Asthma & COPD

Asthma is a chronic inflammatory condition of the airways. The airway inflammation is associated with hyper-responsiveness of the airways and variable airflow obstruction. These physiological changes result in the classic symptoms of intermittent breathlessness, cough and wheeze.

Bronchial hyper-responsiveness: is currently defined as an increase in sensitivity to a wide variety of airway narrowing stimuli.

Types of asthma:

- Allergic asthma
- Seasonal asthma
- Occupational asthma
- Non-allergic asthma
- Exercise induced asthma
- Difficult asthma
- Severe asthma or Brittle asthma
- Adult onset asthma
- Childhood asthma

Aetiology

The aetiology of asthma is complex and not fully elucidated. It is recognized that there is a complex interaction between multiple **genetic and environmental factors**.

Potential triggers of asthma symptoms
Allergens: House dust mite, Animal dander, Moulds, Pollens
Infectious agents: Influenza, Rhinovirus
Drugs: Non-steroidal anti-inflammatory drugs, Beta blockers, Prostaglandins
Occupational: Wheat flour, Soy caster bean, Latex, Formaldehydes, Hair colourants
Other: Sulphites, Nitrogen oxides, Sulphur dioxide, Exercise, Cold air, Stress

Pathophysiology

Asthma is an inflammatory disorder of the airways, and various inflammatory cells and mediators have been identified as playing an important role in the pathophysiology of asthma.

Bronchial hyper-reactivity is recognised as a key feature of asthma pathophysiology. This results in the airways of people with asthma responding to exposure to particular triggers, which vary from person to person. Exposure to triggers causes constriction of the airway smooth muscle, resulting in bronchoconstriction.

Bronchoconstriction is a result of activation of the parasympathetic pathways of the autonomic nervous system. The release of acetylcholine by the postganglionic nerve fibers activates the M3 muscarinic receptors within the airway smooth muscle. Activation of these receptors results in contraction of the smooth muscle and, consequently, constriction of the diameter the airway.

The inflammatory process follows the bronchoconstriction, resulting in the production of excess mucus and oedema within the airway. The combination of bronchoconstriction and inflammatory process leads to narrowing of the airway and the classic symptoms of asthma.

The majority of people with asthma have an inflammatory process driven by **T_H2 processes** that tend to be associated with atopy, allergy, type I hypersensitivity and eosinophilic inflammation. This group of asthma has long been recognized to be responsive to treatment with corticosteroids. The **non-T_H2-driven** asthma is much less established and seems to be associated with a later age of onset, obesity and neutrophilic inflammation. Lack of response to treatment with corticosteroids tends to be a feature of non-TH2-driven asthma.

Clinical signs and symptoms

The classical symptoms of asthma are **cough, wheeze and breathlessness**, which are often induced by exposure to a wide variety of trigger factors. **Acute asthma** attack may present also with **tachypnea.** The frequency and severity of these symptoms is highly variable between individuals and also within individuals. At times the person with asthma may be asymptomatic, whereas at other times the person may have a high level of symptoms potentially requiring hospital admission. Asthma tends to demonstrate **diurnal variation**, generally with increased symptoms at night and early in the morning.

Acute severe asthma is defined as the patient's peak flow reduced to between 33–50% of the patient's predicted, increased respiratory rate of more than 25 breaths/minute, heart rate of more than 110 beats/minute and the patient is unable to complete a sentence in one breath.

Life-threatening asthma is defined as the peak flow being less than 33% of the patient's predicted, oxygen saturation of less than 92%, silent chest, reduced respiratory effort, hypotension and an altered state of consciousness.

Investigations

A. Lung function testing

Lung function testing is a key part of the **diagnosis and monitoring** for people with asthma.
Lung function testing in asthma **aims** to: 1) demonstrate the presence of reversible airflow obstruction and 2) monitor the response to treatment and detect any deterioration in asthma control.
There are a number of different methods for testing lung function:

- **Peak expiratory flow rate (PEFR)** is the maximum airflow rate during forced expiration. A peak flow meter can measure PEFR in a simple portable device that provides a simple and useful method for patients to monitor their asthma. When using a peak low meter, the patient undertakes three forced expirations through the device and records the highest value.

- **Spirometry,** with a spirometer, is preferable to PEFR because it provides a **more accurate** measure of airflow obstruction. When performing spirometry, an individual inhales to maximal inspiration, then exhales maximally to complete expiration. The spirometry provides a graphical representation of the manoeuvre as a volume–time curve. Examination of the spirometry values is important to ensure that the procedure has been performed appropriately. When performing spirometry, the forced expiratory volume in 1 second **(FEV1)** and forced vital capacity **(FVC)** are recorded. This then allows for calculation of the **FEV1/FVC ratio** and also the percentage of predicted values.

- **Forced expiratory volume in 1 second (FEV1):** Volume of air forcibly expired in 1 second.
- **Forced vital capacity (FVC):** Total volume of air forcibly expired at maximum expiration.
- **FEV1/FVC Ratio** (between FEV1 and FVC): Normal ratio >0.7, if ratio <0.7, indicated airflow obstruction. ***Normal individuals can exhale at least 70% of their total capacity in 1 second.***

B. Measurement of airway hyper-responsiveness

The tests aim to demonstrate bronchoconstriction in response to administration of an inhaled challenge. A number of substances can be used as challenges, including histamine, methacholine and mannitol.

C. Measures of airway inflammation

Eosinophilic airway inflammation can be determined either directly by measurement of eosinophils and eosinophilic cationic protein (ECP) in sputum or indirectly by measurement of the same markers in blood. Airway inflammation could also detected by measurement of the fraction of exhaled nitric oxide (FeNO) using a portable device that measures the level of nitric oxide.

D. Other tests

Other tests that can be useful in supporting the diagnosis include measurement of serum IgE and testing for atopy through either skin-prick testing or IgE testing for specific allergens. For individuals with atypical features, consideration should be undertaken for a chest X-ray.

Treatment of Chronic Asthma

GOAL of treatment:

- No daytime symptoms,
- No night-time wakening due to asthma symptoms,
- No requirement for rescue medication,
- No asthma attacks/exacerbations,
- No limitations on activity,
- Normal lung function – FEV1 and/or PEF greater than 80% predicted or best,
- Minimal adverse effects from medication.

1. Short-acting β-agonists

Short-acting β-agonists (SABAs) work by activation of β_2-adrenoceptor in the smooth muscle of the lung to promote bronchodilation. SABAs, such as **Salbutamol** and **Terbutaline**, are the **first-line step** and should be prescribed for all asthma patients and should be used on a when-required basis (on need). Excessive use of SABAs, defined as **more than one canister per month**, has been associated with an increased risk of asthma death. Additionally, oral SABAs are not

recommended due their higher risk of systemic side effects compared with administration via inhalation.

2. Inhaled corticosteroids

Corticosteroids bind to glucocorticoid receptors within the lung and decrease the formation of cytokines, which produce IgE and promote the expression of IgE receptors. They also inhibit the influx of eosinophils into the lung, therefore **reducing overall inflammation**. Inhaled corticosteroids (ICSs) are recommended as the **second step** as a regular **preventative** therapy for all people with asthma, except those with very mild and occasional symptoms, where 'as-required' symptomatic treatment with short-acting β2-agonists alone may be sufficient. Standard doses of ICSs are suggested as 200–400 micrograms/day of Beclomethasone dipropionate (BDP) or equivalent in 24 hours.

The threshold frequency of β2-agonist use which prompts the start of ICSs:

1. Exacerbations of asthma in the past 2 years
2. Using inhaled β2-agonists three times a week or more
3. Symptoms three times a week or more
4. Waking one night a week with symptoms

3. Long-acting β-agonists

Inhaled LABAs are a **first-line addition to ICSs**. The addition of a LABA to a low-dose ICS has been shown to be as effective as increasing the ICS dose and may be associated with fewer side effects.

LABAs, such as **Salmeterol, Formoterol Fumarate and Vilanterol**, are designed to be used **regularly** but have different characteristics in terms of onset and duration of action.

LABAs can exert an effect on β1-receptors in the cardiac muscle, increasing cardiac output and stimulation, leading to tachycardia and arrhythmias. Additionally, they can cause tremor and hypokalemia. Due to the cardiac risks associated with the use of LABAs, it is important to step down treatment where possible for safety.

LABAs should not be used alone without an ICS… why?

Chronic use of LABAs causes tolerance due to down-regulation of β2-adrenoceptors. This is associated with an increased risk of mortality in patients with asthma. Therefore the use of LABAs

alone is contraindicated. The down-regulation of β2-adrenoceptors by chronic use of LABAs can impair the response to SABAs when they are need for acute relief of symptoms during an asthma attack.

On another hand, ICS are used to control the inflammatory processes underlying asthma. Corticosteroids also upregulate β2-adrenoceptor expression. Combination of ICS with LABAs reduces the risk of development of tolerance to β2-adrenoceptor agonists. Therefore, LABAs are only used concomitantly with corticosteroids.

Dose chronic use of SABA increase the risk of mortality…?

Whether or not SABAs increase the risk of mortality is controversial. SABAs being shorter acting and less likely to cause down-regulation of β2-adrenoceptors. When used only intermittently for acute relief of symptoms of asthma, there does not appear to be a clear association between SABA usage and increased mortality. Even when SABAs are used chronically, there is less clearcut evidence for increased mortality. Nevertheless, it would usually be the case that the patient with asthma is advised only to use the SABA intermittently when needed for acute relief of symptoms of asthma rather than chronically to ensure that the β2-adrenoceptors are not down-regulated and are responsive when the SABA is needed for acute relief of the symptoms of an asthma attack.

4. Leukotriene antagonists

They work by **reducing the inflammation in the bronchi**, by **inhibiting leukotriene receptors** in the respiratory mucosa and **reducing sputum eosinophilia**.

Leukotriene antagonists such as **Montelukast and Zafirlukast** are recommended:

- In patients not responding to a LABA or in addition to an ICS/LABA in persistent poor control.
- For people with exercise-induced asthma.
- For patients with allergic rhinitis.

Leukotriene antagonists have mild side effect on GI system.

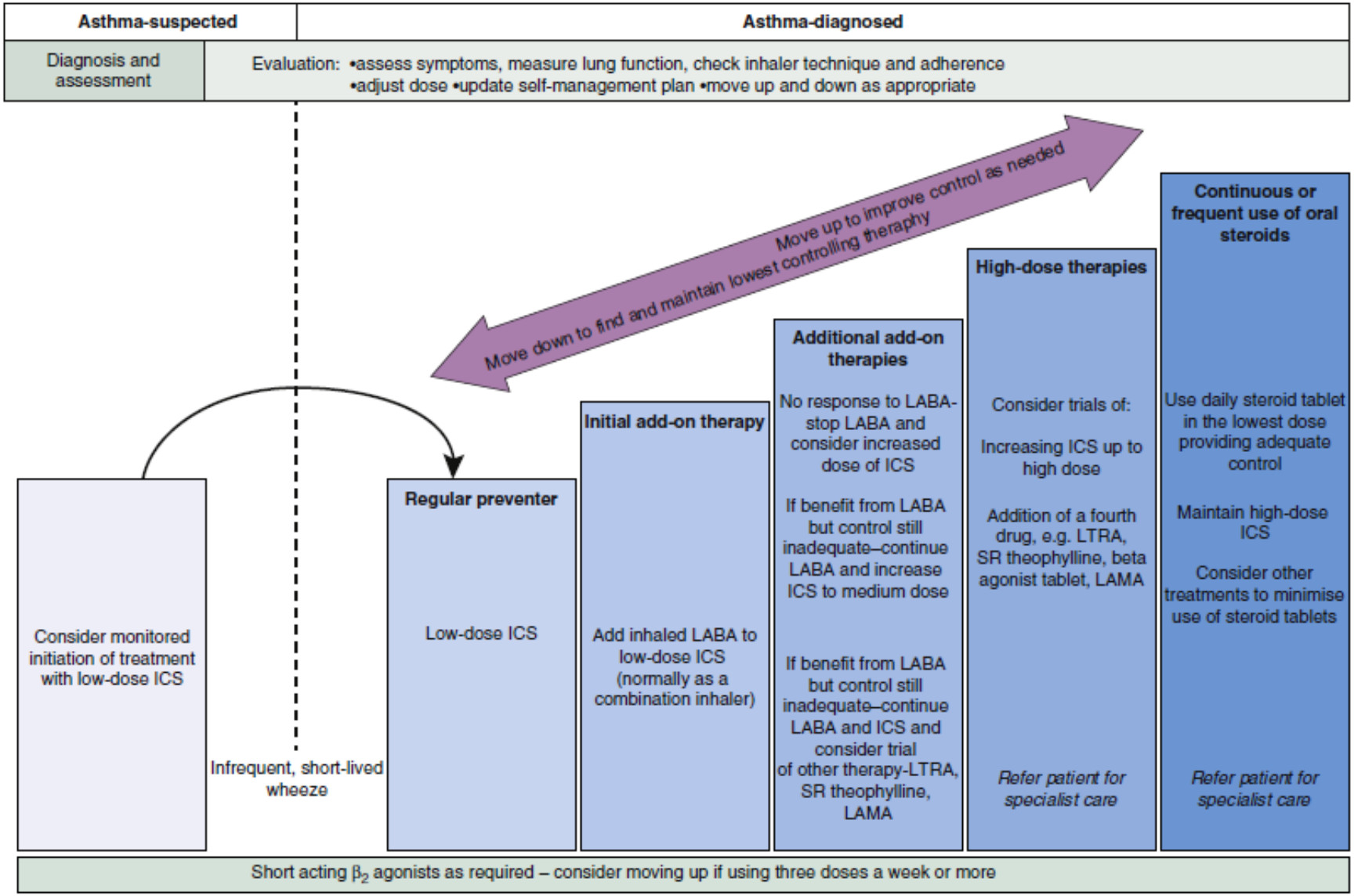

Fig. 25.2 Summary of stepwise management of asthma in adults (BTS and SIGN, 2016).

5. Long-acting muscarinic receptor antagonist

LAMAs work by binding to the **muscarinic M3 receptors** in the smooth muscle of the lung to aid **bronchodilation**.

LAMAs, like **Tiotropium**, considered as the **fourth step** in patients who have not responded to an ICS/LABA combination and in severe asthma, they demonstrated to improve asthma control and quality of life as well as reduce exacerbation frequency in patients with severe asthma.

6. Theophylline preparations

Theophylline and Aminophylline are methylxanthines and work as bronchodilators and stimulate respiration.

Oral theophylline and aminophylline can be used as an **alternative in the same way as the leukotriene antagonists** when patients are unresponsive to LABAs or as an addition to an ICS/LABA combination.

Methylxanthines have a **narrow therapeutic window** and require close monitoring of serum theophylline levels to ensure a therapeutic dose and avoid toxicity.

Normal serum level= 10–20 mg/L (achieved after 5 days).

At toxic levels (>20 mg/L) methylxanthines have side effects on:

- CNS, causing tremor,
- Cardiac muscle α-receptors, results in increased cardiac output and tachycardia,
- Constricting cerebral blood vessels, causing convulsions (care must be taken with epilepsy).

Theophylline is **metabolised using the cytochrome P450** pathway; therefore, its plasma concentration can be decreased by enzyme inducers and increased by enzyme inhibitors. (Check table 25.6 for Drug interactions with theophylline).

7. Biological therapies

Omalizumab is a **humanized monoclonal anti-IgE** antibody being introduced for treatment of allergic asthma and uncontrolled asthma. It tend to reduce the amount of circulating IgE and **reduce the inflammatory response**. It has been shown to significantly reduce the number of exacerbations in patients with severe asthma who have not improved on standard treatments. Omalizumab is administered as a subcutaneous injection two to four times weekly, and it can take up to 12–16 weeks before an effect is felt.

8. Oral corticosteroids

Oral corticosteroids, such as **prednisolone**, **the fifth step of treatment** can be used for **both exacerbations and chronic asthma**. Corticosteroids act by reducing lung inflammation.

Long-term oral corticosteroids should be used at **the lowest dose** possible and regularly reviewed, and patients should be **monitored for risk of adverse effects**.

Patients should be fully informed of the risks of long-term oral steroids (check them in BNF) and about concurrent use of oral corticosteroids with other medicines (see interactions)

Treatment of Acute Asthma Attack

a) **Oxygen**. Patients with severe or life-threatening acute asthma should have their oxygen saturation maintained at 94–98% to treat hypoxia.

b) **Bronchodilators**. Inhaled β -agonists should be administered in emergency situations to treat bronchoconstriction. High doses should be given via the nebulized route where possible (routine monitor for potassium and heart rate). In case of poor control, there is evidence for the addition of nebulised ipratropium (anti-muscarinic) for increased bronchodilation.

c) **Corticosteroids**. Oral prednisolone should be administered after an acute asthma attack at the earliest stage with a dose of 40–50 mg daily. If the oral route is unavailable, then intravenous hydrocortisone may be administered at a dose of 100 mg four times daily until the oral route is available again. Corticosteroid therapy should be continued for at least 5 days but can be extended until the patient's condition has improved.

d) **Intravenous Aminophylline**. May be commenced in severe acute asthma to aid with bronchodilation, although evidence suggests it does not provide additional bronchodilation compared with SABAs.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is defined on the basis of airflow obstruction that is not fully reversible. Certainly, this clinical entity is highly prevalent and familiar, usually in older patients with a significant smoking history. COPD is a leading cause of morbidity and mortality worldwide.

Aetiology

1- Smoking is the commonest cause of COPD

2- Dust and fume exposure can also cause the condition.

3- α_1-antitrypsin deficiency predisposes to early-onset emphysema, mostly in smokers, revealing the importance of the balance between neutrophil-derived proteases and anti-proteases in the development of the condition.

The major risk factors are summarized in Table 26.1

Table 26.1 Risk factors for the development of chronic obstructive pulmonary disease

Risk factor	Comment
Smoking (including tobacco, heroin, cannabis)	Risk increases with increasing consumption, but there is large inter-individual variation in susceptibility.
Age	Lung function impairment progresses with age.
Gender	Male gender was previously thought to be a risk factor, but this may be due to historical higher rates of smoking in men.
Occupation	Development of COPD is associated with occupational dust and fume exposure, including coal mining, farming, grain-handling and the cement and cotton industries.
Genetic factors	Alpha-1 antitrypsin deficiency is the strongest single genetic risk factor, accounting for 1–2% of COPD.
Air pollution	Death rates are higher in urban areas than in rural areas. Indoor air pollution from burning biomass fuel is also a risk factor, particularly in the developing world.
Socio-economic status	COPD has increased prevalence in individuals of low socio-economic status.

Pathology and Pathophysiology

The two pathological components of COPD are **chronic bronchitis and emphysema.**

Emphysema means dilatation of the airways distal to the terminal bronchiole, with loss of alveolar walls and consequent reduction in the surface area of the alveolar membrane. This impairs gas transfer and can be measured in the laboratory by a reduction in the carbon monoxide gas transfer coefficient (DL_{CO}).

Another effect of this tissue damage is a reduction in the traction on airways, increasing lung compliance and making airways prone to collapse during expiration. The tendency is for emphysematous areas to coalesce, which can lead to the formation of large air cysts, called **bullae**. These are most commonly located in the upper zones, occasionally giant bullae can develop and occupy over half of the volume of a lung.

Chronic bronchitis is a chronic cough with sputum production for at least 3 months per year for 2 consecutive years. Pathologically, chronic bronchitis refers to hypertrophy of the mucus-secreting goblet cells in airway walls. This in turn leads to worsening airflow obstruction by luminal obstruction of small airways, epithelial remodeling and alteration of airway surface tension, predisposing to collapse.

At a microscopic level the inflammation is predominantly neutrophilic, and as is usual, this is not responsive to corticosteroids. A relatively small proportion of COPD patients, however, have a significant eosinophilic component to their disease, which is steroid responsive.

Bronchiectasis a damage of bronchial walls due to repeated bronchial infections, leading to loss of elasticity, and dilatation, which develops in a proportion of COPD patients. This tends to be associated with copious sputum production, with repeated infective exacerbations and frequently with the emergence of pathogens more resistant to first-line antibiotics.

Both emphysema and bronchitis combine to impair the ability to expel air from the lungs, leading to hyperinflation of the thorax. The consequent overstretching of intercostal muscles and diaphragm places them at a mechanical disadvantage, reducing their efficiency. Hyperinflation can be exacerbated by exercise, leading to further reduction in efficiency of the respiratory pump, a process known as dynamic hyperinflation.

Cor pulmonale is a hypoxic syndrome refer to peripheral oedema occurring in COPD with type 2 respiratory failure. The hypoxia and hypercabnia eventually lead to pulmonary hypertension and increase right ventricle afterload and consequently right ventricle failure.

Clinical manifestations: Signs and Symptoms

- The earliest symptoms of COPD are **cough** and **expectoration** of sputum.
- Acute infections may lead to episodic **breathlessness** frequently with **wheezing**, which may be appreciated by the patient and by the clinician on auscultation of the chest.
- If emphysema is prominent, the chest becomes visibly hyperinflated, which can also be appreciated by a hyper-resonant percussion note, as part of the clinical examination.
- Other symptoms that may be experienced are **sleep disturbance**, **dry mouth**, **lethargy** and **weight loss** (common in advanced disease).
- If respiratory failure develops, ankle oedema appears, comprising the clinical syndrome of hypoxic cor pulmonale. This may be associated with headache and drowsiness and is clinically associated with a bluish complexion (‘cyanosis’), warm peripheries, a bounding pulse and lapping tremor.

Two COPD stereotypes have been recognized:

Pink puffers tend to have a more emphysematous phenotype, with marked hyperinflation. They maintain normal blood gases at the expense of a high work of breathing and severe breathlessness. These patients are typically thin.

The blue bloater, in contrast, tends to have less obvious hyperinflation and slips into respiratory failure and hypoxic cor pulmonale. These patients are less breathless and tend to be obese. Interestingly, pathologically, the lungs of these two stereotypes are very similar, suggesting that the cause for the difference lies in the central respiratory control of breathing.

Investigations

1- **Spirometry** measure the airflow obstruction. Airflow obstruction is present when the ratio of the (FEV_1) to the (FVC) falls below 70%. The severity of airflow obstruction is assessed by the post-bronchodilator FEV_1 expressed as the percentage of the predicted, according to age and height, and can be graded as shown in Table 26.2.

2- **Lung volume measurements and carbon monoxide** gas transfer (DL_{CO}) can be more precisely quantify the severity of air trapping and emphysema.
3- **Computed tomography (CT)** scanning can be helpful in identifying emphysema, and bronchiectasis.
4- **Plain chest radiography** also used but has both poor sensitivity and specificity for COPD.
5- **Chest X-ray** shows hyperinflated lungs, increased lung markings due to bronchial wall thickening and regions of lucency corresponding to areas of emphysema/bullae.

Table 26.2 Assessment of severity of airflow obstruction

FEV_1	Severity
Greater than 80% predicted	GOLD stage 1: Mild
50–79% predicted	GOLD stage 2: Moderate
30–49% predicted	GOLD stage 3: Severe
<30% predicted	GOLD stage 4: Very severe

FEV_1, Forced expiratory volume in 1 second.
Adapted from GOLD (2017).

Managing of stable COPD

GOAL of treatment

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve quality of life and health status
- Prevent and treat complications such as hypoxaemia
- Prevent and treat exacerbations
- Reduce mortality

Non-pharmacological Therapy

- **Smoking cessation** effective in reducing ill health and prolonging life.
- **Pulmonary rehabilitation,** the rehabilitation program should include exercise training, smoking cessation, nutrition counselling and education.

- **Surgical treatments,** either **Bullectomy** (lung volume reduction surgery), or **lung transplantation.**

Pharmacologic Therapy for stable COPD

- ### Bronchodilators

Bronchodilators are the **mainstay** of treatment for symptomatic COPD, they are effective in reducing exacerbations and improving symptoms. Monotherapy with long-acting bronchodilators (LABA and LAMA) is preferred, combination therapy may be appropriate in patients with FEV_1 less than 60% or patients with frequent exacerbation.

Short-acting bronchodilators (SABA and SAMA) are used to reverse airflow limitation. They are useful for easing symptoms such as wheeze and improve exercise tolerance.

Note: asthma must be confidently excluded before initiating a LABA without an ICS.

- **Theophylline and aminophylline**

Methylxanthines are weak bronchodilators with a narrow therapeutic index. It appears that the benefits of these compounds in COPD may involve other mechanisms, including increasing respiratory drive and exercise tolerance as well as anti-inflammatory effects. These drugs are now being superseded due to their relative lack of effect and poor tolerability.

- ### Corticosteroids

ICS considered **as second line** treatment if bronchodilators failed to control, as well as in severe COPD. ICS improve symptoms, lung function, quality of life, and exacerbation rates in patients with FEV1 < 60%. Combination with LABA appear to be more effective than monotherapy.

- **Other treatments**

- **Vaccinations,** with annual influenza vaccination**.**
- **α 1-antitrypsin augmentation therapy,** recommended for individuals with α 1-antitrypsin deficiency.
- **Mucolytic and AB,** according to patients' requirements.

Management of exacerbations of COPD

a) **Oxygen** therapy, considered for patients with hypoxemia. Adjust oxygen to achieve PaO_2 greater than 60 mm Hg or oxygen saturation (SaO_2) greater than 90%.
b) Bronchodilators. Salbutamol 2.5 mg four times daily is usually adequate with the addition of ipratropium 500 micrograms four times daily as an adjunct.
c) Aminophylline IV, may be used if there is an inadequate response to bronchodilators.
d) Corticosteroids, a course of oral prednisolone 30 mg for 5–7 days only.
e) Antibiotics, Acute infective exacerbations may be bacterial or viral in origin. If the exacerbation is bacterial in origin, suggested by purulent sputum, then antibiotics should be prescribed.