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# ASSESSMENT OF PRESCRIBING PATTERN OF BRONCHODILATORS AND CORTICOSTEROIDS IN THE MANAGEMENT OF COPD

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**Abstract:**

***Introduction***: *Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.*

***Objectives***: *The objective of this study is to assess the prescribing pattern of bronchodilators and corticosteroids on the management of COPD.*

***Conclusion***: *COPD will remain a significant healthcare problem for years to come. Early identification of the disease through primary care screening for the common symptoms in smokers or those exposed to air pollutants or toxins will lead to earlier diagnosis and treatment. Focusing on smoking cessation will have a great impact on the progression of disease. Advancements in treatment will require translation of a more fundamental understanding of the pathophysiologic pathways involved into disease-modifying interventions. At present, management efforts are directed toward improving patients' symptoms and functional limitations through carefully selected treatment modalities.*

**Keywords**: *Chronic obstructive pulmonary disease, Bronchodilators, Corticosteroids, Global Initiative for Chronic Obstructive Lung Disease, Forced expiratory volume in 1 second, Forced vital capacity, pulmonary function test.*

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## INTRODUCTION:

The term "chronic obstructive pulmonary disease "(COPD), also known as chronic obstructive airway disease (COAD) or chronic obstructive lung disease (COLD), includes chronic bronchitis and emphysema.

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases (GOLD, 2009). COPD is a general term that covers a variety of other disease labels including chronic obstructive airways disease (COAD), chronic obstructive lung disease (COLD), chronic bronchitis and emphysema. COPD has been defined (National Institute for Health and Clinical Excellence, 2010) as:

- Airflow obstruction with a reduced $FEV_1$ /FVC ratio of less than 0.7.
- If $FEV_1$ is $\geq 80\%$ of predicted normal, a diagnosis of COPD should only be made in the presence of respiratory symptoms, for example breathlessness or cough.

**Epidemiology:**

COPD is the fifth leading cause of death in the UK and the fourth in the world. It is expected to rise to third position by 2020. It is estimated that over 3 million people have the disease in the UK, with 2 million having undiagnosed COPD (National Clinical Guideline Centre, 2010). COPD is the largest single cause of lost working days in the UK. It is accountable for more than 10% of all hospital admissions and directly costs the NHS around £491 m/year. The burden of COPD on the UK healthcare system exceeds that of asthma and is outlined in Table 1.

Respiratory diseases including chronic bronchitis are more common in areas of high atmospheric pollution and in people with dusty occupations such as foundry workers and coal miners. Areas that are highly industrialized generally have the highest incidence of COPD. The UK has around twice the rate of mortality from respiratory disease compared to the European average.

**Table 1.Annual morbidity and mortality from COPD (National Clinical Guideline Centre, 2010)**

| | Hospital Admissions | GP consultations | Deaths |
|---|---|---|---|
| England and Wales | 130,000 | 1.4 million | 30,000 |

## ETIOLOGY:

Chronic bronchitis is strongly associated with cigarette smoking; but this doesn't exclude persons who have never smoked. Other factors such as pollution or occupational exposures have also been associated with bronchitis. Emphysema is also associated with smoking.

Cigarette smoking causes increased bronchial reactivity and inflammation. Ciliary function is depressed, resulting in decreased clearance of mucus and particles. Macrophage function is similarly inhibited. Release of lysosomal enzymes destroys the connective tissue in the lung.

A history of chronic bronchitis can often be elicited in patients with the centrilobular form of emphysema.

Inborn errors resulting in enzymes deficiencies are rare causes of emphysema. If an imbalance elastase

and elastase inhibitor occurs, alveolar destruction results. A deficiency of $\alpha_1$ trypsin, elastase inhibitor, indicates a genetic basis; as the reason for alveolar wall destruction.

## RISK FACTORS OF COPD:

- Exposure to tobacco smoke: 80-90% cases caused by smoking. Several pharmacological interventions now exist to aid smokers in cessation; these include nicotine replacement therapy, bupropion and varenicline.
- Passive smoking
- Occupational exposure
- Ambient air pollution

- Genetic abnormalities, including a deficiency of alpha 1 anti-trypsin enzyme.

**PATHOPHYSIOLOGY:**

The major pathological changes in COPD affect four different compartments of the lung and all are affected in most individuals to varying degrees.

The normal function of the respiratory system is carried out by the exchange of oxygen and carbon dioxide such that oxygen is delivered to the bloodstream and carbon dioxide is removed to the environment.

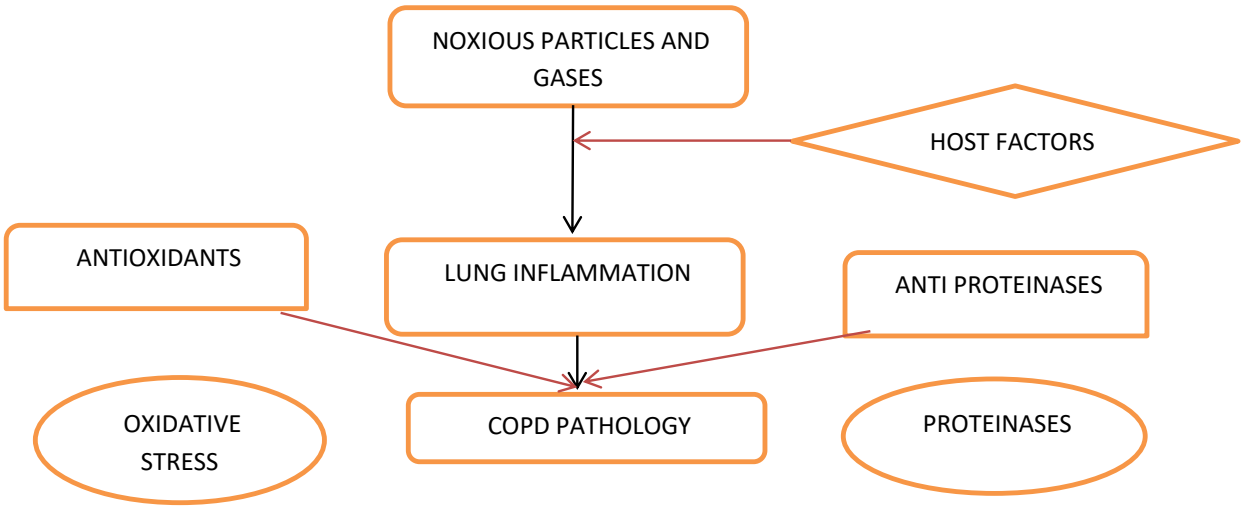
Chronic bronchitis is characterized by the excessive mucus secretion and inflammation in the bronchi that interferes with normal mechanisms to maintain airway integrity. The excessive mucus production is the result of irritation of the airway by smoke or other irritants. With chronic irritation, the mucus glands hypertrophy and their ducts dilate with in bronchial mucosa. Airway obstruction, when present, results from narrowing of the airway by thick, tenacious mucus and from bronchiolar inflammation and edema. Excess mucous results in plugs or consolidations Occlusion of the respiratory exchange units can occur from these plugs, reducing the functional air exchange area and causing destruction of the alveoli. Airway obstruction is not always present in chronic bronchitis but may occur only during exacerbations. Chronic recurrent bacterial infection is common in chronic bronchitis.

Emphysema involves anatomic alteration of the lung resulting in abnormally enlarged distal air spaces in combination with destructive changes in the alveoli. The result is loss of elastic recoil. Elastic recoil contributes significantly to the force of expiration: if decrease, distal airways will collapse during expiration and trap air. Pathologically, there are 2 types of emphysema.

- Centri lobular (centriacinar) emphysema is characterized by deposition of carbon pigment at the center of pulmonary lobule with distal alveoli left intact.
- Pan lobular (panacinar) emphysema is characterized by destruction of all areas of the pulmonary lobule.

  No specific laboratory information is useful in differentiating the various forms of COPD, with the exception of emphysema due to alpha 1 antitrypsin deficiency. This diagnosis is made by a serum protein electrophoresis study. Sputum and blood eosinophilia may be present if the COPD patient also has asthma component.

Emphysema should be suspected in the patient with progressive dyspnea and in the patient with a history of heavy smoking.




**CLASSIFICATION OF COPD:**

❖ Bronchodilators:

1. Sympathomimetic:
   - Salbutamol
   - Salmeterol
   - Terbutaline
   - Isoprenaline
   - Formaterol
   - Bambuterol
2. Methyl Xanthine:

- Theophylline
- Aminophylline

3. Anticholinergic:
   - Ipratropium bromide
   - Tiotropium bromide

❖ Leukotriene antagonist:
- Montelukast
- Zafirlukast

❖ Mast cell Stabilizers:
- Sodium chromoglycate
- Ketotifen

❖ Corticosteroids:

1. Systemic:
   - Hydrocortisone
   - Prednisolone
2. Inhalational:
   - Beclomethasone dipropionate
   - Budesonide
   - Fluticasone propionate
   - Flunisolide
   - Ciclesonide

❖ Anti-IgE antibody:
- Omalizumab

## DRUG THERAPY:

Drug therapy of these disorders involves dilating the airways, reducing inflammation and stabilizing mast cells. Several types of drugs are used, including bronchodilators, corticosteroids and others.

## MECHANISM OF ACTION:

**Bronchodilators:**

Adrenergic stimulate $\beta_2$ adrenergic receptors in bronchial smooth muscle. The receptors stimulate the enzyme adenylcyclase to increase production of cyclic AMP. The increased cyclic AMP produces bronchodilation. So $\beta_2$ adrenergic drugs like epinephrine also stimulate $\beta_1$ receptors in the heart to increase the rate and force of contraction. Cardiac stimulation is an adverse effect when the drugs are given for bronchodilation. Commonly used and preferred beta adrenergic bronchodilators are albuterol act more selectively on $\beta_2$ receptors and cause fewer cardiac effects.

**Short acting bronchodilators:**

Bronchodilators help open airways to make breathing easier.

- ***Albuterol (***Proair HFA, Ventolin HFA)
- ***Levalbuterol (***Xopenex***)***
- ***Ipratropium (***Atrovent HFA)
- ***Albuterol/Ipratropium (***Combivent Respimat)

Side effects: Dry mouth, headache, cough.

Other side effects: tremors (shaking), nervousness, a fast heartbeat.

**Long acting bronchodilators:**

Long acting bronchodilators are medications that are used to treat COPD over a longer period of time. They're usually taken once or twice daily using inhalers or nebulizers. Because these drugs work gradually to help ease breathing, they don't act as quickly as rescue medication. They're not meant to be used in an emergency situation.

- **Aclidinium (**Tudorza)
- **Arformoterol (**Brovana)
- **Formoterol (**Foradil, Perforomist)
- **Glycopyrrolate (**Seebri Neohaler, Lonhala Magnair)
- **Indacaterol (**Arcapta)
- **Olodaterol (**Striverdi Respimat)
- **Revefenacin (**Yupelri)
- **Salmeterol (**Serevent**)**
- **Tiotropium (**Spiriva)
- **Umeclidinium (**Incruse Ellipta)

Side effects: Dry mouth, dizziness, tremors, runny nose, irritated or scratchy throat, upset stomach.

Other side effects**:** blurry vision, rapid or irregular heart rate, an allergy reaction with rash or swelling.

**Methyl xanthines:**

Xanthine (e.g.: theophylline) were formerly thought to increase cyclic AMP by inhibiting the enzyme phosphodiesterase, which metabolizes cyclic AMP. They also increase cardiac output, cause peripheral vasodilation, exert a mild diuretic effect and stimulate the CNS. The cardiovascular and CNS effects are considered as adverse effects. A person suffering from severe COPD, the typical first line treatments like bronchodilators and corticosteroids not found to be effective. In such cases, a drug known as theophylline is prescribed along with a bronchodilator.

*Theophylline* works as an anti-inflammatory drug and relaxes the muscles in airways. It comes as a pill or liquid form.

Side effects: nausea or vomiting, tremors, headache and trouble sleeping.

**Combination drugs:**

Several COPD drugs come as combination medications. These are mainly combinations of either two long-acting bronchodilators or an inhaled corticosteroid and a long-acting bronchodilator.

For people with COPD who experience shortness of breath or trouble breathing during exercise, the American Thoracic Society strongly recommends a long-acting beta agonist (LABA) combined with a long-acting muscarinic antagonist (LAMA).

Triple therapy, a combination of an inhaled corticosteroid and 2 long-acting bronchodilators, is recommended for those who continue to have shortness of breath or trouble breathing and are currently using LABA and LAMA combination therapy. Recommended LABA/LAMA combination bronchodilator therapies include:

- **Aclidinium/ Formaterol** (Duaklir)
- **Glycopyrrolate/ Formaterol** (Bevepsi Aerosphere)
- **Tiotropium/ Olodaterol** (Stiolto Respimat)
- **Umeclidinium / Vilanterol** (Anoro Ellipta)

Combinations of an inhaled corticosteroid and a long acting bronchodilator include:

- **Budesonide/Formaterol** (Symbicort)
- **Fluticasone/Salmeterol** (Advair)
- **Fluticasone/Vilanterol**(Breo Ellipta)

Combinations of an inhaled corticosteroid and 2 long acting bronchodilators, called triple therapy include:

- **Fluticasone/Vilanterol/Umeclidinium** (Trelegy Ellipta)

A 2018 Research Review found that triple therapy reduced flare-ups and improved lung function in people with advanced COPD.

**Roflumilast:**

Roflumilast (**Daliresp**) is a type of drug called a phosphodiesterase-4 inhibitor. It comes as a pill you take once per day. Roflumilast helps relieve inflammation, which can improve air flow to your lungs. Your doctor will likely prescribe this drug along with a long-acting bronchodilator.

Side effects of Roflumilast can include: weight loss, diarrhea, headache, nausea, cramps, tremors, insomnia.

**Mucoactive drugs:**

COPD flare-ups can cause increased levels of mucus in the lungs. Mucoactive drugs help reduce mucus or thin it so you can more easily cough it up. They typically come in pill form and include: carbocysteine, erdosteine, N-acetyl cysteine.

A 2019 study Trusted Source suggested that these medications may help reduce flare-ups and disability from COPD.A 2017 study also found that erdosteine lowered the number and severity of COPD flare-ups.
Side effects: nausea, vomiting, stomach pain.

**Vaccines:**

It's important for people with COPD to get a yearly flu vaccine. The doctor may recommend the pneumococcal vaccine as well. These vaccines reduce your risk for getting sick and can help you avoid infections and other complications related to COPD. A 2018 research review found that the flu vaccine may also reduce COPD flare-ups, but it noted that there were few current studies.

**Antibiotics:**

Regular treatment with antibiotics like azithromycin and erythromycin may help manage COPD. A 2018 research review indicated that consistent antibiotic treatment helped reduce COPD flare-ups. However, the study noted that repeated antibiotic use can cause antibiotic resistance. More studies are needed to determine the long-term effects of regular antibiotic use.

Side effects: hearing loss.

**Cancer medications for copd:**

Several cancer drugs could possibly help reduce inflammation and limit damage from COPD. A 2019 study found that the drug tyrphostin AG825 helped lower inflammation levels in zebrafish. The medication also sped up the rate of death of neutrophils, which are cells that promote inflammation, in mice with inflamed lungs similar to COPD.
Research is still limited on using tyrphostin AG825 and similar drugs for COPD and other inflammatory conditions. Eventually, they may become a treatment option for COPD.

**Biologic drugs:**

In some people, inflammation from COPD may be a result of eosinophilia, or having a higher-than-normal number of white blood cells called eosinophil.

A 2019 study Trusted Source indicated that biologic drugs may be able to treat this form of COPD. Biologic drugs are created from living cells. Several of these drugs are used for severe asthma caused by eosinophilia, including:

- **Mepolizumab** (Nucala)
- **Benralizumab** (Fasenra)
- **Reslizumab** (Cinqair)
- **Dupilumab** (Dupixent)

More research is needed on treating COPD with these biologic drugs.

## MANAGEMENT OF COPD:

The clinical progress of COPD depends on whether bronchitis predominates or emphysema. Most patients with COPD usually have irreversible airway obstruction. Drugs therefore relieve only symptoms without treating underlying pathophysiology. Treatment aims for patients of COPD are:

1. To lessen airflow obstruction
2. To reduce respiratory system and improve quality of life
3. To prevent and treat secondary complications like hypoxaemia, infections and cor pulmonale.

Treatment options are mentioned below:

1. The most important therapeutic intervention is to ask the patient to stop smoking. Pharmacological intervention may also help stop smoking.
2. Influenza vaccine may be given to COPD patients every year and a proper antibiotic therapy should be provided if patient develops purulent sputum.
3. The first-line drug therapy for the treatment of COPD consists of bronchodilators to reduce bronchospasm and wheezing. Short-acting selective $\beta_2$-agonist should be tried initially since they provide rapid relief and low incidence of side effects on inhalation. There are reports that anti-muscarinics are more effective than $\beta_2$-agonists in COPD patients because the predominant airway muscle tone in COPD patients is parasympathetic. However, they have a slower onset of bronchodilatory effects. Hence, various guidelines suggest that COPD patients are benefitted more from a combined therapy. Long-acting $\beta_2$-agonists have no defined place in COPD treatment.
4. A xanthine such as theophylline may also be administered orally in addition to inhaled bronchodilators. Theophylline may improve respiratory muscle function in patients with COPD and because of its positive cardiac inotropic effects could be of value in cor pulmonale also. If lung functions show improvement, theophylline is usually continued as maintenance therapy. Persistent nocturnal symptoms such as cough or wheezing may be helped by night-time use of long-acting theophylline.
5. Some patients of COPD, who are receiving optimal bronchodilator therapy, exhibit a substantial better response further by administering corticosteroids orally (e.g., prednisolone 30-40mg per day orally for 15 days). If objective responses are achieved, the recommended guidelines suggest a continued use of inhalational corticosteroids as these are associated with lesser adverse effects. For the transition from oral to inhaled, the oral glucocorticoids are gradually tapered off and inhaled treatment is started. However, whether glucocorticoids improve the long-term outcome of COPD remains to be confirmed.
6. In the patients with severe COPD and persistent hypoxaemia, the use of domiciliary $O_2$ therapy for 15hrs a day reduces the associated mortality and the risk of complications such as cor pulmonale and neuropsychological impairment.
7. The use of mucolytics or expectorants is controversial though they definitely provide modest benefits in reducing exacerbations.

## OBJECTIVE OF MANAGEMENT CLIENT WITH COPD:

- Relieve symptoms
- Present disease progression
- Reduce mortality and improve exercise tolerance
- Prevent and treat complications

## MEDICAL MANAGEMENT:

Risk reduction is done by smoking cessation. It is the single most effective intervention to prevent COPD or s/low its progression.

**Stable COPD:**

Reduction in the risk of exacerbation, along with symptom management, is the cornerstone of the current strategy for management of COPD. The main components of COPD management are appropriate pharmacotherapy (that addresses both symptom management and exacerbation prevention), promotion of smoking cessation, pulmonary rehabilitation, and regular follow-up monitoring for disease progression.

The GOLD ABCD tool combines symptom severity, using either the COPD Assessment Test score or the modified Medical Research Council scale, together with exacerbation risk, determined by either spirometry-defined airflow limitation or exacerbation history, to categorize patients into disease “risk stratification” groups ABCD to guide pharmacotherapy (Figure 1).

Bronchodilators are central to management of COPD at all levels of severity. GOLD recommends specific treatment options for the initial therapy upon diagnosis of COPD in patients based on their ABCD classification. This initial therapy differs from the follow-up treatment, which is based on current medication(s) and the most treatable trait (e.g., dyspnea or exacerbation); after ensuring correct inhaler technique and adherence to the initial treatment regimen.

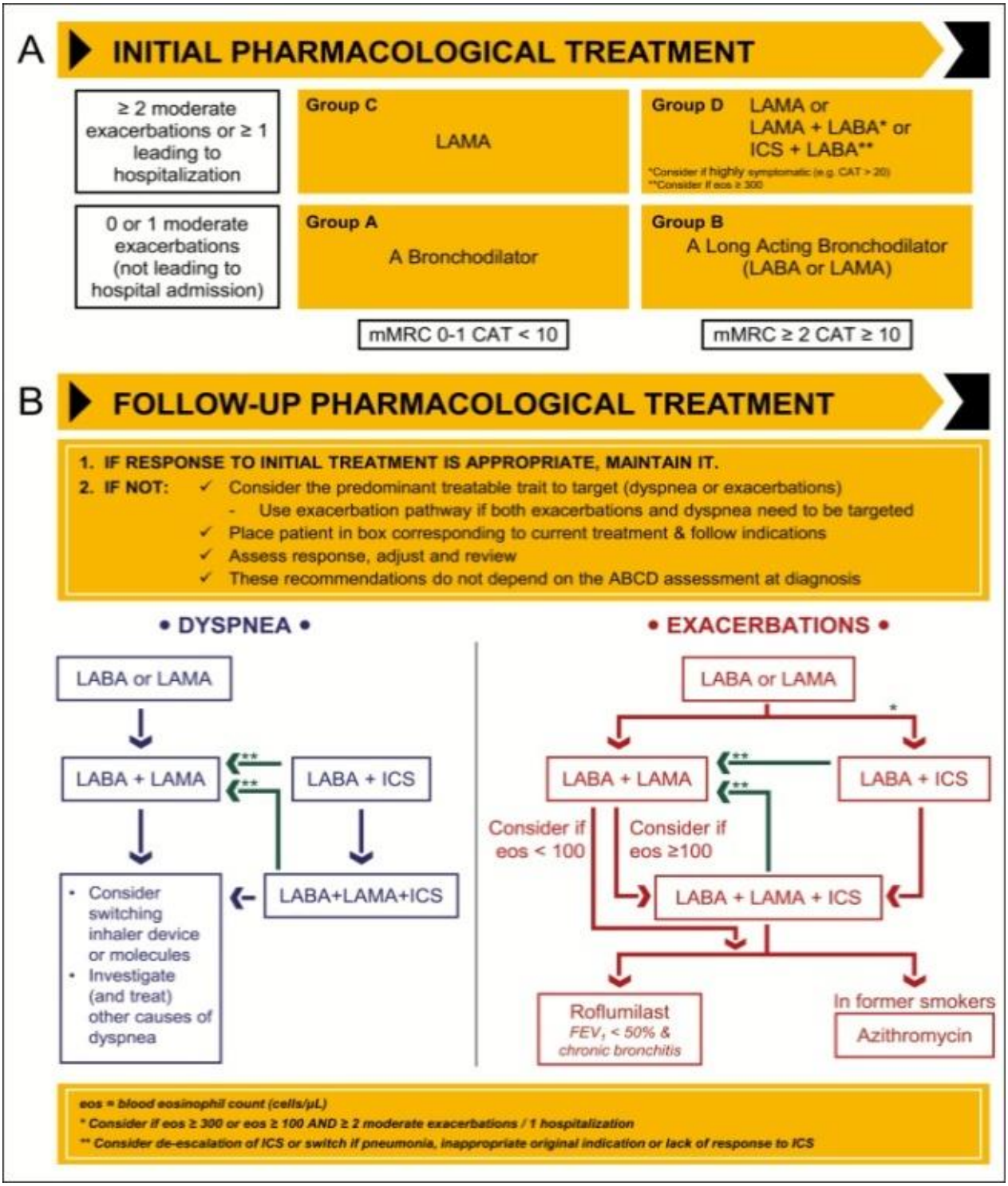



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Figure 1.. Recommended initial (A) and follow-up (B) treatment options. CAT = COPD assessment test, COPD = chronic obstructive pulmonary disease, Eos = eosinophil counts (cells/µL), $FEV_1$ = forced expiratory volume in 1 second, ICS = inhaled corticosteroid, LABA = long-acting $\beta_2$-agonist, LAMA = long-acting muscarinic antagonist, mMRC = modified Medical Research Council.

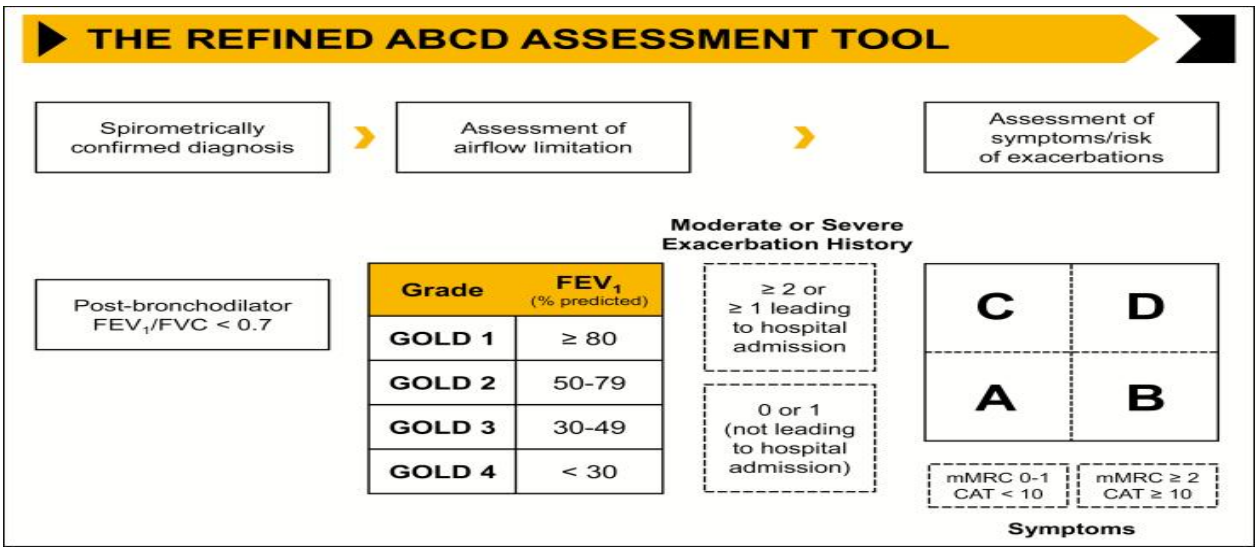


Figure 2.. Updated by GOLD classification of COPD severity. The GOLD guidelines updated in 2019 use exacerbation history and symptom burden to classify patient's future exacerbation risk stratification (ABCD tool). However, the use of spirometry is vital to properly diagnose and gauge a prognosis for the disease. CAT = COPD Assessment Test, COPD = chronic obstructive pulmonary disease, GOLD = Global Initiative for Chronic Obstructive Lung Disease, mMRC = modified Medical Research Council, $FEV_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity

## WARNINGS FOR COPD MEDICATIONS:

Whatever medication doctor prescribes, make sure to take it according to doctor's instructions. If serious side effects, such as an allergic reaction with rash or swelling, contact doctor right away. If difficulty breathing or swelling of the mouth, tongue, or throat, consult to the doctor or contact to the nearest medical services.

Because some COPD medications can affect your cardiovascular system, be sure to tell your doctor if you have an irregular heartbeat or cardiovascular problems.

## CLINICAL PRESENTATION AND DIAGNOSIS:

By the time of presentation for medical attention, patients usually are far advanced in their diseases with symptoms of airway obstruction. The usual presentation of COPD may begin with cough and increased sputum production, reminiscent of chronic bronchitis. The patient may have noticed a decline in exercise tolerance. Weight loss may be reported in obese patient with chronic emphysema. Dyspnea or breathlessness is the sensation of labored or difficult breathing. It occurs later in the course of COPD and maybe worsened by exposure to cold, dampness, pollution or acute infection. There is a close correlation between dyspnea and the degree of airway obstruction in patients with COPD.

Infections due to viruses, *Haemophilus influenza*, *Mycoplasma pneumonia*, *Streptococcus pneumonia* can trigger an acute deterioration in patient status, especially in the patient with chronic bronchitis. Patients with mucus hyper secretion are predisposed to repeated bacterial, viral, or mycoplasma infections. Decreased removal of bronchial secretions physically impairs the defenses of the lungs against infection. The mucus provides a good growth medium for bacteria. Colonization of the airways by these organisms has been clearly demonstrated. There is no conclusive evidence that colonization or recurrent infection contributes to the progression of COPD by contributing to further airway inflammation.

On physical examination certain characteristic signs maybe noted. A prolonged expiratory effect may be seen as a sign of airway obstruction in primary emphysema. These patients may also exhale through pursed lips in an attempt to control the rate of expiration. Grunting can be heard on expiration. The patient may also use the accessory respiratory muscles to aid in breathing. An overall increase in respiration is common. Wheezes maybe heard during bouts of airway obstruction in both chronic bronchitis

and emphysema. An increase in the anteroposterior diameter of the chest and the classic "barrel chest" can be seen in both the diseases. The chest X-ray maybe helpful in emphysematous bullae, or marked vascular changes is present.

| | Chronic Bronchitis ("Blue Bloater") | Emphysema ("Pink Puffer") |
|---|---|---|
| Symptoms | Chronic cough, Heavy sputum production | Dyspnea, minimal cough, minimal sputum production. |
| Weight | Obesity common | Marked weight loss |
| Smoking history | Common | Common |
| Blood gases | Low $PaO_2$ | Normal or slightly low $PaO_2$ |
| | Elevated $PaCO_2$ | Normal or slightly high $PaCO_2$ |
| | Respiratory acidosis | Normal pH or mild respiratory acidosis |
| Cor Pulmonale | Common | Less common |
| Respiratory | Repeated episodes | Rare until end stage |
| Pulmonary function test | Decreased forced expiratory volume ($FEV_1$) | Decreased ($FEV_1$) |
| | Decreased forced vital capacity (FVC) | Decreased (FVC) |
| | Increased residual volume | Greatly increased residual volume |

## PULMONARY FUNCTION TEST:

**Introduction:**

Pulmonary function tests or lung function tests are useful in assessing the **functional status** of the respiratory system both in physiological and pathological conditions. Lung function tests are based on the measurement of volume of air breathed in and out in quiet breathing and forced breathing. These tests are carried out mostly by using spirometer.

**Types of lung function tests:**

Lung function tests are of two types:

1. Static lung function tests
2. Dynamic lung function tests

**Static Function Tests:**

Static lung function tests are based on **volume of air that flows** into or out of lungs. These tests do not depend upon the rate at which air flows. Static lung function tests include static lung volumes and static lung capacities.

**Dynamic Lung Function Tests:**

Dynamic lung function tests are based on time, i.e. the **rate at which air flows** into or out of lungs. These tests include forced vital capacity, forced expiratory volume, maximum ventilation volume and peak expiratory flow.

Dynamic lung function tests are useful in determining the severity of obstructive and restrictive lung diseases.

**Lung volumes:**

Static lung volumes are the volumes of air breathed by an individual. Each of these volumes represents the volume of air present in the lung under a specified static condition (specific position of thorax).

Static lung volumes are of four types:

a) Tidal volume
b) Inspiratory reserve volume
c) Expiratory reserve volume
d) Residual volume

**Tidal volume:**

Tidal volume (TV) is the volume of air breathed in and out of lungs in a single normal quiet respiration. Tidal volume signifies the normal depth of breathing.
Normal value- 500ml (0.5 L)

**Inspiratory reserve volume:**

Inspiratory reserve volume (IRV) is an additional volume of air that can be inspired forcefully after the end of normal inspiration.
Normal value- 3,300ml (3.3L)

**Expiratory reserve volume:**
Expiratory reserve volume (EVR) is the additional volume of air that can be expired out forcefully, after normal expiration.
Normal value- 1,000ml (1L)

**Residual volume:**
Residual volume (RV) is the volume of air remaining in lungs even after forced expiration. Normally, lungs cannot be emptied completely even by forceful expiration. Some quantity of air always remains in the lungs even after the forced expiration.
Residual volume is significant because of two reactions:

1. It helps to aerate the blood in between breathing and during expiration.
2. It maintains the contour of the lungs.

Normal value- 1,200ml (1.2L)

**Lung capacities:**
Static lung capacities are the combination of two or more lung volumes. Static lung capacities are of four types:

a) Inspiratory capacity
b) Vital capacity
c) Functional residual capacity
d) Total lung capacity

**Inspiratory capacity:**
Inspiratory capacity (IC) is the maximum volume of air that is inspired after normal expiration (end expiratory position). It includes tidal volume and inspiratory reserve volume.

IC = TV + IRV
=500 + 3,300 =3,800ml

**Vital capacity (vc):**
Vital capacity (VC) is the maximum volume of air that can be expelled out forcefully after a deep (maximal) inspiration. VC includes inspiratory reserve volume, tidal volume and expiratory reserve volume.

VC = IRV + TV + ERV
= 3,300 + 500 + 1,000 = 4,800 mL

Vital capacity is significant physiologically and its determination is useful in clinical diagnosis.

**Functional Residual Capacity:**
Functional residual capacity (FRC) is the volume of air remaining in lungs after normal expiration (after normal tidal expiration). Functional residual capacity includes expiratory reserve volume and residual volume.

FRC = ERV + RV
= 1,000 + 1,200 = 2,200 mL

**Total Lung Capacity:**
Total lung capacity (TLC) is the volume of air present in lungs after a deep (maximal) inspiration. It includes all the volumes.

TLC = IRV + TV + ERV + RV
= 3,300 + 500 + 1,000 + 1,200
= 6,000 mL

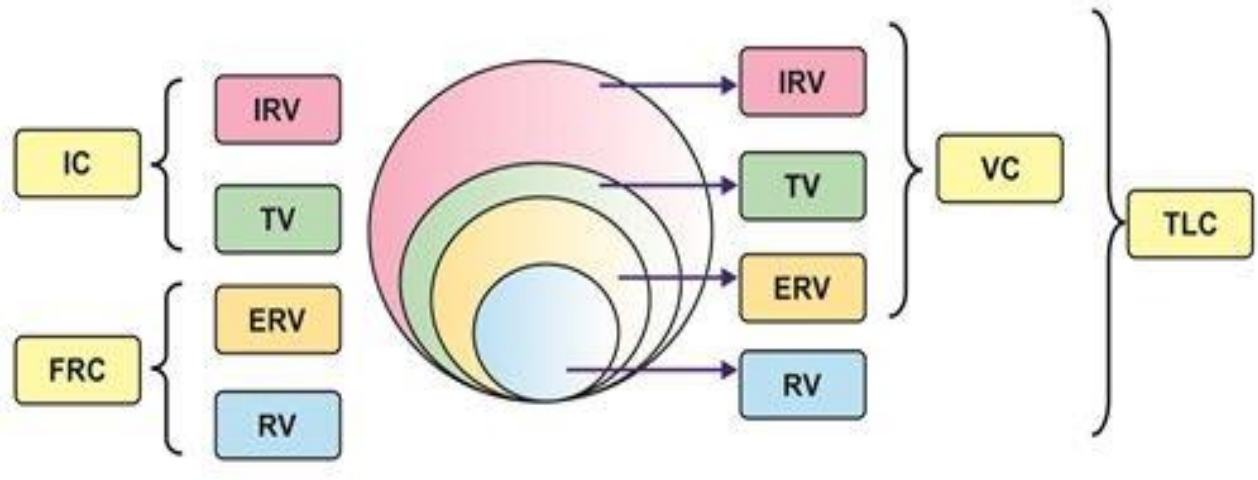


Figure 3. Lung volumes and capacities. TV = Tidal volume, IRV = Inspiratory reserve volume, ERV = Expiratory reserve volume, RV = Residual volume, IC = Inspiratory capacity, FRC = Functional residual capacity, VC = Vital capacity, TLC = Total lung capacity.

**Measurement of lung volumes and capacities:**
Spirometry is the method to measure lung volumes and capacities. Simple instrument used for this purpose is called spirometer. Modified spirometer is known as respirometer. Nowadays plethysmograph is also used to measure lung volumes and capacities.

**Spirometer:**
Spirometer is made up of metal and it contains two chambers namely outer chamber and inner chamber (Fig. 4). Outer chamber is called the **water chamber** because it is filled with water. A **floating drum** is immersed in the water in an inverted position. Drum is counter balanced by a **weight**. Weight is attached to the top of the inverted drum by means of string or chain. A **pen with ink** is attached to the counter weight. Pen is made to write on a **calibrated paper**, which is fixed to a recording device. Inner chamber is inverted and has a small hole at the top. A long metal tube passes through the inner. Upper end of this tube reaches the top portion of the inner chamber. Then the tube passes through a hole at the top of inner chamber and penetrates into outer water chamber above the level of water. A **rubber tube** is connected to the outer end of the metal tube. At the other end of this rubber tube, a mouthpiece is attached. Subject respires through this mouthpiece by closing the nose with a **nose clip**.

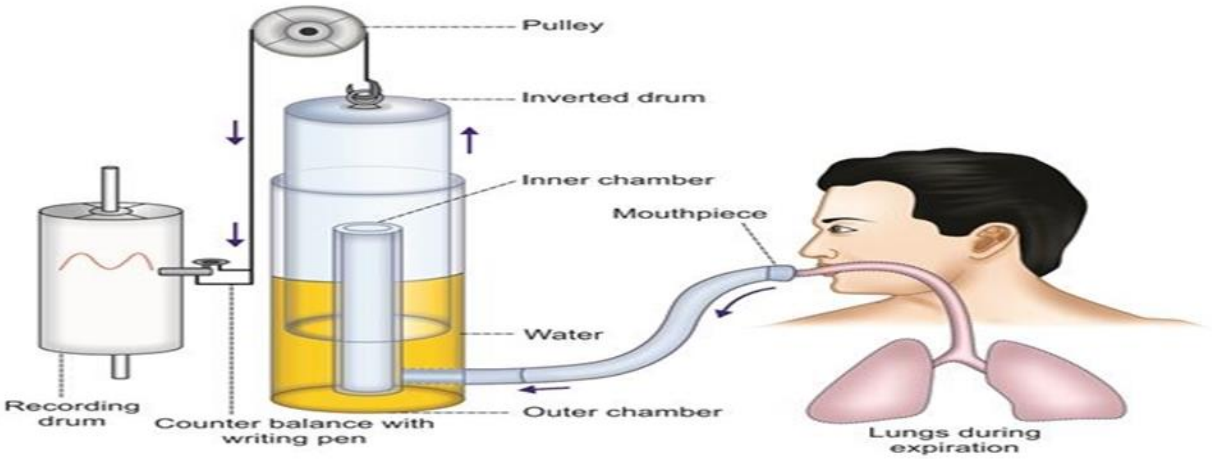


Figure 4. Spirometer; During expiration, the air enters the spirometer from lungs. Inverted drum moves up and the pen draws a downward curve on the recording drum.

When the subject breathes with spirometer, during expiration, drum moves up and the counter weight comes down. Reverse of this occurs when the subject breathes the air from the spirometer, i.e. during inspiration. Upward and downward movements of the counter weight are recorded in the form of a graph. Upward deflection of the curve in the graph shows inspiration and the downward deflection denotes expiration.
Spirometer is used only for a **single breath**. Repeated cycles of respiration cannot be recorded by using this instrument because carbon dioxide accumulates in the spirometer and oxygen or fresh air cannot be provided to the subject.

**RESPIROMETER:**

Respirometer is the modified spirometer. It has provision for removal of carbon dioxide and supply of oxygen. Carbon dioxide is removed by placing soda lime inside the instrument. Oxygen is supplied to the instrument from the oxygen cylinder, by a suitable valve system. Oxygen is filled in the inverted drum above water level and the subject can breathe in and out with instrument for about 6 minutes and recording can be done continuously.

**SPIROGRAM:**
Spirogram is the graphical record of lung volumes and capacities using spirometer. Upward deflection of the spirogram denotes inspiration and the downward curve indicates expiration (Fig.5). In order to determine the lung volumes and capacities, following four levels are to be noted in spirogram:
1. Normal end expiratory level
2. Normal end inspiratory level
3. Maximum expiratory level
4. Maximum inspiratory level

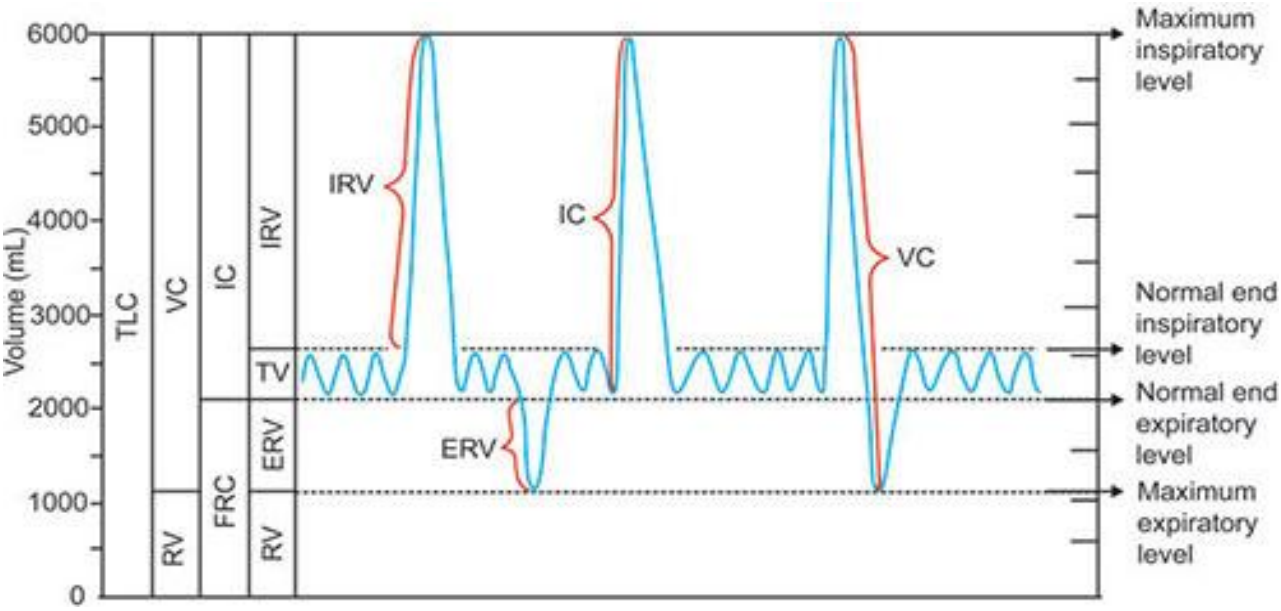


Figure 5. Spirogram. TV = Tidal volume, IRV = Inspiratory reserve volume, ERV = Expiratory reserve volume, RV = Residual volume, IC = Inspiratory capacity, FRC = Functional residual capacity, VC = Vital capacity, TLC = Total lung capacity

## COMPUTERIZED SPIROMETER:

Computerized spirometer is the solid state electronic equipment. It does not contain a drum or water chamber. Subject has to respire into a sophisticated transducer, which is connected to the instrument by means of a cable.

**Disadvantages of Spirometry**

By using simple spirometer, respirometer or computerized spirometer, not all the lung volumes and lung capacities can be measured.

Volume, which cannot be measured by spirometry, is the residual volume. Capacities, which include **residual volume,** also cannot be measured. Capacities that include residual volume are **functional residual capacity** and **total lung capacity**.

Volume and capacities, which cannot be measured by spirometry, are measured by **nitrogen washout technique** or **helium dilution technique** or by **body plethysmograph.**

## PLETHYSMOGRAPHY:

Plethysmography is a technique used to measure all the lung volumes and capacities.

**Measurement of functional residual capacity and residual volume:**

Residual volume and the functional residual capacity cannot be measured by spirometer and can be determined by three methods:

1. Helium dilution technique
2. Nitrogen washout method
3. Plethysmography.

## HELIUM DILUTION TECHNIQUE:

**Procedure to Measure Functional Residual Capacity:**

Respirometer is filled with air containing a known quantity of **helium**. Initially, the subject breathes normally. Then, after the end of expiration, subject breathes from respirometer. Helium from respirometer enters the lungs and starts mixing with air in lungs. After few minutes of breathing, concentration of helium in the respirometer becomes equal to concentration of helium in the lungs of subject. It is called the equilibration of helium. After **equilibration of helium** between respirometer and lungs, concentration of helium in respirometer is determined (Fig. 6).

Functional residual capacity is calculated by the formula:

$$FRC = \frac{V\,(C_1 - C_2)}{C_2}$$

Where,

$C_1$ = Initial concentration of helium in the respirometer,

$C_2$ = Final concentration of helium in the respirometer,

V = Initial volume of air in the respirometer.

**Measured Values:**

For example, the following data of a subject are obtained from the experiment:

1. Initial volume of air in respirometer = 5 L (5,000 mL)
2. Initial conc. of helium in respirometer = 15%
3. Final conc. of helium in respirometer = 10%.

**Calculation:**

From the above data, the functional residual capacity of the subject is calculated in the following way:

$$FRC = \frac{V\,(C_1 - C_2)}{C_2}$$

$$= \frac{5{,}000\,(\frac{15}{100} - \frac{10}{100})}{10/100}\ \text{ml}$$

$$= 2{,}500\ \text{ml}$$

**Procedure to Measure Functional Residual Capacity:**

Subject is asked to breathe normally. At the end of normal expiration, the subject inspires **pure oxygen** through a valve and expires into a Douglas bag. This procedure is repeated for 6 to 7 minutes, until the **nitrogen** in lungs is displaced by oxygen. Nitrogen comes to the **Douglas bag**. Afterwards, following factors are measured to calculate functional residual capacity.

Thus, the functional residual capacity in this subject is 2,500 ml.

**Procedure to Measure Residual Volume**:

To determine functional residual capacity, the subject starts breathing with respirometer after the end of normal expiration. To measure residual volume, the subject should start breathing from the respirometer after forced expiration.

**2. NITROGEN WASHOUT METHOD**:

Normally, concentration of nitrogen in air is 80%. So, if total quantity of nitrogen in the lungs is measured, the volume of air present in lungs can be calculated.

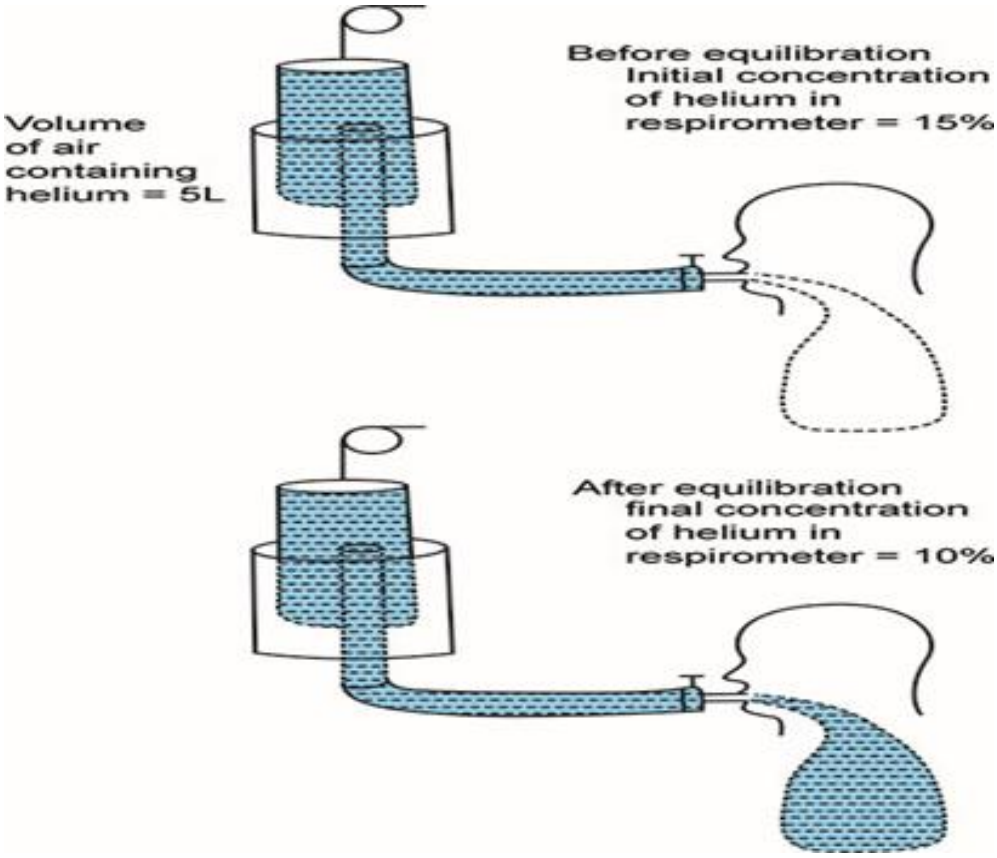


Figure 6. Measurement of functional residual capacity by using helium.

**Calculation:**

i. Volume of air collected in Douglas bag
ii. Concentration of nitrogen in Douglas bag. By using the data, the functional residual capacity is calculated by using the formula:

$$FRC = \frac{C_1 x\, V}{C_2}$$

Where,
V = Volume of air collected
$C_1$ = Concentration of nitrogen in the collected air
$C_2$ = Normal concentration of nitrogen in the air.

**Measured Values:**

For example, the following data are obtained from the experiment with a subject:

**i.** Volume of air collected = 40 L (40,000 mL)
**ii.** Concentration of nitrogen = 5% in the collected air
**iii.** Normal concentration of = 80% nitrogen in the air.

**Calculation:**

From the above data, the functional residual capacity of the subject is calculated in the following way:

$$FRC = \frac{C_1 x\, V}{C_2}$$
$$= \frac{5/100 \times 40{,}000}{80/100}$$
$$= 2{,}500 \text{ mL}$$

Thus, functional residual capacity in this subject is 2,500 ml.

**Procedure to Measure Residual Volume:**

To measure the functional residual capacity, the subject starts inhaling pure oxygen after the end of normal expiration and to determine the residual volume, the subject starts breathing pure oxygen after forceful expiration.

## PLETHYSMOGRAPHY:

Plethysmography is a technique to study the variations in the size or volume of a part of the body such as limb. **Plethysmograph** is the instrument used for this purpose. Whole body plethysmograph is the instrument used to measure the lung volumes including residual volume.

Plethysmography is based on **Boyle's law of gas**, which states that the volume of a sample of gas is inversely proportional to the pressure of that gas at constant temperature.

Subject sits in an airtight chamber of the whole body plethysmograph and breathes normally through a mouthpiece connected to a flow transducer called **pneumotachograph**. It detects the volume changes during different phases of respiration. After normal breathing for few minutes, the subject breathes rapidly with maximum force. During maximum expiration, the lung volume decreases very much. But volume of gas in the chamber increases with decrease in pressure. By measuring the volume and pressure changes inside the chamber, volume of lungs is calculated by using the formula:

$$P1 \times V = P2\ (V - \Delta V)$$

Where,
P1 and P2 = Pressure changes
V = Functional residual capacity.

## VITAL CAPACITY:

**Definition:**

Vital capacity is the maximum volume of air that can be expelled out of lungs forcefully after a maximal or deep inspiration.

**Lung volumes included in vital capacity:**

Vital capacity includes inspiratory reserve volume, tidal volume and expiratory reserve volume.

**Normal value:**

VC = IRV + TV + ERV
= 3,300 + 500 + 1,000 = 4,800 ml.

**Variations of vital capacity:**

**Physiological Variations:**

1. Sex: In females, vital capacity is less than in males
2. Body built: Vital capacity is slightly more in heavily built persons
3. Posture: Vital capacity is more in standing position and less in lying position
4. Athletes: Vital capacity is more in athletes
5. Occupation: Vital capacity is decreased in people with sedentary jobs. It is increased in Person's who play musical wind instruments such as bugle and flute.

**Pathological Variations:**

Vital capacity is decreased in the following respiratory diseases:

1. Asthma
2. Emphysema
3. Weakness or paralysis of respiratory muscle
4. Pulmonary congestion
5. Pneumonia
6. Pneumothorax
7. Hemothorax
8. Pyothorax
9. Hydrothorax
10. Pulmonary edema
11. Pulmonary tuberculosis.

**Measurement:**

Vital capacity is measured by spirometry. The subject is asked to take a deep inspiration and expire forcefully.

## FORCED VITAL CAPACITY:

Forced vital capacity (FVC) is the volume of air that can be exhaled forcefully and rapidly after a maximal or deep inspiration. It is a dynamic lung capacity.
Normally FVC is equal to VC. However in some pulmonary diseases, FVC is decreased.

## FORCED EXPIRATORY VOLUME OR TIMED VITAL CAPACITY:

**Definition**:
Forced expiratory volume (FEV) is the volume of air, which can be expired forcefully in a given unit of time (after a deep inspiration). It is also called timed vital capacity or forced expiratory vital capacity (FEVC). It is a dynamic lung volume.
$FEV_1$ = Volume of air expired forcefully in 1 second
$FEV_2$ = Volume of air expired forcefully in 2 seconds
$FEV_3$ = Volume of air expired forcefully in 3 seconds.

**Normal values:**
Forced expiratory volume in persons with normal respiratory functions is as follows:
$FEV_1$ = 83% of total vital capacity
$FEV_2$ = 94% of total vital capacity
$FEV_3$ = 97% of total vital capacity
After 3rd second = 100% of total vital capacity.

**Significance of determining fev:**
Vital capacity may be almost normal in some of the respiratory diseases. However, the FEV has great diagnostic value, as it is decreased significantly in some respiratory diseases.

It is very much decreased in obstructive diseases like asthma and emphysema. It is slightly reduced in some restrictive respiratory diseases like fibrosis of lungs.

## RESPIRATORY MINUTE VOLUME:

**Definition:**
Respiratory minute volume (RMV) is the volume of air breathed in and out of lungs every minute. It is the product of tidal volume (TV) and respiratory rate (RR).

$$RMV = TV \times RR = 500 \times 12$$
$$= 6{,}000 \text{ ml.}$$

**Normal value:**
Normal respiratory minute volume is 6 L.

**Variations:**
Respiratory minute volume increases in physiological conditions such as voluntary hyperventilation, exercise and emotional conditions. It is reduced in respiratory diseases.

## MAXIMUM BREATHING CAPACITY OR MAXIMUM VENTILATION VOLUME:

**Definition:**
Maximum breathing capacity (MBC) is the maximum volume of air, which can be breathed in and out of lungs by forceful respiration (hyperventilation: increase in rate and force of respiration) per minute. It is also called maximum ventilation volume (MVV).
MBC is a dynamic lung capacity and it is reduced in respiratory diseases.

**Normal value:**
In healthy adult male, it is 150-170L/minute and in females, it is 80-100L/minute.

**Measurement:**
Subject is asked to breathe forcefully and rapidly with a **respirometer** for 15 seconds. Volume of air inspired and expired is measured from the spirogram. From this value, the MBC is calculated for 1 minute.
For example, MBC in 12 seconds = 32 L
NMBC per minute = 60 L× 12 = 160 L

## PEAK EXPIRATORY FLOW RATE:

**Definition:**
Peak expiratory flow rate (PEFR) is the maximum rate at which the air can be expired after a deep inspiration.

**Normal value:**
In normal persons, it is 400 L/minute.

**Measurement:**
Peak expiratory flow rate is measured by using Wright peak flow meter or a mini peak flow meter.

**Significance of determining pefr:**
Determination of PEFR rate is useful for assessing the respiratory diseases especially to differentiate the obstructive and restrictive diseases. Generally, PEFR is reduced in all type of respiratory disease. However, reduction is more significant in the obstructive diseases than in the restrictive diseases.
Thus, in restrictive diseases, the PEFR is 200 L/minute and in obstructive diseases, it is only 100 L/minute.

**Restrictive and obstructive respiratory diseases:**
Diseases of respiratory tract are classified into two types:

1. Restrictive respiratory disease
2. Obstructive respiratory disease.

These two types of respiratory diseases are determined by lung functions tests, particularly FEV.

| Type | Disease | Structures involved |
|---|---|---|
| Restrictive respiratory diseases | Polio myelitis | CNS |
| | Myasthenia gravis | CNS and thoracic cavity |
| | Flail chest (broken ribs) | Thoracic cavity |
| | Paralysis of diaphragm | CNS |
| | Spinal cord diseases | CNS |
| | Pleural effusion | Thoracic cavity |
| Obstructive respiratory diseases | Asthma | Lower respiratory tract |
| | Chronic bronchitis | |
| | Emphysema | |
| | Cystic fibrosis | |
| | Laryngotracheobronchitis | Upper respiratory tract |
| | Epiglottis | |
| | Tumors | |
| | Severe cough and cold with phlegm | |

TABLE: Restrictive and obstructive respiratory diseases

**Restrictive Respiratory Disease:**
Restrictive respiratory disease is the abnormal respiratory condition characterized by difficulty in inspiration. Expiration is not affected. Restrictive respiratory disease may be because of abnormality of lungs, thoracic cavity or/and nervous system.

**Obstructive respiratory disease:**
Obstructive respiratory disease is the abnormal respiratory condition characterized by difficulty in expiration. Obstructive and respiratory diseases are listed in Table mentioned above.

**REVIEW LITERATURE:**

1. **David Price, Daniel West and Katsiaryma Bichel** conducted a study titled **an analysis of real-life prescribing patterns in the management of chronic obstructive pulmonary disease in UK primary-care setting.** The purpose of the study was to evaluate the current management of patients with COPD using a large UK primary-care database.
2. **Sarah E Petite** conducted a study titled **Characterization of chronic obstructive pulmonary disease** prescribing patterns in the United States which was published in *pulmonary pharmacology and therapeutics 49,119-122, 2018.* The aim was to determine the prescribing percentages of medications for COPD in a national, cross-sectional study.
3. **Mirko Di Martino, Nera Agabiti, Lisa Bauleo, Ursula Kirchmaver, Silvia Cascini Riccardo Pistelli, Vittoria Colamesta, Elisabetta Patorno** had conducted a study on the "**Use patterns of long-acting bronchodilators in routine COPD Care: the OUTPUL study** was published in *Journal of Chronic Obstructive Pulmonary Disease 11(4),414-423,2014.* The aim is to describe patterns of drug utilization among patients diagnosed with COPD, to measure continuity and adherence to long-acting bronchodilators therapy and to identify determinants of not receiving long acting bronchodilators continuously.
4. **Zainabath Sazmi, Sanjiv Karale, Sharanya S Rao, Amrutha Sathyan** conducted a study on the **Assessment of prescribing pattern of COPD patients** which was published in *Indian Journal of Pharmacy Practice 15(3),2022.* The objective of the study was to evaluate the prescribing patterns of corticosteroids and bronchodilators in COPD patients and to determine the type of therapy.
5. **Morven Wilkie, Simon Finch, Stuart Schembri** conducted a study titled **Inhaled corticosteroids for chronic obstructive pulmonary disease- the shifting treatment paradigm;** published in *Journal of Chronic*

*Obstructive Pulmonary Disease 12(5),582-590,2015.*

6. **Rachael L Di Santostefano, Tim Sampson, Hoa Van Le** conducted a study on **Risk of pneumonia with inhaled corticosteroid versus long-acting bronchodilator regimens in COPD: A New- User- Cohort Study** which was published in *PloS one 9(5), e 97149, 2014.* The objective was to estimate the association between ICS and pneumonia among new users of ICS relative to inhaled long acting bronchodilator (LABD) mono therapy.
7. **Alejandro Casas, Maria Montes De Oca, Ana MB Menezes, Fernado C Wehrmeister** conducted a study titled **Respiratory medication used in COPD patients from seven Latin American countries: the LASSYC study** and was published on *International journal of chronic obstructive pulmonary disease 13,1545,2018.*
8. **Maria Montes de Oca, Maria Victorina Lopez Varela, Jose Jardim Roberto Stirvulov, Filip Surmont** conducted a study titled **Bronchodilator treatment for COPD in primary care of four Latin American: The multinational, cross-sectional, non-interventional PUMA study** was published in *Pulmonary Pharmacology and Therapeutics 38,10-16,2016.*
9. **Jose Luis Lopez-Campos, Bernardino Alcazas Navarrete, Myriam Calle Rubio** conducted a study titled **Determinants of medical; prescriptions for COPD care: an analysis of the EPOCONSUL** clinical audit was published in *International Journal of Chronic Obstructive Pulmonary Disease 13, 2279, 2018.* The aim was to describe pharmacological prescriptions during a routine clinical visit for COPD and study the determinants of changing therapy.
10. **GUY Brusselle, David Price, Kevin Gruffy dd Jones, Marc Miravitlles, Dorothy L Keininger** conducted a study on **the inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK** which was published in *International Journal of Chronic Obstructive Pulmonary Disease 10, 2207, 2015.* The aim was to determine the prescribing of Triple Therapy (TT) before and after COPD diagnosis; the average time taken to receive TT and the impact of lung function grade, modified Medical Research Council dyspnea score and exacerbation history on the pathway to TT.

## METHODOLOGY:

The study is systematic review of the various literatures which are available on the various sources. The review, discussions were carried out and are concluded.

## DISCUSSION:

The review was carried out with the aim to analyze the prescribing pattern of bronchodilators and corticosteroids in the management of COPD patients, and also to determine the type of therapy i.e., combination or monotherapy commonly preferred in the management of the disease. The review also aims to determine gender and age distribution in COPD patients as well as to evaluate the most common comorbidity associated in the subjects.

## CONCLUSION:

COPD will remain a significant healthcare problem for years to come. Early identification of the disease through primary care screening for the common symptoms in smokers or those exposed to air pollutants or toxins will lead to earlier diagnosis and treatment. Focusing on smoking cessation will have a great impact on the progression of disease. Advancements in treatment will require translation of a more fundamental understanding of the pathophysiologic pathways involved into disease-modifying interventions. At present, management efforts are directed toward improving patients' symptoms and functional limitations through carefully selected treatment modalities.

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