48 *Evolving Trends in the Management of Chronic Obstructive Pulmonary Disease*

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Abstract: Chronic obstructive pulmonary disease (COPD) is a syndrome of progressive airflow limitation caused by chronic inflammation of the airways and lung parenchyma. It stems from tobacco smoking, and indoor air pollution, and bronchospasm is the predominant cause of the symptoms. The condition exhibits expiratory airflow limitation due to abnormalities in the airways and/or lung parenchyma.

The understanding of the pathogenesis and pathophysiology of COPD have presented a number of novel therapeutic opportunities. The management guidelines include assessment and monitoring of the disease, reduction of risk factors and treatment of patients with stable COPD and with those exhibiting infective exacerbations. The diagnosis, though, is suggested by symptoms, it is to be confirmed by spirometry. The airflow limitation is not fully reversible. The severity of the disease is based on the measurements of airflow limitation during forced expiration.

The deterioration of lung functions, and progressive downhill course of COPD should be prevented by smoking cessation, by controlling atmospheric pollution, and by treatment directed to reduce airway obstruction and reduction of its pathologic consequences.

The drugs are administered in a stepwise manner. Beta-2 adrenergic receptor agonists and anti-cholinergic drugs are the mainstay in the therapy for many patients with COPD. Both short-acting and long-acting preparations are used. The future treatment of patients with COPD involves more extensive use of combination of short- and long-acting bronchodilators. Methyl xanthine and cilomilast are other agents used in the management. Inhaled corticosteroids are to be used in selected patients. Antibiotics and oxygen are necessary in the management of acute exacerbations of COPD. In hypoxemic patients with stable chronic COPD, long-term oxygen therapy improves neuropsychiatric functions and reduces mortality. These patients need pulmonary rehabilitation to return to highest possible functional capacity. Lung-volume reduction surgery and lung transplantation are the two surgical procedures available in selected cases.

There are no current therapies that reduce the inevitable progression of COPD. Greater understanding of the cellular and molecular mechanisms of COPD has enabled to develop new molecules to counteract the underlying inflammation and destruction of this relentlessly progressive chronic debilitating disease. Novel treatments are very much needed.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease associated with long-term exposure to toxic gases and particles, mostly related to cigarette smoking. The median prevalence of COPD in India is about 5 percent in men and 2.7 percent in women of age above 30 years.[1] Even though there have been significant advances in the understanding and management of COPD suggesting that the disease may be largely preventable, it remains marginally treatable.

COPD is a syndrome of progressive airflow limitation caused by chronic inflammation of the airways and lung parenchyma.[2] It leads to a gradual decline in lung function and worsening of dyspnea and health status. The guidelines formulated by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in the management of COPD include the following components:[3]

1. Assessment and monitoring of the disease
2. Reduction of risk factors and
3. Treatment of patients with stable COPD.

Assessment and Monitoring of COPD

Successful management of COPD depends on correct diagnosis of COPD that includes two distinct patho-physiologic processes such as chronic bronchitis and emphysema. The pathologic hallmarks of COPD are destruction of the lung parenchyma (pulmonary emphysema), inflammation of the small peripheral airways (respiratory bronchiolitis) and inflammation of the central airways. Most patients with COPD exhibit a mixture of emphysema and chronic bronchitis and they appear normal for a prolonged period of time and present with respiratory symptoms only when the disease has been advanced. This slowly progressive destructive process of the lung is poorly reversible when manifested clinically. Although the disease affects the lungs, it also produces significant systemic consequences, and often associated with significant co-morbid diseases. Systemic effects of COPD involve respiratory and skeletal muscles. There is muscle weakness and fatigue. There is a preferential loss of skeletal muscles especially in the lower extremities and the muscle wasting is increasingly noticed in quadriceps muscle. Patients exhibit weight loss and osteoporosis.

The patients, especially those 40 years or older men who have risk factors of the disease such as history of smoking, are to be screened for COPD. Though the diagnosis is suggested by symptoms, it needs confirmation by spirometry.[3] Cough, sputum, wheeze and dyspnea are the common presenting symptoms. The patients with advanced COPD may exhibit hyperinflation of the chest. However, patients with chronic bronchitis may not exhibit over inflation of the chest. The best physical signs of COPD are a prolonged expiratory phase and decreased, distant breath sounds. Breathing in and out deeply and rapidly with mouth open fails to improve breath sounds.

Advanced emphysema on chest roentgenography exhibits low, flat diaphragm, increased retro-sternal air space, decreased vascular markings in the outer-third of the lung fields, all features of lung hyperinflation. Coarse lung markings and peribronchial cuffing may be present in chronic bronchitis.

COPD is defined as airflow limitation that is not fully reversible, and it is confirmed by spirometry.[3] The airflow limitation is generally progressive. Airflow limitation was to be described 'irreversible'. Of late it has been recognized incorrect. Repeated testing before and after bronchodilator challenge, has shown a significant degree of reversibility at some point of disease in many patients.[4] But it must be noted that the lung function of patients with COPD does not return to normal after bronchodilator challenge. Hence the airflow limitation is 'not fully reversible'.[5]

The severity of COPD is established by measuring the forced expiratory volume in one second (FEV1) and the ratio of FEV1 to forced vital capacity (FVC). The GOLD has introduced a five-stage classification to determine the severity of COPD based on measurements of airflow limitation during forced expiration.[6] Each stage is determined by FEV1 and FVC. Abnormalities in these tests reflect both the reduction in the force available to drive air out of the lung as a result of emphysematous lung destruction and obstruction to airflow in the smaller conducting airways.[7]

The disease begins with an asymptomatic phase in which lung functions deteriorate without associated symptoms. The onset of subsequent symptom phase is variable, but often does not occur until FEV1 has fallen to nearly 50 percent of the predicted normal values.[8] It is intriguing that only 18.5 percent of the patients progress to more severe airflow limitation at 15 years.[9] Thus it is difficult to predict which patients belonging to stage 0 make a progress to an advanced disease. When the patients are symptomatic there is a substantial decline in airflow. They exhibit hyperinflation. It occurs at rest and gets worsened with exercise. This is noted in patients with moderate-to-severe COPD. There is an increase in the functional residual capacity (FRC) placing the respiratory muscles at a mechanical disadvantage. It increases the work of breathing and reduces exercise tolerance. The patients exhibit other physiologic abnormalities that include a reduction in diffusing capacity for carbon monoxide, hypoxemia and alveolar hypoventilation. Though FEV1 does not consistently predict disability or mortality among patients with COPD, it helps in guiding therapy.[6] Spirometry does not provide information about the extrapulmonary effects of COPD.

Stages of COPD according to GOLD[6]

Stages	*Manifestations*	*FEV1(%)*	*Symptoms*
0	At risk	> - 80	–
I	Mild	> - 80	±
II	Moderate	50-79	+
III	Severe	30-49	++
IV	Very severe	< 30	+++

Spirometry is to be performed in all patients at risk to find out asymptomatic airflow limitation. It is advocated to perform spirometry annually in patients with established disease. Such a study helps in the assessment of clinical status and response to therapy. Inspiratory capacity (IC) is a surrogate for lung hyperinflation that is easily obtained from spirometry. The ratio of inspiratory to total lung capacity helps in accurate assessment of COPD than FEV1. It is likely to reflect the functional response and improvement of symptoms and exercise tolerance induced by bronchodilators in COPD.[10]

Often it is considered that there is limitation to evaluate severity of COPD based on lung function. Traditional measurement of lung functions does not evaluate the systemic effects of COPD. There is a constant search to find newer markers to assess the disease. A multi-dimensional grading system, the BODE index (Body mass index, degree of airflow obstruction, a modified MRC dyspnea scale, and exercise capacity based on 6-minute walking test) appears to predict better than FEV1 of the risk of hospitalization and death among patients with COPD.[11] The sum of components provides a score from 0 to 10. The index is widely applicable, simple and requires no special equipment. Serum C-reactive protein is increased in COPD and is related to the presence of co-morbidities. It decreases following administration of steroids.[12]

Risk Factors

Tobacco smoking—both active and passive forms the most important risk factor for COPD. It acts through the generation of oxidative stress and/or reduction of antioxidant capacity. Not all

smokers develop COPD suggesting that genetic factors may be involved. Indoor air pollution is another risk factor. It includes emission from combustion-generated products such as biomass fuels and fossil fuels used for cooking and heating, exposure to biomass pollution from firewood and smoke from burning cow-dung cakes, haystacks, woodchips, crop residues and agricultural wastes in ill-ventilated kitchen, and exposure to occupational dusts and chemicals. Alpha-1 antitrypsin deficiency (PiZZ) is a well documented genetic risk factor, and the condition makes an early onset in usually younger than 40 years.

The patients become symptomatic only after substantial reduction of lung functions. Hence early detection is possible by spirometric evaluation of FEV1 and FVC. An airflow limitation in COPD is characterized by an FEV1 value less than 80% of the predicted normal value and a FEV1/FVC ratio of less than 0.70.[7]

Treatment of Patients with Stable COPD

The deterioration of lung functions, and progressive downhill course of COPD should be prevented by stopping smoking, by control of atmospheric pollution, and by treatment mainly directed to reduce airway obstruction and to reduce its physiologic consequences. The goals of therapy for COPD are to prevent disease progress, relieve symptoms, improve health status, prevent and treat complications and exacerbations, reduce morbidity and prevent or minimize adverse effects from treatment.[5]

Though COPD is predominantly a disorder of respiratory system, it produces significant systemic consequences. Existing therapies for COPD are grossly inadequate. None has been shown to slow the relentless progression of the disease. The drugs and supplemental therapies are used in a stepwise manner as the disease progresses.

Smoking Cessation

All patients with COPD regardless of severity should stop smoking or remain abstinent. The former is advocated for active smokers and the latter for former smokers. Smoking cessation is the most effective way to reduce the rate of natural decline of lung function that occurs with aging.

All persons regardless of smoking status show a decline in FEV1 starting around 30 years of age. It exhibits an accelerated decline in patients with COPD. The normal rate of approximately 30 ml per year becomes nearly 60 ml per year.[13] Thus the patient with COPD who continues to smoke loses lung function twice the rate of a nonsmoker. Following quitting smoking the decline in lung function slows and returns to about the rate of decline of a nonsmoker. Smoking cessation is the single most important intervention to slow the rate of decline in lung function.[14]

Stepwise Treatment

It has been recommended to manage patients with COPD in a stepwise manner by addition of medication (bronchodilators) with increasing severity and worsening of symptoms.[6]

Inhaled Bronchodilators

Inhaled bronchodilators form the cornerstone of pharmacotherapy for COPD patients. These agents help in relief of symptoms, decrease exacerbations of disease and improve the quality of life. They bring about improvement in airflow and hyperinflation, thus a decrease in the work of breathing and improved exercise tolerance. Such a therapy is also recommended for patients with intermittent symptoms. It must be noted that symptomatic improvement is not always reflected by changes in FEV1 and FVC. The drug administered through aerosol gets retained in the airway and causes bronchodilatation and it is not dependent on its plasma levels.

Inhaled bonchodilators are grouped into 2 types (short-acting and long-acting) based on the mechanism or duration of action.

Short-acting bronchodilators: Selective beta-adrenergic receptor agonists combine with the beta-2 receptors on bronchial smooth muscle to increase production of cyclic adenosine monophosphate (cAMP) and cause bronchodilatation. Anticholinergics compete with acetylcholine for the muscarine receptors in the smooth muscle of the bronchial passages and mucous glands. Salbutamol (Beta-2 agonist) and ipratropium (anticholinergic agent) are equally effective bronchodilators and can be used interchangeably in the treatment of mild disease as the first step.[15]

The effect of short-acting beta-2 agonists is felt immediately (< 10 minutes) after inhalation, and reach peak effect in 30 to 60 minutes. The bronchodilator effect disappears in 4-6 hours. 2 puffs of salbutamol, each puff of 90 micrograms, have to be taken through a metered dose inhalator (MDI) every 4 hours. Ipratropium is as effective as beta-2 agonists in patients with stable COPD. It has a slower onset of action taking 30-60 minutes to cause bronchodilation and the maximal effect is noted 2 hours after administration. The total duration of action is for 4 to 6 hours. 2 puffs, each puff of 18 micrograms has to be taken through MDI every 4 hours. It is topically active and there is no significant absorption from the oropharynx and airways.

Orally salbutamol is administered in a dose of 2-4 mg three or four times a day. Other oral preparations are orciprenaline (10-20 mg) and terbutaline (2.5-5.0 mg). The oral preparations on administration show their effect in 15 to 30 minutes reaching a peak in 1 to 3 hours. Oral preparations are advocated to patients who cannot take the drug by aerosol route. The dose used is much larger than that used in aerosol. The bronchodilator effect depends on the plasma concentration achieved. Unlike aerosol which produces dilatation of central airways preferentially, the oral preparation causes dilatation of central and peripheral airways.

Stage I (Mild COPD)

The patients with stage I disease may not exhibit any respiratory symptoms. When respiratory symptoms are present, short-acting bronchodilators (salbutamol and ipratropium) are to be prescribed to reduce symptoms and improve exercise tolerance. It must be noted that the agents do not modify the clinical course, the rate of decline in pulmonary function or survival in patients with COPD.[15]

Stage II (Moderate), III (Severe) and IV (Very Severe) COPD

Long-acting bronchodilators: These patients with COPD are to be given one or more long-acting bronchodilators regularly to produce optimal effect in addition to the as-needed short-acting bronchodilators. There is no difference in action between long-acting anticholinergic agent (Tiotropium bromide) and beta-2 agonist (formoterol fumarate, and salmeterol ximafoate). The duration of action of tiotropium is > 24 hours and one inhalation containing 18 microgram is given through dry powder inhaler (DPI). The duration of action of formoterol lasts 8-12 hours and two puffs each with a dose of 12 microgram has to be given twice a day through DPI. Salmeterol has also similar duration of action and 2 puffs each with 90 micrograms has to be given twice a day through DPI.

The combination of a short-acting anticholinergic with a long-acting beta-agonist or the combination of a long-acting anticholinergic with a short- or long-acting beta-agonist appear to improve lung function and it may be used for patients in whom a single inhaled bronchodilator has failed to provide adequate relief of symptoms. A combination of bronchodilators with different mechanisms of action will give greater bronchodilation than either drug administered singly. One of the widely used combination schedules for treatment of COPD is a short-acting anticholinergic (ipratropium) plus a short-acting beta-agonist (salbutamol, SABA). A long-acting oral, beta adrenergic agonist, bambuterol may be given orally in a dose of 10-20 mg a day. The duration of its action lasts for 24 hours.

Long-acting beta-2 agonists improve health-related quality of life but not the mortality. Tiotropium improves FEV1 significantly. A meta-analysis of 5 published clinical trials involving 3574 patients with moderate-to-severe COPD has shown that tiotropium reduces acute exacerbations compared with either placebo or ipratropium.[16] The clinical trials have shown an overall 25% reduction in acute exacerbations of COPD.[17] Long-acting inhaled bronchodilators are not suitable for the treatment of acute symptoms and short-acting bronchodilators are indicated for relief of acute symptoms.

Methyl Xanthines

Methyl xanthine derivatives are moderately powerful bronchodilators. Theophylline is given orally in a dose of 200-600 mg a day. It reduces dyspnea in some patients by improving contractility and endurance of fatigued diaphragm in a setting of hypoxemia and myocardial contractility. Theophylline is added to inhaled bronchodilator therapy to obtain additional improvement in lung function and symptomatology. Theophylline has significant anti-inflammatory effects in COPD at lower plasma concentrations. It activates histone deacetylases in turn enhancing the anti-inflammatory effect of corticosteroids.[18]

Phosphodiesterase-4 Inhibitors

Phosphodiesterases (PDEs) are intracellular enzymes that inactivate cAMP. Methyl xanthines are nonselective phosphodiesterase inhibitors. PDE-4 sub type is the predominant isoenzyme found in inflammatory cells and it specifically targets cAMP. PDE-4 inhibitors (cilomilast and roflumilast) have shown to be useful in COPD. Cilomilast, a selective PDE-4 inhibitor, administered in a dose of 15 mg twice a day is capable of reducing the inflammatory process in patients with COPD, and maintain pulmonary functions and reduce the rate of exacerbations.[19] In patients with moderate-to-severe COPD, long-term treatment with 250-500 micrograms of roflumilast administered orally appears to improve FEV1 and pulmonary functions and reduce the rate of mild exacerbations.[20] However these agents have a limited therapeutic ratio.

Inhaled Corticosteroids

Inhaled corticosteroids (ICSs) do not appear to bring about substantial changes in airway inflammation in COPD. The clinical trials comparing inhaled corticosteroids (budesonide, fluticasone propionate, triamcinalone) with placebo did not find these agents to appreciably alter the rate of decline in lung function. These agents are able to relieve symptoms and reduce the frequency of exacerbations.[21]

Inhaled corticosteroids appear to provide clinical benefits to some patients with COPD. It is recommended for patients with moderate-to-severe airflow limitation who have persistent symptoms despite optimal bronchodilator therapy. Combinations of inhaled corticosteroids (fluticasone, budesonide) and long-acting beta-agonists (salmeterol, formoterol) have shown to be superior to either drug alone with regard to lung function and frequency of exacerbations.[22,23]

It is recommended to use inhaled corticosteroids in patients who have failed to show improvement or exhibiting frequent exacerbations despite optimal bronchodilator therapy. The treatment should not be persisted if there is no substantial clinical or physiological improvement. It is advisable to assess the spirometric response to a trial of oral corticosteroids in order to identify patients who respond to inhaled corticosteroids. Though it helps in detection of coexistent asthma, it is a poor predictor of the response to inhaled corticosteroids among patients with COPD. Oral corticosteroids are not advocated in the routine management of stable COPD.

GOLD states that regular treatment with ICSs alone or in combination with inhaled long-acting beta-agonists should be prescribed only to patients with severe COPD (FEV1 < 50% of predicted value) and repeated exacerbations requiring treatment with antibiotics and/or oral

corticosteroids.[6] An inhaled corticosteroid (ICS, fluticasone) plus a long-acting beta-agonist (salmeterol, LABA) is a frequently prescribed combination.

Antibiotics

Antibiotics are to be given during infective exacerbations. Quite often, the patients show improvement on empiric therapy for 10 days with amoxicillin, doxycillin, or trimethoprime-sulphamethoxazole. Prophylactic therapy with antibiotics, however does not prevent the occurrence of infection.

New Drugs

Mediator Antagonists

A variety of inflammatory mediators participate in the chronic inflammation and structural alterations noted in COPD. However in presence of a multitude of mediators blocking a single mediator may not be able to exhibit clinical benefit.

Tumor-necrosis factor (TNF)-alpha antagonists: The cytokine TNF-alpha takes part in the pathogenesis of COPD. Its amount is raised both in the sputum and in circulation. Infliximab, a chimeric monoclonal antibody that neutralizes the biologic activities of TNF-alpha has been used in patients with COPD. However it has failed to produce clinically beneficial effects in patients with mild-to-moderate COPD.[24] Long-term administration may induce development of blocking antibodies.

Antioxidants

There is an increased oxidative stress in the patients with COPD and it is more evident during acute exacerbations. As the reactive oxygen species are responsible for such a complication, antioxidants are likely to counter the effects. N-acetyl cysteine provides cysteine for an increased production of glutathione, which has an antioxidant effect.[25]

Retinoic Acid

Animal experiments have shown retinoic acid induces alveolar regeneration. Retinoids are being tried in patients with emphysema in the hope that alveolar regeneration may help in repair of emphysematous lesions in humans.[26]

Extrapulmonary Effects

Weight loss and skeletal muscle dysfunction limit the exercise capacity of patients with COPD. There appears improvement in prognosis in patients with COPD if they regain their body weight. No specific therapy has been formulated as the pathogenesis of the systemic effects of COPD has not yet well understood. Physical rehabilitation and domiciliary oxygen therapy is advocated to overcome sedentary life and tissue hypoxia. A low dose of inhaled steroids are potentially beneficial due to its anti-inflammatory effect.[27] Nutritional supplementation is necessary.

Supplemental Therapy

Pulmonary Rehabilitation

Patients with moderate-to-very severe COPD are likely to benefit by participating in a pulmonary rehabilitation program. These programs, consisting of chest physical therapy, breathing retraining, energy conservation, adequate nutrition and respiratory muscle training, improve health status, quality of life, reduces dyspnea and exercise tolerance. It is appropriate for patients with clinically significant exertional dyspnea.

The patients are instructed to breathe through their nose and breath-out twice as long as they breath-in. The lips should be kept firmly together except the center. While exhaling air, it should be blown-out slowly in a firm steady stream through the center of lips. Among exercises, diaphragmatic breathing and pursed-lip breathing are commonly employed. Breathing exercises increase the strength and coordination of breathing muscle. Deep breathing helps in opening poorly ventilated areas. The diaphragm and abdominal muscles should play an active part. They allow the abdomen to protrude during inspiration causing a greater descent of the diaphragm. After deep inspiration, the patient has to exhale slowly to prevent collapse of airways.

Supplemental Oxygen

Supplemental oxygen is beneficial in patients with COPD especially during acute hypoxic exacerbations. An arterial oxygen tension (PaO_2) of 60 mmHg without respiratory acidosis can be achieved with low fractional inspired oxygen concentration. Nasal supplementation of 2 liters oxygen per minute will help in attaining adequate arterial oxygenation.

The patients with severe COPD having FEV1 of less than 30% of predicted value are to be screened for the need for supplemental oxygen. Supplemental oxygen improves survival in COPD patients who exhibit chronic hypoxemia at rest. Hypoxemia develops as a result of a worsening ventilation-perfusion inequality. The survival benefit is obtained only by use of supplemental oxygen for more than 15 to 18 hours per day. Supplemental oxygen should be adjusted to maintain an oxygen saturation of at least 90% at all times. Pulse oximetry and oxygen titration should be performed at rest, on exertion and during sleep.

In advanced disease, there is occurrence of hypoxemia and hypercapnia. The latter occurs from hypoventilation, increased dead-space ventilation, and increased work of breathing with enhanced production of carbon dioxide. Ventilation-perfusion mismatch and alveolar hypoventilation aggravate hypoxemia. Some patients with alveolar hypoventilation are benefited by inhaled bronchodilators as they help in reducing the work of breathing and improve gas exchange. Noninvasive positive-pressure ventilation in addition to supplemental oxygen may show improvement in dyspnea and quality of life. But the improvement in arterial carbon dioxide levels is quite small.[28]

Heliox

Exertional dyspnea leads to reduction in daily activities. Reduction of dyspnea forms an important therapeutic intervention especially in patients with more severe COPD. Physical training and ambulatory oxygen therapy help in reducing exertional dyspnea. Effects of helium and oxygen (heliox) mixture has been tried to determine its effects on exercise capacity in severe COPD.[29]

Nitrogen in inspired air is replaced with lower density helium. It reduces turbulent flow of resistance in the airway leading to improved ventilation and gas exchange. Reducing inspired gas density can improve exercise performance in COPD as much as increasing inspired oxygen. The effects can be combined as Heliox[28] (72% helium/28% oxygen) to get benefit in patients with more severe airflow obstruction.[29] Heliox mixture is recommended as an adjunct to pulmonary rehabilitation program with severe COPD who are still disabled by dyspnea and are unable to achieve full benefits of training despite pharmacological treatment and ambulatory oxygen therapy.[30]

Surgery

Lung Volume Reduction Surgery (LVRS)

Patients with very severe COPD may benefit from surgical intervention that involves removal of the most damaged areas of the lung. LVRS reduces hyperinflation and it should be considered in patients with severe upper-lobe emphysema and reduced exercise-tolerance not showing

improvement with medical therapy alone. Three clinical trials involving 1321 patients have shown that lung volume reduction surgery improves health-related quality of life and exercise capacity in patients who have an FEV1 of less than 30% of predicted.[31]

Lung Transplantation

Single-lung transplantation is used as a potential surgical intervention for patients with very severe COPD who do not have significant co-morbid conditions. It does not prolong life, but has the potentiality of significantly improving the quality of life in patients with very severe COPD who exhibit an extremely limited functional status due to dyspnea with minimal exertion. This surgical option is considered for patients with end-stage emphysema who have an FEV1 of less than 25% of the predicted normal value after a bronchodilator and who have such complications as pulmonary hypertension, marked hypoxemia, and hypercapnia.[32] The lung implanted in COPD is smaller than the larger diseased lung. Following transplantation, the overinflated chest cavity decreases in size as air-trapping no longer exists.

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