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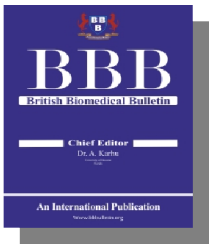

Original

An Insight to Chronic Obstructive Pulmonary Disorder COPD and its Pharmacotherapy

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A R T I C L E I N F O

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A B S T R A C T

COPD is a common, costly, and preventable disease that has implications for global health. It is the fourth leading cause of death in the United States, exceeded only by heart attacks, cancers, and stroke. This can result from several types of anatomical lesions, including loss of lung elastic recoil and fibrosis and narrowing of small airways. Inflammation, edema, and secretions also contribute variably to airflow limitation. Occupational exposure to dusts and chemicals, asthma, age, tobacco smoke and genetic factors likely play a major role and which also account for much of the heterogeneity susceptibility to smoke and other factors. Many factors may play a role, but to date, only α-1 protease inhibitor deficiency has been unambiguously identified. Exposures other than cigarette smoke can also contribute to the development of COPD. Spirometry is recommended in COPD guidelines for the accurate diagnosis of this disease. Wheezing, productive cough, barrel chest and shortness of breath are some of the hallmark signs of COPD. Although COPD cannot be cured but it can be managed my reducing symptoms and improving overall health, WHO and NICE have guidelines regarding COPD which outline management via pharmacotherapy for approaching COPD. The advances in understanding the pathogenesis of COPD have identified the provided therapy for management of this disease, if these guidelines are accurately followed, reduction in further complications or mortality from this ailment can be achieved.

Introduction

Chronic obstructive pulmonary disease, COPD is defined as a long-lasting obstruction of the airways that occurs with chronic bronchitis, emphysema, or both.[1] this obstruction of airflow is progressive in that it happens over time and it is not fully reversible. Whereas asthma is most frequently diagnosed during childhood and is associated with atopy and eosinophilic inflammation, COPD is usually diagnosed during the middle or later life and is associated with neutrophilic inflammation.[1] It has been contemplated that current body of evidence-based medicine for managing asthma and COPD, taking into consideration new approaches to the disease management and taking advantage of what is known about the gene by environment interactions that affect the phenotypic expression of this multifactor disease.[2] Clinical guidelines must be taken into the consideration for the direct assessment of patients with Asthma and COPD. These clinical guidelines help to achieve improved quality of care (and thereby improve outcomes), Decreased practice variations (especially if unnecessary and inappropriate), controlled healthcare costs, faster evidence-based decision making, accelerated application and translation of advances in medical science to everyday clinical practice (especially in large medical practices).

Epidemiological studies of COPD have shown that the disease over time may develop physiologic features that are quite similar to asthma. The rapid rate of decline in pulmonary function, a characteristic of subjects with COPD, may be seen in asthmatic subjects as well. Therefore, the progression in severity of asthma symptoms, and the overlap of symptoms seen in some patients with asthma and COPD have led to a hypothesis that asthma may be a risk factor for the subsequent development of COPD.[3]

Epidemiology of COPD

An estimated 24 million people in the US have airflow limitation, half of them diagnosed with COPD.[4] COPD is the 4th leading cause of death, resulting in 122,000 deaths in 2003-compared with 52,193 deaths in 1980. From 1980 to 2000, the COPD mortality rate increased 64% (from 40.7 to 66.9/100,000).[4] Prevalence, incidence, and mortality rates increase with age. Prevalence is higher in men, but total mortality is similar in both sexes.[5] Incidence and mortality are generally higher in white collar, blue-collar workers, and people with fewer years of formal education, probably because these groups have a higher prevalence of smoking. COPD seems to aggregate in families having of α1-antitrypsin (α1-antiprotease inhibitor) deficiency.[6] COPD is increasing worldwide because of the increase in smoking in developing countries, with rise in infectious diseases and the widespread use of biomass fuels. It caused an estimated 2.74 million deaths worldwide in 2000 and is projected to become one of the top 5 causes of disease burden globally by the year 2020.[6]

Etiology OF COPD

Cigarette smoking is the primary risk factor in most countries, although only about 15% of smokers develop clinically apparent COPD[7]; an exposure history of 40 or more pack-years is especially predictive. Smoke from burning biomass fuels for indoor cooking and heating is an important contributing factor in developing countries[7]. Smokers with pre-existing airway reactivity (defined by increased sensitivity to inhaled methacholine), even in the absence of clinical asthma, are at greater risk of developing COPD than are those without[7]. Low body weight, childhood respiratory diseases, passive cigarette smoke exposure,

air pollution, and occupational dust (eg, mineral dust, cotton dust) or chemical (eg, cadmium) exposure contribute to the risk of COPD but are of minor importance compared with cigarette smoking. Genetic factors also contribute[7]. The best-defined genetic disorder is α1-antitrypsin deficiency, which is an important cause of emphysema in nonsmokers and influences susceptibility to disease in smokers[8]. Polymorphisms in microsomal epoxide hydrolyses, vitamin D–binding protein, IL-1β, IL-1 receptor antagonist, phospholipids A_2 matrix metalloproteinase 9, and ADAM-33 genes are all associated with rapid decline in forced expiratory volume in 1 sec (FEV_1) in selected populations.[9] Inhalational exposures trigger an inflammatory response in airways and alveoli that leads to disease in genetically susceptible people. The process is thought to be mediated by an increase in protease activity and a decrease in antiprotease activity. Lung proteases, such as neutrophil elastase, matrix metallo-proteinases, and cathepsins, break down elastin and connective tissue in the normal process of tissue repair. Their activity is balanced by antiproteases, such as α1-antitrypsin, airway epithelium–derived secretory leukoproteinase inhibitor, elafin, and matrix metalloproteinase tissue inhibitor. In people with COPD, activated neutrophils and other inflammatory cells release proteases as part of the inflammatory process; protease activity exceeds antiprotease activity, and tissue destruction and mucus hypersecretion result. Neutrophil and macrophage activation also leads to accumulation of free radicals, superoxide anions, and hydrogen peroxide, which inhibit antiproteases and cause broncho-constriction, mucosal edema, and mucous hypersecretion. Neutrophil induced oxidative damage, release of profibrotic neuropeptides (eg, bombesin), and reduced levels of vascular endothelial growth factor may contribute to apoptotic destruction of lung parenchyma.[10] Infection, in conjunction with cigarette smoking, may amplify progression of lung destruction. The inflammation in COPD increases with increasing disease severity, and, in severe (advanced) disease, inflammation may not resolve completely with smoking cessation. Neither does this inflammation appear responsive to corticosteroids. Bacteria**,** especially Haemophilus influenzae, colonize the normally sterile lower airways of about 30% of patients with COPD. In more severely affected patients (eg, those with previous hospitalizations), Pseudomonas aeruginosa colonization is common.[11] Smoking and airflow obstruction may lead to impaired mucus clearance in lower airways, which predisposes to infection. Repeated bouts of infection increase the inflammatory burden that hastens disease progression.[7]There is no evidence, however, that long-term use of antibiotics slows the progression of COPD in susceptible smokers.[11]

Pathophysiology of COPD

Pathological changes in COPD occur in the large (central) airways, the small (peripheral) bronchioles, and the lung parenchyma. The pathogenic mechanisms are not clear but most likely involve diverse mechanisms. The increased number of activated polymorphonuclear leukocytes and macrophages release elastases in a manner that cannot be counteracted effectively by antiproteases, resulting in lung destruction. The primary offender has been human leukocyte elastase, with a possible synergistic role suggested for proteinase 3 and macrophage-derived matrix proteinases, cysteine proteinases, and a plasminogen activator. Additionally, increased oxidative stress caused by free radicals in cigarette smoke, the oxidants released by phagocytes, and polymorphonuclear leukocytes all may

lead to apoptosis or necrosis of exposed cells. Accelerated aging and autoimmune mechanisms have also been proposed as having roles in the pathogenesis of COPD. Mucous gland enlargement is the histologic hallmark of chronic bronchitis. The structural changes described in the airways include atrophy, focal squamous metaplasia, ciliary abnormalities, and variable amounts of airway smooth muscle hyperplasia, inflammation, and bronchial wall thickening. Neutrophilia develops in the airway lumen, and neutrophilic infiltrates accumulate in the submucosa.[12] The respiratory bronchioles display a mononuclear inflammatory process, lumen occlusion by mucous plugging, goblet cell metaplasia, smooth muscle hyperplasia, and distortion due to fibrosis. These changes, combined with loss of supporting alveolar attachments, cause airflow limitation by allowing airway walls to deform and narrow the airway lumen. Emphysema has 3 morphologic patterns. The first type, centriacinar emphysema, is characterized by focal destruction limited to the respiratory bronchioles and the central portions of acinus. This form of emphysema is associated with cigarette smoking and is most severe in the upper lobes. The second type, panacinar emphysema, involves the entire alveolus distal to the terminal bronchiole. The panacinar type is most severe in the lower lung zones and generally develops in patients with homozygous alpha1-antitrypsin (AAT) deficiency.[12] The third type, distal acinar emphysema or paraseptal emphysema, is the least common form and involves distal airway structures, alveolar ducts, and sacs.[12] This form of emphysema is localized to fibrous septa or to the pleura and leads to formation of bullae. The apical bullae may cause pneumothorax. Paraseptal emphysema is not associated with airflow obstruction. Both emphysematous destruction and small airway inflammation often are found in combination in individual patients, leading to the spectrum that is known as COPD. When emphysema is moderate or severe, loss of elastic recoil, rather than bronchiolar disease, is the mechanism of airflow limitation.[12] By contrast, when emphysema is mild, bronchiolar abnormalities are most responsible for the deficit in lung function.[12] Although airflow obstruction in emphysema is often irreversible, bronchoconstriction due to inflammation accounts for a limited amount of reversibility.[12] Furthermore, airflow limitation is not the only pathophysiologic mechanism by which symptoms occur. Lung volumes, particularly dynamic hyperinflation, have also been observed to play a crucial role in the development of dyspnea perceived during exercise.[12] In fact, the improvement in exercise capacity brought about by several treatment modalities, including bronchodilators, oxygen therapy, lung volume reduction surgery (LVRS), and pulmonary rehabilitation are more likely due to delaying dynamic hyperinflation rather than improving the degree of airflow obstruction. Additionally, hyperinflation (as defined as the ratio of aspiratory capacity to total lung capacity (IC/TLC) has been observed to predict survival better than forced expiratory volume in 1 second (FEV_1).[12]

In contrast to the eosinophil, which is the most prominent inflammatory cell in persons with asthma, the cellular composition of the airway inflammation in COPD is predominantly mediated by the neutrophils. Cigarette smoking induces macrophages to release neutrophil chemotactic factors and elastases, thus unleashing tissue destruction.[13] Severity of airflow obstruction has correlated with greater induced sputum neutrophilia that is also more prevalent in patients with chronic cough and sputum production and is

associated with an accelerated decline in lung function. Macrophages also play an important role through macrophage-derived matrix metalloproteinases (MMPs).[13] Cigarette smoke causes neutrophil influx and is required for the secretion of MMPs, therefore suggesting that both neutrophils and macrophages are required for the development of emphysema. Studies have also shown that T lymphocytes, particularly $CD8^+$, in addition to the macrophages, play an important role in the pathogenesis of smoking-induced airflow limitation. To support this theory further, a stepwise increase in alveolar inflammation occurs in surgical specimens from patients without COPD versus patients with mild or severe emphysema. Indeed, mounting evidence supports that the deregulation of apoptosis and defective clearance of apoptotic cells by macrophages play a prominent role in airway inflammation, particularly in emphysema.[13] Azithromycin has been shown to improve this macrophage function, providing yet another possible modality of treatment in the future.[13]

Clinical Presentation of COPD

The diagnosis of COPD is made based on the patient's symptoms, including cough, sputum production, and dyspnea, and a history of exposure to risk factors such as tobacco smoke and occupational exposures. Patients may have these symptoms for several years before dyspnea develops and often will not seek medical attention until dyspnea is significant.[14] A diagnosis of COPD should be considered in any patient who presents with chronic cough, sputum production, or dyspnea and who has risk factors for the disease.[15] The presence of airflow limitation should be confirmed with spirometry. Spirometry represents a comprehensive assessment of lung volumes and capacities. The biomarker of COPD is an FEV_1:FVC ratio of less than 70%, which indicates airway obstruction, and a post bronchodilator FEV_1 of less than 80% of predicted confirms the presence of airflow limitation that is not fully reversible.[15] An improvement in FEV_1 of less than 12% following inhalation of a rapid-acting bronchodilator is considered to be evidence of irreversible airflow obstruction. Reversibility of airflow limitation is measured by a bronchodilator challenge.[15]

Although a low peak expiratory flow is consistent with COPD, the use of peak expiratory flow measurements is inadequate for the diagnosis of COPD owing to low specificity and the high degree of effort dependence. Spirometry combined with a physical examination improves the diagnostic accuracy of COPD.[7] Spirometry is also used to determine the severity of the disease, along with an assessment of symptoms and the presence of complications.[15,16] A primary benefit of spirometry is to identify individuals who might benefit from pharmacotherapy to reduce exacerbations. Currently, the GOLD consensus guidelines[16] suggest a four-stage classification system given in table 1.

The 2006 GOLD guidelines were modified to remove the stage 0 category for COPD classification. Patients at risk (stage 0) have normal spirometry but experience chronic symptoms of cough or sputum production and a history of exposure to risk factors.[16] This change was made because of inadequate evidence to identify patients who might progress to stage 1 disease. Patients in the remaining four stages of classification all exhibit the hallmark finding of airflow obstruction, that is, a reduction in the FEV_1: FVC ratio to less than 70%. FVC is the total amount of air exhaled after a maximal inhalation. The extent of reduction in FEV_1 further defines the patient with mild, moderate, severe, or very severe disease. Spirometry is the primary tool in classifying COPD according to severity. However, two

other factors that influence disease severity, survival, and health-related quality are life are body mass index (BMI) and dyspnea. A low BMI is a systemic consequence of chronic COPD and a BMI of less than 21 kg/m^2 is associated with increased mortality.[16] Dyspnea is often the most troublesome complaint for the patient with COPD. Dyspnea can impair exercise performance and functional capacity and is frequently associated with depression and anxiety. Together, these have a significant effect on health related quality of life. As a subjective symptom, dyspnea is often difficult for the clinician to assess.[16] Various tools are available to evaluate the severity of dyspnea. A version of the Medical Research Council scale, modified by the American Thoracic Society, is commonly employed and categorizes dyspnea grades from 0 to 4. The scale is also given in table 2.

Although a physical examination is appropriate in the diagnosis and assessment of COPD, most patients who present in the milder stages of COPD will have a normal physical examination. In later stages of the disease, when airflow limitation is severe, patients may have cyanosis of mucosal membranes, development of "barrel chest" because of hyperinflation of the lungs, an increased respiratory rate and shallow breathing, and changes in breathing mechanics such as pursing of the lips to help with expiration or use of accessory respiratory muscles.[14]

Traditionally patients with severe COPD are divided into two categories, the blue bloaters, who cannot get enough oxygen into their system (hypoxemia) and cannot get carbon dioxide out (hypercapnia). This places a strain on their heart and they develop peripheral edema. The 'blue' derives from the cyanosed appearance of these patients, while 'bloater' comes from the large body build.[14] and the pink puffers who suffer from extreme dyspnoea (breathlessness) and so increase their ventilation. This helps them to maintain their normal carbon dioxide and oxygen levels, however it is very exhausting. The 'pink' is derived from the reddish appearance of the patient due to the exertion of breathing. While the 'puffer', refers to the breathlessness and panting respiration.[14]

Prognosis

For the patient with COPD, the combination of impaired lung function and recurrent exacerbations promote a clinical scenario characterized by dyspnea, reduced exercise tolerance and physical activity, and de-conditioning. These factors lead to disease progression, poor quality of life, possible disability, and premature mortality.[17] COPD is ultimately a fatal disease if it progresses and advanced directives and end-of-life care options are appropriate to consider. The FEV_1 is the most important prognostic indicator in a patient with COPD. The average rate of decline of FEV_1 is the most useful objective measure to assess the course of COPD. The average rate of decline in FEV_1 for healthy, nonsmoking patients owing to age alone is 25 to 30 mL/year.[17] The rate of decline for smokers is steeper, especially for heavy smokers compared with light smokers. The decline in pulmonary function is a steady curvilinear path. The more severely diminished the FEV_1 at diagnosis; the steeper is the rate of decline. Greater numbers of years of smoking and number of cigarettes smoked also correlate with a steeper decline in pulmonary function.[17] Conversely, the rate of decline of blood gases has not been observed to be a useful parameter to assess progression of the disease[17]. Patients with COPD should have spirometry performed at least annually to assess disease progression. The survival rate of patients with COPD is highly correlated to the initial level of impairment in the FEV_1

and to age.[17] Other, less important factors include degree of reversibility with bronchodilators, resting pulse, perceived physical disability, diffusing capacity of lung for carbon monoxide (DLCO), cor pulmonale, and blood gas abnormalities. A rapid decline in pulmonary function tests indicates a poor prognosis. Median survival is approximately 10 years when the FEV_1 is 1.4 L, 4 years when the FEV_1 is 1.0 L, and about 2 years when the FEV_1 is 0.5 L.[18] although arterial blood gas ABG measurements are important, they do not carry the prognostic value of pulmonary function tests. Measurement of ABGs is more useful in patients with severe disease and is recommended for all patients with an FEV_1 of less than 40% of predicted or those with signs of respiratory failure or right-sided heart failure.[18] It is important to recognize that deaths resulting in patients with COPD are not only due to respiratory failure but also due to associated co-morbidities. Cardiovascular complications, as well as lung cancer, are the leading causes of death in patients with COPD.[18]

Clinical Presentation of COPD Exacerbation

Because of the subjective nature of defining an exacerbation of COPD, the criteria used among clinicians varies widely; however, most rely on a change in one or more of the following clinical findings: worsening symptoms of dyspnea, increase in sputum volume, or increase in sputum purulence.[20] Acute exacerbations have a significant impact of the economics of treating COPD as well, estimated at 35% to 45% of the total costs of the disease in some settings. With an exacerbation, patients using rapid-acting bronchodilators may report an increase in the frequency of use.[20] Stages of exacerbations are given in table 3.

An important complication of a severe exacerbation is acute respiratory failure ARF.[20] In the emergency department or hospital, an ABG usually is obtained to assess the severity of an exacerbation.[20] The diagnosis of acute respiratory failure in COPD is made on the basis of an acute change in the ABGs. Defining acute respiratory failure as a PaO_2 of less than 50 mm Hg or a $PaCO_2$ of greater than 50 mm Hg often may be incorrect and inadequate because these values may not represent a significant change from a patient's baseline values. A more precise definition is an acute drop in PaO_2 of 10 to 15 mm Hg or any acute increase in $PaCO_2$ that decreases the serum pH to 7.3 or less.[20] Additional acute clinical manifestations of respiratory failure include restlessness, confusion, tachycardia, diaphoresis, cyanosis, hypotension, irregular breathing, meiosis, and unconsciousness.[21]

Prognosis of Acute Exacerbations of COPD

COPD exacerbations are associated with significant morbidity and mortality. While mild exacerbations may be managed at home, mortality rates are higher for patients admitted to the hospital. In one study of patients hospitalized with COPD exacerbations, in hospital mortality was 6% to 8%.[22] Many patients experiencing an exacerbation do not return to their baseline clinical status for several weeks, significantly affecting their quality of life. Additionally, as many as half the patients originally hospitalized for an exacerbation are re-admitted within 6 months. It is now evident that acute exacerbations of COPD have a tremendous impact on disease progression and mortality.[22] For exacerbations requiring hospitalizations, mortality rates range from 22% to 43% after 1 year, and 36 to 49% in 2 years. [22]

Diagnostic Test for COPD

The diagnostic process for COPD includes a thorough medical history as well as one or more of the following diagnostic procedures. In history examination, patients with COPD usually are current or past smokers over the age of 40 with a history of shortness of breath upon physical exertion and chronic productive cough. The physical examination may show a barrel chest, decreased breath sounds, and wheezing. Signs of right-sided heart failure, such as edema, tender liver, and distended abdomen (caused by fluid accumulation in the abdomen; called ascites may be noted as well.[15] COPD is a diagnosis of history (in the case of chronic bronchitis), or a diagnosis of anatomy (in the case of emphysema). Clubbing of the fingers rarely occurs in COPD and warrants investigation for other causes.[15] Pulmonary function tests are the primary diagnostic tools for COPD, after the medical history and physical examination. These tests demonstrate characteristic abnormalities in lung function that, in the proper clinical context (i.e., medical history, physical examination, chest x-ray) confirm or support the diagnosis of COPD and give some idea of the degree of impairment and prognosis. Lung biopsy is rarely used to diagnose emphysema. There are four components to pulmonary function testing: spirometry, post bronchodilator spirometry, lung volumes, and diffusion capacity.[15] In the initial evaluation, all four components are often performed. Periodically, an individual component, most commonly spirometry, is performed to assess progression of disease and to determine the effectiveness of medication.[15] The most reliable way to determine reversible airway obstruction is with spirometry, a procedure that measures the amount of air entering and leaving the lungs. This simple test can be performed in most physicians' offices, with the patient sitting comfortably in front of the spirometry machine. The machine measures airflow that passes through the inhalation port attached to the machine. The inhalation device is usually a disposable card board tube or a reusable tube that can be sterilized after use. The patient inhales as deeply as possible and forms a seal around the tube with their mouth. Then the patient exhales, as forcefully and rapidly as they can, until they can exhale no more. To be an adequate test, the patient must exhale all the air they possibly can continue exhaling for at least another 6 seconds. Usually, three separate attempts are made and the best result is used for evaluation. Multiple measurements are obtained from this maneuver such as those most commonly used for interpretation are (1) forced expiratory volume after 1 second [FEV_1], (2) forced vital capacity [FVC], and (3) forced expiratory flow at 25%-75% of maximal lung volume [FEF25-75]. They are expressed as percentages of what is predicted for normal lung function, depending on the variables of height, age, race, and sex. COPD produces characteristic results in this test. [15] The amount of air exhaled (forced vital capacity, or FVC) is reduced, compared to a person with normal lung function. Furthermore, the amount of air exhaled during the initial 1 second (FEV1) is reduced to a greater degree than the entire FVC. Therefore, the ratio of air exhaled after 1 second is low compared to the total amount of air exhaled. In healthy lungs, 70%-75% of all the air exhaled after maximum inhalation (FVC) is exhaled within the first second (FEV_1), known as the FEV_1/FVC ratio.[15] In lungs with COPD, the FEV_1/FVC ratio falls below 70%-75%. The absolute value of the FEV_1 is also reduced. The FEV_1 can be reduced in another disease process, termed restrictive ventilatory defects. However, in restrictive ventilatory defects the FVC is reduced proportionally, preserving a normal FEV_1/FVC ratio. The

FEV_1 is used to quantify the severity of obstruction with a FEV_1 < 70% of what is predicted for age, height, weight and race considered mild; < 50% to 69%, moderate; < 35%-49%, severe; and < 35%, very severe. Sometimes the only abnormality is a reduction in the FEF25-75. Isolated reduction in the FEF25-75 is considered an early detector of very mild obstruction. It can also be a normal variant. Spirometry is often repeated after giving the patient a bronchodilator, such as an inhaled beta-agonist. If the FEV_1 (forced expiratory volume after 1 second) improves more than 12%, the obstruction may be reversible or partially reversible. This procedure provides some information on the potential responsiveness of the airways to medication.[15]

It is also useful for determining whether steroid treatment has been beneficial, a few weeks after initiating therapy. Peak expiratory flow rate (PEFR) also can be obtained. PEFR can be compared with readings the patient obtains at home with a peak flow meter. A peak flow meter is a portable device that consists of a small tube with a gauge that measures the maximum force with which one blows air through the tube.[15]

Lung volumes are measured in two ways, gas dilution or body plethysmography.[15] the gas dilution method is performed after the patient inhales a gas, such as nitrogen or helium. The amount of volume in which the gas is distributed is used to calculate the volume of air the lungs can hold. Body plethysmography requires the patient to sit in an airtight chamber (usually transparent to prevent claustrophobia) and inhale and exhale into a tube. The pressure changes in the plethysmograph are used to calculate the volumes of air in the lungs. The most important measurements obtained are residual volume and total lung capacity (TLC). These measurements vary with age, height, weight, and race and are usually expressed as an absolute number and a percentage of what is predicted for a person with normal lung function. A high TLC demonstrates hyperinflation of the lungs, which is consistent with emphysema. Increased residual volume signifies air trapping. This demonstrates an obstruction to exhalation.[15]

Diffusion capacity is a measurement of gases transferred from the alveoli to the capillary. The patient inhales a very small amount (very safe) of carbon monoxide. How much of it is taken into the blood is measured. A reduced diffusion capacity is consistent with emphysema but is seen in a many other lung diseases as well.[15]

Noninvasive method determines the oxygenation of the blood (O_2 sat; normal is greater than 90%) by measuring the amount of light transmitted through an area of skin.[15] The device must be able to read pulsatile flow, so it must pick up a pulse to be accurate. Oximetry is not as accurate as the measurement of arterial blood gases. It is commonly used during exercise and sleep. Exercise oximetry can determine if a patient's oxygen decreases during activity. If so, oxygen therapy with activity may be beneficial. Overnight oximetry is done to see if oxygen concentrations decrease during sleep. Radiology Chest x-ray is an imprecise method of diagnosis of COPD.[15] It is only consistently abnormal in severe cases and should be performed in the initial evaluation to exclude other lung diseases. Findings characteristic of COPD in chest x-ray are hyper inflated lungs with flattened diaphragm, hyper lucent lungs (chest film shows greater than normal film blackening from increased transmission of x-rays), and central pulmonary artery enlargement. Areas of destroyed lung tissue that create large dilated air sacs, termed as bullae's may be seen as well. CT scan may be used to more accurately diagnose emphysema. This is

usually not necessary, however, and abnormal lung anatomy is not always detected.[15]

Arterial blood gases are measured using blood drawn from an artery, usually in the wrist. Blood is usually drawn from a vein, but venous blood is inaccurate for these measurements.[15] Drawing blood from an artery, unfortunately, causes more discomfort. Arterial blood gases are measured to determine the amount of oxygen dissolved in the blood (pO_2), the percentage of hemoglobin saturated with oxygen (O_2 sat), the amount of carbon dioxide dissolved in the blood (pCO_2), and the amount of acid in the blood pH. The oxygen measure may be used to determine whether a patient needs oxygen therapy. The carbon dioxide measure gives some idea of lung function and is especially important to know when starting oxygen therapy. A person suspected of having a genetic deficiency of this enzyme will undergo this test. Alpha-1-antitrypsin deficiencies can also cause liver disease in children, and the level may be measured for that as well. If the level is low, a genetic probe may be used to determine the cause.[15]

Treatment of COPD

To be effective, the clinician should address four primary components of management: assess and monitor the condition; avoidance of or reduced exposure to risk factors; manage stable disease; and treat exacerbations.[23] These components are addressed through a variety of non-pharmacologic and pharmacologic approaches. Patients with COPD should receive education about their disease, treatment plans, and strategies to slow progression and prevent complications.[23] Advice and counseling about smoking cessation are essential, if applicable. Because the natural course of the disease leads to respiratory failure, the clinician should address end-of-life decisions and advanced directives prospectively with the patient and family.[23]

Smoking Cessation

A primary component of COPD management is avoidance of or reduced exposure to risk factors. Exposure to environmental tobacco smoke is a major risk factor, and smoking cessation is the most effective strategy to reduce the risk of developing COPD and to slow or stop disease progression.[24] The cost-effectiveness of smoking cessation interventions compares favorably with interventions made for other major chronic diseases. The importance of smoking cessation cannot be overe-mphasized. Smoking cessation leads to decreased symptomatology and slows the rate of decline of pulmonary function even after significant abnormalities in pulmonary function tests have been detected (FEV_1:FVC <60%).[24] As confirmed by a study, smoking cessation is the only intervention proven at this time to affect long-term decline in FEV_1 and slow the progression of COPD. In this 5-year prospective trial, smokers with early COPD were randomly assigned to one of three groups: smoking-cessation intervention plus inhaled ipratropium three times a day, smoking-cessation intervention alone, or no intervention.[24] All clinicians should take an active role in assisting patients with tobacco dependence in order to reduce the burden on the individual, the individual's family, and the healthcare system. It is estimated that more than 75% of smokers want to quit and that one-third have made a serious effort. Yet complete and permanent tobacco cessation is difficult.[24] Counseling that is provided by clinicians is associated with greater success rates than self-initiated efforts.[24]

Pulmonary Rehabilitation

Exercise training is beneficial in the treatment of COPD to improve exercise tolerance and to reduce symptoms of dyspnea and fatigue.[25] Pulmonary rehabilitation programs are an integral component in the management of COPD and should include exercise training along with smoking cessation, breathing exercises, optimal medical treatment, psychosocial support, and health education.[25] High-intensity training (70% maximal workload) is possible even in advanced COPD patients, and the level of intensity improves peripheral muscle and ventilatory function.[25] Studies have demonstrated that pulmonary rehabilitation with exercise three to seven times per week can produce long-term improvement in activities of daily living, quality of life, exercise tolerance, and dyspnea in patients with moderate to severe COPD.[25] Improvements in dyspnea can be achieved without concomitant improvements in spirometry. Programs using less-intensive exercise regimens (two times per week) are not beneficial.[25]

Immunizations

Vaccines can be considered as pharmacologic agents; however, their role is described here in reducing risk factors for COPD exacerbations.[26] because influenza is a common complication in COPD that can lead to exacerbations and respiratory failure, an annual vaccination with the inactivated intramuscular influenza vaccine is recommended. Immunization against influenza can reduce serious illness and death by 50% in COPD patients. Influenza vaccine should be administered in the fall of each year (October and November) during regular medical visits or at vaccination clinics.[26]

There are few contraindications to influenza vaccine except for a patient with a serious allergy to eggs. An oral antiinfluenza agent (oseltamivir) can be considered for patients with COPD during an outbreak for patients who have not been immunized; however, this therapy is less effective and causes more side effects. The polyvalent pneumococcal vaccine, administered one time, is widely recommended for people from 2 to 64 years of age who have chronic lung disease and for all people older than age 65 years. Thus COPD patients at any age are candidates for vaccination.[26] Although evidence for the benefit of the pneumococcal vaccine in COPD is not strong, the argument for continued use is that the current vaccine provides coverage for 85% of pneumococcal strains causing invasive disease and the increasing rate of resistance of pneumococcus to selected antibiotics.[26] The GOLD guidelines recommend pneumococcal vaccine for all COPD patients age 65 years and older and for patients younger than age 65 years only if the FEV_1 is less than 40% of predicted.[26]

Pharmacotherapy

The primary goal of pharmacotherapy is to control patient symptoms and reduce complications, including the frequency and severity of exacerbations and improving the overall the health status and exercise tolerance of the patient.[27] International guidelines recommend a stepwise approach to the use of pharmacotherapy based on disease severity, which is determined by the extent of airflow limitation and degree of symptoms. The impact of recurrent exacerbations on disease progression is increasingly recognized as an important factor and should be considered.[27] The primary goals of pharmacotherapy are to control symptoms (including dyspnea), reduce exacerbations, and improve exercise tolerance and health status. Pharmacotherapy focuses on the use of bronchodilators to control symptoms.[27] there are several classes of bronchodilators to

choose from, and no single class has been proven to provide superior benefit over other available agents. The initial and subsequent choice of medications should be based on the specific clinical situation and patient characteristics. Considerations should be given to individual patient response, tolerability, adherence, and economic factors. According to the guidelines, patients with intermittent symptoms should be treated with short-acting bronchodilators.[28] When symptoms become more persistent, long-acting bronchodilators should be initiated. For patients with an FEV_1 less than 50% and who experience frequent exacerbations, inhaled corticosteroids should be considered.[29] Short-acting broncho-dilators relieve symptoms and increase exercise tolerance. Long-acting broncho-dilators relieve symptoms, reduce exacerbation frequency, and improve quality of life and health status.[28] Patients have a variety of choices in using inhalational therapies, including metered dose inhalers (MDIs), dry powder inhalers (DPIs), or nebulizers.[30]

Bronchodilators

Bronchodilator classes available for the treatment of COPD include β_2-agonists, anticholinergics, and methylxanthines. There is no clear benefit to one agent or class over others, although inhaled therapy generally is preferred. Bronchodilators generally work by reducing the tone of airway smooth muscle (relaxation), thus minimizing airflow limitation.[28] In patients with COPD, the clinical benefits of bronchodilators include increased exercise capacity, decreased air trapping in the lungs, and relief of symptoms such as dyspnea. However, use of bronchodilators may not be associated with significant improvements in pulmonary function measurements such as FEV_1.[28] In general; side effects of bronchodilator medications are related to their pharmacologic effects and are dose-dependent. Because COPD patients are older and more likely to have comorbid conditions, the risk for side effects and drug interactions is higher compared with patients with asthma. SABA is the initial therapy for COPD. Among these agents, the choices are a short-acting β_2-agonist or an anticholinergic.[28] Either class of agents has a relatively rapid onset on action, relieves symptoms, and improves exercise tolerance and lung function. In general, both classes are equally effective.[28]

Short-acting sympathomimetics vary in selectivity, route of administration, and duration of action. In COPD management, sympathomimetic agents with β_2-selectivity, or β_2-agonists, should be used as bronchodilators. β_2-agonists cause broncho-dilation by stimulating the enzyme adenyl cyclase to increase the formation of cyclic adenosine monophosphate cAMP. Cyclic adenosine monophosphate is responsible for mediating relaxation of bronchial smooth muscle, leading to bronchodilation. In addition, it may improve mucociliary clearance. Although shorter-acting and less-selective β-agonists are still used widely (e.g., metaproterenol, isoetharine, isopro-terenol, and epinephrine), they should not be used owing to their shorter duration of action and increased cardiostimulatory effects.[28] Short-acting, selective β_2-agonists such as albuterol, levalbuterol, and pirbuterol, are preferred for therapy. The preferred route of administration is by inhalation. The use of oral and parenteral β-agonists in COPD is discouraged because they are no more effective than a properly used MDI or DPI, and the incidence of systemic adverse effects such as tachycardia and hand tremor is greater. Administration of β_2-agonists in the outpatient and emergency room settings via inhalers (MDIs or DPIs) is at least as effective as nebulization therapy and usually favored for

reasons of cost and convenience.[28] Albuterol is the most frequently used β_2-agonist. It is available as an oral and inhaled preparation. (S)-Albuterol is considered by some clinicians to be inert, whereas others believe that it may be implicated in worsening airway inflammation and antagonizing the response to (R)-albuterol.[28] Short-acting inhaled β_2-agonists cause only a small improvement in FEV_1 acutely but may improve respiratory symptoms and exercise tolerance despite the small improvement in spirometric measurements. Patients with COPD can use quick-onset β_2-agonists as needed for relief of symptoms or on a scheduled basis to prevent or reduce symptoms. The duration of action of short-acting β_2-agonists is 4 to 6 hours.[28]

Short-acting anticholinergics given by inhalation, such as ipratropium or atropine produce bronchodilation by competitively inhibiting cholinergic receptors in bronchial smooth muscle.[28] This activity blocks acetylcholine, with the net effect being a reduction in cyclic guanosine monophosphate, which normally acts to constrict bronchial smooth muscle. Muscarinic receptors on airway smooth muscle include M_1, M_2, and M_3 subtypes. Activation of M_1 and M_3 receptors by acetylcholine results in bronchoconstriction; however, activation of M_2 receptors inhibits further acetylcholine release. Ipratropium is the primary short-acting anticholinergic agent used for COPD in the United States. Atropine has a tertiary structure and is absorbed readily across the oral and respiratory mucosa, whereas ipratropium has a quaternary structure that is absorbed poorly.[28] The lack of systemic absorption of ipratropium greatly diminishes the anticholinergic side effects such as blurred vision, urinary retention, nausea, and tachycardia associated with atropine. Ipratropium bromide is available as a metered dose inhaler MDI and a solution for inhalation. Ipratropium has a slower onset of action and a more prolonged bronchodilator effect compared with standard β_2- agonists. Because of the slower onset of effect (15 to 20 minutes compared with 5 minutes for albuterol), it may be less suitable for as needed use; however, it is often prescribed in that manner.[28] The most frequent patient complaints are dry mouth, nausea, and an occasional metallic taste.[28]

Long-acting bronchodilators for patients with moderate to severe COPD who experience symptoms on a regular and consistent basis, or in whom short-acting therapies do not provide adequate relief, long-acting bronchodilator therapies are the recommended treatment. Long-acting, inhaled bronchodilator therapy can be administered as a β_2-agonist or anticholinergic.[28] Long-acting broncho-dilators provide similar benefits to short-acting agents. In addition, they reduce exacerbation frequency and improve quality of life. Long-acting, inhaled β_2-agonists offer the convenience and benefit of a long duration of action for patients with persistent symptoms. Both salmeterol and formoterol are dosed every 12 hours and provide sustained bronchodilation. Formoterol has an onset of action similar to albuterol (less than 5 minutes), whereas salmeterol has a slower onset (15 to 20 minutes); however, neither agent is recommended for acute relief of symptoms.[28] The clinical benefits of long-acting inhaled β_2-agonists compared to short-acting therapies include similar or superior improvements in lung function and symptoms, as well as reduced exacerbation rates.[28] The use of the long-acting agents should be considered for patients with frequent and persistent symptoms. Long-acting β-agonists are also useful to reduce nocturnal symptoms and improve quality of life. Formoterol and arformoterol are unique in that they are the first long-acting β_2-agonists available as nebulized solutions.[28]

Long-acting anticholinergics tiotropium bromide, a long acting quaternary anticholinergic agent, has been available in the United States since 2004. This agent blocks the effects of acetylcholine by binding to muscarinic receptors in airway smooth muscle and mucus glands, blocking the cholinergic effects of bronchoconstriction and mucus secretion. Tiotropium is more selective than ipratropium at blocking important muscarinic receptors. Tiotropium dissociates slowly from M_1 and M_3 receptors, allowing prolonged bronchodilation. The dissociation from M_2 receptors is much faster, allowing inhibition of acetylcholine release. Binding studies of tiotropium in the human lung show that it is approximately 10-fold more potent than ipratropium and protects against cholinergic bronchoconstriction for greater than 24 hours. When inhaled, tiotropium is minimally absorbed into the systemic circulation and results in bronchodilation within 30 minutes, with a peak effect in 3 hours. Bronchodilation persists for at least 24 hours, allowing for a once-daily dosing.[28]

Corticosteroids

Corticosteroid therapy has been studied and debated in COPD therapy for half a century; however, owing to the poor risk-to-benefit ratio, chronic systemic corticosteroid therapy should be avoided if possible.[29] Because of the potential role of inflammation in the pathogenesis of the disease, clinicians hoped that corticosteroids would be promising agents in COPD management. However, their use continues to be debated, especially in the management of stable COPD.[29] The antiinflammatory mechanisms whereby corticosteroids exert their beneficial effect in COPD include reduction in capillary permeability to decrease mucus, inhibition of release of proteolytic enzymes from leukocytes, and the inhibition of prostaglandins.[30] Unfortunately, the clinical benefits of systemic corticosteroid therapy in the chronic management of COPD are often not evident, and the risk of toxicity is extensive and far-reaching.[30] Currently, the appropriate situations to consider corticosteroids in COPD include short-term systemic use for acute exacerbations and inhalation therapy for chronic stable COPD. While a small number of COPD patients are considered responders to oral steroids, many of these patients actually may have an asthmatic, or reversible, component to their disease.[30] Long-term adverse effects associated with systemic corticosteroid therapy include osteoporosis, muscular atrophy, thinning of the skin, development of cataracts, and adrenal suppression and insufficiency.[29] The risks associated with long-term steroid therapy are much greater than the clinical benefits.[30] If a decision to treat with long-term systemic corticosteroids is made, the lowest possible effective dose should be given once per day in the morning to minimize the risk of adrenal suppression. If therapy with oral agents is required, an alternate-day schedule should be used.[29,30]

Antitrypsin Replacement Therapy ART

In patients with inherited α1 Antitrypsin AAT deficiency associated emphysema, treatment focuses on reduction of risk factors such as smoking, symptomatic treatment with bronchodilators, and augmentation therapy with replacement AAT.[31] Based on knowledge about the relationship between serum concentrations of AAT and the risk of developing emphysema, the rationale for augmentation therapy is to maintain serum concentrations above the protective threshold throughout the dosing interval. Indirect evidence of AAT activity in the interstitium of the lung has been demonstrated by measuring concentrations of the enzyme in epithelial lining fluid obtained during bronchoalveolar

lavage.[31] Augmentation therapy consists of weekly infusions of pooled human AAT to maintain AAT plasma levels greater than 10 micromolars. Much of the data supporting the use of AAT replacement is based on evidence of biochemical efficacy (e.g., administering the product and demonstrating protective serum concentrations of AAT).[31] Clinical evidence for slowing lung function decline or improving outcomes with augmentation therapy is sparse.[31]

Conflict of Interest

The authors declare no conflict of interests exists.

Author's Contribution

All authors contributed equally in all aspects of the study.

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Table 1. Classification of COPD

Classification of Chronic Obstructive Pulmonary Disease Severity
Stage I: mild FEV1/FVC <70% FEV1 ≥80% With or without symptoms
Stage II: moderate FEV1/FVC <70% 50% <FEV1 <80% With or without symptoms
Stage III: severe FEV1/FVC <70% 30% <FEV1 <50% With or without symptoms
Stage IV: very severe FEV1/FVC <70% FEV1 <30% or <50% with presence of chronic respiratory failure or right heart failure
Where FEV1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity.

Table 2. Modified Medical Research Council (MRC) Dyspnea Scale

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

Table 3. Staging Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Staging Acute Exacerbations of Chronic Obstructive Pulmonary Disease	
Mild (type 1)	One cardinal symptom plus at least one of the following: Upper respiratory tract infection (URTI) within 5 days, fever without other explanation, increased wheezing, increased cough, increase in respiratory or heart rate >20% above baseline
Moderate (type 2)	Two cardinal symptoms
Severe (type 3)	Three cardinal symptoms
Where, Cardinal symptoms include worsening of dyspnea, increase in sputum volume, and increase in sputum purulence.	

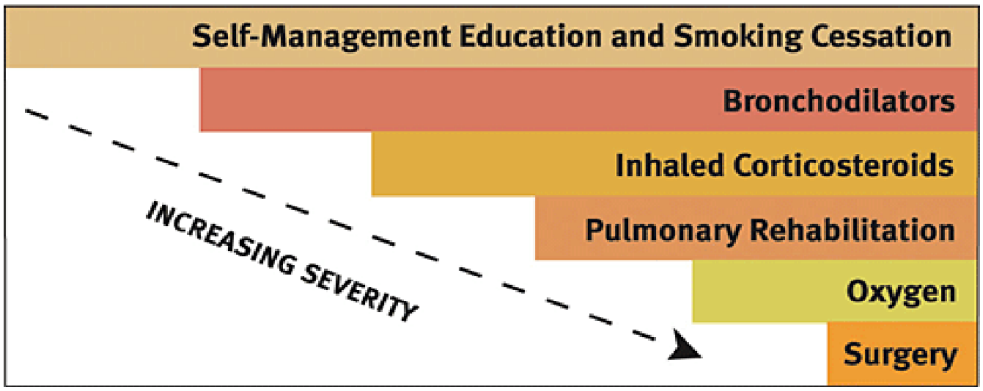

Figure 1. Treatment chart of COPD

Source: www.nhlbi.nih.gov/.../treatment-chart.gif