

Review Article

Chronic Obstructive Pulmonary Disease: An Overview of Epidemiology, Pathophysiology, Diagnosis, Staging and Management

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Abstract: Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease. It is among the fastest growing chronic diseases diagnosed in the world today. COPD is the third most common cause of death in the United States. It is characterized by the development of an inflammatory response of the lungs to noxious substances such as tobacco or air pollution. If the exposure becomes recurrent or persistent, the lungs develop chronic inflammatory response leading to lung parenchymal damage, air trapping and progressive airflow limitation. The Diagnosis of COPD is usually made in the context of symptoms and spirometry evidence of airway obstruction with post bronchodilator spirometry $FEV_1/FVC < 0.70$. Most patients with COPD first seek medical attention when they develop dyspnea. Once the diagnosis of COPD is confirmed, the treatment is geared mainly towards preventing exacerbations and eliminating risk factors and exposures. Several treatment combinations can be used in patients with stable COPD to prevent exacerbations and to improve their quality of life. Patients with COPD exacerbations have to be appropriately diagnosed and promptly treated to prevent complications. Patient's symptoms, the degree of airflow limitation, risk of exacerbations and the presence of comorbidities have to be assessed. Both pharmacological and non-pharmacological interventions have been used in the management of COPD. Appropriate pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. None of the existing medications for COPD have been shown conclusively to modify the long-term decline in lung function.

Keywords: COPD Epidemiology, Pathophysiology, Staging and Diagnosis

1. Introduction and Epidemiology

Chronic obstructive pulmonary disease (COPD) is defined as a common preventable and treatable disease, characterized by airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.¹

COPD is ranked as the third most common cause of death in the United States.² It is a very common and treatable condition that affects 5-22% of the adult population aged 40

and above. COPD is one of the leading causes of hospitalizations and has very high health care cost.³⁻⁵ Gerson et al.⁶ found an overall incidence of 5.9 cases per 1000 person per year of COPD. The lifetime risk of COPD was 26.6% in this study. This risk was higher in men, smokers, people older than forty, and in people living in rural areas. This means far more people will be diagnosed with COPD than with heart failure, acute myocardial infarction and some common cancers.⁶ COPD is reported as the sixth most common cost of death today, but it is predicted to be the third most common cause of death in 2020 due to increasing smoking rates and decreasing in other common causes of

death like ischemic heart disease and infections. The estimates of morbidity, mortality and general burden of COPD are underestimated due to the lack of adequate evidence. Most of the estimates on COPD have not been obtained by consistent methods and there is some evidence that these estimates may be underestimates.⁷⁻⁹ Of note, FEV1/FVC ratio drops with age in healthy people, this may result in over-diagnosis of early COPD in adults of age 50 years and above.⁹ This early stage of COPD does not greatly contribute to the social economic burden of COPD.⁹

2. Pathophysiology

When the lungs are exposed to noxious substances such as tobacco, they develop inflammatory response. If the exposure becomes a recurrent process, the lungs develop chronic inflammatory response, which causes lung parenchymal damage (emphysematous changes) and fibrosis leading to air trapping and progressive airflow limitation.¹

These inflammatory changes with tissue damage and fibrosis are mainly seen in the airways, lung parenchyma, and pulmonary vasculature,¹⁰ and usually get worse with increased exposures. The inflammatory changes noted in patients with COPD are amplified and persist even in the absence of exposures. Specific patterns of inflammation characterized by an increase in CD8+ and Tc1 lymphocytes have been noted in smokers that develop COPD.¹¹ These cells, together with neutrophils and macrophages, release inflammatory mediators and enzymes that interact with structural cells in the airways, lung parenchyma and pulmonary vasculature.¹²

Oxidative stress and an excess of proteinases in the lung further modify the inflammatory response in the lung. Autoantigens and persistent microorganisms have also been noted to play an important role in the inflammatory process.¹³ Patients with COPD have more oxidative stress in their lungs which further worsen COPD exacerbations. Secondly, there is an imbalance between proteases that break down connective tissue components and ant proteases that protect against connective tissue breakage in patients with COPD. Protease-mediated destruction of elastin, which is a major connective tissue component in lung parenchyma is a common finding in patients with emphysema.

Inflammation and narrowing of peripheral airways lead to decreased FEV1. Parenchymal destruction due to emphysema also contributes to airflow limitation. FEV1 and FEV1/FVC ratio directly correlate to the extent of inflammation, fibrosis, and luminal exudates in small airways.¹² This peripheral airway obstruction progressively traps air during expiration, resulting in hyperinflation. Hyperinflation reduces inspiratory capacity, particularly during exercise leading to increased dyspnea and limitation of exercise capacity.¹⁴

Hypoxic vasoconstriction of small pulmonary arteries causes intimal hyperplasia and smooth muscle hypertrophy leading to pulmonary hypertension. Progressive pulmonary hypertension promotes right ventricular hypertrophy and eventually, right-side heart failure.

3. Diagnosis

COPD is a chronic disease which is usually diagnosed clinically, but in the appropriate clinical context, spirometry is needed for definitive diagnosis. A clinical diagnosis of COPD should be considered in all patients who present with dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease.¹ The risk factors include: family history, environmental history and smoking history. The smoking history should include the age at which smoking was initiated, average amount smoked per day since initiation and current smoking status or stop date. Smoke from any forms of tobacco, smoke from home cooking and heating fuels, occupational dusts and chemicals are all important risk factors for the development of COPD.

The diagnosis of COPD is confirmed by a post bronchodilator spirometry FEV1/FVC < 0.70.^{16,15} The clinical signs and symptoms that lead to the clinical diagnosis of COPD include: chronic cough with variability in the production of sputum from day to day and progressively worsening dyspnea.^{16,17} These are also the main symptoms that have to be looked into in order to determine the need for antibiotics. Sputum production may start several years prior to airway limitations confirming the presence of COPD.¹⁷ Some patients have been found to have airway obstructions without the classic symptoms of cough or sputum production.

The first symptom which develops in patients who have been exposed to COPD is a cough. Usually the cough is intermittent, and then progresses to a daily and even to an all-day symptom. The chronic cough in COPD may be unproductive.¹⁸

Sputum production is harder to evaluate. Large amounts of sputum may warrant evaluation for bronchiectasis. Worsening sputum production and purulence may be a sign of bacterial infection leading to COPD exacerbation.¹⁹

The main symptom which causes patients to seek medical attention is dyspnea. Progressively worsening dyspnea is one of the main symptoms of COPD and is usually described as a sense of increased effort to breathe, heaviness, air hunger, or gasping.²⁰

Other non-specific symptoms commonly found in patients with COPD include wheezing and chest tightness. Fatigue, weight loss and anorexia are common in patients with severe and very severe COPD.²¹

A thorough medical history has to be obtained for each patient presenting with a possible diagnosis of COPD. The history should include exposure to noxious substances like tobacco, occupational and environmental factors. The past medical history should include any history of asthma, allergies, nasal polyps, sinusitis, and respiratory infections. A family history of COPD and other chronic medical disease patterns need to be clearly documented. The characteristics of patient's respiratory symptoms, including what times of the year patient usually have symptoms, how long they last and how long ago the patient first experience the symptoms. A history of exacerbations and how many times in a year the patient has been hospitalized is important. All comorbidities should be

evaluated and the impact of COPD on patient's social life, economic activities, feeling of depression or anxiety and any effects on sexual activities need to be appropriately addressed.

Spirometry is the most reproducible and objective measurement of airflow limitation available. Spirometry measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex, and race. The presence of a post bronchodilator FEV₁/FVC < 0.70 confirms the presence of airflow limitation.²²

4. Prognostic Factors

- Male gender
- HIV infection
- Elevated C-reactive protein
- Airways responsiveness
- Cigarette smoking
- Low body-mass index (BMI ≤21)
- Increased airway bacterial load
- Decreased exercise capacity
- Peak oxygen consumption (VO₂), measured by cardiopulmonary exercise testing
- Chest computed tomography showing presence of emphysema

These prognostic factors have been noted to accelerate decline of the lung function as evidenced by a decline in the FEV₁, functional status, exercise tolerance morbidity or mortality of a patient with COPD.^{2, 23-32}

The risk of death in people with COPD is usually calculated using the BODE index. The BODE index is calculated based on four factors: weight (BMI), airway obstruction (FEV₁), dyspnea (Medical Research Council dyspnea score), and exercise capacity (six-minute walk distance).^{2, 30}

5. Staging

The GOLD (Global Initiative for Chronic Obstructive Lung Disease) classification of COPD severity is based on the post

bronchodilator spirometry.³³

Table 1. Gold classification of COPD based on post bronchodilator spirometry.

| Severity of airflow limitation in COPD (based on post bronchodilator FEV ₁) with FEV ₁ /FVC < 0.7 | |
|--|--|
| GOLD 1: MILD | FEV ₁ ≥ 80 percent predicted |
| GOLD 2: MODERATE | 50 percent ≤ FEV ₁ < 80 percent predicted |
| GOLD 3: SEVERE | 30 percent ≤ FEV ₁ < 50 percent predicted |
| GOLD 4: VERY SEVERE | FEV ₁ < 30 percent predicted |

FEV₁: Forced expiratory volume in one second; FVC: Forced vital capacity

This classification does not take into consideration the experience of the patient with COPD.

The revised GOLD classifications use different tools to evaluate the severity of symptoms, risk of exacerbations, and the presence of comorbidities. These are all major factors that contribute to the disease course, prognosis and most importantly to the experience of the patient with COPD.^{3, 35}

GOLD guidelines have proposed several tools to evaluate the severity of symptoms. These tools include:

A: Modified Medical Research Council (mMRC) dyspnea scale which gives a grade from 0 to 4 depending on the description of breathlessness of the patient.

B: COPD Assessment Tool (CAT). This tool has questions on the level of dyspnea and the feeling caused by shortness of breath, the presence of cough and the characteristics of the cough and exercise tolerance.³⁴⁻⁴¹

C: St. George's Respiratory Questionnaire (SGRQ). This is the most widely used tool. This questionnaire has 76 items which focus on three: symptoms, activity, and impact on daily life. It scores each of the components and a total score is given.

In order to assess exacerbations and guide therapy, the GOLD system has combined the symptoms, history of exacerbations and FEV₁ to place patients in 4 groups.¹

Table 2. Gold classification of COPD in 4 groups based on symptoms, history and FEV₁.

| Groups | RISK OF EXACERBATION/SYMPTOMS | SEVERITY OF FLOW BASED ON FEV ₁ | NUMBER OF EXACERBATIONS PER YEAR | mMRC grade | CAT SCORE |
|--------|-------------------------------|--|----------------------------------|------------|------------|
| A | Low risk/less symptoms | GOLD 1 or 2 | 0-1 | 0-1 | <10 |
| B | Low risk/ more symptoms | GOLD 1 or 2 | 0-1 | <2 | 10 or more |
| C | High risk/ less symptoms | GOLD 3 or 4 | 2 or more | 0-1 | <10 |
| D | High risk/more symptoms | GOLD 3 or 4 | 2 or more | <2 | 10 or more |

6. Management

Once a diagnosis of COPD is made, there is no intervention, except for a lung transplant, that will prevent the progression of the disease or decrease mortality.¹ The different aspects that have to be evaluated and managed are shown in figure 1 below. Patients have to be assessed and staged. A baseline spirometry has to be obtained, so that the progression of the disease can be

monitored objectively. Risk factors have to be identified and reduced or eliminated. Even though the patients are staged to determine the severity of their COPD, the treatment has to be individualized. Stable COPD has several treatment options available based on the stages and so patients within the same stage may be on different treatment regimens.^{1, 51, 53, 69} COPD exacerbations impair the patient's quality of life and decrease their health status. The prevention of exacerbations is one of the main goals in the management of COPD. However,

patients will have exacerbations, and the early recognition and prompt treatment of COPD exacerbation, is very beneficial to the overall outcome of the patient.¹

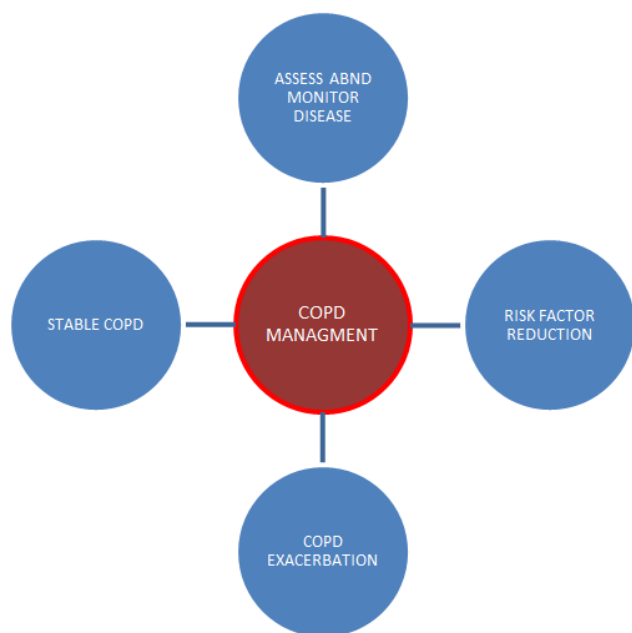


Figure 1. The Components of COPD management.

Table 3. Summary of the Components in the management of COPD.

| |
|--|
| <p>ASSESS AND MONITOR DISEASE:</p> <p>An early diagnosis, a thorough history with attention to exposures to risk factors is necessary.^{1,51,52}</p> <p>Spirometry evidence of airway limitations with or without symptoms (chronic cough, sputum, dyspnea) with FEV1/FVC < 70% and post bronchodilator-FEV1 < 80% predicted.</p> <p>An arterial blood gas is required if FEV1 < 40% predicted or there are clinical signs suggestive of right heart or respiratory failure.</p> <p>REDUCTION OF RISK FACTORS: PREVENT ONSET AND PROGRESSION OF COPD.</p> <p>Decrease exposure to air pollutants, tobacco smoke, occupational dusts and chemicals pollutants.¹</p> <p>Smoking cessation^{1,42} is the most effective and cost savings way to prevent the onset and progression of COPD. Smoking cessation can be approached in several ways ranging from counselling to pharmacologic interventions.^{1,51}</p> <p>MANAGE STABLE COPD: STEPWISE INCREASE IN THERAPY</p> <p>Patient education</p> <p>Smoking cessation</p> <p>Pharmacotherapy: Decrease symptoms and complication</p> <ul style="list-style-type: none"> • Bronchodilators-scheduled/PRN • Inhaled steroids-used in patients with symptomatic COPD with spirometry response to steroids or FEV1 < 50% predicted and repeat exacerbations that need antibiotics and oral steroids. • Chronic steroid therapy is not good in the long term. <p>Exercise Training improves exercise tolerance and decreases both dyspnea and fatigue</p> <p>Long term oxygen therapy, (>15L/d) in patients with chronic respiratory failure decreases mortality.⁵²</p> <p>ELIMINATE, TREAT OR REDUCE EXPOSURE TO THE EXACERBATING FACTORS: Identify the exacerbating factors like infection or air pollution and treat, eliminate or reduce accordingly. A third of COPD exacerbations have no identifiable cause.</p> |
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6.1. Goals of Care

The overall goal of COPD management is to improve the patient's functional status and thus, their health related quality of life in a cost effective manner.^{1, 51, 64} Treatment should be individualized and aimed at preventing or rapidly treating exacerbations, reducing the long term functional decline associated with COPD and reducing hospitalization and mortality.

Table 2 summarizes these goals and diagram 2 demonstrated the factors that should be considered in the overall treatment of patients with COPD. These goals should be achieved with treatments that will cause the minimum side effects for that patient. Comorbidities tend to complicate the treatment of COPD and are a major aspect also in the management of COPD.

Table 4. Management Goals of care.

| GOALS OF CARE IN COPD MANAGEMENT |
|---|
| <ul style="list-style-type: none"> • Prevent COPD from progressing and thus reducing long term lung function decline • Prevent and treat exacerbations • Prevent and treat complications • Relieve symptoms like disabling shortness of breath • Improve exercise tolerance • Improve health status-health related quality of life, reduce hospitalizations • Reduce Mortality |

To achieve these overall goals of care in the management of COPD, a multifaceted approach in treatment has to be taken. The core of this approach is patient education and health care follow up, with the aim of reducing hospital visits.¹

6.2. Management of Stable COPD

The management of patients with stable COPD is generally based on the tenets put forward by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).¹ GOLD recommends management of stable COPD based on disease severity. It divides COPD into 4 stages and treatment is based on the stage of the disease and is individualized for the patient. The goal of care is to decrease exacerbations, control symptoms and improve the patients' quality of life. GOLD approaches the care with pharmacologic and non-pharmacologic therapies.¹

The following aspects have to be carefully assessed when managing patients with stable COPD:

1. Symptoms (Modified Medical Research Council Dyspnea Scale/COPD Assessment Test/ The COPD Control Questionnaire)
2. The degree of airflow limitation-percent predicted FEV1 in patients with FEV1/FVC ratio < 0.7
3. Risk of exacerbations
4. Presence of Comorbidities.

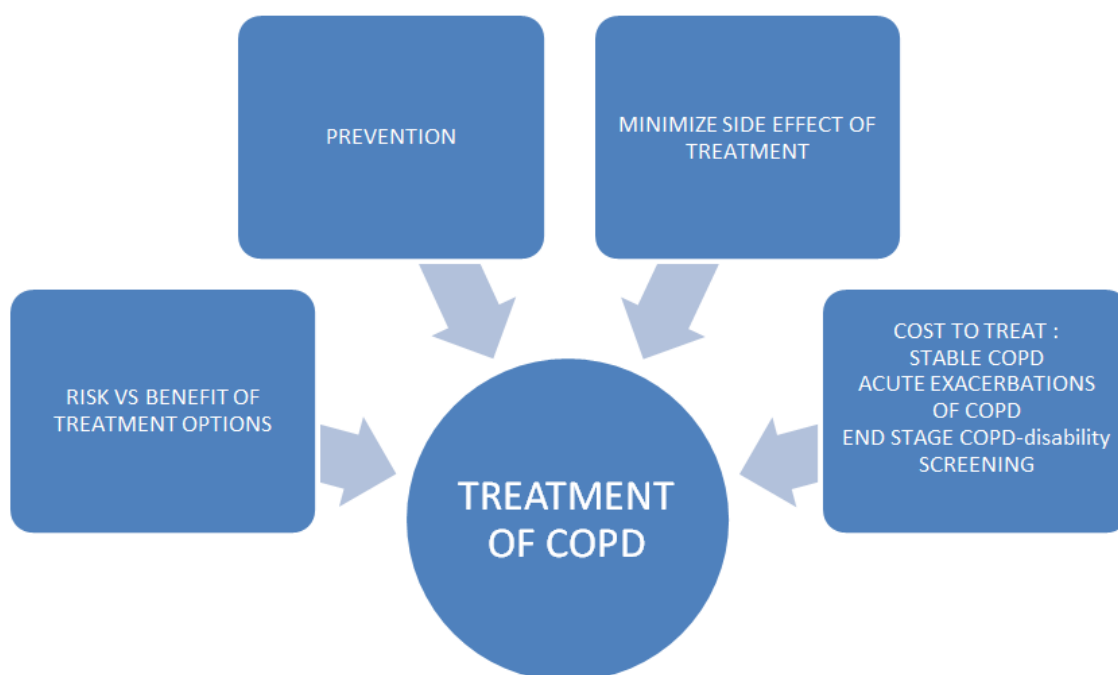


Figure 2. Treatment of COPD: Factors to consider when deciding on the treatment options.

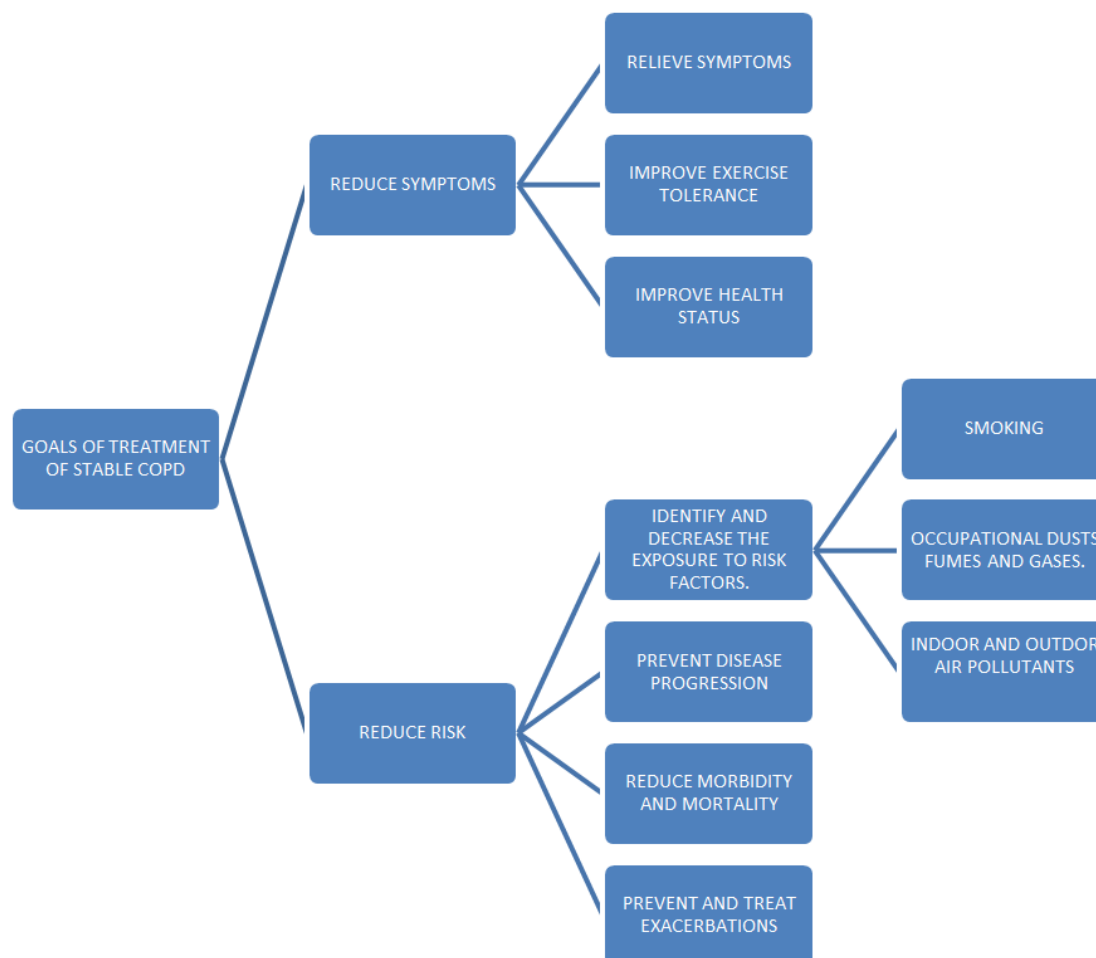


Figure 3. The Goals of Care for Patient with Stable COPD.

6.3. Assessment of Symptoms

6.3.1. Modified Medical Research Council (MMRC) Dyspnea Scale

The patients are required to assess their level of breathlessness and grade it into stages from 0 to 4

Table 5. MMRC Dyspnea scale.

| | |
|---------|--|
| STAGE 0 | I only get breathless with strenuous exercise |
| STAGE 1 | I get short of breath when hurrying on level ground or walking up a slight hill |
| STAGE 2 | On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace |
| STAGE 3 | I stop for breath after walking about 100 yards or after a few minutes on level ground. |
| STAGE 4 | I am too breathless to leave the house or I am breathless when dressing |

6.3.2. The COPD Assessment Test

Table 6. The COPD Assessment Test.

| |
|--|
| <ul style="list-style-type: none"> • I never cough, 0 1 2 3 4 5 I cough all the time. • I have no phlegm (mucus) in my chest at all, 0 1 2 3 4 5 My chest is completely full of phlegm • My chest does not feel tight at all, 0 1 2 3 4 5 My chest feels very tight. • When I walk up a hill or one flight of stairs, I am not breathless, 0 1 2 3 4 5 When I walk up a hill or one flight of stairs I am very breathless. • I am not limited doing any activities at home, 0 1 2 3 4 5 I am very limited doing activities at home. • I am confident leaving my home despite my lung condition, 0 1 2 3 4 5 I am not at all confident leaving my home because of my lung. • I sleep soundly, 0 1 2 3 4 5 I don't sleep soundly because of my lung condition. • I have lots of energy, 0 1 2 3 4 5 I have no energy at all. |
|--|

The MMRC dyspnea scale only measures dyspnea and so other more comprehensive scales such as the CAT scales and the COPD Control Questionnaire have been developed. These are simplified self-administered assessment tools that measure health status and not just shortness of breath. They are reliable, comprehensive, reproducible and applicable worldwide.

The COPD Assessment Test is a simple patient administered validated questionnaire, comprised of 8 items. It has good discriminant properties and covers a wide range of the effects that COPD has on the patient's health. It has proven to be able to demonstrate changes that may occur in the disease and changes that occur in response to treatments. The patient rates the symptoms from absence of the symptom, score 0 to the most severe presentation of that symptom, and score 5. The total score ranges from 0 to 40.

6.3.3. The COPD Control Questionnaire

The COPD Control Questionnaire is a 10 item self-administered questionnaire that may also be used to assess symptoms.

GOLD recommends that patients be placed in categories A-D, based on their risk of exacerbation which is determined by the severity of airflow limitation (GOLD 1-4) (see figure 4 below) and their symptoms (Dyspnea Scales-discussed above). This categorization of patients may be used as a guide for managing patients with stable COPD. Generally, patients should be taught how and when to use their therapies. These are broad categorizations and each patient should be managed on an individual basis. Each patient's treatment should be adjusted based on their response the treatment, their comorbidities and concomitant medications prescribed for their comorbid conditions.

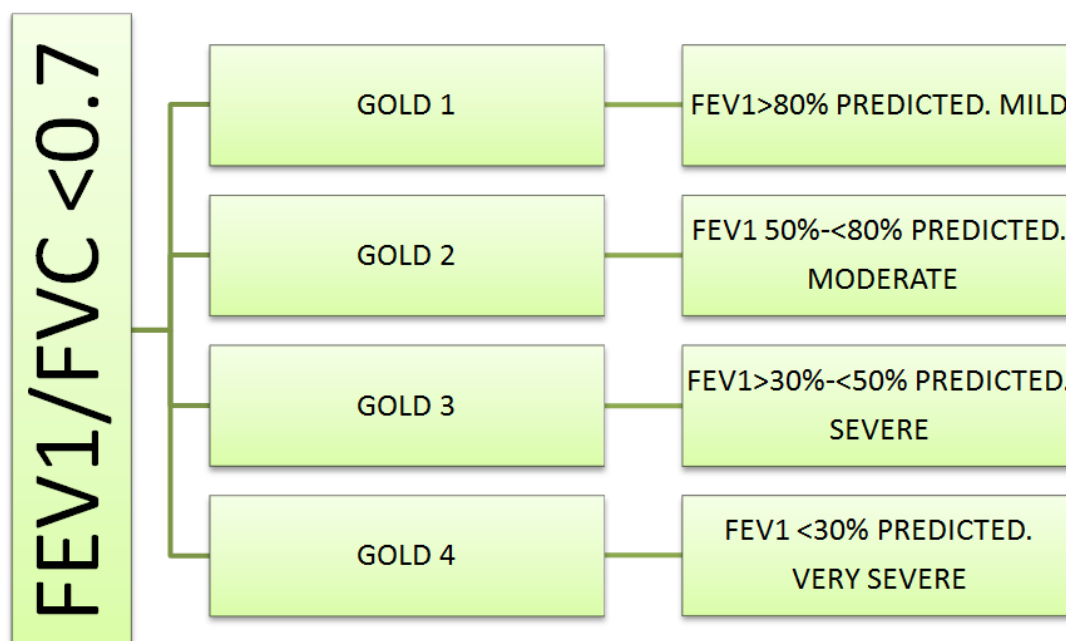


Figure 4. The severity of airflow limitation in COPD based on spirometry post bronchodilator response.¹

Category A:

These patients are at low risk of exacerbations with one or less exacerbation in the previous year. They have mild or infrequent symptoms and they fall into the GOLD 1 or 2 spirometric category.

These patients are best treated with: a short acting bronchodilator as needed, which could be a beta agonist alone, or an anticholinergic bronchodilator alone.

Second choice agents may be a combination of the short acting bronchodilators with a long acting anticholinergic or a long acting beta agonist. The alternative to these options is theophylline.^{1, 46, 50, 51}

Category B:

Patients in category B are more symptomatic and suffer from moderate to severe symptoms, but are at low risk of exacerbations. They also had one or less exacerbation in the previous year, and fall into the GOLD 1 or 2 spirometric categories.

These patients benefit from the use of short acting bronchodilators as needed and pulmonary rehabilitation. Long acting bronchodilators alone or in combination, are the treatment of choice in these patients and there is no evidence to support the use of one particular long acting agent over another. The choice is individualized to the patient's tolerance and symptom relief. Alternatively, theophylline may be used.^{1, 50}

Category C:

Exacerbation risk is increased in these patients, they have two or more exacerbations per year or they may have had one hospitalization for exacerbation. They fall into the GOLD 3 or 4 spirometric stages. Paradoxically, these patients have mild or infrequent symptoms. Again, short acting bronchodilators are used in an acute exacerbation.

It is recommended that they are prescribed regular treatment with a fixed combination of inhaled steroids and a long acting beta agonist or a long acting anticholinergic agent alone.

A second choice would be to use a combination of two long acting agents or inhaled steroids and a long acting anticholinergic agent. Alternatively, if none of the above is available to patients, then a short acting bronchodilator and theophylline may be used.^{1, 46, 50, 51}

Category D:

Patients are at high risk for exacerbations having more than two per year or at least one hospitalization for exacerbation. They are more symptomatic and they fall into the GOLD 3 or 4 spirometric classes.¹

These patients should be prescribed a short acting bronchodilator to use as needed.

First choice of therapy in these patients is a combination of inhaled glucocorticoid and a long-acting beta agonist and /or long acting anticholinergic.

Secondary options include the following: Inhaled steroids, a long-acting beta agonist and a long acting anticholinergic OR Inhaled steroids, a long acting beta agonist and a phosphodiesterase-4 inhibitor OR a long acting anticholinergic and a long acting beta agonist OR a long acting

anticholinergic and a phosphodiesterase 4 inhibitor.

Alternatively carbocysteine, a short acting beta agonist and/or a short acting anticholinergic or theophylline as well as surgical treatments may be considered.^{1, 46, 50, 51}

In all patients with COPD, still smoking, smoking cessation should be encouraged.⁴² Patients should be advised to avoid what they identify as potential triggers and to reduce the risk of exposure to indoor and outdoor air pollutants. Physical activity is recommended for all stable COPD patients, although there is little study based evidence to say how much or what type of activity is beneficial. Pulmonary rehabilitation appears to be beneficial in COPD patients, although more studies are needed in this area. It usually improves the sensation of breathlessness as well as exercise tolerance in patients with COPD. Vaccinations especially flu and pneumonia vaccines should be up to date, per local guidelines.

Patients with COPD who are not responding to therapy and who continue to have symptoms or repeated exacerbations despite optimizing therapy, should be evaluated for other illnesses that could be contributing to their shortness of breath for example congestive heart failure, pulmonary hypertension, smoking, deconditioning etc. Additionally, the use of inhalers should be reassessed and pulmonary rehabilitations should be ordered. These patients should be assessed for exercise induced desaturation and supplemental oxygen may be used if indicated.

6.4. Management of COPD Exacerbations

About 50% of COPD exacerbations are mild and are not reported. The goal of care is to reduce COPD exacerbations that require hospital visits or hospitalizations. Patients who are admitted have an inpatient mortality of about 3-4%.²³ A patient with COPD exacerbation requiring ICU admission has a 43-46% risk of death within a year after hospitalization. The risk of death from an exacerbation increases with the development of respiratory acidosis, presence of comorbidities and the need for ventilatory support.

Table 7. Criteria for hospitalization and admission to the ICU.⁶³

| CRITERIA FOR HOSPITALIZATION | CRITERIA FOR ICU ADMISSION |
|---|----------------------------------|
| 1. Failure of outpatient therapy | 1. Marked lethargy |
| 2. Altered Mental Status | 2. Respiratory muscle fatigue |
| 3. Hypoxia/Hypercarbia | 3 Respiratory failure |
| 4. Unable to take oral medication | 4.Worsening hypoxemia |
| 5. Marked increase in shortness of breath | 5.Marked confusion |
| | 6. Respiratory Acidosis pH<7.3 |
| | 7. Impending respiratory failure |

Pharmacologic interventions are aimed at prevention or reduction of symptoms and exacerbations while improving the patient's health status and exercise tolerance. These interventions do not change the natural progression of the disease and lung function still declines over time. There are several classes of medications available for treatment of COPD. The choice of medication is based on the individual

patient's disease stage, severity of exacerbations, the patient's ability to manipulate devices (Metered Dose Inhalers-MDIs vs Breath Activated or Spacer Devices vs Dry Powder Inhalers-DPI) for delivery of medications, cost effectiveness and the patients' response to the medication.^{1, 51} The success of

the pharmacologic therapy is based on decrease or resolution of symptoms and not on changes in lung function as the disease is expected to remain at baseline or progressively worsen.

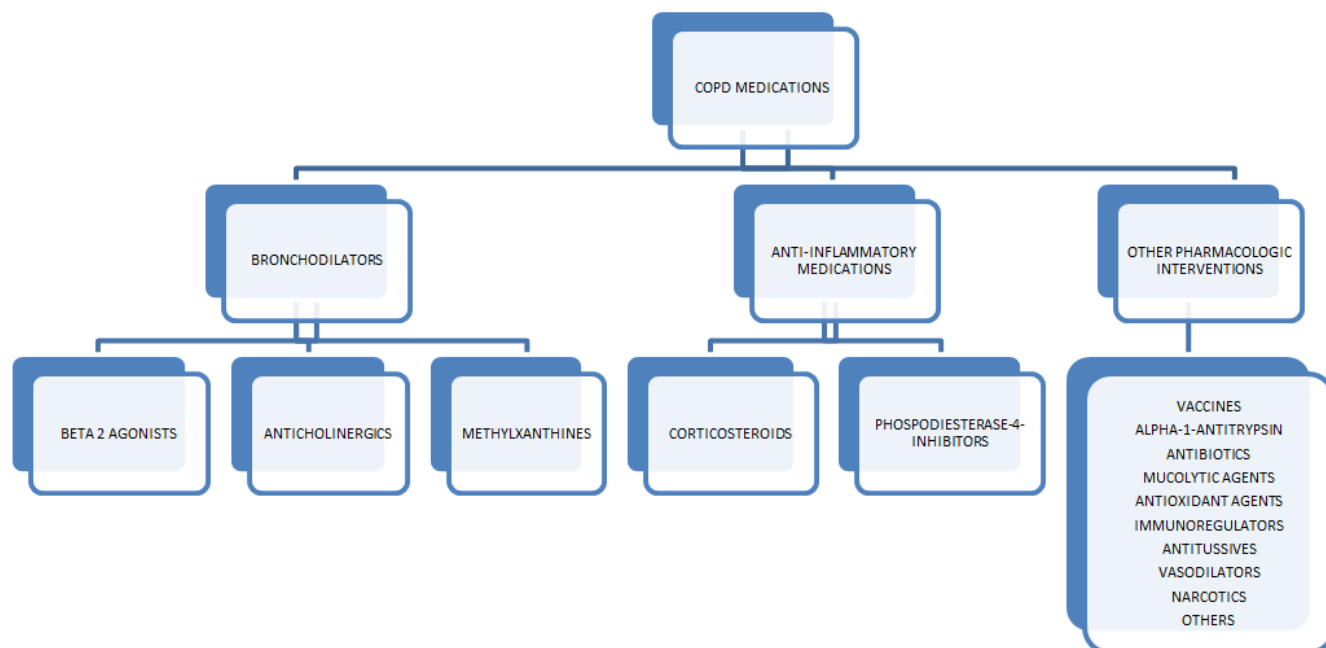


Figure 5. Medications for COPD.

6.4.1. Bronchodilators: Beta 2

Agonists/Anticholinergics/Methylxanthines

Bronchodilators are the foundation drugs for the management of patients with COPD.^{1, 46, 48, 50} They work by changing the tone of the airway muscles, thus increasing the diameter of the airway. The hyper inflated lungs are then able to empty better. Drugs in this category include beta agonists, anticholinergics and theophylline. Bronchodilators studies have shown that these agents cause symptomatic relief, but do not offer any spirometric improvement. With

bronchodilators, patients experience improved exercise capacity and long term improvement in their symptoms. Bronchodilators can be given on a schedule to prevent or reduce exacerbations or as needed to treat acute symptoms. Bronchodilators may be administered by inhalation, orally or parenterally depending on the drug administration routes available. In COPD inhalation is the method of choice as it enhances the direct effect of the bronchodilator on the airway whilst limiting the systemic effect. Inhalation may be by several methods as noted in figure 6.

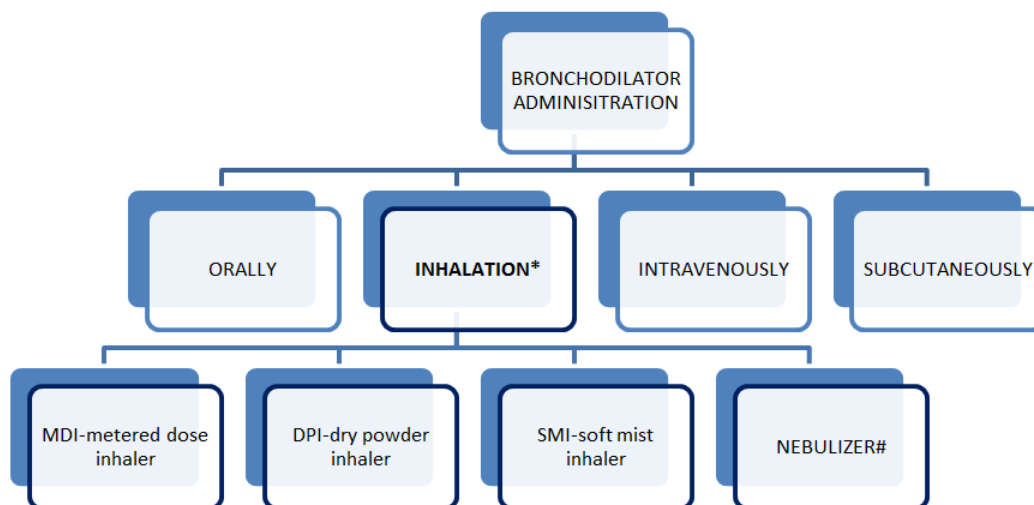


Figure 6. Bronchodilator Administration.

*Inhalation is the method of choice. To ensure the effectiveness of the drug given by this route, the correct inhaler technique should be ensured and patient education should be geared towards optimizing when and how to use their inhalers. The type of inhaler prescribed should be individualized based on the patient's ability to use the inhaler, the presence of comorbidities, the cost of the inhaler and what inhaler is available to be prescribed.

There is no strong evidence to show that nebulizer administration of bronchodilators confers any benefit over other methods of inhalation. Patients do, however report symptomatic relief with nebulizers in the acute setting not achieved with other inhalation methods. The hand held inhalers are cheaper, simpler and easier to carry than nebulizers, which even at their most streamline are bulky.

The beta agonists and anticholinergics may be long or short acting. The long acting bronchodilators are the drug of choice for producing long term symptomatic relief compared to short acting agents. Bronchodilators may be used singly or in combination. There are several formulations of this agent from which to choose.

(i) Beta 2 Agonists

These agents stimulate the beta 2 adrenergic receptors, releasing cyclic AMP resulting in relaxation of airway smooth muscle and thus bronchodilation. Patients feel subjectively better and their FEV1 increases. They may be short acting, wearing off in about four to six hours or long acting agents that last for more than 12 hours. The short acting agents are prescribed as rescue agents and regularly scheduled use is discouraged as there is an increase in adverse side effects without much improvement in lung function exercise capacity or symptoms.¹

Table 8. Long acting beta 2 agonists.

| Long acting beta 2 agonists: positive profile | Long acting beta 2 agonists: negative profile |
|--|--|
| <ul style="list-style-type: none"> • Reduce the risk of exacerbations • Reduce hospitalizations although not consistently • Improve respiratory health status-improve FEV1 and lung volumes • Improve dyspnea • Improve quality of life | <ul style="list-style-type: none"> • Have no effect on mortality rate. • Do not stop the rate of decline of lung function • Dry mouth • Urinary retention • Hypersensitivity reactions • Symptoms of narrow angle glaucoma • Dizziness • Headache • Tremor • Throat irritation |

Side effects of short acting beta 2 adrenergic agonists include palpitations, tremor, hypersensitivity reaction and tachycardia. Additionally, pulmonary vasodilation can worsen ventilation-perfusion matching resulting in a slight fall in arterial PaO₂.

(ii) Anticholinergics

Broncho-motor tone is mostly regulated by the parasympathetic nervous system. Actions in the nervous system are facilitated through nicotinic (N) and muscarinic (M) receptors via the neurotransmitter acetylcholine (Ach). Release of Ach, to act on these receptors, results in bronchoconstriction. These drugs block the acetylcholine effect on muscarinic receptors. There are several muscarinic receptors M1-M5. Short acting anticholinergics mostly block M2 and M3 receptors and long acting anticholinergics act on M3 and M1 receptors.^{1, 48}

The quaternary compounds of this group of agents are used for the treatment of COPD as they are poorly absorbed after oral administration and causes fewer side effects as compared to tertiary compounds such as atropine. There is no appreciable CNS effect. Additionally, as they are poorly absorbed from the lungs, they do not inhibit mucociliary clearance so there is no increased accumulation of lower airway secretions. Poor absorption from the gastrointestinal tract as well as the lung results in little or no change in BP, intraocular pressure and bladder function. The short acting anticholinergics such as ipratropium bromide are preferred over beta-2 agonists and methylxanthines. They are more effective and as compared to beta agonist the cardiac stimulatory effect is minimal. Treatment with anticholinergics results in improvement in exercise tolerance, relief of dyspnea and improvement in quality of life. Treatment does not however change the natural course of the disease as it does not have anti-inflammatory properties and so there is no need to use in asymptomatic patients. The duration of action of these short acting agents is about 6-9 hours.

Ipratropium bromide can be used alone or in combination therapy. It can be delivered by MDI as well as nebulized solution. It has been shown by several studies to be superior to beta-adrenergic agonists because of its minimal side effects compared to its beneficial effects. In combination with beta agonists, the benefits are optimized as there is more bronchodilation achieved compared to the administration of single agents alone. They can be given together, in immediate sequence or separated by an interval as there are no studies to show as yet any benefits of one method over the other. Another short acting anticholinergic is oxitropium bromide and is available as an inhaler and a solution for nebulizer.⁴⁸

Table 9. Benefits of combination short acting bronchodilators.^{43, 48}

| |
|--|
| Benefits of using Ipratropium and beta agonists together |
| Both classes of medication, by different mechanisms, result in bronchodilation. |
| By giving both drugs together, there is a rapid onset of action of the beta agonists and a long term effect due to the activity of the anticholinergic agents. |
| Beta agonists act on the distal small airways and anticholinergics act mostly on the proximal large airways, thus the entire lungs are affected. |

Long acting anticholinergic agents include tiotropium, aclidinium, umeclidinium and glycopyrronium.^{1, 48} The most

commonly used anticholinergic agent to date, is tiotropium. Tiotropium is well tolerated and is associated with:

- A reduction in hyperinflation.
- Decreased shortness of breath.
- Less acute exacerbations of COPD.
- Reduced hospitalizations as a result of exacerbations.
- Improves lung function.
- Improves quality of life.

Table 10. Long acting anticholinergics.^{44, 45, 47, 48}

| DRUGS | MAIN RECEPTORS INHIBITED | DURATION OF ACTION | MODES OF ADMINISTRATION |
|----------------|--|--------------------|--------------------------------------|
| Tiotropium | M1, M3, uncouples from the M2 receptors rapidly. | 24hrs | Dry powder inhaler/Soft mist inhaler |
| Umeclidinium | Mainly at M3 | 24hrs | Dry powder inhaler |
| Aclidinium | Selective at M3 | 12hrs | Dry powder inhaler |
| Glycopyrronium | M1 M3 more so than M2 | 24hrs | Dry powder inhaler |

The side effect profile of anticholinergic agents is safe, mainly due to their poor absorption from the mouth and gastrointestinal tract. The main side effect in this class of drugs is dry mouth. Tiotropium as a soft mist inhaler has been shown in one study to cause an increased risk of mortality compared to placebo. However, another study contradicted this. Aclidinium has been associated most commonly with cough, headache and nasopharyngitis as well as the other anticholinergic side effects of constipation, urinary retention and dry mouth. Glycopyrronium's most common side effects were dry mouth and urinary tract infection.^{1, 48}

(iii) Methylxanthines

Theophylline is the most commonly used drug in this class.^{1, 52} It is not clear exactly how Methylxanthines work, as they are reported to have a wide range of non-bronchodilator effects. The main idea is that they work as nonselective phosphodiesterase inhibitors.

Use of theophylline has been shown to cause a moderate bronchodilator effect. It is metabolized by cytochrome P450 mixed function oxidases. Low doses of theophylline causes a reduction in exacerbations but does not improve post-bronchodilator lung function. Clearance of the drug decreases with age and other drugs and physiologic conditions alter the metabolism of these drugs.

Theophylline has a narrow therapeutic ratio and its adverse effects are dose-related. To achieve maximum effect, the dose of theophylline needed would be toxic. Because they are nonselective phosphodiesterase inhibitors, they have a wide range of toxic effects.

Side effects of methylxanthines

- Cardiac arrhythmias
- Grand mal convulsions
- Headaches
- Insomnia
- Nausea
- Heartburn
- Interactions with frequently used medications: Coumadin
- Overdose

(iv) Combination of bronchodilators

Bronchodilators with different duration of action and mechanism of action may be combined. This may result in an increase of bronchodilation while maintaining the same side effect profile or less so.¹

6.4.2. Steroids

Inhaled and systemic steroids are widely used in the treatment of COPD.^{1, 44} The rationale for doing so is the belief that COPD is an inflammatory condition involving primarily the lung but may be systemic also. There are however controversies surrounding this belief and while the role of steroids in asthma has been proven by several studies, there are no clear studies that this is the case with COPD. Currently the use of steroids in the management of stable COPD is restricted to specific indications, while its use in COPD exacerbation has been demonstrated to have marked beneficial effects on the course of the illness.^{45, 46, 47, 48, 49}

Table 11. Inhaled and systemic corticosteroid profile.

| INHALED CORTICOSTEROIDS | SYSTEMIC CORTICOSTEROIDS |
|--|--|
| The dose response relationship is unknown | Limited for use in patients with acute exacerbations. |
| The long term safety is unknown | Beneficial in patients hospitalized for acute exacerbation of COPD |
| Regular treatment reduces exacerbations | The beneficial dose and duration of treatment are not clearly defined. |
| Regular treatment improves quality of life, lung function and symptoms. | Oral and IV steroids have been found to be equally effective in preventing treatment failure |
| Does not change mortality in patients with COPD | Hasten recovery in acute exacerbations. |
| Do not change the long term fall in FEV1 | There is no study currently to support the use in patients with stable COPD |
| Side effects: increased risk of pneumonia, oral candida, hoarseness, skin bruising | Side effects: infection, hypertension, osteoporosis, weight gain, adrenal suppression, cataracts, glucose intolerance, GI discomfort |

6.4.3. Other Pharmacologic Therapies

Other pharmacological therapies worth mentioning include:

- Phosphodiesterase 4 inhibitors
- Vaccines
- Mucolytics
- Antitussives
- Antibiotics
- Immunoregulators

6.4.4. Non-pharmacologic Interventions

Non-pharmacological interventions are a vital part in the management of COPD. The main non-pharmacological interventions include: smoking, vaccinations, elimination of other risk factors, oxygen therapy and pulmonary

rehabilitation. Nutritional support and palliative care have also been needed in patients with COPD.

Lung volume reduction surgery is beneficial in selected patient groups. Patients with upper lobe emphysema and low exercise tolerance benefit the most from lung volume reduction surgery.⁶⁹ Lung transplant has not shown any statistically significant improvement in mortality as compared to medical therapy because most of the patients who have had transplant surgery are still alive and also some of the patients have been lost to follow up. Patients do have to meet certain criteria in order to be placed on a transplant list.

Palliative care is aimed at relieving suffering in all patients with COPD using non pharmacological and pharmacological management.

Oxygen therapy has been shown to improve both quality of life and survival in COPD patients with hypoxemia.

7. Conclusion

COPD is still clearly a chronic medical condition that warrants more international attention. COPD is both preventable and treatable, but transplant apparently is the only treatable option available at this time. Current pharmacological managements are unable to cure COPD. The main focus of COPD management teams is to increase awareness of COPD among health professionals, health authorities, and the general public. In addition, GOLD 2015 had the main objectives of improving diagnosis, management and prevention, decreasing morbidity and mortality, and finally to stimulate research.

Conflict of Interest

None declared.

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