Seminar

Chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability worldwide. Recognition that the burden of this disorder will continue to increase over the next 20 years despite medical intervention has stimulated new research into the underlying mechanisms, leading to a rational basis for evaluation of existing therapies, and has suggested novel treatment approaches. Tobacco exposure remains the main but not exclusive cause of COPD. Whether the lung is injured by changes in the balance of proteases and antiproteases, tissue damage by oxidative stress, or a combination of the two is still not known. The genetic basis of susceptibility to COPD is now being studied as is the role of computed tomography in the identification of structural damage in individuals with less symptomatic disease. Clinical diagnosis still relies heavily on an appropriate history confirmed by abnormal spirometry. Smoking cessation is possible in a substantial proportion of individuals with symptoms but is most effective if withdrawal is supported by pharmacological treatment. Treatment with long-acting inhaled bronchodilators and, in more severe disease, inhaled corticosteroids reduces symptoms and exacerbation frequency and improves health status. Rehabilitation can be even more effective, at least for a year after the treatment. Recent guidelines have made practical suggestions about how to optimise these treatments and when to consider addition of oxygen, surgery, and non-invasive ventilation. Regular review of this guidance is important if future management advances are to be implemented effectively.

Chronic obstructive pulmonary disease (COPD) is a major global health problem. The Global Burden of Disease Studies[1–3] found that COPD was the sixth commonest cause of death worldwide in 1990 but made the alarming prediction that it would become the third commonest cause of death by 2020 irrespective of public-health intervention. Furthermore, COPD was recognised as being the twelfth greatest cause of chronic morbidity, with a predicted increase to become the fourth most important disability-producing illness by 2020. Data from WHO show that these predictions are likely to be correct; by 2000 COPD had become the fourth leading cause of mortality worldwide.[4] Although the increase has been due mainly to the rapid rise in COPD in less developed countries, the burden in more developed economies such as the USA and western Europe is still substantial. Data from the US National Heart, Lung, and Blood Institute have shown that, in contrast to all other causes of chronic ill-health in the USA, COPD has been steadily increasing in importance during the past two decades.[5] This development is paralleled by an increase in consultations with physicians, across a range of health-care providers.[6] In the UK, there was a progressive increase in COPD diagnosed by general practitioners between 1990 and 1997 and a sharp increase in the number of hospital admissions due to COPD from 1995 onwards (figure 1).[7,8] These changes are not simply due to diagnostic reclassification but reflect a real increase in the burden of COPD.

Surveys of patients who have been diagnosed as having COPD or who have symptoms that suggest chronic bronchitis indicate a significant degree of disability and restriction in daily activities.[9–12] A UK national survey of 2500 patients with COPD found that 73% were unable to undertake activities that were important to them, such as gardening or going out for social functions.[13] These patients have low expectations of the medical care system, and many are uncomplaining despite substantial restrictions due to breathlessness.[14] These patients tend to be slow to seek medical help and are reluctant to press for more public attention to their problems.

During the past decade there have been several important publications that have summarised current opinion and evidence about the management of COPD. These were initially produced by national thoracic societies and subsequently by international organisations.[15–18] The most recent is the Global initiative for chronic Obstructive Lung Disease (GOLD). This project was developed by WHO and the US National Heart, Lung, and Blood Institute and resulted in a document available in full at www.goldcopd.com; an executive summary has also been published.[19] This project was the first to adopt evidence-based criteria for recommendations on specific treatments; as part of the GOLD process, there is a system for regular review and updating of the latest publications to assess how they affect the recommendations already made. The last such review was in July 2003. In addition, the GOLD project aims to increase awareness of COPD globally and to

Search strategy

This seminar is based on a comprehensive review of work published between 1966 and 2002 (Medline, Cochrane Library databases) with the keywords "chronic obstructive pulmonary disease" and the terms "chronic bronchitis", "emphysema but not bronchitis unspecified". The information reviewed inevitably reflects a personal perspective, but the studies selected are those we believe contribute most to the epidemiology, pathobiology, and management of the disease. In the case of treatment studies, large randomised controlled trials were selected when available.

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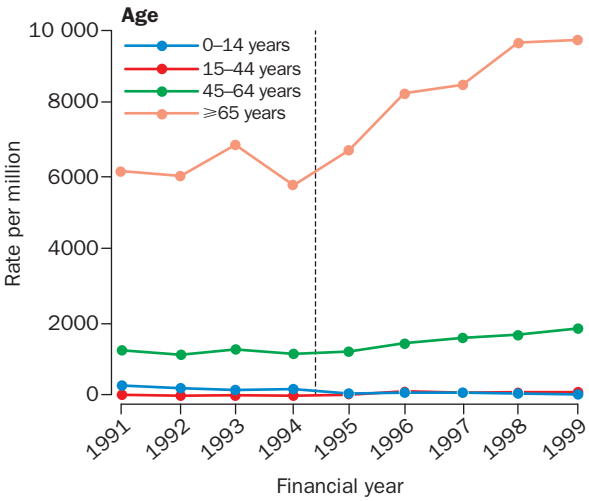

Figure 1: **Admissions due to exacerbations of COPD (asthma excluded) during the 1990s**
Broken line indicates change in ICD code. Adapted from reference 8 with permission

stimulate new research in this previously neglected area. This review is not intended as a substitute for even the summary document in GOLD, but our purpose is to highlight some important issues in which changes are happening now and are likely to continue in the next few years.

Definition

Patients with COPD have been poorly served by clinicians' inability to agree on a simple formulation of their illness that captures both its biology and its effect on their lives. Early attempts relied on epidemiological definitions of chronic cough and sputum production lasting for 3 months over a period of at least 2 years (chronic bronchitis) or on the presence of emphysema in pathological specimens. In practice, neither approach was of much help in clinical management. A major step forward came with the epidemiological studies of Fletcher, Peto, and colleagues,[20,21] which showed that death and disability were related to progressive deterioration in the FEV_1 (forced expiratory volume in 1 s) rather than persistent symptoms of cough and sputum production. Subsequent definitions have emphasised that a diagnosis of COPD requires the presence of airflow obstruction defined as a lower than normal ratio of FEV_1 to FVC (forced vital capacity) or vital capacity (normally <0·7). This definition has been further extended by the GOLD guidelines (panel 1), which recognise for the first time the importance of persistent inflammation and of the inhaled nature of the insult. Although COPD is most commonly associated with cigarette smoking, this is not necessarily the only factor causing the disorder. In many parts of the world, exposure to indoor pollution or biomass fuels can produce identical problems; women who are exposed to smoke from cooking in poorly ventilated conditions are commonly affected.[22–24]

Panel 1: **GOLD definition of COPD**[19]

COPD is characterised by airflow limitation that is not fully reversible. The airflow limitation is in most cases both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

Pathophysiology

Airflow obstruction in COPD arises as a result of variable degrees of narrowing, smooth-muscle hypertrophy, and fibrosis in the respiratory bronchioles[25,26] and loss of elastic recoil pressure due to pulmonary emphysema.[27,28] The physiological abnormalities that accompany these changes are shown in figure 2. The reduction in FEV_1 that defines COPD is due mainly to an increase in resistance in the peripheral airways with a contribution from loss of elastic recoil. Attempts to define consistent COPD phenotypes based on the bronchial or emphysematous clinical syndromes have not been successful, although there is renewed interest in this approach based on the more objective data provided by computed tomography (CT). The inflammatory basis of COPD is now well established. Studies with induced sputum and bronchoalveolar lavage have shown that, compared with smokers without airflow obstruction, COPD patients have more macrophages and neutrophils in these fluids, the former cells predominating in mild disease.[29,30] Biopsy and resection data confirm these findings but also show increased numbers of CD8-positive T lymphocytes in the airway wall.[31–33] The degree of airflow obstruction is correlated with the number of these cells.[33,34] When the number of cells is corrected for lung volume, all cell types increase throughout the airways and alveoli as lung function deteriorates.[34] The inflammation is different from that in bronchial asthma, in which CD4-positive lymphocytes predominate. Thus, these inflammatory characteristics are a more reliable pointer to the presence of COPD than more conventional physiological measurements.[35] They may also explain the differences in response to corticosteroid treatment between asthma and COPD.

Several mechanisms have been proposed to explain why the inflammation occurs and how inhaled insults, particularly cigarette smoke, induce COPD. The processes are not mutually exclusive and some of the possible interactions are summarised in figure 3. The idea that there is an imbalance between the release of proteases from neutrophils and of the antiprotease enzymes that

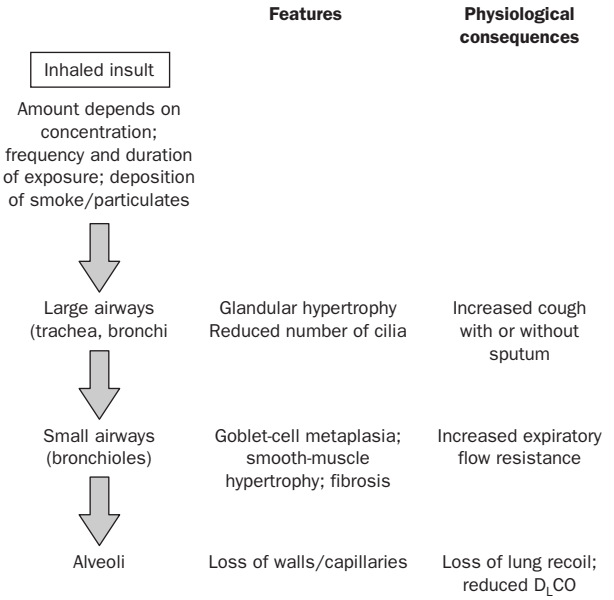

Figure 2: **Pathological processes in COPD and their physiological consequences**
The severity of the inhaled insult varies in a complex way and produces damage of varying severity within different areas of the lung depending on individual exposure and susceptibility. D_LCO=diffusing capacity of carbon monoxide.

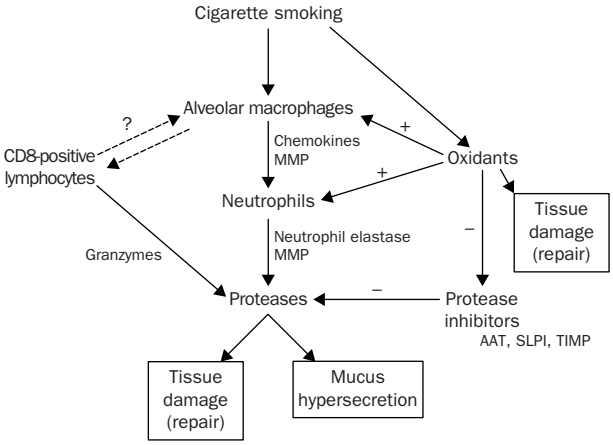

Figure 3: **Potential mechanisms involved in the pathogenesis of COPD**

Some of the more important candidate cells and mediators and some of the potentially large number of interactions between them are shown. The degree of tissue damage is modified by the extent to which repair occurs, which emphasises the dynamic nature of all these processes. Naturally occurring inhibitory enzymes are secreted along with the active proteases. MMP=matrix metalloproteinases; AAT=α_1-antitrypsin; SLPI=secretory leucocyte protease inhibitor; TIMP=tissue inhibitor of metalloproteinases.

prevent elastin digestion arose from the observation that patients deficient in α_1-antitrypsin developed emphysema. This deficiency remains the main genetic disorder causing COPD in people of European descent, although it is still a rare form of the disease.[36]

Another potentially complementary hypothesis proposes that oxidative stress caused by inhaled cigarette smoke can explain the pathological changes in COPD. Findings in patients have now confirmed previous observations of increased oxidative stress in COPD by showing increased amounts of oxidation products in exhaled breath condensates of patients with stable disease.[37,38] Studies in mice exposed to cigarette smoke have shown that the hallmarks of oxidative lung damage and the pathological changes of emphysema can be produced by this stimulus[39] and blocked by pretreatment with superoxide dismutase.[40]

Models of emphysema have also been used to study the effect of specific gene deletions, for example deletion of the gene for matrix metalloproteinase 12 (*MMP12*), which can protect against the development of emphysema during cigarette-smoke exposure.[41] In other studies, genes have been overexpressed; for example, overexpression of interleukin 13 produced mice with a COPD-like illness.[42] Further direct manipulation of the genome is likely to yield greater understanding of the processes regulating inflammation in COPD. Another interesting observation is that emphysema is associated with apoptosis of the alveolar cells, possibly secondary to inhibition of vascular endothelial growth factor.[43] These findings emphasise the dynamic nature of lung damage and its interaction with natural repair mechanisms designed to maintain lung structure, a research area likely to promote better understanding of the mechanisms that lead to progression of COPD.

Genetic factors are likely to be major determinants of susceptibility to COPD, although systematic studies are only now being undertaken. Early-onset emphysema in women has a genetic basis, independent of α_1-antitrypsin status.[44–46] Attempts to link COPD with specific susceptibility genes have had varying degrees of success. Several candidate gene polymorphisms have been proposed, mostly in genes protecting against oxidant injury or involved in the inflammatory cascade. However, these data have not been replicated in other populations.[44] Another approach involving scanning of the whole genome in patients and unaffected siblings is now under way and should identify new gene associations with COPD.

There is increasing recognition that COPD is not simply confined to the lungs but has systemic effects, at least in individuals with more advanced disease.[47] Some consequences (eg, tissue hypoxia in patients with impaired gas exchange) have been recognised for many years. However, COPD patients are also now known to have a high prevalence of osteoporosis irrespective of sex, and many have a low body-mass index, which is an independent predictor of mortality.[48] The skeletal muscles are also abnormal, and reduced muscle strength predicts increased health-care contact irrespective of lung function.[49] Identification of the mechanisms that produce these abnormalities is an active research area.

Physiological consequences

Advances in the biology of COPD have been accompanied by improved understanding of the factors leading to the disabling symptoms, particularly exercise-induced breathlessness. The development of simpler methods that reliably detect expiratory flow limitation during breathing at rest[50] and measure inspiratory capacity and hence end-expiratory lung volume during exercise[51] has enabled a convincing explanation of the origin of dyspnoea, at least in severe disease. Figure 4 shows that in patients with expiratory flow limitation at rest, increases in ventilation during exercise can be achieved only by allowing end-expiratory lung volume to rise. This change correlates with the intensity of dyspnoea during exercise,[51] can be effectively delayed by pretreatment with bronchodilator drugs[52] or by breathing oxygen when exercising,[53] and is most obvious when tidal expiratory flow limitation is detected at rest.[54]

There is renewed interest in the effects of COPD on skeletal muscles such as the quadriceps. Studies with

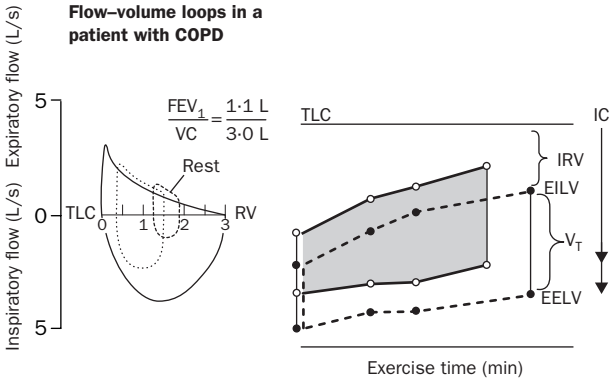

Figure 4: **Tidal flow limitation and dynamic hyperinflation during exercise**

The left panel shows a maximum flow–volume loop of a patient with COPD (spirometry shown). The tidal breathing loop at rest (loop 1 dashed line) is flow limited during expiration; during exercise expiratory flow can be increased only by breathing at a higher lung volume (loop 2 dotted line). Solid line is maximum flow-volume loop (Adapted with permission from Hughes JMB, Pride NB. Lung function tests. London: W B Saunders, 2002.) The right panel shows the lung volumes during exercise in a group of similar COPD patients before (shaded area, solid lines) and after (open area, broken lines) treatment with ipratropium bromide. Since total lung capacity (TLC) is constant during exercise, the inspiratory capacity (IC) allows end-expiratory lung volume (EELV) to be measured. In contrast to the normal situation, in COPD EELV rises as exercise proceeds, as predicted in the left panel. The bronchodilator delays this change in EELV, prolongs exercise time, and reduces dyspnoea at any rate of ventilation. Data redrawn from reference 52 with permission.

Stage	Characteristics
0–at risk	Normal spirometry Chronic symptoms (cough, sputum)
I–mild	$FEV_1/FVC<70\%$ $FEV_1 \geq 80\%$ predicted with or without symptoms (cough, sputum)
II–moderate	$FEV_1/FVC<70\%$ $FEV_1<80\%$ to >50% predicted with or without chronic symptoms (cough, sputum, dyspnoea)
III–severe	$FEV_1/FVC<70\%$ $FEV_1<50\%$ to >30% predicted with or without chronic symptoms
IV–very severe	FEV_1/FVC <70%, FEV_1 <30% predicted

Disease severity in COPD

magnetic resonance spectroscopy have shown that severe acidosis develops in the muscles of COPD patients as they exercise, a change reversed by rehabilitation.[55] Whether this effect results from impaired oxygen delivery to the muscle or to changes in its fibre composition is not clear.

Clinical assessment

The diagnosis of COPD is based on a typical history of persistent progressive symptoms, an appropriate risk factor (eg, cigarette smoking), and a confirmatory spirometric test. Despite much discussion and a clear difference between North America and Europe in its definition,[15,17,18] bronchodilator reversibility testing plays only a small part in the assessment of the COPD patient. A useful feature for confirmation of the diagnosis is that the patient's lung function does not return to normal after bronchodilator administration. However, smaller degrees of reversibility that exceed arbitrary thresholds do not seem to be related to subsequent mortality and contribute little in practice for COPD management.[56]

Current approaches to staging of disease severity use deliberately wide bands of FEV_1 to encompass the different grades because spirometry bears only a loose relation to symptom intensity (table). Use of additional physiological measurements such as the diffusing capacity of carbon monoxide (D_LCO) or static lung volumes allows for better characterisation of the patient but seldom influences management. However, identification of arterial hypoxaemia is important, and blood gases should be measured if the FEV_1 is less than 30% predicted.

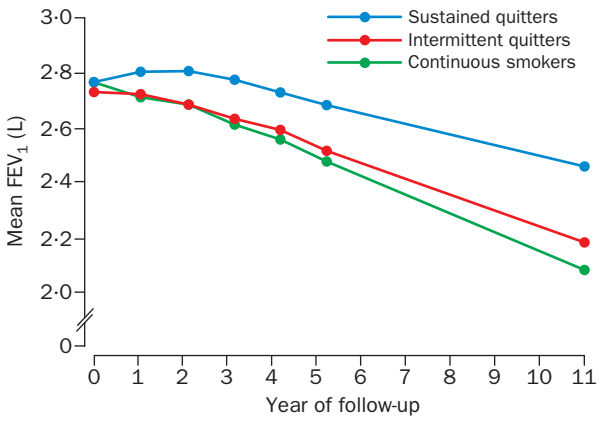

Figure 5: **Decline in lung function in relation to smoking status in COPD**

Lung function in patients with mild COPD who stop smoking completely declines more slowly than those who continue or those who give up intermittently. Data derived from follow-up of the original Lung Health Study cohort.[66] The original small difference in lung function produced by the greater number quitting among patients randomly assigned nicotine replacement therapy is still evident at 11 years.[62]

There is evidence that other non-pulmonary factors including an overall assessment of the patient's well-being, such as health status or the MRC dyspnoea grade, help to predict health-care utilisation[57,58] and possibly mortality[59,60] more accurately than FEV_1 alone. Similarly, recording of body-mass index is simple and prognostically important in more severe disease.[48] Whether quantification of the extent of emphysema by structural techniques such as CT will provide further improvement is less clear, but exercise performance seems to be an important determinant of health status[61] and could usefully be documented in patients with more severe disease. Attempts at synthesising these factors into a more comprehensive staging system are under way, but there is no agreement about how best this can be achieved.

Treatment approaches

These fall into three broad areas: prevention of disease progression, management of stable disease, and management of exacerbations. There is now a much firmer evidence base for many of the management suggestions incorporated in the various guidelines.[15–19]

Prevention of disease progression

Smoking cessation early in the natural history of COPD not only returns the subsequent rate of declining function towards normal but also reduces future mortality,[20] as confirmed by the 11-year follow-up of the original Lung Health Study population[62] (figure 5). Whether this is true in more advanced disease is still unclear, but ex-smokers have better health status than current smokers with a similar degree of lung-function impairment.[63] Although patients with COPD are not easily persuaded to stop smoking, organised smoking cessation programmes can help. Such programmes should include prescription of appropriate agents to reduce tobacco withdrawal symptoms, such as nicotine replacement therapy[64] and bupropion.[65] The original intention-to-treat analysis of the effect of nicotine replacement in the first Lung Health Study was disappointing,[66] perhaps reflecting the effectiveness of counselling in the patients assigned placebo. Bupropion is promising in COPD patients, although to date only 6-month follow-up data have been reported in these patients.

Removal of an affected individual from a polluted environment is easier to propose than achieve, but

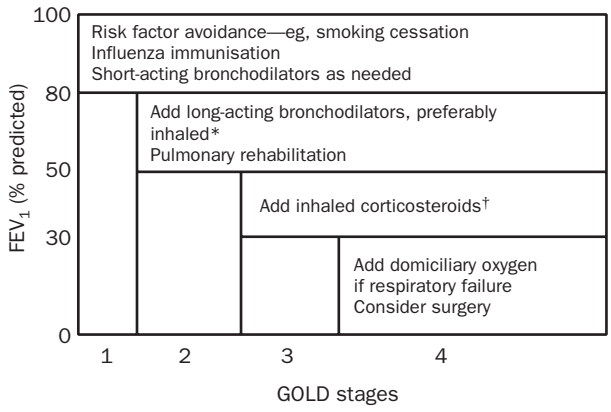

Figure 6: **Stepwise therapy for stable COPD**

Treatment is cumulative and generally determined by spirometric disease severity and symptom intensity. All treatments apply to patients diagnosed as having COPD (ie, FEV_1/FVC ratio <0·70). Treatments in the boxes above each stage should be considered. *If the patient has persistent symptoms. †If the patient has regular exacerbations (eg, three in a 2-year period).

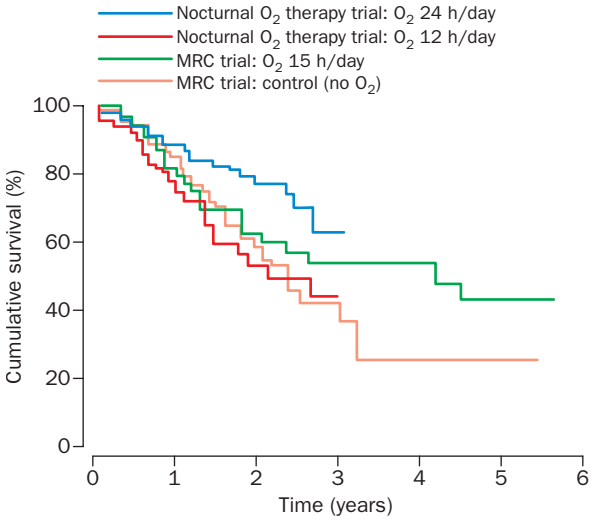

Figure 7: **Survival after treatment with domiciliary oxygen therapy in patients with PaO_2 <7·3 kPa**

Composite plot of data[89,90] indicating that survival can be prolonged by oxygen for 15 h per day and 12 h per night at a higher flow rate. The best survival was in the US patients treated for 24 h per day.

improved ventilation is a potentially useful intervention for some patients.

One issue of special interest is α_1-antitrypsin deficiency, which should be considered in white people with emphysema who have little or no tobacco exposure or disease evident by the age of 50. Substantial progress has been made both in elucidation of the basic molecular biology and in development of replacement therapy programmes, at least in the USA.[67] The value of this treatment remains controversial. A European randomised trial has so far failed to show an effect on lung function with regular replacement therapy but has shown differences in lung CT density.[68] This method of assessing progressive lung damage may be useful in detecting the treatment effect of other drugs designed to modify lung growth, such as retinoids.

Management of stable disease

Management should involve several different treatment approaches and should be directed at control of symptoms, improvement in exercise capacity, and prevention of exacerbations (figure 6).

Since airflow obstruction is a constant feature of COPD, a reasonable approach is to try to maintain effective bronchodilation continuously. This aim is now possible with negligible side-effects by use of long-acting inhaled β agonist or anticholinergic drugs.[69–74] The greater side-effect profile associated with theophyllines has relegated them to a third-line add-on role in treatment. Long-acting inhaled drugs produce more consistent bronchodilation than is achieved by anticholinergics inhaled four times daily[72,74] and are associated with better health status and fewer disease exacerbations.[74] Whether tiotropium is superior to long-acting inhaled β agonists is not clear, although one study suggested this possibility.[75] The value of combining these different drugs in the same patient is still to be tested.

Inhaled corticosteroids are still widely used in COPD, although the scientific basis of this approach remains contentious.[76,77] These drugs do not modify the rate of decline of lung function[78–81] but do reduce the number of exacerbations and decline in health status seen in patients with more severe disease.[63,80] Evidence from large general population databases suggests that treatment with inhaled corticosteroids is associated with fewer hospital admissions and lower mortality.[82,83] However, these reports have significant limitations. Recent large prospective randomised controlled trials suggest that addition of an inhaled corticosteroid to a long-acting inhaled bronchodilator, typically a β agonist, is useful in patients whose FEV_1 is less than 50% predicted and who have a history of regular exacerbation. Combination of these treatments leads to fewer exacerbations, better health status, fewer symptoms, and improved lung function than with either treatment used alone.[84–86]

Pulmonary rehabilitation can be used at any stage of COPD and is very effective.[87–93] Most programmes involve 7–12 weeks of intermittently supervised exercise therapy coupled with general education about COPD. They commonly produce striking improvements in exercise capacity and health status together with a reduction in symptoms and even hospital admission. Unfortunately, the effects tend to wane over the subsequent 18 months, and the optimum way to prevent this loss of effect is still to be determined. Not every patient completes the rehabilitation programme, exacerbations of COPD and poor initial motivation being common reasons for failure.

Oxygen therapy is confined to patients with more severe disease and is used in three distinct ways.[94] In patients whose arterial oxygen partial pressure (PaO_2) is always less than 7·3 kPa, domiciliary oxygen for 15 h per day or more prolongs life (figure 7); no survival benefit is seen with lesser degrees of hypoxaemia.[9,95–97] Oxygen taken while exercising improves endurance[98,99] and is commonly used in this way in the USA. Whether oxygen desaturation is necessary for this benefit to occur is not clear, although prescription of ambulatory oxygen generally requires that desaturation is present. Finally, many patients receive oxygen to control acute episodes of dyspnoea or to use before they exercise. Good evidence to support either practice is lacking, although clinicians often report that patients appreciate having oxygen available at home even if they seldom use it.

The most striking new treatment is lung volume reduction surgery. Two randomised controlled trials have shown that this treatment improves exercise capacity and health status while reducing breathlessness during daily activities.[100,101] The large multicentre National Emphysema Treatment Trial in the USA identified an unacceptable surgical risk in patients with FEV_1 of less than 20% predicted and either D_LCO less than 20% predicted or a homogeneous pattern of emphysema on CT.[102] Survival improved and symptomatic benefits were greater in patients with homogeneous emphysema and low exercise capacity after rehabilitation.[103] The recognition that lung transplantation conveys a symptomatic rather than a survival benefit has affected the priority given to COPD patients in countries where organs are scarce, and fewer patients with COPD are now being given transplants in the UK.[104,105]

Management of exacerbations

The most recent definition for these events is given in panel 2.[106] Exacerbations become progressively more

Panel 2: **Recent consensus definition of an exacerbation of COPD[105]**

An exacerbation of COPD is a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variation, which is acute in onset and necessitates a change in regular medication.

troublesome as baseline lung function declines and patients who have frequent exacerbations have worse health status[107] and may show more rapid deterioration in lung function than those who seldom have exacerbations.[108] Previous viral infection accounts for about 30% of exacerbations,[109] with bacterial infection present in 30–50% of cases, depending on the severity of the episode.[110,111] Persistent bacterial infection is associated with more intense airway inflammation,[112] whereas patients with symptoms of chronic bronchitis are more likely to have recurrent exacerbations.[113] Although prophylactic antibiotic treatment does not reduce exacerbation frequency, influenza vaccination is beneficial and should be offered routinely at the appropriate season.

Management of exacerbations still focuses on increases in bronchodilator therapy, antibiotics for some patients, and the addition of oral corticosteroids. Antibiotics are helpful if there is an increase in dyspnoea, coughing, and the volume and purulence of the sputum. Several randomised controlled trials have shown that, compared with placebo, oral and nebulised corticosteroids accelerate the rate of improvement in lung function during an exacerbation, and that oral corticosteroids can reduce the length of the hospital stay.[114–117] Treatment with 30 mg prednisolone for 7–10 days is sufficient; higher doses used in other studies are unnecessary. Controlled oxygen therapy is needed for patients who need admission to hospital but the use of an unnecessarily high inspired concentration of oxygen leads to potentially dangerous degrees of acidosis.[118] However, the recognition that hospital admission is closely related to the presence of comorbidities and respiratory acidosis[119] allows the identification of patients who can be safely managed in the community with appropriate nurse support and conventional medical therapy as outlined above.[120–122] This technique can also be adapted to reduce the duration of hospital stays in patients who initially need admission.[123] It is preferred by patients[124] and is cost-saving.

If respiratory acidosis develops, non-invasive positive-pressure ventilation offers a useful alternative to conventional positive-pressure ventilation and can reduce the workload in intensive-care units.[125] It is most effective when the pH is between 7·30 and 7·35;[126] it can reduce both the risk of nosocomial pneumonia and duration of stay in the intensive-care unit.[127] It appears to be less effective in more acidotic patients who ideally should undergo conventional positive-pressure ventilation, provided it is ethically reasonable to do so and in line with their stated wishes.

Panel 3: **Future progress in COPD**

Pathogenesis

Characterising phenotype by biomarkers—eg, exhaled air condensate or CT scanning for emphysema
Identification of candidate susceptibility genes
Clarification of the basis of corticosteroid resistance
Relating data from knock-out/knock-in mouse models of disease to human beings

Clinical

Improved detection of tidal flow limitation—eg, by forced oscillation techniques
Development of comprehensive staging systems that describe disease impact by additional indices apart from FEV_1

Treatment

More specific forms of smoking cessation therapy
Corticosteroids with less systemic bioavailability
Phosphodiesterase IV inhibitors—eg, cilomilast, roflumilast, which may reduce inflammation in COPD
Chemokine inhibitors that reduce inflammation non-specifically
Effective antioxidant molecules with better bioavailability that counter oxidative damage related to inflammation/exacerbation
Retinoids that may promote alveolar regeneration
Anti-TNFα drugs that reduce systemic inflammation
Nutriceuticals that act as supplements to intramuscular energy supplies in exercising muscle
Medical lung volume reduction via a bronchoscope with implanted one-way valves or surgical openings in the airway (spiracles)
Identification of the role of lower respiratory tract in promoting disease progression and frequent exacerbation and the effect of abolishing this colonisation

Future progress

The next 5 years should see improvements in our understanding of many areas relevant to COPD. A selection of some of the more promising areas is given in panel 3.

The epidemiology of the disease will continue to change with a steady rise in the number of cases identified among women. A more comprehensive description of the physiological abnormalities accompanying expiratory flow limitation at rest is likely, as well as the development of simpler ways to detect this feature. The use of CT to diagnose emphysema will increase and with it the uncertainty about the importance of emphysema in individuals who have little or no lung-function abnormality. Most clinical trials will use existing therapies in different combinations, although the effect, if any, of these treatments on mortality should be clarified when the TORCH (Towards a Revolution in COPD Health) study is reported in 2007. Undoubtedly, some novel treatments directed at controlling inflammation in COPD will reach the proof-of-principle stage,[128] although the attrition rate continues to be high among the leading candidate molecules. Screening of suitable candidate compounds would be greatly helped if we knew more about the value of disease markers such as induced sputum or exhaled breath condensates as surrogates for future disease progression.

For most patients the major advances in care will come from the systematic application of existing knowledge to their treatment and the availability of proven treatment in a readily accessible form.

Conflict of interest statement
PMAC has received research funding from several pharmaceutical companies with an interest in COPD and has spoken at meetings sponsored by companies including GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Altanta Pharma, Schering Plough, and Novartis.

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References

1 Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997; **349:** 1269–76.
2 Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997; **349:** 1436–42.
3 Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997; **349:** 1498–504.
4 Murray CJL, Lopez AD, Mathers CD, Stein C. The Global Burden of Disease 2000 Project: global programme on evidence for health policy discussion, paper number 36. Geneva: WHO, 2001.

5 National Heart, Lung and Blood Institute. NHLBI Morbidity and Mortality Chartbook, 2002. Bethseda: US Department of Health and Human Services, Public Health Service, 2002. (available from www.nhlbi.nih.gov/resources/docs/02_chtbk; accessed May 13, 2003).

6 National Centre for Health Statistics. National hospital interview survey. Vital and Health Statistics, series 10 (issues from 1974 to 1997).

7 Soriano JB, Maier WC, Egger P, et al. Recent trends in physician diagnosed COPD in women and men in the UK. *Thorax* 2000; **55:** 789–94.

8 Lung and Asthma Information Agency. Trends in emergency hospital admissions for lung disease. Fact sheet 2001/4. London: St George's Hospital Medical School.

9 Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St George's respiratory questionnaire. *Am Rev Respir Dis* 1992; **145:** 1321–27.

10 McSweeny AJ, Grant I, Heaton RK, Adams KM, Timms RM. Life quality of patients with chronic obstructive pulmonary disease. *Arch Intern Med* 1982; **142:** 473–78.

11 Ketelaars CA, Schlosser MA, Mostert R, et al. Determinants of health-related quality of life in patients with chronic obstructive pulmonary disease. *Thorax* 1996; **51:** 39–43.

12 Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Comparison of discriminative properties among disease-specific questionnaires for measuring health-related quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; **157:** 785–90.

13 Morgan MDL, Threlfall E, Sanders D, Walden IM, Britton M. Living with COPD: results of the British Lung Foundation survey. European Respiratory Society Congress, Berlin, Sept 22–26, 2**001:** abstr 3266.

14 Rennard S, Decramer M, Calverley PMA, et al. The impact of COPD in North America and Europe in 2000: the patients perspective of the Confronting COPD International Survey. *Eur Respir J* 2002; **20:** 1–7.

15 American Thoracic Society. Standards for the diagnosis of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987; **136:** 225–44.

16 Canadian Thoracic Society Working Group. Guidelines for the assessment and management of chronic obstructive pulmonary disease. *Can Med Assoc J* 1992; **147:** 420–28.

17 European Respiratory Society Task Force. Optimal assessment and management of chronic obstructive pulmonary disease. *Eur Respir J* 1995; **8:** 1398–420.

18 COPD Guidelines Group of the Standards of Care Committee of the British Thoracic Society. BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997; **52:** S1–28.

19 Pauwels RA, Buist AS, Calverley PMA, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary. *Am J Respir Crit Care Med* 2001; **163:** 1256–76.

20 Fletcher C, Peto R.The natural history of chronic airflow obstruction. *BMJ* 1977; **1:** 1645–48.

21 Peto R, Speizer FE, Cochrane AL, et al. The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease: results from 20 years of prospective observation. *Am Rev Respir Dis* 1983; **128:** 491–500.

22 Pandey MR, Regmi HN, Neupane RP, Gautam A, Bhandari DP. Domestic smoke pollution and respiratory function in rural Nepal. *Tokai J Exp Clin Med* 1985; **10:** 471–81.

23 Pandey MR. Prevalence of chronic bronchitis in a rural community of the hill region of Nepal. *Thorax* 1984; **39:** 331–36.

24 Perez-Padilla R, Regaldo J, Vedal S, Pare P, Sansores R, Seman M. Exposure to biomass smoke and chronic airway disease in Mexican women: a case-control study. *Am J Respir Crit Care Med* 1996; **154:** 701–06.

25 Cozio M, Ghezzo H, Hogg JC, et al. The relations between structural changes in small airways and pulmonary function tests. *N Engl J Med* 1978; **298:** 1277–81.

26 Thurlbeck WM, Wright JL. Chronic airflow obstruction, 2nd edn. Hamilton: BC Dekker, 1999.

27 Penman RW, O'Neill RP, Begley L. The progress of chronic airway obstruction in relation to measurements of airway resistance and lung elastic recoil. *Am Rev Respir Dis* 1970; **101:** 536–44.

28 Colebatch HJ, Finucane KE, Smith MM. Pulmonary conductance and elastic recoil relationships in asthma and emphysema. *J Appl Physiol* 1973; **34:** 143–53.

29 Keatings VM, Collins PD, Scott DM, Barnes PJ. Differences in interleukin-8 and tumor necrosis factor-alpha in induced sputum from patients with chronic obstructive pulmonary disease or asthma. *J Respir Crit Care Med* 1996; **153:** 530–34.

30 Pesci A, Balbi B, Majori M, et al. Inflammatory cells and mediators in bronchial lavage of patients with chronic obstructive pulmonary disease. *Eur Respir J* 1998; **12:** 380–86.

31 Turato G, Zuin R, Miniati M, et al. Airway inflammation in severe chronic obstructive pulmonary disease: relationship with lung function and radiologic emphysema. *Am J Respir Crit Care Med* 2002; **166:** 105–10.

32 Saetta M, Baraldo S, Corbino L, et al. CD8+ve cells in the lungs of smokers with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; **160:** 711–17.

33 O'Shaughnessy TC, Ansari TW, Barnes NC, Jeffery PK. Inflammation in bronchial biopsies of subjects with chronic bronchitis: inverse relationship of CD8+ T-lymphocytes with FEV_1. *Am J Respir Crit Care Med* 1997; **155:** 852–57.

34 Retamales I, Elliott WM, Meshi B, et al. Amplification of inflammation in emphysema and its association with latent adenoviral infection. *Am J Respir Crit Care Med* 2001; **164:** 469–73.

35 Fabbri LM, Romagnoli M, Corbetta L, et al. Differences in airway inflmmation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; **167:** 418–24.

36 Lomas DA, Mahadeva R. Alpha 1 antitrypsin polymerisation and the serpinopathies: pathobiology and prospects for treatment. *J Clin Invest* 2002; **110:** 1585–90.

37 Corradi M, Montuschi P, Donnelly LE, Pesci A, Kharitonov SA, Barnes PJ. Increased nitrosothiols in exhaled breath condensate in inflammatory airway diseases. *Am J Respir Crit Care Med* 2001; **163:** 854–58.

38 Montuschi P, Collins JV, Ciabattoni G, et al. Exhaled 8-isoprostane as an in vivo biomarker of lung oxidative stress in patients with COPD and healthy smokers. *Am J Respir Crit Care Med* 2000; **162:** 1175–77.

39 D'Armiento J, Dalal SS, Okada Y, Berg RA, Chada K. Collagenase expression in the lungs of transgenic mice causes pulmonary emphysema. *Cell* 1992; **71:** 955–61.

40 Nishikawa M, Kakemizu N, Ito T, et al. Superoxide mediates cigarette smoke-induced infiltration of neutrophils into the airways through nuclear factor-kappa B activation and IL-8 mRNA expression in guinea pigs in vivo. *Am J Respir Cell Mol Biol* 1999; **20:** 189–98.

41 Hautamaki RD, Kobayashi DK, Senior RM, Shapiro SD. Requirement for macrophage elastase for cigarette smoke-induced emphysema in mice. *Science* 1**997: 277:** 2002–04.

42 Zheng T, Zhu Z, Wang Z, et al. Inducible targeting of IL-13 to the adult lung causes matrix metalloproteinase–and cathepsin-dependent emphysema. *J Clin Invest* 2000; **106:** 1081–93.

43 Kasahara Y, Tuder RM, Cool CD, Lynch DA, Flores SC, Voelkel NF. Endothelial cell death and decreased expression of vascular endothelial growth factor and vascular endothelial growth factor receptor 2 in emphysema. *Am J Respir Crit Care Med* 2001; **163:** 737–44.

44 Sandford AJ, Silverman EK. Chronic obstructive pulmonary disease: 1–susceptibility factors for COPD the genotype-environment interaction. *Thorax* 2002; **57:** 736–41.

45 Silverman EK, Chapman HA, Drazen JM, et al. Genetic epidemiology of severe, early-onset chronic obstructive pulmonary disease. Risk to relatives for airflow obstruction and chronic bronchitis. *Am J Respir Crit Care Med* 1998; **157:** 1770–78.

46 McCloskey SC, Patel BD, Hinchliffe SJ, Reid ED, Wareham NJ, Lomas DA. Siblings of patients with severe chronic obstructive pulmonary disease have a significant risk of airflow obstruction. *Am J Respir Crit Care Med* 2001; **164:** 1419–24.

47 Agusti A. Systemic effects of chronic obstructive pulmonary disease. *Novartis Found Symp* 2001; **234:** 242–49.

48 Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; **157:** 1791–97.

49 American Thoracic Society/European Respiratory Society. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; **159:** S1–40.

50 Milic-Emili J. Expiratory flow limitation: Roger S Mitchell Lecture. Chest 2000; **117:** 219S–23S.

51 O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; **164:** 770–77.

52 O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; **160:** 542–49.

53 O'Donnell DE, D'Arsigny C, Webb AK. Effects of hyperoxia on ventilatory limitation during exercise in advanced chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; **163:** 892–98.

54 Diaz O, Villafranca C, Ghezzo H, et al. Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. *Eur Respir J* 2000; **16:** 269–75.

55 Sala E, Roca J, Marrades RM, et al. Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; **159:** 1726–34.

56 Hansen EF, Phanareth K, Laursen LC, Kok-Jensen A, Dirksen A. Reversible and irreversible airflow obstruction as predictor of overall mortality in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; **159:** 1267–71.

57 Osman LM, Godden DJ, Friend JA, Legge JS, Douglas JG. Quality of life and hospital re-admission in patients with chronic obstructive pulmonary disease. *Thorax* 1997; **52:** 67–71.

58 Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; **54:** 581–86.

59 Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002; **121:** 1434–40.

60 Domingo-Salvany A, Lamarca R, Ferrer M, et al. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; **166:** 680–85.

61 Dowson LJ, Newall C, Guest PJ, Hill SL, Stockley RA. Exercise capacity predicts health status in alpha-1-antitrypsin deficiency**.** *Am J Respir Crit Care Med* 2001; **163:** 936–41.

62 Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med* 2002; **166:** 675–79.

63 Spencer S, Calverley PMA, Burge PS, Jones PW. Health status deterioration in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; **163:** 122–28.

64 Lancaster T, Stead L, Silagy C, Sowden A. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. *BMJ* 2000; **321:** 355–58.

65 Tashkin D, Kanner R, Bailey W, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001; **357:** 1571–75.

66 Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anti-cholinergic bronchodilator on the rate of decline of FEV1: the Lung Health Study. *JAMA* 1994; **272:** 1497–505.

67 Carrell RW, Lomas DA. Alpha1-antitrypsin deficiency: a model for conformational diseases. *N Engl J Med* 2002; **346:** 45–53.

68 Dirksen A, Dijkman JH, Madsen F, et al. A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. *Am J Respir Crit Care Med* 1999; **160:** 1468–72.

69 Rennard SI, Anderson W, ZuWallack R, et al. Use of a long-acting inhaled beta 2-adrenergic agonist, salmeterol xinafoate, in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; **163:** 1087–92.

70 Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. *Am J Respir Crit Care Med* 1997; **155:** 1283–89.

71 Dahl R, Greefhorst LAPM, Nowak D, et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 164; **5:** 778–84.

72 Mahler DA, Donohue JF, Barbee RA, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest* 1999; **115:** 957–65.

73 Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obsrtructive pulmonary disease *Eur Respir J* 2002; **19:** 217–24

74 Vincken W, van Noord JA, Greefhorst AP, et al; Dutch/Belgian Tiotropium Study Group. Improved health outcomes in patients with COPD during 1 year's treatment with tiotropium. *Eur Respir J* 2002; **19:** 209–16.

75 Donohue JF, van Noord JA, Bateman ED, et al. A 6 month placebo controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002; **122:** 47–55.

76 Calverley PMA. Inhaled corticosteroids are beneficial in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; **161:** 341–42.

77 Barnes PJ. Inhaled corticosteroids are not beneficial in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; **161:** 342–44.

78 Pauwels RA, Lofdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. *N Engl J Med* 1999; **340:** 1948–53.

79 Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999; **353:** 1819–23.

80 Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; **320:** 1297–303.

81 The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease: *N Engl J Med* 2000; **343:** 1902–909.

82 Sin DD, Tu JV. Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med 2001*; **164:** 580–84.

83 Soriano JB, Vestbo J, Pride NB, Kiri V, Maden C, Maier WC. Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. *Eur Respir J* 2002; **20:** 799–805.

84 Mahler DA, Wire P, Horstman D, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the diskus device in the treatment of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; **166:** 1084–91.

85 Calverley PMA, Pauwels R, Vesbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; **361:** 449–56.

86 Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003; **21:** 74–81.

87 American Thoracic Society. Pulmonary rehabilitation. *Am J Respir Crit Care Med* 1999; **159:** 1666–82.

88 British Thoracic Society Standards of Care Subcommittee on Pulmonary Rehabilitation. Pulmonary rehabilitation. *Thorax* 2001; **56:** 827–34.

89 Goldstein RS, Gort EH, Stubbing D, Avendano MA, Guyatt GH. Randomised controlled trial of respiratory rehabilitation. *Lancet* 1994; **344:** 1394–97.

90 Wijkstra PJ, Van Altena R, Kraan J, Otten V, Postma DS, Koeter GH. Quality of life in patients with chronic obstructive pulmonary disease improves after rehabilitation at home. *Eur Respir J* 1994; **7:** 269–73.

91 Young P, Dewse M, Fergusson W, Kolbe J. Improvements in outcomes for chronic obstructive pulmonary disease (COPD) attributable to a hospital-based respiratory rehabilitation programme. *Aust N Z J Med* 1999; **29:** 59–65.

92 Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. *Am J Respir Crit Care Med* 1999; **160:** 1248–53.

93 Griffiths TL, Burr ML, Campbell IA, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000; **355:** 362–68.

94 Royal College of Physicians. Domiciliary oxygen therapy services: clinical guidelines and advice for prescribers. London: Royal College of Physicians, 1999.

95 Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980; **93:** 391–98.

96 Medical Research Council Working Party. Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* 1981; **1:** 681–86.

97 Gorecka D, Gorzelak K, Sliewinski P,Tobias M, Zielinski J. Effect of long-term oxygen therapy on survival of patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 1997; **52:** 674–79.

98 Roberts CM, Bell J, Wedzicha JA. Comparison of the efficacy of a demand oxygen delivery system with continuous low flow oxygen in subjects with stable COPD and severe oxygen desaturation on walking. *Thorax* 1996; **51:** 831–34.

99 Ram FS, Wedzicha JA. Ambulatory oxygen for chronic obstructive pulmonary disease (Cochrane Review). In: *The Cochrane Library*. Issue 2. Oxford: Update Software, 2003.

100 Criner GJ, Cordova FC, Furukawa S, et al. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; **160:** 2018–27.

101 Geddes D, Davies M, Koyama H, et al. Effect of lung-volume-reduction surgery in patients with severe emphysema. *N Engl J Med* 2000; **343:** 239–45.

102 National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med* 2001; **345:** 1075–83.

103 National Emphysema Treatment Trail Research Group. A randomised trial comparing lung volume reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; **348:** 2059–73.

104 Hosenpud JD, Bennett LE, Keck BM, Edwards EB, Novick RJ. Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. *Lancet* 1998; **351:** 24–27.

105 Anyanwu AC, Rogers CA, Murday AJ; for Steering Group.

Intrathoracic organ transplantation in the United Kingdom 1995–99: results from the UK cardiothoracic transplant audit. *Heart* 2002; **87:** 449–54.

106 Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest* 2000; **117** (suppl 2)**:** 398S–401S.

107 Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; **157:** 1418–22.

108 Donaldson GC, Seemungall TAR, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; **57:** 847–52.

109 Seemungal TS, Harper-Owen R, Bhowmic A, et al. Symptoms, inflammatory markers and respiratory viruses in acute exacerbations and stable COPD. *Am J Respir Crit Care Med* 2001; **164:** 1618–23.

110 Monso E, Ruiz J, Rosell A, et al. Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med* 1995; **152:** 1316–20.

111 Soler N, Torres A, Ewig S, et al. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 1998; **157:** 1498–505.

112 Sethi S, Muscarella K, Evans N, Klingman KL, Grant BJ, Murphy TF. Airway inflammation and etiology of acute exacerbations of chronic bronchitis. *Chest* 2000; **118:** 1557–65.

113 Patel IS, Seemungal TAR, Wiks M, Lloyd-Owen SJ, Donaldson GC, Wedzicha JA. Relationship between bacterial colonisation and the frequency, character and severity of COPD exacerbations. *Thorax* 2002; **57:** 759–64.

114 Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med* 1996; **154:** 407–12.

115 Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet* 1999; **354:** 456–60.

116 Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1999; **340:** 1941–47.

117 Maltais F, Ostinelli J, Bourbeau J, et al. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Am J Respir Crit Care Med* 2002; **165:** 698–703.

118 Plant PK, Owen JL, Elliott MW. One-year period prevalence study of respiratory acidosis in acute exacerbations of COPD: implications for the provision of non-invasive ventilation and oxygen administration. *Thorax* 2000; **55:** 550–54.

119 Connors AF Jr, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. *Am J Respir Crit Care Med* 1996; **154:** 959–67.

120 Gravil JH, Al-Rawas OA, Cotton MM, Flanigan U, Irwin A, Stevenson RD. Home treatment of exacerbations of chronic obstructive pulmonary disease by an acute respiratory assessment service. *Lancet* 1998; **351:** 1853–55.

121 Davies L, Wilkinson M, Bonner S, Calverley PM, Angus RM. Hospital at home versus hospital care in patients with exacerbations of chronic obstructive pulmonary disease: prospective randomised controlled trial. *BMJ* 2000; **321:** 1265–68.

122 Skwarska E, Cohen G, Skwarski KM, et al. Randomized controlled trial of supported discharge in patients with exacerbations of chronic obstructive pulmonary disease. *Thorax* 2000; **55:** 907–12.

123 Cotton MM, Bucknall CE, Dagg KD, et al. Early discharge for patients with exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Thorax* 2000; **55:** 902–06.

124 Ojoo JC, Moon T, McGlone S, et al. Patients' and carers' preferences in two models of care for acute exacerbations of COPD: results of a randomised controlled trial. *Thorax* 2002; **57:** 167–69.

125 British Thoracic Society Standards of Care Committee. Non-invasive ventilation in acute respiratory failure *Thorax* 2002; **57:** 192–211.

126 Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet* 2000; **355:** 1931–35.

127 Brochard L, Mancebo J, Wysocki M, et al. Non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; **333:** 817–22.

128 Compton CH, Gubb J, Nieman R, et al. Cilomilast, a selective phosphodiesterase-4 inhibitor for treatment of patients with chronic obstructive pulmonary disease: a randomised, dose-ranging study. *Lancet* 2001; **358:** 265–70.