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Understanding COPD and Its Effective Treatment Strategies

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Introduction

Chronic obstructive pulmonary disease (COPD) is common and is mostly due to smoking. From the clinical perspective, it is a combination of chronic bronchitis and emphysema. Productive cough for 3 or more months for at least 2 consecutive years is labelled as chronic bronchitis. In emphysema there is abnormal enlargement of the air spaces distal to the terminal bronchioles along with destruction of their walls. Though COPD cannot be cured, effective treatment strategies can alleviate symptoms, improve the quality-of-life, and also reduce the mortality risk. COPD prevalence in India (2021) is 7.4%.

Definition

- COPD is a disease state characterised by 'non fully reversible' or 'fixed' airflow obstruction. Airflow limitation is the hallmark of COPD. This has been highlighted in the GOLD classification which focuses on the decrease in FEV_1.
- There is minimal or no reversibility with bronchodilators.
- There is progressive airflow limitation with an abnormal inflammatory response of the lung to noxious substances (pollutants) and gases.
- There is minimal variability in day-to-day symptoms.
- For all practical purposes, the vicious triad of COPD consists of asthma, chronic bronchitis, and emphysema. Therefore, any patient presenting in the OPD/clinic with dyspnoea, chronic cough, or sputum production and/or a history of exposure to the various risk factors should be considered as having COPD.

Aetiology and Risk Factors

- More than 90% cases are smokers with history of >20 packs per year
- COPD is increasing in frequency globally, more so in many developing countries, due to the high incidence of outdoor and indoor air pollution: smoking, environmental and occupational pollution from dust, particulate matter, chemicals, and use of biomass fuel for cooking and heating
- Longstanding asthma
- Recurrent infections of the respiratory tract
- Genetic inheritance: Alpha1-antritrypsin deficiency (AATD) – causing emphysema
- Low socio-economic status
- Older age group and female gender have increased susceptibility

Pathophysiology

- Mucous gland hyperplasia – particularly in the larger airways, with mucus hypersecretion leading to chronic productive cough. Mucosal damage from smoke also causes:
  - Squamous metaplasia – Normal ciliated columnar epithelium is replaced by squamous epithelium.
  - Loss of ciliary function – Causing impairment of the normal functioning of the mucociliary escalator, thus causing chronic productive cough.
- Chronic inflammation and fibrosis of small airways – CD8 lymphocyte, macrophage, and neutrophil infiltration occurs with release of pro-inflammatory cytokines. Moreover, airway inflammation is perpetuated by recurrent infections.
- Emphysema – is caused by alveolar wall destruction which leads to irreversible enlargement of the air spaces distal to the terminal bronchiole, i.e., the acinus, causing loss of elastic recoil and thus hyperinflated lungs.
- Thickened pulmonary arteriolar wall and remodelling – occurs as a result of hypoxia. This causes increased pulmonary vascular resistance, pulmonary hypertension, and impaired gas exchange.
- Most common bacterial pathogens seen in COPD

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exacerbations are: *Streptococcus pneumoniae, Haemophilus influenzae, Moxarella catarrhalis*. In case of any patient not showing expected improvement within 3 - 7 days of appropriate empirical antibiotic therapy, it is advisable to get a sputum culture and sensitivity test done.

Clinical features

- Dyspnoea
- Productive cough
- Decreased exercise tolerance
- Wheeze

Signs of COPD

Significant airflow obstruction could be present before the patient becomes aware of it.

- Raised respiratory rate (RR).
- Barrel chest (Hyperexpanded).
- Expiratory time is prolonged to >5 sec., along with pursed lip breathing.
- Accessory muscles of respiration are in use.
- Quiet breath sounds – especially in the lung apices, with or without wheeze.
- Quiet heart sounds – due to overlying hyperinflated lung.
- Basal crepitations may be heard.
- Features of Cor Pulmonale and CO_2 retention:
  - Raised JVP
  - Ankle oedema
  - Warm peripheries
  - Bounding pulse
  - Plethoric conjunctivae
  - Polycythaemia
  - Flapping tremor – if CO_2 is acutely raised.

Investigations

- Pulmonary function test (PFT) with reversibility; or instant assessment with a Mini Peak Flow Meter – The quickest, easiest, and cheapest test to perform in the clinic in all patients above 5 years of age.
  - Obstructive spirometry and flow volume loops.
  - FEV_1 is reduced to <80% predicted. FEV_1 can assess the progression of COPD, but not the degree of dyspnoea.
  - $FEV_1/FVC < 0.7$
  - Minimal reversibility with bronchodilator (<10 - 15%) and steroids.
  - Total lung volume, FRC, and residual volume are increased because of emphysema, air trapping, and loss of elastic recoil.
  - Reduced TLCO and kCO due to decrease in surface area available for gas diffuse as a result of emphysema.
- Chest X-ray (PA View)
  - To rule-out any other lung conditions – cancer, bronchiectasis.
  - 'Black lung sign' – lung fields are hyperinflated with attenuation of peripheral vasculature and more than 7 posterior ribs are visible.
  - Ribs appear more horizontal.
  - Bullae may be seen, usually in the apices. Due to absence of lung markings, large bullae could be mistaken for a pneumothorax. An HRCT chest will clear any doubts.
- Blood tests
  - CBC – to rule-out anaemia.
  - Alpha-1-antitrypsin (AAT) levels – to rule-out a genetic cause.
  - CRP – could be raised in COPD, but falls after treatment with steroids.

Diagnosis

- Clinical clues – H/o smoking, progressive dyspnoea, and irreversible airflow obstruction on spirometry.
- D/D – Asthma – Responsive to both bronchodilators and steroids (Table I).
- Breathlessness – Persistent and progressive in COPD, but variable in asthma.
- Chronic productive cough – Common in COPD, but uncommon in asthma.
- Diurnal/day-to-day variability of symptoms (night-time waking with SOB/wheeze) is more in asthma.

Severity of COPD

- Mild (Stage I): FEV_1 (forced expiratory volume in 1 second) is >80% of predicted and FEV_1/FVC (forced

Table I: Differentiating characteristics of COPD and Asthma

Characteristics	Chronic Obstructive Pulmonary Disease	Asthma
Age	• >35 years	• <20 years
Symptom pattern	• Chronic cough and sputum precedes onset of dyspnoea, regardless of triggers	• Episodes related to triggers such as exercise, emotions including laughter, dust or exposure to allergens
	• Good and bad days but daily symptoms and exertional dyspnoea always present	• Symptoms worsen during night or early morning
Lung function	• Persistent airflow limitation	• Variable airflow limitation
Time course	• Symptoms gradually worsen over time	• Seasonal variation in symptoms present
	• Limited relief can be provided by rapid-acting bronchodilator treatment	• Demonstrates immediate response to bronchodilator or to inhaled corticosteroid over weeks

vital capacity) <0.7. These patients may or may not be symptomatic (cough or sputum).

- Moderate (Stage II): FEV_1 is 50 - 80% of predicted and FEV_1/FVC <0.7. FRC is increased and TLCO is decreased. These patients could be symptomatic (cough, sputum, SOB).
- Severe (Stage III): FEV_1 is 30 - 50% of predicted and FEV_1/FVC <0.7. TLCO is reduced. Hypoxia is present with signs of cor pulmonale. Patient is symptomatic and may need hospitalisation.
- Very Severe (Stage IV): FEV_1 is <30% of predicted and FEV_1/FVC <0.7.

Pharmacological Management

For COPD patients who are clinically stable, the main aim is to relieve symptoms and prevent or reduce exacerbations. Treatment in COPD should be increased gradually and stepwise. All exacerbations of COPD will need extra medication and support.

Routinely used drugs in bronchial asthma and COPD

- Bronchodilators
  - Sympathomimetics –
    - Salbutamol (SABA)
    - Levosalbutamol (SABA)
    - Terbutaline (SABA)
    - Salmeterol (LABA)
    - Formoterol (LABA)
    - Arformoterol (LABA)
    - Indacaterol (LABA)
  - Methylxanthines –
    - Theophylline
    - Aminophylline
    - Choline theophyllinate
    - Hydroxyethyl theophylline
    - Doxophylline
    - Roflumilast (PDE_4 inhibitor)
  - Anticholinergics –
    - Ipratropium bromide (Bronchodilator)
    - Tiotropium bromide (LAMA)
    - Glycopyrrolate (LAMA)
    - Leukotriene antagonists
  - Montelukast
  - Zafirlukast
    - Mast cell stabilizers
  - Sodium cromoglycate
  - Ketotifen
- Corticosteroids
  - Inhalational (ICS) –
    - Beclomethasone dipropionate
    - Budesonide
    - Fluticasone propionate
    - Flunisolide
    - Ciclesonide
  - Systemic (Oral/Intravenous) –
    - Hydrocortisone
    - Prednisolone
    - Other glucocorticoids
- Anti-IgE antibody
  - Omalizumab

For all practical purposes, drugs are divided into 'Controllers' and 'Relievers':

1. CONTROLLERS (Preventers/Prophylactic drugs)
    - Inhaled Glucocorticoids:
        - Beclomethasone, Budesonide, Fluticasone
    - Long-acting inhaled β-2 agonists (LABA):
        - Salmeterol, Formoterol
    - Theophylline: Sustained-release formulation
    - Leukotriene Modifiers:
        - Montelukast, Zafirlukast, Pranlukast, Zyleutin
    - Cromones:
        - Sodium Cromoglycate, Nedocromil sodium
    - Long-acting oral β-2 agonists:
        - Salbutamol, Terbutaline
    - Oral/Systemic Glucocorticosteroids
2. RELIEVERS (which relieve bronchoconstriction)
    - Rapid/short-acting inhaled β-2 agonist (SABA) drugs: Salbutamol, Terbutaline, Fenoterol
    - Inhaled anticholinergics:
        - Ipratropium bromide, Oxitropium
    - Short-acting oral β-2 agonists:
        - Salbutamol, Terbutaline
    - Short-acting methylxanthines:
        - Theophylline, Aminophylline
    - Systemic glucocorticosteroids
    - Others:
        - Epinephrine
        - Adrenaline

Bronchodilators

- Simple PFT may not show significant reversibility of FEV_1 with bronchodilator. However, in the long-term, bronchodilators do provide therapeutic benefit as evidenced by decreasing the dyspnoea and thereby reducing the hyperinflation of the chest.
- First, give a short-acting β-2 agonist (SABA) for symptom relief.
- If no relief, give a short-acting β-2 agonist with with a short-acting anti-cholinergic.
- If patient is still symptomatic, give a regular long-acting bronchodilator with/without an anti-cholinergic.
- Oral methylxanthines – Theophylline – can be continued as maintenance therapy along with inhaled bronchodilators and inhaled steroids – to be continued only if symptoms improve. May have an anti-inflammatory effect but watch for toxicity in the elderly.
- When used with a spacer device, inhaled therapy provides sufficient bronchodilator doses in most patients. Patient's inhaler technique should be checked once by the attending physician.
- Nebulisation – is to be used in patients who are incapable of using inhalers. Only those who show clinical benefit from nebuliser therapy may continue with its long-term use at home with a combination of salbutamol and ipratropium. Also, nebulisation is known to have a placebo effect too!

Inhaled corticosteroids (ICS)

- All patients with FEV_1 <60% predicted with h/o >2 exacerbations every year treated with antibiotics and/or oral steroids, should be prescribed inhaled corticosteroids (ICS). Ideally used in combination with a bronchodilator, inhaled steroids do reduce the severity and frequency of exacerbation in severe COPD, but have not helped in slowing the decline in lung function.
- Patients should be made aware and warned about steroid side-effects.

Inhaled combinations of bronchodilators and steroids to manage COPD

These are available as metered dose inhalers:-

1. Single-inhaler dual therapy (SIDT) combination containing –
    - ICS (inhaled corticosteroid) + LABA (long-acting β-2 agonist), or LABA + LAMA (long-acting muscarinic receptor antagonist). The combination of ICS + LABA contains Formoterol fumarate 6 mcg + Budesonide 100/200/400 mcg. The combination of LABA + LAMA contains Formoterol fumarate 12 mcg + Glycopyrronium bromide 25 mcg. Glycopyrronium bromide – also known as Glucopyrrolate – blocks the muscarinic acetylcholine receptors in the bronchial smooth muscles with its action lasting up to 24 hours, thereby providing sustained bronchodilatation. These combination inhalers are indicated for maintenance treatment of airflow obstruction in COPD – including chronic bronchitis and emphysema.

2. Single-inhaler triple therapy (SITT) combination – for patients who remain uncontrolled, leading to moderate-to-severe exacerbations. The SITT is a newer development and has shown benefits in effectively preventing exacerbations due to improved efficacy, reduced inhaler use, and enhanced compliance. This combination inhaler contains –

    - LABA + LAMA + ICS – Indicated for maintenance treatment to prevent and relieve symptoms associated with COPD. The three drugs being used are Fluticasone furoate 100 mcg + Umeclidinium 62.5 mcg + Vilanterol 25 mcg. The mechanism of action of these 3 drugs is as follows:

        - Vilanterol (LABA) – Causes smooth muscle relaxation in the airways by binding to β-2 adrenergic receptors, leading to bronchodilatation and increased airflow. It also boosts the anti-inflammatory properties of corticosteroids.
        - Fluticasone furoate (ICS) – Inhibits the inflammatory cell response and cytokine production leading to a reduction in airway inflammation, thus helping prevent exacerbations associated with chronic inflammation. Also, corticosteroids elevate the expression of β-2 receptors and protect them from downregulation when exposed to LABAs.
        - Umeclidinium (LAMA) – Prevents smooth muscle constriction in the airways by blocking acetylcholine receptors. Apart from preventing bronchoconstriction, this action also widens the airways.

Even then, acute exacerbations of COPD (AECOPD) usually require hospitalisation.

Oral steroids

- Needed in cases of severe COPD exacerbation. In such cases, since it is usually difficult to discontinue oral steroids, try to taper down the dose to the lowest possible.
- Danger of osteopenia and osteoporosis should be avoided by suitable prophylaxis with calcium and vitamin D supplementation.

Oxygen – short-term therapy via cylinder or long-term via oxygen concentrator for:

- Patients in respiratory failure (PaO_2 <7.3 kPa or PaO_2 of 7.3 - 8 kPa) with features of secondary polycythaemia, pulmonary hypertension, or peripheral oedema – need to be given oxygen for at least 15 hours daily (including sleep time).
- Low flow oxygen (2 - 4 lit./min) via nasal prongs is generally quite adequate.

Vaccination

- Seasonal influenza vaccine – administered annually.
- Both types of pneumococcal vaccines – once in 5 years: PPSV23 (pneumonia polysaccharide vaccine) and PCV13 (pneumonia conjugate vaccine).

Antibiotics – No role of prophylaxis.

Mucolytics

- Helpful in patients with chronic productive cough and have shown reductions in COPD exacerbations.
- Reduce sputum viscosity and facilitate expectoration.
- Give for 4-weeks and continue if there is improvement.

Asthma-COPD Overlap Syndrome (ACOS)

Patients showing persistent airflow limitation plus one or more features of asthma (wheezing, bronchial hyperresponsiveness, or sputum eosinophilia) are labelled as ACO. Though uncommon, it worsens symptoms, exacerbations and quality-of-life (QoL), and increases the use of rescue drugs.

Eosinophilic ACO responds better to ICS + LABA than LABA alone, reducing hospitalisation and improving mortality outcomes. GINA (2023) advocates ICS + LABA as first-line therapy for most ACO patients.

Summary of treatment

- Any patient in acute exacerbation (i.e., too breathless to talk + respiratory rate >24/min + SpO_2 <90%) should be referred for emergency management to a hospital.
- Primary treatment: Quit Smoking. After stabilizing the acute condition with appropriate measures, refer the patient to a Tobacco De-addiction Centre.
- If there is shortness of breath (SOB) only on strenuous physical exertion without any previous h/o hospitalisation, prescribe MDI Salbutamol (ASTHALIN) – 2 puffs SOS/QID.
- If there is shortness of breath (SOB) even at rest or on mild activity without any previous h/o hospitalisation, prescribe:

- Short-acting β-Agonist (SABA) – MDI Salbutamol (ASTHALIN) – 2 puffs SOS/QID.
- Long-acting β-Agonist (LABA) Salmeterol + LAMA (Tiotropium bromide).

- If there is history of any previous hospitalisation, start the following MDIs:
  - Salbutamol – 2 puffs SOS/QID
  - LABA + LAMA + ICS (Fluticasone or Budesonide)
- In a case of exacerbation, add an antibiotic, preferably Azithromycin 500 mg OD x 5 days.
- For cough with expectoration – Syp. Bromhexine 10 mL TDS.
- For dry cough – Syp. Noscapine.
- May add bronchodilator Tab. Doxofylline 400 mg BDS or Tab. Acebrophylline 100/200 mg BDS.
- If there is no relief or improvement, refer to the Medicine Emergency of the nearest hospital.

Non-pharmacological management

For patients who are clinically stable:

1. Cessation of smoking
2. Education
3. Diet
4. Pulmonary rehabilitation
5. Psychological and social support

- Cessation of smoking
  - Decreases the smoking-related decline in lung function.
  - Nicotine replacement therapy may be tried to aid smoking cessation.
- Education
  - Improves the will to quit smoking and manage one's illness.
- Pulmonary rehabilitation – Is initiated on an OPD basis to reduce recurrent hospital admissions, improve exercise tolerance and quality-of-life. Patients with COPD tend to have reduced muscle mass in the lower limbs as compared with healthy same-age controls. Reduction in muscle mass is, by itself, reflective of the severe nature of the COPD and its systemic effects.
  - To improve muscle mass, a graded exercise programme is initiated.
  - Patient is guided and educated about lifestyle modifications and breathing techniques are taught.
- Diet
  - To minimise respiratory effort, obese patients are advised and guided to lose weight.
  - Nutritional supplementation – Very breathless patients could be in a catabolic state due to a low calorific intake. This may cause the BMI to fall, which thereby causes a deterioration in the pulmonary functions, reduction in diaphragm mass, fall in exercise capacity, leading to increased mortality risk. Improving muscle mass and body weight should be a top priority – achieved by a well-balanced diet and nutritional supplementation.
- Psychological and social support
  - Patients with COPD are seen to show remarkable improvement with practical support and a psychologically encouraging and cheerful environment in the home and day care centre.
  - Care givers should make special efforts to keep the patients free from any form of mental stress, anxiety, and depression.

An Approach to COPD in the clinic

- Establish diagnosis and assess severity – PFT, CXR.
- Rule-out other causes for symptoms – anaemia, pulmonary embolism, ILD, pneumothorax, large emphysematous bullae, arrhythmia, heart failure, thyroid dysfunction, mental depression.
- Counsel the patient to quit smoking.
- Review the ongoing treatment of COPD – optimise the doses of bronchodilators and/or inhaled corticosteroids.
- Assess for the need to nebulise – with SABA/LABA/ICS.
- Check SpO_2 and go for ABG if SpO_2 <92% – assess whether LTOT (long-term oxygen therapy) is needed.
- Check vaccination status.
- Decide if the patient needs pulmonary rehabilitation.

Steroid trial to help distinguish asthma from COPD

- Needed only if the diagnosis is unclear.
- Method: Measure FEV_1 and slow VC (vital capacity) before and after:–

- Either a high dose ICS for 6 - 8 weeks,
- Or a 2-week course of oral prednisolone – 30 mg/day.

>15% increase in FEV_1 implies steroid reversibility – therefore patient is likely to be an asthmatic.

>15% increase in slow VC points to markedly reduced air-trapping – s/o significant asthma.

Bronchodilator reversibility test to help distinguish asthma from COPD

- Firstly, check the FEV_1. Then administer a SABA (short-acting β-2 agonist) inhaled via a spacer or via a nebulizer. After 15 - 20 minutes of this inhalation, check the FEV_1 again.
- Now subtract the pre-test value from the post-test value and then divide the difference by the pre-test value, and express as a percentage increase from baseline. >15% increase or >200 mL is indicative of bronchodilator reversibility.
- Before going for bronchodilator reversibility testing, avoid short-acting bronchodilator in the preceding 6 hours, a long-acting bronchodilator in the preceding 12 hours, or a long-acting anticholinergic or a sustained release theophylline in the preceding 24 hours.

COPD exacerbations

- Diagnosis is practically clinical.
- Result in mild symptoms in those with relatively preserved lung function.
- Can result in marked morbidity in patients with limited respiratory reserve.
- A large number of patients fail to regain their pre-morbid lung function and/or quality-of-life after an exacerbation.
- Patients who suffer frequent exacerbations, show a more rapid FEV_1 decline than those who have fewer exacerbations.
- Frequency of exacerbations increases with the severity of COPD.
- Exacerbations are more frequent in winter – likely because viruses have a better survival in the cold and people crowd together indoors.

Summary of management of acute exacerbation of COPD

- First assess severity of exacerbation:–
  - Measure RR, SpO_2, FEV_1, BP, pulse for tachycardia.
  - Check for peripheral perfusion, level of consciousness, mental state.
- Exclude a pneumothorax – clinically and/or radiologically.
- In a hypoxic patient, administer controlled oxygen (24 - 35%) via a Venturi facemask – aim should be SaO_2 88 - 92%; also, salbutamol nebulisation.
- Establish an IV line.
- Check ABG.
- Get an ECG done.
- Send requisition for CXR.
- Blood tests: CBC (for WCC), CRP, RBS, KFT (for potassium), etc.
- Optimise volume status.
- If possible, take a short history: to know the patient's normal functional status, e.g., exercise tolerance and need for assistance in day-to-day activities. Check previous hospital notes (for severity of disease; and to find out if previously decisions were taken regarding ventilation or resuscitation.
- Bronchodilator nebulisation – Salbutamol 2.5 - 5 mg + Ipratropium 500 mcg on arrival and 4 - 6 hourly thereafter. Run the nebuliser with air, not oxygen.
- Oxygen therapy to be continued – try to maintain saturations between 80% and 90%.
- ABG to be repeated after 60 minutes to ensure improvement if patient is hypoxic or acidotic. Repeat ABG if there is clinical deterioration.
- Antibiotics may be considered if sputum is purulent, patient has fever, and there are changes in the chest x-ray.
- Systemic steroids – Prednisolone 30 mg/day for 1 - 2 weeks – may be added in cases of exacerbations who are hospitalised or more breathless.
- IV aminophylline may be considered if patient is not showing improvement with nebulisations.
- Consider intensive care – a consultant-led decision with the patient and family – intensive mechanical ventilation. Document all this in the medical notes in the patient's case file. Also consider resuscitation status.
- Consider NIV (non-invasive ventilation) – pH <7.3, hypoxia, hypercapnia, patient conscious.
- Consider doxapram – an intravenous respiratory

stimulant – if NIV is not available or is not tolerated.

- Consider non-invasive ventilation (NIV) – supports patients who are in exacerbation, conscious, and having respiratory acidosis (pH <7.35), hypoxia, and hypercapnia.
- Intubation in ICU if no response to medication – Consider invasive mechanical ventilation.
- DVT prophylaxis.
- Early mobilization – to prevent muscle wasting.
- Nutritional support.

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