Current Trends in the Management of Chronic Obstructive Pulmonary Disease

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide, with an increasing prevalence and mortality. It is the fourth or fifth highest cause of death in developed countries. In Malaysia, the prevalence of smoking is 47% in the adult male population while 3% of the adult female population smoke. As tobacco consumption continues to rise in this part of the world, a continuously expanding population of COPD patients is anticipated. This has important socioeconomic implications on the quality of life of the patients and imposes a major burden on our health care system.

Treatment of COPD

Significant advances have been made in the treatment of COPD over the past decade. The treatment of COPD is directed at reducing airflow obstruction to improve symptoms, preventing and managing complications such as respiratory tract infection, accelerating recovery when exacerbations occur, improving life quality, and increasing survival. Only two interventions have been shown to increase survival of smokers who develop COPD. The first is smoking cessation, which is beneficial at all stages of the disease. The second is long-term oxygen therapy which improves the quality of life and increases life expectancy of patients with chronic respiratory failure (Table I) as demonstrated by the MRC and Nocturnal Oxygen Therapy Trial. The goals of other interventions are to relieve symptoms and to improve quality of life.

The respiratory societies of various countries including the European Respiratory Society (ERS), the American Thoracic Society (ATS) and the British Thoracic Society (BTS) have published and implemented guidelines for the management of COPD. The Malaysian Thoracic Society has also developed its guidelines on COPD management which were published in a recent issue of this journal. A review of the literature and consensus of expert opinion have been used as a basis for the development of all these guidelines. The quality of the evidence supporting the different recommendations is variable (Table I). The World Health Organization and the National Heart Lung and Blood Institute (NHLBI) of the United States have also initiated the Global Initiative for Obstructive Lung Disease (GOLD) project. This is similar in design to the global programme on asthma, Global Initiative for Asthma (GINA), and aims to develop guidelines for the management of COPD.

As regards management, there is strong agreement between the various guidelines. All support diagnostic spirometry with bronchodilator testing. Spirometry is also important in screening for asymptomatic cases among smokers. Most patients with COPD present to doctors with moderate to severe disease. Since the damage is irreparable, early detection is crucial, preferably before symptoms develop, so that intervention at an earlier stage can be taken. Disease severity is based on spirometric measurement of the forced expiratory volume in 1 second (FEV1) although there is some disagreement among the various guidelines on FEV1 ranges for the various categories of severity.
Table I
Evidence-based Interventions in Stable COPD*

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
<th>Grade of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
<td>↓ FEV₁ decline, ↓ mortality</td>
<td>A</td>
</tr>
<tr>
<td>Inhaled β₂-agonists (short-/long-acting)</td>
<td>↑ FEV₁, ↑ exercise tolerance, ↓ symptoms</td>
<td>A</td>
</tr>
<tr>
<td>Inhaled anticholinergics</td>
<td>↑ FEV₁, ↑ exercise tolerance, ↓ symptoms</td>
<td>A</td>
</tr>
<tr>
<td>Oral theophylline</td>
<td>Small ↑ FEV₁, ↑ QoL</td>
<td>A/B</td>
</tr>
<tr>
<td>Long term oxygen therapy</td>
<td>↓ mortality</td>
<td>A</td>
</tr>
<tr>
<td>Oxygen as required</td>
<td>↓ symptoms</td>
<td>C</td>
</tr>
<tr>
<td>Pulmonary rehabilitation</td>
<td>↑ QoL, ↑ exercise tolerance</td>
<td>A</td>
</tr>
<tr>
<td>Lung volume reduction surgery</td>
<td>↑ FEV₁, ↑ exercise tolerance, ↑ QoL</td>
<td>B</td>
</tr>
</tbody>
</table>

*Grading of recommendations 33

A = Evidence from meta-analysis of randomised controlled trials or evidence from at least one randomised controlled trial
B = Evidence from well conducted clinical studies but no randomised trials
C = Expert opinion often with no direct study data
↓ = reduced
↑ = increased
FEV₁ = forced expiratory volume in 1 second
QoL = quality of life

**Smoking cessation**

All the guidelines emphasise smoking cessation which has been shown by well-designed controlled trials (Table I) to modify the decline in lung function in patients with mild and moderate COPD. The natural history of COPD, elegantly described by Fletcher and Peto, is that a proportion (15 - 20%) of cigarette smokers have an annual loss of FEV₁ that is larger than for non-smokers. Quitting smoking is associated with a reduction in the accelerated rate of decline in FEV₁. That smoking cessation can decrease the rate of decline of lung function is substantiated in the prospective Lung Health Study carried out by the National Heart Lung and Blood Institute (NHLBI) of the United States which showed that smoking cessation reduces the accelerated decline in lung function. This prospective study with a follow up of 5 years comprised nearly 6,000 male and female smokers aged 35 - 60 years with mild COPD. The study was carried out (1) to evaluate whether smoking cessation intervention would have a decelerating effect on the decline in FEV₁ in a population followed up longitudinally, and (2) to determine if bronchodilator therapy with ipratropium bromide could alter the rate of loss of lung function. One third of the patients were treated with usual care and two thirds of them received an intensive smoking cessation intervention. The smoking cessation intervention group was further divided into two groups, one of which received a placebo inhaler and the other group, ipratropium bromide inhaler. Continuing smokers showed a steady decline in FEV₁. In those who quit, there was an initial improvement in FEV₁ followed by a decline at a rate significantly less than that of the continuing smokers and approximating that expected for normal non-smokers. In the smoking cessation group, treatment with ipratropium was associated with a small, but statistically significant, improvement in lung function. After this improvement, however, lung function in the ipratropium group declined at the same rate as that in the placebo group. This means that ipratropium bromide treatment does not affect the rate of long-term decline in lung function in COPD patients. The improvement in lung function associated with ipratropium therapy persisted as long as the ipratropium therapy was continued.
Bronchodilator therapy

Airway obstruction is generally not reversible in COPD, but bronchodilators including short and long acting \(\beta\)-agonists and anticholinergic drugs may reduce dyspnoea and improve quality of life even in the absence of significant changes in spirometric variables\(^{12,13}\). Extensive studies of inhaled \(\beta\)-agonists and anticholinergics confirm their value as bronchodilators in COPD (Table I). The Combivent Study Group showed that combining an anticholinergic with a \(\beta\)-agonist resulted in higher efficacy than either drug used alone\(^{14}\). However, FEV\(_1\) is not the only relevant outcome as both symptoms and exercise performance can improve, even in patients where the change in lung function is small.

In the stepwise pharmacological management of COPD, patients with mild, intermittent symptoms are treated with inhaled short-acting \(\beta\)-agonists used when necessary. In the second step, patients with mild-to-moderate, persistent symptoms are prescribed an anticholinergic agent (ipratropium bromide) to be inhaled regularly every 6 - 8 hours to provide background bronchodilation and a short-acting inhaled \(\beta\)-agonist can be administered P.R.N. for acute relief of symptoms or can be taken regularly. The next step is to consider the addition of oral sustained-release theophylline and/or oral sustained-release \(\beta\)-agonist if step 2 fails or if there are increased symptoms. Inhaled long-acting \(\beta\)-agonists can be tried in the individual patients. Long-term studies have shown poor adherence of COPD patients to inhalation therapy, particularly if administration is recommended more than once or twice a day. Long-acting inhaled \(\beta\)-agonists such as salmeterol and formoterol, and long-acting anticholinergic (tiotropium, not yet available) may improve patient compliance with treatment as they need to be administered only once or twice a day. In step 4 (i.e. for patients with the most severe COPD), trial of oral corticosteroids should be considered if there is objective improvement in FEV\(_1\), low dose oral steroids or high dose inhaled steroids may be prescribed.

While the ATS\(^\circ\) suggests initial therapy with an anticholinergic if regular therapy is required and a \(\beta\)-agonist if P.R.N. therapy is all that is needed, the ERS\(^8\) and the BTS\(^9\) offer no preference between these two types of bronchodilators. All the guidelines support the role of combination therapy with an anticholinergic and a \(\beta\)-agonist. Evidence for the use of theophylline is less clear (Table I).

What are the roles of inhaled and oral corticosteroids in COPD?

Although corticosteroids greatly reduce airway inflammation in asthma and are the first line components of maintenance treatment in patients with asthma, the precise role of corticosteroids in COPD has yet to be established. Oral corticosteroids are widely used in acute exacerbations of COPD, although their effect has been assessed in few studies. It is common practice to use a 7 - 14 day course of prednisolone 30mg/day. The use of systemic corticosteroids is justified if the patient is already on oral corticosteroids, if there is a previously documented response to oral corticosteroids, if the airflow obstruction fails to respond to increased bronchodilator therapy, or if this is the first presentation of airway obstruction\(^{10}\). A recent randomised double blind study showed that a nine day treatment with tapering dose of oral prednisone (60mg for three days, 40mg for three days, and 20mg for three days) accelerates recovery in terms of lung function and reduces the rate of treatment failures\(^{11}\).

All the COPD guidelines emphasise the need to document corticosteroid responsiveness before prescribing oral corticosteroids for long-term use. The ERS\(^8\) and BTS\(^9\) provide recommendations for the use of inhaled corticosteroids. A recent placebo controlled randomised trial by Paggiaro PL, et al.\(^{16}\) assessed the effect of 500µg of inhaled fluticasone twice daily in 281 patients with COPD (bronchodilator reversibility had to be less than 15% to minimise chances of including patients with asthma) over six months. In this short-term study, fluticasone produced mild but significant improvement in symptoms, lung function (as measured by peak expiratory flow rate and FEV\(_1\)), and six-minute walking distance and reduced the number of moderate to severe exacerbations (Table II). However, long-term trials of at least 2 years’ duration have found that inhaled corticosteroids are beneficial 'for only three to six months\(^{17,18}\). A major flaw in some of these studies was that no distinction was made between patients with COPD and asthma. Renkema and colleagues\(^9\) studied
### Table II
Randomised Placebo Controlled Trials on the use of Inhaled Corticosteroids in Stable COPD

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients and Their Characteristics</th>
<th>Active treatment (duration)</th>
<th>Findings</th>
</tr>
</thead>
</table>
| EUROSCOP38                         | 912 mild COPD (mean FEV₁ of 77% predicted) who continued smoking | Budesonide 400 μg B.D. (3 years) | 1. FEV₁ increased during first 6 months of the study.  
2. Non-significant effect on subsequent FEV₁ decline.  
3. Quality of life not measured. |
| ISOLDE                             | Severe COPD (mean FEV₁ of 50% predicted) 48% were still smoking at trial entry | Fluticasone 500 μg B.D. (3 years) | 1. Non-significant improvement in FEV₁ decline.  
2. Number of exacerbations reduced.  
3. Benefit in terms of quality of life. |
| Copenhagen City Lung Study27       | 290 mild and moderate COPD 76% were current smokers | Budesonide 1200 μg per day for the first six months followed by 800 μg per day for the next 30 months | No benefit on any outcome measure. |
| Paggiarro PL, et al.13             | 281 (FEV₁ 35 - 90% predicted)              | Fluticasone 500 μg B.D. (6 months) | 1. Improvement in symptoms  
2. Improvement in PEFR and FEV₁.  
3. Improvement in 6 minute walking distance.  
4. Number of moderate and severe exacerbations reduced. |
| Van Grunsven PM, et al.22          | Meta-analysis of 3 studies Active treatment: 95 patients Placebo: 88 patients | Beclomethasone 1500 μg/day or Budesonide 1600 μg/day (2 years) | 1. Beneficial effect on prebronchodilator FEV₁.  
2. No benefit on exacerbation rate |

The effects of budesonide 1.6mg or budesonide 1.6mg plus oral prednisolone compared with placebo for 2 years in 58 patients with COPD. The two active treatments significantly reduced pulmonary symptoms, but had no significant effect on decline of lung function or the frequency or duration of exacerbations. In a four-year study of 28 COPD patients with a rapid decline in FEV₁ (146ml/year), beclomethasone 800μg/day slowed the rate of decline, improved symptoms and reduced exacerbations, without altering bronchial hyperresponsiveness17. Three important large, parallel group, placebo controlled studies (Table II): the European Respiratory Society study on Chronic Obstructive Pulmonary Disease (EUROSCOP)38, the study on Inhaled Steroids in Obstructive Lung Disease (ISOLDE) conducted in the United Kingdom and the Copenhagen City Lung Study22 have been reported at scientific meetings but not all have been published. All three studies used similar definitions of COPD and excluded patients with a clinical diagnosis of asthma or significant
bronchodilator responsiveness. The principal outcome measure for all three studies was longitudinal decline in FEV\textsubscript{1} over three years. None of these long-term studies showed an unequivocal difference in the FEV\textsubscript{1} decline slope between treatment groups. The Copenhagen study showed no evidence of any difference at all between groups, whilst the EUROSCOP and ISOLDE studies both showed reductions in the FEV\textsubscript{1} decline slope which were not statistically significant when analysed in the whole study group. Health effects measures, such as quality of life, are an important outcome in their own right and the ISOLDE study which used the St. George's respiratory questionnaire showed reduced rates of decline in the scores in each domain. Exacerbations of COPD are related to the severity of the disease and to increasing age. They were only common in the ISOLDE group and were significantly reduced by active treatment. The ISOLDE study showed that exacerbations were increased in the eight weeks after stopping inhaled corticosteroids in the 55% taking them prior to the run in period.

The differences between the findings of these three studies could be due to the differences in severity of COPD, inhaled corticosteroids working best for those with the most severe disease. Alternatively, it could be due to a dose-related effect, the ISOLDE study using a significantly higher relative dose than the other two studies. A meta-analysis\textsuperscript{22} (Table II) of three previous small studies on the long-term effects of inhaled corticosteroids in clearly defined moderate to severe COPD (FEV\textsubscript{1} 45 - 55% of predicted) showed a significant beneficial effect on prebronchodilator FEV\textsubscript{1}, in terms of its preservation. However, there was only a tendency towards an effect on postbronchodilator FEV\textsubscript{1} during two years of treatment with relatively high daily dosages of inhaled corticosteroids (i.e. 1500µg of beclomethasone or 1600µg of budesonide daily). No beneficial effect was seen on the exacerbation rate. A daily dose of 1500 or 1600µg of the inhaled corticosteroids was more effective than 800µg, but only a small number of subjects (eight) received this lower dose in this meta-analysis and the authors stated that the result should be interpreted with caution. Nevertheless, it is probable that the dosage of inhaled budesonide in the EUROSCOP study and the Copenhagen City Lung Study might have been too low to show an effect.

In COPD, the largely neutrophilic and lymphocytic inflammation seems to take place in the peripheral airways while in asthma the predominantly eosinophilic inflammation is located mainly in the central airways. These two considerations might explain the need for a higher dosage of inhaled corticosteroids in moderate to severe COPD compared with moderate asthma. Furthermore, COPD has mixed pathology, including emphysema, small airways disease, and changes in mucous glands and goblet cells. It is likely that different pathologies respond differently to inhaled corticosteroids.

Based on available data, there is evidence that high dose inhaled corticosteroids improve lung function, reduce the number of exacerbations and inhibit the progressive decline in health status in advanced COPD but they do not have an effect on the long-term progressive FEV\textsubscript{1} decline. So high dose inhaled corticosteroids may be prescribed to COPD patients who have frequent exacerbations requiring repeated courses of oral steroids and for improvement of symptoms and quality of life in patients with severe COPD.

The role of antibiotics in the treatment of COPD exacerbations

Patients with COPD have, on average, three exacerbations per year. It remains debatable whether COPD exacerbations should be treated with antimicrobial agents. Two important prognostic factors that indicate that treatment is required urgently are frequent exacerbations and significant comorbidity, particularly cardiopulmonary disease\textsuperscript{23}. Antibiotics have been shown to benefit (hastens resolution of acute exacerbations) only if the patient has at least two of three cardinal symptoms which include increased dyspnoea, increased sputum volume, and development of purulent sputum\textsuperscript{24-26}. Although viral infection, environmental pollution including cigarette smoke, and allergic reactions can lead to exacerbations, as many as 50% of these episodes are due to bacterial infection\textsuperscript{27}. The three most likely bacteria in order of importance are Haemophilus influenzae (the most common pathogen), Streptococcus pneumoniae and Moraxella catarrhalis\textsuperscript{10,28}. These three organisms account for 70% of all infective COPD exacerbations, the remaining 30% being caused by viruses\textsuperscript{29} and atypical bacteria. Other Gram-negative
Table III

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
<th>Grade of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral antibiotics</td>
<td>↓ infection, ↑ PEFR/FEV₁</td>
<td>A</td>
</tr>
<tr>
<td>Controlled oxygen</td>
<td>↑ PaO₂, ↓ mortality</td>
<td>C</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>↑ FEV₁, ↓ hospital stay</td>
<td>A</td>
</tr>
<tr>
<td>NIPPV</td>
<td>↓ mortality, ↓ hospital stay</td>
<td>A</td>
</tr>
</tbody>
</table>

*Grading of recommendations⁶³
A = Evidence from meta-analysis of randomised controlled trials or evidence from at least one randomised controlled trial
B = Evidence from well conducted clinical studies but no randomised trials
C = Expert opinion often with no direct study data
↓ reduced
↑ increased
PEFR peak expiratory flow rate
FEV₁ forced expiratory volume in 1 second
NIPPV non-invasive positive pressure ventilation

bacteria such as Pseudomonas aeruginosa have been isolated from patients with more severe COPD⁶⁰. This may partly be explained by the coexistence of unsuspected bronchiectasis⁶¹.

A total of 270 studies have examined the effects of antibiotics and suggested that they are beneficial but only six of these trials were randomised (Table III). There are a large number of antibiotics available to treat COPD exacerbations. Newer agents have a better spectrum of activity and/or better pharmacokinetics. Such newer antibiotics include β-lactams combined with a β-lactamase inhibitor, second- and third-generation cephalosporins, azalides, and fluoroquinolones. In recent years, there has been a steady rise in the frequency of β-lactamase production by H. influenzae. Almost all strains of M. catarrhalis, at least in Europe and North America produce β-lactamase and are therefore, resistant to aminopenicillins⁶². More recently, strains of penicillin- and macrolide-resistant pneumococci due to alteration of penicillin-binding proteins have emerged. In Malaysia, a nation-wide survey involving seven centres revealed that 17% of H. influenzae isolates produce β-lactamase and 8% of S. pneumoniae isolates are penicillin-resistant⁶⁳. Certainly, the widespread use of antibiotics has led to increased resistance.

The target organisms in COPD exacerbations are mostly H. influenzae in mild exacerbations and in severe exacerbations there are fewer H. influenzae and larger percentage of other organisms including gram negative bacteria. Inexpensive antibiotics are usually adequate in most cases; the newest brands are rarely appropriate⁶⁴. Amoxicillin, tetracycline or cotrimoxazole are first choice unless used with poor response prior to admission. For more severe exacerbations, or if there is lack of response to these agents, second line antibiotics such as a second or third generation cephalosporin, a β-lactam/β-lactamase inhibitor combination, a new macrolide, or a fluoroquinolone can be considered. Unless there is a contraindication, oral rather than intravenous antibiotics should be used. New antibiotics are more expensive, but they could be more cost-effective in severe COPD patients in whom failure rates are higher with standard antibiotic therapy and failure might have more serious consequences.


CONTINUING MEDICAL EDUCATION


MCQs on Current Trends in the Management of Chronic Obstructive Pulmonary Disease

1. The following societies have published guidelines on the management of COPD
   A. The American Thoracic Society
   B. The British Thoracic Society
   C. The European Respiratory Society
   D. The Malaysian Thoracic Society
   E. The Asian Pacific Society of Respirology

2. The following interventions have a beneficial effect on the long-term progressive decline in FEV₁ in COPD patients
   A. Inhaled ipratropium bromide
   B. Long-term oxygen therapy
   C. Oral corticosteroids
   D. Prophylactic antibiotics
   E. Smoking cessation

3. The following interventions prolong the survival of COPD patients
   A. Inhaled bronchodilators
   B. Inhaled corticosteroids
   C. Long-term oxygen therapy
   D. Oral theophylline
   E. Smoking cessation

4. In patients with severe COPD, there is evidence that treatment with high dose inhaled corticosteroids
   A. Improves lung function
   B. Improves symptoms
   C. Enhances the quality of life
   D. Reduces the number of acute exacerbations
   E. Slows down the accelerated rate of FEV₁ decline

5. In COPD exacerbations
   A. *Streptococcus pneumoniae* is the most frequently isolated pathogen from the respiratory tract
   B. Treatment with oral antibiotics results in more rapid resolution of symptoms
   C. Fluoroquinolones are the antibiotics of choice in all patient categories
   D. Treatment with oral corticosteroids improves lung function
   E. Controlled oxygen therapy should be used