Management of chronic obstructive pulmonary disease

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Recognising COPD

Chronic obstructive pulmonary disease (COPD) is characterised by chronic airflow limitation (obstruction), not fully reversible, some significant extrapulmonary effects and important co-morbidities, all of which may contribute to the severity of the disease. Co-morbidity may be myocardial infarction, osteoporosis, respiratory infection, bone fractures from osteoporosis, depression, diabetes, sleep disorders, anaemia and glaucoma.

COPD is an important cause of death and morbidity worldwide. The estimated prevalence of COPD varies from 7% to 19% around the world. It is also true that COPD remains underdiagnosed.

Risk factors

Smoking remains the most important risk factor. Alpha-1-antitrypsin deficiency (rare) is an important genetic risk factor seen in premature, early COPD (young age), but siblings of patients with severe COPD also have an increased risk (other genetic factors). Air pollution, outdoor but also indoor, such as heating and cooking with biomass fuels (wood, charcoal, vegetable matter, animal dung and coal) are important risks for the development of COPD, as are occupational chemicals. People exposed to biomass smoke have an odds ratio of 2.44 [95% confidence interval (CI) 1.9 to 3.33] for developing COPD. Exposure to pollution and respiratory infections during early childhood may contribute to reduced lung function in adulthood. Pulmonary tuberculosis is an important risk factor. It is estimated that 25-45% of patients with COPD have never smoked, but were exposed to other risk factors, noticeably the use of biomass fuels.

Recognition of early disease

COPD should be considered in any patient with chronic persistent progressive dyspnoea and/or chronic cough and/or phlegm production who smokes and has at least a 10 pack-year history (or exposure to another risk factor). The public health message is: chronic cough and sputum are not normal. However, in clinical practice many patients only present when they become dyspnoeic.

Spirometry for confirmation. A post-bronchodilator forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio of ≤ 0.70 implies persistent, not fully reversible airflow obstruction, i.e. COPD. Currently this is the gold standard for diagnosis. Use of this fixed ratio may sometimes lead to overdiagnosis, especially in the elderly. Peak expiratory flow measurement is not appropriate for the diagnosis of COPD.

Once the diagnosis is made, the measured FEV1, expressed as a percentage of the predicted value, is used to classify the severity of COPD in four stages [Global Initiative for Obstructive Lung Disease (GOLD) stages]:

- Stage I (mild): FEV1 ≥ 80% of predicted; in this stage the individual may be unaware of the existence of COPD
- Stage II (moderate): FEV1 ≥ 50% to < 80% of predicted
- Stage III (severe): FEV1 > 30% to < 50% of predicted
- Stage IV (very severe): FEV1 < 30% of predicted or < 50% predicted and there is chronic respiratory failure and/or right heart failure.

Arterial blood gas measurement is recommended when the FEV1 in a stable patient is ≤ 50% of predicted normal or when the patient has signs suggestive of respiratory failure or right heart failure.

Chest radiography. A chest radiograph is useful as it may reveal the following:

- Lung cancer, also commonly due to smoking
- Signs of hypertension
- Complications of COPD, e.g. pneumothorax
- Co-morbid disease, e.g. left heart failure.

Lung computed tomography is sometimes needed when the diagnosis is in doubt.

Management aims

Prevention of disease progression

Patients should be advised to avoid air pollution and any other risk factors, including smoking. Smoking cessation is one of the most cost-effective and important measures and has been shown to
reduce the rate of decline in lung function, particularly the decline in FEV₁.

There are some indications that treatment of early COPD in stage II disease with tiotropium inhalation may slow the decline of FEV₁, despite the fact that 69% of patients in the Understanding Potential Long-term Impacts on Function with Tiotropium trial (UPLIFT) were on long-acting β agonists and 72% were on inhaled corticosteroids.

**Treatment of airflow obstruction**

Airflow obstruction (airflow limitation) in COPD is not fully reversible and is usually progressive. Many patients with COPD show significant, albeit partial, reversibility following administration of a bronchodilator. Bronchodilators, especially long-acting ones, are the mainstay of the treatment of COPD and include inhaled β₂ agonists and inhaled anticholinergics (tiotropium). Long-acting bronchodilators are more effective than short-acting bronchodilators. Oral theophylline may be added, in low doses, to avoid toxicity. Bronchodilators can improve FEV₁ (as shown by an increase in FEV₁ on bronchodilator testing) but even if the FEV₁ does not improve, some meaningful symptomatic improvement can be achieved in reduction of hyperinflation and dynamic hyperinflation with a consequent improvement in the quality of life. Combining bronchodilators may improve the effectiveness. Long-acting bronchodilators, e.g. tiotropium and long-acting β agonists (LABA) are more effective and convenient when used as regular therapy. Tiotropium may be used as a first-line long-acting bronchodilator treatment in COPD (South African guidelines) or may be used in combination with LABAs because of their different mechanisms of action. Tiotropium improves quality of life and reduce acute exacerbations and hospitalisations, which have also been shown with LABAs.

**Reduction or prevention of acute exacerbations**

There is no standard, universally acceptable definition for a COPD exacerbation, but commonly patients present with an acute increase in dyspnoea, cough and sputum volume, and purulence of sputum that warrants a change in regular medication (antibiotics and steroids are added). Some of these episodes may be managed outside the hospital, but many episodes warrants hospitalisation. As COPD severity increases, so does the frequency of the episodes of acute exacerbations.

**Tiotropium (long-acting antimuscarine drug)**

In a Cochrane systematic review of nine trials involving 6 584 patients, tiotropium compared to placebo or ipratropium (short-acting antimuscarine) reduced acute exacerbations by 18% (95% CI 10-25%), numbers to treat 25 (95% CI 13 to 34) and related hospitalisations by 33% (95% CI 14-47%), numbers to treat 34 (95% CI 25 to 100). In the four-year UPLIFT trial, tiotropium reduced exacerbations by 14% (P <0.001), even when given on top of LABAs and inhaled corticosteroids.

**Long-acting β₂ agonists**

A Cochrane systematic review of 1 741 patients showed that 50 μg salmeterol, compared to placebo, reduced acute exacerbations by 28% (95% CI 10-43%). In the Towards a Revolution in COPD Health (TORCH) trial in 6 112 patients, salmeterol vs. placebo reduced acute exacerbations by 15% (P < 0.001).

**Inhaled corticosteroids**

A meta-analysis of 11 trials involving 8 164 patients showed a moderate reduction of acute exacerbations of 18% (95% CI 8-27%), but with a subgroup analysis suggesting that the benefit occurred only in those patients with FEV₁ < 50% predicted.

The following has become the indication for the use of inhaled corticosteroids (ICS) in COPD: FEV₁ < 50% of predicted and/or patient with repeated acute exacerbations. The use of ICS increases the likelihood of pneumonia in patients with COPD, a relative risk increase of 1.60 (95% CI 1.33-1.92).

**Combined long-acting β₂ agonist and ICS**

A Cochrane meta-analysis of seven trials (5 708 patients) showed a reduction in acute exacerbations of 9% (95% CI 3-15%). A systematic review of 18 studies (12 446 patients) found that the combination of LABA plus ICS is not better than LABA alone in preventing acute severe exacerbations, but the combination is marginally better in preventing moderate exacerbations. The INSPIRE trial (a study of interferon γ-1b for idiopathic pulmonary fibrosis) of 1 323 patients found no difference in the rate of exacerbations when tiotropium was compared to the use of LABA plus ICS as a combination.

**Tiotropium combined with long-acting β₂ agonist and ICS**

There are not enough data on triple therapy to construct a meta-analysis or to promote the use of it as first-line treatment. Many patients in practice may very well end up using triple therapy, i.e. ICS, LABA and tiotropium.

**Tiotropium vs. salmeterol**

In a recent trial directly comparing tiotropium to salmeterol, tiotropium significantly reduced the time to the first COPD exacerbation by 17% (95% CI 10-23%), and significantly reduced the annual number of acute exacerbations by 11% (95% CI 4-17%). The incidence of serious side-effects, including death, was identical.

**Symptomatic relief**

There is evidence that lung volumes, especially dynamic hyperinflation during exercise or during walking, are important in the generation of symptoms such as dyspnoea, and effort limitation is recommended in patients with more advanced COPD. All categories of bronchodilators and all long-acting bronchodilators, some better than others, have been shown to improve exercise capacity and improve the quality of life without necessarily producing significant changes in FEV₁. They achieve this by reducing or delaying dynamic hyperinflation. Tiotropium has also been shown to improve the effectiveness of pulmonary rehabilitation when added to the pulmonary rehabilitation programme.
Pulmonary rehabilitation

Pulmonary rehabilitation reduces symptoms, improves quality of life, and increases physical and emotional participation in everyday activities. The problems specifically addressed by rehabilitation include physical deconditioning, relative social isolation, altered mood status (especially depression), muscle wasting and weight loss.

Oxygen therapy

The long-term use of oxygen (> 15 hours every day) in COPD patients, who have resting hypoxaemia when in a stable state, has been shown to increase survival.

Ventilatory support

Long-term noninvasive positive-pressure ventilation (NIPPV) combined with long-term oxygen therapy may benefit a few selected patients.

Surgical treatment

Bullectomy, lung volume reduction surgery and lung transplantation are available for highly specific selected patients.

Other measures

Vaccines. Influenza vaccines can reduce serious illness and death in COPD patients. Pneumococcal vaccine should be given to COPD patients older than 65 years.

Antibiotics. There is no benefit of prophylactic, continuous use of antibiotics. Antibiotics are useful during the treatment of an acute exacerbation of COPD.

Mucolytics. The overall benefit is very small and the widespread, routine use is not recommended.

Antioxidant agents. One trial has shown some benefit of N-acetylcysteine in patients not treated with ICS but, on average, not much benefit has been shown as yet.

Antitussives. Cough has a significant protective role in COPD and guidelines do not recommend the routine use of antitussives.

Vasodilators. Nitric oxide is not indicated in stable COPD.

Narcotics. Oral opioids are effective to treat severe dyspnoea in advanced COPD. Nebulised opioids have not been properly evaluated. The serious adverse effects of opioids limit the benefits.

Management of co-morbidities

Patients with COPD should also have their cardiovascular risk evaluated using a risk score such as the Framingham Risk Score. Appropriate therapies should then be initiated (e.g. statins, blood pressure reduction). The specific uses of statins or aspirin to reduce the systemic inflammatory nature of COPD have not been formally tested in a randomised trial. Standard therapy for the other comorbidities is necessary.

Guidelines

The South African Guidelines for the Management of Chronic Obstructive Pulmonary Disease: 2011 should be consulted and used in clinical practice.

Conclusion

Recognition of the risk factors for COPD, especially smoking, and early diagnosis based on lung function tests are critical components of an effective management plan. Smoking cessation is the single most cost-effective therapy. Long-acting bronchodilators and possibly early introduction of a long-acting anticholinergic drug (tiotropium) may significantly influence the disease and overall significantly improves the quality of life, even though the FEV₁ may not improve significantly. Inhaled corticosteroids should be introduced when the FEV₁ is below 50% of the predicted value, and when the patient has repeated exacerbations (for example three in the last three years). Later on patients often require combination therapy.

References