Chronic Obstructive Pulmonary Disease (COPD)

Pathogenesis of COPD : (IHLL)

1- **I**nflammation & fibrosis of the bronchial wall,
2- **H**ypertrophy of the submucosal glands and hypersecretion of mucus

} Both lead to obstruction of airflow & cause : **mismatching of ventilation & perfusion.**

3- **L**oss of alveolar tissue → decreases the surface area for gas exchange.
4- **L**oss of elastic fibers → leads to airway collapse.

Normally *the elastic fibers have 2 functions:*

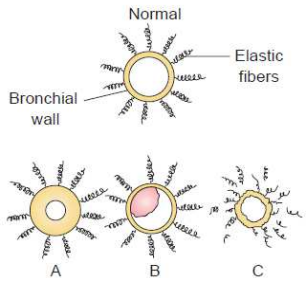
1- Recoil of elastic fibers that were stretched during inspiration provides the force needed to move air out of the lung during expiration.
2- Elastic fibers are attached to the airways,providing radial traction to hold airways open during expiration

In persons with COPD : the loss of elastic fibers causes:

1- Predisposes to airway collapse.
2- Increases air trapping.
3- Impairs the expiratory flow rate.

The term *COPD* encompasses **two** types of obstructive airway disease:

- **Emphysema,** with enlargement of air spaces and destruction of lung tissue.
- **Chronic obstructive bronchitis,** with obstruction of airways.



(Top) Normal bronchial airway with elastic fibers that provide traction and hold the airway open.

(Bottom) Obstruction of the airway caused by :
(**A**) hypertrophy of the bronchial wall,
(**B**) inflammation and hypersecretion of mucus
(**C**) loss of elastic fibers that hold the airway open

Chronic Bronchitis

Definition :

Chronic productive cough of more than 3 months' duration for more than 2 consecutive years .

➔ *Typically,the cough has been present for many years, with a gradual increase in acute exacerbations that produce frankly purulent sputum.*

Types :

1- **Simple bronchitis** → Chronic bronchitis without airflow obstruction.
2- **Chronic obstructive bronchitis**→ chronic bronchitis with airflow obstruction.

Causes :

- It's associated with chronic irritation from **smoking & recurrent infections.**

In chronic bronchitis, **airway obstruction** is caused by :

1- Inflammation of the major and small airways.
2- There is edema and hyperplasia of submucosal glands and excess mucus excretion into the bronchial tree.

Emphysema

Normally, the lung is protected by antiprotease enzymes as : **α1-antitrypsin**

Two recognized causes of emphysema : →

In smokers in whom COPD develops :
- Inadequate antiprotease production and release to neutralize
- Excess protease production

1- Increased elastase production:

- Cigarette smoke stimulate **movement of inflammatory cells into the lungs**, → resulting in **increased release of proteinases as: elastase** (serine elastase from neutrophils / metalloelastase from alveolar macrophages) → that digests elastin resulting in breakdown of elastin and other alveolar wall components.

2- Inherited deficiency of α1-proteinase inhibitor (α1 – antitrypsin):

- Accounts for 1% of all cases of COPD.
- More common in young persons before age of 40 years .
- Smoking & repeated respiratory tract infections, → decrease **α1**-antitrypsin levels→ risk for emphysema .
- Human **α1**-antitrypsin is available for replacement therapy.

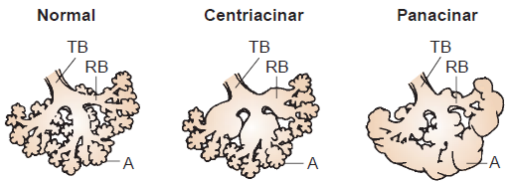
Emphysema is characterized by :

1- **Loss of lung elasticity**
2- **Destruction of the alveolar walls and capillary beds.**
3- **Abnormal enlargement of the air spaces distal to the terminal bronchioles,**
Enlargement of the air spaces leads to → **hyperinflation of the lungs** → produces an increase in (TLC).

There are two commonly recognized types of emphysema:

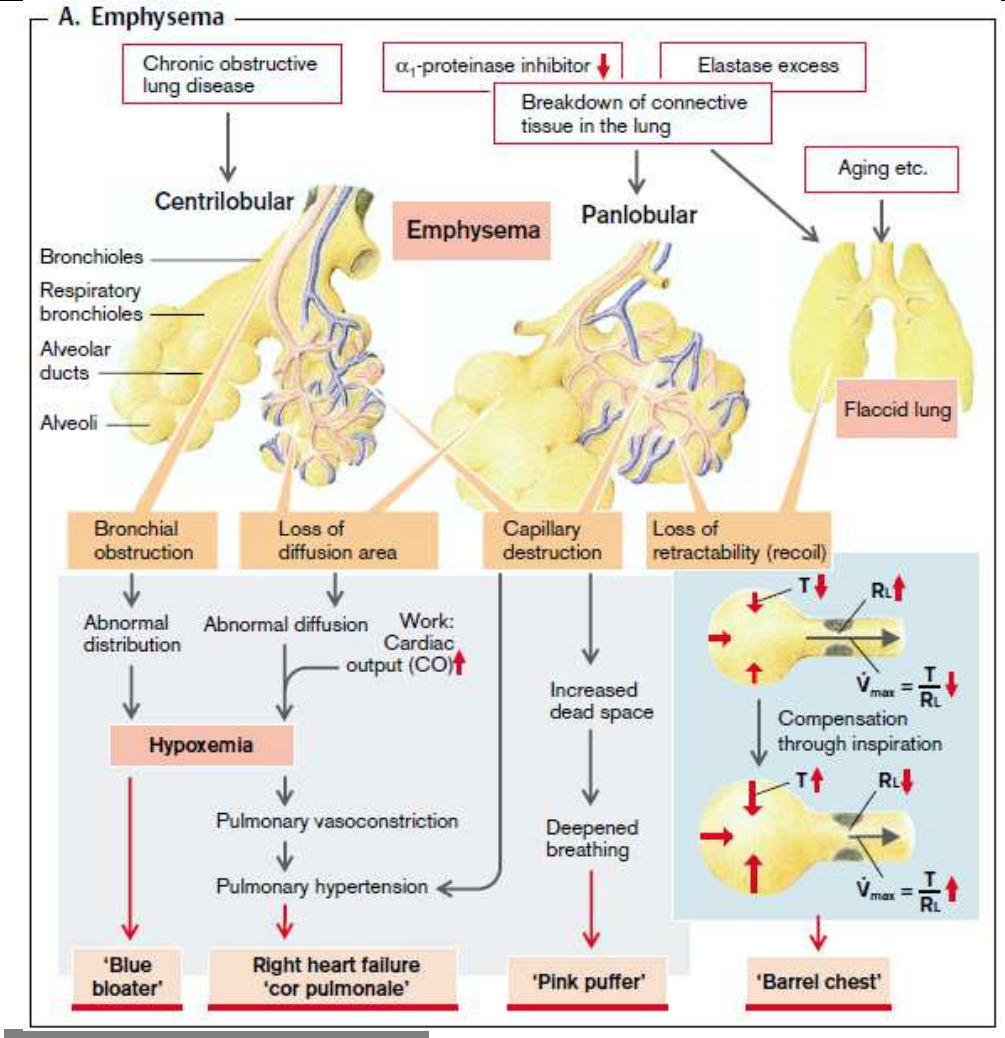
1- Centriacinar :

- Affects the bronchioles in the central part of the respiratory lobule (terminal bronchioles (TB) & respiratory bronchioles (RB)), with initial preservation of the alveolar ducts and sacs.
- Most common type of emphysema.
Seen predominantly in male smokers.
- Centriacinar changes in upper parts of the lung.



2- Panacinar

- Produces initial involvement of the peripheral alveoli → Later extends to involve the more central bronchioles.
- More common in persons with **α1**-antitrypsin deficiency.
Also found in smokers in association with centrilobular emphysema.
- Panacinar changes are seen in lower parts of the lung



Clinical Manifestations

1. Dyspnea : In Emphysema & chronic bronchitis

- Persons with emphysema have **marked dyspnea and struggle to maintain normal blood gas levels** with increased ventilatory effort (overventilate) , including prominent use of the accessory muscles.
- The seated position,which stabilizes chest structures and allows for maximum chest expansion and use of accessory muscles, is preferred

2. Productive chough : In Chronic Bronchitis

- **Cough is productive** of thick, purulent sputum owing to→ ongoing local inflammation & infection.
- **Sputum viscosity is increased** largely as a result of presence of free DNA (of high molecular weight and highly viscous) from lysed cells.
- **Hemoptysis** → with increased inflammation and mucosal injury.
- **Cough is much less effective** owing to → 1- narrow airway caliber & 2- greater volume and viscosity of secretions.

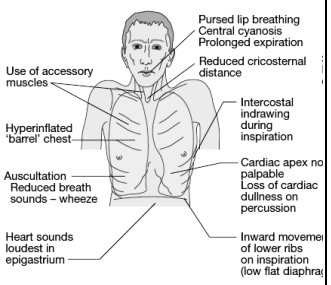
3. Breath sounds :

In Emphysema :
- Decreased in intensity of breathing sound → reflecting decreased airflow.
- Wheezes, when present , are of diminished intensity - Crackles & rhonchi, in superimposed processes as infection

In Chronic Bronchitis : Persistent airway narrowing & mucus obstruction :
- Produce localized or diffuse wheezing (responsive to bronchodilators).
- Prolonged expiratory time .
- Inspiratory & expiratory coarse crackles : ↑ mucus production + defective mucociliary clearance → excessive secretions in the airways.

4. Cardiac examination :

- Tachycardia → as in chronic bronchitis, especially with exacerbations of bronchitis or hypoxemia.
- Pulmonary hypertension → If hypoxemia is significant and chronic,,, Cardiac examination may reveal :
  - Prominent pulmonary valve closure (increased P_2, pulmonary component of the 2nd heart sound) or
  - Elevated jugular venous pressure AND peripheral edema resulting from Rt heart failure.



5. Imaging :

- Hyperinflation with → 1- flattened hemidiaphragms 2- ↑ anteroposterior chest diameter.
- Parenchymal destruction produces : attenuated peripheral vascular markings.
- Pulmonary hypertension produces : proximal pulmonary artery dilation .
- Cardiac size may be increased, suggesting right heart volume overload.
- Cystic or bullous changes.

6. Pulmonary function tests :

In Emphysema :
- The loss of elastic recoil in lung tissue supporting the airways results in increased dynamic compression of airways, (especially during forced expiration)→ all flow rates are reduced:**With premature airway collapse, FEV_1, FVC, FEV_1/FVC (FEV_1% ratio) ↓.**
- **"Expiratory flow-volume curve" shows substantial limitation in flow**.

In Chronic Bronchitis :
- Diffuse airway obstruction is demonstrated as a global reduction in expiratory flows & volumes. **FEV_1, FVC, FEV_1/FVC (FEV_1%) ↓.**
- **expiratory flow-volume curve" shows substantial limitation in flow**.
- **Increased RV and FRC**, reflecting *air trapped in the lung* as a result of :
  a- Diffuse airway obstruction (chronic bronchitis)
  b- Early airway closure caused by loss of elastic recoil (emphysema)
- **TLC is increased** → substantial amount of this increase comes from gas trapped in poorly lung units, including bullae.

7. Arterial blood gases :

In Emphysema : (Emphysema is a disease of alveolar wall destruction)
- The loss of the alveolar capillaries creates: **areas of high ventilation relative to perfusion.**
- They may ***able to maintain nearly normal PO_2 and PCO_2 levels*** despite advanced disease
- **Hypercapnia, respiratory acidosis, and a compensatory metabolic alkalosis** are *common in severe disease.*

In Chronic Bronchitis :
- In contrast to persons with emphysema, those with chronic obstructive bronchitis are ***unable to maintain normal blood gases by increasing their breathing effort*** → **" Ventilation-perfusion mismatching "** is common in chronic bronchitis.
- **Hypoxemia** (arterial PO2 levels fall below 55 mm Hg) at rest tends to be more profound than in emphysema → causes reflex vasoconstriction of the pulmonary vessels → persons with chronic obstructive bronchitis develop **pulmonary hypertension** and, eventually, **right-sided heart failure with peripheral edema (*i.e.,* cor pulmonale).**
- **Hypercapnia, Cyanosis, respiratory acidosis, and a compensatory metabolic alkalosis**.

8. **Polycythemia :** Chronic hypoxemia (especially in chronic bronchitis) is associated with erythropoietin-mediated increase in **hematocrit**.

The mnemonics **"pink puffer" and "blue bloater"** used to differentiate the clinical manifestations of **:**
Emphysema & Chronic obstructive bronchitis (In practice, differentiation between the two types is often difficult)
A major difference between the pink puffers & the blue bloaters is the respiratory responsiveness to the hypoxic stimuli.

- **Chronic obstructive bronchitis** is characterized by **excessive bronchial secretions and airway obstruction that causes mismatching of ventilation & perfusion** → Thus, persons with chronic bronchitis are unable to compensate by increasing their ventilation; → instead, **hypoxemia & cyanosis** develop. (These are **blue bloaters, or nonfighters**).
  - In centrilobular emphysema a ***distribution abnormality*** also develops, because of differing resistances in different bronchioles → resulting in ***hypoxemia***.
  - Patients with centrilobular emphysema are called **"blue bloaters"** .

Centrilobular emphysema :

- **Pulmonary emphysema :** there is a **proportionate loss of ventilation & perfusion area** in the lung.
  - These persons are **pink puffers, or fighters** able to overventilate and thus maintain relatively normal blood gas levels ***until late in the disease.***
  - In panlobular emphysema , an ***enlargement of the functional dead space*** forces them to ***breathe more deeply***.
  - Patients with panlobular emphysema are called are called **"pink puffers".**

Panlobular emphysema :

1- Reduced elastic recoil: leads to

The lung's reduced ability to retract (*flaccid lung*) can lead to **obstructive lung disease**, because :

reduced elastic recoil (increased compliance) of the lung requires an increase in intrathoracic pressure for expiration, resulting in compression of the intrathoracic airways → massive **increase in flow resistance.**

- **Positive pressure in alveoli :**
  1- **Reduced lung's elastic recoil** generates the positive pressure in the alveoli :
  - With loss of lung elasticity and hyperinflation of the lungs → greater intrathoracic pressure is necessary for expiration because compliance and resistance are increased → This causes **compression of the bronchioles** →so, **airway pressure increases further**.
  - The airways often collapse during expiration because pressure in surrounding lung tissues exceeds airway pressure → Air becomes trapped in lungs, producing an increase in the anteroposterior dimensions of the chest, the so-called *barrel chest*.
  - Elastic recoil can be raised by increasing the inspiratory volume → leading to a *shift in the resting position* toward inspiration (*barrel chest*).
  - Pursed-lip breathing, → increases the resistance to the outflow of air, → preventing airway collapse by increasing airway pressure.

  2- **External compression** produces positive pressure in the alveoli by contraction of expiratory muscles, BUT this will **also compress the bronchioles** → thus bring a massive **increase in flow resistance.**

THUS :

Maximal expiratory flow rate (V max) is a function of the ratio between *elastic recoil (K)* and resistance (RL) .

- **Respiratory function :**
  - If tidal volume(TV) remains constant :
    1- ↑ functional residual capacity (FRC) 2- ↑ residual volume (RV) 3- ↑ dead space.
  - Vital capacity (VC) is ↓ because of the reduced expiratory volume.

2- Bronchial obstruction : leads to

1- ↓ maximum breathing capacity ($\dot{V}$ max)
2- ↓ FEV1 .
3- differing ventilation of various alveoli results in ***abnormal distribution*** → resulting in : **Hypoxemia.**

3- Loss of alveolar wall : leads to

1- **diminished diffusion area** → ***abnormal diffusion*** of gases → resulting in : **Hypoxemia .**

The hypoxia of underventilated alveoli leads to →vasoconstriction, → increased pulmonary vascular resistance, → **pulmonary hypertension**, → an **increased right ventricular load (cor pulmonale)**.

4- Loss of pulmonary capillaries : leads to

1- ***increase in functional dead space***
2- ***increased pulmonary artery pressure and vascular resistance*** → **with development of " *cor pulmonale*"**

- *The fluid retention and peripheral oedema is due to failure of excretion of sodium and water by the hypoxic kidney rather than Rt. heart failure.*
- *With severe fluid overload,* → ***tricuspid incompetence*** *may develop with :*
elevated jugular venous pressure (JVP) / ascites / upper abdominal discomfort due to liver swelling.

Investigations

1- Lung function tests:
- **Show evidence of airflow limitation** : FEV_1: FVC ratio is reduced /and PEFR is low.
  In many patients the airflow limitation is partly reversible (usually a change in FEV_1 of <15%), and it can be difficult to distinguish between COPD and asthma.
- **Lung volumes :** be normal or increased;
- **Carbon monoxide gas transfer factor:** is low when significant emphysema is present.

2- Chest X-ray : see above in clinical manifestations

3- High-resolution CT scans : when the plain chest X-ray is normal.

4- Haemoglobin level and PCV : can be elevated as a result of persistent hypoxaemia (2ry polycythaemia).

5- Blood gases :
- **At rest** → normal - **On exercise** → patients desaturate .
- **In more advanced cases** → 1- resting hypoxaemia and 2- hypercapnia.

6- Sputum examination :
- Strep. pneumoniae and H. influenzae are the only common organisms to produce acute exacerbations.
- Occasionally, Moraxella catarrhalis may cause infective exacerbations.

7- Electrocardiogram: is often normal, BUT In advanced pulmonary hypertension :
- P wave is tall (P pulmonale) . - Right bundle branch block (RBBB) - Rt. ventricular hypertrophy.

8- Echocardiogram : is useful to assess cardiac function where there is disproportionate dyspnoea.

9- α_1-Antitrypsin : levels & genotype are worth measuring in: 1- premature disease or 2- lifelong non-smokers.

Acute exacerbations of COPD → Presence of hypercarbia (P_{CO_2} >45 mmHg) has important implications for treatment (discussed below).

- Exacerbations are **episodes of increased dyspnea and cough and change in the amount and character of sputum.**
- They may or may not be accompanied by other signs of illness, including **fever, myalgias, and sore throat**.
- Presence of **cyanosis, peripheral oedema or alteration in consciousness** → indicates the need for referral to hospital.

1- Oxygen : (In patients with an exacerbation of severe COPD, high concentrations of oxygen may cause respiratory depression & worsening acidosis)
- The aim is maintaining : **PaO2** > 60 mmHg or **SaO2** between 88% & 92% without worsening acidosis.

2- Bronchodilator s :
- Nebulised short-acting β2-agonists (salbutamol) **combined with** anticholinergic agent (ipratropium).
- These may be administered separately or together.

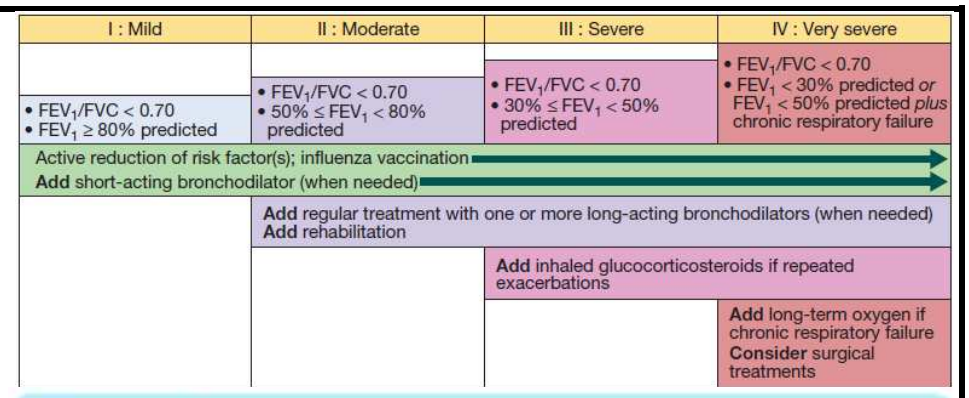
3- Glucocorticoids :
- 1- Reduce length of stay 2- hasten recovery 3- reduce chance of subsequent exacerbation or relapse for a period of up to 6 m.
- The GOLD guidelines recommend : **oral prednisolone (30 mg) for a period of 2 weeks.**

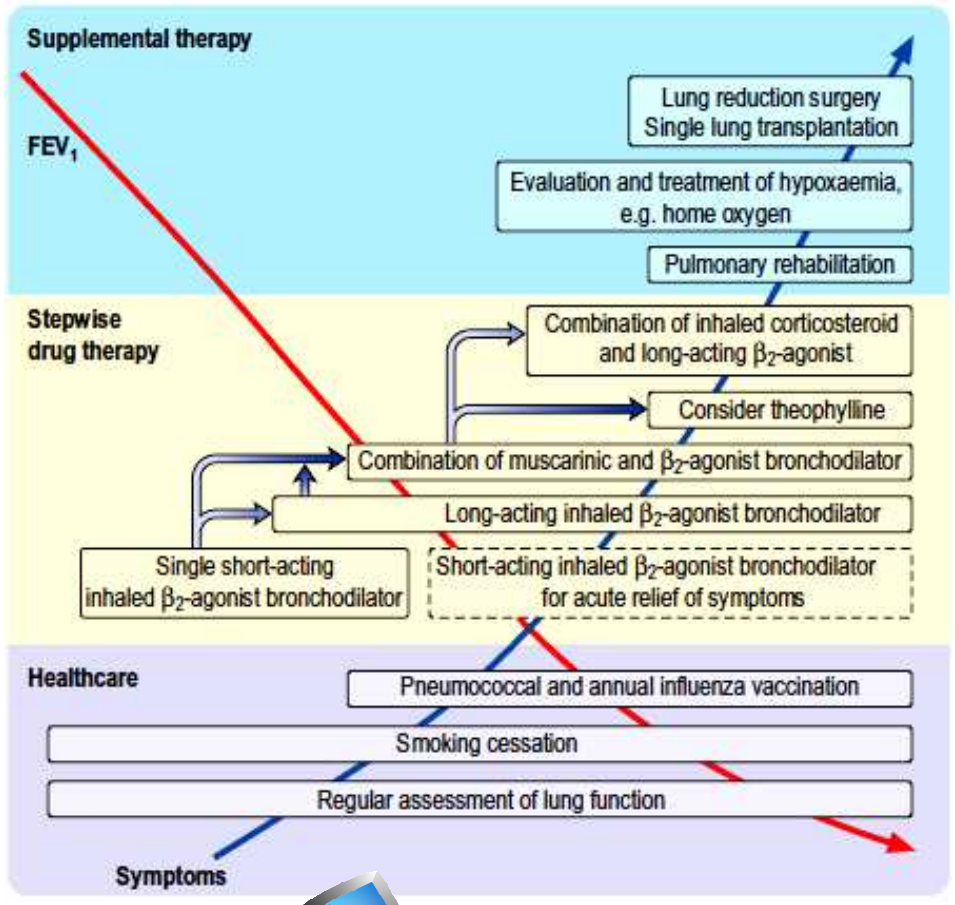
4- Antibiotics :
- Patients with COPD are frequently colonized with potential respiratory pathogens (*s. pneumoniae*, *H. influenzae*, *M. catarrhalis)*.
- Indications: **Currently recommended for patients reporting increase in sputum purulence, sputum volume or breathlessness.**
- Regimens : **Aminopenicillin or a macrolide**. / **Co-amoxiclav** if β-lactamase-producing organisms susceptible.

5- Mechanical Ventilatory Support :

A) **Noninvasive positive-pressure ventilation (NIPPV)** :
- Indications: If, despite above measures, patient remains **tachypnoeic, hypercapnic ,acidotic (PaCO2 > 45 mmHg / pH < 7.35)**
- Its use is associated with reduced requirements for mechanical ventilation and reduced mortality

B) **Invasive Mechanical Ventilation** :
- Indications:
  1- Severe respiratory distress despite initial therapy, 2- life-threatening hypoxemia, 3- severe hypercarbia and/or acidosis, 4- markedly impaired mental status 5- respiratory arrest 6- hemodynamic instability





MedicoNotes www.mediconotes.com

Pharmacotherapy

Reducing exposure to noxious particles & gases	• Complete cessation of smoking is accompanied by → 1- improvement in lung function 2- deceleration in the rate of FEV1 decline . • Pharmacologic approaches: **1- Bupropion** **2- Nicotine replacement therapy** as: gum, transdermal patch, inhaler **3- varenicline**, nicotinic acid receptor agonist/antagonist.
Bronchodilators	- Bronchodilator therapy is central to the **management of breathlessness.** - Compound bronchodilators, a selective β2 agonist and an antimuscarinic agent, are used. - Oral bronchodilator therapy may be used in patients who cannot use inhaled devices efficiently. - Significant improvements in breathlessness may be reported, despite minimal changes in FEV1 → reflecting improvements in lung emptying that reduce dynamic hyperinflation .
β-Adrenergic agonists	• **In mild COPD :** Short-acting β2-agonists → **Salbutamol or Terbutaline** . • **In moderate & severe COPD :** long-acting β2 agonists → **Formoterol or salmeterol** .
Antimuscarinic drugs	• **In mild COPD :** Short-acting → **Ipratropium bromide** (improves symptoms and produces acute improvement in FEV_1). • **In moderate & severe COPD :** long-acting → **Tiotropium bromide** (improve symptoms and reduce exacerbations BUT does not affect the decline in FEV1).
Theophyllines	• **Theophylline preparations**: improve breathlessness and quality of life, BUT their use is limited by : 1- side-effects 2- unpredictable metabolism 3- drug interactions.
Phosphodiesterase inhibitors	• **Roflumilast** is an inhibitor with anti-inflammatory properties. → It is used as an adjunct to bronchodilators for the maintenance treatment of COPD patients.
Corticosteroids **Combination of :** - Corticosteroid with - Long-acting β_2 agonist may protect against lung function decline BUT does not improve overall mortality.	**Inhaled Corticosteroids (ICS)** • **Indications :** - Recommended in patients with **severe disease (FEV1 < 50%) who report two or more exacerbations requiring antibiotics or oral steroids per year .** • **Effects :** - Reduce the frequency and severity of exacerbations. - Regular use is associated with a small improvement in FEV1 (but ICS do not alter the natural history of the FEV1 decline). **Oral Corticosteroids** **Prednisolone** 30 mg daily should be given for 2 weeks • **Indications :** - Useful **during exacerbations** (BUT maintenance therapy contributes to osteoporosis "other side effects" should be avoided) . • **effects :** - If there is objective evidence of a substantial **degree of improvement in airflow limitation (FEV1 increase >15%),** → prednisolone should be discontinued and replaced by : inhaled corticosteroids (beclometasone 40 µg twice daily adjusted according to response)
Oxygen therapy **Long-term oxygen therapy (LTOT)**	• **long-term domiciliary oxygen therapy (LTOT) will benefit patients who have:** Arterial blood gases measured in clinically stable patients on optimal medical therapy *on at least two occasions 3 weeks apart* : **1- PaO2 < 55 mmHg** irrespective of PaCO2 and **FEV1 < 1.5 L** **2- PaO2 55–60 mmHg** plus **secondary polycythaemia**, **pulmonary hypertension, peripheral oedema or nocturnal hypoxaemia** **3- Carboxyhaemoglobin of <3% (i.e. patients who have stopped smoking).** → **Use : at least 15 hrs/day at 2–4 L/min** → **Aim : to achieve → *Pa*O2 > 60 mmHg *or* SaO2 > 90 %** • **A fall in pulmonary artery pressure** : was achieved if oxygen was given for 15 hours daily, • **Substantial improvement in mortality:** was only achieve if oxygen was given for 19 hours daily.
Other measures	**1- Vaccination:** → **1- Influenza vaccine (annually) 2- Polyvalent pneumococcal vaccine (single dose)** **2- Mucolytic therapy :** →**4-week trial of Carbocysteine** (Reduce sputum viscosity + can reduce the number of acute exacerbations) . **3- Diuretic therapy:** → This is necessary for all oedematous patients. **4- α1-Antitrypsin replacement**:→Weekly or monthly infusions of **α1-antitrypsin** have been recommended for : **1-patients with serum levels below 310 mg/L & 2-abnormal lung function.** **5- Heart failure** : → should be treated. **6- Secondary polycythaemia** :→ requires **venesection** if the PCV is >55% **7- Sensation of breathlessness:** → an be reduced by either **promethazine** or **dihydrocodeine** Although opiates are the most effective treatment for intractable breathlessness they depress ventilation and carry the risk of respiratory failure.

Nonpharmacologic Therapies

Pulmonary rehabilitation	• **Exercise** should be encouraged at all stages • **Multidisciplinary programmes** that incorporate: **1-** Physical training **2-** Disease education and nutritional counselling reduce symptoms **3-** Improve health status and enhance confidence.
Surgical intervention	**1- Bullectomy :** - Patients in whom large bullae compress surrounding normal lung tissue, who otherwise have minimal airflow limitation and a lack of generalised emphysema, → considered for bullectomy. **2- Lung volume reduction surgery (LVRS) :** Patients with : - **Predominantly upper lobe emphysema - with preserved gas transfer - No evidence of pulmonary hypertension,** → benefit from **lung volume reduction surgery (LVRS),** in which: *peripheral emphysematous lung tissue is resected → with the aim of reducing hyperinflation and decreasing the work of breathing.*
Lung Transplantation	• Candidates for lung transplantation: **1- <65 years 2- have severe disability despite maximal medical therapy 3- free of comorbid conditions** (liver, renal diseases). • In contrast to LVRS, the anatomic distribution of emphysema *AND* presence of pulmonary hypertension are not *contraindications to lung transplantation.*