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Review :

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic Obstructive Pulmonary Disease (COPD) is a major and increasing global health problem that is predicted to become the third most common cause of death and the fifth most common cause of disability in the world by 2020.[1] In India, COPD is the commonest lung disorder following pulmonary tuberculosis and is equally prevalent in rural and urban areas.

Chronic obstructive pulmonary disease is characterized by slowly progressive development of airflow limitation that is poorly reversible in sharp contrast to asthma in which there is a variable airflow obstruction that is usually reversible spontaneously or with treatment.[2] A new definition of COPD has recently been adopted by the global initiative on Obstructive Lung Disease (GOLD)[3] "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of lung to noxious particles and gases".

Chronic obstructive pulmonary disease includes chronic obstructive bronchitis with fibrosis and obstruction of small airways, and emphysema with enlargement of airspaces, destruction of lung parenchyma, loss of lung elasticity and closure of small airways. Chronic bronchitis, by contrast is defined by a productive cough of more than three months duration for more than two successive years; this reflects mucus hypersecretion and is not necessarily associated with airflow limitation. Most patients with COPD have all three mechanisms (chronic obstructive bronchitis, emphysema, and mucus plugging.)

The most common cause of COPD is cigarette smoking but there are several other risk factors including air pollution (particularly indoor air pollution from burning fuels), poor diet and occupational exposure.[4]

COPD and asthma both involve inflammation in the respiratory tract but there are marked differences in the nature of the inflammatory process with differences in inflammatory cells, mediators, response

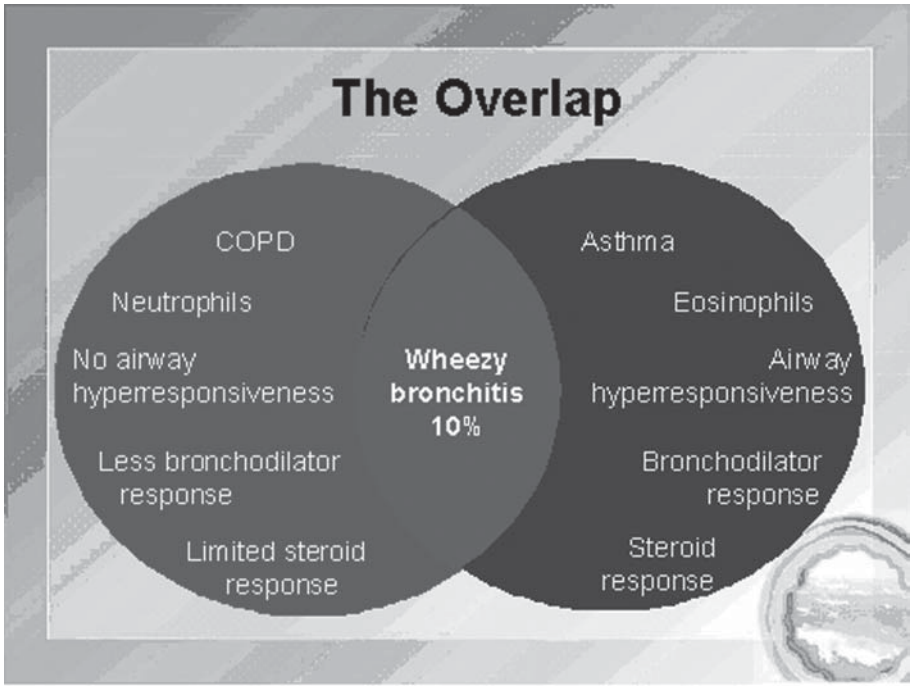


Fig. 1

to inflammation, anatomic distribution, and response to antiinflammatory therapy. Some patients appear to share the characteristics of COPD and asthma however.

There have been important advances in understanding the cellular and molecular mechanisms of COPD. The inflammatory response differs from that of asthma, with a marked increase in numbers of macrophages in the alveoli, neutrophils in airspaces and cytotoxic CD8 + lymphocytes in small airways and alveoli.[5] This inflammatory process leads to the characteristic fibrosis and narrowing of small airways and alveolar destruction or emphysema which together lead to airflow limitation and hyperinflammation.[6] Fig 1 shows the overlap between COPD and asthma.

Asthma and COPD are different diseases, but some patients show features of both diseases, (Dutch hypothesis). Approximately 10% of patients with COPD have asthma and will share inflammatory features between these diseases. This overlap group may be termed wheezy bronchitis. In practice it is important to recognize these patients because they may require treatment for both diseases to optimize symptom control.

Risk factors for COPD

Cigarette smoking

Cigarette smoking is a major risk factor for mortality from chronic bronchitis and emphysema. Hooka and bidi smoking is just as harmful as cigarette smoking. Smoking impairs the mucociliary defence mechanisms of the lung and produces hypertrophy and hyperplasia of the mucus-secreting glands. It also induces polymorphonuclear leucocyte injury by releasing proteolytic enzymes. Acute increase in airways resistance is also encountered following inhalation of smoke as a result of stimulation of submucous receptors and vagally – mediated smooth muscle contraction.

Air pollution

Some investigators have reported increased respiratory symptoms in those living in urban compared to rural areas, which may relate to increased pollution in urban settings. However, the relationship of air pollution to chronic airflow obstruction remains unproven. With high rates of COPD reported in non smoking women in many developing countries, indoor air pollution, usually associated with cooking, has been suggested as a potential contributor. In India, indoor air pollution caused by burning of cowdung and wood for cooking is also blamed as a contributory factor.

Airway responsiveness and COPD

A tendency for increased bronchoconstriction in response to a variety of exogenous stimuli, including methacholine and histamine is one of the defining features of asthma. However, many patients with COPD also share this feature of airway hyperresponsiveness. Increased airway responsiveness is clearly a significant predictor of subsequent decline in pulmonary function. Thus, airways hyperresponsiveness is a risk factor for COPD.

Respiratory infections

These have been studied as potential risk factors for the eventual development of COPD in adults, childhood respiratory infections have also been assessed as potential predisposing factors for the eventual development of COPD. The impact of adult respiratory infections on decline in pulmonary function is controversial, but significant long term reductions in pulmonary functions are not typically

seen following an episode of bronchitis or pneumonia.

Occupational exposures

Increased respiratory symptoms and airflow obstruction have been suggested as resulting from general exposure to dust at work. Several specific occupational exposures, including coal mining, gold mining, cotton textile dust, have been suggested as risk factors for chronic airflow obstruction.

Passive or Second –hand smoke exposure

Exposure of children to maternal smoking results in significantly reduced lung growth. In utero tobacco smoke exposure also contributes to significant reductions in post natal pulmonary function. Although passive smoke exposure has been associated with reductions in pulmonary function, the importance of this risk factor in the development of the severe pulmonary function reductions in COPD remains uncertain.

Pathology of COPD

Emphysema and small airway pathology are both present in most persons with COPD, and their relative contributions to obstruction vary from one person to another. Small airway obstruction likely contributes more to initial obstruction, with emphysema predominating later in the course. In chronic bronchitis, mucus-producing glands in the submucosa of large airways show hypertrophy and hyperplasia. The Reid index, which indicates the ratio of thickness of the submucosal glands to that of the bronchial wall, is thus increased. Small non-cartilagenous airways also show pathological changes. Inflammatory damage to small airways and surrounding alveoli occurs in relatively early stages of the disease.

In emphysema, gas - exchanging units (acini) of the lung distal to the terminal bronchiole are affected, and the changes are classified according to the pattern of involvement into centrilobar and panacinar types. Panacinar emphysema involves both the central and the peripheral portions of the acini.

Cigarette smoke exposure may affect the large airways, small airways and the alveolar space. Changes in large airways cause cough and sputum, while changes in the small airways and alveoli are responsible for physiologic alterations.

Clinical features of COPD

History - The three most common symptoms in COPD are cough, sputum production and exertional dyspnea. Many patients have such symptoms for months or years before seeking medical attention. Although the development of airflow obstruction is a gradual process, many patients date the onset of their disease to an acute illness or exacerbation. A careful history however, usually reveals the presence of symptoms prior to the acute exacerbation.

Activities involving significant arm work, particularly at or above shoulder level, are particularly difficult for patients with COPD. Conversely, activities that allow the patient to brace the arms and use accessory muscles are better tolerated. Examples of such activities include pushing a shopping cart, walking on a treadmill or pushing a wheelchair. As COPD advances, the principal feature is worsening dyspnoea on exertion with increasing intrusion on the ability to perform vocational or avocational activities. In most advanced stages, patients are breathless doing activities of daily living.

Physical findings – In early stages of COPD, patients may have an entirely normal physical examination. Current smokers may have stains of active smoking, including an odour of smoke and nicotine staining of fingernails. In patients with more severe disease, signs include expiratory wheezing and barrel chest. Patients with severe airflow obstruction may also exhibit use of accessory muscles of respiration. Patients with predominant emphysema are classically referred to as 'pink puffers', a reference to the lack of cyanosis, the use of accessory muscles and pursed lip breathing. Patients with a clinical syndrome of chronic bronchitis are classically labeled as 'blue bloaters', a reference to fluid retention and more marked cyanosis. Typically, patients have elements of each and cannot be simply classified. Advanced disease may be accompanied by systemic wasting, significant weight loss, bitemporal wasting and diffuse loss of subcutaneous adipose tissue.

Key Indicators for COPD Diagnosis (Table 1)

Chronic cough	Present intermittently or every day often present throughout the day; seldom only nocturnal
Chronic sputum production	Present for many years, worst in winters. Initially mucoid – becomes purulent with exacerbation
Dyspnoea that is	Progressive (worsens over time) Persistent (present every day) Worse on exercise Worse during respiratory infections
Acute bronchitis	Repeated episodes
History of exposure to risk factors	Tobacco smoke (including beedi) occupational dusts and chemical smoke from home cooking and heating fuel

The most prominent symptom of COPD is dyspnoea, which is largely caused by hyperinflation of the lungs as a result of small airway collapse due to emphysema and narrowing due to fibrosis, so that alveoli are not able to empty. Hyperinflation induces an uncomfortable sensation and induces exercise intolerance. This leads to immobility and deconditioning and results in poor health status. Other common symptoms of COPD are cough and sputum production as a result of mucus hypersecretion. The systemic features of COPD may be seen in patients with severe COPD. These are weight loss (cachexia, lassitude, muscle wasting, polycythemia, anemia and depression) which may require treatment.[8]

Diagnosis of chronic obstructive pulmonary disease (COPD) :

A chest radiograph should be done at initial assessment. The lungs are hyperinflated, the diaphragmics flattened, vascular markings are increased and the heart size is marginally increased or is tubular in predominant emphysema (Fig 2).

In clinical practice chronic obstructive pulmonary disease is still underdiagnosed mainly because of the underutilization of pulmonary function tests.[7] Spirometry is important for initial diagnosis and

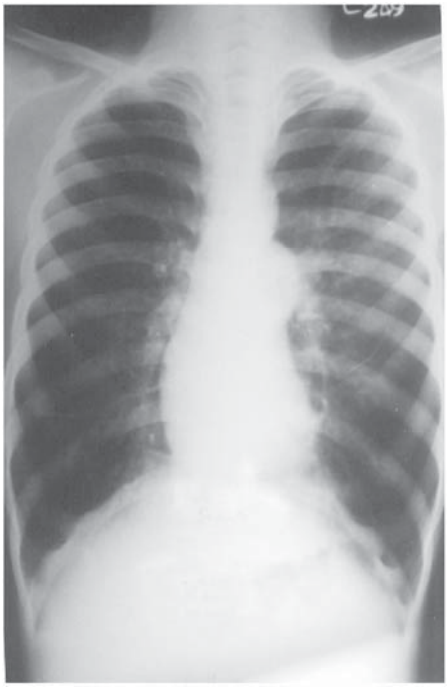


Fig. 2

assessment of severity but less useful to assess disability during routine follow-up, as it is poorly related to symptoms. A chest radiograph should be done at initial assessment. A bronchodilator test is also important; typically COPD patients have less than 12% (or less than 200ml) increase after a short acting bronchodilator. In patients with more severe disease, it may be useful to measure lung volumes particularly total lung capacity and residual volume. Inspiratory capacity is more closely related to symptoms than is forced expiratory volume in 1 second (FEV1). Arterial blood gases are indicated in more severe cases.
Fig. [3, 4].

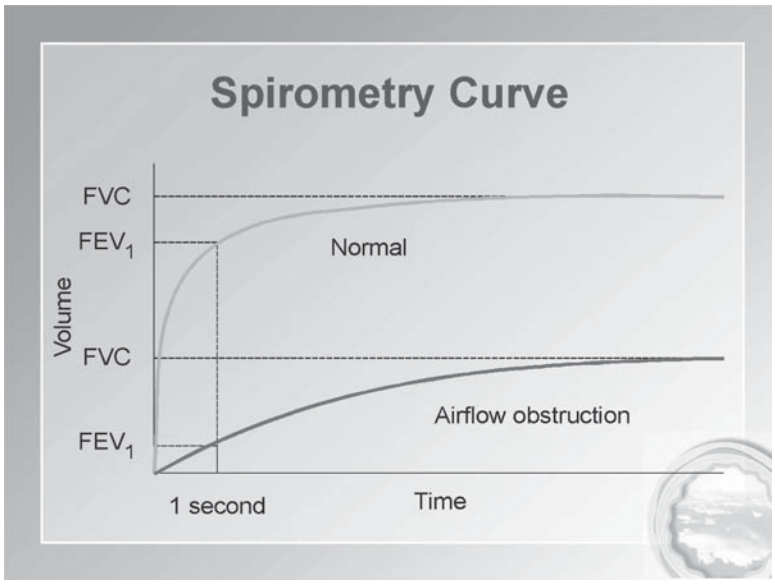


Fig. 3

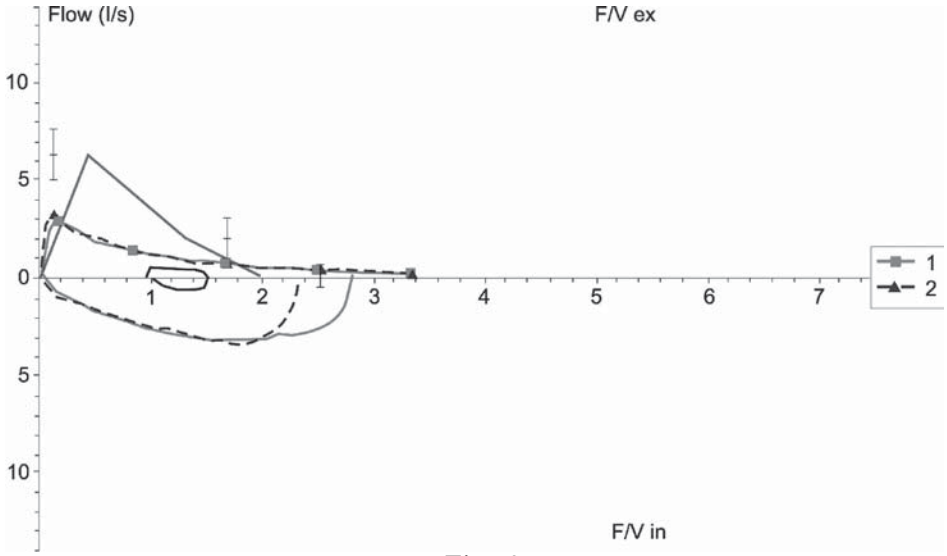


Fig. 4

Overview of Management of COPD

The aims of therapy of COPD are :

- Prevent disease progression
- Reduce symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat exacerbations
- Prevent mortality

Appropriate therapy for COPD patients depends upon early diagnosis assessment of the severity of disease in individual patients (Table 2).

Classification of COPD (Table 2)

Stage 0:	**At Risk**	• Chronic cough and sputum production; lung function is still normal.
Stage I:	**Mild COPD**	• Mild airflow limitation **(FEV1/FVC < 70% but FEV1 >80% predicted)** and usually chronic cough and sputum production and dyspnoea on unaccustomed activity.
Stage II	**Moderate COPD**	• Worsening airflow limitation **(FEV1 <80% and >30% predicted)**, and usually the progression of symptoms, with shortness of breath typically developing on accustomed activity.
Stage III	**Severe COPD**	• Severe airflow limitation **(FEV1 < 30% predicted)** or the presence of respiratory failure or clinical signs of right heart failure

Complications of Chronic Obstructive Pulmonary disease

Acute bronchitis, pneumonia, pulmonary thromboembolism and concomitant left ventricular failure may worsen otherwise stable COPD.

Pulmonary hypertension, cor pulmonale and chronic respiratory failure are common in advanced COPD.

Spontaneous pneumothorax occurs in a small fraction of patients with emphysema.

Hemoptysis may result from chronic bronchitis or may signal bronchogenic carcinoma.

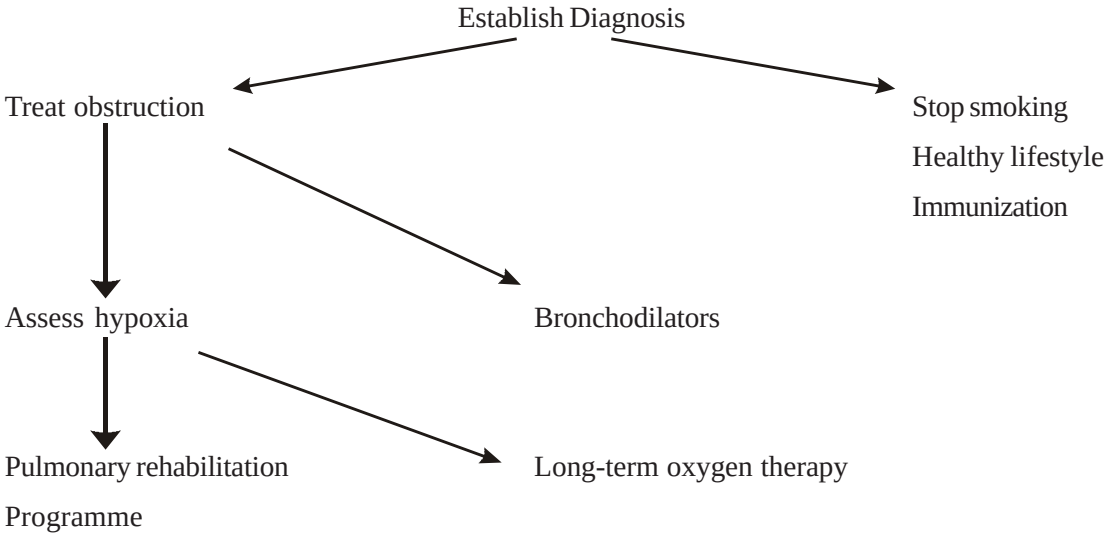
Pharmacotherapy for Stable COPD (Table - 3)

Bronchodilators	**Steroids**
Short-acting beta$_2$-agonist – Salbutamol	
Long-acting beta$_2$-agonist - Salmeterol and Formoterol	Oral – Prednisolone
Anticholinergics – Ipratropium	Inhaled - Fluticasone
Methylxanthines - Theophylline	Budesonide

Management of COPD

Appropriate therapy for COPD patient depends upon diagnosis and healthy life-style (limiting inhaled risk factors, adequate diet, regular exercise, and limited alcohol consumption) and annual vaccination against influenza are mandatory for all patients with COPD. Bronchodilators are the mainstay of drug therapy for COPD and the most common agents used are inhaled anticholinergics and / or ß2-agonists. Inhaled corticosteroids may be prescribed in severe COPD; for patients with severe COPD or for patients with frequent exacerbations.

Health education, dietary advise and exercise training programmes benefit patients with COPD, and are best used as components within comprehensive pulmonary rehabilitation program.



All patients should be encouraged to stop smoking. The mainstay of treatment however is bronchodilators to reduce symptoms.

Pharmacotherapy of COPD

Smoking cessation

It has been shown that middle aged smokers who were successfully able to stop smoking experienced a significant improvement in the rate of decline in pulmonary function, returning to annual changes similar to that of non smoking patients. Thus, all patients with COPD should be strongly urged to quit and educated about the benefits of smoking. There are two pharmacologic approaches to the problem – bupropion, originally developed as an antidepressant medication and nicotine replacement therapy.

Bronchodilators

In general, bronchodilators are used for symptomatic benefit in patients with COPD. The inhaled route is preferred for medication delivery as the incidence of side effects is lower that that seen with the use of parenteral medication delivery.

Anticholinergic agents

While regular use of Ipratropium bromide does not appear to influence the rate of decline of lung function, it has been reported to improve symptoms and produce acute improvement in FEV1. Side effects are minor, and a trial of inhaled anticholinergics is recommended in symptomatic patients with COPD. Tiotropium bromide is a new drug in this group, and can be used for long term once daily maintenance therapy of bronchospasm associated with COPD.

Beta agonists

These drugs provide symptomatic benefit. The main side effects are tremors and tachycardia. Long acting inhaled beta agonists, such as salmeterol, have benefits comparable to Ipratropium bromide. Their use is more convenient than short-acting agents. The addition of a beta agonist to inhaled anticholinergic therapy has been demonstrated to provide incremental benefit.

Inhaled glucocorticoids

Several recent trials have failed to find a beneficial effect for the regular use of inhaled glucocorticoids on the rate of decline of lung function, as assessed by FEV1. Patients studied included those with mild to severe airflow obstruction and current ex-smokers. Patients with significant acute response to inhaled beta agonists were excluded from these trials.

Inhaled glucocorticoids were demonstrated to reduce the frequency of exacerbations by 25-30%, but their use has been associated with increased rates of oropharyngeal candidiasis and an increased rate of loss of bone density.

A trial of inhaled glucocorticoids should be considered in patients with frequent exacerbations, defined as two or more per year, and in patients who demonstrate a significant acute reversibility in response to inhaled bronchodilators.

Parenteral corticosteroids

The chronic use of oral glucocorticoids for the treatment of COPD is not recommended because of unfavourable risk benefit ratio. The chronic use of oral glucocorticoids is associated with significant side effects, including osteoporosis, weight gain, cataract, glucose intolerance, and increased risk of infection.

A recent study demonstrated that patients tapered off chronic low-dose prednisone (approx 10 mg/day) did not experience any adverse effect on the frequency of exacerbations, health-related quality of life, or lung function. On average, patients lost about 4.5 kg when steroids were withdrawn.

Theophylline

Theophylline produces modest improvements in expiratory flow rates and vital capacity and a slight improvement in arterial oxygen and carbon dioxide levels in patients with moderate to severe COPD. Nausea is a common side effect, tachycardia and tremor have also been reported.

Modified release preparations of theophylline are more commonly used as they reduce adverse effects and the need for frequent dosing, especially in patients with a rapid theophylline clearance. Sustained release theophylline improves arterial oxygen hemoglobin saturation during sleep in COPD patients and is a first line agent for those with sleep related breathing disorders. Theophylline improves dyspnea, exercise performance, and pulmonary function in many stable COPD patients. Its benefits may result from anti-inflammatory properties and extrapulmonary effects on diaphragm strength, myocardial contractility, and renal function.

Oxygen

Supplemental oxygen is the only therapy demonstrated to decrease mortality in patients with COPD. For patients with resting hypoxemia (resting oxygen saturation less than 88% or less than 90% with signs of pulmonary hypetension or right heart failure) the use of oxygen has been demonstrated to have a significant impact on mortality. Various delivery systems are available, including portable systems that patients may carry to allow mobility outside the home.

Supplemental oxygen is commonly prescribed for patients with exertional hypoxemia or nocturnal hypoxemia.

Other agents

N-acetyl cysteine has been used in patients with COPD for both its mucolytic and antioxidant properties. The latter aspect of its use is the subject of ongoing trials.

Specific treatment in the form of alpha1 Anti trypsin (AT) augmentation therapy is available for individuals with severe alpha1 AT deficiency. Despite heat treatment of this product, and the absence of reported cases of viral infection from therapy, hepatitis B vaccination is recommended prior to starting augmentation therapy. Although biochemical efficacy of alpha1 AT augmentation therapy has been shown, a randomized controlled trial of alpha1 AT augmentation therapy has never proven the efficacy of augmentation therapy in reducing decline of pulmonary function.

THE GOLD'S STEPWISE APPROACH BASED ON THE SEVERITY OF DISEASE IS AS FOLLOWS :

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy proposes a stepwise approach to pharmacological management of COPD[2,9] the incremental steps in treatment correspond to stages of increasing severity of COPD, as defined by symptoms and signs together with spirometry evaluation. Since COPD is usually progressive, the 'step-down' approach used in treatment of asthma is not usually applicable in COPD. The responses to treatment of individual patients are variable, and all patients with COPD should be monitored regularly with time.

For COPD patients at GOLD Stages I, it is appropriate to give inhaled short-acting anti-cholinergics (Ipratropium bromide) and/or short-acting ß2-agonists (salbutamol and terbutaline) on an 'as required' basis for the relief of symptoms.

At GOLD Stages II-IV, regular therapy with long-acting bronchodilators should be given rather than with short-acting ß2-agonists. The once-daily anticholinergic, tiotropium bromide, or the long-acting ß2-agonists (LABAs) are modern convenient choices for regular therapy. Tiotropium bromide is inhaled once daily, while the LABAs salmeterol and formoterol are inhaled twice daily. Combining bronchodilators may improve efficacy for some patients, and this may cause less risk of side-effects than by increasing the dose of a single bronchodilator. Bronchodilators may have relatively small effects on FEV1 compared to benefit in terms of symptoms and health-related quality of life.

Theophylline slow-release (SR) may be used in refractory cases as both a bronchodilator and an anti-inflammatory. Theophylline is a reserve therapy because it has a narrow therapeutic ratio, and monitoring of serum theophylline levels is generally required.

GOLD (2003) recommends regular treatment with inhaled corticosteroids for symptomatic patients with a postbronchodilator FEV1 < 50% predicted and repeated exacerbations (e.g. three exacerbations in the past 3 years). Patients with a postbronchodilator FEV1 of < 50% predicted have severe (stage III) or very severe (stage IV) COPD. However, regular treatment with inhaled corticosteroids does not modify the long-term decline of FEV1 (natural history) of patients with COPD. An increased incidence of skin bruising and decreased bone density have been reported with higher doses of inhaled corticosteroids in COPD.

Systemic steroids and antibiotics are only indicated as short courses to treat certain types of more severe exacerbations.

Combined inhaled corticosteroids and LABAs within a single inhaler (Salmeterol with fluticasone propionate; or : formoterol with budesonide) have been shown to be more effective than the individual components, in terms of improved lung function and decreased exacerbations. It is important to treat common complications of COPD such as respiratory failure, cor-pulmonale, muscle wasting and cachexia. Oxygen therapy increases survival in patients with severe COPD and respiratory failure. Because long-term oxygen therapy (LTOT) is expensive, patients should be carefully assessed before this therapy is recommended. LTOT should be given for at least 15 hours a day to achieve benefit. The indications are PaO2 < 55 mmHg corresponding to SaO2 < 88%, pulmonary hypertension, peripheral edema, polycythemia (hematocrit > 55%), nocturnal hypoxemia.[10,11]

In some patients of COPD, surgical intervention may be considered. Originally heart-lung transplantation was used in patients with end-shape emphysema, but more recently single lung transplantation (SLT) has become a favoured technique. Lung volume reduction surgery has become popular for the treatment of severe emphysema. Bullectomy is considered in patients with localized large bulla.[12]

Miscellaneous COPD Therapy

Vaccination : Influenza vaccine is recommended for all patients with COPD, there is convincing evidence that influenza vaccine reduced frequency of acute exacerbations in patients with COPD. It should be given once a year. Pneumococal vaccine may be used to protect against development of pneumococcal infection but there is insufficient evidence to suspect general use in COPD patients.[13,14]

Bronchomunal : is a mixture of bacterial products that activate macrophage function. There is some evidence that it may reduce the severity of acute exacerbations of COPD. But it cannot be recommended on a routine treatment.[2,12] Mucolytics - various mucolytic therapies may be used to increase the ease of mucus expectoration. The commonly used mucolytics are carbocysteine, bromhexine, ambroxol, ardostine and such expectorants as guaiphenesin and potassium iodide.

Antioxidants :

Since oxidant damage may be critical in the pathophysiology of COPD, antioxidant therapy is logical, but the GOLD guidelines do not recommend use of antioxidants. N-acetyl-cysteine (NAC) was originally developed as a mucolytic, but has well documented antioxidant effects. NAC may therefore be useful in long-term management of COPD.[17]

Surgery for COPD

Lung transplantation

Experience with both single and bilateral sequential lung transplantation for severe COPD is extensive. Requirements for lung transplantation are severe lung disease, limited activities of daily living, exhaustion of medical therapy, ambulatory status, potential for pulmonary rehabilitation, limited life expectancy without transplantation, adequate function of other organ systems, and a good social support system. The two year survival rate after lung transplantation for COPD is 75%. Complications include acute rejection, opportunistic infection and obliterative bronchiolitis.

Substantial improvements in pulmonary function and exercise performance have been noted after transplantation.

Lung volume reduction surgery (LVRS or reduction pneumoplasty)

This is an experimental surgical approach to relief of dyspnoea and improvement in exercise tolerance in patients with advanced diffuse emphysema and lung hyperinflation. Bilateral resection of 20-30% of lung volume in selected patients results in modest improvements in pulmonary function, exercise performance and dyspnoea. The duration of any improvement and any mortality benefits remains uncertain. Prolonged air leaks occur in up to 50% of patients postoperatively. Mortality rates in centres with largest experience with lung volume reduction surgery remain 4% - 10%.

Bullectomy

Bullectomy is an older surgical procedure for palliation of severe dyspnoea in patients with severe bullous emphysema. In this procedure, the surgeon removes a very large emphysematous bulla that demonstrates no ventilation or perfusion on lung scanning and compresses adjacent lung that has preserved function. Bullectomy can now be performed with a carbon dioxide laser via thoracoscopy.

Prognosis of COPD

The median survival of patients with severe COPD (FEV1 less than or equal to 1) is about four years. The degree of pulmonary dysfunction (as measured by FEV1) at the time the patient is first seen is probably the most important predictor of survival.

Dyspnoea at the end of life can be extremely uncomfortable and distressing to the patient and family. Dyspnoea can be effectively managed with a combination of medications and mechanical interventions. As the patients near the end of life, meticulous attention to palliative care is essential.

Summary[18] :

COPD is an increasing and major global health problem. It is important to diagnose it early and treat it to prevent decline in lung function and prevent mortality. GOLD guidelines recommend a multidisciplinary stepwise approach. It involves increasing the intensity of treatment depending on increasing severity of the disease (Fig 5). All patients should be encouraged to give up smoking and should also receive influenza vaccine. Pulmonary rehabilitation may be helpful in improving health status and reducing hospitalization in patients with more severe disease.

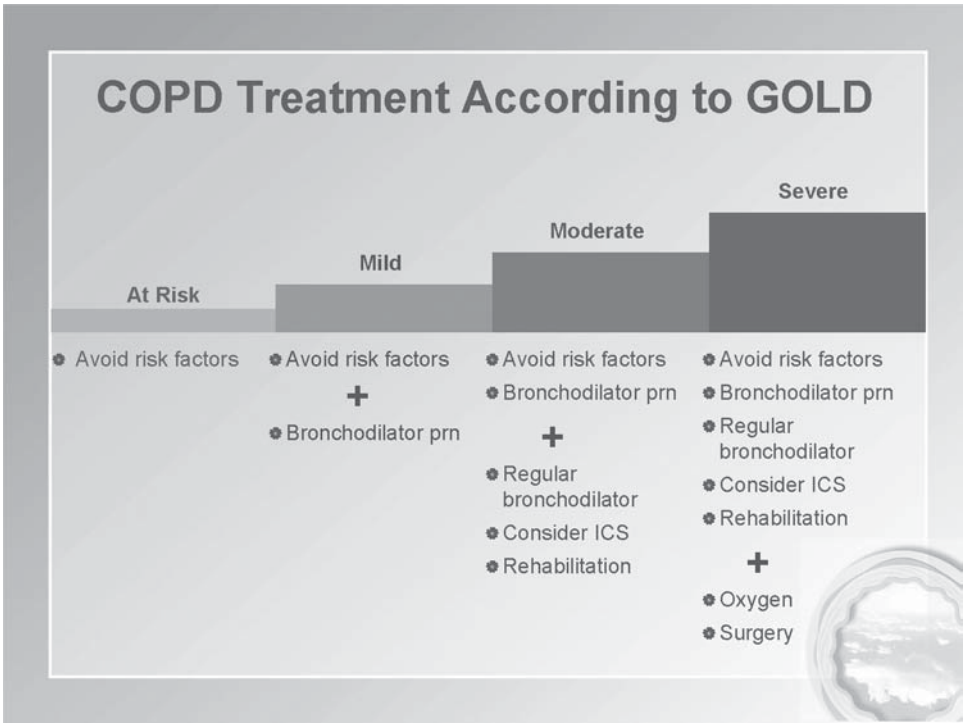


Fig. 5

EXACERBATION OF COPD

Exacerbations are a prominent feature of the natural history of COPD. Exacerbations are commonly considered to be episodes of increased dyspnoea and cough and change in the amount and character of sputum. They may or may not be accompanied by other signs of illness, including fever, myalgias, and sore throat. Self reported health-related quality of life correlates with frequency of exacerbations more closely than it does with the degree of airflow obstruction. The frequency of exacerbations increase as airflow obstruction increases; patients with moderate to severe airflow obstruction [GOLD stages III, IV] have one to three episodes per year.

What is an exacerbation?

COPD exacerbations have been defined according to the presence of specific symptoms, changes in symptoms, and the need for medical intervention. Each of these approaches has advantages and disadvantages (Table 1).

Definition: symptom-based and action-driven

One of the earliest and most widely known definitions of COPD exacerbations is that proposed by ANTHONISEN et al in 1987. This definition is based on the presence of three specific symptoms in patients with COPD, namely increased dyspnoea, sputum volume and sputum purulence. These sub-types of exacerbations were defined: type 1, occurrence of all three symptoms; type 2, occurrence of two out of the three symptoms; and type 3, occurrence of one of the three symptoms in addition to at least one of the following: recent upper respiratory infection, fever, increased wheezing, increased cough, or increased respiratory or heart rate. This definition suffers from the disadvantage of being based on ill-defined, subjective symptoms. Moreover, it was designed specifically for a study of the effectiveness of antibiotic therapy in the treatment of infectious exacerbations. It has yet to be determined whether this definition is generally applicable to all exacerbations and/or useful for studying other treatments. Exacerbations are heterogenous in presentation and, though these three symptoms are important, they will not identify exacerbations in all patients.

In 2000, a consensus panel of respiratory physicians from Europe and the USA suggested that an exacerbation of COPD should be defined as “a sustained worsening of the patient’s condition, from the stable state and beyond normal day to day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD.”

Exacerbations were respectively defined as mild, moderate or severe depending on whether the patient could manage the exacerbation alone, felt the need for additional medical assistance, or required hospitalization. As this definition invariably leads to symptom-defined exacerbations, it is not surprising that some large-scale studies have recently relied on symptomatic changes to define exacerbations. Subsequently, it was recommended that the general definition should be amended to include exacerbations that did not necessitate a change in treatment. Thus, an exacerbation was defined as “a sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations that may warrant additional treatment”.

More recently, researchers have used pure ‘action-based’ (requiring specific medical intervention) definitions of COPD exacerbations. Instead of specifying particular symptom criteria, large-scale studies have defined COPD exacerbations as a worsening of respiratory symptoms that required treatment with oral corticosteroids, antibiotics, or both, and/or hospitalization due to respiratory

symptoms. Mild exacerbations have also been defined in an action based manner, in terms of increased bronchodilator use.

Exacerbations defined by this relatively objective approach are easily recognized and can be registered accurately. For this reason, action-based definitions are, at present, favoured as outcome measures in clinical studies of medical interventions. In addition, this approach will isolate the more severe exacerbations that result in high levels of morbidity, mortality and healthcare resource use, particularly if hospitalization is stipulated. Hence, such definitions may be of particular interest to healthcare payers and decision-makers.

Predicting exacerbations

A high frequency of exacerbations in one year within an individual is predictive of a similar number the following year. However, there is no reliable way of predicting when exacerbations will occur. COPD symptoms often change shortly before an exacerbation. For example, in a recent 1 year study, mean symptom scores (shortness of breath, cough, chest tightness, night-time awakenings) recorded by patients on diary cards clearly increased in the days preceding exacerbations.

Precipitating causes and strategies to reduce frequency of exacerbations

A variety of stimuli may result in the final common pathway of airway inflammation and increased symptoms that are characteristic of COPD exacerbations. Bacterial infections play a role in many, but by no means all, episodes. Viral respiratory infections are present in approximately one-third of COPD exacerbations. In a significant minority of instances, no specific precipitant can be identified.

Despite the frequent implication of bacterial infection, chronic suppressive or ‘rotating’ antibiotics are not beneficial in patients with COPD. This is in contrast to their apparent efficacy in patients with significant bronchiectasis. In patients with bronchiectasis due to cystic fibrosis, suppressive antibiotics have been shown to reduce frequency of hospital admissions.

The role of anti-inflammatory therapy in reducing exacerbation frequency is less well studied. Chronic oral glucocorticoids are not recommended for this purpose. Inhaled glucocorticoids did reduce the frequency of exacerbations by 25% to 30% in large clinical trials. It is important to realize that patients with significant pulmonary function reversibility to inhaled bronchodilators were excluded from these trials. Thus, the use of inhaled glucocorticoids should be considered in patients with frequent exacerbations or those who have an asthmatic component, i.e. significant reversibility on pulmonary function testing or marked symptomatic improvement after inhaled bronchodilators.

Patient Assessment

The practitioner should attempt to establish the severity of the exacerbation as well as the severity of preexisting COPD. The more severe either of these two components, the more likely that the patient will require hospital admission. The history should include quantification of the degree of dyspnoea by asking about breathlessness during activities of daily living and typical activities for the patient. The patient should be asked about fever, change in character of sputum; any ill contacts; and associated symptoms such as nausea, vomiting, diarrhoea, myalgias, and chills. Inquiring about the frequency and severity of prior exacerbations can provide important information. Specific attention should be focused on tachycardia, tachypnea, use of accessory muscles, signs of perioral or peripheral cyanosis, the ability to speak in complete sentences, and patient’s mental status. The

chest examination should establish the presence or absence of focal findings, degree of air movement, presence or absence of wheezing, asymmetry in the chest examination (suggesting large airway obstruction or pneumothorax mimicking an exacerbation), and the presence or absence of paradoxical motion of the abdominal wall.

Patients with severe underlying COPD who are in moderate or severe distress or those with focal findings should have a chest x-ray. Approximately 25% of x-rays in this clinical situation will be abnormal, with the most frequent findings being pneumonia and congestive heart failure. Patients with advanced COPD, those with a history of hypercarbia, those with mental status changes (confusion, sleepiness), or those in significant distress should have an arterial blood gas measurement. The presence of hypercarbia, defined as a PCO_2 > 45 mmHg, has important implications for treatment.

Implications for treatment

A simple way to reduce the risk of exacerbations is to ensure that patients receive influenza vaccinations. In elderly patients with chronic lung disease, combined influenza and pneumococcal vaccination reduced the risk of hospitalization for pneumonia or influenza by approximately 50%, and the risk of death by 70%. Smoking cessation, but not smoking reduction, is also effective in this regard. A recent population-based, observational study in Denmark showed that smoking cessation reduced the risk of hospitalization for COPD exacerbations by almost 50%.

Antibiotics are only useful in exacerbations with a bacterial aetiology. The classic study by ANTHONISEN et al, showed a substantial reduction in the risk of deterioration in patients whose exacerbations were treated with antibiotics. Recent research has also demonstrated a reduced relapse rate in patients treated with antibiotics. The presence of purulent, green sputum appears to be highly predictive of a bacterial infection and, by implication, a favourable response to antibiotics.

Short courses of oral corticosteroids can reduce the severity and duration of COPD exacerbations. However, longer courses should be avoided for reasons of safety and tolerability. Indeed, maintenance therapy with oral steroids in patients with severe COPD may confer a dose-related, increased risk of mortality.

Inhaled corticosteroids

International, randomized, placebo-controlled studies have shown that inhaled corticosteroids (ICS) reduce the frequency and severity of exacerbations in patients with moderate-to-severe COPD. For example, in the 3 year Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study involving 751 patients, inhaled fluticasone propionate (500 µg twice daily) increased FEV1, reduced the frequency of exacerbations requiring medical intervention by 25%, and slowed the rate of health status decline compared with placebo. Subsequent analysis revealed that the reductions in exacerbations occurred only in patients with moderate to severe COPD, as defined by a post-bronchodilator FEV1 of < 50% predicted.

Population-based, observational studies have shown that ICS are associated with reduced hospitalization and mortality rates in patients with COPD.

Bronchodilator and ICS combination therapy

Bronchodilator therapy with long-acting ß2-agonists (LABA) or anticholinergic mediators improves lung function and health status and reduces exacerbations in patients with COPD. As ICS reduce

the frequency of exacerbations and, possibly, mortality, combining these treatments would be expected to confer added benefits to patients. Complementary effects of LABA and ICS on the inflammatory cascade and on reducing bacterially induced mucosal damage have been demonstrated in vitro. In patients with asthma, adding LABA to ICS therapy improves symptoms and lung function and reduces the frequency of exacerbations and use of rescue medications.

By reducing the frequency of COPD exacerbations, LABA and ICS combination therapy may slow down the disease process. In the aforementioned observational study conducted in the UK, LABA and ICS combination therapy was associated with a 41% reduction in the risk of hospitalization or death, compared to respective reductions of 16% and 10% with ICS and LABA alone.

Oxygen

Supplemental Oxygen should be supplied to keep arterial saturations > 90%. Hypoxic respiratory drive plays a small role in patients with COPD.

Mechanical Ventilatory Support

Recent studies have demonstrated that the initiation of noninvasive positive pressure ventilation (NIPPV) in patients with respiratory failure, defined as PCO2 > 45 mmHg, results in a significant reduction in mortality, need for intubation, complications of therapy, and hospital length of stay. Contraindications to NIPPV include cardiovascular instability, impaired mental status or inability to cooperate, copious secretions or the inability to clear secretions, craniofacial abnormalities or trauma precluding effective fitting of mask, extreme obesity, or significant burns.

Invasive (conventional) mechanical ventilation via an endotracheal tube is indicated for patients with severe respiratory distress despite initial therapy, life – threatening hypoxemia, severe hypercapnia and/or acidosis, markedly impaired mental status, respiratory arrest, hemodynamic instability, or other complications. The goal of mechanical ventilation is to correct the aforementioned conditions. Factors to consider during mechanical ventilatory support include the need to provide sufficient expiratory time in patients with severe airflow obstruction and the presence of auto-PEEP (positive end-expiratory pressure) which can result in patients having significant respiratory effort to trigger a breath during a demand mode of ventilation. The mortality of patients requiring mechanical ventilatory support is 17-30% for that particular hospitalization. For patients aged greater than 65 years admitted to intensive care unit for treatment, the mortality doubles over the next year to 60%, regardless of whether mechanical ventilation is required.

Conclusions

Exacerbations of COPD can be defined in numerous ways depending on the needs of the researcher, the clinician, the healthcare administrator, or the patient. Although consensus definitions for COPD exacerbations exist, current evidence suggests that, when studying effects of interventions, a workable definition of an exacerbation is likely to be one based on medical intervention rather than symptoms. In terms of their impact, exacerbations are associated with more rapid decline in lung function, sustained impairment of functionality and health status, high levels of hospitalization and mortality, and substantial direct healthcare costs and indirect societal costs. As severe exacerbations are associated with the worst prognosis and the highest healthcare costs, these may be of greatest priority for research.

A greater awareness of the mechanism underlying exacerbations, and their impact on health outcomes and costs, is necessary to encourage optimal treatment. Interventions that are effective in preventing or treating exacerbations, such as combination therapy with inhaled corticosteroids and long-acting ß2-agonists, have the potential to significantly reduce the impact of chronic obstructive pulmonary disease on patients and society.

PULMONARY REHABILITATION IN COPD PATIENTS

Respiratory rehabilitation is increasingly recognized as an important part of the management of patients with chronic obstructive pulmonary disease (COPD). The widespread application of such programmes should be preceded by evidence of directly attributable improvements in function. Respiratory rehabilitation relieves dyspnoea and improves the control over COPD. These improvements are clinically important. The value of the improvement in exercise capacity is not clear. Respiratory rehabilitation is an effective part of care in patients with COPD.

Pulmonary rehabilitation has gradually become the “gold standard” for patients with severe lung disease, especially chronic obstructive pulmonary disease (COPD). Because some newer therapeutic strategies, such as lung volume reduction surgery and lung transplantation, require well-conditioned patients, pulmonary rehabilitation is now considered essential for many patients formerly deemed untreatable.

Pulmonary rehabilitation is increasingly recognized as an important component of the comprehensive management of patients with severe symptomatic lung disease

The goal of rehabilitation is to restore a patient to the fullest medical, mental, emotional, social, and vocational potential possible. The most important aspect of rehabilitation is that the treatment be individualized. While appreciation of individual needs is crucial to the success of rehabilitation programs, the wide variations from patient to patient make objective evaluations difficult.

Well-controlled studies have shown significant improvement in various outcomes, including increased exercise capacity, improved quality of life, decreased dyspnoea, and fewer hospital admissions, when rehabilitation is used.

Pulmonary rehabilitation has two major objectives:

- To control, alleviate and, if possible, reverse the symptoms and pathophysiologic processes leading to respiratory impairment
- To improve the quality of, and attempt to prolong, the patient’s life

In the broadest sense, pulmonary rehabilitation attempts to provide comprehensive respiratory care for patients with pulmonary disease. From a practical point of view, a multidisciplinary approach and a structured rehabilitation program work best.

The practical goals are listed below

Reduce work of breathing

Improve pulmonary function

Normalize arterial blood gases

Alleviate dyspnea

Increase efficiency of energy use

Correct poor nutrition

Improve exercise performance and activities of daily living

Restore a positive outlook

Improve emotional state

Decrease health-related costs

Lengthen survival

Rehabilitation therapy basically consists of exercise, ventilatory therapy, ventilatory muscle training, and respiratory muscle resting. Nutritional and psychological support are also required.

Exercise

Exercise training is the most important component of a pulmonary rehabilitation program. Training improves exercise endurance in these patients.

Lower extremity exercise: Two recent controlled trials support the theory that pulmonary rehabilitation is better than conventional treatment in symptomatic COPD patients. After rehabilitation, patients showed a greater increase in distance walked, maximal work, and oxygen uptake and a decrease in lactate production and perception of dyspnoea when compared with controls.

Results in patients selected for lung transplantation show that rehabilitation improves performance to a degree not achieved with any other form of therapy. The data support exercise as a crucial component in the rehabilitation of patients with severe lung disease.

Upper extremity exercise: In general, arm training improves task-specific performance. It has been concluded that unsupported arm exercise may be effective for pulmonary rehabilitation because such exercises condition muscles used in activities of daily living.

Ventilatory therapy

This includes controlled breathing techniques (diaphragmatic breathing, pursed-lip breathing, and forward-bending exercises) and chest physical therapy (postural drainage, chest percussion, and vibration). The controlled breathing exercises help decrease dyspnoea, and chest drainage enhances removal of secretions. Benefits include less dyspnoea and anxiety, fewer panic attacks, and improved sense of well-being.

Ventilatory muscle training: Specific respiratory muscle training can improve strength and endurance. Because inspiratory muscles tend to be weakened in patients with COPD, the role of respiratory muscle training in these patients has been viewed with great interest. Strength training has limited clinical significance.

Evaluation of nutrition

Many patients with emphysema are thin, emaciated and, in fact, malnourished. Although evidence is lacking as to unequivocal benefits of improved nutrition on the respiratory system, most authorities agree that deficiencies should be corrected whenever possible. Treatment of anemia could improve oxygen-carrying capacity, and adjusting electrolyte imbalances could improve cardiopulmonary performance. Similarly, simple measures, such as encouraging the patient to take small amounts of food at frequent intervals, may alleviate abdominal distention and dyspnoea after meals. Oxygen

saturation during meals should also be evaluated and can be corrected by using supplemental oxygen while eating.

Psychological support

Most patients with advanced lung disease have minor but frequent psychological problems, especially reactive depression and anxiety. Fortunately, these are likely to improve with rehabilitation that encourages activity. Simple measures, such as being able to exercise under the supervision of supportive specialists, often alleviate symptoms, including dyspnoea and fear. Evidence shows that 15 to 20 rehabilitation sessions that include education, exercise, physical therapy, and breathing and relaxation techniques are more effective in reducing anxiety than a similar number of psychotherapy sessions. Nonetheless, a patient with major psychological problems occasionally requires primary psychiatric evaluation and treatment.

Conclusions

Many patients with chronic lung diseases benefit from pulmonary rehabilitation, and any patient with moderate to severe symptoms should be considered a candidate. Even the most severely ill patients, including those awaiting lung transplantation and those about to undergo lung volume reduction surgery, show improvements in pulmonary function with individualized training and support.

The most effective programs include patient education, exercise, nutrition guidance, psychological support, and a number of therapeutic options, such as breathing training and chest physical therapy. Primary care physicians can provide an important service by incorporating pulmonary rehabilitation in the care of patients with breathing disorders.

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