



Current Perspectives on Management of COPD

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Epidemiology

Chronic Obstructive Pulmonary Disease (COPD) is currently the 4th leading cause of death in Hong Kong and USA, and its mortality rate has been on the rise over the past 30 years whilst that of coronary heart disease and stroke have dramatically declined during the same period. It is estimated that by 2020, COPD will become the 5th most prevalent disease worldwide and the 3rd most common cause of death in many countries. In Hong Kong, COPD ranks third after cancer and renal failure in the number of patients admitted to HA hospitals. According to the Hong Kong Adult Lung Function Study, of the 409 smokers and ex-smokers studied, 21% was found to have spirometric evidence of COPD (Ip, unpublished data). More importantly, nearly two-thirds of the COPD population had at least moderate disease based on the extent of lung function impairment, and yet many remained undiagnosed and under-treated.

According to the revised GOLD guidelines (Global Initiative for Chronic Obstructive Lung Disease) published in 2003, COPD is defined as a disease state characterised by airflow limitation that is not fully reversible, is usually progressive, and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The single most important risk factor for COPD is smoking, and about 14% of smoking males develop COPD sometime in their lives. The cardinal symptoms of COPD are chronic cough, usually productive of mucoid sputum, and progressive dyspnoea. Spirometry typically shows a reduction in FEV1/FVC to 70% or less of the normal value, and the severity of COPD is based on the percentage of FEV1 relative to the normal value.

Management

The goals of effective COPD management are to prevent disease progression, relieve symptoms, and to prevent and treat exacerbations so as to reduce mortality. There have been exciting developments in both pharmacological and non-pharmacological modalities in the management of COPD in the past decade.

Smoking Cessation

Smoking is the relevant risk factor in over 90% of COPD patients, and smoking cessation remains the only effective measure that can modify the disease progression by reducing the rate of decline in lung function (Scanlon et

al. *AM J Respir Crit Care Med* 2000;161:381-90). Up to 40% of smokers in USA attempt to quit smoking every year but the success rate is only 5%. Nicotine replacement therapy increases quit rate to 10-15% but its use in ischaemic heart disease is relatively contraindicated. Bupropion reduces nicotine dependence by increasing dopaminergic activity in the brain via catecholamine uptake blockade. When given alone, Bupropion was recently shown to achieve quit rate of 30% after 1 year and this was increased further to 35% when combined with nicotine replacement therapy (Jorenby et al. *N Engl J Med* 1999). In COPD patients, Bupropion was able to achieve point prevalence quit rate of 30-35% over 6 months (Tashkin et al. *Lancet* 2001). Besides pharmacotherapy, regular counselling to enhance self-confidence is pivotal in achieving successful smoking abstinence. Smokers should be encouraged to quit smoking and appropriate smoking cessation strategies given to help prevent further deterioration in lung function.

Bronchodilator

Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms. The absence of acute bronchodilator response does not preclude a long term favourable bronchodilator response in some patients (Tashkin and Kesten *Chest* 2003;123:1441-9). The principal bronchodilators are β -agonists and anticholinergics; both cause functional improvement in FEV1 but combination of the two drugs leads to more beneficial bronchodilation than the individual component given alone and does not produce tachyphylaxis over 3 to 6 months (Combivent Inhalation Aerosol Study Group 1994). The main disadvantage of these drugs is their short duration of action of only 4-6 hours necessitating frequent dosing up to 4 times a day, and its effectiveness is greatly influenced by patients' compliance.

Whilst long-acting β -agonists have been used in the management of persistent asthma for some time, its benefit in COPD has only been established recently. Salmeterol has been shown to improve FEV1 and reduce exacerbation in COPD patients compared to placebo and the extent of improvement could be further enhanced by the combination with Ipratropium (Van Noord et al. *Eur Respir J* 2000;15:878-85). Similarly, Formoterol has been found to cause more pronounced and sustained bronchodilation up to 12 hours in COPD patients compared with Ipratropium (Wadbo et al. *Eur Respir J* 1999;14:Suppl. 30, 381s) and





theophylline. Tiotropium is a long-acting anti-cholinergic bronchodilator, and its long duration of action is due to the high affinity for the Muscarinic 3 (M3) receptor on airway smooth muscle cells resulting in prolonged bronchodilation up to 36 hours. In a study of 536 moderate-severe COPD patients over 1 year, Tiotropium was significantly better than Ipratropium in the improvement in lung function and quality of life (Vincken et al. *Eur Respir J* 2002;19:209-16). In other studies of 6 to 12 months duration, Tiotropium was able to reduce exacerbation by 25% and hospitalisation by 35% (Vincken et al. *Eur Respir J* 2002;19:209-16, Casaburi et al. *Eur Respir J* 2002;19:217-24). Tiotropium is also the only bronchodilator that has been shown to improve exercise tolerance in moderate-severe COPD, which translates to significant improvement in quality of life (O'Donnell 2004).

The current GOLD guidelines recommend the use of short-acting bronchodilators for symptom relief in all grades of COPD, and regular use of long-acting bronchodilator in moderate or severe disease.

Steroid

The airway inflammation in COPD is mediated predominantly by neutrophils and it is not as steroid responsive as in the asthmatic airway where eosinophils and lymphocytes are key cells in the inflammatory cascade. The role of inhaled steroid in COPD has not been defined until a few years ago. A meta-analysis of the use of inhaled steroid in COPD found that in moderate-severe COPD, inhaled steroid was able to reduce exacerbation by about 25% (Alsaeedi A et al. *Am J Med* 2002;113:59-65); however, its effect on the rate of decline in lung function remains controversial (MacNee and Calverley, *Thorax* 2003;58:261-5, Sutherland et al. *Thorax* 2003;58:937-41). There is currently no evidence to recommend the use of inhaled steroid in mild and moderate COPD. Combination therapy of inhaled steroid with long-acting-agonist has been shown to improve lung function more than either component alone, and there is some evidence to suggest that combination therapy is superior in terms of reduction of exacerbation and improvement in quality of life as well (Calverley P et al. *Lancet* 2003;361:449-456; Szafranski W et al. *Eur Respir J* 2003;21:74-81)

Short courses of oral steroid of 2-3 weeks often lead to symptomatic and objective improvement in about 10% of COPD patients. However, the positive response to oral steroid is a poor predictor of response to maintenance inhaled steroid. In acute exacerbation, short courses of oral steroid have been shown to improve outcome and reduce hospital stay. Long term oral steroid should not be used as it has no survival benefit and may lead to myopathy that contributes to muscle weakness and worsens respiratory failure in severe COPD.

Anti-oxidant

Exposure of the COPD airway to cigarette smoke and other noxious agents results in increased oxidative stress that perpetuates the underlying airway inflammation. The defence mechanism against oxidative stress is relatively deficient in COPD. N-Acetylcysteine is an anti-oxidant

that has been shown to reduce exacerbation by about 22% in patients with moderate-severe COPD who have not been on inhaled steroid (Decramer et al. *Eur Respir J* 2001; 17:329) and may be an alternative to inhaled steroid in some patients.

Pulmonary rehabilitation

Pulmonary rehabilitation is a multi-disciplinary approach to increase physical and emotional participation in daily activities and thereby reducing symptoms of dyspnoea and improvement in quality of life in COPD. Compared to control, pulmonary rehabilitation has been shown to significantly reduce hospitalisation rate, and improve health status and exercise capacity (Griffiths et al. *Lancet* 2000;355:362).

Its benefit is sustainable and can be seen across all grades of severity of COPD. Pulmonary rehabilitation should be offered to COPD patients with moderate and severe disease.

Lung volume reduction surgery

Lung volume reduction surgery (LVRS) is the surgical removal of the most diseased portion of lungs thereby thus allowing the remaining more functional lung units to expand and participate in ventilation and gas exchange. By improving lung mechanics and gas exchange, LVRS has been shown to reduce dyspnoea and improve lung function in some end-stage emphysematous patients, and these palliative effects were sustainable according to a recent long-term follow up study (Ciccone et al. *J Thorac Cardiovas Surg* 2003; 125(3):513-5). Patients with predominantly apical disease and poor baseline exercise capacity appear to benefit most from LVRS (National Emphysema Treatment Trial Research Group. *N Engl J Med* 2003; 348(21):2059-73)

Conclusion

COPD is a chronic debilitating illness that is increasing in prevalence worldwide. A significant proportion of COPD patients in our community remain under-diagnosed and many under-treated. New developments in the pharmacological as well as non-pharmacological treatment modalities in recent years have been shown to improve lung function, reduce exacerbation, and improve quality of life. Practitioners should become more aware of the disease and its treatment strategies so that morbidity and mortality related to COPD can be reduced in the future.

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