Journal of Clinical Respiratory Diseases and Care

Managing Severe COPD: Addressing the Challenges with Latest Trends and Treatment Options (Part I: Pharmacological Management)

Khajotia RR[1]* and Sree Raman K[2]

[1]Department of Internal Medicine and Pulmonology, International Medical University, Seremban, Malaysia
[2]Hospital Tuanku Ja'afar, Seremban, Malaysia

Abstract

Managing severe (GOLD 3 and GOLD 4) COPD requires patience and tenacity, both on the part of the patient and the treating physician. Though not an easy task, a thorough understanding by the discerning physician of the latest diagnostic and treatment options available, prognosis and expected quality of life (which is essentially individualized for each patient), goes a long way in the meaningful management of such patients. Essentially, management of severe COPD involves monitoring the disease process closely, reducing existing risk factors such as smoking and occupational exposure (dusts, irritants, toxic vapours and fumes), managing the patient while he is in a stable or baseline state, preventing and treating complications, and managing acute exacerbations, as and when they occur. Besides medical management, an ongoing programme in pulmonary rehabilitation is also critically important in improving the patient's effort tolerance and lung functions, thereby reducing symptoms and improving the overall quality of life. Finally, end-of-life decision making and advanced directives are critically important, both to the patient and the treating physician, in the final stages of the disease process.

In this review article we have detailed the various treatment options available for patients with severe COPD, and the clinical challenges commonly encountered during the course of management.

Keywords: Severe COPD; Chronic bronchitis; Emphysema; Long-term oxygen therapy; Non-invasive ventilation (NIV); Invasive mechanical ventilation; Pulmonary rehabilitation

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a condition characterised by chronic inflammation of the airways and lung parenchyma which is accompanied by progressive worsening of airflow limitation that is poorly reversible [1-3]. COPD is most certainly one of the major causes of chronic morbidity and increasing incidence of mortality in the modern world. Essentially, COPD encompasses two conditions, namely, chronic bronchitis and emphysema. While chronic bronchitis is clinically characterised by cough with expectoration for three months of a year for two consecutive years in a patient in whom other causes of a chronic cough (such as bronchiectasis) have been excluded, and which may precede or follow the development of airflow limitation [4,5], emphysema is defined as abnormal and permanent dilatation of the airways distal to the terminal bronchioles, with destruction of the airspace walls [6]. In chronic bronchitis the productive cough is believed to be due to hypersecretion of mucus, and some studies have shown that mucus hypersecretion is accompanied by airflow obstruction, as a result of narrowing of the peripheral airways [7]. While emphysema may very occasionally be present in a patient without airway obstruction, it is most often seen in patients with moderate to severe airflow limitation [8,9].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD), a project initiated by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) defines COPD as follows [8]:

"Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is 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."

Risk Factors

Globally, cigarette smoking is the most commonly encountered risk factor for COPD.

Overall, the risk for developing COPD is directly proportional to the total burden of inhaled noxious particles that an individual encounters during his lifetime. These include tobacco smoke encountered through cigarettes, pipes, cigars and environmental tobacco smoke (ETS), occupational dusts and chemicals such as irritants, vapours and fumes, indoor air pollution from biomass fuels used for cooking and heating in poorly ventilated buildings and outdoor air pollution.

Other risk factors which are responsible for far fewer cases of COPD include a severe hereditary deficiency of alpha-1 antitrypsin [10].

Pathology

The predominant pathologic changes seen in COPD involve the airways, lung parenchyma and pulmonary vasculature. These mainly depend on the predominant underlying disease (chronic bronchitis or emphysema) and severity of the underlying condition [8]. Airways abnormalities in COPD include chronic inflammation, increase in the number of goblet cells, mucus gland hyperplasia, fibrosis, narrowing

and reduction in the number of small airways, and airway collapse due to the loss of tethering caused by alveolar wall destruction [9]. In addition, chronic inflammation in chronic bronchitis and emphysema is characterized by the presence of CD8+ T-lymphocytes, neutrophils, and CD68+ monocytes/macrophages in the airways [10-13]. Lung parenchymal changes in emphysema affect structures distal to the terminal bronchiole, which include the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli, known collectively as the acinus. Consequently, the part of the acinus that is affected by permanent dilation or destruction determines the subtype of emphysema in a particular patient, namely, proximal acinar, centrilobular, panacinar, or distal acinar emphysema.

In patients with COPD, pulmonary vasculature changes such as intimal hyperplasia, smooth muscle hypertrophy and smooth muscle hyperplasia occur due to chronic hypoxic vasoconstriction of the small pulmonary arteries and arterioles. In addition, destruction of the alveoli due to emphysema leads to a loss of the pulmonary capillary bed with resultant pruning of the distal pulmonary vasculature. This is usually detected radiologically using computed tomographic methods [14].

Physiological Changes

The predominant physiological deterioration in a patient with COPD includes a rapid decline in the forced expiratory volume in one second (FEV_1) from the normal rate seen in adults (of approximately 30 ml per year), to nearly 60 ml per year [3,15].

In COPD, the disease progression usually begins with an asymptomatic phase in which lung function deteriorates without significant accompanying symptoms. The onset of symptoms in patients with COPD usually does not occur until the FEV_1 has fallen to approximately 50% of the normal predicted value [3,16].

Another common physiologic abnormality that is seen in patients with severe (stages III and IV) COPD is hyperinflation, which is commonly present at rest and worsens on exercise. This results in an increase in the residual volume (RV) and the functional residual capacity (FRC).

Consequently, this results in an increase in the work of breathing and reduced exercise tolerance. Reduction in the diffusing capacity for carbon monoxide (DLCO), hypoxemia, and alveolar hypoventilation also occur in such patients.

Diagnosis

Early detection of COPD can be easily missed with disappointing consequences. Hence, a diagnosis of COPD should be considered in any patient with progressive dyspnoea accompanied by chronic cough and sputum production, especially if exposed to additional risk factors such as cigarette smoking or noxious fumes. Consequently, it is also imperative that complete lung function studies (including FEV_1, FEV_1/FVC, FVC, RV, TLC, RV/TLC and DLCO) be carried out when airflow obstruction is initially suspected. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has stated that initial airflow limitation in COPD is characterized by an FEV_1 of less than 80% of the normal predicted value alongwith an FEV_1/FVC ratio of less than 0.70 [16]. Besides GOLD, most other guidelines such as the European Thoracic Society, American Thoracic Society and the British Thoracic Society recommend that treating physicians use a combination of factors such as severity of symptoms and signs, and deterioration in physiological functions, while determining the severity of COPD [16-

19] although these guidelines slightly differ in their interpretation about what constitutes mild, moderate and severe COPD.

Prognosis depends on the stage of the disease and data from longitudinal studies conducted, show increased mortality in moderate and severe stages of the disease.

In defining what constitutes COPD, it is important to understand how chronic bronchitis, emphysema and bronchial asthma are interrelated, as per the GOLD guidelines.

The defining points about their interrelationship have been classified into the following subsets:

- Patients with bronchial asthma whose airflow obstruction is completely reversible on spirometry are not considered to have COPD.

- In some patients it is difficult to differentiate bronchial asthma from chronic bronchitis and emphysema, when airflow obstruction does not remit completely. Such patients with unremitting asthma are now classified as having COPD. However, it is believed that the aetiology and pathogenesis of the COPD in these patients is possibly different from that of patients with chronic bronchitis or emphysema.

- Chronic bronchitis and emphysema with airflow obstruction commonly occult together [20] and some of these patients may also have coexistent bronchial asthma.

- Patients with bronchial asthma may develop a chronic productive cough, either spontaneously or due to exposure to inhalants such as cigarette smoke or allergens. In the US, such patients are often referred to as having asthmatic bronchitis or the asthmatic form of COPD, although the term 'asthmatic bronchitis' has not been officially endorsed in clinical practice guidelines.

- Patients with chronic bronchitis or emphysema, or both, who do not have evidence of airflow obstruction on spirometry, are not considered to have COPD [21,22]. However, since cough and sputum are abnormal in these patients (even though the lung functions are normal), they were classified as patients at risk for developing COPD, and hence categorised as GOLD Stage 0, in the original GOLD classification [23]. However, this stage was deleted in the 2006 revision over doubts about whether it is a progressive condition [24].

- Finally, patients with airflow obstruction due to other aetiological disorders such as bronchiectasis, cystic fibrosis or obliterative bronchiolitis, are not considered to have COPD [25].

Differential diagnoses

The differential diagnoses of COPD include a wide variety of conditions. Hence, prior to arriving at a definitive diagnosis of COPD, it is essential to consider some important medical conditions. These include:

Congestive heart failure (CHF): Congestive heart failure (CHF) may present with dyspnoea and wheezing and hence may be difficult to differentiate from COPD. However, symptoms of orthopnea and paroxysmal nocturnal dyspnea, accompanied by the presence of fine late-inspiratory crepitations bilaterally at the lung bases on auscultation, along with typical chest radiographic findings, can lead to a definitive diagnosis of CHF.

Peak expiratory flow rate (PEFR) is a reasonable bedside

investigation that may be used to distinguish chronic obstructive pulmonary disease (COPD) from CHF. If the PEFR is ≤ 150-200 L/min the patient is likely to be having an acute exacerbation of COPD, while higher PEFR readings are indicative of congestive heart failure.

According to a study, CHF–related acute dyspnea can be distinguished from pulmonary-related conditions such as COPD and bronchial asthma, by the presence of a 'comet-tail sign' on lung ultrasonography. For this, eight zones of the lungs are scanned (two anterior and two lateral zones on each side of thorax) and the presence of three or more B lines (comet tail signs) in each of the eight zones is indicative of CHF. B lines are essentially hyperechoic reverberation artefacts that originate at the pleural line and extend vertically to the bottom of the screen. A positive ultrasound examination [26-28] requires two or more positive zones bilaterally, of the eight zones measured. The accuracy of this sign is such that absence of a comet-tail sign correctly rules out heart failure–related dyspnea even in patients with a history of heart failure [26].

Chronic asthma: An acute exacerbation of adult-onset severe asthma may be difficult to distinguish from COPD, in older patients. However, an important distinguishing factor is a good bronchodilator response on spirometry and normal diffusion capacity for carbon monoxide (DLCO) in such patients.

Bronchiolitis obliterans: Bronchiolitis obliterans is a condition that occurs in the younger population who does not smoke, and may also be seen in patients with collagen-vascular diseases. The high-resolution computerized tomographic (HRCT) chest scan characteristically shows areas of mosaic attenuation without evidence of hyperinflation or other radiographic signs of emphysema.

Pneumothorax: Pneumothorax is a condition that may be difficult to rule out clinically from emphysema, as there would be diminished chest wall movements, hyperresonance on percussion and diminished air entry, in both conditions. However, in a pneumothorax the clinical signs are mostly localised to one hemothorax, unlike in emphysema where the signs are generalised. Chest radiography will help rule out a pneumothorax. However, in case of a large bulla in a patient with emphysema, an HRCT chest scan may be additionally required.

Other differential diagnoses: Pulmonary embolism, bronchiectasis, diffuse panbronchiolitis, pneumonia, tuberculosis and carcinoma of the bronchus.

Stages of COPD

Previously, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines used forced expiratory volume in 1 second (FEV_1), as a percentage of the predicted value, to stage disease severity. However, it was later realised that while FEV_1 is only one component in determining the severity of COPD, patients with the same percentage predicted value of FEV_1 may have significantly different severity of symptoms, risk of exacerbations, exercise tolerance, quality of life and chronic morbidity and mortality, resulting in a significantly different long-term prognosis for each patient. Hence, taking into consideration this important aspect, the severity of symptoms, risk of exacerbations, presence of comorbidities, and prognosis are now included in the new staging system of the revised GOLD classification [8,29].

In order to determine the severity of symptoms, the GOLD guidelines suggest using instruments such as the modified Medical Research Council (mMRC) dyspnea scale, the Clinical COPD Questionnaire and the COPD Assessment Tool (CAT) [8,30,31].

One commonly used questionnaire is the St. George's Respiratory Questionnaire (SGRQ), which incorporates three main components, namely, symptoms, activity, and impact on daily life, along with and a total score.

The gold guidelines: The gold guideline uses a combination of factors, namely, history of acute exacerbations, severity of symptoms, and FEV_1 (percent predicted value) to assess the risk for future exacerbations and to guide therapy [8].

Severity of symptoms is assessed using the modified Medical Research Council (mMRC) or COPD assessment test (CAT) [8]. The future risk of exacerbations is determined from the number of acute exacerbations in the previous 12 months.

If the patient has had zero or one exacerbation in the past 12 months, it implies a low future risk of exacerbations. However, two or more exacerbations suggest a high future risk [8]. Stratification of the severity of lung function impairment is based on the post bronchodilator FEV_1, using the GOLD classification.

These three components are then combined into four groups, namely:

- Group A: Low risk, less symptoms: GOLD 1 or GOLD 2 (mild or moderate airflow limitation) and/or 0 to 1 exacerbation per year and mMRC grade 0 to 1 or CAT score <10.

- Group B: Low risk, more symptoms: GOLD 1 or GOLD 2 (mild or moderate airflow limitation) and/or 0 to 1 exacerbation per year and mMRC grade>2 or CAT score ≥ 10.

- Group C: High risk, less symptoms: GOLD 3 or GOLD 4 (severe or very severe airflow limitation) and/or ≥ 2 exacerbations per year and mMRC grade 0 to 1 or CAT score<10.

- Group D: High risk, more symptoms: GOLD 3 or GOLD 4 (severe or very severe airflow limitation) and/or ≥ 2 exacerbations per year and mMRC grade>2 or CAT score ≥ 10.

The COPD Foundation system uses a staging system that includes seven criterion for determining severity [32,33]. These are based upon assessment of spirometry, regular symptoms, frequency of exacerbations in the past one year, oxygenation levels, emphysema, as determined on computed tomography chest scans, presence of chronic bronchitis, and other coexistent morbidities. The COPD Foundation uses five spirometric grades:

1. SG 0: Normal spirometry

2. SG 1: Mild, postbronchodilator FEV_1/FVC ratio<0.7, $FEV_1 ≥ 60\%$ predicted

3. SG 2: Moderate, postbronchodilator FEV_1/FVC ratio<0.7, $30\% ≤ FEV_1<60\%$ predicted

4. SG 3: Severe, postbronchodilator FEV_1/FVC ratio<0.7, $FEV_1<30\%$ predicted

5. SG U: Undefined, postbronchodilator FEV_1/FVC ratio>0.7, $FEV_1<80\%$ predicted

Management of severe (GOLD 3 and GOLD 4) COPD

Successful management of severe COPD entails close monitoring and careful assessment of the patient's condition. Assessment includes a detailed history of exposure to risk factors such as smoke and noxious fumes. A past history of bronchial asthma, allergies, respiratory

infections in childhood and other coexistent respiratory diseases should be elicited, along with family history of COPD and other chronic respiratory diseases.

In case of severe COPD, it is also essential to elicit history of acute exacerbations in the past and their frequency, along with the need for hospitalisation, if any. At the time of presentation, an assessment of the pattern of development of the symptom complex should be noted as it helps in defining the management plan. An initial assessment also needs to be made regarding the effect of the present level of disease on the patient's quality of life. For this, presence of comorbidities, if any, need to be detected. These include heart disease, diabetes mellitus, hypertension, malignant conditions, osteoporosis and musculoskeletal disorders, which may restrict the patient's mobility and freedom of movement.

Finally, the patient's family and social support levels must be assessed, as COPD is a chronic disorder which requires long-term supportive care. It should also be determined to what extent exposure to risk factors such as cigarette smoke and other noxious inhalants can be reduced.

When the patient presents to the physician with an acute exacerbation of severe COPD, it is essential to accurately assess the severity of the condition in order to determine the appropriate treatment. Defining an exacerbation, it can be termed as "an event in the natural course of the disease which is characterised by a change in the patient's baseline dyspnoea, cough and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication, in a patient with underlying COPD [34]".

In addition to the above mentioned parameters which help in determining the severity of an exacerbation, arterial blood gas (ABG) values too are important in assessing severity.

Respiratory failure is suspected and mechanical ventilation is indicated if, in addition to clinical evidence of respiratory fatigue and depression, the arterial blood gases show evidence of moderate-to-severe respiratory acidosis (pH<7.36) accompanied by hypercapnia ($PaCO_2$>50 mmHg, >6.7 kPa), moderate-to-severe hypoxia, (PaO_2 is<60 mmHg, <8 kPa) and a fall in oxygen saturation (SaO_2<90%).

Chest radiograph is a very important investigation as it helps in identifying the presence of hyperinflation, infection (denoted by the presence of a consolidation), and other complications such as a pneumothorax, localised collapse (due to mucoid impaction), enlarged cardiac size, left heart failure (denoted by the presence of Kerley-B lines at the lower zones of the lungs bilaterally and/or minimal bilateral pleural effusion), or the presence of a tumour mass.

Electrocardiogram is an essential investigation in all patients with an acute exacerbation of severe COPD. Patients with COPD may show evidence of right-axis deviation, right ventricular or biventricular hypertrophy, 'p' pulmonale and transient cardiac arrhythmias due to hypoxia or electrolyte abnormalities. Full blood count (FBC) detects evidence of infection and polycythemia. Serum electrolytes help in detecting hyponatremia and hypokalemia. Sputum analysis is useful in detecting the presence of infection.

Although acute exacerbations of COPD, defined by increased symptoms and worsening lung function, are a common cause of hospital admission, patients may be treated at home either transiently prior to hospital admission, or on a more permanent basis due to the resistant nature of the condition or due to social and economic reasons.

Home/Outpatient management of severe COPD

Home management is usually reserved for patients who have severe COPD which is relatively resistant to most treatment options. Such patients are usually managed by a combination therapy which includes, nebulisation with bronchodilators, anticholinergics and steroids, metered dose inhalers, oral medication and controlled long-term oxygen therapy (LTOT) using mobile oxygen cylinders or oxygen concentrators. Long-term oxygen therapy should be given for a minimum of 15 hours per day. LTOT when administered for 15 hours or more per day, retards the progression of the disease process, slows the development of pulmonary hypertension and reduces the incidence of cor pulmonale and consequent biventricular failure. While administering home oxygen therapy, it should be remembered that patients with type II respiratory failure have chronically elevated $PaCO_2$ levels and hence their normal hypercapnoeic drive is severely blunted. The only remaining respiratory drive in such patients is the hypoxic drive. If such patients are given high-flow oxygen (4-6 liters/min), there is a risk that the hypoxic drive would also get blunted resulting in the patient going into respiratory depression and consequent respiratory failure. Hence, controlled oxygen should be given to such patients, in a dose of 1-2 liters/min through nasal prongs or as 24%-28% via a venturi mask.

In severely resistant cases of COPD, non-invasive ventilation may be resorted to at home, if in spite of all the above-mentioned measures, the blood gas parameters are not well-maintained and the patient continues to remain hypoxic and retains CO_2. Non-invasive ventilation is usually delivered by a CPAP or a BiPAP. A BiPAP is preferable as here the inspiratory and expiratory pressures can be separately adjusted, unlike with a CPAP where the oxygen is delivered at the same pressure during both inspiration and expiration. Patient education plays an important role in the outpatient management of severe COPD. Good patient education helps in the understanding of the chronic nature of the illness and consequently improves the patient's ability to cope with the illness. It helps in motivating the patient to quit smoking and in the understanding of advance directives and end-of-life issues.

Indications for hospital admission in patients with severe COPD

1. Inadequate response to outpatient management.

2. Patient is unable to cope with day-to-day household activities.

3. Insufficient home support.

4. Marked increase in intensity of breathlessness, resulting in sudden development of resting dyspnoea

5. Deteriorating general condition of the patient with development of tachycardia, cyanosis, peripheral oedema, acute confusion, drowsiness, flapping tremors, bounding pulse, conjunctival oedema, tachyarrythmias.

6. Fall in SaO_2<90%, H^+>45, PaO_2<50 mmHg.

7. Significant comorbidities such as cardiac failure, diabetes mellitus, malignancy, pneumonia.

Inpatient (hospital) management of severe COPD

Inpatient management is needed for patients with severe COPD who have an acute, unremitting exacerbation which necessitates urgent hospital admission.

The treatment plan in these patients include a combination of pharmacologic measures, as follows:

Inhaled bronchodilators: They form a mainstay in the treatment of patients with severe COPD. Patients with severe COPD obtain symptomatic relief from breathlessness following the use of inhaled bronchodilators. Short-acting β_2-adrenergic agonists such as terbutaline, salbutamol (albuterol), fenoterol and levalbuterol alongwith short-acting anticholinergics such as ipratropium bromide or oxitropium bromide, may be used singly and in combination. When given together, they are combined in a single inhaler (Table 1).

Long-acting bronchodilators are now commonly used, but a short-acting bronchodilator should be provided for emergency treatment.

Inhaled long-acting β_2-agonists such as salmeterol, indacaterol and formoterol provide sustained bronchodilatation for about 12 hours, while the inhaled long-acting anticholinergic agent tiotropium provides bronchodilatation for at least 24 hours [35]. Randomized trials in exacerbation-prone, symptomatic patients who have FEV_1 values less than 60% of the predicted value [35-38] has shown that when used as monotherapy, both classes of long-acting bronchodilators show similar beneficial effects and improve the respiratory health status according to patient scores on the St. George's Respiratory Questionnaire when compared with a placebo.

Long-acting β_2-agonists and anticholinergics also reduce the risk of exacerbations by 15 to 20%, which is believed to be their most important clinical benefit [36-38]. Both classes of drugs have also been shown to reduce hospitalizations, although the reductions have not been consistent [37,38].

Adverse effects associated with short-acting β_2-adrenergic agonists include, tremors, palpitations, tachycardia and hypersensitivity reactions. Patients on long-term inhaled salbutamol are especially troubled by tremors of the hands, tachycardia and palpitations unlike patients on long-term inhaled terbutaline.

Adverse effects attributable to ipratropium bromide usually include, dry mouth, cough and blurring of vision (Table 1).

However, adverse reactions associated with long-acting β_2-agonists are minor and include throat irritation, dizziness, headache and mild tremors. Long-term use of tiotropium is known to cause urinary retention, dry mouth, narrow-angle glaucoma and occasional hypersensitivity reactions.

Inhaled corticosteroids: Inhaled corticosteroids are widely used in the treatment of COPD. While its chronic use is not known to decelerate the long-term decline in FEV_1, it has been shown to reduce the frequency of exacerbations by 15 to 20% in symptomatic patients with an $FEV_1 < 50\%$ of the predicted value, thereby reducing morbidity and improving the quality of life. The combination of an inhaled corticosteroid with a long-acting β_2-agonist reduces frequency of exacerbations by an additional 10% as compared with either therapy used alone [38]. Oral and upper-airway thrush and dysphonia are common adverse effects seen in patients with long-term inhaled corticosteroid use. Another adverse effect observed in one study [39] was an increased incidence of pneumonia. However, the significance of these results is doubtful as chest radiographs were not used to diagnose pneumonia in these patients and there was no increase in the incidence of mortality.

Metered-dose inhalers (MDI) are also commonly used to deliver the medication in these cases. However, in an acute exacerbation, the large aerosol particles (usually >6 microns in diameter) released from an MDI may remain in the pharynx and not reach the tracheobronchial tree in any significant concentration, due to severe bronchospasm. In such cases, it is recommended to use a spacer device along with the inhaler. The spacer device negates the need for proper triggering on the part of the patient. In addition, the large aerosol particles released from the MDI condense onto the walls of the spacer, thereby allowing the smaller-sized aerosol particles to enter deep into the tracheobronchial tree. Using the spacer device, 40% more aerosol particles reach the airways as compared to MDI alone.

However, if the inhaled bronchodilators, anticholinergics and corticosteroids delivered via an MDI along with a spacer device still do not have the desired effect in a patient with an acute exacerbation, they should then be delivered as a nebulized solution via an ultrasonic nebuliser, as it delivers aerosol particles far smaller than 6 microns in size, which can penetrate deep into the tracheobronchial tree, thereby helping to relieve symptoms of breathlessness in an acute exacerbation.

While nebulized solutions of a short-or-long-acting β2-agonist may be combined with anticholinergic, nebulized solutions of corticosteroids is usually given alone, in order to obtain the desired effect. Hence, nebulisation therapy with a β_2-agonist and an anticholinergic may be alternated with corticosteroid therapy, in a patient with an acute exacerbation of COPD (Table 1).

Systemic corticosteroids: Current guidelines and data from clinical trials recommend the use of systemic corticosteroids in the treatment of acute exacerbations of COPD [40,41]. However, the literature review suggests that specific recommendations might not be optimal because of the heterogeneity of the trials. But studies have undoubtedly shown that corticosteroids are effective in improving airflow by increasing FEV_1 and PaO_2. It is also observed that use of systemic corticosteroids decreases the $PaCO_2$, and improves the arterial pH, especially over the first 72 hours [42,43]. Consequently, it has been observed that the use of systemic corticosteroids reduces breathlessness, frequency of relapse, and duration of hospital stay.

Multiple trials on the use of systemic corticosteroids have been conducted which have been heterogeneous, often having multiple limitations. Hence, it is difficult to draw definitive conclusions. Various trials included different corticosteroids and sometimes a combination, including hydrocortisone (intravenous), methylprednisolone (oral and intravenous), and oral prednisone, making it difficult to recommend only one corticosteroid [42,43]. Some studies have also compared the efficacy of oral versus neubulized corticosteroids (Table 1).

a) Intravenous corticosteroids: In severe exacerbation of COPD, intravenous corticosteroids help to relieve symptoms of breathlessness and improve lung function. Hydrocortisone 50-100 mg qds may be given depending on the clinical condition of the patient. Alternatively, methylprednisolone 125 mg may be given intravenously every 6 hours for 72 hours, followed by oral prednisone (30-40 mg), tapered over 2 weeks [44].

Studies have shown a decrease in treatment failure rates, shorter duration of hospital stay, and and a significant improvement in FEV_1 in patients treated with intravenous corticosteroids. Intravenous methylprednisolone in hospitalized patients appears to reduce treatment failure rates with minimal adverse side-effects [44] (Table 1).

b) Oral corticosteroids: While short term use of oral corticosteroids is known in patients with an acute exacerbation of severe COPD, long-term use is not recommended due to the unacceptable incidence of adverse effects. Usually tab. Prednisolone is administered in a dose of 30-40 mg per day for 7-10 days, following the tapering of intravenous hydrocortisone or methylprednisolone.

Medication	Inhaler (MDI/DPI) (microgram)	Nebulizer mg/ml	Oral	Injectable	Adverse reactions	Duration of action
Beta-2 agonists						
Short-acting						
Fenoterol	100-200 (MDI)	1	0.05% syrup			4-6 hours
Levalbuterol	45-90 (MDI)	0.21-0.42				6-8 hours
Salbutamol	100-200 (MDI and DPI)	5	5 mg(tab) 0.024% (syrup)	0.1,0.5	Palpitation, tremor, tachycardia,	4-6 hours
Terbutaline	400-500 (DPI)		2.5, 5 mg (tab)			4-6 hours
Long-acting						
Formoterol	4.5-12	0.01+			Dizziness, headache, tremors	12+
Arformoterol		0.0075				12+
Indacaterol	150-300 (DPI)					24
Salmeterol	25-50 (MDI and DPI)				Dizziness, tremors, headache, throat irritation,	12+
Anticholinergics						
Short-acting						
Ipratropium bromide	20,40 (MDI)	0.25-0.5			Dry mouth, cough, blurred vision	6-8
Oxitropium bromide	100 (MDI)	1.5			Dry mouth, cough, blurred vision	7-9
Long-acting						
Tiotropium	18 (DPI), 5 (SMI)				Dry mouth, urinary retention, narrow-angle glaucoma	24+
Combined short-acting beta-2 agonists and anticholinergic in one inhaler						
Fenoterol/Ipratropium	200/80 (MDI)	1.25/0.5				6-8
Salbutamol/Ipratropium	75/15 (MDI)	0.75/0.5			Palpitation, tachycardia, tremor, dry mouth, cough, blurred vision	6-8
Inhaled Corticosteroids						
Beclomethasone	50-400 (MDI and DPI)	0.2-0.4			Sore throat, dysphonia, headache, nasopharyngitis, oral thrush, possible pneumonia	
Budesonide	100,200,400 (DPI)	0.2,0.25, 0.5			Oral thrush, dysphonia, sore throat, pharyngitis	
Fluticasone Propionate	50-500 (MDI and DPI)				Oral thrush, sore throat, dysphonia, nasopharyngitis	
Combined long-acting beta-2 agonist and corticosteroids in one inhaler						
Formoterol/budesonide	4.5/160, 9/320 (DPI)				Sore throat, headache, dysphonia, throat irritation, nasopharyngitis, oral thrush	
Salmeterol/Fluticasone propionate	50/100, 250,500 (DPI) 25/50, 125,250 (MDI)				Sore throat, headache, dysphonia, throat irritation, nasopharyngitis, oral thrush	
Systemic Corticosteroids						
Prednisolone			5-60 mg (tab)		Hyperglycemia, GI bleeding, infections, muscular weakness, fractures, delirium	
Methylprednisolone			4,8,16 mg (tab)	125mg (IV)	Hyperglycemia, GI bleeding, infections, muscular weakness, fractures, delirium	
Hydrocortisone				50,100, 150, 200 mg (IV)		
Methylxanthines						
Theophylline (SR)			100-800 mg (tab)		Nausea, vomiting, tremors, atrial tachyarythmias, seizures	Up to 24 hours
Aminophylline				125,250,500 mg (IV)	Nausea, vomiting, atrial tachyarythmias, palpitations, seizures	Up to 24 hours
Phosphodiesterase-4 inhibitors						
Roflumilast			500 mcg			24 hours
MDI= Metered Dose Inhaler, DPI= Dry Powder Inhaler						

Table 1: Formulations and Dosages of medications used in the management of COPD.

It should be noted that long-term use of systemic corticosteroids increases the risk of hyperglycemia with some patients requiring insulin therapy. Besides this, gastrointestinal bleeding, infections, muscular weakness, fractures, development of cushingoid features and delirium may also occur in patients on long-term corticosteroids.

In conclusion, in treatment of severe COPD, systemic corticosteroids reduce airflow obstruction, relieve symptoms of breathlessness, reduce incidence of treatment failure, decrease frequency of relapse, and consequently decrease the overall duration of stay in hospital.

In order to prevent the occurrence of potential side-effects,

systemic corticosteroid therapy should be administered in the lowest possible dose and for the minimum duration of time, in order to achieve the maximum therapeutic benefit. For this purpose, it is recommended that hospitalized patients be given an initial dosage of systemic corticosteroids such as intravenous hydrocortisone or methylprednisolone, rather than than 30-40 mg of oral prednisolone initially for 7–10 days, as suggested in the GOLD guidelines.

c) Methylxanthines: Methylxanthines such as theophylline and aminophylline may occasionally be used to treat severe COPD whose exacerbations are difficult to control. In such patients regular plasma theophylline levels must be monitored and should not exceed 12 micrograms per millilitre. When given intravenously, the patient should be carefully monitored for adverse reactions which include, nausea and vomiting (if injected rapidly), tremors, insomnia, transient multifocal atrial tachyarrhythmia and rarely seizures. It is always preferable to administer aminophylline as bolus intravenous injections. 125 mg or 250 mg of aminophylline is usually admixed with 30ml of 5% dextrose or normal saline and given intravenously, slowly over a period of 30 minutes. Rapid administration of aminophylline usually results in symptoms of nausea, vomiting and tremors which are transient and subside gradually.

Phosphodiesterase-4 inhibitors: In patients with moderate-to-severe COPD, the phosphodiesterase-4 inhibitor, Roflumilast reduces the severity of acute exacerbations when used in combination with oral corticosteroids. Similar results are also seen when Roflumilast is combined with long-acting bronchodilators.

Antibiotics: An acute exacerbation of severe COPD is commonly due to bacterial infections as evidenced by the presence of increasing cough, purulent expectoration and fever. However, it is known that exacerbations may be due to viral infections of the upper respiratory tract or may be non-infective. Even so, a meta-analysis of controlled trials of antibiotics in COPD has shown a statistically significant benefit from antibiotics in terms of improvement in clinical symptoms lung functions and overall morbidity [45].

When compared with placebo, antibiotics are shown to decrease the risk of treatment failure (defined as no resolution or clinical deterioration) by approximately 50% in severe COPD [35,46] and are known to be most effective when sputum purulence is present.

The main pathogens responsible for causing exacerbations in COPD include respiratory bacterial pathogens, respiratory viruses and atypical bacteria (Table 2). Among the typical bacteria, nontypeable *Haemophilus influenzae* (NTHI), *Streptococcus pneumoniae*, and *Moraxella catarrhalis* are the most common [47]. These three pathogens are exclusively human pathogens that are transmitted between patients. In a healthy individual, these pathogens are confined to the upper respiratory tract without causing any symptoms. However, since patients with COPD have compromised lung defense mechanisms, these pathogens get established in the lower respiratory tract causing acute exacerbations.

Among the viruses, Rhinovirus and Respiratory Syncytial Virus (RSV) [48] are predominantly responsible for acute exacerbations in patients with COPD, possibly because of diminished respiratory reserve.

A risk categorisation approach has been recommended by some investigators in the early empiric antibiotic treatment of an acute exacerbation. For this, the three cardinal symptoms identified are:

1. Increasing breathlessness,
2. Increasing sputum quantity, and
3. Increasing sputum purulence.

If one of the above cardinal symptoms is present, it is defined as a mild exacerbation, while if 2 or all 3 of the cardinal symptoms are present, it is defined as moderate or severe exacerbation, respectively. Mild exacerbations are usually treated symptomatically and antibiotics are prescribed only if symptoms worsen. However, in moderate to severe exacerbations, it is important to distinguish the 'uncomplicated' (simple) patient from the 'complicated' one. Uncomplicated patients are defined as those who do not have any risk factors to suggest a poor outcome, while complicated patients have one or more of the following risk factors which could suggest a poor outcome, namely, age >65yrs, FEV1<50% of predicted value, co-morbid cardiac conditions such as heart failure, ischaemia, cardiomyopathies, valvular disorders, or three or more exacerbations in the previous one year [49,50]. The choice of antibiotics for patients with uncomplicated COPD include an advanced macrolide (azithromycin, clarithromycin), a cephalosporin (cefuroxime, cefpodoxime or cefdinir), doxycycline, trimethoprim/sulfamethoxazole or a ketolide (telithromycin). Amoxicillin alone is no longer considered an appropriate antibiotic for an acute exacerbation as there is a high incidence of β-lactamase production among NTHI and M catarrhalis. In complicated patients, suitable antibiotics include fluoroquinolone such as moxifloxacin, gemifloxacin and levofloxacin, or a combination of amoxicillin and clavulanate.

In choosing an appropriate antibiotic, it is also important to note that exposure to an antibiotic within the past 3 months is a mitigating factor in considering the use of the same antibiotic again. Hence, the choice of the antibiotic should be from a different class of agents from the one prescribed within the past 3 months. The antibiotic prescribed in hospitalised patients with severe COPD is usually administered intravenously, however, at times it may be given orally. It is important that the course of antibiotics is completed and not discontinued midway. Usually, an antibiotic in an acute exacerbation is administered for 7-10 days. A successful response to antibiotic treatment is considered if there is a reduction in breathlessness, reduction in the quantity of sputum production, reduced sputum purulence, subsidence of fever and normalisation of total white cell count. Other important factors to be considered while prescribing antibiotics include safety and tolerability of the agent, drug interactions and cost of treatment.

Oxygen therapy: On admission to hospital, oxygen may be initially administered via nasal prongs or face mask. In patients with COPD, controlled oxygen therapy should be administered. Oxygen is delivered in a dose of 1-2 liters/min through nasal prongs or as 24%-28% via a venturi mask (Figure 1). While on oxygen therapy, patient should be monitored for any signs of clinical deterioration and the ABG should

Type of Organism	Percentage of exacerbations	Pathologic species
Bacteria	45%-55%	Nontypeable Haemophylus Influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, pseudomonas spp. Enterobacteriaceae, haemophilus haemolyticus, haemophilus parainfluenzae, staphylococcus aureus
Viruses	30%-40%	Rhinovirus, Respiratory syncytial virus (RSV), Influenza, Parainfluenza, Adenovirus, Coronavirus
Atypical bacteria	5%-15%	Chlamydia pneumoniae, Mycoplasma pneumoniae

Table 2: Pathogens commonly isolated in severe acute exacerbations of COPD.

Figure 1: A 44-year-old patient with severe COPD, cor pulmonale and decompensated congestive cardiac failure, on a venturi mask.

be repeated after 30 minutes to look for improvement in the blood gas parameters.

Aim of oxygen therapy is to maintain the SaO_2 between 94%-98% in patients with type I respiratory failure and between 88%-92% in patients with type II respiratory failure, while increasing the PaO_2 levels above 60 mmHg. In addition, in patients with type II respiratory failure, an attempt should be made to maintain the $PaCO_2$ levels at or near 45 mmHg.

Since patients with type II respiratory failure have chronically elevated $PaCO_2$ levels, their normal hypercapnoeic drive is blunted. The only respiratory drive remaining in such patients is the hypoxic drive. Consequently, if such patients are given high-flow oxygen (4-6 liters/min), there is a risk that the hypoxic drive would also get blunted resulting in the patient going into respiratory depression and consequent respiratory failure. Hence, controlled oxygen should be given to such patients, in a dose of 1-2 liters/min through nasal prongs or as 24%-28% oxygen via a venturi mask. In severe COPD, the patient may continue to deteriorate with worsening of his clinical symptoms, signs and investigative parameters, including ABG. If the patient continues to deteriorate, and the arterial blood gas levels worsen, a decision may need to make about the need for non-invasive ventilation (NIV).

References

1. American Thoracic Society (1995) Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152: S77-S121.

2. Barnes PJ (2000) Chronic obstructive pulmonary disease. N Engl J Med 343: 269-280.

3. Rand SE, Cherniack RM (2004) Management of Chronic Obstructive Pulmonary Disease. N Engl J Med 350: 2689-2697.

4. Celli BR, MacNee W, ATS/ERS Task Force (2004) Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 23: 932.

5. Elbehairy AF, Raghavan N, Cheng S, Yang L, Webb KA, et al. (2015) Physiologic characterization of the chronic bronchitis phenotype in GOLD grade IB COPD. Chest 147: 1235.

6. Rennard SI (1998) COPD: overview of definitions, epidemiology, and factors influencing its development. Chest 113:235S.

7. Vestbo J, Prescott E, Lange P (1996) Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Am J Respir Crit Care Med 153: 1530-1535.

8. (2014) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Revised 2014. Global Initiative for Chronic Obstructive Lung Disease.

9. McDonough JE, Yuan R, Suzuki M (2011) Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N Engl J Med 365: 1567.

10. Eriksson S (1965) Studies in alpha 1-antitrypsin deficiency. Acta Med Scand Suppl 432: 1-85.

11. Aoshiba K, Nagai A (2004) Differences in airway remodeling between asthma and chronic obstructive pulmonary disease. Clin Rev Allergy Immunol 27:35.

12. Turato G, Zuin R, Miniati M, Baraldo S, Rea F, et al. (2002) Airway inflammation in severe chronic obstructive pulmonary disease: relationship with lung function and radiologic emphysema. Am J Respir Crit Care Med 166: 105-110.

13. Cosio MG, Saetta M, Agusti A (2009) Immunologic aspects of chronic obstructive pulmonary disease. N Engl J Med 360: 2445.

14. Estépar RS, Kinney GL, Black-Shinn JL, Bowler RP, Kindlmann GL, et al. (2013) Computed tomographic measures of pulmonary vascular morphology in smokers and their clinical implications. Am J Respir Crit Care Med 188: 231.

15. Anthonisen NR, Connett JE, Murray RP (2002) Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 2002;166:675-679.

16. Fabbri LM, Pauwels RA, Hurd SS, GOLD Scientific Committee (2004) Global strategy for the diagnosis, management and prevention of COPD: 2003 update. Eur Respir J 22: 1-2.

17. (1995) Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152: S77-S121.

18. Siafakas NM, Vermeire P, Pride NB (1995) Optimal assessment and management of chronic obstructive pulmonary disease (COPD). Eur Respir J 8: 1398-1420.

19. (1997) BTS guidelines for the management of chronic obstructive pulmonary disease. Thorax 52: S1-S28.

20. (1990) Obstructive lung disease. Med Clin North Am 74: 547.

21. Rosenbloom J, Campbell EJ, Mumford R, Saldeen T, Senior RM, et al. (1991) Biochemical/immunologic markers of emphysema. Ann N Y Acad Sci 624: 7-12.

22. Petty TL, Silvers GW, Stanford RE (1987) Mild emphysema is associated with reduced elastic recoil and increased lung size but not with air-flow limitation. Am Rev Respir Dis 136: 867-871.

23. (2005) Global initiative for chronic obstructive lung disease (GOLD). Workshop report: Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease.

24. (2006) Global initiative for chronic obstructive lung disease (GOLD). Workshop report: Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease.

25. O'Brien C, Guest PJ, Hill SL, Stockley RA (2000) Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. Thorax 55: 635.

26. Prosen G, Klemen P, Strnad M, Grmec S (2011) Combination of lung ultrasound (a comet-tail sign) and N-terminal pro-brain natriuretic peptide in differentiating acute heart failure from chronic obstructive pulmonary disease and asthma as cause of acute dyspnea in prehospital emergency setting. Crit Care 15: R114.

27. Cardinale L, Volpicelli G, Binello F, Garofalo G, Priola SM, et al. (2009) Clinical application on lung ultrasound in patients with acute dyspnea: differential diagnosis between cardiogenic and pulmonary causes. Radiol Med 114: 1053-1064.

28. Volpicelli G, Mussa A, Garofalo G, Cardinale L, Casoli G, et al. (2006) Bedside

lung ultrasound in the assessment of alveolar-interstitial syndrome. Am J Emerg Med 24: 689-696.

29. Lange P, Marott JL, Vestbo J, et al. (2012) Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. Am J Respir Crit Care Med 186: 975.

30. Jones PW, Tabberer M, Chen WH (2011) Creating scenarios of the impact of COPD and their relationship to COPD Assessment Test (CAT™) scores. BMC Pulm Med 11: 42.

31. Gupta N, Pinto LM, Morogan A, Bourbeau J (2014) The COPD assessment test: a systematic review. Eur Respir J 44: 873.

32. Rennard S, Thomashow B, Crapo J, Yawn B, McIvor A, et al. (2013) Introducing the COPD Foundation Guide for Diagnosis and Management of COPD, recommendations of the COPD Foundation. COPD 10: 378.

33. Qaseem A, Wilt TJ, Weinberger SE, Hanania NA, Criner G, et al. (2011) Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med 155: 179.

34. Pocket guide to COPD diagnosis, management and prevention. Updated 2010. Global Initiative for Chronic Obstructive Lung Disease (GOLD).

35. Niewoehner DE (2010) Outpatient management of severe COPD. N Engl J Med 362: 1407-1416.

36. Wilt TJ, Niewoehner D, Kim CB, RL Kane, A Linabery, et al. (2005) Use of spirometry for case finding, diagnosis, and management of chronic obstructive pulmonary disease (COPD): structured abstract. Rockville, MD: Agency for Healthcare Research and Quality.

37. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, et al. (2008) A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 359: 1543-1554.

38. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, et al. (2007) Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 356: 775-789.

39. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E (2008) Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 300: 2407-2416.

40. O'Donnell DE, Aaron S, Bourbeau J, Hernandez P, Marciniuk DD, et al. (2007) Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease—2007 update. Can Respir J 14: 5B-32B.

41. The National Collaborating Centre for Chronic Conditions (2004) Chronic obstructive pulmonary disease: national clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 59: 1-232.

42. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ (1996) Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. Am J Respir Crit Care Med 154: 407-412.

43. Quon BS, Gan WQ and Sin DD (2008) Contemporary management of acute exacerbations of COPD: a systematic review and meta-analysis. Chest 133: 756-766.

44. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, et al. (1999) Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. N Engl J Med 340: 1941-1947.

45. Saint S, Bent S, Vittinghoff E, Grady D (1995) Antibiotics in chronic obstructive pulmonary disease exacerbations: a meta-analysis. JAMA 273: 957-960.

46. Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC (2006) Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2: CD004403-CD004403.

47. Eldika N, Sethi S (2006) Role of nontypeable Haemophilus influenzae in exacerbations and progression of chronic obstructive pulmonary disease. Curr Opin Pulm Med 12: 118-124.

48. Seemungal T, Harper-Owen R, Bhowmik A, Moric I, Sanderson G, et al. (2001) Respiratory viruses symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164: 1618-1623.

49. Balter MS, La Forge J, Low DE, Mandell L, Grossman RF, et al. (2003) Canadian guidelines for the management of acute exacerbations of chronic bronchitis. Can Respir J. 10: 3B-32B.

50. (2007) [GOLD] Global Initiative for Obstructive Lung Disease. Global Initiative for Obstructive Lung Disease.

51. Miravitlles M, Murio C, Guerrero T, Gisbert R (2002) Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. Chest 121: 1449-1455.