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Management of Chronic Obstructive Pulmonary Disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality and morbidity throughout the world. It is the only cause of death among the top ten causes that is increasing and is expected to become the third leading cause of death in the world by 2020. A diagnosis of COPD should be considered in any patient with a history of exposure to risk factors for the disease and/or the presence of chronic cough, sputum production or dyspnea. Patients with COPD are categorized into 5 stages based on their pulmonary function tests and symptoms. Smoking cessation is the single most effective way to stop the progression of COPD and prolong life. Pharmacologic management of stable COPD includes the use of bronchodilators (β-2 agonists, anticholinergics and methylxanthines) and inhaled corticosteroids. Other adjunctive measures include vaccination, oxygen therapy, pulmonary rehabilitation and certain surgical measures like bullectomy and lung transplantation. Management of acute exacerbations includes the use of systemic steroids, antibiotics, bronchodilators and oxygen therapy. During very severe exacerbations, patients may need ventilatory support.

Keywords: Chronic obstructive pulmonary disease; Smoking; Bronchodilators; Corticosteroids; Oxygen therapy; Lung transplantation

Introduction

Chronic obstructive pulmonary disease (COPD) is associated with an abnormal inflammatory response of the lungs to noxious particles or gases and is characterized by a progressive limitation of expiratory airflow due to airway obstruction that is not fully reversible.

At least 20 million adults in the United States suffer from this condition, and it leads to about 16 million physician office visits, 1.5 million Emergency Room visits and half a million hospitalizations each year. In the United States, more than 125,000 deaths can be attributed to COPD each year, making it the fourth leading cause of death [1]. Worldwide, this condition leads to almost 3 million deaths annually and is currently the fifth leading cause of death in the world. It is the only cause of death among the top ten causes that is increasing and it is expected to become the third leading cause of death in the world by 2030 [2,3].

While most cases of COPD are caused by smoking, the majority of chronic smokers will not develop COPD. Up to 15-20% of cases occur in lifetime nonsmokers, and these might be related to certain other risk factors such as air pollution, occupational exposure, and alpha-1-antitrypsin deficiency. Some studies have suggested that women are more susceptible to the effects of tobacco smoke than men [4].

Management

There are 4 components to the management of COPD.

1. Assess severity and monitor disease.
2. Reduce risk factors.
3. Manage stable COPD.
4. Manage exacerbations.

Assessment of severity and monitoring of disease

A diagnosis of COPD should be considered in any patient with a history of exposure to risk factors for the disease and/or the presence of chronic cough, sputum production, or dyspnea. The diagnosis should then be confirmed by spirometry. Unfortunately, the majority of patients with COPD are undiagnosed in the community, and most patients are first identified when they present with an exacerbation. In view of the fact that early intervention can modify the natural history of COPD, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends that spirometry should be performed in all current or ex-smokers over the age of 40 years who either cough several times on most days or get out of breath more easily than others of similar age. This will help to detect disease in relatively asymptomatic patients, define severity and prognosis in symptomatic patients, and monitor the progression of disease.

Patients with COPD are categorized on the basis of their pulmonary function tests (PFTs) including forced expiratory volume in 1 second (FEV1)/ forced vital capacity (FVC).

Stage 0 (at risk)	: Normal PFTs; chronic cough/sputum production
Stage 1 (mild)	: FEV1/FVC < 70%; FEV1 > 80%
Stage 2 (moderate)	: FEV1/FVC < 70%; FEV1 50-80%
Stage 3 (severe)	: FEV1/FVC < 70%; FEV1 30-50%
Stage 4 (very severe)	: FEV1/FVC < 70%; FEV1 < 30% or FEV1 < 50% + chronic respiratory failure

Reduction of risk factors

Smoking cessation: Smoking cessation is the single most effective way to stop the progression of COPD and prolong life. The Lung Health Study demonstrated that the decline in lung function among smokers was directly related to their smoking habits (Figure 1) [5].

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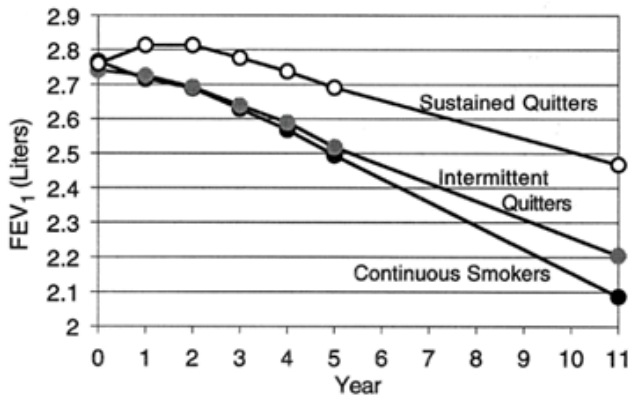

Figure 1: Loss of lung function over the years of study among sustained quitters (*open symbols*), continuing smokers (*closed symbols*), and intermittent smokers (*gray symbols*). Average values of postbronchodilator forced expiratory volume in 1 second (FEV_1) are shown, expressed in absolute terms. Reprinted by permission from Reference 5.

While the vast majority of current smokers report that they want to quit, less than 7% of smokers who attempt to quit remain smoke-free after 1 year. The average smoker will try to quit six to nine times in a lifetime. The five A's of smoking cessation are:

1. Ask about and document tobacco use at every visit.
2. Advise strongly to quit at every visit.
3. Assess willingness to quit.
4. Assist the patient in quitting with counseling and pharmacotherapy.
5. Arrange follow-up contact.

Therapy for smoking cessation should include a combination of two or more of the following:

1. Pharmacotherapy
   - First line: bupropion, varenicline
   - Second line: nortriptyline, clonidine
2. Nicotine replacement: patch, gum, inhaler, spray, lozenges, sublingual tablets
3. Counseling

Management of stable COPD

Existing medications for COPD should be used mainly to control symptoms as none of them have been shown to modify the long-term decline in lung function. The management of stable COPD should be characterized by a stepwise increase in treatment depending on the severity of the disease [Table 1].

Bronchodilators: These drugs should be used either on an as-needed basis for symptom relief or on a regular basis to prevent or reduce symptoms. They have been shown to increase exercise capacity in patients with COPD even when there is no significant change in FEV1 [6,7].

There are three classes of bronchodilators:

1. β-2 agonists
   - Short-acting: albuterol, terbutaline
   - Long-acting: salmeterol, formoterol
2. Anticholinergics
   - Short-acting: ipratropium
   - Long-acting: tiotropium
3. Methylxanthines: theophylline, aminophylline

Stage	0: At risk	I: Mild	II: Moderate	III: Severe	IV: Very Severe
	Avoidance of risk factors; influenza vaccination				
		Short-acting bronchodilators as needed			
			Regular treatment with long-acting bronchodilators		
				Inhaled steroids	
					Oxygen, surgical treatments

Table 1: Therapy at each stage of chronic obstructive pulmonary disease.

β-2 agonists: Short-acting β-2 agonists along with short-acting anticholinergics, either alone or in combination, form the first line of therapy in patients with COPD. These drugs have been shown to increase airflow and decrease hyperinflation. In addition, they decrease dyspnea, especially during acute exacerbations, and increase exercise tolerance leading to an improvement in quality of life indices.

Delivery by a metered-dose inhaler (with a spacer if needed), in equal doses, is almost always as effective as delivery via a nebulizer. Combined preparations of a short-acting β-2 agonist and an anticholinergic improve effectiveness and decrease risk of side-effects.

Long-acting preparations are more convenient and have been shown to have a positive impact on quality of life indices and acute exacerbations, but are more expensive. Apart from their bronchodilating ability, long-acting β-2 agonists have been shown to inhibit mast cell mediator release, decrease airway permeability and bacterial adhesion and increase mucociliary clearance. The Towards a Revolution in COPD Health (TORCH) trial established the role of salmeterol in decreasing exacerbation rates and improving lung function and health-related quality of life [8]. Although there was a reduction in mortality with the use of salmeterol, it was not statistically significant. In addition, the well documented safety concern with the use of salmeterol in asthmatics has made physicians wary of using this drug in COPD as well. As a result, salmeterol is almost exclusively prescribed in conjunction with inhaled corticosteroids in patients with COPD [9].

Anticholinergics: These agents work by competitively inhibiting muscarinic receptors and by reducing vagal tone to the airways. In addition, they may block the reflex bronchospasm seen in gastro-esophageal reflux disease and following exposure to irritants, and may also decrease mucus secretion.

The long-acting anticholinergic agent tiotropium has been shown to have a significantly greater affinity for the M1, M2 and M3 muscarinic receptors than the short-acting anticholinergic drug ipratropium. Clinically, when compared to ipratropium, tiotropium has been shown to lead to a more prolonged increment in FEV1 after administration and has also been shown to reduce exacerbation rates by more than 25% [10].

Methylxanthines: Slow release preparations of theophylline are effective in patients with COPD, but due to its potential toxicity, inhaled bronchodilators are preferred. A meta-analysis showed that theophylline improved FEV1, FVC, and gas exchange when compared to placebo [11].

Corticosteroids: Inhaled corticosteroids (ICS) work by a variety of mechanisms, some of which are not completely understood. One of their main roles is to decrease inflammatory cells which include eosinophils, T-lymphocytes, mast cells, and dendritic cells. Other beneficial mechanisms include decreasing chemotactic peptides and adhesion molecules.

While some studies have shown that ICS have no effect on the decline in FEV1, other studies have shown that the use of high-

dose ICS does slow the rate of lung function decline in patients with COPD [12,13]. Use of ICS have also been shown to reduce the rate of exacerbations by about 25-30%, but this beneficial effect was modified by disease severity, with a greater benefit being seen in patients with a lower FEV1 [9,14]. Although studies have not shown any effect of ICS on all-cause mortality, patients on ICS have had a slower decline in health status [15].

At the present time, ICS are appropriate for symptomatic COPD patients with an FEV1 < 50% predicted and repeated exacerbations. ICS combined with a long-acting β-2 agonist is more effective than the individual components [16-20]

A short course of oral steroids is a poor predictor of the long-term response to ICS and should not be used to determine treatment [21]. Long-term treatment with oral steroids is not recommended in COPD and every attempt should be made to discontinue steroids in the "steroid-dependent" patient [22]. Moreover, long-term systemic steroids may contribute to respiratory failure by leading to steroid myopathy which in turn contributes to muscle weakness and decreased functionality [23,24].

Phosphodiesterase Type 4 inhibitors : Rofumilast is approved in the United States for patients with COPD and a history of exacerbations. A randomized trial showed that rofumilast improved pre-bronchodilator FEV1 and decreased the rate of moderate to severe exacerbations [25]. Also, in another trial, when patients with moderate to severe COPD were randomly assigned to a combination of roflumilast plus salmeterol or tiotropium and compared to patients receiving either salmeterol or tiotropium alone, roflumilast significantly improved the pre-bronchodilator FEV1 [26].

Chronic antibiotic therapy: Randomized controlled trials have shown that patients with COPD receiving macrolide antibiotics have fewer exacerbations, and that this might be due to their anti-inflammatory effect along with their antibiotic effect [27,28]. However, due to the concern for developing resistance, daily antibiotic therapy is not recommended at this time pending further studies.

Vaccines: Influenza vaccination should be recommended to all patients with COPD at least once a year as it can significantly reduce serious illness and death [29]. Although pneumococcal vaccination has not been clearly shown to improve morbidity or mortality, the Centers for Disease Control and prevention (CDC) recommends administering the pneumococcal vaccine to all patients with COPD [30,31].

Oxygen therapy: The Nocturnal Oxygen Therapy Trial Group demonstrated that in hypoxemic patients with COPD, continuous oxygen (O_2) therapy (nearly 18 hours/day) is associated with a lower mortality than is nocturnal (12 hours/day) O_2 therapy [32].

However, O_2 has not been shown to be beneficial in patients with moderate hypoxemia (PaO_2 56-65 mm Hg) who do not have evidence of peripheral edema, polycythemia (hematocrit > 55%), or cor pulmonale [33].

There might, however, be certain other benefits to O_2 therapy that have been recently uncovered. A study has suggested that the hypoxemia in patients with COPD leads to activation of tumor necrosis factor-alpha (TNF-α). This may be a factor contributing to the weight loss in patients with the disease, thereby potentially suggesting that O_2 therapy will lower TNF-α and lead to less wasting [34].

Chronic hypoxemia may lead to increased nervous system activity [35]. Patients with severe nocturnal hypoxemia exhibit elevated plasma norepinephrine levels which were reduced if whole night oxygenation was normalized with O_2 therapy [36]. Thus apart from decreased wasting, O_2 therapy can lead to decreased pulmonary vascular resistance and decreased skeletal muscle dysfunction.

Unfortunately, on one hand while studies have shown that O_2 therapy remains underutilized in patients for COPD, other studies have demonstrated that once a patient is started on O_2 therapy, a re-evaluation of the need for the O_2 is done in less than 20% of patients. In one study, when 237 patients receiving home O_2 were re-evaluated, 41% did not meet criteria for home O_2 [37].

Pulmonary rehabilitation: A study of 200 patients with disabling chronic lung disease, 167 of whom had COPD, demonstrated that pulmonary rehabilitation led to an improvement in exercise capacity (walking ability) and in health status (quality of life) indices [38].

Surgical therapy

Bullectomy: In select patients, this procedure is effective in improving lung function and reducing dyspnea. Criteria for bullectomy include [39]:

1. The bulla must occupy at least 50% of the hemithorax.
2. The bulla must displace adjacent lung tissue.
3. There must be evidence of poor perfusion on the side of the bulla with relatively good perfusion on the contralateral side.
4. There must be no evidence of chronic purulent bronchitis.

Lung volume reduction surgery (LVRS): This is a surgical procedure in which parts of the lung are resected to reduce hyperinflation. LVRS improves physiology by increasing elastic recoil, respiratory muscle function and flow, and by decreasing lung volume and dead space, although there is a variable effect on gas exchange. Studies indicate that survival is probably not altered by LVRS, but it has been shown to improve exercise capacity, probably more than with rehabilitation alone. Currently, it is an experimental palliative surgical procedure not recommended for widespread use.

Lung transplantation: In select patients with very advanced COPD, lung transplantation has been shown to improve functional capacity and quality of life. Criteria for lung transplantation include FEV1 < 35%, predicted, PaO_2 < 60 mm Hg, $PaCO_2$ > 50 mm Hg, and secondary pulmonary hypertension [40].

Management of exacerbations

Bronchodilators: A short-acting β-2 agonist is the preferred bronchodilator for the treatment of COPD exacerbations. If a prompt response does not occur, addition of an anticholinergic is recommended even though the effectiveness of this combination is controversial [41]. Similarly, the role of aminophylline in the treatment of COPD exacerbations is controversial and should be considered only in more severe exacerbations. Close monitoring of serum theophylline levels should be then be done to avoid side effects.

Corticosteroids: Systemic steroids help to restore lung function more quickly and shorten recovery time [42]. The dosages and routes of administration of systemic steroids used in studies have varied widely from 30 mg once daily of oral prednisolone to 125 mg every 6 hours of intravenous methylprednisolone [43,44]. However, the current consensus and recommendation is that 40 mg of oral prednisolone for 10 days is adequate to treat most cases of COPD exacerbation. More prolonged treatment does not result in greater efficacy and increases the risk of side effects. Nebulized ICS may be an alternative to oral steroids in the treatment of milder, non-acidotic exacerbations [45].

Antibiotics: The tracheo-bronchial trees of about one-third of patients with COPD are colonized with bacteria. The bacteria involved in an acute exacerbation include Hemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Hemophilus parainfluenzae, enteric bacilli, and Pseudomonas species. Recent studies using polymerase chain reaction (PCR) have also demonstrated the presence of viruses (rhinovirus, influenza, and parainfluenza) and atypical organisms like mycoplasma and chlamydia.

Molecular typing of sputum isolates from 81 patients with COPD followed over a 56-month period showed that the isolation of a new strain of Hemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae was associated with a significantly increased risk of an exacerbation, thus supporting the causative role of bacteria in exacerbations of COPD [46].

However, due to the absence of many well-designed clinical studies, the role of antibiotics in COPD exacerbation remains debated. One study of 362 exacerbations in 173 patients over 3.5 years demonstrated that there was a significant benefit associated with antibiotic treatment over placebo [47]. On the other hand, a study of 278 patients who had an acute exacerbation of chronic bronchitis showed that there was no difference between antibiotic therapy and placebo [48]. The problems with most of the studies have been that they were not stratified for steroid use. However, a review of all the studies would suggest an overall beneficial effect of using antibiotics, and most authorities would recommend their use if a patient experiences increased dyspnea associated with increased volume and purulence of their sputum.

Oxygen therapy: Supplemental oxygen should be used to achieve adequate levels of oxygenation (PaO_2 > 60 mm Hg or SaO_2 > 90%). As CO_2 retention can occur insidiously, an arterial blood gas should be checked 30 minutes after initiation of therapy to ensure that an acute respiratory acidosis has not developed. Venturi masks deliver oxygen more accurately than nasal prongs but are more uncomfortable for the patient.

Ventilatory support: During very severe COPD exacerbations, patients may need ventilatory support which can be achieved by either:

1. Noninvasive positive pressure ventilation or
2. Conventional mechanical ventilation

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