Review Article

Chronic Obstructive Pulmonary Disease (COPD)

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Chronic obstructive pulmonary disease (COPD) is a common disease with high global morbidity and mortality. COPD involves accelerated ageing of the lungs and an abnormal repair mechanism that might be driven by oxidative stress. Acute exacerbations, which are mainly triggered by viral or bacterial infections, are important as they are linked to a poor prognosis. The mainstay of the management of stable disease is the use of inhaled long-acting bronchodilators, whereas corticosteroids are beneficial primarily in patients who have coexisting features of asthma, such as eosinophilic inflammation and more reversibility of airway obstruction. Apart from smoking cessation, no treatments reduce disease progression.

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Chronic Obstructive Pulmonary Disease (COPD) is currently the fourth leading cause of death in the worldbut is projected to be the 3rd leading cause of death by 2020[1]. Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population[2].

Epidemiology :

COPD affects more than 400 million people worldwide. The reported prevalence of COPD is highly variable ranging from 0.2% in Japan to 37% in the United States. The prevalence of COPD in India according to INSEARCH (Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults) studies was 3.67% (4.46 and 2.86% among males and females, respectively). In India about more than 3 crore population suffering from COPD. In India, COPD causes about 500,000 deaths per year[3].

Definition :

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases[4]. The chronic airflow limitation that is characteristic of COPD is caused by a mixture of small airways disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema).

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Pathogenesis — Inflammation is present in the lungs, particularly the small airways, of all people who smoke. Besides inflammation, two other processes are involved in the pathogenesis of COPD – an imbalance between proteases and antiproteases and an imbalance between oxidants and antioxidants (oxidative stress) in the lungs..

This amplified response may result in mucous hypersecretion (chronic bronchitis), tissue destruction (emphysema), and disruption of normal repair and defence mechanisms causing small airway inflammation and fibrosis (bronchiolitis)(Figs 1&2).

Risk factor for COPD — Hithertomost of the studies on COPD have primarily focused on smoking asa risk factor[5]. Smoking was established as a causative risk factor for COPD by the findings of Fletcher and Peto's 8-year prospective study of 792 men, and the larger and longer Framingham cohort offspring study confirmed these results[6]. More evidence is emerging to suggest that other risk factors are also important for disease.

Other Risk Factors :

Indoor air pollution /Biomass fuel exposure — Biomass fuels, wood smoke, charcoal, crops, dry plants,

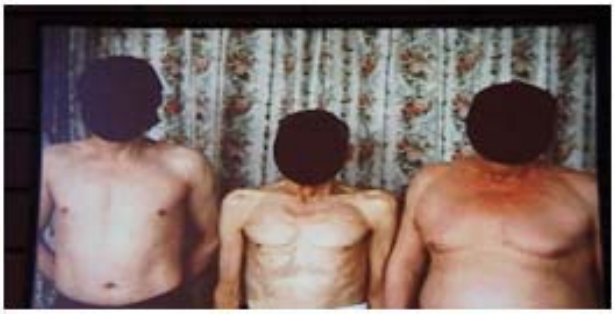

Fig 1 — Showing Morphology of COPD and Asthma Patients

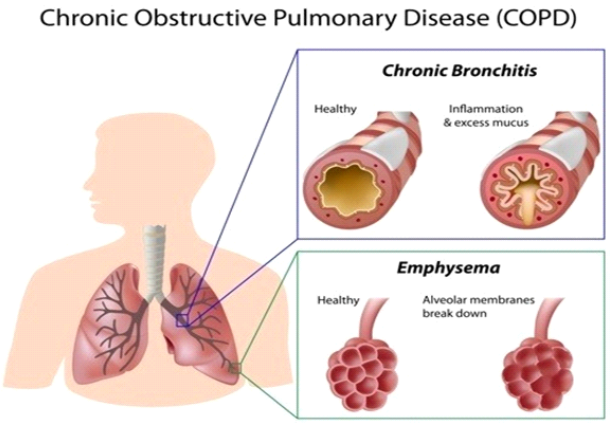

Fig 2 — Pathogenesis of Chronic Bronchitis and Emphysema of COPD patients

and dung are being used for cooking in developing countries. Biomass fuel still continues to be used in about 50% of homes worldwide. It is estimated that 3 billion people are exposed to indoor smoke from the burning of biomass fuel and are at risk for its adverse respiratory effects[7].

Outdoor air pollution — The association between high concentrations of outdoor air pollutants and COPD exacerbations and worsening of pre-existing COPD is supported by strong evidence.

Occupational exposures — Occupational exposure to vapours, gases, dusts or fumes is associated with the development of COPD.

Genetic factors — The genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin (AATD), a major circulating inhibitor of serine proteases. Genetics[8,9,10] together with environmental factors could influence this susceptibility. Single genes, such as the gene encoding matrix metalloproteinase 12 (*MMP-12*) and glutathione *S*-transferase have been related to a decline in lung function[11].

Age and sex —Age is often listed as a risk factor for COPD. Advancing age more than 40 years are prone to COPD because of aging of the airways and parenchyma .In the past reported that COPD prevalence and mortality are greater among men than women, but more recent data from developed countries has reported that the prevalence of COPD is now almost equal in men and women, probably reflecting the changing patterns of tobacco smoking .

Lung growth and development — Any factor that affects lung growth during gestation and childhood has the potential risk of developing COPD like low birth weight and smoking.

Socioeconomic status — Poverty is consistently associated with airflow obstructionand lower socioeconomic status is associated with high risk of COPD[12,13].

Asthma and airway hyper-reactivity — Asthma may be a risk factor for the development of chronic airflow limitation and COPD.

Chronic bronchitis — Presence of chronic bronchitis has been associated with an increased likelihood of developing COPD

Respiratory Infections — severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood. Tuberculosis has also been identified as a risk factor for COPD.Itis both a differential diagnosis for COPD and a potential comorbidity[14].

Symptoms :

COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, a history of recurrent lower respiratory tract infections and/or a history of exposure to risk factors for the disease

Diagnosis :

COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis in this clinical context[15]; the presence of a post-bronchodilator FEV1/ FVC<0.70 confirms the presence of persistent airflow limitation and thus of COPD in patients with appropriate symptoms and significant exposures to noxious stimuli. Spirometry is the most reproducible and objective measurement of airflow limitation. It is a noninvasive and readily available test.

Assessment :

The goals of COPD assessment are to determine the level of airflow limitation, its impact on the patient's health status and the risk of future events (such as exacerbations, hospital admissions or death), in order to, eventually, guide therapy. To achieve these goals, COPD assessment must consider the following aspects of the disease separately:

- The presence and severity of the spirometric abnormality
- Current nature and magnitude of the patient's symptoms
- History of moderate and severe exacerbations and future risk
- Presence of comorbidities

Classification of severity (Tables 1&2).

Differential Diagnosis :

Major differential diagnosis is asthma. In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques (Table 3).

Table 1 — Gold Guideline 2019

In patient with FEV1/FVC <0.70		
GOLD1	MILD	FEV1 > 80%predicted
GOLD2	MODERATE	>50%FEV1<80% predicted
GOLD3	SEVERE	>30%FEV1<50% predicted
GOLD4	VERY SEVERE	<30% predicted

Table 2 — *Classification of severity according to Indian Guideline*[15]

Severity	Post-bronchodilator Fev1 % Predicted	mMRC Grade	Exacer-bation frequency	Complication: PO2<60mmHg Pco2>50mmHg Haemotocrit>55% Cor-pulmonale
Mild	≥80%	<2	<2	No
Moderate	50%-79%	≥2	<2	No
Severe	<50%	≥2	≥2	Yes

Table 3 — *Differential Diagnosis of COPD.*

Differential diagnosis	Suggestive symptoms
Asthma	Onset in childhood,variable symptoms day by day,allergic rhinitis and/or eczema present, family history of asthma
Congestive heart failure	Chest Xray showed dilated heart, pulmonary edema, PFT indicate volume restriction
Bronchiectasis	Copious amount of sputum, associated with bacterial infection etc.
Pulmonary Tuberculosis	Onset all ages Chest X ray shows lung infiltrates, microbiological confirmation
Obliterative bronchiolitis	Onset at younger age, nonsmoker may have history of rheumatoid arthritis or fume exposure, CT on expiration shows hypodens area
Diffuse pan bronchiolitis	Most commonly seen in male non smoker, history of sinusitis in all patients
Post tubercular sequelae	History of tuberculosis, younger age
Topical pulmonary eosinophilia	Short Duration of clinical history, peripheral eosinophilia etc

Composite Assessment of COPD :

The impact of COPD on an individual patient combines the symptomatic assessment with the patient's spirometric classification and/or risk of exacerbations.[16] In the revised assessment scheme patients should undergo spirometry to determine the severity of airflow limitation (ie, spirometric grade) (Table 1). They should also undergo assessment of either dyspnea using mMRC(modified Medical research council) or symptoms using COPD assessment tool (CAT). Finally, their history of moderate and severe exacerbations (including prior hospitalizations) should be recorded. Groups A to D provides information regarding symptom burden and risk of exacerbation which can be used to guide therapy (Table 4).

Goals of management of COPD :

(1) Reduce symptoms

Table 4 — *Group of COPD*

≥2 moderate exacerbations or ≥1 leading to hospitalization	Group C	Group D
0 or 1 moderate exacerbations not leading to hospitalization	Group A MmRC 0-1 CAT<10	Group B MmRC ≥2 CAT ≥10

(2) Reduce risk of exacerbation

(3) Identify and reduce risk factors

(A) Pharmacological therapy for stable COPD

Pharmacological therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and health status[17].

(1) Bronchodilators

A. Beta2-agonists (Short-acting beta$_2$-agonists : Salbutamol/levosalbutamolLong-acting beta$_2$-agonists : Salmeterol / Formoterol Ultra long acting beta 2 agonists : Indacaterol

B. AnticholinergicsShort-acting anticholinergics : IpratropiumLong-acting anticholinergics : Tiotropium/ Glycopyrronium

C. Methylxanthines

(2) Inhaled corticosteroids (ICS)

(3) Oral glucocorticoids

(4) Phosphodiesterase-4 (PDE4) inhibitors-Roflumilast

(5) Antibiotics

(6) Mucolytic (mucokinetics, mucoregulators) and antioxidant agents (NAC, carbocysteine)

Management of Group A :

All Group A patients should be offered bronchodilator treatment based on its effect on breathlessness. This can be either a short- or a long-acting bronchodilator.

Management of Group B :

Initial therapy should consist of a long acting bronchodilator. Long-acting inhaled bronchodilators are superior to short-acting bronchodilators taken as needed ie, *pro re nata* (prn) and are therefore recommended.

There is no evidence to recommend one class of long-acting bronchodilators over another for initial relief of symptoms in this group of patients. In the individual patient, the choice should depend on the patient's perception of symptom relief. For patients with severe breathlessness initial therapy with two bronchodilators may be considered.

Management of Group C :

Initial therapy should consist of a single long acting bronchodilator. In two head-to-head comparisonsthe tested LAMA was superior to the LABA regarding exacerbation

prevention therefore starting therapy with a LAMA in this group.

Management of Group D :

In general, therapy can be started with a LAMA as it has effects on both breathlessness and exacerbations.

For patients with more severe symptoms especially driven by greater dyspnea and/or exercise limitation, LAMA/LABA may be chosen as initial treatment based on studies with patient reported outcomes as the primary endpoint where LABA/LAMA combinations showed superior results compared to the single substances .An advantage of LABA/LAMA over LAMA for exacerbation prevention has not been consistently demonstrated, so the decision to use LABA/LAMA as initial treatment should be guided by the level of symptoms. In some patients, initial therapy with LABA/ICS may be the first choice; this treatment has the greatest likelihood of reducing exacerbations in patients with blood eosinophil counts e" 300 cells/µL. LABA/ICS may also be first choice in COPD patients with a history of asthma. ICS may cause side effects such as pneumoniaso should be used as initial therapy only after the possible clinical benefits versus risks have been considered.

The strategy for management of stable COPD is shown in Table 5 is in very simple way according toIndian Guidelines for diagnosis and management of chronic obstructive pulmonary disease: Joint Indian Chest Society(ICS)/ National College of Chest Physician (NCCP) (Table 5).

(B) Non Pharmacology Management of COPD

1. Education and Self Management
2. Smoking Cessation
3. Control of air pollution
4. Switching to clean fuel for cooking –LPG poor people can take advantage of "UJJWALA YOJNA".
5. Vaccination
6. Oxygen therapy
7. Pulmonary rehabilitations including yoga and pranayama

(C) Bronchoscopy guided management

(D) Surgery

8. Lung volume reduction surgery
9. Lung transplantation

Table 5 — *Management of Stable COPD*

Category	First Choice	Alternative Choice	Add-on Therapy
Mild	SABA or SAMA	Methylxanthines	_____
Moderate	LAMA	LABA	
Severe	ICS plus LABA	LAMA plus LAMA	ICS plus LABA or add Methylxanthines

Treatment of Stable COPD :

Non-pharmacological :

(1) Education and Self Management

(2) Smoking Cessation

Smoking cessation has the greatest capacity to influence the natural history of COPD. If effective resources and time are dedicated to smoking cessation, long-term quit success rates of up to 25% can be achieved[18]. Besides individual approaches to smoking cessation, legislative smoking bans are effective in increasing quit rates and reducing harm from second-hand smoke exposure.A five-stepprogram for intervention

- ASK Tobacco use status is queried and documented at every clinic visit
- ADVICE strong and personalized manner urge every tobacco user to quit
- ASSESS Ask every tobacco user if he or she willing to quit at this time
- ASSIST Aid the patient in quitting
- ARRANGE Schedule follow up contact

(3) Vaccinations –

Influenza vaccination can reduce serious illness (such as lower respiratory tract infections requiring hospitalization) and death in COPD patients[19].

Pneumococcal vaccinations, PCV13 and PPSV23, are recommended for all patients ≥65 years of age .PCV 13 Followed by PPSV23 at the interval of one year. The pneumococcal polysaccharide vaccine 23 (PPSV23) is also recommended for younger COPD patients with significant comorbid conditions including chronic heart or lung disease.

(4) Pulmonary Rehabilitation including yoga and pranayam–

Pulmonary rehabilitation is defined as acomprehensive intervention based on thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, self-management intervention aiming at behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors[20].

Supervised exercise training at least twice weekly is recommended, and this can include any regimen from endurance training, interval training, resistance/strength training; upper and lower limbs ideally should be included as well as walking exercise; flexibility, inspiratory muscle training[21] and neuromuscular electrical stimulation can also be incorporated. Yoga and pranayama training has a positive effect on improving lung function and exercise capacity and could be used as an adjunct pulmonary

rehabilitation program in COPD patients[22,23].

(5) Oxygen Therapy – The long-term administration of oxygen (>15 hours per day) to patients with chronic respiratory failure has been shown to increase survival in patients with severe resting hypoxemia[24].

Bronchoscopy Guided Management :

Endoscopic lung volume reduction (ELVR) is an emerging management for advanced COPD. Valve implants, coil implants, biological LVR, Bronchial thermal Vapour ablation and airway stents are used to induce lung deflation with the ultimate goal of improving respiratory mechanics and chronic dyspnea[25].

Surgical Interventions :

VRS Volume reduction surgery is a surgical procedure in which parts of the lungs are resected to reduce hyperinflation, making respiratory muscles more effective pressure generators by improving their mechanical efficiency. LVRS increases the elastic recoil pressure of the lung and thus improves expiratory flow rates and reduces exacerbations. LVRS has been demonstrated to result in higher mortality than medical management in severe emphysema patients with an FEV1 ≤20% predicted and either homogeneous emphysema high resolution computed tomography or a DLCO of d" 20% of predicted.[26]

Bullectomy — Bullectomy is an older surgical procedure for bullous emphysema. Removal of a large bulla that does not contribute to gas exchange and is, or has been, responsible for complications decompresses the adjacent lung parenchyma. Pulmonary hypertension, hypercapnia and severe emphysema are not absolute contraindications for bullectomy. [27]

Lung transplantation — In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve health status and functional capacity but not prolong survival. Over 70% of lung transplants conducted in COPD patients are double lung transplants; the remainder are single lung transplants[28]. Bilateral lung transplantation has been reported to provide longer survival than single lung transplantation in COPD patients, especially those <60 years

COPD and Systemic Effects :

Recently, besides the typical pulmonary pathology of COPD (ie, chronic bronchitis and emphysema), several effects occurring outside the lungs often associated with extra pulmonary abnormalities and have been described as the so called systemic effects of COPD[29].

Malnutrition contributes to respiratory muscle weakness resulting in increased frequency of hospitalization, cor pulmonale and increased mortality[30,31].

COPD is associated with many comorbid diseases, which may be pulmonary or extrapulmonary (coronary vascular disease, congestive heart failure, diabetes mellitus, metabolic syndrome, obstructive sleep apnea, skeletal muscle dysfunction, cachexia, osteoporosis, depression, lung cancer[32-34]. Comorbid diseases in COPD are independently associated with a higher risk of hospitalization and mortality.

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