simple and effective, is the preferred diagnostic study to confirm the diagnosis in such cases. It is important to bear in mind that chronic respiratory symptoms may precede the development of measurable airflow limitation. An appreciable number of smokers with normal spirometry have other demonstrable signs of lung disease, including emphysema, airway wall thickening, and air trapping [199].

Patients at risk for COPD (because of one or a combination of factors) but with normal spirometric values may be in the pre-COPD stage of mild disease. Such patients should be encouraged to make lifestyle changes that include smoking cessation and avoidance of exposures injurious to the lungs. Clinical follow-up with annual spirometry is also important for monitoring potential disease progression and the early detection of persistent airflow limitation [10].

The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on the patient's health status, and the risk of exacerbations in order to guide therapy [199]. The COPD Assessment Test (CAT) is a patient-completed questionnaire that complements current approaches to assessing COPD [196]. The test consists of eight items evaluating the presence of COPD symptoms and the extent of their impact on activities of daily living. Each question is answered with a number from 0 to 5 depending on the level of impairment. The corresponding score is an indicator of impact of the disease on the patient's life. Patients periodically complete the CAT questionnaire to detect changes and trends in disease course.

MRC BREATHLESSNESS SCALE	
Grade	**Degree of Breathlessness Related to Activities**
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness, stops after about a mile, or has to stop after 15 minutes when walking at own pace
4	Stops for breath after walking about 100 yards or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

Source: Reprinted with permission from Stenton C. The MRC breathlessness scale. Occup Med (Lond). 2008;58(3):226-227. *Table 5*

ASSESSMENT OF SYMPTOMS

Symptoms of COPD, with a few exceptions, usually arise in a particular pattern. The principal symptoms in mild COPD are chronic cough and sputum production. These symptoms are usually ignored, in some cases for years, and are often attributed to poor conditioning and old age. In moderate COPD, the airflow limitation worsens, leading to dyspnea and limiting the patient's daily activities [46]. This is the point at which the patient usually seeks medical care and may be diagnosed with COPD. However, some patients will not recognize COPD symptoms or seek medical help even at this stage. As the disease progresses, airflow limitation worsens. The symptoms of cough and sputum production persist, dyspnea worsens, and other systemic complications, such as cor pulmonale, weight loss, and respiratory failure, may supervene. The diagnosis is usually forthcoming when the patient with progressive breathlessness and exercise intolerance seeks medical help, or an episode of superimposed bronchitis or pneumonia leads to respiratory failure and the recognition of an acute-on-chronic pulmonary disorder.

There are also a number of nonspecific symptoms and signs that, if present, can help in diagnosis of COPD, including [46]:

- Weight loss
- Exercise intolerance
- Waking at night
- Ankle swelling
- Fatigue
- Occupational hazards
- Hemoptysis
- Chest pain

Hemoptysis and chest pain are not common in COPD and should always prompt an evaluation for other related comorbidities, such as infection and malignancy.

Dyspnea

The insidious onset and progression of dyspnea is so characteristic as to be a hallmark symptom of COPD. The majority of patients who seek medical opinion do so because of dyspnea and its associated disability and anxiety. As discussed, breathlessness is initially only noted on increased physical activity, such as running up a flight of stairs or walking. However, as the disease progresses and lung function worsens, breathlessness can be experienced even with slight physical effort. Finally, dyspnea will interfere with activities of daily living and even at rest. The degree of dyspnea varies from patient to patient, but it is usually not difficult to distinguish the dyspnea of COPD from that due to other causes. The Medical Research Council (MRC) Breathlessness Scale can be used to evaluate the impact of dyspnea on a patient's health status (***Table 5***) [197]. This questionnaire not only relates well to other measures of health status but also predicts future mortality risk.

POSSIBLE CAUSES OF CHRONIC COUGH WITH NORMAL CHEST X-RAY
Intrathoracic
COPD
Bronchial asthma
Central bronchial carcinoma
Left heart failure
Tuberculosis
Bronchiectasis
Interstitial lung disease
Cystic fibrosis
Extrathoracic
Gastroesophageal reflux disease (GERD)
Postnasal drip syndrome
Certain medications (e.g., angiotensin-converting enzyme [ACE] inhibitors)
Source: Compiled by Author *Table 6*

Cough

Chronic cough, usually the first symptom of COPD to develop, is often initially attributed to smoking or environmental exposures. In early stages, the cough usually comes and goes, but later it is present almost every day or even the entire day. Some patients have significant airflow limitation even in absence of cough. However, there are other possible causes of chronic cough, and chest x-ray and differential diagnosis is necessary (***Table 6***).

Sputum Production

Individuals with COPD usually expectorate or swallow small quantities of sputum after coughing spells. Regular sputum production for three or more months in two consecutive years is indicative of chronic bronchitis. Patients producing copious amount of sputum may have underlying bronchiectasis.

Wheezing and Chest Tightness

As noted, wheezing and chest tightness are nonspecific symptoms of COPD. They may be present in the early stages of COPD, becoming more prominent in the later stages of the disease.

Additional Features in Severe Disease

Weight loss and anorexia are frequently present in advanced stages of COPD and are important prognostic markers. Therefore, these symptoms should be thoroughly investigated. In severe cases, coughing spells may cause patients to experience cough syncope (caused by rapid increases in intrathoracic pressure) or can cause rib fractures, especially in osteoporotic patients. Those persons with COPD who develop cor pulmonale usually develop ankle swelling.

MEDICAL HISTORY

As with any illness, a careful history is critical in determining the correct diagnosis. The goals of history taking are to identify possible causes of dyspnea and other symptoms and to screen for COPD risk factors. An inadequate history may result in misdiagnosis or delayed diagnosis, with ramifications on disease course. A comprehensive medical history of an individual presenting with COPD symptoms should include:

- Long-term exposure to risk factors, such as smoking or occupational and environmental exposures
- Past medical history, including asthma, allergy, respiratory infections in the past (especially in childhood), sinusitis or nasal polyps, and other respiratory illnesses
- Family history of COPD or other chronic respiratory disease
- Pattern of symptoms of COPD (e.g., development in adulthood, increasing dyspnea or breathlessness, frequent "winter colds," restricted social life)
- History of previous hospitalizations or exacerbations for respiratory illnesses
- Presence of comorbid conditions, such as chronic heart disease, malignancy, musculoskeletal disorders, or osteoporosis
- Medical treatments
- Impact of the disease on the patient's life, including restricted activity, absenteeism at work, financial impact, and depression or anxiety

- Family and social support available
- Possibilities for COPD risk factor reduction, particularly smoking cessation

This sample list may seem daunting, especially in the context of a brief office visit. However, it is critical that a detailed history be obtained. It may be more efficient to have a questionnaire available for patients to fill out while they are waiting or even prior to the office visit.

Language barriers can be a serious consideration when engaging a patient and elucidating possible causes of COPD symptoms. When a patient does not speak the same language as the clinician, a professional interpreter should be consulted to ensure accurate communication. Use of professional interpreters has been associated with improvements in communication (errors and comprehension), utilization, clinical outcomes, and satisfaction with care.

PHYSICAL EXAMINATION

A physical examination is an important component of the diagnosis of COPD, but it is seldom diagnostic. Physical signs of airflow limitation are generally absent in the early stages of the disease, developing only later when there is a significant reduction in lung function [16; 17]. Patients may have several physical signs indicative of COPD, but absence of these signs does not exclude diagnosis.

Inspection

Shallow and rapid breathing with respiratory rate of more than 20 breaths per minute may be noted [17]. The presence of central cyanosis is hard to visualize in artificial light and in darker-skinned patients, but it may be present in severe cases. Ankle or lower leg edema may be a sign of cor pulmonale.

Common chest wall abnormalities indicative of pulmonary hyperinflation (emphysema) may be seen in COPD, such as "barrel-shaped" chest, relatively horizontal ribs, and protruding abdomen. Flattening of the hemidiaphragms may be evident on percussion over the posterior chest or noted on chest x-ray.

Patients with advanced COPD/emphysema often show pursed-lip breathing, which slows expiratory flow and allows better lung emptying [18]. Patients in the later stages of COPD use accessory muscles (e.g., scalene and sternocleidomastoid muscles) to force breaths. Resting muscle activation while lying supine can also be seen in these patients.

Palpation and Percussion

Palpation and percussion are of limited value but may disclose a subtle degree of increased A-P diameter and increased resonance. Pulmonary hyperinflation will make the heart apex beat more difficult to detect. Hyperinflation also causes downward displacement of the liver, and it is easy to palpate this organ even with no enlargement.

Auscultation

Patients with COPD often have diminished breath sounds on auscultation [47]. The presence of wheezes during quiet breathing indicates airflow limitation. But, it is important to note that wheezing heard only after forced expiration is not diagnostic for COPD. Inspiratory crackles are also not diagnostically important in COPD.

In patients with pulmonary hypertension, the heart sounds may be distant and the pulmonary component of the second heart sound may be loud. Generally, heart sounds are best heard over the xiphoid area.

MEASUREMENT OF AIRFLOW LIMITATION (SPIROMETRY)

Every patient with known or suspected COPD should undergo spirometry in order to quantify the level of airflow obstruction. It is an important tool both for the diagnosis of COPD and to rule out conditions that may mimic COPD. Although spirometry does not provide a complete picture of the overall effect of COPD on a patient's health, it remains the gold standard for the diagnosis and periodic monitoring of the disease—it provides a standardized, reproducible, and objective measurement of airflow limitation (***Table 7***) [176; 199].

CONSIDERATIONS IN PERFORMING SPIROMETRY
Preparation
Spirometers need calibration on a regular basis.
Spirometers should produce hard copy or have a digital display of the expiratory curve to permit detection of technical errors or have an automatic prompt to identify an unsatisfactory test and the reason for it.
The supervisor of the test needs training in its effective performance.
Maximal patient effort in performing the test is required to avoid underestimation of values and hence errors in diagnosis and management.
Bronchodilation
Possible dosage protocols are 400 mcg beta2-agonist, 160 mcg anticholinergic, or the two combined. FEV1 should be measured 10 to 15 minutes after a short-acting beta2-agonist is given, or 30 to 45 minutes after a short-acting anticholinergic or a combination.
Performance
Spirometry should be performed using techniques that meet published standards.
The expiratory volume/time traces should be smooth and free from irregularities.
The recording should go on long enough for a volume plateau to be reached, which may take more than 15 seconds in severe disease.
Both FVC and FEV1 should be the largest value obtained from any of three technically satisfactory curves, and the FVC and FEV1 values in these three curves should vary by no more than 5% or 150 mL, whichever is greater.
The FEV1/FVC ratio should be taken from the technically acceptable curve with the largest sum of FVC and FEV1.
Evaluation
Spirometry measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex, and race.
The presence of a postbronchodilator FEV1/FVC <0.70 confirms the presence of airflow limitation.

Source: Reprinted from the Global Strategy for Diagnosis, Management, and Prevention of COPD 2016, © Global Initiative for Chronic Obstructive Lung Disease (GOLD), all rights reserved. Available from http://www.goldcopd.org. *Table 7*

Spirometry accurately measures the volume of air forcibly exhaled from the point of maximal inspiration (FVC) and the volume of air exhaled during the first second of this maneuver (FEV1). The ratio of these two measurements is then calculated. Spirometry measurements are evaluated by comparison with reference values based on the individual's age, height, sex, and race. Patients with COPD typically show a reduction in both FEV1 and FVC, with the degree of abnormality correlated with disease severity [48]. The presence of airflow limitation is generally defined by a postbronchodilator FEV1/FVC ratio less than 0.70; however, it is important to note that there are no universally applicable reference values for FEV1 and FVC.

Spirometry should be performed after administrating short-acting inhaled bronchodilator (e.g., 400 mcg salbutamol) to minimize variability. Findings should be compared to age-related normal values in order to prevent overdiagnosis of COPD in the elderly [21]. Peak expiratory flow may also be used as a measure of airflow limitation. Data from the U.S. National Health and Nutrition Examination Survey suggest that peak expiratory flow is highly sensitive and can detect more than 90% of COPD cases. However, this measurement has poor specificity and should not be the only diagnostic test [49].

The role of screening spirometry for COPD is controversial. There are insufficient data to demonstrate the efficacy of screening spirometry in the general population [50].

DIFFERENTIAL DIAGNOSIS OF COPD	
Diagnosis	**Suggestive Features**[a]
COPD	Onset in mid-life Symptoms slowly progressive Long history of tobacco smoking Breathlessness or dyspnea during exercise Largely irreversible airflow limitation
Asthma	Early onset, often in childhood Family history of asthma Symptoms at night/early morning and vary from day to day Presence of allergy, rhinitis, and/or eczema Largely reversible airflow limitation
Bronchiectasis	Copious amount of purulent sputum Generally associated with bacterial infection Coarse crackles or clubbing on auscultation Bronchial dilation and thickening of bronchial wall on chest x-ray/CT
Congestive heart failure	Fine basilar crackles on auscultation Dilated heart and pulmonary edema on chest x-ray Pulmonary function tests show volume restriction with no airflow limitation
Tuberculosis	Onset all ages Lung infiltrate visible on chest x-ray Microbiologic confirmation of *Mycobacterium tuberculosis* High local prevalence of tuberculosis
Diffuse panbronchiolitis	Majority of patients are men and nonsmokers Chronic sinusitis Diffuse small centrilobular nodular opacities and hyperinflation on chest x-ray and/or HRCT
Obliterative bronchiolitis	Onset in younger age, nonsmokers May have history of rheumatoid arthritis or exposure to fumes CT on expiration shows hypodense areas
[a]These signs/symptoms/features tend to be characteristic of the respective diseases but are not present in every case. CT = computed tomography, HRCT = high-resolution CT.	
Source: [200]	*Table 8*

Spirometry requires patients' cooperation, and therefore, it is unsuitable for patients who are unconscious, heavily sedated, or incapable of vigorous respiratory efforts. It is also not appropriate for children younger than 6 years of age.

DIFFERENTIAL DIAGNOSIS

A range of pulmonary and systemic conditions should be considered in the differential diagnosis of COPD (***Table 8***) [200]. Some patients are assumed to have coexisting asthma and COPD because a clear distinction between the two cannot be made using current methods and techniques. In such cases, management is similar to that of asthma. Other potential conditions are typically easier to distinguish from COPD and include heart failure, tuberculosis, and bronchiectasis. The differential diagnosis of these conditions and possible comorbidities may require additional testing.

SPIROMETRIC CLASSIFICATION OF COPD SEVERITY BASED ON POSTBRONCHODILATOR FEV1[a]	
GOLD Stage	**Spirometric Finding**
1 (mild)	FEV1 ≥80% predicted
2 (moderate)	50% ≤ FEV1 <80% predicted
3 (severe)	30% ≤ FEV1 <50% predicted
4 (very severe)	FEV1 <30% predicted
[a]In patients with FEV1/FVC <0.70 FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, GOLD = Global Initiative for Chronic Obstructive Lung Disorder.	
Source: Reprinted from the Global Strategy for Diagnosis, Management, and Prevention of COPD 2016, © Global Initiative for Chronic Obstructive Lung Disease (GOLD), all rights reserved. Available from http://goldcopd.org. *Table 9*	

ASSESSMENT OF COPD SEVERITY

Assessment of COPD severity is based on the patient's level of symptoms, the degree of the spirometric abnormality, and the presence of complications such as respiratory failure, cor pulmonale, weight loss, and arterial hypoxemia. Spirometric classification of COPD categorizes the stage of disease progression based on postbronchodilator FEV1, FEV1/FVC ratio, and presence of respiratory failure (***Table 9***) [176; 199].

Presence of airflow limitation is crucial for assessing COPD severity, but it is not the only measure. Several studies have observed that individuals with early COPD experience at least one respiratory symptom (e.g., dyspnea, cough, sputum production, wheezing), even with relatively minor or no spirometric abnormality [51]. Presence of such respiratory symptoms can help in identifying high-risk individuals, but it is important to remember that not all individuals will go on to develop COPD [29]. When evaluating symptomatic patients, apart from severity of airflow obstruction, the severity of dyspnea, the presence or absence of cachexia, and the capacity for carrying out activities of daily living are the major indicators of prognosis and overall health status.

The severity of a patient's dyspnea is a reliable indicator of COPD severity and health status, particularly in the elderly, and this parameter can be determined using the mMRC or MRC scale. Objectively measured exercise intolerance or impairment, as assessed by a reduction in self-paced walking distance or during incremental exercise testing in a laboratory, is a powerful prognostic marker as well [30; 52; 53]. The ratio of inspiratory capacity to total lung capacity determined by plethysmograph may also be helpful in determining disease prognosis [54]. Patients experiencing weight loss and reduction in arterial oxygen tension are at increased risk for mortality [55; 56]. Some have proposed using a combination of these variables when staging COPD and determining prognosis.

The BODE index is a multidimensional grading method used to assess clinical risk in patients with COPD based on four factors: body mass index (BMI), obstruction, dyspnea, and exercise (***Table 10***) [5; 57]. It is a better prognostic marker of subsequent survival than any other component alone [5; 57]. Each component of the BODE index is graded and a score out of 10 is obtained; higher scores are indicative of greater mortality risk. This method reflects the effect of both pulmonary and extrapulmonary factors on prognosis and survival in COPD.

VARIABLES AND POINT VALUES USED FOR THE COMPUTATION OF THE BODY MASS INDEX, DEGREE OF AIRFLOW OBSTRUCTION AND DYSPNEA, AND EXERCISE CAPACITY (BODE) INDEX				
Variable	**Points on BODE Index**			
	0	**1**	**2**	**3**
FEV1 (% of predicted)	≥65	50–64	36–49	≤35
Distance walked in six minutes	≥350 m	250–349 m	150–249 m	≤149 m
Modified Medical Research Council dyspnea scale score	0–1	2	3	4
Body mass index	>21	≤21	—	—
FEV1 = forced expiratory volume of air in one second.				
Source: Reprinted with permission from Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005-1012. *Table 10*				

ADDITIONAL INVESTIGATIONS FOR PATIENTS WITH MODERATE-TO-SEVERE COPD	
Investigation	**Role**
Serial domiciliary peak flow measurements	To rule out asthma if there is diagnostic doubt
Transfer factor for carbon monoxide (TLCO)	To investigate symptoms that are disproportionate to the spirometric impairment
Alpha-1 antitrypsin	In case of early onset, minimal smoking history, or family history
Computed tomography (CT) scan of the thorax	To investigate symptoms that are disproportionate to the spirometric impairment To investigate abnormalities present on a chest radiograph To assess indication for surgery
Electrocardiogram	Assessment of cardiac status if features of cor pulmonale
Pulse oximetry	To assess oxygen therapy requirement Presence of cyanosis, or cor pulmonale, or if FEV1 <50% predicted
Echocardiogram	Assessment of cardiac status if features of cor pulmonale
Sputum culture	To identify organisms if sputum is persistently present and purulent
Source: Reproduced from Chronic obstructive pulmonary disease: national clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax. 2004;59(Suppl I):1-232, with permission from BMJ Publishing Group Ltd. *Table 11*	

ADDITIONAL INVESTIGATIONS

For patients diagnosed with moderate (stage 2) COPD or more severe disease, other investigations should also be considered (***Table 11***) [201]. This includes bronchodilator reversibility testing, chest x-ray, arterial blood gas measurement, and alpha-1 antitrypsin deficiency screening.

Bronchodilator Reversibility Testing

Bronchodilator and oral corticosteroid reversibility testing are not accurate in predicting disease progression, whether indicated by decline in FEV1, worsening of health status, or number of exacerbations in persons with COPD [58; 59]. However, minor deviation in initial airway caliber can lead to different classification of reversibility status depending on the day of testing, and the lower the prebronchodilator FEV1, the greater the chance of a patient being classified as reversible [59].

Imaging

Abnormal findings detected on chest x-ray are often not definitive for diagnostic purposes. It is helpful in ruling out other conditions, such as lung carcinoma, and for confirming significant comorbidities, such as heart failure. Possible radiologic changes associated with COPD include:

- Signs of hyperinflation (e.g., flattened diaphragm on the lateral chest film, an increase in the volume of the retrosternal air space)
- Hyperlucency of the lung fields
- Reduction in vascular markings

Computed tomography (CT) of the chest has advanced understanding of COPD and has an important role in the clinical assessment of selected patients. Chest CT can identify the presence and extent of disease patterns that impact prognosis and influence the management of patients with COPD [10]. CT imaging features that are associated with adverse clinical outcomes include early interstitial lung abnormalities, bronchiectasis, presence and pattern of emphysema, airway wall thickness, and expiratory gas trapping [224]. The addition of expiratory CT scans has enabled measurement of small airway disease. Chest CT also may reveal extrapulmonary findings of importance, such as coronary artery calcification, cardiac chamber enlargement, and early-stage lung cancer. The presence of predominantly upper-lobe emphysema on CT imaging identifies the patient who is a good candidate for surgical lung-volume reduction [60].

Arterial Blood Gas Measurement

In patients with advanced COPD, analysis of arterial blood gases while the patient is breathing room air provides oxygenation status of the individual. If the resting oxygen saturation is less than 90%, then prompt measurement of arterial blood gases is necessary to assess the need for supplemental oxygen [199]. The test should be undertaken in stable patients with FEV1 <50% predicted or in patients with suspected cor pulmonale or respiratory failure.

Screening for Alpha-1 Antitrypsin Deficiency

White patients who experience COPD at a young age (i.e., younger than 45 years) or who have a positive family history of COPD may be screened for alpha-1 antitrypsin deficiency. A serum concentration of alpha-1 antitrypsin less than 15% to 20% of the normal expected value indicates a high probability of homozygous alpha-1 antitrypsin deficiency.

RISK REDUCTION

The identification, reduction, and control of risk factors are essential for the prevention and management of COPD. As discussed, the prominent COPD risk factors are cigarette smoking and exposure to dust and/or all types of air pollutions and irritants. As the most important risk factor for COPD, tobacco smoking prevention and cessation programs should be implemented and encouraged universally. Exposure to all types of air pollutants should also be curtailed as much as possible.

SMOKING PREVENTION AND CESSATION

A dramatic increase in public awareness concerning the dangers of secondhand smoke has corresponded to social demand for smoking restrictions. There is broad public support in the United States for smoking restrictions in many public places, including childcare centers, hospitals, shopping malls, convenience stores, fast-food restaurants, and indoor sporting events [202].

Efforts to regulate tobacco products include the World Health Organization's Framework Convention on Tobacco Control. Additionally, legislation has been passed to give the FDA regulatory authority over tobacco. The main reason for these proposals is to minimize death and disease caused by tobacco smoke by reducing the prevalence of its use and the toxicity of its products. Based on scientific studies and tobacco industry documents, it is believed that tobacco products could be made less toxic if their design, content, emissions, and manufacturing were better controlled [203].

Nationwide polls reveal broad public support for increased taxing of tobacco [204]. Since 2002, the average state cigarette tax has increased from 43.4 cents to $1.65 per pack [205]. In February 2009, President Obama signed a 61.66-cent federal cigarette tax increase into law, bringing the federal cigarette tax to $1.01 [206]. As of 2019, the CDC reported an average national retail price of $7.65 per pack of cigarettes [207]. Increasing the cost of tobacco not only decreases tobacco use by creating a larger economic barrier to smoking, it also motivates people to try to quit.

The 2009 federal tax increase on the sale of cigarettes is expected to yield several health benefits. Projected benefits and cost savings include an increase in the number of children alive today who will not become smokers (1,992,000) and $493.3 million in five-year healthcare savings from fewer smoking-caused myocardial infarctions and strokes [206; 208].

Though the state and local governments and employers provide protection from tobacco smoke at work, private homes are not subject to such regulation. Educational strategies are needed to increase awareness of personal and childhood tobacco exposure both in and out of the home. As with the business microenvironment, air quality cannot be maintained if smoking is allowed indoors, even with additional ventilation and air-cleaning devices.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The ACCP and the Canadian Thoracic Society suggest including smoking cessation counseling and treatment using best practices as a component of a comprehensive clinical strategy to prevent acute exacerbations of COPD.

(https://journal.chestnet.org/article/S0012-3692(15)38941-8/fulltext. Last accessed October 25, 2022.)

Strength of Recommendation/Level of Evidence: 2C (Weak recommendation, low- or very-low-quality evidence)

Smoking Cessation

Behavioral Modifications

Behavioral interventions are nonpharmacologic treatments delivered directly to individual smokers [209]. The main disadvantage of this approach is that relatively few smokers (about 5%) are interested in attending specific classes at any given time [210]. Therefore, group sessions appear to be the most cost-effective approach to delivering smoking cessation interventions [211]. Although relatively few patients want to go to classes, healthcare professionals should still have a list of referral smoking cessation clinics in their area for those smokers who express an interest in attending them and for those who have failed to respond to other approaches. Simple computer-tailored cessation messages may also be an effective alternative for behavioral support, doubling the cessation rates. This concept has been incorporated into patient support programs provided by several manufacturers of smoking cessation products [210].

There are several behavioral interventions that have empirical support, such as multicomponent coping skills training (e.g., coping response therapy, problem-focused treatment, relapse prevention training, and cognitive-behavioral therapy). This training includes social support and didactic information about nicotine dependence, withdrawal symptoms, and situations that are risks for relapse (e.g., alcohol use, negative moods, or presence of other smokers) as well as training in the use of cognitive and behavioral responses to cope with urges to smoke that reduce the risk of relapse [212; 213]. Aversive therapy for smoking cessation, known as rapid smoking, involves smokers in a controlled clinical setting who deeply inhale on cigarettes at six-second intervals. Up to nine cigarettes would be smoked per treatment session to produce strong aversive reactions to cigarettes [214]. Aversive cigarette use greatly declined after the introduction of nicotine-replacement therapies (NRTs), but it has been rediscovered and is being investigated as an aftercare strategy to reduce cravings and prevent relapse [215].

Another behavioral treatment, scheduled reduced smoking, involves three weeks of gradually reduced nicotine intake. In contrast with other smoking cessation strategies involving reduction of smoking, the patient does not control when and where smoking will occur. Rather, an algorithm is used to determine when each cigarette is to be smoked based on the passage of time [216].

Pharmacotherapy

The first-line pharmacologic interventions for smoking cessation are NRT, bupropion, and varenicline [217; 218]. However, no pharmacotherapy has been approved for use among pregnant or nursing women. The five forms of NRT available are the patch, gum, lozenge, nasal spray, and inhaler.

The nicotine transdermal system, otherwise known as the patch, releases nicotine steadily during an extended period, with blood levels rising within the first 2 to 4 hours and then remaining relatively constant between 8 and 24 hours after application, depending on the product used [219]. Nicotine chewing gum is a type of NRT that may aid in smoking cessation and/or quitting smokeless tobacco. Chewing allows nicotine to be delivered quickly into the bloodstream. Typically available in either 2- or 4-mg doses, nicotine chewing gum is expected to last one to two hours.

The nicotine lozenge is similar to a hard candy. It slowly dissolves in the mouth (for 20 minutes or so) to release nicotine to the brain more quickly than the patch. A 2-mg sublingual nicotine tablet has shown efficacy in several studies and has been approved in Europe to manage nicotine withdrawal [220; 221; 222].

Nasal nicotine spray was approved by the FDA in 1997. Available by prescription, each spray contains 0.5 mg of nicotine, and a dose is defined as one spray in each nostril. In clinical trials, subjects were allowed to take up to five doses/hour, with a maximum of 40 doses/day (40 mg of nicotine). The cessation rates in trials with nicotine nasal spray at one year ranged from 15% to 25% [63; 64; 65].

The FDA also approved a nicotine inhalation system consisting of a mouthpiece and a nicotine-containing cartridge. Available with a prescription, each inhaler contains 10 mg of nicotine and 1 mg of menthol, of which 4 mg of nicotine can be extracted and 2 mg are systemically available. Shallow or deep puffing results in similar nicotine absorption.

Quitting smoking can be a difficult process, even with use of NRT. When subjects were given denicotinized cigarettes along with IV saline or nicotine, the variable most responsible for craving satisfaction, psychologic reward, and craving reduction was the denicotinized cigarette [66]. When ad libitum smoking of preferred brands was also allowed, the combination of nicotine-less cigarette and bolus IV nicotine were the most effective in lowering craving, negative affect, and total amount smoked [67]. Sensations in the tongue, nose, back of mouth, throat, windpipe, and chest showed strong correlation between nicotine-less cigarettes and the usual brand smoked by the subjects, perhaps explaining the strong effects on smoking suppression observed [66]. Therefore, it is important to recognize that while NRT is a key part of cessation therapy, it does not address all aspects of smoking behavior.

Bupropion is an atypical antidepressant that has both dopaminergic and adrenergic actions [68]. In 1998, the slow-release preparation of bupropion became available as a prescription item specifically for smoking cessation, with the trade name Zyban. This treatment could be appropriate for smokers who do not wish to use an NRT or for those whose treatment with NRT has failed. Unlike NRT, smokers begin bupropion treatment one week prior to cessation. The suggested dosage is 300 mg/day, and the duration of treatment is 7 to 12 weeks [69].

Another non-nicotine therapy for smoking cessation is varenicline tartrate (Chantix), a partial agonist selective for nicotine acetylcholine receptor subtypes. Released in 2006, varenicline is available in monthly dose packs (0.5-mg and 1-mg tablets) and is approved for a 12-week course of treatment [217].

The two second-line drugs for smoking cessation are clonidine and nortriptyline [218]. Clonidine is an antihypertensive medication that is administered orally or transdermally. It appears to increase the smoking cessation rate by approximately 11%; however, clonidine is known to produce such side effects as dry mouth, dizziness, sedation, and orthostatic hypotension [70]. Clonidine has not been approved by the FDA for smoking cessation but has been used with individuals who have failed NRT or bupropion. Nortriptyline is a tricyclic antidepressant that has been used to assist smoking cessation, although this is an unlabeled use [218].

OCCUPATIONAL EXPOSURES

In the United States, approximately 19% of COPD in smokers and up to 31% of COPD in nonsmokers is associated with exposure to occupational dust and fumes [76]. The COPD burden may be greater in regions where exposure to inhaled particles, fumes, and gases is more common. Many occupations, especially those involving exposure to chemical, mineral, and biologic fumes or dusts, have been linked with increased risk of developing COPD. The risks associated with these exposures may be reduced or controlled through a number of strategies, including [77; 78; 79]:

- Proper implementation, monitoring, and enforcement of strict norms to control airborne exposure in the workplace
- Adequate education for people who are directly or indirectly involved with occupational airborne exposure (e.g., workers, managers, physicians, legislators)

All employers, employees, and policy decision-makers should be aware of the harmful effects of cigarette smoking and airborne exposure to dust and fumes.

It should be stressed that primary prevention can easily be achieved by eliminating or reducing exposures to various substances in the workplace. Secondary prevention involves surveillance and early case detection. Both of these approaches are essential to prevent and control the risk of COPD from workplace exposures.

INDOOR AND OUTDOOR AIR POLLUTION

People are exposed to various indoor and outdoor environments throughout the day, and each environment has its own distinctive set of air contaminants and potentially harmful particulates. Exposure to air pollution can be decreased by the joint effort of individuals and society.

National and local governments establish air quality standards. Policies should be geared toward reducing pollution levels global and locally and protecting employees with occupational exposures (e.g., with personal protective equipment).

Proper and adequate ventilation should be provided in kitchens to reduce pollution. Face masks should be provided in workplaces with a high risk of exposure to toxic gases, fumes, and particles. Reducing workplace emissions and improving ventilation measures are also recommended in order to ensure cleaner and safer air quality in the workplace.

People with advanced COPD should avoid going outdoors when air pollution increases or air quality is poor. All patients should refrain from outdoor exercise during periods of increased air pollution.

MANAGEMENT OF STABLE COPD

The pharmacologic treatment of stable COPD is intended to reduce symptoms and the risk of exacerbations and improve exercise tolerance and quality of life. The GOLD guidelines recommend a stepwise increase in treatment guided by the severity of disease and by the patient's preference and response to therapy [199]. For treatment purposes, severity is categorized in reference to degree of airflow limitation, severity of dyspnea and other symptoms, and the frequency of exacerbations (the number reflects the degree of airflow limitation [by spirometry] and the letter reflects severity of symptoms) (***Table 12***) [199]. Clinical considerations include:

- Severity and frequency of exacerbations
- Degree of airflow limitation
- Severity of symptoms

GOLD GUIDELINES FOR STEPWISE MANAGEMENT OF COPD BY SEVERITY					
Treatment Step	**Symptom Grade**				
	Stage 0 (At Risk)	**Stage 1/A (Mild)**	**Stage 2/B (Moderate)**	**Stage 3/C (Severe)**	**Stage 4/D (Very Severe)**
Step 1	Avoidance of risk factors				
Step 2		Offer short-acting or long-acting bronchodilator to reduce breathlessness			
Step 3			Initiate regular treatment with one or a combination of long-acting bronchodilators Begin rehabilitation		
Step 4				Utilize single or combination long-acting bronchodilator Add inhaled corticosteroids if repeated exacerbations	
Step 5					Add macrolide in former smokers Consider roflumilast if patient has chronic bronchitis

Source: [199] *Table 12*

- Presence of one or more complications
- Presence of respiratory failure
- Presence of comorbidities
- Health status
- Total number of medications required to manage COPD

PHARMACOTHERAPY

Pharmacotherapy is used to both control and prevent COPD symptoms. Effective treatment will reduce the frequency and severity of COPD exacerbations, increase exercise capacity, and improve overall health status.

Currently, there is no medication for COPD that can prevent the long-term deterioration in lung function that is the hallmark of the disease. However, there are many drugs that can improve symptoms and provide relief to the patient (***Table 13***) [199].

As noted, treatment usually increases in a step-up pattern and is cumulative, meaning the number of medications used increases as the patient's condition deteriorates. Regular treatment should be maintained at the same level for a long duration of time. Aggressive treatment is required only if significant side effects occur or COPD symptoms worsen.

Each individual responds differently to treatment and will experience a varying degree of side effects. Careful monitoring is required to ensure that the goal of treatment is met. If it is not, a step up is warranted [80].

The treatment regimen for the patient with COPD should be patient-specific. However, the step-up guidelines for therapy provide a useful framework for decisions to escalate treatment. Patients with mild (stage 1) COPD experiencing few or intermittent symptoms may require only a short-acting inhaled bronchodilator used as needed. Otherwise, the initial drug of choice for patients with mild disease and no exacerbations is a long-acting muscarinic antagonist. If there is more severe dyspnea and airway obstruction, as with stage 2 to 4 COPD, combining the muscarinic agent with a selective long-acting beta2-agonist is more effective [10; 199].

MEDICATIONS COMMONLY USED IN THE MANAGEMENT OF COPD					
Drug	**Inhaler (mcg)**	**Solution for Nebulizer (mg/mL)**	**Oral**	**Vials for Injection (mg)**	**Duration of Action (hours)**
Short-acting beta2-agonists					
Fenoterol	100–200 (MDI)	1	0.05% (syrup)	–	4–6
Levalbuterol	45–90 (MDI)	0.21, 0.42	–	–	6–8
Salbutamol (albuterol)	100, 200 (MDI & DPI)	5	5 mg (pill), 0.024% (syrup)	0.1, 0.5	4–6
Terbutaline	400, 500 (DPI)	–	2.5 mg, 5 mg (pill)	–	4–6
Long-acting beta2-agonists					
Arformoterol	–	0.0075	–	–	12
Formoterol	4.5–12 (MDI & DPI)	0.01	–	–	12
Indacaterol	75–300 (DPI)	–	–	–	24
Olodaterol	5 (SMI)	–	–	–	24
Salmeterol	25–50 (MDI & DPI)	–	–	–	12
Tulobuterol	–	–	2 mg (transdermal)	–	24
Short-acting muscarinic antagonists					
Ipratropium bromide	20, 40 (MDI)	0.25–0.5	–	–	6–8
Oxitropium bromide	100 (MDI)	1.5	–	–	7–9
Long-acting muscarinic antagonists					
Aclidinium bromide	322 (DPI)	–	–	–	12
Glycopyrronium bromide	44 (DPI)	–	–	–	24
Tiotropium	18 (DPI), 5 (SMI)	–	–	–	24
Umeclidinium	62.5 (DPI)	–	–	–	24
Combination short-acting beta2-agonist plus muscarinic antagonist in one inhaler					
Fenoterol/ipratropium	200/80 (MDI)	1.25/0.5	–	–	6–8
Salbutamol/ipratropium	100/20 (SMI)	–	–	–	6–8
Combination long-acting beta2-agonist plus muscarinic antagonist in one inhaler					
Formoterol/aclidinium	12/340 (DPI)	–	–	–	12
Indacaterol/glycopyrronium	85/43 (DPI)	–	–	–	24
Olodaterol/tiotropium	5/5 (SMI)	–	–	–	24
Vilanterol/umeclidinium	25/62.5 (DPI)	–	–	–	24
Methylxanthines					
Aminophylline	–	–	200–600 mg (pill)	240	Variable, up to 24
Theophylline (SR)	–	–	100–600 mg (pill)	–	Variable, up to 24
Inhaled corticosteroids					
Beclomethasone	50–400 (MDI & DPI)	0.2–0.4	–	–	–
Budesonide	100, 200, 400 (DPI)	0.2, 0.25, 0.5	–	–	–
Fluticasone	50–500 (MDI & DPI)	–	–	–	–
Combination long-acting beta2-agonist plus corticosteroid in one inhaler					
Formoterol/beclometasone	6/100 (MDI & DPI)	–	–	–	–
Formoterol/budesonide	4.5/160 (MDI), 9/320 (DPI)	–	–	–	–
Formoterol/mometasone	10/200, 10/400 (MDI)	–	–	–	–
Salmeterol/fluticasone	50/100, 250, 500 (DPI)	–	–	–	–
Vilanterol/fluticasone furoate	25/100 (DPI)	–	–	–	–
Systemic corticosteroids					
Prednisone	–	–	5–60 mg (pill)	–	–
Methylprednisolone	–	–	4, 8, 16 mg (pill)	–	–
Phosphodiesterase-4 inhibitors					
Roflumilast	–	–	500 mcg (pill)	–	24
MDI = metered-dose inhaler, DPI = dry-powder inhaler, SMI = soft-mist inhaler, SR = sustained release.					
Source: [199; 225; 226]					*Table 13*

The addition of theophylline may help control symptoms in patients using a regular long-acting bronchodilator. Short-acting bronchodilators may be prescribed for stage 2 – 4 COPD in order to address exacerbations. Nebulized therapy is not suitable for stable patients unless it has more beneficial effects than standard dose therapy. Inhaled corticosteroid, used in combination with a long-acting beta2-agonist or a long-acting anticholinergic, is recommended for patients who have progressed to stage 3 or 4 (severe to very severe) COPD. This combination appears to reduce the risk of exacerbations and improve the overall health status in patients with advanced disease. Long-term treatment with oral corticosteroids is not recommended [199].

Bronchodilators

Bronchodilators are the cornerstone of treatment of COPD and are recommended as first-line therapy in patients with demonstrable airflow limitation or other symptoms. They are effective in significantly improving COPD symptoms and quality of life, predominantly by emptying trapped air through the dilatation of distal airways. However, bronchodilators offer symptomatic relief only and do not modify the disease process. They are prescribed on an as-needed basis for symptomatic relief (short-acting) or on a regular basis (long-acting) to reduce or prevent COPD symptoms. Short-acting bronchodilators often result in medical noncompliance due to the problems caused by multiple dosing. This has shifted the focus to the development of long-acting and ultra-long-acting bronchodilators that can induce sustained bronchodilation (12 to 24 hours). This once- or twice-daily dosing regimen improves compliance. As such, long-acting inhaled bronchodilators (i.e., beta2-agonists and muscarinic antagonists [LAMA]) now form the backbone of COPD management [176; 177; 178].

For patients with stable COPD, respiratory symptoms, and FEV1 <60% predicted, the ACP, the ACCP, the ATS, and the ERS recommend treatment with inhaled bronchodilators.

(https://www.thoracic.org/statements/resources/copd/179full.pdf. Last accessed October 25, 2022.)

Strength of Recommendation: Strong (Benefits clearly outweigh risks and burden)

The side effects of bronchodilators are dose dependent and typically predictable. Adverse effects are more common in older patients and those with advanced COPD and comorbidities. However, they usually resolve promptly after medication withdrawal.

Bronchodilators increase FEV1 and affect other spirometric variables, usually by relaxing smooth muscle tone in the airway. They improve lung emptying, reduce dynamic hyperinflation at rest and during exercise, and increase exercise performance (***Table 14***) [8]. The degree of these changes, particularly in more advanced COPD, is difficult to predict from the improvement in FEV1. While these drugs reduce impedance to air flow and improve the efficiency of expiration, lung elastic recoil remains unchanged. Bronchodilators that act predominantly on the smooth muscles of the airway do not have a significant impact on the decline of lung function or disease prognosis.

Inhaled bronchodilators require attention to training in inhaler technique for proper drug delivery. The choice of inhaler device and bronchodilator depends on:

- Cost
- Availability
- Prescribing healthcare provider
- Physical and mental condition of the patient

Inhaled bronchodilators are administered via metered-dose inhaler, dry powder inhaler, or nebulizer (jet or ultrasonic).

RATIONALE FOR THE USE OF BRONCHODILATORS IN COPD	
Physiologic Effects	**Clinical Effects**
Airway smooth muscle relaxation	↓Breathlessness (↓airway resistance, ↓hyperinflation)
Bronchodilation (improve FEV1, lung volumes)	↑Exercise tolerance (↓dynamic hyperinflation)
Decreased air trapping and dynamic hyperinflation	↑Sleep quality (↓nocturnal bronchospasm)
Nonbronchodilator effects (e.g., stimulation of mucociliary transport)	↑Health-related quality of life
	↓Frequency of acute exacerbations

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Hanania NA, Donohue JF. Pharmacologic interventions in chronic obstructive pulmonary disease: bronchodilators.
Proc Am Thorac Soc. 2007;4(7):526-534. *Table 14*

Metered-dose inhalers rely on a mixture of medication, preservatives, and liquid propellant gas to deliver medicine into the lungs in aerosol form. Some metered-dose inhalers discharge medication after a trigger is pressed, but newer versions are breath activated. For patients with poor coordination or impaired hand function, such as those with arthritis or with a history of stroke, breath-activated devices may improve medication delivery. The drawback of the breath-activated inhalers is that a lack of air may make device triggering difficult. Some patients require the assistance of a spacer when using an inhaler.

Breath-activated dry powder inhalers incorporate the same benefits as other breath-activated inhalers; patients are not required to coordinate inhaling with releasing medication. Some dry powder inhalers have a different delivery system involving the insertion of a capsule with medicated, fine powder into the canister. Depending upon the patient's ability to breathe in deeply, variable amounts of medication may be inhaled. Another concern involves the effect of humidity on dry powder, which may influence dose strength.

The nebulizer acts as a vaporizer or humidifier, delivering microdroplets of asthma medication in spray form and allowing a patient to breathe it in through a mouthpiece or face mask. Larger doses from nebulizers may increase the risk of side effects, and studies have shown metered-dose inhalers to be as effective as nebulizers in delivering medication to the lungs [71; 72]. Wet nebulizers are usually not prescribed for regular treatment of COPD because they are more expensive and need regular maintenance [81].

Three classes of bronchodilators are available for the treatment of COPD and may be used alone or in combination: beta2-agonists, muscarinic antagonists (also referred to as anticholinergics), and methylxanthines. All classes of bronchodilators exhibit a similar effect on FEV1 with identical dose of medication. Toxicity with bronchodilators is dose dependent.

Beta2-Agonists

Beta2-agonists stimulate beta2-adrenergic receptors, resulting in increases in cyclic adenosine monophosphate and bronchodilation. Inhaled beta2-agonists produce a rapid bronchodilator effect, a response observed more quickly in asthma patients than those with COPD. Short-acting beta2-agonists produce bronchodilation for a duration of not more than 4 to 6 hours, while long-acting agents, such as salmeterol and formoterol, produce bronchodilation for more than 12 hours [87]. More recently, vilanterol and olodaterol were approved for use in the treatment of COPD. These novel beta2-agonists have 24-hour duration of action, allowing for once-daily dosing [86; 226].

It has been observed that increasing the dose of either a beta 2-agonist or a muscarinic antagonist by an order of magnitude, particularly when given via wet nebulizer, offers subjective relief in acute episodes of COPD but is not necessarily beneficial in stable disease [199]. Rather than increasing dose for increased disease severity, another agent should be added to the treatment regimen.

In rare cases, inhaled beta2-agonists can cause resting sinus tachycardia and cardiac arrhythmias in patients with COPD [199]. At higher doses, these agents can cause exaggerated somatic tremor in the elderly. In fact, the risk of all adverse effects increases in a dose dependent manner, so the dose should be monitored carefully. Hypokalemia may occur, particularly when beta2-agonists are given together with a thiazide diuretic. Some patients experience a mild reduction in partial pressure of oxygen (PaO_2) if short- and long-acting beta2-agonists are administered together. Despite the concerns raised related to beta2-agonists in the management of asthma, further detailed study has found no association between beta2-agonist use and an accelerated loss of lung function or increased mortality in COPD [199].

Muscarinic Antagonists

Muscarinic antagonists act to block acetylcholine's effect on M3 receptors. Short-acting muscarinic antagonists also alter neurotransmission at the pre-ganglionic junction and block M2 receptors. Tiotropium, a long-acting muscarinic antagonist, is M3- and M1-muscarinic receptor selective and is effective for more than 24 hours [88; 89; 90]. Short-acting inhaled anticholinergics produce bronchodilation for a longer duration than short-acting beta2-agonists, but their use is generally limited to the treatment of exacerbations.

Regular use of muscarinic antagonists, both short- and long-acting, improves overall clinical and health status, enhances the effectiveness of pulmonary rehabilitation, and reduces the rate of exacerbations [84; 85]. These agents are often the preferred bronchodilators for COPD due to their greater efficacy and minimal cardiac stimulatory effects compared to those of beta2-agonists.

Muscarinic antagonists are comparatively safer to use and have fewer side effects than other available bronchodilators. The main side effects result from antimuscarinic activity and include xerostomia and a bitter, metallic taste. Studies indicate an increased risk for cardiovascular events, specifically heart failure, acute coronary syndrome, or dysrhythmias) associated with the muscarinic antagonist ipratropium bromide, making tiotropium the preferred agent [91]. Acute glaucoma has been observed in a few patients after wet nebulization with a face mask. These drugs do not have any effect on mucociliary clearance, and there is no increased risk of respiratory infection.

Methylxanthines

Methylxanthines have weak bronchodilator and respiratory stimulant properties. Both of the available methylxanthines (aminophylline and theophylline) are administered orally and have variable durations of action (up to 24 hours). The inhaled bronchodilators are preferred over these oral agents, as the latter tends to be less predictable and more toxic. Although useful for some patients, the methylxanthines are a third-line option in the treatment of stable COPD [199].

The therapeutic ratio of methylxanthines is small, meaning that near-toxic doses are often required to achieve efficacy. Side effects include nausea, headache, heartburn, insomnia, cardiac arrhythmias, and convulsions. The risk of overdose (accidental or intentional) is high with these agents. Several drugs and other factors affect the metabolism of methylxanthines, including anticonvulsants, quinolone antibiotics, alcohol, nicotine, and erythromycin [104].

Combination Bronchodilator Therapy

Combining bronchodilators can improve the impact of therapy with similar or fewer adverse effects. The combination of a beta2-agonist and a LAMA has been shown to be more effective than monotherapy with either agent [126; 146; 147; 148; 149; 150; 151; 152]. This is believed to be related to the synergistic effect of combining the different mechanisms of action. One of the disadvantages of such an

approach is delivery of LAMA and long-acting beta2-agonists at different locations in the lung, which results in a lowering of their synergistic potential.

Bronchodilator Research

The single molecule GSK961081 has dual properties of both antimuscarinic and beta2-agonist agents and is being investigated for its bronchodilator effect. This molecule can deliver the drugs to the same location, leading to optimum synergistic effect [180].

Discovery of novel classes of bronchodilator drugs has proved to be difficult. The focus has shifted to developing drugs that inhibit the contractile machinery in airway smooth muscle, including rho kinase inhibitors, myosin light chain kinase inhibitors, and direct smooth muscle myosin inhibitors. Even as research focuses on novel approaches to address the underlying pathophysiology of COPD, management of the disease remains largely palliative, with minimal impact on the inflammatory process that ultimately leads to a decline in lung function.

Corticosteroids

Corticosteroids, both oral and inhaled, have a limited role in the treatment of COPD except for exacerbations. Although used in the past to identify patients who would be more likely to respond to inhaled steroids, a number of studies have observed that improvement on a short course of oral corticosteroids is not a reliable predictor of the long-term response [199]. Therefore, it is difficult to recommend a therapeutic trial with oral corticosteroids in late stage (moderate to very severe) COPD.

Some retrospective studies have evaluated the effect of oral corticosteroids on long-term FEV1 changes in patients with moderate to very severe COPD [154; 155]. However, long-term oral treatment is not recommended for patients with COPD because of numerous side effects and limited therapeutic benefit. Extended use of systemic corticosteroids can result in a variety of adverse effects, including steroid myopathy, respiratory failure, osteoporosis, and Cushing syndrome.

Although regular treatment with inhaled corticosteroids does not result in the long-term reduction of FEV1 in patients with COPD, it does reduce the frequency of exacerbations and positively impacts overall health status in certain patients [92; 93; 94; 95]. Withdrawal from such treatment may result in COPD exacerbations in these patients [96]. Treatment with inhaled corticosteroids can be recommended for patients with advanced COPD (FEV1 <50%) with frequent exacerbations. Some pooled studies observed that this treatment reduces mortality, but this observation requires further evidence [97]. An inhaled corticosteroid in combination with a long-acting beta2-agonist has a higher efficacy than either drug alone [98; 99].

Reversal of Corticosteroid Resistance

There is mounting evidence that resistance to corticosteroid treatment is the result of a reduction in histone deacetylase-2 (HDAC2) due to oxidative and nitrative stress [188]. Reversal of this corticosteroid resistance by increasing the expression and activity of HDAC2 may be beneficial in the treatment of COPD.

Animal studies have shown that low-dose oral theophylline may increase HDAC2 expression in alveolar macrophages and restore steroid responsiveness in patients with COPD [189]. Further studies may provide novel therapeutic strategies to restore corticosteroid responsiveness with fewer side effects and adverse effects.

Antioxidants. Patients with COPD have increased oxidative stress, especially during exacerbations. Oxidative stress lowers steroid responsiveness by reducing HDAC2 activity and expression, and antioxidants may reverse corticosteroid resistance and reduce inflammation. Glutathione-based antioxidants are weak and easily inactivated by oxidative stress; therefore, researchers are now focusing on more potent and stable antioxidants, such as superoxide dismutase mimics and nicotinamide adenine dinucleotide phosphate oxidase inhibitors [190].

Macrolides. Azithromycin taken on a regular basis has been shown to reduce the frequency of exacerbations in former smokers with COPD prone to exacerbations. In a double-blind, placebo-controlled trial involving patients with three or more COPD exacerbations the previous year, 500 mg azithromycin three times per week for one year was associated with a significant reduction in the adjusted exacerbation rate per year (1.94 vs. 3.22 exacerbations in the placebo group) [192]. The decision to administer a macrolide on a chronic basis should take into account the potential risks of ototoxicity and the induction of respiratory tract bacterial resistance [199].

Alternative Anti-Inflammatory Treatments

Because inflammation in COPD lungs is predominantly corticosteroid-resistant, alternative anti-inflammatory treatment is often required [184; 185]. The majority of broad-spectrum anti-inflammatory agents are systemic in nature, and there are doubts over the safety of such drugs. Therefore, an inhaled delivery may be the optimum mode to increase efficacy and decrease side effects.

Phosphodiesterase-4 (PDE4) is the principal PDE expressed in neutrophils, T-cells, and macrophages, indicating that PDE4 inhibitors would be effective in controlling inflammation in COPD [186]. Oral PDE4 inhibitors have good potential because there are fewer compliance issues and easy availability. Roflumilast, a selective PDE4 inhibitor that inhibits lung inflammation and emphysema, has been developed and approved for treatment of COPD. It is an orally administered drug found to marginally improve FEV1 compared to tiotropium [181]. Roflumilast is recommended for patients with moderate and severe COPD and chronic bronchitis who have frequent exacerbations treated with systemic corticosteroids [199]. However, PDE4 inhibitors have gastrointestinal side effects, such as nausea, diarrhea, reduced appetite, and weight loss. Roflumilast should be avoided in underweight patients.

NONPHARMACOLOGIC TREATMENT

Immunizations

Influenza and pneumococcal vaccines are effective in preventing some of the infections that cause COPD exacerbations and should be administered to all patients with COPD. Annual vaccination against influenza reduces the incidence of serious illness and mortality [100]. Influenza vaccines containing killed or live, inactivated viruses have a greater efficacy in elderly patients with COPD and therefore are highly recommended. Because of antigenic drift, newly attuned vaccines are developed each year in order to assure appropriate efficacy; therefore, the patient with COPD should be immunized against influenza annually [101].

Pneumococcal vaccines have improved over time by broadening the coverage of serotypes in the vaccine to include those that cause the most common invasive infections. At present, the CDC recommends either a single dose of 20-valent pneumococcal conjugate vaccine (PCV20) (Prevnar 20) or one dose of PCV15 may be administered followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) given at least one year after the PCV15 dose [102]. A minimum interval of eight weeks between PCV15 and PPSV23 can be considered for adults with COPD to minimize the risk of invasive pneumococcal disease caused by serotypes unique to PPSV23 in these vulnerable groups [102; 103]. Current information, schedules, and guidance for adult immunizations is maintained by the CDC at https://www.cdc.gov/vaccines/schedules.

Alpha-1 Antitrypsin Augmentation Therapy

Alpha-1 antitrypsin augmentation therapy (i.e., weekly infusion of alpha-1 antitrypsin protein from healthy donors) is suitable for young patients who have severe hereditary alpha-1 antitrypsin deficiency and emphysema [199]. However, this therapy is quite expensive and is available in only a few countries. It is not recommended for patients without alpha-1 antitrypsin deficiency.

Rehabilitation

Pulmonary rehabilitation is a multidisciplinary and comprehensive intervention that is individually tailored for patients with COPD. Its principal goals are to:

- Reduce COPD symptoms
- Optimize physical and emotional status
- Reduce healthcare costs by controlling and reversing various dysfunctions (reducing the need for hospitalization)
- Improve overall quality of life
- Improve activities of daily living

The ACP, the ACCP, the ATS, and the ERS recommend that clinicians should prescribe pulmonary rehabilitation for symptomatic patients with an FEV1 <50% predicted.

(https://www.thoracic.org/statements/resources/copd/179full.pdf. Last accessed October 25, 2022.)

Strength of Recommendation: Strong (Benefits clearly outweigh risks and burden)

Pulmonary rehabilitation can address nonpulmonary conditions that are not addressed by the medical management of COPD, including:

- Muscle weakness and wasting
- Exercise deconditioning
- Depression
- Relative social isolation
- Weight loss

Addressing and treating such problems can disrupt the "vicious circle" in COPD, leading to overall improvement in all aspects of COPD. Patients involved in pulmonary rehabilitation experience an 11% increase in peak oxygen consumption, an 18% increase in peak workload, and an 87% increase in endurance time [105].

Exercise training programs are beneficial at all stages of COPD and can improve exercise tolerance and reduce symptoms of dyspnea and fatigue. Pulmonary rehabilitation requires a multidisciplinary approach involving a number of health professionals from different specialties and may be conducted in outpatient, inpatient, or home settings.

The following factors should be considered in choosing patients for pulmonary rehabilitation [199]:

- Functional status: Overall benefits are observed in patients with a number of disabilities, although chair-bound patients with COPD seldom respond.
- Motivation: Highly motivated patients perform well and are preferred in outpatient programs.
- Severity of dyspnea: Grading of dyspnea with the aid of the MRC questionnaire can be helpful in identifying and selecting patients who can benefit from rehabilitation. Patients with MRC grade 4 dyspnea may not benefit from pulmonary rehabilitation.
- Smoking status: There is no evidence that smokers benefit less than nonsmokers; however, continuing smokers have a greater likelihood of quitting pulmonary rehabilitation programs than nonsmokers.

Program Components

The components of pulmonary rehabilitation vary widely from program to program, but a comprehensive pulmonary rehabilitation program includes proper exercise training, nutrition counseling, and education.

Bicycle ergometry or treadmill exercise is usually the best option to evaluate exercise tolerance, with measurement of maximum heart rate, maximum work performed, and maximum oxygen consumption. Another simple approach is the self-paced, timed walking test (e.g., six-minute walking distance).

These tests require at least one practice session before the interpretation of data. Shuttle walking tests are easier to perform than treadmill tests and provide more detailed information compared to a self-paced test. Exercise training lasts 10 to 45 minutes per session and can be performed daily or weekly. Severely disabled patients should use a simple wheeled walking aid, as it improves walking distance and dyspnea [107]. Other modes of improving outcomes include use of oxygen during exercise, exercising while breathing heliox gas mixtures, unloading the ventilatory muscles while exercising, or use of pursed lip breathing [108; 109]. Anabolic steroids, specific strength training, and the use of neuromuscular electrical stimulation are also being investigated for their perceived benefits in COPD rehabilitation programs [106].

Studies have observed that programs involving less than 28 sessions demonstrate inferior results compared to those with longer treatment periods [199]. The minimum duration of an effective rehabilitation program is six weeks. But long-term beneficial effects are not usually maintained after cessation of rehabilitation regardless of program [110].

Patients who are not able to participate in a formal rehabilitation program should be encouraged to exercise on their own. The addition of upper limb exercises or other strength training to aerobic training is beneficial in improving strength; however, it has no beneficial effect on overall quality of life or exercise tolerance [199].

Nutritional status is a key determinant of morbidity and mortality, disability, symptom severity, and overall prognosis in an individual with COPD, and nutrition counseling is an important part of rehabilitation. Approximately 25% of patients with stage 2 – 4 (moderate to very severe) disease have a low BMI and fat-free mass. Reduced BMI is associated with increased mortality in patients with COPD. Healthcare providers should identify and correct the factors responsible for reduced calorie intake and take steps to improve overall nutrition status in such cases. Patients should be advised to take frequent, small meals, especially those who experience dyspnea while eating. Proper dental hygiene and correction of poor dentition is also vital.

Improvement in the nutritional status of patients with COPD leads to an increase in respiratory muscle strength. However, the cost-effectiveness of this treatment is controversial. Increased calorie intake and an exercise regimen can also be beneficial in patients with COPD without significant nutritional depletion [111]. Anabolic steroids increase body weight and lean body mass in patients with weight loss, but they are not effective in increasing exercise capacity [113; 114].

As noted, the majority of pulmonary rehabilitation programs include an educational component. However, the benefits of continuing patient education have not been established.

Assessment and Follow-Up

Baseline and outcome evaluation should be assessed to quantify individual benefits and scope for improvement. This should include:

- Detailed history
- Physical examination
- Evaluation by spirometry pre- and postbronchodilator drug
- Assessment of overall health status and impact of dyspnea
- Evaluation of exercise capacity

In patients with COPD who suffer from muscle wasting, lower limb strength and inspiratory and expiratory muscle strength should be evaluated. Patient history and physical examination are not useful in outcome assessment but are the principal criteria for baseline status and establishing entry suitability.

Several questionnaires are being used to aid in the assessment of health and mental health status, including questionnaires that are specifically designed for patients with COPD. The Medical Outcomes Study Short Form, the Dyspnea Management Questionnaire, and/or the Hospital Anxiety and Depression Scale (HADS) may be useful to improve identification and management of COPD symptoms [112; 129; 130].

Oxygen Therapy

Oxygen therapy is one of the main nonpharmacologic treatments for stage 4 COPD and can be administered as long-term continuous therapy, therapy during exercise, or therapy to relieve acute dyspnea.

The primary goal of oxygen therapy is to maintain or increase the baseline PaO_2 to at least 8.0 kPa (60 mm Hg) at sea level and rest and/or to produce an oxygen saturation (SaO_2) of at least 90%, which will protect vital organ function by ensuring sufficient delivery of oxygen. Long-term oxygen therapy (i.e., more than 15 hours per day) has been shown to improve survival in patients with chronic respiratory failure [199]. It also has a positive effect on lung function, hemodynamics, exercise tolerance, hematologic characteristics, and mental health [115]. Oxygen therapy may also prevent the progression of pulmonary hypertension.

Long-term oxygen therapy is usually indicated in stage 4 COPD for patients who have [199]:

- $PaO_2 \leq 7.3$ kPa (55 mm Hg) or $SaO_2 \leq 88\%$, with or without hypercapnia confirmed twice over a three-week period
- PaO_2 between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg) or SaO_2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%)

Oxygen is usually delivered by a facemask, with inspiratory flow rates ranging between 24% and 35%. During air travel, patients should be instructed to increase the flow by 1–2 L/min. The facemask allows appropriate and accurate titration of oxygen, which is especially beneficial in patients who are susceptible to CO_2 retention. However, facemasks are readily dislodged and hinder eating and conversation, so many patients prefer nasal cannulae. Oxygen delivery by nasal cannulae necessitates additional blood gas monitoring.

More sophisticated and specialized methods of oxygen delivery are available but should only be used in specialized facilities. Long-term home oxygen therapy may be provided from a fixed oxygen concentrator with plastic piping, allowing the patient to use oxygen at home. Duration of treatment should be at least 15 hours per day, preferably longer.

The ACP, the ACCP, the ATS, and the ERS assert that use of supplemental oxygen for 15 or more hours daily can help improve survival in patients with COPD who have severe resting hypoxemia ($PaO_2 \leq 55$ mm Hg or $SaO_2 \leq 88\%$).

(https://www.thoracic.org/statements/resources/copd/179full.pdf. Last accessed October 25, 2022.)

Strength of Recommendation: Strong (Benefits clearly outweigh risks and burden)

An extra supply of oxygen should be given to allow patients to go outdoors for an appropriate period of time and to exercise while maintaining oxygen saturation greater than 90%. Oxygen therapy during exercise can increase endurance and/or reduce the degree of end-exercise dyspnea or breathlessness. However, studies have observed that ambulatory oxygen therapy has a poor compliance in patients with COPD [116].

Supplemental home oxygen is generally the most expensive component of outpatient therapy for patients who require it. Oxygen concentrator devices may be less expensive than cylinder delivery systems.

Ventilatory Support

Noninvasive ventilation, via the use of both negative and positive pressure ventilation devices, is extensively used to treat acute exacerbations of COPD. Noninvasive ventilation should be the treatment of choice for persistent hypercapnic ventilatory failure during COPD exacerbations in spite of optimal medical treatment [199]. Negative pressure ventilation is not recommended for the chronic management of stage 4 COPD with or without CO_2 retention.

Data do not support combination noninvasive intermittent positive pressure ventilation (NIPPV) with long-term oxygen therapy [117]. However, the addition of NIPPV can reduce CO_2 retention and improve dyspnea in some patients [118].

Possible complications of NIPPV include nasal congestion, nasal bridge ulceration, and facial skin erythema. In addition, contraindications for NIPPV include:

- Respiratory arrest
- Unstable cardiovascular activity (e.g., cardiac arrhythmias, hypotension, myocardial infarction)
- Impairment of mental status, increased somnolence, inability to cooperate
- Copious and/or viscous secretions with high risk for aspiration
- Recent history of facial or gastroesophageal surgery
- Fixed nasopharyngeal abnormality and craniofacial trauma
- Severe burns
- Morbid obesity

Surgical Interventions

Surgical intervention may be indicated for selected patients with severe COPD and decreased exercise endurance that is responding poorly to medical management. CT evaluation of lung anatomy helps determine whether surgical intervention will be of benefit. Patient selection criteria vary by the surgical technique, but in general, patients who undergo surgical intervention have stage 4 COPD.

There is a limit beyond which it is inadvisable to perform surgery for high-risk patients, as the risks outweigh the perceived benefits. Patients undergoing pneumonectomy with a preoperative FEV1 <2 L or 50% predicted and/or a carbon monoxide diffusing capacity (DLCO) <50% predicted have a high risk of postoperative respiratory failure [119]. Patients with poor lung function should be thoroughly investigated for regional distribution of perfusion and exercise capacity [120]. Surgery should not be performed during COPD exacerbations.

Postoperative pulmonary complications are a principal element of the increased risk associated with surgery in patients with COPD. The main risk factors are smoking, age, poor health, obesity, and COPD severity. All COPD candidates for lung resection should undergo a number of tests prior to surgery, including:

- Static lung volume
- Forced spirometry with bronchodilator response
- Arterial blood gases at rest
- Diffusing capacity

Bullectomy

Bullectomy is an older procedure that may be of use for patients with COPD and bullous emphysema. It involves the resection of a large, nonfunctional bulla that is compressing the adjacent lung parenchyma.

Thoracoscopic bullectomy is beneficial in reducing dyspnea and improving lung function [132]. It may also reduce hemoptysis, infection, and chest pain and facilitate re-expansion of a compressed lung region. A thoracic CT scan, arterial blood gas measurement, and comprehensive lung function tests are required before making a decision for bullectomy. Indications for this surgical intervention include the absence of significant hypoxemia, normal or near normal diffusing capacity, and evidence of regional reduction in perfusion with good perfusion in the remaining lung. Several other factors predict a positive or negative outcome with bullectomy (***Table 15***) [73].

Lung Volume Reduction Surgery

Lung volume reduction surgery (LVRS) is a surgical procedure in which damaged parts of the lung are resected to reduce hyperinflation, thus improving efficacy of respiratory muscles. LVRS also improves expiratory flow rates by increasing the elastic recoil pressure of the lung. LVRS is considered for patients with bilateral emphysema on HRCT and severe

FACTORS ASSOCIATED WITH FAVORABLE OR UNFAVORABLE OUTCOME IN CLASSICAL BULLECTOMY		
Parameter	**Favorable**	**Unfavorable**
Clinical	Rapid progressive dyspnea despite maximal medical therapy Ex-smoker	Older age Comorbid illness Cardiac disease Pulmonary hypertension >10% weight loss Frequent respiratory infections Chronic bronchitis
Physiological	Normal FVC or slightly reduced FEV1 >40% of predicted Little bronchoreversibility High trapped lung volume Normal or near normal DLCO Normal PaO_2 and $PaCO_2$	FEV1 <35% of predicted Low trapped gas volume Decreased DLCO
Imaging		
Chest x-ray	Bulla >1/3 hemithorax	Vanishing lung syndrome Poorly defined bullae
CT scan	Large and localized bulla with vascular crowding and normal pulmonary parenchyma around bulla	Multiple ill-defined bullae in underlying lung
Angiography	Vascular crowding with preserved distal vascular branching	Vague bullae; disrupted vasculature elsewhere
Isotope scan	Well-localized matching defect with normal uptake and washout for underlying lung	Absence of target zones, poor washout in remaining of lung
CT = computed tomography, DLCO = carbon dioxide diffusing capacity of the lung, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity.		
Source: Reprinted with permission from Martinez FJ. Surgical therapy for chronic obstructive pulmonary disease: conventional bullectomy and lung volume reduction surgery in the absence of giant bullae. Semin Respir Crit Care Med. 1999;20:351-364. Table 15		

obstruction with hyperinflation and air trapping [194]. As with bullectomy, certain characteristics may indicate the likelihood of a favorable or unfavorable outcome with LVRS (***Table 16***) [73].

Lung Transplantation

Lung transplantation is a therapeutic option in appropriately selected patients with very advanced COPD. Criteria for referral for lung transplantation include COPD with a BODE index exceeding 5. Recommended criteria for listing include a BODE index of 7–10 and at least one of the following [199]:

- History of exacerbation associated with acute hypercapnia (partial pressure of carbon dioxide [$PaCO_2$] >6.7 kPa or 50 mm Hg)
- Pulmonary hypertension, cor pulmonale, or both despite oxygen therapy
- FEV1 <20% predicted with either DLCO <20% predicted or homogenous distribution of emphysema

Patients must remain symptomatic despite optimal medical treatment in order to be considered for transplant. In addition, prognosis should be assessed. Only patients with predicted disease-related survival equal to or less than the predicted survival after transplantation should be selected [194]. Transplantation improves lung function, exercise capacity, quality of life, and survival in patients with end-stage disease [133].

FACTORS ASSOCIATED WITH FAVORABLE OR UNFAVORABLE OUTCOME IN LUNG VOLUME REDUCTION SURGERY		
Parameter	**Favorable**	**Unfavorable**
Clinical	Age <75 years Clinical picture consistent with emphysema Not actively smoking (for at least three to six months) Severe dyspnea despite maximal medical treatment including pulmonary rehabilitation Requiring <20 mg prednisone a day	Age >75 to 80 years Comorbid illness which would increase surgical mortality Clinically significant coronary artery disease Pulmonary hypertension (PA systolic >45 mm Hg, PA mean >35 mm Hg) Severe obesity or cachexia Surgical constraints Previous thoracic procedure Pleurodesis Chest wall deformity
Physiologic	FEV1 after bronchodilator <45% predicted Hyperinflation (i.e., RV >150%, TLC >100% predicted) PaO_2 >6 kPa (45 mm Hg) $PaCO_2$ <8 kPa (60 mm Hg) Postrehabilitation six-minute walk >140 meters Low post-rehabilitation maximal achieved cycle ergometry watts	FEV1 <20% predicted and DLCO <20% predicted Decreased inspiratory conductance High post-rehabilitation cycle ergometry maximal achieved wattage
Imaging	High-resolution computed tomography confirming severe emphysema, ideally with upper lobe predominance	Homogeneous emphysema and FEV1 <20% predicted Non-upper lobe predominant emphysema
DLCO = carbon dioxide diffusing capacity of the lung, FEV1 = forced expiratory volume in one second, PA = alveolar pressure, PaO_2 = arterial oxygen tension, $PaCO_2$ = arterial carbon dioxide tension, RV = residual volume, TLC = total lung capacity.		
Source: Reprinted with permission from Martinez FJ. Surgical therapy for chronic obstructive pulmonary disease: conventional bullectomy and lung volume reduction surgery in the absence of giant bullae. Semin Respir Crit Care Med. 1999;20:351-364. Table 16		

The number of lung transplantations performed is curtailed by a shortage of donor organs. To address this, specialized centers are adopting the single-lung technique. Common complications of this procedure include:

- Acute rejection
- Bronchiolitis obliterans
- Cytomegalovirus infection
- Fungal and bacterial infection
- Operative mortality
- Lymphoproliferative disease and lymphomas

Lung Regeneration

Despite making strides in understanding the mechanism and pathophysiology of COPD, treatment strategies have not changed significantly in the last few decades. However, the possibility of lung regeneration is offering a hope of cure. Lung regeneration has the potential to replace or repair nonfunctional tissue via restoration of functional alveoli and alveolar ducts. Advances made in the field of stem cells (embryonic and adult-derived) and the ability to differentiate them into chosen cell types offer a glimpse into the future of lung regeneration. Two main approaches are being evaluated for possible reversal of structural disease:

- Extrinsic cell therapy: Exogenous stem cells, paracrine effects of stem cells, and ex vivo tissue engineering
- Intrinsic cell therapy: Small molecules used to induce lung regeneration through actions on intrinsic populations of cells

Extrinsic Cell Therapy

Human exogenous stem cells can differentiate into type II pneumocytes and can possibly regenerate lung parenchyma, including alveoli. Sophisticated technologies and methods are being used to produce pure populations of exogenous stem cells, which is necessary to prevent the development of teratomas. However, there are two major hurdles for the development of this therapy. The first is an ethical issue, as stem cells are extracted from human embryos, which has been controversial in the United States. The second hurdle is risk of rejection, because the differentiated type II cells would not be autologous. The use of autologous adult stem cells can solve both these problems. Direct administration of differentiated type II cells is better than intravenous administration of mesenchymal stem cells [182].

Endogenous stem cell therapy avoids complications related to extrinsic cell therapy, particularly rejection. Tissue-specific stem cell populations have the capability to regenerate lung parenchyma. Research is being done to induce lung tissue regeneration without utilizing specific stem cell populations [182].

Retinoic Acid

Retinoic acid, particularly all-trans-retinoic acid (ATRA), plays an important role in fetal lung development and increases alveolar septation. ATRA also restores the normal lung structure in rats with emphysema. However, ATRA has not definitely shown beneficial effects in patients with emphysema [183].

MANAGEMENT OF EXACERBATIONS

A COPD exacerbation is an acute, persistent deterioration of a patient's symptoms from their usual baseline (beyond normal day-to-day variations) that requires a change in medication [121]. The characteristic clinical presentation is that of acute or subacute onset of breathlessness, cough, increased sputum volume, and a change in sputum color (purulence). Exacerbations may be classified according to clinical presentation based on the number of symptoms and/or healthcare resources utilized. Exacerbations have a major impact on patient health, and recovery often takes several weeks.

About 50% of COPD exacerbations can be attributed to intercurrent bronchial infection [122]. Ambient low-level colonization of the tracheobronchial tree by common respiratory bacterial pathogens (e.g., *S. pneumoniae*, *H. influenzae*) is common in patients with COPD. Studies have shown that exacerbations are associated with a new strain of one of these pathogens and an increase in the bacterial population of the lower airways as evidenced by quantitative cultures. Targeted antimicrobial therapy is known to speed clinical resolution [25].

Approximately 10% of patients admitted for a hypercarbic COPD exacerbation have a fatal outcome. Patients requiring mechanical support have a mortality rate of 40% after one year, and all-cause mortality following hospitalization for a COPD exacerbation jumps to 49% after three years [199].

COPD exacerbations lead to a more rapid decline in lung function, reduce quality of life, and impose a heavy socioeconomic cost burden because of subsequent hospitalizations. In one cost analysis, the annualized mean COPD-related cost of care ($12,765) for a patient with severe COPD exacerbations was nearly 10 times higher than that for a patient with COPD and no exacerbations ($1,425) [123]. Therefore, exacerbations should ideally be prevented or detected early and promptly treated in order to reduce adverse effects and minimize

FACTORS TO CONSIDER WHEN DECIDING WHERE TO TREAT THE PATIENT WITH COPD EXACERBATION		
Factor	**Treat at Home**	**Treat in Hospital**
Able to cope at home	Yes	No
Breathlessness	Mild	Severe
General condition	Good	Poor/deteriorating
Level of activity	Good	Poor/confined to bed
Cyanosis	No	Yes
Worsening peripheral edema	No	Yes
Level of consciousness	Normal	Impaired
Already receiving long-term oxygen therapy	No	Yes
Social circumstances	Good	Living alone/not coping
Acute confusion	No	Yes
Rate of onset	Insidious or gradual	Rapid
Significant comorbidity (particularly cardiac disease and insulin-dependent diabetes)	No	Yes
SaO_2 <90%	No	Yes
Changes on chest radiograph	No	Present
Arterial pH level	≥7.35	<7.35
Arterial PaO_2	≥7 kPa	<7 kPa
PaO_2 = partial pressure of oxygen, SaO_2 = oxygen saturation.		
Source: Reprinted from National Institute for Health and Care Excellence. Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (Partial Update). With permission from National Institute for Health and Care Excellence. *Table 17*		

hospitalization risk. Strategies to prevent exacerbations include regular exercise, smoking cessation, compliance with an optimal medication regimen, avoiding periods of high environmental pollution, and influenza virus and pneumococcal immunization [199]. If hospitalization can be avoided with home care, this is best (***Table 17***) [9].

ASSESSMENT OF SEVERITY

The principal symptom of an exacerbation is increased breathlessness, often accompanied by chest tightness, wheezing, increased cough and sputum production, and change of the color and/or tenacity of sputum. Certain nonspecific symptoms are common, including malaise, worsening fatigue, decreased exercise tolerance, palpitations, somnolence, and mild confusion. An increase in sputum volume and shift toward purulence is indicative of bacterial infectious bronchitis. Prominent fever or shaking chills should raise suspicion of pneumonia.

The severity of an exacerbation is assessed on the basis of a patient's medical history prior to exacerbation, physical examination, symptoms, pre-existing comorbidities, arterial blood gas measurements, and other laboratory tests [198]. Key indicators for assessing severity of an exacerbation include:

- Severity and frequency of attacks of breathlessness and cough
- Volume and color of the sputum
- Limitation of activities of daily living

Acute changes in arterial blood gas measurements during and prior to an exacerbation are also important indicators. Altered mental status during an exacerbation in stage 4 COPD requires urgent assessment in the hospital.

Spirometry

Patients experiencing an exacerbation of COPD may have difficulty performing even a simple pulmonary function test such as spirometry. Spirometric measurements are not reliable during an acute exacerbation and thus are not recommended.

Pulse Oximetry and Arterial Blood Gas Measurement

Pulse oximetry is helpful in determining a patient's need for supplemental oxygen therapy during exacerbations. Accurate arterial blood gas measurement is also crucial to assess the severity of an exacerbation, especially in patients requiring hospitalization for their COPD. Respiratory failure is characterized by a PaO_2 <8.0 kPa (60 mm Hg) and/or SaO_2 <90% with or without $PaCO_2$ >6.7 kPa (50 mm Hg) when breathing room air. Mechanical ventilation is indicated when there is moderate-to-severe respiratory acidosis (pH ≤7.35) plus hypercapnia ($PaCO_2$ >6–8 kPa or 45 – 60 mm Hg) in a patient with COPD and severe dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces [199].

Pulmonary embolism (without infarction) has a similar clinical presentation to an exacerbation of COPD, and it may be difficult to distinguish between the two, particularly in patients with advanced COPD who may already have developed clinical, radiographic, and electrocardiographic (ECG) signs of right heart strain. A history of transient syncope, hypotension, or an inability to increase PaO_2 greater than 8.0 kPa (60 mm Hg) despite high-flow oxygen should raise suspicion for pulmonary embolism. The two conditions are not mutually exclusive; in fact, cor pulmonale is a risk factor for pulmonary embolism. Treatment for both, at least initially, may be the best option when pulmonary embolism is suspected and the diagnosis is unclear.

Chest X-Ray and ECG

Chest radiographs with posterior/anterior and lateral views, combined with ECG, are helpful in differentiating other diseases that can mimic COPD exacerbations. These include cardiac arrhythmias, right ventricular hypertrophy, and myocardial ischemia.

Other Laboratory Tests

A complete blood count may detect polycythemia (i.e., hematocrit >55%) or bleeding, but white blood cell counts do not provide any concrete information regarding exacerbations. Antibiotic treatment should be initiated promptly if there is fever or purulent sputum. Bacterial infections with *S. pneumoniae*, *H. influenzae*, or *Moraxella catarrhalis* are most frequently involved in COPD exacerbations. A sputum culture and an antibiogram are required when antibiotic treatment is ineffective against a COPD exacerbation.

Abnormal biochemical test results can be linked to COPD exacerbations and comorbid conditions. Common test abnormalities include metabolic acid-base disorder, electrolyte disturbance, and poor glucose control.

DIFFERENTIAL DIAGNOSIS

Approximately 10% to 30% of patients considered to have an acute exacerbation of COPD have atypical clinical features or are refractory to treatment. Such cases require a thorough re-evaluation for other medical disease or conditions that can worsen symptoms or imitate COPD exacerbation. As an example, one study reported that 49 of 197 patients (25%) admitted to the hospital with an initial diagnosis of COPD exacerbation were subsequently found to have sustained an acute pulmonary embolism [227]. Common differential diagnosis considerations include:

- Congestive heart failure
- Pneumothorax
- Pneumonia
- Cardiac arrhythmia
- Pleural effusion
- Pulmonary embolism

Elevated serum levels of brain-type natriuretic peptide together with other clinical indications can help detect patients with acute dyspnea secondary to congestive heart failure [124]. Noncompliance with prescribed medications can also result in increased symptoms that may be confused with a true COPD exacerbation.

OUTPATIENT MANAGEMENT

Patients with early mild-to-moderate COPD exacerbation can often be managed in the outpatient setting. The goals of therapy are to control infection, reduce inflammation and airway trapping, and restore overall respiratory compensation. The usual strategy is to combine antibiotic and enhanced bronchodilator therapy with a brief course of corticosteroids.

Patients and their relatives are increasingly interested in home care for end-stage COPD, although studies of the cost-effectiveness of this approach have produced mixed results [223]. Nurse-administered home care (hospital-at-home care) has been found to be an effective alternative to hospitalization in select patients with exacerbations without acidotic respiratory failure. However, the exact criteria for home management as opposed to hospital treatment remain unclear and vary according to healthcare setting.

Bronchodilator Therapy

Beta2-agonists are highly effective in the home management of COPD exacerbations. Increasing the dose and/or frequency of beta2-agonists is beneficial in such cases. There is insufficient data to compare efficacy of different classes of short-acting bronchodilators; bronchodilator therapy delivered by metered-dose inhaler with a spacer and by handheld nebulizer yield similar clinical responses.

Corticosteroids

For patients experiencing an exacerbation, systemic corticosteroids act by improving lung function, shortening recovery time, improving hypoxemia, and reducing the risk of early relapse, treatment failure, and duration of hospital stay. If the patient's baseline FEV1 is less than 50% predicted corticosteroids may be added to the bronchodilator(s) to improve the response to treatment. A regimen commonly used is prednisone 30 – 40 mg daily for 7 to 10 days. There is little reason to taper the dosage as exogenous steroids administered for less than 10 days rarely causes significant adrenal suppression.

Antibiotics

Antimicrobial therapy is indicated for patients who present with all the cardinal features of a COPD exacerbation, but if there is little change in sputum volume and no shift toward purulence, then, absent fever, antibiotics are unlikely to be of benefit. Sputum culture requires 48 to 72 hours for meaningful results and thus is of limited usefulness in outpatient management of COPD. The selection of a specific antimicrobial should be made in consideration of the patient's age, severity of airway obstruction, comorbidities, and anticipated respiratory bacterial pathogens [25]. Amoxicillin/clavulanate or trimethoprim/sulfamethoxazole is a good choice for many patients; a macrolide or tetracycline has the advantage of covering atypical pathogens such as mycoplasma and *Chlamydia* species. A respiratory fluoroquinolone is preferred in patients with comorbidities, recent hospital discharge, or recent use of other antimicrobials.

HOSPITAL MANAGEMENT

The patient with COPD exacerbation usually presents to the emergency department or physician's office. The first priority is to assess the degree of respiratory failure and need for supplemental oxygen and support of ventilation. The mortality risk from COPD exacerbation is closely linked to the development of respiratory acidosis, the presence of significant comorbidities, and the need for intermittent or continuous mechanical ventilation. Features that indicate a need for hospital assessment/admission include:

- Severe underlying COPD
- Marked increase in intensity of symptoms
- Onset of new physical signs such as cyanosis or peripheral edema

- Exacerbation refractory to initial medical treatment
- Frequent exacerbations
- Significant comorbidities
- Uncertain diagnosis
- Newly occurring cardiac arrhythmias
- Older age
- Inadequate home support

Immediate admission to an intensive care unit (ICU) is indicated for the patient who exhibits any of the following:

- Severe dyspnea or breathlessness that does not respond adequately to initial emergency treatment
- Persistent or worsening hypoxemia (PaO_2 <5.3 kPa or <40 mm Hg), severe or worsening hypercapnia ($PaCO_2$ >8.0 kPa or >60 mm Hg), and/or severe or worsening respiratory acidosis (pH <7.25) despite supplemental oxygen and noninvasive ventilation
- Altered mental status (e.g., coma, confusion, lethargy)
- Need for invasive mechanical ventilation
- Hemodynamic instability (i.e., need for vasopressors)

Most patients with a COPD exacerbation who present to a hospital emergency department will require some degree of supplemental oxygen therapy. Arterial blood gas determination should be performed (on room air) in patients whose oxygen saturation is less than 90%. If there is hypoxia without hypercapnea, low-flow oxygen is indicated, with the goal of achieving a PaO_2 value of 60 to 65 mm Hg (oxygen saturation: 91% to 94%) [10]. If clinical and laboratory features indicate that the exacerbation is life threatening, the patient should be admitted to the ICU immediately. Otherwise, patients with moderate-to-severe COPD may be managed initially in the emergency department to assess response to treatment and determine the need for hospitalization. In addition to treatment with bronchodilators, corticosteroid, antimicrobials, and supplemental oxygen, emergency department- and hospital-based care often includes the following adjunctive measures:

- Adequate and accurate fluid administration with monitoring of fluid balance
- Proper nutrition with supplementation as required
- Prophylaxis of deep vein thrombosis
- Respiratory therapy to facilitate clearance of bronchial secretions (pulmonary toilet)

Mechanical chest percussion and postural drainage may be helpful in patients producing more than 25 mL sputum per day or who present with lobar atelectasis.

Controlled Oxygen Therapy

Controlled oxygen therapy is a main component of the hospital treatment of acute COPD exacerbations. Careful titration of supplemental oxygen is essential to improve the patient's hypoxemia. Safer levels of oxygenation (PaO_2 >8.0 kPa/60 mm Hg or SaO_2 >90%) can be easily attained in uncomplicated COPD exacerbations; however, there is a danger of CO_2 retention that can develop insidiously. Arterial blood gases should be measured 30 to 60 minutes after the initiation of oxygen therapy to ensure adequate levels of oxygenation without acidosis or CO_2 retention. Compared to nasal prongs, Venturi masks provide more accurate delivery of controlled oxygen but are less well tolerated by patients.

Bronchodilator Therapy

A short-acting inhaled beta2-agonist administered by nebulizer every one to four hours is usually the bronchodilator of choice for initial treatment of COPD exacerbations. The addition of a muscarinic antagonist is recommended if prompt relief is not provided by the beta2-agonist. Methylxanthines may be considered as second-line intravenous therapy when there is insufficient response to short-acting bronchodilators [199].

Corticosteroid

Corticosteroid, administered orally or intravenously, is recommended for moderate-to-severe acute exacerbations [199]. A dose equivalent to 30 – 40 mg prednisone daily is commonly used for a 7- to 10-day period [104; 199]. Corticosteroid therapy for longer than two weeks is rarely necessary, and extended use increases the risk of adverse effects.

Antibiotics

As noted, acute exacerbations frequently occur in association with viral and/or bacterial upper respiratory infections. As a practical matter, most patients receive empirical antimicrobial therapy, and studies have observed a small beneficial effect of antibiotics on lung function in COPD exacerbations [199]. One clinical trial demonstrated a significant beneficial effect of antibiotics in patients who presented with increased breathlessness, sputum volume, and sputum purulence [199].

Based on the available evidence, antibiotics should be prescribed for patients with cough accompanied by increased sputum volume and purulence, increased dyspnea, and/or fever. Patients experiencing COPD exacerbation that necessitates mechanical ventilation (invasive or noninvasive) should also receive antibiotics.

The bacterial pathogens most commonly associated with COPD exacerbations are *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*. Atypical pathogens, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, have also been detected in patients with COPD exacerbations. As FEV1 declines and patients have more frequent exacerbations and/or comorbid diseases, infections with *H. influenzae* and *M. catarrhalis* become more frequent. *Pseudomonas aeruginosa* is a consideration in patients with severe airway limitation or history of bronchiectasis [199].

The mode of administration depends on the ability of the patient to eat and the pharmacokinetics of the antibiotic. The oral route is the preferred mode of administration, but hospitalized patients should be treated parenterally, switching to the oral route when clinical stabilization permits. The initial selection of therapy, pending results of sputum culture, should address the most likely pathogens, taking into account local antimicrobial resistance patterns.

Respiratory Stimulants

Respiratory stimulants are not prescribed for patients with COPD and acute respiratory failure. However, doxapram, a nonspecific but relatively safe respiratory stimulant, may be used only in cases when noninvasive intermittent ventilation (NIV) is not available or not recommended [125]. For these patients, doxapram can increase tidal volume and respiratory rate.

Ventilatory Support

COPD exacerbations cause bronchoconstriction, airway inflammation, increased mucus production, and loss of elastic recoil, all of which reduce passive functional residual capacity at the end of expiration, shrink dynamic hyperinflation, and increase breathing effort [128]. These deficits may be managed with ventilator support in certain patients. The principal goals of ventilatory support are to reduce breathing load and to encourage efficient gas exchange and alveolar ventilation, which in turn decreases mortality and morbidity and relieves symptoms.

Ventilatory support can be categorized as:

- NIV: Uses either negative or positive pressure devices
- Invasive mechanical ventilation: Provided by orotracheal tube or tracheostomy

Noninvasive Intermittent Ventilation

NIV is indicated for persistent hypercapnic ventilatory failure during exacerbations refractory to medical treatment. It should be provided only by specialized staff experienced and educated in this field.

Several clinical studies have successfully demonstrated the efficacy of NIV in acute respiratory failure, with success rates of 80% to 85% [126]. NIV decreases the rate of respiration, incidence of respiratory acidosis, severity of dyspnea or breathlessness, duration of hospitalization, and mortality and intubation rates [127]. NIV is not preferred for patients whose primary diagnosis is cardiac failure or pneumonia; however, it may be indicated in patients with these complications if escalation to intubation and ventilation is perceived to be inappropriate.

The selection criteria for NIV are based on clinical observations and gas exchange measurements. Patients with moderate-to-severe dyspnea with signs of increased breathing load (i.e., use of accessory muscles and paradoxical abdominal motion) and tachypnea (>25 breaths per minute) as well as moderate-to-severe acidosis (pH ≤7.35) and/or hypercapnia ($PaCO_2$ >6.0 kPa OR 45 mm Hg) are considered candidates for NIV [199]. Relative contraindications include [199]:

- Respiratory arrest
- Life-threatening hypoxemia
- Unstable cardiovascular status (e.g., cardiac arrhythmias, myocardial infarction, hypotension)
- Altered mental status or inability to cooperate (e.g., low Glasgow coma score)
- High aspiration risk, vomiting
- Viscous or copious secretions
- Recent history of facial or gastroesophageal surgery
- Craniofacial trauma
- Bowel obstruction
- Fixed nasopharyngeal abnormalities
- Severe burns
- Morbid obesity

Certain factors are useful predictors of failure of NIV. These include:

- Hypercapnic respiratory failure
- No overall improvement or worsening pH within one to two hours of effective NIV therapy
- Minimal improvement in oxygenation after one to two hours of effective NIV therapy
- Multi-organ failure
- Lack of response or cooperation
- Hypoxemia
- Respiratory failure
- Older age

Invasive Mechanical Ventilation

With the advent of better and more sophisticated technology, a number of indications for invasive mechanical ventilation are now being effectively treated with NIV. However, some patients will require more intensive ventilatory support. The indications for initiating invasive mechanical ventilation during exacerbations of COPD include:

- Unable to tolerate NIV or NIV failure (or exclusion criteria)
- Severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Tachypnea (>35 breaths per minute)
- Life-threatening hypoxemia
- Severe acidosis (pH <7.25) and/or hypercapnia ($PaCO_2$ >8.0 kPa or 60 mm Hg)
- Respiratory arrest
- Somnolence or altered mental status
- Cardiovascular complications (e.g., hypotension, shock)
- Other complications (e.g., sepsis, metabolic impairments, pneumonia, massive pleural effusion, pulmonary embolism)

The choice of whether or not to initiate invasive ventilation may also be influenced by non-medical factors. Cultural and psychologic aspects should be considered, as should any financial limitations. The major risks associated with mechanical ventilation are increased susceptibility to ventilator-acquired pneumonia (particularly when multidrug-resistant organisms are present), pulmonary barotrauma, and failure to wean to spontaneous ventilation [199]. However, ventilator-associated fatalities among patients with COPD and respiratory failure are comparatively fewer than among patients ventilated for non-COPD causes.

Weaning off mechanical ventilation can be difficult and potentially dangerous in patients with COPD. The key determinant of mechanical ventilatory dependency is the balance between the respiratory load and the ability of the respiratory muscles to deal with this load. The best method to wean patients from ventilator still remains unclear.

Hospital Discharge and Follow-Up

There are no clear guidelines for the optimal duration of hospitalization for patients with COPD exacerbation. Patients may be considered for discharge if they meet the following criteria:

- Inhaled beta2-agonist therapy required less often than every four hours
- Able to eat and sleep without frequent awakening by dyspnea
- Able to walk across room (if previously ambulatory)
- Clinically stable for 12 to 24 hours
- Arterial blood gases stable for 12 to 24 hours
- Patient (or home caregiver) fully understands correct use of medications
- Follow-up and home care arrangements made (e.g., visiting nurse, oxygen delivery, meal provisions)
- Able to manage successfully at home

Patients hospitalized with COPD exacerbations may be discharged earlier if visits by a home nurse are ensured. In patients who experience hypoxemia during a COPD exacerbation, arterial blood gas measurements and/or pulse oximetry should be conducted before discharge and in the following three months. Long-term supplemental oxygen therapy may be necessary in hypoxemic patients. Strategies to prevent future exacerbations should be evaluated before hospital discharge, with greater emphasis on smoking cessation, vaccination, medical compliance, inhaler technique, and recognition of exacerbation symptoms.

Patients should be scheduled for follow-up four to six weeks after discharge. Follow-up should include an assessment of the patient's ability to manage in his or her usual environment, FEV, inhaler technique, and understanding of the recommended treatment plan. Patients with stage 4 COPD should be assessed for the need for long-term oxygen therapy and/or home nebulizer.

The use of long-acting inhaled bronchodilators, inhaled corticosteroids, and combination inhalers should be specifically considered. Long-acting inhaled bronchodilators reduce the number of exacerbations and hospitalizations and delay the time of first/next hospitalization. Early outpatient pulmonary rehabilitation immediately following discharge is a safe and effective way to improve exercise capacity and health status. Social problems should be identified and discussed in detail if the patient experiences persisting disability.

MONITORING AND ASSESSMENT

COPD is a progressive disease, and lung function will deteriorate over time even with the best available medical care. Airflow limitation, together with symptoms and objective measures, should be monitored periodically to guide modification of treatment and identification of any complications that may arise during the course of the disease. Comorbidities are frequently present in COPD and often complicate COPD management and vice versa.

The number of visits required for monitoring increases with disease progression. Ongoing or periodic monitoring and assessment in COPD guarantees that the goals of treatment are being achieved and should include evaluation and assessment of:

- Risk factors (particularly tobacco smoking)
- COPD progression and complications
- Response and adherence to drug therapy and other medical treatments
- History of exacerbation(s)
- Comorbidities

PROGRESSION OF COPD AND COMPLICATIONS

After a diagnosis of COPD has been established, follow-up visits should include a physical examination and discussion of symptoms, particularly development of any new symptoms or worsening of previous symptoms. Periodic spirometry measurements are necessary to monitor the patient's decline in lung function, although it should not be done more than once a year unless there is a significant increase in symptoms or a complication. Other pulmonary function tests, such as flow-volume loops, inspiratory capacity, DLCO measurements, and measurement of lung volumes are usually not required in a routine assessment. However, these tests may provide information about the overall impact of the disease and may be beneficial in electing patients for surgery and in resolving diagnostic doubts. A number of exercise tests, such as treadmill and cycle ergometry and six-minute and shuttle walking tests, can be conducted to assess exercise capacity, but these are mainly conducted concurrently with pulmonary rehabilitation programs.

Only patients with respiratory failure require assessment of pulmonary artery pressure; otherwise, its measurement is not recommended. The development of respiratory failure is indicated by a PaO_2 less than 8.0 kPa (60 mm Hg) with or without $PaCO_2$ greater than 6.7 kPa (50 mm Hg) in arterial blood gas measurements while breathing air at sea level. Patients may be screened with pulse oximetry and arterial blood gases if SaO_2 is less than 92%.

Measurement of inspiratory muscle force is helpful in evaluating patients when dyspnea or hypercapnia cannot be explained by LFTs or in suspected cases of peripheral muscle weakness. Individuals with COPD may have increased inspiratory muscle force when other assessments of lung mechanics are equivocal.

Cor Pulmonale

Pitting ankle edema and elevated jugular venous pressure are the most common findings in patients with COPD and cor pulmonale. Because fluctuations in intrathoracic pressure are common, it is usually difficult to evaluate jugular venous pressure in patients with COPD. Several other studies, such as MRI, echocardiography, electrocardiography, and radionucleotide scintigraphy, are crucial for diagnosing cor pulmonale in these patients. Sleep studies may be necessary if cor pulmonale or hypoxemia develops with relatively mild airflow limitation or when sleep apnea is suspected.

Hematocrit

Anemia affects approximately 25% of patients with COPD [61]. Smokers usually develop polycythemia in the presence of arterial hypoxemia, which is indicated by increase in hematocrit of more than 55%. However, a low hematocrit signifies a poor prognosis in patients receiving long-term oxygen therapy [62].

THERAPY COMPLIANCE AND EFFECTIVENESS

Each follow-up visit should include a thorough discussion of the current treatment plan in order to adjust the treatment appropriately with disease progression. Careful monitoring of drug dosage, compliance, appropriate inhaler technique, and safety and efficacy of the treatment is essential in patients with COPD. Adherence to prescribed pharmacotherapy can be improved with thorough patient education, optimized pharmacotherapy choices (e.g., longer acting agents), and regular monitoring of treatment effectiveness.

EXACERBATION HISTORY

Each COPD exacerbation should be recorded during periodic assessments, including the severity, frequency, and possible causes. Documentation of symptoms indicative of exacerbation (e.g., increased sputum volume, purulent sputum, acutely worsening dyspnea) is of utmost importance. The severity of a COPD exacerbation can be gauged by the greater need for bronchodilator therapy, steroids, and antibiotics. All emergency or unscheduled visits to healthcare providers and telephone calls for assistance should also be noted. A note should be made in case intubation or any other emergency care was provided to the patient during hospitalization. Proper documentation of all the hospital summaries should also be done.

COMORBIDITIES

Comorbidities are common in COPD, and include bronchial carcinoma, ischemic heart disease, and osteoporosis. Some comorbidities will develop independently, but the majority develop in the presence of COPD. Other conditions, such as diabetes and arthritis, become more prevalent as the patient ages. Comorbidities are difficult to treat in presence of COPD, because it can increase the degree of disability and polypharmacy may result in untoward drug-drug interactions. It is imperative that comorbidities be identified and treated according to evidence-based guidelines.

COMORBIDITIES

For years, the role and significance of comorbidities in COPD was not properly understood. However, studies have increasingly demonstrated the relationship of comorbidities and COPD severity and outcomes. It is yet to be ascertained if nonpulmonary interventions targeting systemic inflammatory burden, osteoporosis, cardiovascular disease, anemia, or malnutrition can change the natural course of COPD. In addition, more research is necessary to better understand the influence of COPD and different COPD management strategies on these comorbidities.

Comorbidities commonly seen in patients with COPD include pulmonary hypertension, cardiac disease, lung cancer, diabetes, osteoporosis, metabolic syndrome, and psychologic disorders (***Table 18***) [74]. Tobacco smoking is a predominant risk factor for COPD and many of its comorbidities, which makes the relationship complicated. Studies have confirmed a strong independent relationship between COPD and its comorbidities, especially with cardiovascular disease [135; 136; 137]. It has also been observed that systemic inflammation plays a key role in many chronic medical diseases, which may indicate a shared etiology [136]. A number of such comorbidities are now regarded as part of the nonpulmonary sequelae of COPD and are crucial in comprehending the real burden of COPD and developing more effective management strategies.

CARDIOVASCULAR DISEASE

Cardiovascular disease is a common cause of death and hospitalization in patients with COPD and is observed even in mild cases of COPD. Both diseases have the common risk factors of cigarette smoking, advanced age, low socioeconomic status, and sedentary lifestyle.

Patients with COPD carry an increased burden of cardiovascular disease, cardiac arrhythmia, and cardiac failure when compared to the general population. In a cross-sectional analysis, COPD was associated with increased risks of cardiovascular disease and diabetes as well as an increased rate of myocardial ischemia and stroke. Curkendall et al. observed that the prevalence of all cardiovascular diseases was greater in patients with COPD compared with control subjects and that the risk of hospitalization and mortality due to cardiovascular causes was increased in patients with COPD [131].

Patients with COPD and cardiac disease have been found to have worse lung function, poorer quality of life, and a need for more medications and more health resources with greater expenditure compared to patients without heart disease [140].

COPD AND THE PREVALENCE OF COMORBIDITIES					
Comorbidity	Prevalence by Source				
	van Manen et al. (n=1,145)	Mapel et al. (n=200)	Soriano et al. (n=2,699)	Sidney et al. (n=45,966)	Walsh and Thomashow (n=3,000)
Arthritis	36%	22%	28%	—	70%
Cardiac	13%	65%	22%	18%	50%
Hypertension	23%	45%	—	18%	52%
Diabetes	5%	12%	—	2%	16%
Hyperlipidemia	—	—	—	9%	51%
Psychiatric disorders	9%	17%	10%	—	38%
Gastrointestinal	15%	32%	26%	—	62%
Cancer	6%	18%	4%	—	4%
Osteoporosis	—	—	—	—	32%

Source: Reprinted with permission from Chatila WM, Thomashow BM, Minai OA, Criner GJ, Make BJ. Comorbidities in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2008;5(4):549-555. *Table 18*

Approximately 20% to 32% of patients with COPD have coexisting cardiac failure [138]. Cardiac failure is often difficult to diagnose in patients with COPD due to the similar symptomatology and decreased efficacy of echocardiography. Assessment of the natriuretic peptides is generally helpful in detecting cardiac failure in patients with acute dyspnea; however, they have a vague diagnostic role in stable disease and cannot exclude comorbid COPD.

Possible contributing factors include systemic inflammation, hypoxia, acidosis, autonomic dysfunction, and hemodynamic impairments. Impaired lung function is a major risk factor for cardiac arrhythmia and cardiovascular disease, and patients with COPD have increased arterial stiffness [162].

Medications commonly used in the treatment of COPD can also increase cardiac morbidity and mortality. In addition, some patients with COPD on beta-blockers will experience deterioration of lung function, but avoidance of beta-blockers may lead to increased cardiovascular events, particularly in high-risk individuals [199]. In contrast, bronchodilators may cause tachyarrhythmia. Analysis from the TOwards a Revolution in COPD Health (TORCH) study did not indicate increased cardiovascular risk from use of the bronchodilator salmeterol at the standard dose [139]. However, further investigation must be done before reaching any conclusion.

Data from a multicenter, prospective, cross-sectional study of cardiovascular disease observed a direct relationship between the extent of emphysema and impairment of left ventricle filling, stroke volume reduction, and lowering of cardiac output in healthy individuals [156]. In COPD, cardiac failure has an adverse effect on morbidity and prognosis. A cohort study observed that comorbid heart failure was a strong predictor of all-cause mortality over long-term follow-up [141]. It was also a major risk factor for death from respiratory failure and for respiratory admissions.

Management

Beta-Blockers

Beta-blockers are effective in helping to control hypertension and coronary artery disease, but practice guidelines generally indicate that these agents are contraindicated in patients with COPD [199]. This was based primarily on case reports of acute bronchospasm precipitated by high doses of noncardioselective beta-blockers, but evidence increasingly supports the use of cardioselective beta-blockers for the management of cardiovascular comorbidities in patients with COPD [161]. A Cochrane review found that cardioselective beta-blockers were safe and effective in patients with COPD with cardiac failure and should not be withheld, even in the presence of severe airflow limitation [142]. Short et al. observed a reduction in all-cause mortality in patients with COPD being treated with beta-blockers [143]. Beta-blocker use was also not associated with a decline in lung function. Among study participants, use of beta-blockers reduced the risk of cardiac death, respiratory death, oral corticosteroid use, and respiratory-related hospitalizations.

Statins

Statins have the beneficial effect of lowering lipid levels in patients with COPD with cardiovascular disease. Statins have been shown to reduce all-cause mortality, COPD-related mortality, and the need for respiratory-related urgent care [163]. Several single studies have observed a reduction in the number of exacerbations, exertional dyspnea, and inflammation and a minimal decline in lung function [163].

PULMONARY EMBOLISM

As with cardiac failure, overlapping symptoms may make pulmonary embolism difficult to diagnose in patients with COPD. Experts suggest that pulmonary embolism should be suspected in patients with COPD who present with acute exacerbation with no evident cause. Because it is a potentially fatal condition with high mortality, early detection and classification is vital to initiating the optimum treatment.

Clinical features that favor a diagnosis of pulmonary embolism (over COPD exacerbation) include sudden-onset dyspnea, tachypnea, pleuritic chest pain, an absence of fever or sputum change, and new-onset hemoptysis. Patients with large or recurrent pulmonary embolism may have cyanosis, circulatory instability, and in some cases, respiratory failure. Physical examination may be of limited utility in differentiating between COPD and pulmonary embolism in patients with acute respiratory distress. A pleural friction rub may be heard on auscultation over the affected part of the lung when embolism is accompanied by infarction. The past history may provide useful clues to the possibility of pulmonary embolism (e.g., previous deep vein thrombosis or pulmonary embolism, recent unilateral leg swelling or discomfort, and/or underlying malignancy). Laboratory and imaging findings, such as spiral CT and ventilation/perfusion scans, in combination with clinical symptoms and signs provide the best means for reaching the diagnosis. The decision to pursue diagnostic imaging studies, which can be expensive and time consuming, requires some clinical judgment of pretest probability. Clinical assessment tools have been devised to assist clinicians in this decision process. Two such tools are the Wells Scoring System and the Revised Geneva Scoring System [170; 171]. These systems assess a combination of clinical symptoms/signs and risk factors to determine likelihood of pulmonary embolism.

Management

Anticoagulation is the mainstay of pulmonary embolism treatment in all cases. This involves the administration of anticoagulants such as unfractionated heparin, low-molecular-weight heparin, or fondaparinux. Warfarin, acenocoumarol, or phenprocoumon therapy is started within several days of this initial treatment.

Systemic thrombolysis is highly effective in treating pulmonary embolism, especially massive and submassive pulmonary embolisms. Commonly used fibrinolytic drugs to address thrombolysis include streptokinase, urokinase, and recombinant tissue

plasminogen activators such as alteplase, reteplase, and tenecteplase. Surgical or catheter embolectomy is indicated when fibrinolytic drugs fail to induce improvement, thrombolysis is contraindicated, or persistent pulmonary vascular obstruction is present.

PNEUMONIA

Pneumonia is the most common comorbid condition in patients with COPD. Pneumonia can present as a part or a trigger of COPD exacerbations; however, there are important clinical differences between pneumonia and acute COPD exacerbations without pneumonia. COPD exacerbation with pneumonia has a more rapid onset of symptoms, more severe illness, longer length of hospital stay, and higher rate of ICU admission and mortality compared to an exacerbation without pneumonia [144].

It is crucial to differentiate COPD exacerbations from pneumonia in order to initiate proper management. Prompt initiation of antibiotic therapy provides significant benefits in patients with pneumonia. Corticosteroids are the mainstay for acute exacerbations of COPD; however, their role in the management of patients with COPD with pneumonia is not clearly defined [146; 147]. Treatment with salmeterol and fluticasone to manage COPD exacerbations may increase the risk of pneumonia [145].

LUNG CANCER

Lung cancer and COPD are thought to be interlinked by the pathobiology of COPD rather than the shared risk factor of exposure to smoking. Although COPD and lung cancer are closely associated to smoking, patients with airway obstruction are more susceptible to developing lung cancer regardless of degree of smoking [148]. The incidence of lung cancer in the presence of moderate-to-severe airway obstruction does not differ significantly among ex-smokers and current smokers.

MUSCULOSKELETAL DYSFUNCTION

Musculoskeletal dysfunction limits exercise tolerance and increases disability in patients with COPD. Research indicates that patients with COPD have a decreased capacity to sustain repetitive muscular contractions, with rapid onset of muscle fatigue [149]. Patients with COPD have muscle fiber atrophy and decreased activity of aerobic enzymes. Some studies have observed lower survival rates in underweight patients with COPD, while other studies have indicated that loss of fat-free mass may be a more accurate measure of functional debilitation than other indicators, such as BMI [150]. The increased incidence of musculoskeletal dysfunction is attributed to multiple factors, including:

- Corticosteroid use
- Longer periods of reduced activity
- Malnutrition
- Oxidative stress
- Systemic inflammation

Prolonged bed rest results in loss of muscle strength at a rate of 1% to 1.5% per day, and some patients with COPD may become cachectic or malnourished [172]. Ongoing systemic inflammation and oxidative stress can ultimately lead to muscle wasting and reduced exercise capacity. In one study, CRP levels were elevated in patients with COPD and correlated inversely with six-minute walk distance [151]. Another study revealed that elevated CRP levels were associated with inferior quality of life and limited exercise capacity in patients with severe COPD [152].

Management of musculoskeletal dysfunction involves preventing or minimizing deconditioning and avoiding systemic corticosteroid treatment. Other possible interventions include:

- Pulmonary rehabilitation
- Nutritional supplementation (e.g., dietary supplements, vitamins)
- Hormone replacement (experimental with no proven efficacy)

OSTEOPOROSIS

Several factors make patients with COPD prone to osteoporosis, including old age, smoking, restricted physical activity, low BMI, undernutrition, hypogonadism, and prolonged use of corticosteroids. Systemic corticosteroids are the most common cause of drug-related osteoporosis, and long-term use of systemic corticosteroids may lead to osteoporosis, hypertension, diabetes, muscle dysfunction, and adrenal insufficiency [134]. However, some studies have observed a significant association between COPD and osteoporosis/osteopenia regardless of corticosteroid use, and the risk for osteoporosis appears to increase with COPD disease severity [173; 174; 175]. Daily calcium and vitamin D supplementation (1,000–1,500 mg and 400–800 IU, respectively) and lifestyle modification with pulmonary rehabilitation may be beneficial in the management of osteoporosis in patients with COPD.

People with a smoking history or advanced COPD and those being treated with continuous high-dose inhaled corticosteroids or low-to-medium dose inhaled corticosteroids with frequent courses of oral corticosteroids are considered at high risk for osteoporosis and should be screened. Risedronate (5 mg/d) or alendronate (5–10 mg/d) is the recommended first-line therapy for the prevention and treatment of osteopenia and osteoporosis [104]. Screening for metabolic abnormalities and hormonal deficiencies should be considered.

GASTROESOPHAGEAL REFLUX

There is an increased prevalence of gastroesophageal reflux disease (GERD) and other esophageal disorders in patients with COPD, and GERD symptoms are more frequent in patients with COPD compared to control subjects [153]. Severity of COPD is also correlated to severity of GERD symptoms [153]. Still, there is not enough evidence to establish the exact nature and significance of the relationship between COPD and GERD. It is believed that *Helicobacter pylori* may play an important role in increasing airway inflammation [154].

The most common symptoms of GERD are heartburn, dysphagia, and regurgitation; less frequent symptoms include odynophagia (sore throat), increased salivation, chest pain, and nausea. Symptoms may be controlled by avoiding food two hours before bedtime and elevating the head of the bed. Sleeping on the left side also reduces nighttime reflux episodes [155]. In terms of pharmacotherapy, proton pump inhibitors are the most effective in treating in GERD. Other agents that can help are gastric H2-receptor blockers, antacids, sucralfate, and prokinetics. In severe cases, surgery may be necessary, and Nissen fundoplication is the standard surgical option.

DIABETES

Approximately 2% to 16% of patients with COPD have comorbid diabetes [74]. Studies have found that a reduction in lung function is a risk factor for developing diabetes [157; 158]. In addition, CRP and inflammatory cytokines (e.g., tumor necrosis factor-alpha [TNF-a], interleukin-6), are elevated in COPD and in diabetes, indicating a possible joint etiology. One study found that patients with poor glycemic control who were hospitalized for acute COPD exacerbation had a significantly higher mortality than those with normal blood glucose levels [159]. Even after hospital discharge, diabetes remains a risk factor for mortality in these patients [160]. It is not clear whether tighter glucose control would improve COPD outcomes.

ANEMIA

Hematopoietic suppression in COPD, similar to other chronic inflammatory diseases, is probably mediated by three different mechanisms:

- Shortened life span of red blood cells
- Bone marrow erythropoietin resistance
- Impairment of iron homeostasis

Smoking, malnutrition, and systemic inflammation likely play an important role in inducing these mechanisms. Systemic inflammation in COPD is characterized by elevated levels of interleukin-6,

interleukin-8, CRP, and TNF-a, with the latter two probably playing a crucial role in the mechanisms implicated in anemia.

Anemia is common in patients with COPD and is linked to greater mortality, comorbidity, and health expenditures [165]. Studies indicate that anemia is present in 8% to 33% of patients with COPD. A study by John et al. revealed significantly elevated CRP and erythropoietin levels in anemic compared with nonanemic patients with COPD [164]. Risk factors for anemia in patients with COPD include:

- More severe airway obstruction
- Lower BMI
- Older age
- Other comorbidities

Treating anemia with blood transfusion has a positive impact on clinical and physiologic parameters in patients with COPD [179]. However, the role of pharmacotherapy in the treatment of anemia in patients with COPD is not clear.

ASPIRATION

Aspiration of food and/or liquids can lead to recurrent exacerbations and complications in patients with COPD. Some patients experience impaired breathing-swallowing coordination and are at risk of aspiration, which in turn increases the risk of COPD exacerbation.

Diagnosis of aspiration can easily be made with an adequate history from the patient and his or her caregiver(s). Treatment generally involves training in safe and proper swallowing techniques. Patients should be advised to:

- Sit upright, especially when eating
- Take a small quantity of food at a time
- Avoid talking when eating
- Chew adequately
- Drink thickened fluids
- Drink with dry foods
- Use a straw

SUMMARY

COPD has become a global health problem and is increasing worldwide, especially in underdeveloped and developing countries [166]. This chronic debilitating disease is now one of the leading causes of mortality and disability, with a prevalence of approximately 10% in individuals older than 40 years of age in most countries [167]. COPD also leads to significant economic burden on people and society.

Despite making rapid strides in understanding the pathophysiology of COPD, the natural history of this condition and its treatment strategies have not changed significantly in recent decades. There are no drug therapies capable of preventing disease progression or reducing mortality. However, researchers now have a better understanding of COPD, which is resulting in identification of novel targets for new drugs and treatments [168; 169].

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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