Review Article

COPD : A Case Based Approach to the Clinician in Light of GOLD 2021

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Chronic obstructive pulmonary disease (COPD) is considered to be one of the most important causes of mortality and morbidity across the globe. Many people suffering from this poorly reversible condition often have a state of chronic ill health, reduced life-span either from the disease itself or secondary to its complications. Hence proper evaluation of every COPD patients and early identification of complication are of utmost importance to prevent such calamities. This article will guide the clinicians about the approach to such patients in day to day practice.

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Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease which is a major cause of chronic morbidity and mortality throughout the world[1]. It is a disease state characterized by persistent limitation of airflow combined with presence of respiratory complaints, that is not completely reversible and those are either due to abnormality in the airway or alveoli. The main aetiology is thought to be related to a considerable exposure to toxic or noxious particles such as smoking, and also influenced by different host factors, combined with some of the congenital and developmental anomalies of the lung. COPD includes chronic bronchitis, emphysema and small airway disease[2]. In most of the patients, it is usually associated with or complicated by some comorbidities, which in most cases, are responsible for the worsening of the clinical course of the disease.

Editor's Comment :

- Smoking cessation is the cornerstone of therapy in patients with COPD.
- Appropriate and judicious use of inhalers should be encouraged in every COPD patient.
- Proper management of the associated comorbidities and complications along with timely management of exacerbations are of paramount importance.

Case Scenarios :

Case 1 :

A 63-year-old retired gentleman with a smoking history of one pack per day for last 33 years presented in the out-patient department (OPD) with the complaint of productive cough with greenish sputum for last several days. He also had breathlessness and fatigue. He had sought care in OPD for similar symptoms two or three times annually in the last decade. A diagnosis of COPD was made 6 years ago, and a short actingâ2-agonist (SABA) was initiated following which his symptoms got relieved and he felt much better. Recently the symptom of breathlessness is interfering with his lifestyle. Recovering from exacerbations takes longer time than before, which is often 2 weeks. During his last visit, FEV1 was 54% predicted. He is on ACE-inhibitor for hypertension for last 15 years. On examination, he was febrile; there was tachycardia (heart rate 110/min), blood pressure of 112/72mm Hg, respiratory rate of 26/min, oxygen saturation of 96% on room air.

Further Course in OPD, Outcome and Follow-up :

On careful examination, predominantly expiratory wheeze with scattered crackles were noted over both lungs. Jugular venous pressure was not raised and examinations of the cardiovascular system were within normal limits. Basic blood parameters were within normal limits, except neutrophilic leucocytosis. Patient was counselled to stop of smoking and yearly vaccination. He was treated with oral antibiotics, paracetamol. As per GOLD guidelines he was offered long acting muscarinic antagonist (LAMA) in inhaled form. He was taught about proper inhalation technique and was advised to continue SABA on as and when required basis. He was asked to revisit after 7days. During this his cough and fever subsided and his generalised condition got improved. He was asked to continue use of two inhalers as advised previously and

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remain in close follow up.

Case 2 :

A 54-year-old lady with a history of smoking presented to the emergency department with severe shortness of breath and cough. Her FEV1 was 35% (predicted) at the recent outpatient visit. She retired from her office job 5 years ago because of her breathlessness. She had quit smoking 5 years ago. Over the years she had suffered multiple exacerbations requiring antibiotics and inhaled steroids, but no hospital admission. Previously her symptoms had been controlled with bronchodilators, inhaled steroids and nebulisers as and when required. In addition to inhaled long-acting â2-agonist/ inhaled steroid combination and a long-acting anti-muscarinic, she is taking acebrophylline, N-acetyl-cysteine, and oral steroids without experiencing any beneficial effect.

Further Course in Hospital :

On examination, patient was alert, conscious and cooperative. Temperature was raised (100.8ºF). Accessory muscles of respiration were working. Patient was unable to speak in a complete sentence. Tachycardia and tachypnea were there. Chest examination revealed presence of wheezing, bronchial breath sound over mid zone of left lung. Blood investigation revealed neutrophilic leucocytosis. Chest X-ray showed hyperinflation of both lung field and a dense homogenous shadow involving mid zone of left lung. Supplemental oxygen therapy given and arterial blood gas was analysed. Hypoxemia improved with oxygen. Nebulisation with beta agonist and muscarinic antagonist was given along with parenteral antibiotics. Systemic steroids were initiated for 14 days. Following this treatment there was clinical as well as radiological improvement. She was discharged with LABA and Long Acting Muscarinic Antagonist (LAMA) in inhaler form and was advised to remain in regular follow up.

Risk Factors :

The following factors are thought to increase the risk for developing COPD :

- Tobacco smoke: Persons who smoke cigarettes on regular basis have more respiratory symptoms and pulmonary function defects and have higher chances of mortality than non-smokers. Other varieties of tobacco related products such as water pipe, cigar, and marijuana are considered as the incriminating factors for the development of COPD, besides outdoor air pollution.
- Occupational exposures
- Outdoor air pollution
- Genetic factors: Congenital deficiency of the protein alpha-1 antitrypsin (A1AD or AATD); mutation in the gene responsible for the synthesis of glutathione-S-transferase or matrix metallo-proteinase-12 is associated with deterioration of pulmonary function and increased chances of developing COPD[4].
- Age and sex: Increasing age and female gender are known risk factors
- Developmental defects of lung, chronic bronchitis and childhood infections.

Diagnosis and Clinical Assessment in COPD :

The diagnosis of COPD should be considered in any patient having shortness of breath associated with chronic cough with sputum production and history of recurrent lower respiratory tract infections, combined with presence of at least one of the known risk factors. The presence of persistent airflow limitation is suggested by a **post-bronchodilator FEV1/FVC <0.70** thus confirming the diagnosis of COPD in the background of specific symptoms and usual risk factors.[5] Presence of co-existent chronic diseases like ischemic heart disease, cardiomyopathy, metabolic syndrome, osteoporosis, depression, anxiety, and lung malignancy, should be properly evaluated and managed. The cardinal features that indicate COPD are as follows:

- **Dyspnea :** Usually progressive in nature, persistent, worse with exercise.
- **Chronic cough :** Intermittent, occasionally non-productive and associated with wheeze.
- **Chronic sputum production**
- **Presence of risk factors,** suggestive family history or history of childhood infections
- **Clinical examination findings :** In early stages of COPD, patients usually have an entirely normal physical examination. Polycythemia can be seen frequently. Tachypnea, increased activity of accessory muscles of respiration and cyanosis may indicate exacerbation. Expiratory wheeze and vesicular breath sound with prolonged expiratory phase may be present.

Investigations[6] :

- **Basic blood parameters :** Complete blood count; C-reactive protein; urea and creartinine; liver function test; blood glucose; electrocardiogram
- **Spirometry :** This is required to make the diagnosis in proper clinical context.
- **Chest imaging :** Chest X-ray features showing bullae, paucity of parenchymal findings, or hyperlucency of lung fields are suggestive of emphysema. It can also detect any alternative

diagnosis or co-existent pathology such as pneumothorax or cardiomegaly. Computed tomography (CT) thorax is not routinely performed except some special situations (to detect the complications such as lung cancer and bronchiectasis). CT scan is also needed before planning some surgical procedures like lung transplant or lung volume reduction surgery.

- **Lung volumes and diffusion capacity :** Air trapping in COPD patients leads to an increased residual volume, and with gradual worsening in airflow limitation, increment of the total lung capacity (static hyperinflation) occurs. Body plethysmography (more accurate), or helium dilution technique (less accurate) may be used to detect such changes.
- **Pulse oximetry and arterial blood gas analysis :** Oximetry may be used for evaluation of peripheral arterial-oxygen saturation of a patient and it is a reliable tool to assess any need for supplemental oxygen. It is generally used in patients with clinical signs of congestive cardiac failure or respiratory failure. Arterial blood gas analysis should be performed when the oximetry reading is <92% on room air.
- **Exercise testing and physical activity assessment :** A reduction in the self-paced walking distance or at the time of incremental exercise testing in laboratory; may be considered as a powerful objective evidence of impairment of health status and poorer prognosis; Both the unpaced 6-minute walk test and paced shuttle walk test[2,3] may be used. Laboratory testing using treadmill ergometry may help in diagnosing co-existent cardiac ailments.
- **Screening of Alpha-1 Antitrypsin Deficiency (AATD) :** The WHO recommends screening in areas with high prevalence of AATD and when the usual risk factors are absent.

Differential diagnosis of COPD (Table 1) :

Table 1 — *The differential diagnosis of COPD*[5]

Diagnosis	Suggestive feature
Asthma	Early age of onset, symptoms worse at night/early morning, seasonal variation of symptoms, history of allergy, rhinitis, eczema; and family history of asthma
Congestive cardiac failure	Orthopnea, pedal swelling, raised JVP, third heart sound on examination, cardiomegaly in chest imaging, pulmonary edema
Tuberculosis	Constitutional symptoms like weight loss, anorexia, night sweats; Chest X-ray showing patchy opacity or cavitary lesions, and microbiological evidence.
Bronchiectasis	Large volume of purulent sputum, bacterial infections common, CT chest shows bronchial dilatation, bronchial wall thickening.

Airflow Limitation Severity :

The classification of airflow limitation severity in COPD with specific spirometric cut-off has been depicted in Table 2[5].

Table 2 — *Spirometry classification of COPD*

In patients with FEV1/FVC < 0.7		
CATEGORY	SEVERITY	SPIROMETRY (% predicted)
GOLD-1	Mild	FEV1 ≥ 80%
GOLD-2	Moderate	50% ≤ FEV1 < 80%
GOLD-3	Severe	30% ≤ FEV1 < 50%
GOLD-4	Very severe	FEV1 < 30%

Assessment of COPD :

Initially COPD was thought to be a disease mainly characterized by breathlessness. A simple standardized measurement of breathlessness such as the Modified Medical Research Council (MMRC) Questionnaire is commonly used for assessment of respiratory symptoms. However, this is well-recognized fact that COPD has a greater impact on the quality of life of a patient beyond dyspnea. Moreover, the COPD Assessment Test (CAT) and the COPD Control Questionnaire (CCQ) can be used to assess such patients in a comprehensive manner.

Combined COPD Assessment :

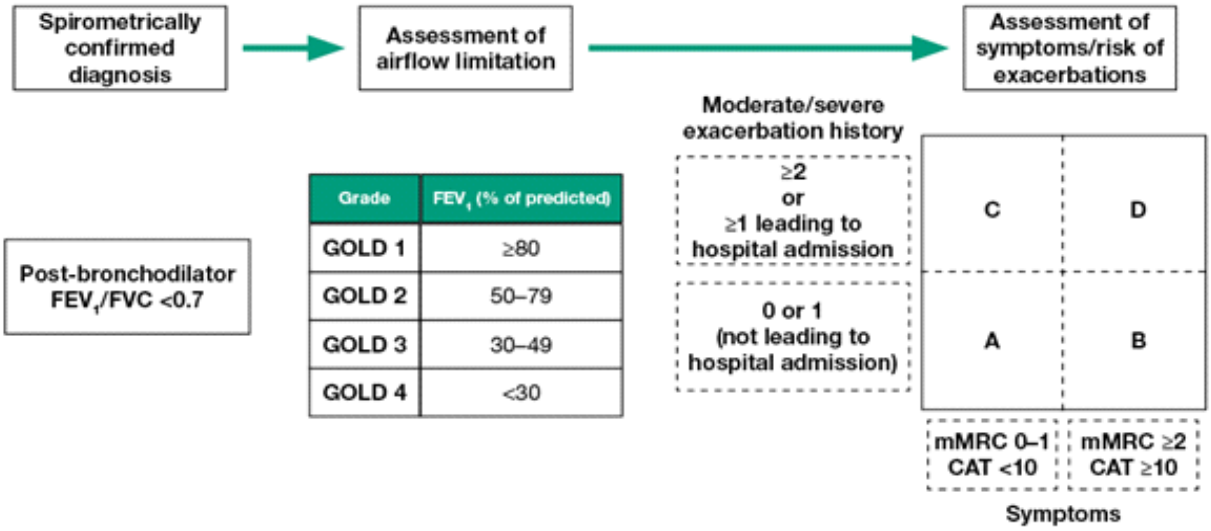
A combination of spirometry, along with patient symptoms and exacerbations history, may be used as an assessment tool. It remains vital not only for the diagnosis but also for prognostication and consideration of alternative therapeutic approaches. This new approach for assessment has been depicted in Fig 1.

Management :

- **Initial management :**

(1) Smoking cessation: It is the cornerstone in management of COPD. Pharmacotherapy combined with the nicotine replacement enhances a long duration of abstinence. Legal actions against smoking, and proper counselling when delivered by skilled healthcare professionals, have been seen to improve quit rates. However, the safety and efficacy of e-cigarettes as an aid for smoking cessation is quite uncertain at present.

(2) Vaccination: Seasonal Influenza vaccination has been seen to significant reduce recurrent hospitalizations, lower respiratory tract



FEV_1=forced expiratory volume in the first second; FVC=forced vital capacity; mMRC=modified Medical Research Council dyspnoea questionaire; CAT=COPD assessment test.

Fig 1 — Assessment in a COPD patient

infections and mortality. Pneumococcal vaccination has also been proved to be beneficial. Use of 23-valent pneumococcal polysaccharide vaccine (PPSV23) has a proven role in reduction of the risk of community acquired pneumonia in patients with COPD of <65 years of age and FEV1 <40% predicted and in presence of concomitant chronic diseases. In case of adults e"65 years, 13-valent conjugated pneumococcal vaccine (PCV13) has proved to be efficacious in reducing the chances of severe pneumococcal disease. Tdap vaccination (dTaP/dTPa) has been recommended by the CDC in patients of COPD to protect them against tetanus, pertussis, and diphtheria, only applicable to those who had not taken this in adolescence[7].

- **Pharmacotherapy :**

(1) Bronchodilators : Inhaled bronchodilators are key to symptomatic management in COPD patients and given on regular basis. Regular and as needed short acting beta agonist (SABA) and short acting muscarinic antagonist (SAMA) are seen to be associated with symptomatic improvement along with an increase in FEV1. Long acting beta agonist (LABA) and long acting muscarinic antagonist (LAMA) have a significant role in improvement of shortness of breath, lung function, general health status, and reduction in exacerbation rates.[8] Combined treatment with LABA and LAMA has been associated with a significant symptomatic improvement along with increase in FEV1 and reducing exacerbations, when compared to the monotherapy. Currently available LABA- formoterol, salmeterol and indacaterol; SAMA- ipratropium bromide and oxitropium bromide; LAMA- tiotropium, aclidinium and glycopyrronium.

(2) Anti inflammatory therapy :

- **Inhaled corticosteroid (ICS) :** ICS when combined with LABA, is seen to be more efficient than individual treatment in improving health status, lung function and reduction in the frequency of exacerbations. Triple inhaled therapy in the form of LABA/LAMA/ICS significantly improves overall lung function, quality of life and reduces exacerbation in comparison to the individual components.
- **Oral glucocorticoids :** Long term use of oral steroids has many adverse effects with no proven benefits except in exacerbation.
- **PDE4 inhibitors :** In patients with severe COPD with history of exacerbation and chronic bronchitis, PDE 4 inhibitor may improve lung function and exacerbations.
- **Antibiotics :** Evidence suggests long term Azithromycin therapy reduces exacerbation but it is associated with increasing bacterial resistence and hearing impairments.
- **Mucoregulators and antioxidants :** Mucolytics commonly used such as N-acetyl-cysteine, carbo-cysteine reduces exacerbation in selected patients.

(3) Oxygen therapy in stable COPD : Long term oxygen therapy (LTOT) has a survival benefit in patients with severe resting hypoxemia and routine supplemental oxygen therapy has no proven value in stable COPD patients without severe resting hypoxemia. Supplemental oxygen should be titrated according to the patient's clinical status and arterial blood gas

parameters to achieve a target saturation of 88-92%.

(4) Interventional therapies in COPD : Lung volume reduction surgery, bullectomy, transplantation, bronchoscopic interventions such as endobronchial valve, lung coils, vapour ablation

The treatment algorithm of stable COPD is depicted in Figs 2 and 3.

Management of Exacerbation :

An exacerbation of COPD is defined as sudden deterioration of existing respiratory symptoms that mandates additional therapy. As the symptoms are mostly non-specific to COPD, therefore relevant differential diagnoses should be kept in mind (Table 3).

COPD may be exacerbated by several factors with respiratory tract infection being the most common incriminating factor. The goal for treatment of COPD exacerbation is to manage the current event appropriately and aggressively, and to prevent such episodes in future.

Management of serious but not life threatening exacerbation:

- After initial assessment administer supplemental oxygen, obtain serial arterial and venous blood gas, pulse oxymetry measurement.
- Bronchodilators : For the treatment of acute exacerbation, short-acting inhaled beta2-agonists (SABA), with or without short-acting anticholinergics (SAMA) are preferred as initial bronchodilators.

♦ Increase dose and or frequency

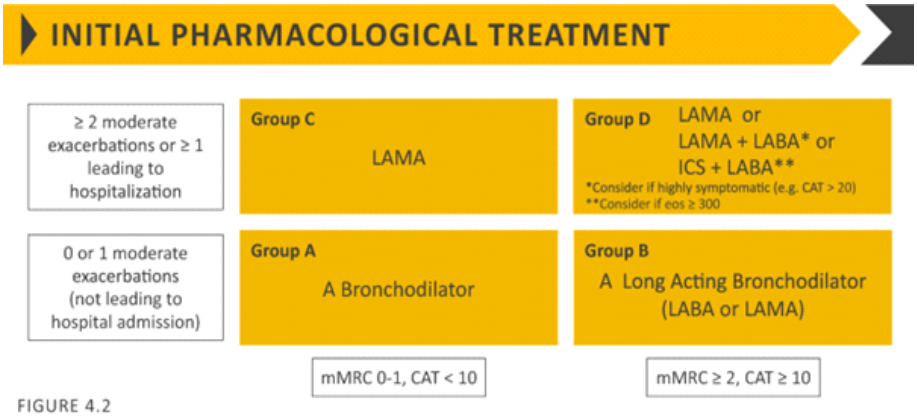


Fig 2 — Initial pharmacological treatment of stable COPD (adapted from GOLD 2021)
Abbreviations : EOS: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.

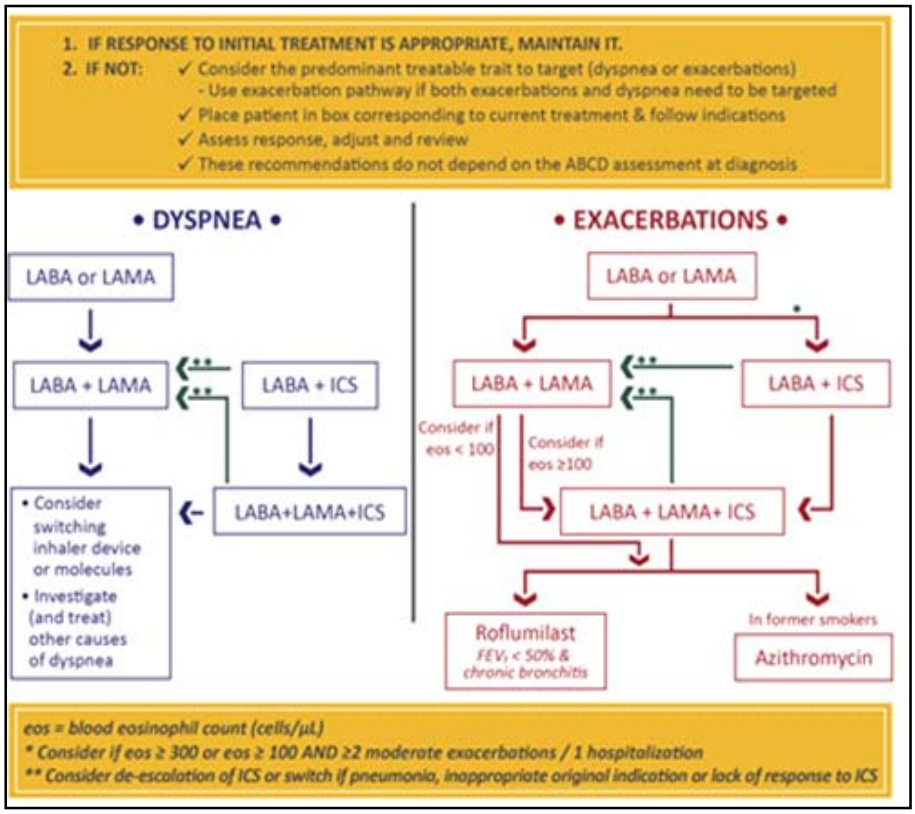


Fig 3 — Follow-up pharmacological treatment of stable COPD (adapted from GOLD 2021)

Table 3 — *Differentials of exacerbation*

Clinical Conditions	Relevant investigation
Pneumonia	Chest Xray, CRP, Pro-calcitonin
Pleural effusion	Chest X-ray or ultrasound
Pneumothorax	Chest Xray or CT chest
Pulmonary embolism	D-dimer and or Doppler lower limb; Chest CT
Pulmonary edema (Cardiogenic)	ECG, cardiac enzymes
Arrythmias (Atrial fibrillation or flutter)	ECG

of short acting bronchodilators

- ♦ Combine short acting beta2 agonist and anticholinergics
- ♦ Consider long acting bronchodilators when patients are stable
- ♦ Use spacers or air driven nebulisers when possible

• Oral corticosteroids: Systemic corticosteroid has a proven benefit on lung function (FEV1), oxygenation and reduction of hospital stay. The usual duration should not exceed 5-7 days.

• Consider oral antibiotics if bacterial infection is present. Antibiotics, when indicated, reduce the hospital stay, fasten recovery, reduce early relapse, and treatment failure. Duration of therapy should not exceed 5-7 days.

• Consider non invasive ventilation (NIV): It should be considered as the first mode of ventilation in patients of COPD with acute respiratory failure in absence of any absolute contraindication.

• In every case : Careful monitoring of the fluid balance. Low molecular weight heparin should be used for thrombo-prophylaxis

• Prompt identification and treatment of co-existing conditions such as heart failure, pulmonary embolism etc.

• Early initiation of maintenance therapy with long-acting bronchodilators (if possible before hospital discharge).

• Appropriate measures for prevention of exacerbation.

Indication for Invasive Ventilation :

- • Inability to tolerate no-invasive ventilation
- • In patients of post-respiratory/cardiac arrest
- • Altered sensorium, restlessness or agitation which cannot be adequately controlled with sedatives
- • Persistent vomiting or aspiration
- • Presence of hemodynamic instability without any response to fluids/vasopressors
- • Severe supraventricular/ventricular arrhythmia

COPD and Comorbidities[9]:

COPD is often associated with some chronic diseases (comorbidities) which may be significantly related to the outcome, health status, and prognosis of such patients. Management of COPD patients with chronic diseases is no different from the usual protocol, however these comorbidities must be treated simultaneously. Cardiovascular diseases comprises major portion of all comorbidities in COPD. Lung cancer is not very uncommon in patients of COPD and it is associated with increase in adverse outcome and mortality. Osteoporosis and psychiatric disorders such as depression and anxiety are common and often under-diagnosed, and their presence is often associated with poorer prognosis. Gastroesophageal reflux (GERD) is a common precipitating factor for exacerbations.

COVID -19 and COPD :

Stable COPD patients having a new respiratory symptom or worsening of the existing symptoms, presence of fever, or any COVID-19 related symptoms, should always be evaluated promptly to exclude SARS-CoV-2, irrespective of the severity of symptoms. Restriction of spirometry should be considered during the rapid surge in COVID-19 cases in the community. It should only be performed in selected cases for diagnosis, and/or assessment of lung function needed before elective surgery or interventional procedures. Patient's education regarding the COVID-19 and its management is of paramount importance.

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