ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 12| Issue: 1| January2026|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2025: 8.691 || ISI Value: 1.188

A REVIEW ON COPD CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

The noncommunicable chronic obstructive pulmonary disease (COPD) ranks among the top five leading causes of death worldwide. It is a preventable chronic disease that has become a major public health concern globally, as well as in India. To improve the pharmacotherapies management of COPD and to increase awareness about the prevalence of the disease, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has updated recommendations for the disease, base" on the current clinical effect. The present GOLD guideline endorses inhaled corticosteroids (ICS) combined with long-acting Bagonists (LABA) for a subgroup of patients. The article is an attempt to clearly define patient profiles that stand to benefit from ICS/LABA, LABA/long-acting muscarinic antagonists (LAMA), and ICS/LABA/LAMA combination therapy based on current clinical evidence. The discussion is presented under the following headings:

(i) *Disease burden worldwide, as well as in India;*
(ii) *Clinical symptoms and diagnosis of disease; (in) risk factors leading to the development of disease;*
(iii) *Pharmacotherapies agents for COPD;*
(iv) *Current updated recommendations from GOLD guidelines;*
(v) *Subgroup of patients who can benefit from various combinations of therapeutic agents; and*
(vi) *Comparative Analysis of clinical studies on various GOLD guideline-suggested combination therapies.*

KEYWORDS: COPD, emphysema, bronchodilators, asthma, Antimuscarinic, beta blocker, smoking, cardiovascular, lung, expiration, inhaler.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a poorly reversible disease of the lungs that is one of the major causes of morbidity and mortality worldwide. In the United States, it is the fourth leading cause of death after heart disease, cancer, and cerebrovascular disease.[1] By 2020, it is projected to become the third leading cause of death worldwide. Contrary to the trends for other major chronic disease in the United States, the prevalence of and mortality from COPD have continued to rise the death rates double between 1970 and 2002 and for the first time in 2000, mortality figures for women surpassed those for men. COPD is a characteristic by limitation of airflow which is caused by chronic bronchitis or emphysema oftenly accompanying with long term tobacco smoking.[2] This is typically a slowly progressive in de and largely irreversible process, which comprises of increased resistance to airflow. Loss of elastic recoil, decreased flow rate of expiration and overinflation of the lung.

The degree of bronchodilatory response at the time of testing, however, does not predict the degree of clinical benefits to the patient and this bronchodilators are given irrespective of the acute response obtained in the pulmonary function laboratory. COPD exhibits some following characteristics features.

1. Pathological changes that leads to reduction in the expiratory air flow.
2. They do not exhibit major reversibility in response to drugs.
3. The condition is accompanying with abnormal inflammatory response of the lungs to noxious particles or gases.
4. The principle cause of COPD is cigarette smoking. In which both active and passive smoking have been concerned. Other risks are air pollution and occupational exposure.

The airways are lined by muscle and elastic tissue. In a healthy lung, the Call in springy tissue between the airways acts as packing and pulls on the airways to keep them open. With COPD, the airways are narrowed because:[3]

- the lung tissue is damaged so there is less pull on the airways
- mucus blocks part of the airways
- the airway lining becomes inflamed and swollen

COPD

Definition

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung disease state characterised by chronic respiratory symptoms and airflow limitation that is not fully reversible. It encompasses emphysema, bronchiolitis, and chronic

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bronchitis. The airflow limitation is often progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases. It is primarily caused by cigarette smoking. Although COPD affects the lungs, it also has significant systemic consequences. Exacerbations or comorbidities are important contributors to the overall condition prognosis in individual patient. [4]

COPD comprise a diverse group of clinical syndrome that share the common features of limitations of expiratory airflow. [5]The American thoracic society defines COPD in terms of chronic bronchitis and emphysema. Chronic bronchitis is characterized by the clinical symptoms of excessive cough and sputum production; emphysema refers to chronic dyspnea, resulting from enlarged air spaces and destruction of the lung tissue. The GOLD initiative defines COPD as "a disease state characterized by airflow limitations that is not fully reversible.[6] The airflow limitations is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases." Asthma is also characterized by airflow obstruction and inflammation, but in addition it involves hyperresponsiveness of the airways to stimulus; therefore, the reversibility of functional deducts in asthma differentiates it form COPD.[7]

Causes

1. Chronic obstructive pulmonary disease (COPD) is caused due to several factors that narrow the airways. Below are the causes of COPD:
2. Smoking cigarette
3. Cigar, pipe, and other tobacco-based smoke
4. Exposure to more allergens in the air
5. Passive smoking
6. Dusts or vapors of chemicals from the workplace or surroundings
7. Air pollution
8. Alpha one antitrypsin deficiency, a rare hereditary autosomal recessive disease.
9. Normal alveoli
10. Lung Damaged

Symptoms

1. getting short of breath easily when you do everyday things such as going for a walk or doing housework
2. having a cough that lasts a long time
3. wheezing in cold weather
4. producing more sputum or phlegm than usual



Fig 1. Emphysema

Epidemiology

COPD is the third leading cause of death worldwide, causing 3.23 million deaths in 2019, with 90% of deaths in low- and middle-income countries. Globally, deaths from COPD increased by 23% from 1990 to 2017 and COPD and related deaths are estimated to increase to 5.4 million by 2060. COPD is more common in older people, especially those aged 65 years and older. COPD prevalence is highest in the World Health Organization region of the Americas and lowest in the South-East Asia and Western Pacific regions. The pooled global prevalence is 15.7% in men and 9.93% in women.[8] The prevalence of COPD in the US was estimated at 14% post-bronchodilator test results based on data from 2007 to 2010. The death rate due to COPD in the US increased over 100% between 1969 and 2013. A 2019 National Health Interview Survey revealed that the prevalence of COPD in US adults was greater in those living in non-metropolitan areas than in metropolitan areas, at 8.0% and 4.0%, r[9]

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Previously, most studies reported that the prevalence and mortality of COPD are greater in men than in women. However, data from 2012 to 2013 from developed countries suggest that COPD prevalence is now almost equal in men and women, probably due to different patterns of cigarette smoking. Some studies have also suggested that women may have a greater risk of airflow obstruction than men despite exposure to a similar dose of tobacco.

An international study reported that the prevalence of COPD in never-smokers is 12.2%. This may be due to air pollution or indoor burning of solid fuels in low- and middle-income countries. In the US, the prevalence of COPD in never-smokers is 2.2%. Many of these cases are attributed to workplace exposures such as in the mining industry and in food preparation and serving.[10]

Diagram

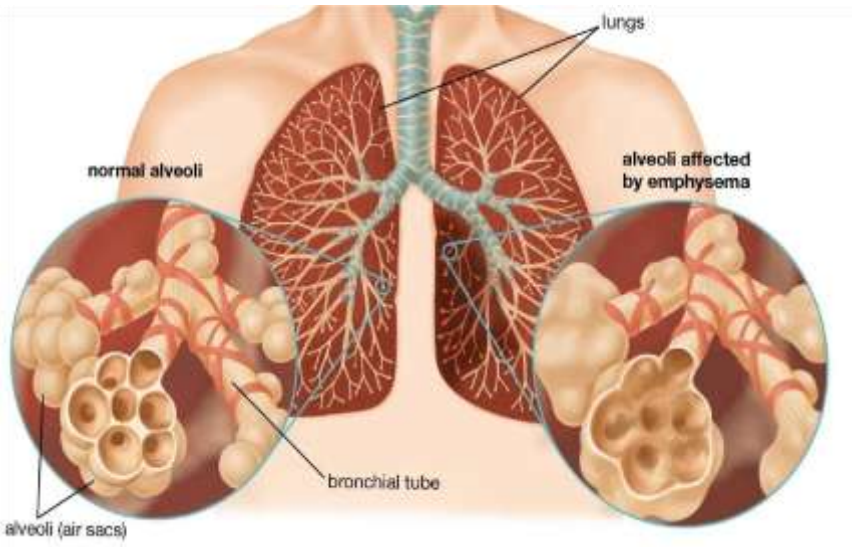


Fig 2. Alveoli effect by Emphysema

Pathophysiology

Chronic obstructive pulmonary disease (COPD) is known to have complex pathogenesis and is a critical form of slowly progressive pathological changes that occurs in pulmonary system resulting in the central and peripheral airway and parenchymal destruction.[11] It is also believed that since the bronchial tree is healthy or COPD individuals is not sterile, the lung microbiome and the bacterial community also participates and manipulates in the inflammatory response and the pathogenesis of the chronic obstructive pulmonary disease. Toxic smoke and chemical particles also influence inflammatory mechanisms and induce COPD exacerbations and functional alterations in the pulmonary system. The pathogenesis of chronic obstructive pulmonary disease is often described based on architecture alterations and morphological changes that are triggered by inflammatory mediators. The histopathological features differ in all chronic obstructive pulmonary disease according to the new pathological alteration triad of COPD.

The hallmark of COPD is chronic inflammation that affects central and peripheral airways, lung parenchyma and alveoli, and pulmonary vasculature. Repeated injury and repair leads to structural and physiological changes. The inflammatory and structural changes in the lung increase with disease severity and persist after smoking cessation.[12]

The main components of these changes are narrowing and remodeling of airways, increased number of goblet cells, enlargement of mucus-secreting glands of the central airways, alveolar loss, and, finally, vascular bed changes leading to pulmonary hypertension. Any relief from overthe-counter cough preparations. Evidence suggests that the host response to inhaled stimuli generates the inflammatory reaction responsibleHEfor the changes in the airways, alveoli, and pulmonary blood vessels. Activated macrophages, neutrophils, and leukocytes are the core cells in this process. Oxidative stress and an excess of proteases amplify theRYeffects of chronic inflammation. Airway remodeling thickens the epithelium, lamina propria, smooth muscle, and adventitia of airways less than 2 mm in diameter, leading to progressive loss of patent terminal and transitional bronchioles. Growing evidence implicates eosinophils, a leukocyte usually involved in allergic disease, in the COPD inflammatory cascade. Elastin breakdown and subsequent loss of alveolar integrity causes emphysema. Ciliary dysfunction and increased goblet cell size and number lead to excessive mucus secretion.[13]

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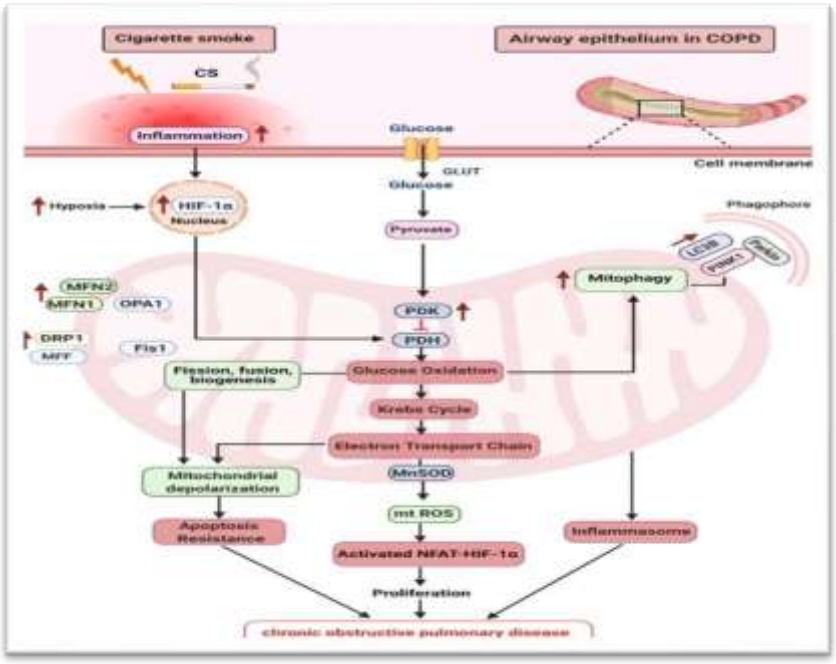


Fig 3. Pathophysiology of COPD

Pharmacological Treatments

Pharmacological treatment for COPD is intended to improve exercise tolerance and general health status and lessen the burden of symptoms and the frequency and severity of exacerbations Bronchodilators, systemic corticosteroids, and antibiotics are the primary treatment options used in the management plan for acute exacerbations of COPD in the hospital setting.

1. Bronchodilators

Bronchodilators are considered one of the mainstays in treating COPD at all levels of severity. They include beta-2 agonists and antimuscarinics drugs.

Tiotropium, a LAMA, has been shown to reduce risk of exacerbation versus placebo or other maintenance treatments. Newer LAMAs, such as aclidinium, glycopyrronium, and umeclidinium, have at least comparable efficacy to tiotropium, in terms of change from baseline in trough FEV, transitional dyspnoea index focal score, St George's Respiratory Questionnaire score, and rescue medication use. Revefenacin is a nebulised LAMA approved for the maintenance treatment of moderate to severe COPD.

There is a suggestion of increased cardiovascular-related mortality in some studies of patients taking short-acting muscarinic antagonists and in some studies of patients taking LAMAs. One study concluded that aclidinium was not associated with an increase in major adverse cardiovascular events, compared with placebo. A population-based cohort study found that older men with COPD newly started on LAMAs are at increased risk of urinary tract infections.

2. Short-acting bronchodilator

If you only get short of breath when you're active, your doctor will give you a short-acting bronchodilator. This will help your breathing quickly and the effects last for 4 to 6 hours.

3. Long-Acting Bronchodilator

If you're breathless daily, you'll be prescribed a 9-acting bronchodilator. This may take longer to have an effect, but the effects last longer – 12 to 24 hours. There are two main types of long-acting drugs. They are called long-acting anti-muscarinic (LAMA) and longacting beta agonist (LABA). Most people with COPD who are breathless will benefit from taking both kinds. Sometimes they come in separate inhalers and sometimes in combinations. You may get on better with one or another version, but in general they are all thought to be equally effective.

4. Beta-2 Agonists

Beta-2 agonists improve symptoms of COPD exacerbation and FEV1 by activating beta-2 adrenergic receptors, which relax the smooth muscle of the airways, thus raising cyclic adenosine monophosphate(cAMP) and functionally opposing bronchoconstriction. Beta-2 agonists are of two types: short-actingbeta-2 agonists (SABAs) and long-acting beta-2 agonists (LABAs). The short-acting are salbutamol(albuterol), levalbuterol, terbutaline, and fenoterol. Long-acting beta-2 agonists significantly reduce these verity of dyspnea, rate of exacerbation, and number of hospitalizations. However, these medicines haven impact on mortality or decline in lung function. The drugs are further classified according to their duration of action and daily dosage. Some are used twice a day, which

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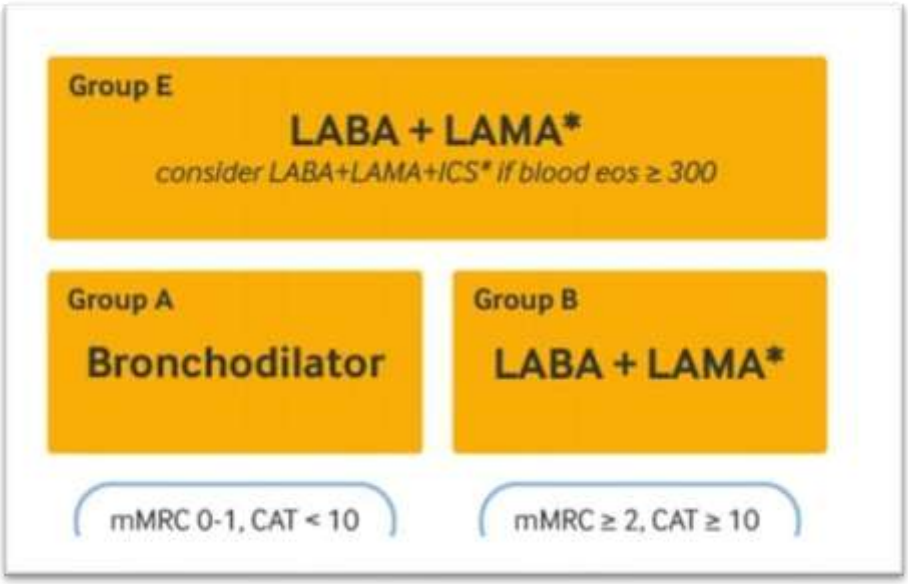
includes formoterol and salmeterol, while indacaterol, oladaterol, and vilanterol are required once a day as they have a duration of action of24 hours. In addition to the clinical benefits, beta-2 agonists possess several harmful effects, too, such as sinus tachycardia, palpitations, somatic tremors, variations in blood pressure, hypokalemia, and increased oxygen consumption.

5. Antimuscarinic

Antimuscarinic drugs cause bronchodilation by inhibiting the acetylcholine effects on muscarinic 3 (M3) muscarinic receptors in smooth airway muscles. Ipratropium and oxitropium are two examples of short-acting antimuscarinics (SAMAs) that additionally block the inhibitory neuronal receptor M2, potentially contributing to vagally induced bronchoconstriction. Tiotropium, glycopyrroniumbromide, aclidinium, and umeclidinium are a few examples of long-acting muscarinic antagonists (LAMAs), which prolong the duration of the bronchodilator effect by prolonged binding to M3 muscarinic receptors and quicker dissociation from M2 muscarinic receptors. Unlike beta-2 agonists, these drugs havefewer side effects, which are not severe and are similar to all drugs in this class. It includes dry mouth, urinary symptoms, and a bitter and metallic taste.

6. Initial pharmacologic treatment of COPD

In the initial management of COPD exacerbations, SABAs with or without SAMA are highly preferred, regardless of the inadequacy of high-quality evidence from randomized controlled trials. Moreover, as per the GOLD 2023 report, no clinical evidence determines the advantageous role of LABAs with or without LAMAs in acute exacerbations of COPD. However, it is recommended to start these drugs during exacerbations or as soon as possible before hospital discharge. Dual LABA therapy and LAMA are highly preferred in moderate-tosevere exacerbations or patients requiring hospitalization. It is also evident from a Cochrane systematic review and network meta-analysis that the combination therapy of LABA in conjugation with LAMA was considered the top-ranked therapy for reducing the exacerbation of COPD



7. Beta Blockers

The effects of beta (β)-receptor activation are countered by beta blockers, which bind specifically to beta-receptors and prevent beta-receptor agonists from binding to those receptors. Beta blocks are divided into cardio-selective and non-selective blockers as per different receptor subtypes. Non-selective β-blockers, including propranolol and carvedilol, act on both β-1 and β-2 receptors, whereas cardio selective β-1blockers such as atenolol, bisoprolol, and metoprolol have a 20-fold higher affinity for β-1 receptors as compared to β2 receptors, which makes them less susceptible to causing bronchoconstriction .When respiratory conditions are present, review articles and practice recommendations demonstrate a clinical reluctance to administer selective beta-1 blockers; however, a Cochrane review found that beta-1blockers did not impair beta agonist responsiveness or the ability to treat COPD . Different observational studies have shown evidence that suggests that β blockers cause a marked reduction in hospital admissions, mortality, hospital visits, especially in the emergency room (ER), and COP exacerbations in patients with COPD with or without cardiovascular disease (CVD). Despite various studies showing the positive effects of β-blockers, especially cardio selective β1 blockers, on COP exacerbation and mortality, the recent LD report 2023 recommended that selective β1 blockers should only be used in patients having COPD concomitantly with a CVD.

8. Inhaler

If you are given inhaled medicine to take regularly make sure that you use it every day as prescribed, even if you feel well. This can also reduce the risks of a flare-up. You can take your inhaled medicine in different ways. These include different sorts of inhalers:

- Dry powder inhalers – suck in as hard as you can then hold your breath for ten seconds

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- Pressurised metered dose inhalers – they produce a puff of medication like an aerosol – use a slow deep breath in and hold your breath for up to ten seconds
- Spacers – these attach to pressurised metered dose inhalers to help you breathe in the drug more effectively
- Nebulizers – these devices turn the medicine into a mist that you can breathe in. They're used in an emergency when you need large doses of inhaled medicine, such as during a flareup. Most people don't need such a big dose and get as much benefit from normal inhalers as long as they use them correctly with a spacer.

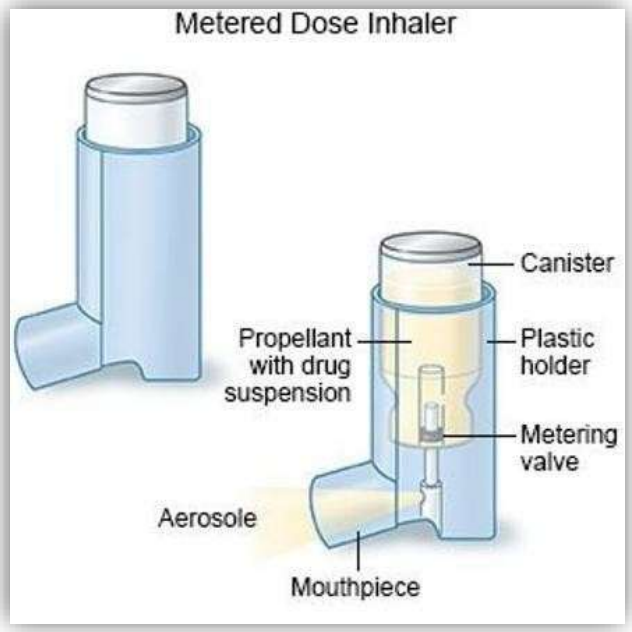


Fig 4. Metered Dose Inhaler

Side Effects from Medications

It's not common to get side effects from inhaled drugs, as the dose is usually very small. Steroid inhalers can sometimes make your voice hoarse or give you a fungal Infection, called thrush, in your mouth. You can reduce the risk by using your inhaler correctly and rinsing your mouth out after every time you use it, Steroid tablets can help during flare-ups but cause side effects if taken at a high dose or for a long time. Long-term treatment is not usually recommended. Side effects include increased appetite, difficulty sleeping, diabetes, weakening of the bones (osteoporosis), thin skin that bruises easily, cataracts and severe mood changes.

- **Oxygen therapy and ventilatory support**.

GOLD guidelines recommend long-term oxygen therapy in stable patients who have:

PaO2 ≤7.3 kPa (55 mmHg) or SaO2 <88%, with or without hypercapnia confirmed twice over a 3-week period; or
PaO, between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO2 of 88%, if there is evidence of pulmonary hypertension, peripheral oedema suggesting congestive cardiac failure, or polycythaemia (haematocrit >55%).

Guidelines from the American Thoracic Society (ATS) recommend prescribing longterm oxygen therapy for at least 15 hours per day in adults with COPD who have severe chronic resting room air hypoxaemia. The ATS defines severe hypoxaemia as either:

- PaO, ≤7.3 kPa (55 mmHg) or oxygen saturation as measured by pulse oximetry (SpO2) ≤88%; or
- PaO2 7.5 to 7.9 kPa (56-59 mmHg) or SpO2 of 89% plus one of the following: oedema, haematocrit ≥55%, or P pulmonale on an ECG.

For patients prescribed home oxygen therapy, the ATS recommends that the patient and their carers should receive instruction and training on the use and maintenance of all oxygen equipment and education on oxygen safety, including smoking cessation, fire prevention, and tripping hazards

Supplemental oxygen should be titrated to achieve SaO, ≥90%. The patient should be reassessed after 60-90 days to determine whether oxygen is still indicated and is therapeutic. Among different therapeutic modalities in COPD, the only two factors that improve survival are smoking cessation and oxygen supplementation.

Oxygen therapy helps to minimise pulmonary hypertension by decreasing pulmonary artery pressure, and improves exercise tolerance and quality of life. It has been shown to improve survival.

Surgery

 Lung volume reduction procedures few percent of people with emphysema and COPD may benefit from a lung volume reduction procedure to reduce the amount of air trapped in their

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lungs. This can involve an operation to remove the worst affected area of lung or putting valves into the airways with a fiber-optic camera to block the worst area off. This allows the remaining healthier parts of the lungs to work better so that you can breathe more easily. If you've had pulmonary rehabilitation and are still limited by breathlessness, ask your doctor if you might be suitable for a lung volume reduction procedure. Your GP can refer you to a specialist center.

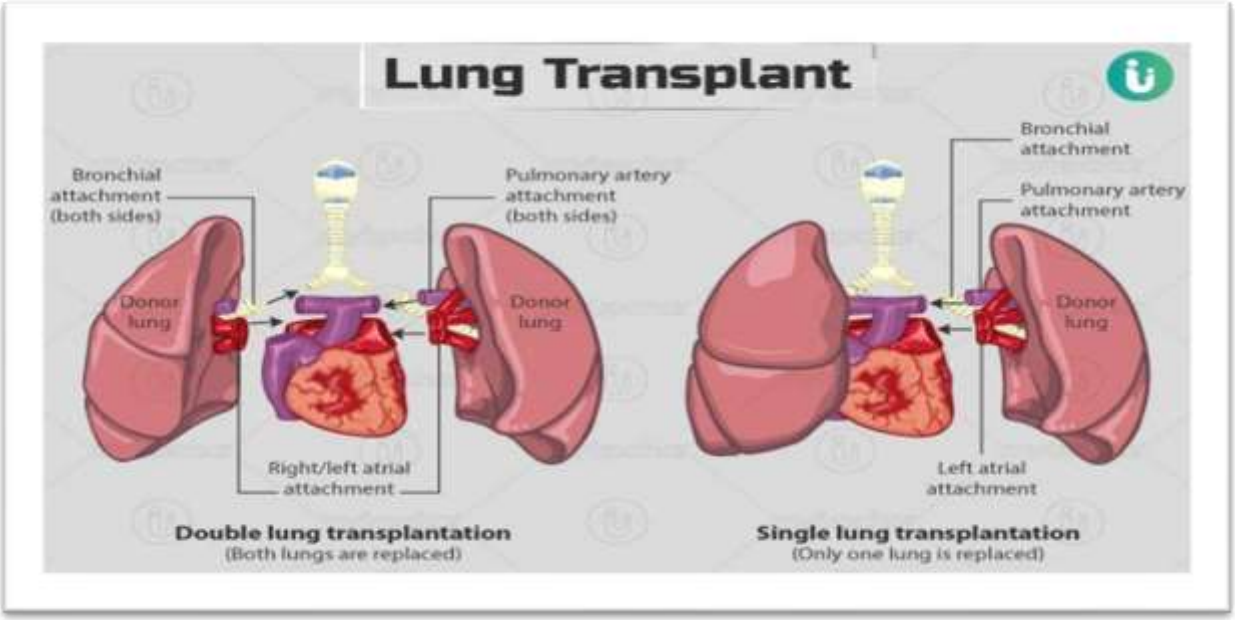


Fig 5. Lung Transplant

Lung Transplant

Lung Transplant Is A High-Risk major operation and is only suitable for a small number of people. Currently, there are not enough donor lungs available to meet demand. Whether you can be considered for a lung transplant depends on factors that influence the chance of a successful outcome. These include your general health and fitness, other medical conditions that mean that you would not be able to cope with the procedure and whether you are over- or under-weight. You will also need to have not smoked for at least 6 months. There is no strict age cut-off, but it's unusual for people with COPD to have a transplant much ki over 60 years old.

CONCLUSION

Chronic obstructive pulmonary disease (COPD) is a complex disease with multiple pathogenic mechanisms. Clinically. Patients will receive better management outcomes when physicians understand the clinical setting on taking a history, physical examination, and performing laboratory and imaging workups. Moreover, COPD treatment depends on the severity of the disease. Physicians must determine and understand COPD GOLD assessment strategies to adopt appropriate inpatient and outpatient management plan for the patient.

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