REVIEW SERIES

Chronic obstructive pulmonary disease • 7: Management of COPD

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A review of the management of COPD is presented, with particular emphasis on the effect on the approach to management of new information which has become available in the 5 years since the BTS guidelines on COPD were published. A major problem is the effective implementation of what is already known, and allocation of the resources necessary to make this available to all who might benefit.

In December 1997 the BTS published its first and, to date, only guideline on the management of chronic obstructive pulmonary disease (COPD) in a supplement to *Thorax*.[1] This was not an evidence based document since, at that time, much of the evidence would have been graded C (based on non-randomised clinical trials) or, at best, B (based on limited randomised controlled trials). Since then considerable new clinical data have been published which have clarified some of the contentious clinical management issues in COPD, although many still remain, some of which are the subject of ongoing clinical trials. This review summarises the management of COPD, with particular emphasis on new information published since the BTS guidelines on COPD which has affected the approach to management of this condition.

DEFINITION AND ASSESSMENT

The most recent COPD guideline from the Global Initiative on Chronic Obstructive Lung Disease (GOLD) recognises as part of the definition of the condition that there is "an abnormal inflammatory response" in the lung to noxious gases or particles,[2] and this suggests the need for effective anti-inflammatory treatment in COPD.

However, the diagnosis of COPD remains a clinical one, confirmed by the measurement of airflow limitation using spirometric tests (a post-bronchodilator forced expiratory volume in 1 second (FEV_1) <80% predicted in combination with a ratio of FEV_1 to forced vital capacity (FVC) of <70% which is not fully reversible). Similarly, assessment of severity of the disease and hence the need for treatment is still, in the most recent guidelines, based around the level of the percentage of the predicted FEV_1. Previous assessments of disease severity have used arbitrary boundaries based on the percentage predicted FEV_1. It is now clear that the FEV_1 does not fully describe disability in COPD and that additional measurements are necessary to fully assess this. These include measurement of breathlessness such as the MRC dyspnoea scale[3] and an assessment of the systemic effects of COPD such as nutritional status, easily measured as the body mass index (BMI), which is known to relate to survival.[4 5] Measurement of health status using respiratory disease specific questionnaires provide a more complete picture of the impact of the disease status than the FEV_1, but is too complex for routine use.[6 7]

It is also increasingly clear that short term changes in the FEV_1 in response to either bronchodilators or corticosteroids[8 9] are a poor predictor of symptomatic benefit in moderate to severe COPD. The FEV_1 may not be the best outcome measure to gauge the effectiveness of treatment in COPD since, by definition, changes in FEV_1 would be expected to be small. Thus, measurement of health status,[10] dyspnoea,[11], exercise performance,[12] or exacerbation rates[13 14] may be important outcome measures in COPD.

The types of treatment used have not changed greatly in the last 5 years, but which approach to use and when is now rather different.

SMOKING CESSATION

Smoking cessation remains the most important intervention in modifying the course of the disease[15] and is cost effective.[16 17] Nicotine dependency is a chronic relapsing condition which may require repeated interventions.[18] Most patients have several attempts at quitting before they finally give up.

Even brief counselling is effective in producing quit rates of around 5%.[17] It is essential that healthcare professionals *ask* about cigarette smoking at every opportunity; that they *advise* all smokers to quit; and that they *assess* their willingness to quit and provide appropriate advice on the method of quitting, including pharmacological treatment.[19] This should be done for every smoker at every visit to a healthcare professional.[20] Follow up contact in person or by telephone should be arranged.

Several effective smoking cessation pharmacotherapies now exist. Nicotine replacement therapy in any form (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge) is effective in increasing long term quit rates.[21] Several studies have shown the effectiveness of the antidepressant bupropion with counselling and support in producing increased long term quit rates at 1 year of 30%.[22] The effectiveness of bupropion has also been shown in smokers with COPD.[23]

BRONCHODILATORS

Prevention and relief of symptoms by regular use of bronchodilators remains central to the management of COPD.[23–25] There is now compelling

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evidence, at least in more severe COPD, that a major benefit of bronchodilator therapy is to improve lung emptying during expiration. This reduces dynamic hyperinflation at rest and during exercise and so improves exercise performance.[12] The degree to which this occurs is not readily predictable from the improvement in FEV_1 after an acute bronchodilator trial.[8 26] Assessment of the effectiveness of bronchodilators is therefore best done by asking simple questions about changes in their symptoms. The choice between β agonists, anticholinergic drugs, theophylline or combination therapy depends on individual symptomatic responses. Combining bronchodilators may improve efficacy and decrease side effects compared with increasing the dose of a single bronchodilator.[27]

Long acting inhaled β agonists such as salmeterol and formoterol have a duration of action of 12 hours and significantly improve symptoms, exercise capacity, and health status in patients with COPD.[28–30] A new long acting once daily anticholinergic agent, tiotropium, produces benefits of equivalent or greater size[31] and is likely to be a useful addition to treatment for COPD. Both long acting β agonists and long acting anticholinergic agents reduce exacerbation rates in COPD,[32 33] raising important questions as to what determines these events. There is no evidence of tachyphylaxis with these long acting bronchodilators and they are well tolerated. To date there are no data about the combination of different classes of long acting drugs, although short acting anticholinergic agents can be usefully combined with long acting β agonists.[34]

High doses of nebulised bronchodilators are still widely prescribed in severe COPD, but the BTS guidelines on nebuliser treatment[35] recommends that the appropriateness of their use should be assessed by a respiratory specialist. It is recommended that the response to high dose bronchodilators via a spacer device should be assessed before trying long term nebulised treatment.

Theophyllines remain somewhat controversial in the management of stable COPD. Their mode of action as a non-selective phosphodiesterase inhibitor is still controversial but they have been shown to produce bronchodilatation in COPD[36 37] with a variable effect on exercise tolerance and symptoms.[38–41] The narrow therapeutic index of theophyllines limits their use. They have a slow onset of action and are used as maintenance treatment rather than for rapid relief of symptoms. Newer more specific phosphodiesterase inhibitors, particularly of phosphodiesterase 4 (PDE4) inhibitors, have been shown to improve lung function in COPD[42] and may also reduce exacerbation rates.[43] However, the results of further studies are awaited before these drugs can be confidently recommended.

Given that long acting bronchodilators taken once/twice daily produce the same or better relief of symptoms than regular short acting bronchodilators, it is sensible to introduce these drugs earlier in the management plan in patients with COPD when they require regular treatment for symptom relief. Theophyllines can be considered in patients who remain symptomatic despite long acting bronchodilators, but clear evidence of improvement in symptomatology should be obtained before continuing these drugs, given the more complex management involved in administering them safely.

INHALED CORTICOSTEROIDS

Whether inhaled corticosteroids have an anti-inflammatory effect in patients with COPD remains controversial. The variable effects of corticosteroids on airway inflammation may reflect the heterogeneity of the disease and also the reproducibility of markers of inflammation.[44 45] What is clear is that these drugs do not modify the natural history of COPD, as measured by the rate of decline in FEV_1 (fig 1). Four large randomised controlled trials (EUROSCOP,[46] Copenhagen City Lung study,[47] ISOLDE,[14] and Lung Health Study 2[48]) all found

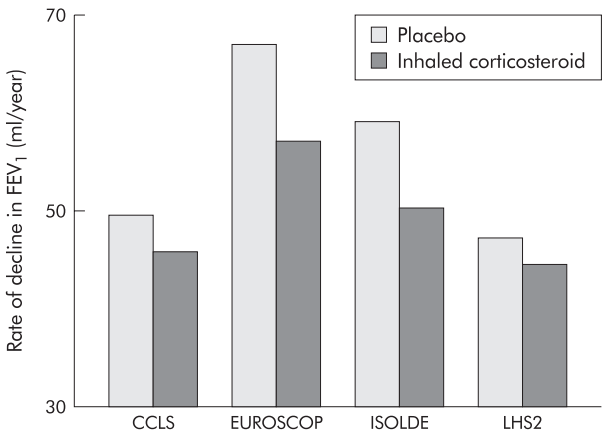

Figure 1 Rate of decline of lung function in four 3 year randomised trials of inhaled corticosteroids and placebo in patients with a range of severity of chronic obstructive pulmonary disease. CCLS=Copenhagen City Lung Study; EUROSCOP=European Respiratory Society Study of COPD; LHS2=Lung Health Study 2; ISOLDE=Inhaled Steroids in Obstructive Lung Disease. Full references are given in the text. In no case was there a statistically significant difference between the treatments.

that inhaled corticosteroids had non-significant effects on the decline in FEV_1 in patients with mild and moderately severe COPD. One of these studies[14] in patients with more severe COPD showed a reduction in exacerbations (from 1.33 to 0.99 per year, a reduction of 25%), which supports results in an earlier smaller study which showed a reduction in severity of exacerbations with inhaled corticosteroid.[49] From these studies it is concluded that inhaled corticosteroids should be recommended to patients who have a demonstrable FEV_1 response to a trial of corticosteroids or in those with moderate to severe disease (FEV_1 <50% predicted) with repeated acute exacerbations (a reasonable number would be two or more exacerbations per year) requiring treatment with antibiotics or oral corticosteroids. The precise dose required to reduce exacerbations in patients with moderate to severe COPD is not known but, on present evidence, a higher dose of inhaled corticosteroids should be given to achieve such an effect.

The effects of a combination of inhaled corticosteroids and long acting β agonists are being studied at present. Data currently in press indicate that combining a long acting β agonist and an inhaled corticosteroid produces significantly greater improvement in symptoms and pulmonary function than either alone, with equivalent reductions in exacerbation frequency. Full analysis of these data will be needed before a firm recommendation about optimal treatment can be made.

VACCINES

Vaccination can reduce severe complications and mortality from influenza in older patients, including those with COPD, and is recommended to be given once in the autumn or twice in autumn and winter each year.[50 51] Pneumococcal vaccine has been used in patients with COPD and can reduce complications of pneumonia in elderly patients, but there are insufficient data to support its general use in patients with COPD.[52–54]

ANTIBIOTICS

Several large scale control studies have shown that prophylactic or continuous antibiotics have no effect on the frequency of exacerbations in COPD,[55–57] nor is there any effect of antibiotic prophylaxis during winter periods.[58] Thus, present evidence does not support the use of antibiotics as a prophylaxis against bacterial infections or exacerbations of COPD.

MUCOLYTIC DRUGS

Mucolytic drugs (ambroxol, erdosteine, carbocysteine, iodinated glycerol) have recently undergone a meta-analysis by the Cochrane collaborative group and have been shown to produce a statistically significant reduction in the number of exacerbations of chronic bronchitis compared with placebo.[59] These studies are of relatively short duration, over a period of 2–6 months, in patients with mild COPD (FEV_1 >50% predicted) and therefore the general use of mucolytic drugs in COPD is not yet recommended.

ANTIOXIDANT AGENTS

Oxidant related lung damage is an important mechanism contributing to lung damage in COPD. Antagonising these effects is an attractive treatment strategy, and the antioxidant and mucolytic drug N-acetylcysteine has been shown to reduce the frequency of COPD exacerbations in most studies.[60] Results of a long term randomised control trial to both assess the effect of N-acetylcysteine on the decline in FEV_1 in COPD patients and in reduction of exacerbations are awaited. However, at present this drug is not licensed for use in COPD, at least in the UK.

REHABILITATION

A large number of clinical trials have now shown that pulmonary rehabilitation is beneficial in COPD.[61–63] Benefits include an increased exercise capacity, reduction in the sensation of breathlessness, improvement in health status, and reduction in the number of hospital admissions, all of which have been shown in randomised control trials. If exercise training is maintained, these benefits can be sustained.[64 65] Whether repeated rehabilitation courses enable patients to maintain benefits gained in the initial course is still a matter of debate. Rehabilitation programmes are effective in inpatients, outpatients and in those treated at home.[65–68] Availability and cost may determine the setting which is used, an outpatient setting being the least expensive. There is also evidence which indicates that rehabilitation may reduce the length of hospital stay.[65–67] A comprehensive review of the evidence for rehabilitation and advice on how to lobby for funding is available.[69]

There are relatively few centres in the UK with access to pulmonary rehabilitation to date, but it is hoped that this will improve in the near future. It is therefore important to discuss the merits of regular exercise with patients with COPD and to provide leaflets and advice about exercises and lifestyle issues for these patients.

OXYGEN THERAPY

The indications for domiciliary oxygen therapy have changed in the last 5 years and there are now good data to suggest that less hypoxaemic patients do not benefit from domiciliary oxygen,[70] nor do those showing isolated nocturnal desaturation with more preserved daytime gas tensions.[71] This probably reflects the slow rate of deterioration in pulmonary haemodynamics recently observed in these patients.[72] In contrast, breathing oxygen during exercise improves endurance time by reducing dynamic hyperinflation even in those who do not desaturate.[73]

LUNG VOLUME REDUCTION SURGERY

The initially surprising observation that removing lung can increase exercise capacity[74] has been repeatedly confirmed and reflects a combination of reduced dynamic hyperinflation, improved diaphragm function, and improved pulmonary elastic recoil.[75 76] The effectiveness of treatment has been confirmed in two randomised controlled trials with up to 12 month follow up.[77 78] The effects on symptoms can persist for several years thereafter.[79] However, the large National Emphysema Treatment Trial in the US has shown that patients with an FEV_1 or carbon monoxide transfer factor (T_{LCO}) of <20% predicted or a homogeneous distribution of emphysema on the CT scan have a higher mortality with surgical than with conservative medical treatment.[80]

EXACERBATIONS OF COPD

Exacerbations of COPD are important clinical events. There is no agreed definition on what constitutes an exacerbation, but a recent proposal was "a variation in symptoms above the normal day to day variation which causes a change in a patient's medications".[81] Exacerbations of COPD worsen health status[82] and are expensive. The number of exacerbations is related to disease severity, patients with moderate severe disease (FEV_1 <50% predicted) having 1–2 exacerbations per year.[14 82] Several factors determine which treatment is used and in what setting.

The severity of the exacerbation depends on the underlying severity of the COPD. In patients with mild COPD, exacerbations are associated with increased breathlessness accompanied by cough and sputum production and may often be managed outwith hospital. Severe COPD exacerbations are often associated with respiratory failure which may prove fatal and require hospital admission. The common causes of exacerbations are infection (bacterial[83 84] and viral[85]) which is present in around 50% of cases. Other factors such as pollution and temperature may also lead to exacerbations.[86] However, in about one third of severe exacerbations no obvious cause can be found.[87] The decision to treat an exacerbation at home or in hospital is influenced by the severity of symptoms, the severity of the underlying COPD, and the ability of the patient to cope at home. Recent trials have shown that about 30% of patients referred for hospital admission with exacerbations of COPD could be successfully treated at home with immediate or early supported discharge and nurse led home care.[88–91] Patients prefer this form of treatment[92] which has been successfully extended to facilitate the discharge of those initially requiring hospitalisation.[89]

Treatment at home involves increasing bronchodilators, if necessary given by nebuliser, and appropriate antibiotic therapy usually given if two or more of the following symptoms are present: increasing breathlessness, increasing sputum purulence, increasing sputum volume.[93] The choice of antibiotics should reflect local patterns of antibiotic sensitivity but parenteral therapy is not usually needed.

Systemic glucocorticoids shorten recovery time, restore lung function more quickly when given during an exacerbation of COPD, and are given to patients with moderate/severe exacerbations of COPD.[90 94 95] The optimum dose and duration of treatment is not known but a reasonable compromise is to give 30 mg prednisolone for 7–10 days. Nebulised budesonide produces similar improvements in lung function to oral corticosteroids, but whether the additional expense is justified in all cases is unclear.[96] Hospital care is increasingly focused on the management of respiratory failure and associated co-morbidities, especially given the increased use of early discharge protocols (see above). Inadvertent oxygen toxicity due to excessively high flow rates in the emergency room is still a widely prevalent problem that could be addressed by increasing the awareness of the risk to the patient.[97] Non-invasive positive pressure ventilation (NIPPV) has been shown to be an effective alterative to intermittent positive pressure ventilation (IPPV) in the ICU[98] and is applicable in the general ward when nurses are appropriately trained.[99] By avoiding nosocomial pneumonia it can reduce hospital stay and patient morbidity, but is probably less effective than IPPV in patients with a pH persistently <7.30.[99] Survival after IPPV is not as poor as some imagine, but the cost implications of providing this in all cases remain substantial. Good patient care involves discussion of end of life issues and the formulation of an advanced directive to guide both physicians and relatives in their expectations of

care. How and when this should be done remains unresolved and is likely to vary between different healthcare systems.

CONCLUSIONS

Much can now be done to improve the well being of patients with COPD and to reduce the risk and duration of hospitalisation. The next 5 years should produce equally substantial steps forward in care. However, the major problem remains the effective implementation of what we do know and allocation of the resources necessary to make this available to all who could benefit. Achieving this should be a major goal of the pulmonary community.

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