

# Chronic Obstructive Pulmonary Disease (COPD): A Review of the Clinical Management

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## ABSTRACT

**Background:** Chronic Obstructive Pulmonary disease (COPD) is one of the most common chronic respiratory diseases which contribute significantly to the burden of non-communicable diseases. With the increasing prevalence of COPD in developing countries a good knowledge of the diagnosis and adequate management are important tools for both primary care and specialist physicians to ensure appropriate treatment.

**Methods:** Review of the available literature on the subject was done through Medline and Google search utilising the following keywords COPD; epidemiology; pathogenesis and management.

**Result:** Spirometry is an important tool in the diagnosis and staging of COPD. Various treatment targets aimed at improving breathing and the quality of life in patients are available.

**Conclusion:** New therapies that have the potential to improve disease outcome are urgently needed.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disorder characterised by airflow limitation. It is usually asymptomatic in the early stages and this account for a low prevalence of the mild disease. Early detection of COPD is relevant because adequate treatment reduces exacerbations and improves quality of life. This manuscript discusses the early detection and

management of stable COPD as well as the exacerbations.

The diagnosis of COPD is dependent on an accurate clinical evaluation process which identifies the key clinical features through history taking and physical examination.

A history of suspected COPD should include the assessment of possible aetiological risk factors and suggestive symptoms such as chronic cough, breathlessness and weight loss. Tobacco smoking, is often quantified in 'pack-years' i.e. the average number of sticks of cigarette smoked per day divided by 20 multiplied by the number of years of cigarette smoking. There is a dose-response relation between smoking duration and lung function decline<sup>1</sup>. Several studies have found that more than 20 pack-years substantially increases the risk of COPD<sup>2,3</sup>. Other airway exposures such as dust, chemicals or fumes, which are often occupation related, should also be evaluated. Indoor air pollution from biomass fuel is relevant in developing countries especially among women<sup>4</sup>. Other risk factors for COPD that can easily be evaluated by history taking or reviewing the medical file are: low birth weight, asthma, respiratory tract infections including tuberculosis and a family history of COPD<sup>5,6</sup>.

Physical examination has limited application in the diagnosis of COPD. Findings such as diminished breath sounds due to hyper-inflation and 'wheezing' on lung auscultation due to airflow limitation have a higher positive than negative predictive values and can therefore not exclude COPD<sup>7</sup>. Other physical manifestations of COPD, including barrel chest, accessory muscle use<sup>8</sup>, weight loss<sup>9</sup>, peripheral oedema<sup>10</sup>, prolonged forced expiratory time, laryngeal height, and subxyphoid apical impulse<sup>11</sup> are

usually confined to severe COPD.

**Spirometry:** The diagnosis of COPD should be considered in any patient who has the following: symptoms of cough; sputum production; or dyspnoea; or history of exposure to risk factors for the disease. The diagnosis requires spirometry; a post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <0.7 confirms the presence of airflow limitation that is not fully reversible<sup>5</sup>. **Patient assessment:** Patients can be assessed using clinical features, spirometry, functional impairment and risk of exacerbation.

Several validated questionnaires are available for the assessment of COPD symptoms. Two of are widely used; the Modified British Medical Research Council questionnaire (mMRC)<sup>12</sup> and the COPD assessment test (CAT)<sup>13</sup>. The mMRC assesses disability due to difficulty in breathing and classifies COPD into five categories based on the severity of dyspnoea. The CAT is an eight item test that has scores ranging from 0 to 40. The test measures overall well being and correlates well with other tests of wellbeing<sup>14</sup>.

Spirometry is useful in the classification of the disease. Using spirometry COPD can be classified into four stages<sup>5</sup> (see table 1).

Severity	Post-bronchodilator FEV1/FVC	FEV1 % predicted
Grade 1 Mild	<0.7	>80
Grade 2 Moderate	<0.7	50-80
Grade 3 Severe	<0.7	30-50
Grade 4 very severe	<0.7	<30

Spirometric classification has proved useful in predicting health status<sup>15</sup>, development of exacerbations<sup>16,17</sup> and mortality<sup>18</sup>.

**Table 1: Spirometric classification of COPD according to the global initiative for chronic (GOLD) 2011 report.**

**Exacerbations:** COPD has a natural history with many episodes of acute worsening of symptoms, called exacerbations. These exacerbations seem to accelerate the decline in

lung function, leading to reduced physical activity and poor quality of life. Two methods can be used to determine a patient's risk for exacerbations; GOLD spirometric classification with GOLD stage 3 and 4 carrying a high risk<sup>5</sup> and an individual patient's history of exacerbations. A history of two or more exacerbations in the previous year indicates a high risk<sup>19</sup>.

**Combined Assessment:** There appears to be a weak correlation between lung function, symptoms and health related quality of life<sup>16</sup>. Thus a single mode assessment may not adequately capture the essence of the disease. A proper understanding of the impact of COPD on a patient may need to combine the spirometric classification with the symptomatic assessment and the risk of exacerbations. The GOLD 2011 report proposes a system based on spirometry, symptoms and risk of exacerbations<sup>5</sup>. Patients can be stratified into four groups;

**A. Low risk with less symptoms**

Typically such patients will be GOLD stage 1 or 2 and or 0-1 exacerbations per year with mMRC 0-1 or CAT <10

**B. Low risk more symptoms**

Typically such patients will be GOLD stage 1 or 2 and or 0-1 exacerbations per year with mMRC ≥ 2 or CAT ≥10.

**C. High risk less symptoms**

Typically such patients will be GOLD stage 3 or 4 and or ≥2 exacerbations per year with mMRC 0-1 or CAT <10

**D. High risk more symptoms**

Typically such patients will be GOLD stage 3 or 4 and or ≥2 exacerbations per year with mMRC ≥2 or CAT ≥10.

Another combined scoring system utilises several of the indicators of disease severity such as airflow limitation, exercise impairment, weight loss, reduced arterial oxygen tension etc. taken together to provide a robust indicator for disease severity and mortality: The Body mass index, Obstruction, Dyspnoea and Exercise (BODE) composite score is a multidimensional ten-point scale in which higher scores indicate increased severity has been found to be a better predictor of mortality than any single variable<sup>20</sup>.

Other investigations: A chest X-ray of a patient with COPD may show evidence of hyperinflation with flattening of the diaphragm, narrowing of the mediastinum, pruning of the vascular markings, increased lucency of the lung fields and increase in the volume of the retrosternal airspace<sup>5</sup>. A chest X-ray is limited in its use for diagnosis but may help to rule out other respiratory conditions.

A chest CT scan is not routinely recommended for COPD diagnosis but may be useful in excluding other respiratory conditions. It is particularly useful in patient evaluation prior to surgery especially if the distribution of tissue damage is not uniform<sup>21</sup>.

There is usually air trapping early in the course of the disease and this will manifest as an increase in the residual volume (RV). As the condition progresses, static hyperinflation occurs and this will manifest as an increase in total lung capacity (TLC) these changes are best detected by body plethysmography. There is also a reduction in the diffusion capacity for carbon monoxide ( $DL_{CO}$ )<sup>5</sup>.

Pulse oximetry should be performed in stable patients with  $FEV_1 < 35\%$  predicted or with clinical signs suggestive of respiratory failure or right heart failure. If the oxygen saturation is less than 92% while breathing room air, measurement of arterial blood gases should be performed<sup>22</sup>.

In patients less than 45 years who develop COPD it is recommended that they are screened for  $\alpha_1$ -antitrypsin deficiency especially if they are Caucasian. Family members with this disorder may be discovered<sup>23</sup>.

Exercise testing is an important way to evaluate functional impairment in COPD. Two methods are commonly used; the six minute walk un-paced walk test<sup>24</sup> and the paced shuttle walk test<sup>25</sup>. They are also useful in assessing effectiveness of pulmonary rehabilitation.

## Differential Diagnosis

In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques and it is assumed that asthma and COPD coexist in these patients<sup>5</sup>. In such cases, management is similar to that of asthma. Other conditions to be distinguished from COPD include; congestive heart failure, bronchiectasis, tuberculosis, obliterative bronchiolitis and diffuse panbronchiolitis.

## Management:

The major goals of therapy include symptom relief, improvement in exercise tolerance, improvement in health status, prevention of disease progression prevention and treatment of exacerbations, and reduce mortality. An integrated approach to treatment in a stepwise fashion should combine health care maintenance and use of drug and supplemental therapies as the disease progresses.

## Non-Pharmacological Therapy

**Smoking cessation:** This is the most important intervention in COPD patients who continue to smoke. An earlier study by Fletcher et. al. in West London in the 1960s showed that the annual decline in  $FEV_1$  in ex-smokers on average approached the levels in healthy never smokers<sup>26</sup>. This finding has been confirmed in more recent studies such as “the lung health study” where 5887 patients with early COPD were randomised to receive smoking cessation and no intervention. The study found that an aggressive smoking intervention program significantly reduced the age-related decline in  $FEV_1$ <sup>27</sup>. Other studies have also shown improvement in symptoms with smoking cessation but achieving and maintaining smoking cessation in patients with COPD is usually challenging<sup>28</sup>.

## Improved air Quality

Poor air quality has been linked to an increase in morbidity and mortality from COPD<sup>26</sup>. It is therefore rational to expect an improvement in air quality to lead to a reduction in the morbidity and mortality from COPD. Chapman et. al. in a study to assess the effects of improved coal stove on the incidence of COPD in China found that



there was a significant reduction in the incidence of COPD in households with an improved stove compared with those without one with the relative risk of developing COPD being 0.58 (95% CI 0.49 to 0.70,  $P < 0.001$ ) in men and 0.75 (95% CI 0.62 to 0.92,  $P = 0.005$ ) in women<sup>29</sup>. Romieu et al. in a study to assess the effects of improved biomass stoves in Central Mexico found that there was a reduction in symptoms of respiratory disease as well as in lung function decline which was comparable to cigarette smoking cessation<sup>30</sup>.

**Physical activity and pulmonary rehabilitation:** The extent to which quality of life is impaired is reflected in patient's symptoms, decreased functional status, and frequency of exacerbations. Exercise intolerance resulting from breathlessness or fatigue is often the chief symptom reported by patients with COPD. The degree of exercise intolerance directly correlates with the disease severity, but exercise intolerance may also be present in patients with only mild disease<sup>31</sup>. COPD often has extrapulmonary manifestations. Principal among these systemic manifestations is skeletal-muscle dysfunction<sup>32</sup>. Pulmonary rehabilitation does not directly improve lung mechanics or gas exchange<sup>33</sup>. Rather, it optimizes the function of other body systems so that the effect of lung dysfunction is minimized<sup>34</sup>. Pulmonary rehabilitation involves exercise training, patient education, psychosocial and behavioural training, training on breathing techniques, and nutritional advice. The model for pulmonary rehabilitation is a multi-disciplinary programme. It may be a hospital-based outpatient program, home-based, community-based or an inpatient setting. The team is usually headed by a Medical Director who is a Pulmonologist and will also have an educational, physical and respiratory therapist. Other members of the team will include a nutritionist, a psychologist and a social worker<sup>34</sup>. Benefits derivable from pulmonary rehabilitation include: improved exercise capacity, reduced severity of dyspnea, and improvement in health-related quality of life<sup>35</sup>. Other benefits include reductions in hospitalization<sup>36</sup> and other measures of health care use<sup>37</sup>.

**Vaccination:** Decisions on vaccination in COPD patients depends on local policies and availability of these vaccines. Although there is little evidence of a direct benefit of vaccination in patients with COPD, some authors recommend that pneumococcal vaccination and annual influenza vaccination be offered to all patients in an attempt to reduce both disease-specific mortality and mortality from all causes<sup>38</sup>.

### **Pharmacological Therapies:**

**Inhaled Bronchodilators:** Inhaled bronchodilators are the foundation of pharmacotherapy for COPD because of their capacity to alleviate symptoms, decrease exacerbations of disease, and improve the quality of life<sup>39-42</sup>. These drugs also improve airflow and hyperinflation<sup>43,44</sup>, thereby decreasing the work of breathing and improving exercise tolerance. Inhaled bronchodilators can be grouped according to mechanism or duration of action. Short-acting  $\beta$ -2 -adrenergic-receptor agonists such as salbutamol and cholinergic-receptor antagonists such as ipratropium result in bronchodilation for four to six hours<sup>45</sup>. Long-acting  $\beta$ -2 -adrenergic-receptor agonists such as formoterol and salmeterol have an effect that lasts for 8 to 12 hours, and the long-acting anticholinergic agent tiotropium has a duration of effect of more than 24 hours<sup>46</sup>. In stable disease, administration by means of a metered-dose or dry-powder inhaler is preferred. For patients with mild airflow limitation and intermittent symptoms, a single short-acting inhaled bronchodilator relieves symptoms and improves airflow. Salbutamol and ipratropium are equally effective for mild disease as the first step in a series of measures for treating patients with COPD<sup>47</sup>. Patients who are symptomatic with moderate airflow limitation are likely to require regularly scheduled bronchodilation with a long-acting bronchodilator as initial therapy. Formoterol, salmeterol, and tiotropium all have a prolonged duration of effect and are superior to short-acting bronchodilators in reducing symptoms and the frequency of exacerbations and in improving the quality of life<sup>48</sup>. Treatment may be initiated with either a long-acting anticholinergic agent or a  $\beta$ -2 agonist, since

there is little evidence to suggest clinically significant differences between pharmacologic classes. Combination bronchodilator therapy i.e. an anticholinergic agent with a  $\beta$ -agonist may be considered for patients in whom a single inhaled bronchodilator has failed to provide adequate relief<sup>49</sup>.

**Theophylline:** For patients who continue to be symptomatic despite combined inhaled bronchodilator therapy, theophylline may be added because of its capacity to provide additional improvement in lung function and symptoms when added to inhaled bronchodilators<sup>50,51</sup>. Frequent monitoring for supra-therapeutic levels, adverse drug reactions, and drug interactions is critical due to its narrow therapeutic index.

**Inhaled corticosteroids (ICS):** The exact role ICS in the management of stable COPD is subject to controversy. Many studies have shown that ICS do not significantly modify airway inflammation in COPD<sup>52</sup>. Studies comparing inhaled corticosteroids with placebo found that these drugs do not appreciably reduce the rate of decline in lung function<sup>53</sup>. The absence of an effect on lung function as well as differences in inflammatory phenotype between COPD and asthma<sup>52</sup>, has led some investigators to conclude that ICS are ineffective in the management of COPD. However, some trials have demonstrated that treatment with ICS may offer some benefits as it alleviates patient's symptoms<sup>54</sup>, reduces the frequency of exacerbations<sup>16</sup>, and improves health status<sup>55</sup>. The combination of inhaled corticosteroids and long-acting  $\beta$ -agonists has been observed to be superior to placebo or either drug alone with regard to lung function, frequency of exacerbations, symptoms, and health status<sup>56</sup>.

### Recommendations

Pharmacological therapy in COPD is used to reduce the symptoms, reduce the frequency and severity of exacerbations, improve exercise tolerance and well being of the patients. The currently available medications have not been shown to conclusively alter the decline in lung function of the patients. The 2011 GOLD report

proposed a model for the initial pharmacological management of patients according to individualised assessment of symptoms and exacerbation risk<sup>5</sup>.

### Group A patients

As required short acting bronchodilator is recommended as first choice. Second choice will be a combination of short acting bronchodilators or the introduction of a long acting bronchodilator.

### Group B

A scheduled long acting bronchodilator is recommended as first choice. Second choice will be a combination of long acting bronchodilators. An alternative therapy is the combination of an inhaled short acting bronchodilator and a systemic theophylline.

### Group C

An ICS combined with a long acting bronchodilator is first choice. Second choice will be a combination of long acting bronchodilators.

### Group D

As in group C patients, an ICS combined with a bronchodilator is recommended as first choice. Second choice will be a combination of an ICS, a long acting  $\beta$ -2-agonist and a long acting anticholinergic.

### Oxygen therapy

As COPD progresses, hypoxemia develops as a result of a worsening ventilation– perfusion mismatch. Trials have shown that mortality can be reduced by treatment with long term oxygen therapy (LTOT) i.e. supplemental oxygen for 15 or more hours per day<sup>57,58</sup>. LTOT is generally introduced in GOLD Stage IV patients who have PaO<sub>2</sub> at or below 7.3 kPa (55 mm Hg) or SaO<sub>2</sub> at or below 88%, with or without hypercapnia. Patients who have PaO<sub>2</sub> between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg), or SaO<sub>2</sub> of 88% and above may be eligible for LTOT if there is evidence of pulmonary hypertension, congestive cardiac failure, or polycythemia (hematocrit > 55%)<sup>5</sup>. The primary goal of oxygen therapy is to increase the baseline PaO<sub>2</sub> to at least 8.0 kPa (60 mm Hg) at sea level and rest, and/or produce an SaO<sub>2</sub> at least 90%, which will preserve vital organ function by ensuring

adequate delivery of oxygen.

### **Ventilatory Support:**

Non-invasive positive pressure ventilation (NIPPV) is not routinely recommended for stable COPD patients but if combined with LTOT may be of some benefit to patients with pronounced daytime hypercapnia. It can also have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental function of COPD patients<sup>59</sup>.

### **Surgery**

Lung-volume-reduction surgery (LVRS) can reduce hyperinflation and should be considered in patients with severe upper-lobe emphysema and poor exercise tolerance who are not doing well with medical therapy alone<sup>60</sup>. In carefully selected patients, bullaectomy is effective in reducing dyspnea and improving lung function<sup>61</sup>. Single-lung transplantation is an alternative surgical option for patients with end-stage emphysema who have an FEV1 that is less than 25% of the predicted normal value after optimal medical therapy and who have such complications as pulmonary hypertension, marked hypoxemia and hypercapnia<sup>62</sup>. Surgical techniques generally do not improve survival.

### **Acute exacerbation of COPD (AECOPD)**

An exacerbation of COPD can be defined as an event in the natural course of the disease characterized by a sudden or on occasion gradual change in the patient's baseline symptoms of dyspnea, cough, and/or sputum that is beyond normal day-to-day variations<sup>63</sup>.

The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution. High concentrations of bacteria have been recovered from the lower airway of more than half of patients with AECOPD<sup>64,65</sup>. Acquisition of a new infection is strongly associated with the occurrence of an AECOPD. The most frequently encountered bacterial organisms as newly acquired infection are *H. influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, or *Pseudomonas aeruginosa*.<sup>66-68</sup>. In about a third of cases, the etiology of severe

AECOPD cannot be identified. Studies using a combination of cultures, serologic tests, and polymerase-chain-reaction (PCR) assays reveal that viruses can be detected in up to two thirds of AECOPD. A range of respiratory viruses has been shown to cause exacerbations. The most common viruses associated with AECOPD are rhinoviruses, but in more severe cases requiring hospitalization, influenza viruses are more common<sup>69-70</sup>. AECOPD caused by the combination of viruses and bacteria are more severe and are associated with higher levels of inflammatory markers than infection caused by viruses or bacteria alone<sup>71</sup>.

The management of mild AECOPD in the home setting involves increasing the dose and/or frequency of existing short-acting bronchodilator therapy, preferably with a  $\beta_2$ -agonist. If not already used, an anticholinergic can be added until the symptoms improve<sup>5</sup>. Systemic steroids are beneficial in the management of AECOPD as they shorten recovery time, improve lung function and hypoxemia<sup>72</sup>.

In the hospital emergency room, management of AECOPD will include the provision of supplemental oxygen therapy and to determine whether the exacerbation is life threatening. If the episode is life threatening, the patient should be admitted to the hospital's intensive care unit (ICU) immediately. Otherwise, the patient may be managed in the emergency department or hospital ward.

Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Supplemental oxygen should be titrated to improve the patient's hypoxemia. Adequate levels of oxygenation ( $\text{PaO}_2 > 8.0$  kPa, 60 mm Hg, or  $\text{SaO}_2 > 90\%$ ) are easy to achieve in uncomplicated exacerbations, but carbon dioxide ( $\text{CO}_2$ ) retention can occur insidiously due to loss of hypoxic respiratory drive with little change in symptoms. After commencing oxygen, arterial blood gases should be checked 30-60 minutes later to ensure satisfactory oxygenation without  $\text{CO}_2$  retention. Venturi masks offer more accurate delivery of controlled oxygen than



other delivery devices<sup>5</sup>.

Short-acting inhaled  $\beta_2$ -agonists are usually the preferred bronchodilators for treatment of AECOPD. Methylxanthines are considered second-line medications. They are administered when there is inadequate or insufficient response to short-acting bronchodilators<sup>73</sup>.

Antibiotics should be given to Patients with exacerbations of COPD with the following three cardinal symptoms: increased dyspnea, increased sputum volume, and increased sputum purulence. Patients with exacerbations of COPD with two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms should also receive antibiotics<sup>74</sup>. Patients with a severe AECOPD that requires mechanical ventilation will also require antibiotics<sup>5</sup>. The choice of antibiotics should be based on the local microbial resistance pattern. A recommended initial empirical regimen is an aminopenicillin with or without clavulanic acid, a macrolide or tetracycline<sup>5</sup>.

Ventilatory support includes both non-invasive intermittent ventilation using either negative or positive pressure devices and invasive mechanical ventilation by endotracheal tube or tracheostomy. NIPPV has been studied in several randomized controlled trials in acute respiratory failure, consistently providing positive results with success rates of 80-85%<sup>75</sup>. These studies provide evidence that NIPPV improves respiratory acidosis, decreases respiratory rate, severity of breathlessness, and length of hospital stay. More importantly, the need for ICU admission and invasive manoeuvres is reduced by this intervention<sup>76</sup>.

The indications for initiating invasive mechanical ventilation will include; inability to tolerate NIPPV or NIPPV failure, severe dyspnea, respiratory frequency > 35 breaths per minute, life-threatening hypoxemia, severe acidosis (pH < 7.25) and/or hypercapnia (PaCO<sub>2</sub> > 8.0 kPa, 60 mm Hg), respiratory arrest, somnolence, impaired mental status, cardiovascular complications such as hypotension and shock, other complications

such as metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion<sup>5</sup>.

Further treatments that can be used in the hospital include: fluid administration, accurate monitoring of fluid balance is essential; nutrition supplementation when needed; deep venous thrombosis prophylaxis.

Observational studies have identified advanced age, severe airflow obstruction, recurrent exacerbations, and coexisting cardiac disease as predictors of poor clinical outcomes in AECOPD<sup>77</sup>.

Due to the adverse effects of AECOPD on the long term outlook in COPD, prevention or the reduction of future exacerbations is a rational goal. New bacterial colonisation of the airway is implicated in more than 50% of AECOPD as such antibiotic prophylaxis may reduce the frequency of AECOPD. Macrolide antibiotics have immunomodulatory, anti-inflammatory, and antibacterial effects and are the ideal candidates for prophylaxis in chronic inflammatory respiratory disease<sup>78</sup>. Randomised trials have been carried out to evaluate the effect of azithromycin prophylaxis on the frequency of AECOPD in selected patients. Albert et. al. observed that azithromycin given at 250mg per day for one year decreased the frequency of exacerbations in COPD patients and improved the quality of life but there with increased incidence of macrolide resistance and hearing loss<sup>79</sup>. Currently antibiotics prophylaxis is not recommended by any professional body<sup>5</sup>.

## CONCLUSION

The prevalence of COPD is increasing especially in developing countries and its share of global mortality is also rising. Early diagnosis is important in improving the quality of life but this may be difficult to achieve in developing countries that lack diagnostic facilities. Currently only smoking cessation has been shown to modify the disease progression. New therapies that have the potential to improve disease outcome are urgently needed. As always, prevention is better than cure.

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