Clinical Management of COPD

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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. COPD is a common disease worldwide with similar trends in the East and the West. It is a disease with significant morbidity and incurs heavy utilisation of health care resources. The prevalence of COPD varied from 11.4 to 26.1% according to a recent multi-city study that surveyed the population with spirometry. The economic burden of COPD to the society is enormous. In 2005, COPD ranked second as a respiratory cause for hospitalisation and in-patient bed days in Hong Kong. In those >75 years of age, the hospitalisation rate for COPD was as high as 2,225/100,000. The prevalence of moderate COPD, using the spirometric reference of FEV1/FVC ratio of <70%, among 1,008 elderly HK Chinese (age ≥60 years) in the community, were 19.6% and 11.9% in the male and female subjects respectively. In this article, we will review the clinical management of COPD.

Management of Stable COPD Patients

The Global Initiative for Obstructive Lung Disease (GOLD) guideline has classified COPD into 4 different stages of severity according to the lung function of the patients, with recommendations on treatment for each stage of the disease (Figure 1).

1. Avoidance of Risk Factor

It has been projected by the WHO that the total mortality of COPD would increase by 30% over the next 10 years unless successful strategies are implemented to reduce the risk factors of COPD, particularly tobacco use. By 2030, COPD is estimated to become the fourth leading cause of death worldwide. Smoking cessation is by far the single most effective and cost effective way to reduce exposure to COPD risk factors. Smoking cessation can reduce the rate of accelerated FEV1 decline that exists in smokers with COPD. Clinician’s advice and intervention, coupled with the use of appropriate drugs such as nicotine replacement therapy, bupropion and varenicline can improve the quit rate of the patients.

2. Influenza and Pneumococcal Vaccinations

Infection of the respiratory tract is a common cause of acute exacerbation of COPD (AECOPD) and repeated exacerbations can lead to more rapid deterioration in the lung function and quality of life of these patients. The GOLD 2007 guideline has recommended routine prophylaxis with pneumococcal and influenza vaccines for the COPD patients.

3. Bronchodilators

Bronchodilators are the therapeutic mainstay for patients with COPD. Short-acting bronchodilators alone or in combination may be sufficient to control symptoms in patients with Stage I disease (Figure 1). The principal bronchodilator treatments are 2-agonists, anticholinergics, and methylxanthines. For patients with stage 2 disease and above, regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators.

Anti-cholinergic Agent

Tiotropium is a long-acting once daily inhaled anti-cholinergic agent for treatment of more severe COPD patients. Tiotropium can improve lung function, dynamic hyperinflation and symptoms in COPD patients. In addition, it can reduce exacerbations and improve the quality of life of the patients. A large scale clinical trial evaluating the impact of tiotropium
on the rate of long term lung function decline and mortality is underway.17

**Long Acting Beta-agonist**
Salmeterol and formoterol are long acting beta-agonists that can offer more sustained improvements in pulmonary function, chronic dyspnoea and quality of life than short-acting bronchodilators in patients with moderate to severe COPD.18 In the Towards a Revolution in COPD Health (TORCH) trial, salmeterol therapy was associated with reduced frequency and severity of exacerbation when compared to placebo.19

**4. Inhaled Corticosteroid**
Regular treatment with inhaled corticosteroid (ICS) alone does not modify the long term rate of decline of FEV1 in patients with COPD. However, for the symptomatic COPD patients with FEV1 <50% predicted (Stage III and IV COPD patients, Figure 1) and repeated exacerbations (e.g. 3 times in the last 3 years), regular use of ICS is associated with a reduction in frequency of AECOPD.1 Furthermore, withdrawal of ICS may lead to exacerbations in some patients.20 There is some concern over the use of ICS as the likelihood of pneumonia appears increased in the COPD patients.19

**5. Combination Inhaled Steroid and LBAB**
Several studies that have explored the role of combination therapy have shown significant improvements over single agents alone, but addition of ICS was associated with an increased risk of pneumonia.21,22 In the TORCH trial, salmeterol in combination of fluticasone could improve lung function, health status and decrease the frequency of exacerbations when compared to placebo, salmeterol alone, or fluticasone alone.19 Salmeterol plus fluticasone however, failed to achieve a statistically significant decrease in mortality when compared to placebo over a study period of 3 years.19

**6. Theophyllines**
Theophylline has some bronchodilatation and anti-inflammatory effects on the airway. Due to its potential systemic toxicity and narrow therapeutic index, inhaled bronchodilators are preferred when available. Theophylline may be considered as an add-on therapy when symptoms persist in patients with more severe disease despite the use of other treatments.

**7. Mucokinetic Agents**
These drugs aim to decrease sputum viscosity and adhesiveness in order to facilitate expectoration.24 In clinical trials of COPD patients, there are conflicting data whether the mucokinetic agents are useful. A large trial on oral acetylcysteine failed to document any substantial benefit.24 However, a recent trial on carbocisteine found that the numbers of exacerbations per patient per year declined significantly in the carbocisteine group when compared against the placebo group.24 In fact, both the above mentioned mucokinetic agents also have some anti-oxidant effects.

**8. Non-pharmacological Therapy**
**Pulmonary Rehabilitation**
The American Thoracic Society (ATS)/ European Respiratory Society (ERS) have defined pulmonary rehabilitation as “an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualised treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimise functional status, increase participation, and reduce health care costs through stabilising or reversing systemic manifestations of the disease.”25 Patients with COPD often have decreased physical activity as exertion can worsen dyspnoea. This relative inactivity will lead to progressive deconditioning and may further initiate a vicious cycle, with dyspnoea becoming problematic at even lower physical demands. Pulmonary rehabilitation aims to break the cycle.

Pulmonary rehabilitation consists of physical conditioning (e.g. training of the upper and lower limb muscles), breathing retraining, education, and psychological support. Pulmonary rehabilitation has been carefully evaluated in a large number of clinical trials and their benefits include improvement in exercise capacity and health-related quality of life. In addition, pulmonary rehabilitation can reduce the perceived intensity of breathlessness, number of hospitalisations and days in the hospital, and anxiety and depression associated with COPD.1,26

**Oxygen Therapy**
In patients with cor pulmonale, long-term oxygen therapy (LTOT) may improve secondary polycythaemia, right heart failure, neuropsychiatric function, and exercise performance, in addition to prolonging survival if usage is at least 15 hours each day.27 LTOT should be considered for patients with COPD who have chronic respiratory failure when assessed at least twice during a stable period of 3 to 4 weeks apart, and who have an arterial oxygen tension (PaO2) of ≥7.3kPa (54.8mmHg) or an arterial oxygen saturation (SaO2) of 88%, with or without hypercapnia while breathing air. In patients with a PaO2 of >7.3 kPa, treatment with oxygen confers no survival advantage. LTOT should be prescribed if 7.3 kPa<PaO2<8kPa (60mmHg) or SaO2 is 89%, in the presence of one of the following complications: secondary polycythaemia (haematocrit >55%), right heart failure, or pulmonary hypertension. However, this treatment is generally not recommended for patients who continue to smoke. The dose of oxygen should be adjusted to achieve a PaO2 of ≥8kPa at sea level, or SaO2 of ≥90% during rest, exercise, and sleep.

**Surgical Treatments**
In carefully selected cases, bullectomy is effective in reducing dyspnoea and improving lung function in patients with COPD who have large bullae (e.g. occupying 30% or more of the hemithorax) that cause significant compression of surrounding pulmonary parenchyma.

Lung volume reduction surgery (LVRS) is a form of palliative surgery in which parts of the lung are resected to reduce hyperinflation. This allows the respiratory muscles to be more effective pressure generators by improving their mechanical efficiency (as measured by length/tension relationship, curvature of the diaphragm, and area of apposition). In addition, LVRS increases the elastic recoil pressure of the lungs and thus improves expiratory flow rates. LVRS can potentially benefit
carefully selected patients with COPD who have an FEV\(_1\) of 20-25% of the predicted value, hyperinflated lungs with a high residual volume (RV)/total lung capacity (TLC) ratio, and a heterogeneous distribution of emphysema on high-resolution CT showing as upper lobe predominance. LVRS may improve symptoms and pulmonary function for several years in carefully selected patients with severe emphysema. The procedure involves excision of 20% to 30% of the volume of each lung by thoracotomy or video assisted thoracoscopy.\(^{26,29}\)

Newer techniques with the use of endobronchial valve (a one-way valve that prevents air from entering into the isolated emphysematous segment while allowing the venting of expired gas and drainage of bronchial secretions distal to it) may be performed via bronchoscopy to achieve lung volume reduction.\(^{30}\) Lung transplantation (double or single) may improve the quality of life, functional capacity, and may be considered in relatively young patients who have very limited exercise tolerance, poor lung function (eg FEV\(_1\) <35% predicted, PaO\(_2\) <7.3 to 8 kPa, arterial carbon dioxide tension [PaCO\(_2\)] >6.7 kPa), and secondary pulmonary hypertension.

**Management of Acute Exacerbations**

AECOPD is characterised by a sustained worsening of symptoms from stable condition that is acute in onset and this worsening of symptoms is beyond the day to day variation of symptoms as experienced by the patients. The symptoms usually include increased breathlessness, sputum purulence or increased sputum volume and in some patients, these are accompanied by other problems such as increasing cough, wheeze, chest tightness or fatigue. Infectious agents are recognised as a major pathogenic factor in AECOPD.\(^{10-12}\) Other contributing factors for exacerbations include air pollution\(^{13}\), low temperature, and interruption of regular treatment.

Patients with mild acute exacerbations can be managed as out-patients, whereas more severe cases require hospitalisation. The major components in managing AECOPD include the use of short acting inhaled beta-2 adrenergic agonist, anti-cholinergic bronchodilator, systemic corticosteroid, and antibiotic.\(^{1}\) In some patients, controlled oxygen therapy and/or non-invasive positive pressure ventilation (NPPV) may be beneficial. More severe exacerbations may require invasive mechanical ventilation.

Bronchodilator provides symptomatic relief of lung hyperinflation, with improvement of shortness of breath, chest tightness and wheeze. The advantage of using inhaled short acting beta-2 adrenergic agonists for AECOPD is its fast onset of bronchodilatation. Anticholinergic bronchodilator is often used in combination with beta adrenergic agonists to produce bronchodilatation in excess of that achieved by either agent alone. Meta-analyses have shown no difference in the efficacy of delivering the bronchodilator therapy via a nebuliser over inhalation via a spacer device for patients with AECOPD.\(^{32}\) There is currently no strong evidence to support the use of long acting bronchodilators in the treatment of exacerbations. The role of aminophylline in the treatment of AECOPD remains controversial. Recent studies have suggested that low dose theophylline (at plasma concentrations below 10 mg/l) has some anti-inflammatory effect on the COPD airway.\(^{33,34}\) The proposed mechanism of its inflammatory effect includes reversal of steroid resistance of the airway by restoring the activity of histone deacetylase to normal levels.\(^{35}\) However, the meta-analyses have failed to confirm the clinical benefits in terms of improvement of lung function and symptoms of patients with AECOPD treated with aminophylline.\(^{36}\) In addition, there is a significant increase in adverse events such as nausea and vomiting in the aminophylline-treated patients.\(^{36}\)

Systemic (oral or intravenous) glucocorticosteroid therapy is recommended for treating AECOPD as it significantly reduces treatment failure and the need for additional medical treatment.\(^{37,38}\) Use of systemic corticosteroid for patients hospitalised for AECOPD accelerates the rate of lung function improvement and improves the sensation of dyspnoea over the first 72 hours of treatment although its use is associated with an increased rate of drug related adverse reactions.\(^{38}\) The GOLD guideline recommends a 10-14 day course of 30-40 mg/day of oral prednisolone for treatment of AECOPD.\(^{1}\)

Patients experiencing AECOPD with clinical signs suggestive of airway bacterial infection (eg., increased sputum volume and change of colour of sputum, and/or fever) may benefit from antibiotic treatment.\(^{1}\) In Hong Kong, beta-lactamase activity was noted in 10.1% and 54.5% of the admissions with positive sputum culture for *Haemophilus influenzae* and *Moraxella catarrhalis* respectively. At least intermediate resistance to penicillin was noted in 69.0% of hospital admissions with sputum that grew *Streptococcus pneumoniae*.\(^{10}\) The Hong Kong Interhospital Multi-disciplinary Programme on Antimicrobial Chemotherapy (IMPACT) guideline in 2005 has recommended oral/intravenous amoxicillin-clavulanic acid or amoxicillin/sulbactam as the anti-microbial therapy for patients with AECOPD.\(^{39}\) Alternative antibiotics include cefotaxime or a new anti-Gram positive fluoroquinolone. A recent Cochrane review has also supported the use of antibiotic therapy for patients who are moderately or severely ill with AECOPD with increased cough and sputum purulence, as antibiotic treatment is associated with reduction in mortality, treatment failure and sputum purulence.\(^{40}\)

Controlled oxygen therapy is needed for hypoxic patients. In patients with decompensated hypercapnic respiratory failure, the use of NPPV can decrease mortality and need for intubation. In addition, NPPV has led to a reduction in treatment failure, and a more rapid improvement within the first hour in both respiratory rate and pH in blood gas measurement. Furthermore, the hospital length of stay and complications associated with treatment for AECOPD are both reduced in the NPPV treatment group when compared to medical treatment alone.\(^{41}\)

**Conclusion**

In summary, COPD is an important disease which imposes a heavy burden on the society. Proper management of the patients may improve their quality of
life, dyspnoea, and exercise capacity and prevent disease progression. Prompt treatment of acute exacerbations is important whereas preventive strategies (such as the use of long-acting bronchodilators, inhaled corticosteroid, pulmonary rehabilitation, seasonal influenza vaccination) to reduce recurrent exacerbations of COPD are needed to improve the health status of these patients.

References

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