

Foreword

This project was initiated by the Standards of Care Committee of the British Thoracic Society. A core group of individuals produced background papers which were collated into a single document. This was discussed over a two day period by a larger group which included respiratory physicians from both teaching and district general hospitals across the UK, geriatricians, general practitioners, nurses, and public health physicians. Advice was also sought from the Breathe Easy section of the British Lung Foundation.

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Glossary of terms used in this document:

FEV ₁	forced expiratory volume produced in first second	PaO ₂	arterial oxygen tension
FVC	forced vital capacity	Paco ₂	arterial carbon dioxide tension
VC	slow vital capacity	SaO ₂	arterial oxygen saturation
FRC	functional residual capacity	LTOT	long term oxygen treatment
TLC	total lung capacity	NIPPV	non-invasive intermittent positive pressure ventilation
TlCO	diffusing capacity for carbon monoxide or gas transfer factor		

Summary of guidelines

1 This document was initiated by the Standards of Care Committee of the British Thoracic Society and summarises the views of many individuals and organisations (page S1). These views are based on a combination of clinical judgement and a review of the literature conducted by the participants as well as a critical reappraisal of the recommendations of published international guidelines. These guidelines are intended to provide a benchmark for current best practice in the care of patients with chronic obstructive pulmonary disease and permit the local development of rational cost effective care.

2 Definitions

- (a) Chronic obstructive pulmonary disease (COPD) is a general term which covers many previously used clinical labels that are now recognised as being different aspects of the same problem.
- (b) Diagnostic labels encompassed by COPD include:
- chronic bronchitis
 - emphysema
 - chronic obstructive airways disease
 - chronic airflow limitation
 - some cases of chronic asthma.
- (c) COPD is a chronic, slowly progressive disorder characterised by airways obstruction ($FEV_1 < 80\%$ predicted and FEV_1/VC ratio $< 70\%$) which does not change markedly over several months. The impairment of lung function is largely fixed but is partially reversible by bronchodilator (or other) therapy.
- (d) Most cases are caused by tobacco smoking (page S5).
- (e) COPD causes significantly more mortality and morbidity than do other causes of airflow limitation in adults (page S5).

3 Diagnosis of COPD

- (a) The diagnosis is usually suggested by symptoms (see below) but can only be established by objective measurement, preferably using spirometric tests.
- (b) Unlike asthma, airflow limitation in COPD as measured by the FEV_1 can never be returned to normal values. However, treatment can improve both symptoms and measured airflow limitation.
- (c) The symptoms and signs vary with the severity of the disease.

Category of COPD	FEV_1 (% predicted)	Symptoms and signs
Mild	60–80	No abnormal signs Smoker's cough Little or no breathlessness
Moderate	40–59	Breathlessness (\pm wheeze) on moderate exertion Cough (\pm sputum) Variable abnormal signs (general reduction in breath sounds, presence of wheezes)
Severe	<40	Breathlessness on any exertion/at rest Wheeze and cough often prominent Lung overinflation usual; cyanosis, peripheral oedema and polycythemia in advanced disease, especially during exacerbations.

4 Assessment of stable COPD

- (a) In general, spirometric testing is preferred to peak expiratory flow (PEF) recordings. If the latter are used, serial recordings over one week are needed to confirm the absence of variability (pages S8, S22). Bronchodilator reversibility testing is helpful in excluding patients with chronic asthma, but many patients with COPD show some degree of response to bronchodilators.
- (b) A positive spirometric response to bronchodilators or corticosteroids is considered to be present when the FEV_1 increases by 200 ml and 15% of the baseline value.
- (c) A substantial bronchodilator response suggests the possibility of asthma. Bronchodilator tests vary from day to day and are not clearly related to the extent of subsequent symptomatic benefit when the patient is treated with the drug tested.
- (d) A trial of oral corticosteroids is indicated in assessing moderate to severe disease. This usually comprises spirometric tests before and after 30 mg of prednisolone taken as a single dose daily for two weeks. Subjective improvement is not a satisfactory end point. Objective

improvement is seen in 10–20% of cases using the criteria described above for bronchodilators.

- (e) A chest radiograph excludes other pathologies but cannot positively diagnose COPD. In some patients bullae can be identified (page S9).
- (f) More complex investigations are not normally indicated except in difficult cases.
- (g) Estimation of arterial blood gas tensions in severe COPD is necessary to identify patients with persistent hypoxaemia with or without hypercapnia (page S9).

5 Treatment of stable COPD

PHARMACOLOGICAL

(a) Mild disease

- Bronchodilator therapy: short acting β_2 agonist or inhaled anticholinergic as required (page S10) depending upon symptomatic response.

(b) Moderate disease

- Bronchodilator therapy: as for mild disease but regular therapy with either drug or a combination of the two may be needed.
- A corticosteroid trial should be considered in all patients.

(c) Severe disease

- Combination therapy with a regular β_2 agonist and anticholinergic; the addition of other agents (see below) should be considered.
- Consider a corticosteroid trial.
- Assess for home nebuliser using the BTS guidelines.

(d) Other considerations

- Inhaler technique should be optimised and an appropriate device selected to ensure efficient delivery.
- Theophyllines are of limited value in the routine management of COPD.
- At present, evidence on the value of long acting β_2 agonists in COPD is limited and they should only be considered if objective evidence of improvement is available.
- There is no role for other anti-inflammatory drugs in the management of COPD.

NON-PHARMACOLOGICAL

- Smoking cessation is essential at all stages of the disease (page S10).
- Participation in an active smoking cessation programme leads to a higher sustained quit rate, especially when nicotine replacement therapy is included.
- Smoking cessation cannot restore loss of lung function but can prevent the accelerated decline seen in many patients with COPD (fig 2).
- Exercise should be encouraged where possible (page S12).
- Obesity and poor nutrition both require treatment (page S12).
- Vaccination against influenza is recommended, especially for moderate to severe disease (page S12).

6 In more advanced disease

- Dyspnoea can be assessed by a variety of scales (page S13).
- Dyspnoea improves with bronchodilators but is hard to suppress with sedative/opiate drugs at safe doses.
- Pulmonary rehabilitation including outpatient-based programmes have been shown to improve exercise performance and reduced breathlessness. This should be considered in moderate/severe disease (page S13).
- Short burst oxygen is often given to reduce breathlessness but the evidence for this is lacking (page S13).
- In hypoxaemic patients LTOT prolongs life (page S13).
- LTOT should only be prescribed if objectively demonstrated hypoxia ($P_{aO_2} < 7.3$ kPa) or high cylinder use (more than two per week) is present (page S14).
- Surgery is indicated for recurrent pneumothoraces and isolated bullous disease. Lung volume reduction surgery may be useful in selected patients (page S14).
- Depression should be identified and treated. Assessment of the patient's social circumstances and the support available is valuable in management (page S14).

- Travel is possible by land and sea in virtually all cases but air travel may be hazardous if the PaO_2 breathing air is <6.7 kPa. The availability of oxygen on the chosen flight should be checked (page S14).

7 Factors for consideration by the GP

- In general practice the consultation rates relating to COPD per 10 000 population rise from 417 at age 45–64 to 886 at age 65–74 and 1032 at age 75–84, values that are 2–4 times the equivalent rates for angina.
- In managing COPD the GP needs to consider:
 - smoking cessation
 - assessment in well man or woman clinics for smokers aged 40 and over
 - access to spirometric tests
 - hospital referral/follow up.

8 Indications for specialist referral (page S15)

A specialist opinion may be helpful at any stage of the disease. The principal reasons are summarised below:

Reason	Purpose
● Suspected severe COPD	● To confirm diagnosis and optimise treatment
● Onset of cor pulmonale	● To confirm diagnosis and optimise treatment
● Assessment for O_2 therapy	● To measure blood gases
● Assessment in accordance with nebuliser guidelines	● To exclude inappropriate prescriptions
● Assessment of oral corticosteroids	● To justify the need for long term treatment or to supervise withdrawal
● Bullous lung disease	● To identify and assess candidates for surgery
● <10 pack years smoking	● To confirm/exclude diagnosis
● Rapid decline in FEV_1	● To encourage early intervention
● COPD in patient less than 40 years	● To identify α_1 -antitrypsin deficiency, consider therapy and screen family
● Uncertain diagnosis	● To make a diagnosis
● Symptoms disproportionate to lung function deficit	● To look for other explanations
● Frequent infections	● To exclude bronchiectasis

Figure 3 summarises the management of stable COPD at each stage of the disease.

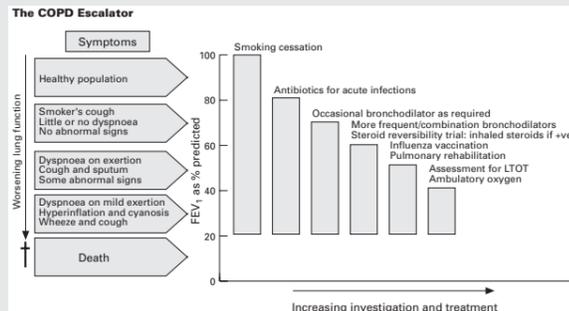


Figure 3 The COPD escalator. Summary of the principal components of a management plan for COPD. Note that, as disease severity increases, symptoms and signs become more obvious whilst the number of treatments used rises.

9 Presenting features of acute exacerbations of COPD

- Worsening of previous stable condition
- Increased wheeze
- Increased dyspnoea
- Increased sputum volume
- Increased sputum purulence
- Chest tightness
- Fluid retention

10 Questions to ask in deciding whether to treat at home or in hospital (page S16)

- Able to cope at home?
- Absence of cyanosis?
- Normal level of consciousness?

- Mild breathlessness?
- Good general condition?
- Not receiving LTOT?
- Good level of activity?
- Good social circumstances?

The greater the number of negative answers, the greater is the likelihood that admission to hospital is needed.

11 Home treatment of acute exacerbations (page S16)

- Add or increase bronchodilators (consider if inhaler device and technique are appropriate).
- Prescribe an antibiotic if two or more of the following are present:
 - increased breathlessness;
 - increased sputum volume;
 - development of purulent sputum.
- Oral corticosteroids may be prescribed in some cases. These should not be used unless:
 - the patient is already on oral corticosteroids;
 - there is a previously documented response to oral corticosteroids;
 - airflow obstruction fails to respond to an increase in bronchodilator dosage;
 - this is the first presentation of airflow obstruction.

12 Follow up of patients treated at home (page S17)

- If patient deteriorates, reassess and consider need for hospital treatment. If not fully improved in two weeks consider chest radiography and hospital referral.
- Measurement of FEV_1 .
- Reassessment of inhaler technique and patient's understanding of recommended treatment regime.
- Emphasise potential benefits of lifestyle management (smoking, weight, exercise).

13 Hospital treatment of an acute exacerbation (page S17)

- Hospital treatment of an acute exacerbation is as for home treatment except:

Drug	Criteria	Action
Broncho-dilator	Moderate exacerbation	Nebulised β_2 agonist or ipratropium bromide. If no response, consider iv aminophylline.
	Severe exacerbation	Nebulised ipratropium bromide and β_2 agonist in combination. If no response, consider iv aminophylline.
Oxygen	Moderate/severe exacerbation	Given in ambulance or on arrival, 24–28% mask 2 l/min by nasal prongs. Check blood gases within 60 minutes of starting oxygen, modify flow rate according to PaO_2 and pH.

- If pH is <7.26 and PaCO_2 is rising consider ventilatory support (page S19). This may be by intubation and intermittent positive pressure ventilation (IPPV) or non-invasive IPPV, although the latter is probably best initiated at a higher pH and is only suitable in cooperative patients without excessive secretions. An alternative is the use of intravenous doxapram.
- IPPV is likely to be appropriate when (page S19):
 - there is a clear basis for the current deterioration;
 - it is the first episode of respiratory failure;
 - there is an acceptable quality of life/habitual level of activity;
 - the patient has not previously had a full medical assessment;
 - there are few if any co-morbidities.
- A senior doctor must make the decision *not* to institute ventilatory support.
- Neither age nor the PaCO_2 predict survival (page S19).

14 Follow up of acute exacerbations

For all patients follow up assessment 4–6 weeks after discharge from hospital should include:

- patient's ability to cope;
- measurement of FEV_1 ;
- reassessment of inhaler technique and patient's understanding of recommended treatment regime;
- need for LTOT and/or home nebuliser usage in patients with severe COPD;
- follow up thereafter is as for stable COPD (page S15).

1

Introduction

Terminology

Chronic obstructive pulmonary disease (COPD) is the internationally preferred term that includes all the clinical labels and acronyms shown below, either alone or in combination.

- Emphysema
- Chronic bronchitis
- Chronic obstructive bronchitis
- Chronic airflow limitation (CAL)
- Chronic airflow obstruction (CAO)
- Chronic airways obstruction (CAO)
- Non-reversible obstructive airways disease (NROAD)
- Chronic obstructive airways disease (COAD)
- Chronic obstructive lung disease (COLD)
- Some cases of chronic asthma

The clinical diagnosis of COPD is suggested by symptoms, but can only be established firmly by an objective measurement indicating airflow obstruction. The critical feature that characterises COPD is the inability to reverse this airflow limitation fully. Appropriate treatment can, however, lead to some improvement in both measured airflow obstruction and/or clinically important symptoms.

These guidelines are intended to:

- help general practitioners, practice nurses and district nurses to recognise, characterise and hence treat patients with COPD appropriately, and to suggest when the use of secondary services can be most helpful;
- help hospital physicians (respiratory, general medical and geriatrician), nurses and physiotherapists to recognise and provide a more uniform and logical approach to care at each stage of COPD and thus to use resources in the most rational way;
- help purchasers of health care to define the quality and quantity of services necessary for patients with COPD (see box 1).

Where there is a lack of evidence in these guidelines we have declared current opinion.

Goals of the COPD guidelines

Early and accurate diagnosis
Best control of symptoms
Prevention of deterioration
Prevention of complications
Improved quality of life

Box 1

Definitions

Chronic obstructive pulmonary disease (COPD) is a chronic, slowly progressive disorder characterised by airflow obstruction (reduced FEV₁ and FEV₁/VC ratio) that does not change markedly over several months. Most of the lung function impairment is fixed, although some reversibility can be produced by bronchodilator (or other) therapy.

Thus, a diagnosis of COPD in clinical practice requires:

- a history of chronic progressive symptoms (cough and/or wheeze and/or breathlessness);
- objective evidence of airways obstruction, ideally by spirometric testing, that does not return to normal with treatment.

Usually a cigarette smoking history of more than 20 pack-years is obtained, although COPD does occur rarely in non-smokers.

COPD arises from varying combinations of airway disease and pulmonary emphysema; it is difficult to define the relative importance of each in an individual patient. The presence of "chronic cough and sputum production for at least three months of two consecutive years in the absence of other diseases recognised to cause sputum production" was used by the MRC¹ as an epidemiological definition of "chronic bronchitis" but does not necessarily signify the presence of airways obstruction or a diagnosis of COPD. The mortality and most of the morbidity associated with COPD relates to the airways obstruction and not the chronic mucus hypersecretion.²

The differentiation of severe COPD from chronic severe asthma is difficult since some degree of improvement in FEV₁ (reversibility) can often be produced by bronchodilator therapy. Moreover, the pathological changes of bronchial asthma in the large airways can co-exist with those of COPD which predominantly affects small airways.³ Whether such an association occurs more frequently than expected by chance is not clear. However, some patients with COPD have pathological evidence of non-asthmatic inflammation within their airways that may respond to anti-inflammatory treatment. The presence or absence of cough and sputum, wheeze at any time of day or night, a partial response to bronchodilators, or a family history of chest disease are unhelpful in differentiating between chronic asthma and COPD.⁴

The term COPD is not conventionally used to include other specific conditions that can cause airways obstruction such as cystic fibrosis, bronchiectasis, or bronchiolitis obliterans.

Aetiology and natural history

The single most important cause of COPD is cigarette smoking.⁵ The greater the total

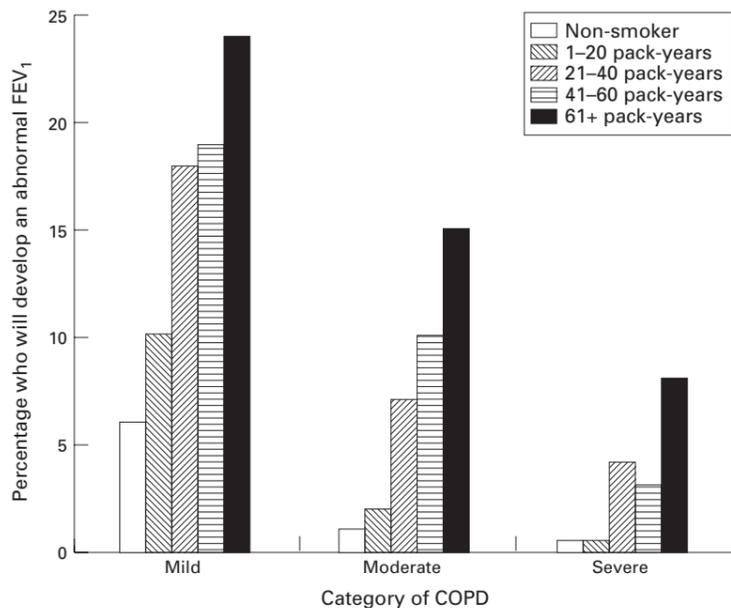


Figure 1 Proportion of individuals who will develop each grade of airways obstruction for each of five different levels of cigarette consumption. Reproduced from Burrows *et al* with permission.

tobacco exposure, the greater the risk of developing COPD (fig 1).⁶ Smoking dominates all other aetiological factors. A small additional contribution to the severity of COPD has been reported in patients who work in dusty environments^{7,8} or those who live in cities.⁹ However, these effects remain contentious. Deficiency of α_1 -antitrypsin, an antiprotease enzyme, is associated with emphysema in non-smokers but the risks of this are greatly magnified in enzyme-deficient subjects who smoke.¹⁰ Other currently proposed risk factors include poor nutrition in utero¹¹ and pre-existing bronchial hyperresponsiveness.^{12,13}

Fletcher and colleagues^{14,15} showed that, while chronic bronchitis and progressive airways obstruction were both related to inhaling cigarette smoke, the two conditions were distinct with respect to prognosis. Sputum production without airways obstruction is not associated with increased mortality^{2,14} and, if

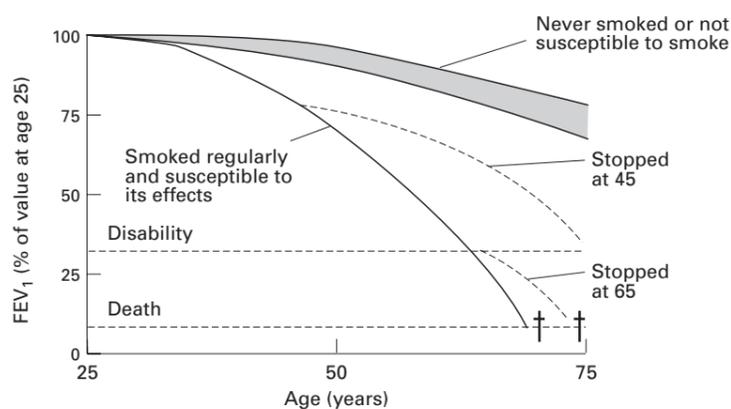


Figure 2 Model of annual decline in FEV₁ with accelerated decline in susceptible smokers. On stopping smoking subsequent loss is similar to that in healthy non-smokers. Modified from Fletcher and Peto.¹⁵

the smoker stops smoking, in 90% of cases the sputum production will cease.¹⁶

The best guide to the progression of COPD is the change in FEV₁ over time (fig 2). FEV₁ declines with normal ageing at about 30 ml/year and this increases to an average of 45 ml/year in smokers.¹⁴ However, the individual susceptibility to cigarette smoking is very wide, such that approximately 15% of smokers will develop clinically significant COPD whilst approximately half will never develop any symptomatic physiological deficit.¹⁶

The prognosis is inversely related to the age of the patient and directly to the FEV₁,¹⁸⁻²⁰ with the post-bronchodilator FEV₁ correlating better with survival than the pre-bronchodilator value.² Thus, three year survival figures have been estimated as²¹:

- aged <60 and FEV₁ >50% predicted = 90%
- aged >60 and FEV₁ >50% predicted = 80%
- aged >60 and FEV₁ 40-49% predicted = 75%

A community survey of COPD in Tucson, Arizona²² showed that the fall in FEV₁ in COPD was 70 ml per year with a 10 year survival of about 30%. Patients with atopy had a significantly better survival than did irreversible non-atopic patients.

Stopping smoking produces only small improvements in the FEV₁ but the subsequent fall in FEV₁ slows to the rate of 30 ml/year found in healthy non-smokers.^{2,17} There is no evidence that acute exacerbations of COPD lead to an increasing rate of decline in FEV₁. The effect of the FEV₁ on prognosis is seen in all grades of severity of COPD.

No drug treatment has been shown to affect the natural history of COPD. The Lung Health Study¹⁷ showed that treatment with ipratropium had a small but significant beneficial effect on FEV₁ whilst the treatment was continued, but that there was no effect on the five year decline in FEV₁. Prospective studies of the effect of long term inhaled steroids on the decline in FEV₁ are expected to report over the next two years.

With severe disease hypoxaemia develops with an increase in pulmonary artery pressure leading to the development of right ventricular hypertrophy or cor pulmonale. Pulmonary hypertension in COPD is slowly progressive²³ and its presence implies a poor prognosis,²⁴ although it may not have a direct effect on mortality. Long term oxygen therapy is the only treatment known to improve the prognosis in patients with severe COPD and hypoxaemia.²⁵

Disease burden

In 1992 there were 26 033 deaths in England and Wales attributed to COPD, chronic bronchitis, or emphysema which accounts for 6.4% of all male and 3.9% of all female deaths. In comparison, 1791 died of asthma.²⁶

COPD is a major cause of morbidity with frequent use of both GP and hospital services.

The estimated annual health service workload due to chronic respiratory disease in an average UK health district of 250 000 people greatly exceeds that for asthma (table 1).²⁷

In a survey of all medical admissions to a UK health region 25% of admissions were due to respiratory diseases and over half of these were COPD.²⁸ A survey of medical and geriatric admissions to another UK region found that, for those aged 65–74 years, 7.3% of male and 3.2% of female admissions had COPD.²⁹ The use of health services increases steeply with age. In general practice annual consultation

Table 1 Annual health service workload due to chronic respiratory diseases in an average UK health district

	<i>Hospital admissions</i>	<i>Inpatient bed days</i>	<i>General practice consultations</i>
Chronic bronchitis, emphysema and COPD	680	9600	14 200
Asthma	410	1800	11 900

rates for COPD per 10 000 population rise from 417 at age 45–64 to 886 at age 65–74 and 1032 at age 75–84, values that are 2–4 times the equivalent rates for angina.³⁰

2

Diagnosis and management of stable COPD

The presence of symptoms can be extremely variable in patients with COPD; a firm diagnosis can only be made by objective measurement of airways obstruction with spirometric tests. COPD is a progressive disorder that necessarily passes through mild and moderate phases before becoming severe. Mild disease may be present in completely asymptomatic individuals. A patient who presents with severe disease has been “missed” by the health services earlier in the disease course. Table 2 summarises the main features of each stage; for fuller information please refer to the appropriate section. A justification of the spirometric levels used to define the degrees of severity appears in Appendix 1. Figure 3 summarises the range of therapies available for the treatment of COPD and the approximate stage in the illness when they may be introduced. Exacerbations of COPD do not represent a worsening of the underlying disease process producing COPD but are caused by the addition of a second (often infective) process to

the existing defect. The combination of the two problems often causes enough symptoms for the patient to ask for medical help.

Presentation

In patients with mild COPD there are few or no symptoms.³¹ A history of morning cough, recurrent respiratory infections, or shortness of breath on vigorous exertion or manual labour should alert the doctor to the possibility of COPD. Routine screening, especially of smokers, and occupational surveillance schemes can identify airways obstruction at an early stage before troublesome symptoms develop.

Moderate COPD can present with a wide range of respiratory symptoms although there are few clinical signs. There is no single typical pattern but possibilities include combinations of some or all of the following:

- cough and sputum production, especially if the sputum becomes discoloured;

The COPD Escalator

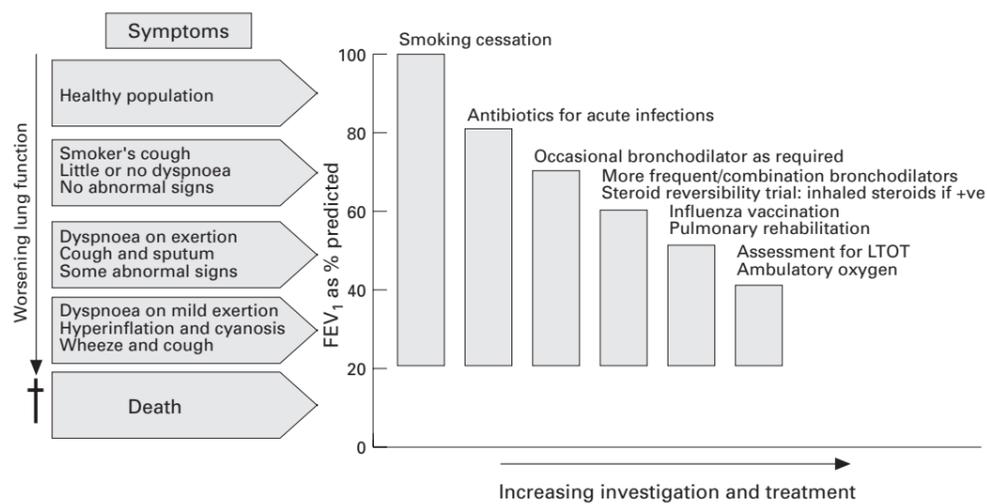


Figure 3 The COPD escalator. Summary of the principal components of a management plan for COPD. Note that, as disease severity increases, symptoms and signs become more obvious whilst the number of treatments used rises.

Table 2 Classification, diagnosis and management of COPD

	Clinical state	Results of measurements	Use of health care resources
Mild	Smoker's cough, but little or no breathlessness. No abnormal signs	FEV ₁ 60–79% predicted, FEV ₁ /VC and other indices of expiratory flow mildly reduced	Unknown – presymptomatic within the community
Moderate	Breathlessness (± wheeze) on exertion, cough (± sputum) and some abnormal signs	FEV ₁ 40–59% predicted, often with increased FRC and reduced TLCO. Some patients are hypoxaemic but not hypercapnic	Known to GP with intermittent complaints
Severe	Breathlessness on any exertion. Wheeze, cough prominent. Clinical overinflation usual, plus cyanosis, peripheral oedema and polycythaemia in some	FEV ₁ <40% predicted with marked overinflation. TLCO variable but often low. Hypoxaemia usual and hypercapnia in some	Likely to be known to hospital and by GP, with frequent problems and hospital admissions

- breathlessness (\pm wheeze) on moderate exertion such as physical work or climbing hills;
- acute worsening of symptoms associated with an infective exacerbation;
- routine screening of a patient who was either tolerating the symptoms as part of the normal ageing process or as an “expected” consequence of smoking – for example, “smoker’s cough”.

Patients with severe COPD are usually troubled by progressively disabling breathlessness or with complications (such as the development of oedema) or with an acute exacerbation with or without respiratory failure. Although usually severely breathless on minimal exertion or at rest, an individual patient’s perception of breathlessness varies considerably for the same degree of airflow limitation³² and this may be particularly poor in old age.³³ Cough and wheeze are almost invariably present but are poor predictors of severity. “Pink and puffing” and “blue and bloated” are clinical patterns which indicate, in the former, a patient who maintains relatively normal blood gas tensions until a late stage of the disease at the expense of severe breathlessness and, in the latter, a patient who develops hypoxaemia often with hypercapnia and pulmonary hypertension, cor pulmonale, and peripheral oedema. These terms describe a minority of patients at either end of the clinical spectrum. The terms do not differentiate between the “emphysematous and bronchitic” patient types and most patients lie between these extremes.

Assessment

HISTORY

In all patients assessment should include a clinical history and documentation of the smoking history (see box 2). A specific record of exercise tolerance should also be made in order to monitor future changes in breathlessness.

A past history of childhood wheeze or bronchitis, pertussis, atopy, pneumonia, and tuberculosis can each suggest alternative diagnoses.

EXAMINATION

Clinical examination and non-pulmonary investigations are likely to be normal in patients with mild disease. In patients with moderate disease the respiratory system may appear nor-

mal or there may be wheezes (rhonchi) or features of overinflation. The degree of airways obstruction cannot be predicted from symptoms or signs.³⁴

In patients with severe disease the following physical signs may be present. None is sufficiently diagnostic to remove the need for objective confirmation of the diagnosis.

- signs of chronic overinflation (loss of cardiac dullness, decreased cricosternal distance, increase in the AP diameter of the chest);
- rhonchi, especially on forced expiration;
- loss of weight is common but may also indicate occult carcinoma;
- central cyanosis, but its absence does not exclude minor degrees of hypoxaemia;
- flapping tremor, bounding pulse, drowsiness (signs of hypercapnia) may occur during acute exacerbations, but a high PaCO₂ can occur in patients with stable severe COPD without these signs;
- peripheral oedema may indicate the presence of cor pulmonale which is of prognostic significance;³⁵
- raised jugular venous pressure, right ventricular heave, loud pulmonary second sound, tricuspid regurgitation. These are signs associated with pulmonary hypertension but can be modified or masked by overinflation.

Investigations

ASSESSING AIRWAYS OBSTRUCTION WITH SPIROMETRIC TESTS

The diagnosis rests on objective demonstration of airways obstruction by spirometric testing. This test should be performed on all patients with suspected COPD, both to confirm the diagnosis and to plan appropriate treatment. Changes in FEV₁ occurring naturally or after treatment are distributed in absolute terms which can make interpretation of percentage changes in the bronchodilator response difficult. Further information on the physiology and how to measure FEV₁ are given in Appendix 1.

- An abnormal FEV₁ (<80% of predicted) with an FEV₁/VC ratio of <70% and little variability in serial peak expiratory flow (PEF) strongly suggests COPD.
- A normal FEV₁ effectively excludes the diagnosis.
- More than 20% variability in the absolute measurements of serial PEF may suggest asthma, but when PEF is low the spontaneous variability of the measurement may exceed this.
- A normal PEF (>80% predicted) does not exclude mild COPD and, in general, PEF underestimates the severity of COPD (see Appendix 1).

CHEST RADIOGRAPHY

A chest radiograph is not needed for the diagnosis of mild COPD and is only indicated if

Smoking history

The smoking history should include both the number smoked, for how long, and an estimate of total pack-years of smoking.
One pack of 20 cigarettes smoked per day for one year = one pack-year

Total pack-years =

$$\frac{(\text{No. cigarettes smoked/day})}{20} \times \text{no. years of smoking}$$

Box 2

another diagnosis is being considered. It is not possible to diagnose mild emphysema radiographically.³⁶ However, the incidence of co-existing diseases with moderate and severe COPD is relatively high so a chest radiograph at first presentation can help to identify emphysematous bullae and to exclude serious underlying diagnoses such as lung cancer which may have precipitated the presentation.

Repeat chest radiographs are not needed routinely but should be performed if new symptoms develop because there is an increased incidence of lung cancer in these patients.³⁷

REVERSIBILITY TESTING TO BRONCHODILATORS
Reversibility tests to bronchodilators (box 3) should be performed at all stages of COPD

Bronchodilator reversibility testing

The objectives of these tests are both diagnostic and prognostic

- to detect those whose FEV₁ increases substantially and are thus really asthmatic;
- to establish the post-bronchodilator FEV₁ which is the best predictor of long term prognosis.²

Tests should be performed when patients are clinically stable and free from infection. Patients should not have taken inhaled short acting bronchodilators in the previous six hours, long acting β agonists in the previous 12 hours, or sustained release theophyllines in the preceding 24 hours.

The preferred outcome measure is the change in FEV₁ because its reproducibility is well known and is greater than that of the PEF (see Appendix 1).

Response to bronchodilator

Spirometric values should be measured before and after an adequate dose of inhaled bronchodilator. The dose should be selected to be high on the dose/response curve and is usually given by nebuliser to be certain it has been inhaled. An alternative less convenient technique would be to give a similar dose with multiple inhalations from a metered dose inhaler and large volume spacer. A recommended dosage protocol would be:

- before and 15 minutes after 2.5–5 mg nebulised salbutamol or 5–10 mg terbutaline;
- before and 30 minutes after 500 μ g nebulised ipratropium bromide; or
- before and 30 minutes after both in combination.

Interpretation

- An increase in FEV₁ that is both greater than 200 ml and a 15% increase over the pre-bronchodilator value is significantly greater than the natural variability of the FEV₁^{40,41} and is the most established definition of reversibility.
- The post-bronchodilator FEV₁ provides information about prognosis and can be used as a marker against which to assess future treatment.
- A negative FEV₁ response does not preclude benefit from bronchodilators in terms of improved walking distance or a reduction in the perception of breathlessness.

Box 3

Corticosteroid reversibility testing

Response to corticosteroids

Spirometric values should be measured before and at the end of a course of oral prednisolone (e.g. 30 mg per day) taken for two weeks, or a course of inhaled steroid (e.g. beclomethasone 500 μ g twice daily or equivalent) taken for six weeks.⁴⁵ The criteria for an FEV₁ response are as for bronchodilators.

A less studied alternative is to use the change in mean PEF measured over the first five days and last five days of the steroid course, accepting a rise of 20% in *mean* PEF as significant. Results of reversibility testing should be clearly documented in the notes and be easily available for future reference.⁴⁵

Interpretation

A positive response to corticosteroids justifies prescription of regular inhaled steroids. The response to bronchodilators or corticosteroids can set a target against which to compare future therapy.

Box 4

since even patients with severe airflow obstruction can demonstrate reversibility.³⁸ Patients who show a bronchodilator response are more likely to respond to a trial of oral or inhaled corticosteroids.³⁹

REVERSIBILITY TESTING TO CORTICOSTEROIDS

An oral corticosteroid reversibility study is usually not required in patients with mild disease who are using a bronchodilator for relief of symptoms up to once per day but should be performed in patients with mild disease with greater bronchodilator usage and in all patients with moderate or severe disease (box 4). Even patients with severe airflow obstruction can demonstrate reversibility.⁴²

Trials of oral corticosteroids will produce a significant spirometric response (defined as above) in 10–20% of patients with clinically stable COPD.⁴³ A response of 200 ml or more in FEV₁ after steroids suggests a better prognosis over five years.⁴⁴ Some patients will report a short term improvement in “well being” but, unlike the assessment of reversibility to β_2 agonists, the trial should not be considered positive unless lung function has also improved in view of possible long term side effects.

OTHER LUNG FUNCTION TESTS

In patients with mild and moderate COPD it is unlikely that any further investigations will be necessary. In those with severe disease the following tests may be useful.

Arterial blood gas tensions

Hypoxaemia and hypercapnia are common and measurement of arterial blood gas tensions should be considered in all patients with severe disease. Pulse oximetry may reduce the need for blood gas tension measurements if the SaO₂

is more than 92%,⁴⁶ but should not replace direct arterial blood sampling when the patient is deteriorating clinically or when complications develop.

CT scanning

CT scanning can be used to quantify the extent and distribution of emphysema. However, its clinical value is currently restricted to the assessment of bullous emphysema.⁴⁷

Electrocardiography

The electrocardiogram provides useful information about the presence of ischaemic heart disease but is an insensitive method of assessing right ventricular hypertrophy.⁴⁸ Electrocardiographic criteria for right ventricular hypertrophy are modified by overinflation.

Exercise tests

These are of no routine diagnostic value but may be useful as a marker of progress in structured rehabilitation programmes.

Haematology

Correction of unsuspected anaemia (from another cause) may improve the symptoms of COPD. Polycythaemia (haematocrit >47% in women or >52% in men) may be present and should not be assumed to be secondary without measurement of arterial blood gas tensions. Venesection may be considered if the packed cell volume is greater than 50%.³¹

Sputum

The routine culture of non-purulent sputum samples is unhelpful.

Management

STOPPING SMOKING

This is the single most important way of affecting outcome in patients at all stages of COPD.^{25,14}

Patients with mild or moderate disease should have the implications of their continued smoking explained to them. Those continuing to smoke are certain to lose FEV₁ at an accelerated rate that cannot be prevented by drug therapy, and worsening disability is highly likely.

Stopping smoking is just as important in severe COPD as at earlier stages of the disease.⁵ Although lost function cannot be restored, those who stop smoking will deteriorate more slowly and have a better chance of benefiting from treatments such as LTOT.⁴⁹

Even brief advice from health professionals can help patients to stop smoking (box 5). The reported success rate of different anti-smoking methods varies from 10% to 30%. Repeated advice and encouragement is often needed.

Drug therapy

BRONCHODILATORS

Bronchodilators are the cornerstone of symptomatic treatment for the reversible component of airways obstruction. They probably act by reducing bronchomotor tone and hence airway resistance in patients with COPD^{57,58} and by reducing the level of pulmonary overinflation. Inhaled agents given in small doses are as efficacious as oral preparations, have fewer side effects and are therefore preferred.

Single dose reversibility tests in the laboratory are useful in diagnosing COPD and for obtaining prognostic information from the post-bronchodilator FEV₁. However, such tests do not predict the degree of symptomatic benefit an individual will obtain from prolonged bronchodilator use.⁵⁹ The usefulness of a particular bronchodilator for any individual can only be assessed by a therapeutic trial, accepting either better lung function or subjective symptom improvement as end points. Bronchodilators can improve the FEV₁, FVC, or exercise tolerance independently of each other.⁶⁰ An increase in FVC does not reliably predict an improvement in symptoms.⁶⁰

Short acting β_2 adrenergic agonists

Short acting β_2 agonists have a relatively rapid onset of action and are recommended for use "as required" for symptom relief. Used before exercise they can increase exercise tolerance in some patients with COPD.⁶¹

Some patients (particularly the elderly) may prefer to take regular doses three or four times daily. Although concern has been expressed about a possible detrimental effect of regular β_2 agonist use in COPD,⁶² the evidence is not strong enough to advise against this practice. There is little evidence of tachyphylaxis to β_2 agonists in patients with COPD, but there is disagreement on whether older patients with COPD are less likely to respond to these agents.^{59,63}

Stopping smoking

- Smoking cessation reduces the accelerated rate of decline of FEV₁ (see fig 2).⁵¹
- Sudden cessation of smoking may have a better success rate than gradual reduction of cigarette intake.⁵²
- Medical advice and behavioural intervention⁵³ is effective in those with high motivation.
- Nicotine chewing gum⁵⁴ or nicotine skin patches are effective,⁵⁵ especially if used in conjunction with a smoking cessation clinic.
- Knowing that the patient has really stopped smoking may be useful especially for reinforcement. Several methods can be used – for example, monitoring of breath carbon monoxide levels, blood carboxyhaemoglobin estimation, or by measuring urinary cotinine levels.⁵⁶

Box 5

Long acting β_2 agonists

There is only limited evidence on the efficacy of long acting β_2 agonists in COPD.^{64 65} Until more data are available their use should be limited to patients with a demonstrable bronchodilator response to β_2 agonists and their use monitored by assessment of both symptoms and FEV₁.

Evidence is lacking to support the use of sustained release oral β_2 agonists in COPD.

Anticholinergic drugs

Most clinical studies suggest that anticholinergic drugs such as ipratropium bromide are as efficacious as β_2 agonists in patients with COPD,^{66 67} and some studies suggest a greater and more prolonged bronchodilator response than β_2 agonists.^{67 68} The addition of ipratropium to a β_2 agonist may enhance exercise tolerance more than can be achieved by either drug alone.⁶⁹

Delivery devices

Metered dose inhalers are the cheapest delivery device currently available. However, if the patient cannot use a metered dose inhaler correctly then a more expensive device is justifiable. A recent study showed that 76% of patients with COPD made important errors when using their metered dose inhaler whilst 10–40% made similar errors with a dry powder inhaler, depending on the device used.⁷⁰ Inhaler technique must be demonstrated to the patient before prescribing inhalers and should be rechecked before changing or modifying inhaled treatments.

Home nebuliser therapy

There is controversy over the use of home nebuliser treatment in patients with COPD.^{70 71} Most patients can be treated with bronchodilators delivered by metered dose inhalers and spacers or by dry powder devices. A few with severe disease may benefit from high dose bronchodilator treatment⁷² which is more conveniently given by a nebuliser. The results of clinical trials comparing metered dose inhalers and nebulisers in stable patients with COPD are inconsistent.^{73 74} Treatment is expensive and may have important side effects.

Nebulisers should only be supplied to patients who have been assessed fully by a respiratory physician who is able to advise on the risk/cost benefit. The assessment should include ensuring that the diagnosis is correct, that optimal use has been made of metered dose and dry powder inhalers, that patients respond to the nebuliser, and that drugs should be preceded by a home trial with peak expiratory flow measurements.⁷⁵ An appropriate regime is contained in the BTS guidelines for nebuliser therapy.⁷⁶ These guidelines stress the need for adequate technical support and follow up to be available whenever a home nebuliser is prescribed.

There is no general agreement as to whether regular use (four times daily) or “as required

up to four times daily” treatment should be used. Dosage regimes should be tailored to individual patient’s needs and to side effects.

Theophyllines

Theophyllines are only modest bronchodilators in COPD^{77 78} with a variable effect on exercise tolerance and symptoms^{79–83} which is only statistically significant at the upper end of the therapeutic range. Oral theophyllines have a slow onset of action. Sustained release preparations are preferred since they have more predictable pharmacokinetics.

Non-bronchodilator effects of theophylline in COPD include improving the strength and effectiveness of respiratory muscles which may explain the reported improvement in exercise tolerance in some patients. However, this and other non-bronchodilator effects – such as improved right ventricular performance, augmentation of respiratory drive, and anti-inflammatory actions – are of questionable clinical significance.

The therapeutic index of theophyllines is narrow and some patients experience side effects even within the therapeutic range.⁸⁴ Infection, hypoxia, smoking, and other drugs affect theophylline clearance and make the control of theophylline dosage difficult, necessitating measurement of plasma theophylline 4–6 hours after dosing.

These problems limit the value of theophyllines in COPD. The risk/benefit ratio has to be carefully considered in each patient and in most cases a trial of theophyllines is best reserved for patients in whom other treatments have failed to control symptoms adequately.

Which bronchodilator?

Beta agonists used “as required” can be tried first in view of their more rapid relief of symptoms. If β agonists do not control symptoms adequately or if regular maintenance therapy is desired, an anticholinergic can be added or substituted.

Combination bronchodilator therapy has the potential advantage of convenience and improved patient compliance. However, combinations of a β_2 agonist and an anticholinergic drug should only be used if the single drugs have been tried and have failed to give adequate symptom relief. Combinations should only be continued if there is good subjective or objective evidence of benefit. Symptom severity and subjective benefit as reported by the patient are better guides to improvement in quality of life than are short term changes in spirometric values after bronchodilators.

The addition of oral theophylline should only be considered if inhaled treatments have failed to provide adequate relief.

A summary of the use of bronchodilators at each stage of COPD is given in box 6.

CORTICOSTEROIDS

The presence of inflammatory changes in the airways of patients with COPD provides a

Bronchodilator therapy at each stage of COPD

At all stages patients must be taught how and when to use their treatments and there should be a review of treatments being prescribed for other conditions. Beta-blocking agents (including eyedrop formulations) should be avoided.

Patients with mild disease

- Patients with no symptoms – no drug treatment.
- Patients with symptoms – a *trial* of an inhaled β agonist *or* an anticholinergic taken as required by an appropriate inhaler device may be useful.⁸⁵ If these drugs are ineffective, they should be stopped.

Patients with moderate disease

- Symptomatic patients will benefit from inhaled bronchodilators.
- The level of treatment depends on the degree of symptoms and their effect on lifestyle.
- Most will be controlled on a single drug, a few will need combination treatment.
- Oral bronchodilators are not usually required.

Patients with severe disease

- Most will justify combination of β_2 agonist and anticholinergic bronchodilators if they derive increased benefit from this combination.
- Theophyllines can be tried but must be monitored for side effects.
- Some patients will request “stronger” therapy. The dose-response curve is limited by the maximum bronchodilation available. High dose treatment including nebulised drugs should only be prescribed after a formal assessment.

Box 6

rationale for the use of corticosteroids.⁸⁶ However, the relationship between these changes, pulmonary function, and the therapeutic response is not clearly established.^{87,88} The issue of whether a response to 30 mg of prednisolone over two weeks predicts a sustained improvement on lower maintenance oral doses or inhaled corticosteroids awaits further studies.⁴⁵ Uncontrolled retrospective studies in COPD suggest that long term oral corticosteroids may slow the decline in FEV₁^{89,90} but this treatment is not recommended in view of significant side effects from systemic corticosteroids. Preliminary data suggesting an improvement in FEV₁ and reduction in the decline in FEV₁ over one year of treatment with inhaled beclomethasone⁹¹ await confirmation in long term studies.

On present evidence, inhaled steroids (up to the equivalent of 1000 μ g beclomethasone, 800 μ g budesonide, or 500 μ g fluticasone/day) should be given to patients who show an objective response to corticosteroids, either oral or inhaled. Patients with substantial responses to an oral steroid trial justify treatment according to the guidelines on the management of chronic asthma.⁹² Those who do not respond should not continue on steroid therapy.

OTHER AGENTS

There is no evidence to support the use of prophylactic antibiotics given either continuously or intermittently in patients with COPD.

There is no role for other anti-inflammatory drugs such as sodium cromoglycate or nedocromil sodium, antihistamines, or mucolytics in COPD. Mucolytic drugs^{93,94} are used widely in continental Europe but are not in the National Formulary in the UK for use in COPD, since trials of their effectiveness have produced variable results.^{94,95} Further studies are required before these drugs can be recommended. Other drugs such as the respiratory stimulant almitrine (not presently licensed in the UK) are of interest^{96,97} but side effects have precluded their use.

It is unclear whether the mild increase in pulmonary arterial pressure which is slowly progressive in most patients with stable COPD has a causal association with mortality or is merely a reflection of the severity of the disease.⁹⁸ There is no evidence that pulmonary vasodilators have any role in patients with COPD and pulmonary hypertension.⁹⁸

Other aspects of management

EXERCISE

Since patients with mild disease have few symptoms, they should be encouraged to continue with all their usual activities which will include all but the most strenuous jobs. Exercise is both safe and desirable. In patients with moderate and severe COPD exercise should be encouraged within the limitations of their airways obstruction. Breathlessness on exertion may be distressing to some patients but is not dangerous and many patients can continue their activities and interests in spite of their impairment.⁹⁹ Patients with moderate COPD can often continue in employment as long as it does not involve heavy manual work.

NUTRITION

Weight reduction in obese patients will reduce the energy requirements of exercise and thus improve the ability of patients to cope with their disability. Appropriate dietary advice and support should be offered.

Malnutrition is common in patients with severe COPD and may contribute to mortality.^{100,101} Although nutritional support for patients with COPD seems logical, controlled trials of its effect on morbidity, quality of life, hospital admissions, and mortality are not available. Selection criteria for patients and a cost-benefit analysis is needed before this treatment can be recommended.

VACCINATION

Influenza vaccine is recommended for chronic respiratory diseases including COPD,¹⁰² but studies to show the relative efficacy of influenza vaccine in mild, moderate, and severe COPD are lacking. Patients who are elderly (but not specifically having COPD) have been shown

to have a 70% reduction in mortality from influenza following vaccination.¹⁰³ This implies that vaccination in severe COPD is likely to be effective. Further studies specific to mild and moderate COPD are needed.¹⁰⁴ Pneumococcal vaccine is available and the current capsular polyvalent polysaccharide may be of value,¹⁰⁵ but no studies specific to COPD have been performed so it cannot yet be formally recommended.

Additional management primarily for those with severe COPD

TREATMENT OF DYSPNOEA

Breathlessness can be assessed clinically from the patient's ability to perform specific tasks – for example, climbing stairs, shopping, or walking around the house – and can be quantified using a visual analogue scale or the Borg scale.¹⁰⁶ These are useful for short term assessments such as the effects of a drug. More detailed information about the long term effects of breathlessness can be obtained using quality of life scores¹⁰⁷⁻⁹ or specific breathlessness questionnaires such as the baseline and transitional dyspnoea indices.¹¹⁰

Bronchodilators are the most effective treatment for breathlessness and can improve exercise tolerance even in patients without measurable bronchodilatation.¹¹¹

Short bursts of oxygen from a cylinder via a face mask are widely prescribed to relieve breathlessness. There are no data to support or refute this practice, but good data are available on the use of long term oxygen therapy (see below).

Other drugs such as dihydrocodeine,^{112 113} diazepam,¹¹⁴ and nebulised morphine have been studied but with unconvincing or negative results. Such sedatives are potentially unsafe, are generally poorly tolerated, and are not recommended for routine use. However, some patients in the terminal stages may benefit from management similar to that used for malignant disease, using sedatives to control intolerable symptoms. Such decisions require expert opinion and assessment.

PULMONARY REHABILITATION

Rehabilitation has been defined as “the restoration of the individual to the fullest medical, mental, emotional, social and vocational potential of which he/she is capable”.¹¹⁵ The rationale behind pulmonary rehabilitation is to prevent deconditioning and to allow the patient to cope with his/her disease.¹¹⁶ It is essential that treatment directed at reversible airflow limitation is optimised before considering rehabilitation. Rehabilitation has been shown to be effective in prospective randomised clinical studies^{117 118} and in a recent meta-analysis of the literature.¹¹⁹

Outcomes of rehabilitation programmes include measuring improvement in lung function or exercise tolerance, although benefit may not always be apparent in these variables.¹²⁰ Psychosocial factors contribute to disability in

COPD.¹²¹ Quality of life assessment is important in assessing the outcome and is most easily measured by a health profile questionnaire.¹⁰⁶ The outcome should also be assessed in terms of the longevity of benefit and an analysis of the cost-benefit ratio.¹²² Patient compliance with the programme should also be addressed.

Meta-analysis of studies of respiratory muscle training alone has provided little evidence of a clinically important benefit in COPD.¹²³

Patients with moderate to severe COPD may be considered for pulmonary rehabilitation programmes. Rehabilitation protocols are currently being developed and evaluated in the UK and are predominantly hospital based. Although some patients undoubtedly benefit from rehabilitation, facilities are limited and, until more UK data are available, firm recommendations as to who should be treated cannot be made.

Teaching patients about their disease is part of all rehabilitation protocols, and all patients may benefit from fuller explanation of the disease processes, the effects of treatment, how and when to use inhalers, and when to ask for help. Many patients with severe COPD are dependent on relatives and carers who also need to know what they can expect from and ask of the patient.

LONG TERM OXYGEN THERAPY

Two trials of long term oxygen therapy (LTOT) in patients with COPD and chronic hypoxaemia^{124 125} showed:

- improved survival – in the MRC study five year survival improved from 25% to 41% with 15 hours of oxygen therapy per day;
- less secondary polycythemia;
- prevention of progression of pulmonary hypertension;
- an improvement in neuropsychological health.

These studies have been used to produce UK recommendations as to which patients should be prescribed oxygen concentrators¹²⁶ (see box 7). When home oxygen is arranged, the type of facility (concentrator and/or portable oxygen) and the recommended flow rate should be recorded.

The long term survival in patients with COPD on LTOT is inversely related to the FEV₁. A long term follow up of patients on LTOT showed that survival improved to 62% at five years, but was only 26% at 10 years.²⁵ The progressive disturbances in the pulmonary circulation were arrested in this cohort but the accelerated late mortality was still associated with the severity of the airflow obstruction. For a very few patients with nasal problems, or in those with refractory hypoxaemia or severe desaturation on exercise, continuous oxygen can be delivered by the more technically difficult transtracheal route.¹²⁷

Prescription of LTOT¹²⁶

- In England and Wales LTOT can be prescribed by the general practitioner but it is recommended that all patients considered for LTOT are assessed by a respiratory physician. In Scotland LTOT is prescribed only by respiratory physicians.
- Arterial blood gas measurements should be made when the patient is clinically stable and on optimal medical treatment, on at least two occasions three weeks apart. Failure to do this results in the inappropriate prescription of domiciliary oxygen.^{128 129}
- Patients with COPD who have a P_{aO_2} of <7.3 kPa, with or without hypercapnia, and an FEV_1 of <1.5 litres should receive LTOT.
- If the P_{aO_2} is between 7.3 and 8.0 kPa and there is evidence of pulmonary hypertension, peripheral oedema or nocturnal hypoxaemia, LTOT should be considered. Patients prescribed LTOT should have stopped smoking because benefit is unlikely in continuing smokers,⁵ and because oxygen and smoking can be dangerous.
- Blood gas tensions should be measured with supplemental oxygen to ensure that the set flow is achieving a P_{aO_2} of >8 kPa without an unacceptable rise in P_{aCO_2} .
- LTOT must be given for at least 15 hours daily to achieve benefit.^{124 125} LTOT is best provided by an oxygen concentrator and nasal prongs. The oxygen concentrator should be set at a flow of 2–4 l/min depending on the blood gas assessments.
- Studies have highlighted problems with the use of LTOT and emphasise the need for six monthly follow up and re-assessment which can be best arranged by a respiratory health worker visiting the patient's home.¹³⁰

Box 7

AMBULATORY OXYGEN THERAPY

Ambulatory oxygen therapy can improve exercise tolerance and breathlessness and may allow greater compliance and longer hours of usage of LTOT. Improvement with ambulatory oxygen therapy may be related to the degree of arterial oxygen desaturation on exercise.¹³¹

Portable cylinders are the only form of ambulatory oxygen therapy available in the UK and provide two hours of use at 2 l/min. Liquid oxygen is not available at present on prescription in the UK. There are no firm criteria for selecting patients for ambulatory oxygen therapy. However, it has been suggested that prescriptions should be based on a documented fall in arterial oxygen saturation of more than 4%, below 90% on a standard walking test, and associated with an improvement in exercise tolerance or breathlessness with ambulatory oxygen therapy.¹³¹ However, good evidence to support this is lacking.

SURGERY IN THE MANAGEMENT OF COPD

Surgical treatments are applicable for a very small number of patients with COPD. Full specialist physiological assessment is mandatory and many assessed will be turned down. In selected patients, particularly those who are

young with α_1 -antitrypsin deficiency, lung transplantation (usually single lung) may be recommended¹³² but problems with late bronchiolitis obliterans after transplantation remain.¹³³

Surgical removal or ablation of expanding or very large bullae may be indicated in some patients¹³⁴ and can lead to prolonged improvements in FEV_1 . Recent reports from the USA have described lung volume reduction surgery (LVRS) in which various forms of surgical ablation of severely affected areas of emphysematous lung have been used. Indications are still evolving but LVRS would seem to be most applicable to patients with severe disease in whom there is a very marked increase in FRC and air trapping.¹³⁵

Other issues

DEPRESSION

Depression is very common, especially in advanced disease, and contributes to the perceived symptom intensity and social isolation. It can be treated with antidepressants.¹³⁶

TRAVEL

Many patients with severe COPD ask for advice about travel. The doctor should enquire about the detail of the proposed holiday and then assess the potential problems of the journey and whether the patient's needs can be met. Travel on land or by sea presents few problems provided that help is available for transfers at stations and ports. Aircraft are pressurised to the equivalent of 900–2400 metres above sea level which reduces the ambient PO_2 to 15–18 kPa.¹³⁷ Patients with COPD who are hypoxic at rest at sea level will become more hypoxic during a journey by air, although the clinical significance of this is not known.

Many patients with chest disease do travel successfully and most emergencies in flight are not respiratory.¹³⁸ Relative contraindications to travel include hypercapnia or gross hypoxia while breathing air (P_{aO_2} <6.7 kPa). A history of previous pneumothorax or the presence of emphysematous bullae suggests a risk of further pneumothorax as the poorly ventilated air spaces fail to respond to the changes in pressure, particularly on descent. Most major airlines, but not most charter operators, are able to supply supplementary oxygen as well as support to get dyspnoeic passengers to and from the aircraft if warned in advance.

The doctor should ensure that the patient has sufficient medication to last the holiday, and may consider providing an emergency supply of antibiotics in case of an exacerbation. Within the UK it is usually possible to make arrangements with a local chemist for a temporary supply of oxygen cylinders for patients on LTOT. However, many patients on LTOT can cope without their oxygen for short periods without detriment.

Health care costs

Within the European Community and a number of other countries costs of health care are met for all residents under reciprocal agree-

ments, but such agreements do not extend to North America and most private travel insurance will not cover an existing problem. The risk of receiving substantial medical bills will deter many patients from such travel.

REFERRAL FOR A SPECIALIST OPINION

A specialist opinion may be helpful at any stage of the disease. Referral may be to establish the diagnosis, to exclude other pathology, to reassure the patient, to reinforce the need to stop smoking, to optimise treatment, or to assess the need for the more complex and expensive therapies appropriate to severe COPD. The principal reasons are summarised in box 8.

Follow up of patients with stable COPD

MILD AND MODERATE DISEASE

Follow up of patients with mild or moderate COPD will usually take place in primary care and should include:

- highlighting in the case record the diagnosis of COPD and the values of spirometric tests performed at diagnosis;
- supervision of smoking cessation;
- documenting the effects of each drug treatment as it is tried;
- recording changes in spirometric parameters measured opportunistically at intervals.

A loss of 500 ml over five years will select out those rapidly progressing patients who may need specialist referral and investigation. Routine isolated PEF measurements are of little value because of the discordance between PEF and FEV₁ (see Appendix 1)

SEVERE DISEASE

Patients with severe COPD are likely to have frequent exacerbations leading to hospital admissions. They often have complex problems with co-morbidities, may be on high levels of

Indications for specialist referral	
<i>Reason</i>	<i>Purpose</i>
Therapeutic advice:	
Suspected severe COPD	Confirm diagnosis and optimise therapy
Onset of cor pulmonale	Confirm diagnosis and optimise therapy
Assessment for oxygen therapy	Optimise therapy and measure blood gases
Assessment for nebuliser therapy	Exclude inappropriate prescriptions
Assessment for oral corticosteroids	Justify need for long term treatment or to supervise withdrawal
Bullous lung disease	Identify candidates for surgery
A rapid decline in FEV ₁	Encourage early intervention
Diagnostic advice:	
Aged under 40 years or a family history of α_1 -antitrypsin deficiency	Identify α_1 -antitrypsin deficiency, consider therapy and screen family
Uncertain diagnosis	Make a diagnosis
Symptoms disproportionate to lung function deficit	Look for other explanations
Frequent infections	Exclude bronchiectasis

Box 8

treatment, and need monitoring for LTOT. Shared care between the hospital and GP is the usual pattern although there are no data to show how care should be provided to achieve the best combination of clinical and cost effectiveness. All of the recommendations for mild/moderate disease apply and, in addition, the Royal College of Physicians has suggested that respiratory health worker posts are created to help with the management of patients with chronic respiratory diseases.¹³⁹ Their duties should include visiting the patient at home to advise on both psychosocial and respiratory problems and to improve compliance with treatment.¹⁴⁰

3

Management of acute exacerbations of COPD

Presentation

Acute exacerbations of COPD present as a worsening of the previous stable situation.¹⁴¹ Important symptoms include:

- increased sputum purulence
- increased sputum volume
- increased dyspnoea
- increased wheeze
- chest tightness
- fluid retention.

The exacerbation is a new respiratory event or complication superimposed upon established COPD. The new event in COPD is most often an infection but can also be the development of peripheral oedema. Differential diagnoses to be considered in each patient include:

- pneumonia
- pneumothorax
- left ventricular failure/pulmonary oedema
- pulmonary embolus
- lung cancer
- upper airway obstruction.

Management of an acute exacerbation in the community

ASSESSMENT

Many patients can be managed at home but some require inpatient support and the decision whether or not to admit is complicated (see box 9).

A confident diagnosis of an exacerbation of COPD in a patient who does not need admission and who responds to treatment does not require further acute investigations.

TREATMENT IN GENERAL PRACTICE

The principles of managing acute exacerbations of COPD in general practice are summarised in box 10.

Antibiotics

These are widely used but have been shown to be effective only if the patient has at least two of the three features shown in box 10.¹⁴² A maximum of seven days of treatment is sufficient. The choice of antibiotic should follow locally produced guidelines derived from local bacteriological sensitivity data. Recently in-

Deciding whether to treat an acute exacerbation at home or in hospital

	<i>Treat at home</i>	<i>Treat in hospital</i>
Ability to cope at home	Yes	No
Breathlessness	Mild	Severe
General condition	Good	Poor – deteriorating
Level of activity	Good	Poor/confined to bed
Cyanosis	No	Yes
Worsening peripheral oedema	No	Yes
Level of consciousness	Normal	Impaired
Already receiving LTOT	No	Yes
Social circumstances	Good	Living alone/not coping
Acute confusion	No	Yes
Rapid rate of onset	No	Yes
Also available at hospital		
Changes on the chest radiograph	No	Present
Arterial pH level	≥ 7.35	<7.35
Arterial PaO ₂	≥ 7 kPa	<7 kPa

The more of the referral indicators that are present, the more likely the need for admission to hospital.

Box 9

roduced expensive new brands are not usually appropriate.

BRONCHODILATORS

Beta agonists and/or anticholinergic drugs should be added to the treatment regimen or the dosage increased if there is evidence of worsening airflow obstruction. The inhaled route is preferable, but the doctor should ensure that the patient has a device he or she can use effectively. Nebulisers are usually not required.¹⁴³

Management of the acute exacerbation

- 1 Add or increase bronchodilators (consider if inhaler device and technique are appropriate)
- 2 Antibiotic if two or more of:
 - increased breathlessness
 - increased sputum volume
 - development of purulent sputum
- 3 Oral corticosteroids in some cases (see text).

Box 10

CORTICOSTEROIDS

Oral corticosteroids should not be used for acute exacerbations in the community unless:

- the patient is already on oral corticosteroids;
- there is a previously documented response to oral corticosteroids;
- the airflow obstruction fails to respond to an increase in bronchodilator dose;
- this is the first presentation of airflow obstruction.

Oral corticosteroids are given usually in a dose of 30 mg per day for one week. They should not normally be continued long term. There is a need for further research into the place of oral corticosteroids in the context of an acute exacerbation of COPD.

FOLLOW UP OF THE ACUTE EPISODE MANAGED AT HOME

A further review after an acute exacerbation is merited if the patient fails to respond fully to treatment when a chest radiograph and possibly hospital referral may be indicated. The follow up visit represents an opportunity to help the patient to plan for the future and to try to prevent further exacerbations. Advice on smoking, lifestyle, activity levels and weight, and a review of medication should follow the recommendations for the management of stable COPD described above.

Management of an acute exacerbation of COPD in hospital**ASSESSMENT IN THE ACCIDENT AND EMERGENCY DEPARTMENT**

Patients may self-refer or be referred by their GP. The same indicators as in the previous section (see box 9) apply in deciding whether the patient should be admitted or discharged home directly. The indicators will have differing importance for different patients.

If a patient is to be discharged directly from the Accident & Emergency department the following extra safeguards should be considered:

- the patient should have adequate support to be able to cope at home;
- the patient (or carer) should understand the treatment prescribed and the use of any delivery devices;
- sufficient medication should be supplied to last until the next opportunity for consultation with the GP (or specialist).

The patient's GP should be informed of the visit to the Accident & Emergency department within 48 hours.

History

Particular note should be made of:

- the known exercise tolerance (which should include a careful record both of how in-

dependent the patient is under normal circumstances and during the exacerbation);

- current treatments, especially the use of nebulisers and LTOT;
- time course of the current exacerbation;
- the patient's social circumstances and quality of life, especially whether living alone/alone with support/with family plus an indication of the suitability of the accommodation;
- number of previous admissions in the past five years, including admissions to the intensive therapy unit;
- smoking history.

Signs

Signs suggesting a significant deterioration include those of infection (pyrexia, frankly purulent sputum), severe airways obstruction (audible wheeze, tachypnoea, use of accessory muscles), peripheral oedema, cyanosis and/or confusion.

INVESTIGATIONS ON ADMISSION

Urgent out of hours investigations should always include measurement of arterial blood gas tensions, noting the inspired oxygen concentration (F_{iO_2}), and a chest radiograph.

Investigations within the first 24 hours should include a full blood count, urea and electrolytes, and ECG. An initial FEV_1 and/or peak flow should be recorded and a serial peak flow chart started as soon as possible. If the sputum appears purulent, it should be sent for culture and if pneumonia is suspected, blood cultures are recommended.

It is probable that pulmonary emboli are more common than is usually recognised in severe COPD¹⁴⁴ but the benefit of prophylactic anticoagulation treatment has not been evaluated.

INITIAL TREATMENT**Oxygen (box 11)**

The aim of treatment with oxygen is to achieve a P_{aO_2} of at least 6.6 kPa without a fall in pH to below 7.26 (secondary to a rise in P_{aCO_2}).

Oxygen therapy

- In patients with a history of COPD aged 50 years or more, do not give an F_{iO_2} of more than 28% via a Venturi mask or 2 l/min via nasal cannulae until the arterial gas tensions are known.
- Check blood gases within 60 minutes of starting oxygen and within 60 minutes of a change in inspired oxygen concentration.
- If the P_{aO_2} is responding and the effect on pH is modest, increase the inspired concentration of oxygen until the P_{aO_2} is above 7.5 kPa.
- If the pH falls (secondary to a rise in P_{aCO_2}), consider alternative strategies.

Box 11

A pH below 7.26 is predictive of a poor outcome.¹⁴⁵ There is no evidence that humidification is necessary.

Patients may have been given oxygen in the ambulance or on arrival in the A & E department. For patients aged over 50 years the maximum initial inspiratory oxygen concentration should be 28% via a Venturi mask.¹⁴⁶ Venturi masks deliver the most predictable levels of inspired oxygen. Concentrations from nasal prongs are less predictable¹⁴⁷ but prongs are less easily dislodged and may be better tolerated.¹⁴⁸

If the patient is initially acidotic or hypercapnic measurement of blood gas tensions should be repeated within 60 minutes. If the inspired oxygen maintains or improves P_{aO_2} without causing a deterioration in pH, then the inspiratory concentration can be increased and the blood gas tensions rechecked until the P_{aO_2} is >7.5 kPa.¹⁴⁴ Monitoring by oximetry may be satisfactory if the arterial blood gas tension measurements have shown that the P_{aCO_2} and pH are both normal and the patient remains stable with no fall in S_{aO_2} .

Measurement of arterial blood gas tensions should be repeated at any time if the clinical situation deteriorates.

Bronchodilators

Nebulised bronchodilators should be given on arrival and at 4–6 hourly intervals thereafter^{149–151} but may be used more frequently if required (see also British Thoracic Society guidelines on nebuliser treatment⁷⁶). Many hospitals power nebulisers from a wall mounted oxygen supply but in patients with COPD the nebuliser should be driven by compressed air if the P_{aCO_2} is raised and/or there is a respiratory acidosis. Oxygen can continue to be given by nasal prongs at 1–2 l/min during nebulisation in order to prevent the fall in oxygen saturation that sometimes occurs with the use of nebulisers.

For moderate exacerbations a β agonist (salbutamol 2.5–5 mg or terbutaline 5–10 mg) or an anticholinergic drug (ipratropium bromide 0.25–0.5 mg) should be given. For severe exacerbations or if the response to either treatment alone is poor, then both may be administered.¹⁵² A response to nebulised bronchodilators in the acute situation does not imply long term benefit. Formal assessment after recovery from the acute episode is still required (see section on nebuliser treatment on page S11).

If the patient is not responding intravenous methylxanthines by continuous infusion (aminophylline 0.5 mg/kg per hour) should be considered. If given, blood levels of theophylline should be measured on a daily basis. There is, however, a paucity of evidence on the effectiveness of theophylline in this situation.¹⁵³

Nebulised bronchodilators should be continued for 24–48 hours or until the patient is improving clinically. Bronchodilators can then be given by metered dose aerosol or dry powder inhalers.

Antibiotics

The indications are the same as for exacerbations in general practice and should be

Choosing an antibiotic in acute exacerbations of COPD

- Common antibiotics will usually be adequate; the newest brands are rarely appropriate. Thus, amoxycillin or tetracycline are first choice unless used with poor response prior to admission.
- For more severe exacerbations, or if there is lack of response to the above agents, several second line alternatives can be considered including a broad spectrum cephalosporin or one of the newer macrolides.

Box 12

given if two or more of the three features described in box 10 are present. In addition, all patients with acute on chronic respiratory failure (pH <7.35) should receive antibiotics.

The three most likely pathogens in order of importance are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. Atypical pathogens are not usually a problem although evidence is emerging that *Chlamydia pneumoniae* may occasionally be found.¹⁵⁴

The choice of antibiotic depends on the local antibiotic policy and pattern of pathogens in the local laboratory, as well as on the antibiotic treatment prior to admission. Oral rather than intravenous antibiotics should be used unless there is a contraindication to oral treatment (see box 12 for a possible approach to antibiotic choice).

In severe exacerbations of COPD sputum culture and sensitivity may be of considerable value. If the chest radiograph shows evidence of pneumonia the patient should be treated according to the British Thoracic Society guidelines on pneumonia.¹⁵⁵

Corticosteroids

Whether systemic corticosteroids alter the course of an acute exacerbation in hospital remains unclear. One study reported benefit with methylprednisolone over 72 hours¹⁵⁶ but it is not known if these data extrapolate to benefits such as earlier discharge or extend to all COPD exacerbations in hospital. It is common practice to use a 7–14 day course of systemic corticosteroids (prednisolone 30 mg/day or 100 mg hydrocortisone if the oral route is not possible). This approach is certainly justified if:

- the patient is already on oral corticosteroids;
- there is a previously documented response to oral corticosteroids;
- the airflow obstruction fails to respond to an increase in bronchodilator dosage;
- this is the first presentation of airways obstruction.

Corticosteroids should be discontinued after the acute episode, usually after 7–14 days of treatment, unless they have been shown to be effective when the patient is clinically stable or there is a definite indication for long term treatment. Clinical improvement from an ex-

acerbation while on oral corticosteroids does not necessarily indicate the need for long term inhaled corticosteroids, the requirement for which should be assessed separately.

Diuretics

Diuretics are indicated if there is peripheral oedema and a raised jugular venous pressure.

Anticoagulants

The only firm recommendation that can be made is to follow the advice of the Thromboembolic Risk Factors Consensus Group who recommend prophylactic subcutaneous heparin for patients with acute on chronic respiratory failure.¹⁵⁷

Physiotherapy

There are few data to support or refute the use of chest physiotherapy to ease problems of sputum retention in acute exacerbations of COPD.¹⁵⁸ It is not recommended in acute on chronic respiratory failure.

Managing respiratory failure and the need for intermittent positive pressure ventilation (IPPV)

Ventilatory support, either as non-invasive intermittent positive pressure ventilation (NIPPV) or invasive intermittent positive pressure ventilation via an endotracheal tube (IPPV) should be considered in a patient with a pH of less than 7.26 and a rising PaCO₂ who fails to respond to supportive treatment and controlled oxygen therapy.¹⁴⁵

The specialist facilities for NIPPV support via nasal masks are only available in some hospitals at present. NIPPV has been shown in randomised controlled trials to reduce the number of patients requiring IPPV and the length of stay in hospital^{159,160} and to be of most value if used earlier than recommended above.^{161,162} Confused patients and those with a large volume of secretions are less likely to respond well to NIPPV.

The decision to institute or to withhold ventilatory support must be made by a senior person with as much information as possible about the patient's pre-morbid state. Factors to be considered are shown in box 13 and to these should be added the patient's wishes if known – for example, as in a living will – and those of close relatives.

Supportive therapy used to try to avoid the need for intubation and IPPV includes the use of intravenous doxapram and non-invasive respiratory support. If either is tried, the patient's condition needs to be closely monitored since a significant proportion will still need intubation and IPPV.

Doxapram, a respiratory stimulant, may be considered in patients with an acidosis (pH <7.26) and/or hypercapnia and hypoventilation.¹⁴⁵ It can tide the patient over for 24–36 hours until the underlying cause – for example, an infection – is controlled. The use

Factors to encourage use of IPPV

- A demonstrable remedial reason for current decline – for example, radiographic evidence of pneumonia or drug overdosage.
- The first episode of respiratory failure.
- An acceptable quality of life or habitual level of activity.

Factors likely to discourage use of IPPV

- Previously documented severe COPD that has been fully assessed and found to be unresponsive to relevant therapy.
- A poor quality of life – for example, being housebound, in spite of maximal appropriate therapy.
- Severe co-morbidities – for example, pulmonary oedema or neoplasia.

N.B. Neither age alone nor the PaCO₂ are a good guide to the outcome of assisted ventilation in hypercapnic respiratory failure due to COPD. A pH of >7.26 is a better predictor of survival during the acute episode.¹⁴⁵

Box 13

of doxapram may decline as the facilities for NIPPV increase.

Misconceptions about the difficulty of weaning from a ventilator should not preclude intubation and IPPV. The five year outcome of patients with COPD who suffer respiratory failure is better than many doctors appreciate and does not depend on the acute level of PaCO₂.¹⁶³ The mean survival of patients who were hypercapnic on admission but who later became normocapnic was 2.9 years.¹⁶³

Monitoring and management as the patient recovers

In addition to the routine hospital observations, the following should be considered:

- FEV₁ should be recorded before discharge from hospital;
- peak flow should be recorded twice daily until clinically stable;
- in patients presenting with hypercapnic respiratory failure and those with a low PaO₂ on admission the arterial blood gas tensions should be checked on air before discharge. This gives a guide to the need for later formal re-assessment for LTOT therapy.

As the clinical condition improves (less dyspnoea, better PEF, improved SaO₂) the nebulised bronchodilator can be changed to the patient's usual inhaler, ideally at least 24–48 hours before discharge. Antibiotics usually do not need to be continued for more than seven days. If oral corticosteroids have been used they can usually be stopped abruptly after seven days unless there are positive reasons for long term usage (see page S12).

Planning for discharge

Patients with severe COPD often have repeated hospital admissions. Discharge planning should

Table 3 Financial help available to patients with COPD in the UK

	Number of rates at which benefit is paid	Criteria for being eligible	Means tested	Special conditions
<i>Patients under 65 years:</i>				
Disability living allowance – mobility (DLA-M)	2	Ability to walk ● lower rate if can walk but need to be accompanied. ● higher rate if unable or virtually unable to walk.	No	Disabled for more than 3 months and needed for more than 6 months. If terminally ill, benefit can be obtained immediately.
Disability living allowance – personal care (DLA-P)	3	Ability to self care ● the highest and middle rates if care needed day and night.	No	As above
Disability working allowance (DWA)	1	Earning capacity limited	Yes	Must be working at least 16 hours per week and be receiving other benefits, renewable 6 months
Invalid care allowance (ICA)	1	Severe disability	No	Benefit to the carer who helps for more than 35 hours per week. Patient must be receiving DLA at middle or high rate
Industrial injuries disablement benefit	10 (and supplements also available)	Loss of physical ability (compared with person of same age and sex) ● due to an accepted industrial injury or prescribed disease.	No	Prescribed diseases include occupational asthma and, in coal miners only, COPD
Incapacity benefit	3	Physical ability but a concurrent depressive illness should not be overlooked.	No	Replaces sickness benefit after 6 months. Allows other benefits to be claimed. Severe cardiorespiratory failure usually exempts person from "all work test".
Severe disablement allowance	1 (and an age supplement)	Incapable of working for more than 196 days ● due to loss of physical ability (compared with person of same age and sex)	No	For those not able to receive incapacity benefit, who are 80% disabled or receiving DLA at high rate or war pension. Disability may need to be assessed by review of medical notes.
War disablement pension	Variable	Conditions aggravated by service in HM forces (during or within 7 years)	No	Contact War Pension hotline, 12 supplements available
Community care grant	Variable	Necessitates move to new accommodation or adaptation of current property	No	One off benefit from local authority
<i>Patients over 65 years:</i>				
Industrial injury benefit		As for under 65 years		
War pension		As for under 65 years		

aim to improve the ability of patients to cope within their limitations at home and to reduce the need for future admissions. A multi-disciplinary approach is needed to consider the following medical and social factors.

Medication

- A review of all medication (including non-respiratory treatments)
- Inhaler technique
- Ensuring that the patient knows how and when to take his/her medication
- For the few patients discharged on a nebuliser, the specific reasons for continuing nebulised treatment should be recorded.

Social factors and ability to manage at home

- Assessment of mobilisation and giving preliminary instruction in rehabilitation
- Assessment of home needs such as shopping, cleaning, obtaining medication, and provision of equipment to assist in daily living.
- Financial assessment: patients with COPD may be eligible for financial help from a number of different benefits.

SOCIAL AND FINANCIAL HELP

In the UK patients with COPD may be entitled to benefits from the Department of Social Security. The entitlement is related to the degree of disability of the patient, but the level of disability required before a claimant is entitled to benefit is not clearly defined. As a

guide any person whose exercise tolerance is less than 100 yards might be entitled to a benefit. When completing any application forms the applicant should always give the time taken to do any task mentioned on the form and also point out any other disability which might enhance the likelihood of a benefit being paid.

Benefits are divided into those available for patients above or below 65 years of age and a few that are independent of age such as mobility allowances and the orange badge scheme to help with car parking. A number of the benefits mentioned below have an additional mobility component which can be claimed including exemption from vehicle excise duty and concessions on rail fares. Most benefits go to the patient but a number are available to the carer.

The more important benefits and how they relate to severe COPD are outlined in table 3. Benefits are claimed through the Benefits Agency whose address and telephone number are available in the telephone directory. If a doctor receives a request for a report this should always describe how the patient is disabled and handicapped by the condition. Basic lung function results with measurements of reversibility are helpful in confirming a claim for disability. If in doubt, a Medical Advisor is available in all the regions of the UK.

ANTI-SMOKING ADVICE

For those still smoking before admission, advice should be repeated and documented.

OXYGEN THERAPY (AND NIPPV)

A decision to provide LTOT should not be made on the basis of hypoxia during the acute

episode alone (see management of stable COPD, page S13). Use of assisted ventilation (NIPPV) on a chronic basis is confined to a few specialist centres and is still being evaluated.

PATIENT EDUCATION

The patient should be fully informed about the nature of his/her condition and its treatment. It is probably useful for the patient to have a written record of the treatment, FEV₁ and PEF readings, and the usual level of PaO₂ and PaCO₂. Where possible, information leaflets such as those produced by the Breathe Easy Group of the British Lung Foundation should be provided. Discussion should include planning how the patient should respond to future episodes and who should be contacted.

Planned follow up in hospital or by general practitioner

Follow up arrangements are required for all patients 4–6 weeks after discharge. At the first follow up visit (either by a respiratory physician in the hospital outpatient department or by a GP with an interest in COPD) assessment should include:

- the patient's ability to cope;
- measurement of FEV₁;
- re-assessment of inhaler technique and of the patient's understanding of recommended treatment regime;
- in severe COPD the need for long term oxygen therapy and/or home nebuliser usage;
- advice on smoking cessation as necessary.

Follow up thereafter is as for stable COPD described on page S15.

Appendix 1: Physiology

Measurement of FEV₁

WHY IS THE FEV₁ THE MEASUREMENT OF CHOICE?

The FEV₁ is strongly recommended as the measurement of choice in COPD for the following reasons:

- It is a reproducible and objective measurement with well defined normal ranges that allow for the effects of age, race, and sex.
- It can be measured relatively easily and quickly and at all stages of the disease.
- The forced expiratory manoeuvre records not only FEV₁ but also FVC. An FEV₁/FVC ratio of less than 70% is diagnostic of airways obstruction. If the ratio is normal (>70%) and the test was performed well, the pattern is not obstructive and the diagnosis is not COPD. PEF measurements cannot differentiate whether values are low because of obstruction or restriction.
- The variance of repeated measurements in the same person is well documented and is low. In COPD the variability of the FEV₁ between testing occasions is of the same absolute order (about 170 ml).⁴¹ Hence, if values change by more than 200 ml it is unlikely that the difference is due to chance.
- Studies of mortality and of disability have shown that the FEV₁ predicts future mortality¹⁸⁻²² and relates best to the severity of breathlessness.
- The absolute value of the FEV₁ is better related to prognosis and disability than is the FEV₁/VC ratio. This may be because the measurement of VC in COPD is subject to error, especially when the expiratory manoeuvre is not continued for more than six seconds.⁴⁰
- Serial measurements provide evidence of the disease progression.
- In COPD the relationship between PEF and FEV₁ is poor and it is not possible to predict FEV₁ from the PEF or vice versa.¹⁶⁴
- PEF may underestimate the degree of airways obstruction in COPD.

Thus, FEV₁ is the measurement of choice. However, PEF may have some value when used serially in a single individual, especially in those with an asthmatic component to their COPD, and changes in mean PEF (recorded over several days) can be useful.

HOW SHOULD FEV₁ BE MEASURED?

Obtaining a spirometer

There are many competent spirometers available. Most cost less than an ECG machine and adhere to US recommended standards.¹⁶⁵ Some measure volume directly while others derive volume from the airflow. There are

varying degrees of computerised reports. The most important considerations when buying and using a spirometer are:

- the spirometer will need calibrating (volumetric devices weekly and flow based devices at least daily) with a three litre syringe;
- the spirometer should produce a hard copy of the tests which should be large enough for any computer reported values to be checked from the graphs. A volume/time plot is mandatory, a flow volume plot is optional. It should be possible to superimpose traces to compare easily the different attempts by an individual;
- a spirometer is of limited value without trained staff who are able to perform the test to the published standards.¹⁶⁵ Poorly trained staff can produce misleading results;
- electronic spirometers without a hard copy tracing may lead to underestimation of the FEV₁ and FVC because it is not possible to verify the reliability of the test.

Reporting the results

Before interpreting the test values the following criteria should be satisfied:

- there are at least three technically satisfactory readings;
- the expiratory volume/time traces are smooth, convex upwards, and free from irregularities that suggest either variable sub-maximal effort or coughing;
- there are at least two readings of FEV₁ that are within 100 ml or 5% of the other;
- the recording has been continued long enough for a volume plateau to be reached on the volume-time plot. This can take up to 15 seconds in patients with severe COPD. Abbreviated efforts will underestimate FVC.

The best FEV₁ and best FVC values should be reported as the result and compared with the predicted normal value (based on age, height and sex).⁴⁰

IMPLEMENTING THESE RECOMMENDATIONS

Since most general practices do not at present possess a spirometer and do not have trained technicians, some clear health service planning will be needed. Three options are:

1. To provide open access for general practice to the lung function laboratory at each district general hospital in a similar fashion to radiographic services. Some additional staffing would be needed, but the equipment and expertise and quality control are already in place in the hospital service.
2. To provide spirometry in individual practices. Many practices will be cautious of spending £1000 or more on equipment that will

not be heavily used and will have difficulty obtaining appropriate training for staff. The cost effectiveness of this will depend upon the size of the practice. In small practices adequate quality control of testing procedures will not be easy to achieve.

3. To provide a mobile community spirometry service. The cost effectiveness of this will need to be compared with either of the options above.

Justification of mild, moderate, and severe categorisation of COPD

COPD describes a spectrum of disease progressing from the earliest symptomless stages through to respiratory failure. The medical requirement of patients increases with increasing severity and the group considered that COPD could usefully be divided into three stages which approximated to their health care requirements. The precise boundaries chosen are inevitably rather arbitrary and were selected for the following reasons:

- Values of FEV₁ above 80% are within two standard residuals of the predicted mean⁴⁰ and, although it is possible for airway obstruction (FEV₁/VC ratio <70%) to be present if the VC is high, the clinical significance of this is probably marginal.
- Choice of 40% and 60% levels: the American Thoracic Society, in assessing levels of respiratory disability, adopted these levels as the indicators of mild, moderate, and severe respiratory disability.⁹⁹ Clinical studies of patients with COPD recruited from UK hospital outpatient departments have reported mean FEV₁ levels of about 35% of predicted,⁴⁴⁵ whereas a study of patients with COPD recruited from general practice had a mean FEV₁ of 50% predicted.⁶²
- The European Respiratory Society guidelines¹⁶⁶ also divide COPD into three categories of severity but have chosen 90%, 70%, and 50% as defining levels of FEV₁. In contrast, the American Thoracic Society document¹⁶⁷ has selected 80%, 50%, and 35% of predicted as their demarcation levels. They do not cite any further justification. These levels may reflect the different styles of medical practice in Europe and the United States, though precise demarcation remains arbitrary.

These data, coupled with the clinical experience of the Guidelines Committee, were considered sufficient to justify adopting the British definitions of mild, moderate, and severe disease.

Thus, the following severity ranges were established:

- Mild COPD: presymptomatic within the community and usually unknown to the doctor. This group is defined as having an FEV₁ of 60–79% of predicted with an abnormal FEV₁/FVC ratio of <70%.
- Moderate COPD: these patients will usually have presented to their GP with intermittent chest problems and may be finding work difficult. Their FEV₁ is 40–59% of predicted.
- Severe COPD: these patients are likely to have significant symptoms and to have intermittent admissions to hospital. Their FEV₁ is below 40% of predicted.

Other tests of respiratory function

Static lung volume measurement documents the degree of overinflation and may be useful when assessing patients for surgery (particularly thoracic surgery) and for research studies.

Diffusing capacity or gas transfer factor for carbon monoxide (TLCO) is said by some to be helpful in distinguishing asthma from emphysema and is recommended for that purpose in the European guidelines.¹⁶⁶ However, its value in planning treatment is less clear. The TLCO did not discriminate between patients who did or did not respond to an oral steroid trial.⁴

Static and dynamic compliance are not easy to measure and, although the latter may be abnormal even before there has been a detectable change in FEV₁, neither has been shown to be of practical clinical value. They remain research tools.

Bronchial hyperreactivity is characteristic of asthma. A degree of hyperreactivity is often seen in patients with COPD but whether this reflects the geometric effect of a reduced starting FEV₁ or is a true increase remains uncertain, as does its clinical role.

The above tests, together with others such as measurement of the ventilatory response to carbon dioxide and tests of respiratory muscle function, may all be useful when assessing the difficult patient or when evaluating new drugs or treatments.

Appendix 2: Pathology

Patients with COPD exhibit a variety of pathological changes throughout the bronchial tree and alveoli, reflecting differences in duration of exposure and response to cigarette smoke.¹⁶⁸ Changes in mucus gland thickness relate to sputum production but not to loss of respiratory function. Most airflow limitation is due to a combination of mechanical obstruction in the small airways and loss of pulmonary elastic recoil due to emphysema. In addition, reduction of the alveolar attachments around the walls of the small airways makes these airways more likely to collapse during expiration.

Emphysema is defined as a permanent destructive enlargement of the air spaces distal to the terminal bronchioles.¹⁶⁹ Smokers are prone to develop centriacinar emphysema where the respiratory bronchioles, alveolar ducts, and alveoli at the centre of the acinus are destroyed. Some subjects also develop panacinar emphysema where the whole of the acinus is destroyed.

Centriacinar emphysema is associated with more small airways disease and less loss of elastic recoil for any level of respiratory function.¹⁷⁰ Paraseptal emphysema occurs close to

connective tissue septae and usually leads to blebs on the lung surface which predispose to pneumothorax or to giant bullae within the lung substance.

The presence of inflammatory cells within the airway wall and lumen of both large and small airways provides a rationale for the use of anti-inflammatory treatment, at least in some cases.^{87 168} Airway eosinophilia is associated with a measurable bronchodilator response to β agonists and relatively less emphysema for any degree of airflow limitation.⁸⁷ Whether clinical markers of inflammation can identify such patients is still unclear, but past results are not encouraging.¹⁶⁸ Nonetheless, these pathological data confirm that bronchodilator reversibility is possible even in the presence of lung pathology thought to be irreversible.

Circulatory changes are confined to advanced disease when persistent arterial hypoxaemia has developed.¹⁴⁴ Pulmonary vascular remodelling is now thought to accompany medial thickening of the pulmonary arterial wall secondary to hypoxia and to explain why these changes do not resolve with long term oxygen therapy.¹⁷¹

Appendix 3: Health care provision for the management of COPD

Smoking cessation policies

Each health district should ensure that the implementation of anti-smoking strategies and policies is a prominent part of its health promotion programme.

District general hospitals should have

- a specified respiratory physician with responsibility for COPD;
- facilities for spirometric tests in all routine clinics and spirometric testing should also be available to patients from general practitioners;
- nursing staff on the wards who have received training in the assessment and management of patients with COPD;
- sufficient high dependency and, preferably, intensive care facilities to permit the management of patients with respiratory failure in hospitals accepting patients with acute exacerbations;
- a specialised respiratory nurse attached to each district hospital with responsibility for liaising over the care plans with primary care;
- care planning should involve physiotherapy, occupational therapy, respiratory rehabilitation staff, and social services;
- resources to develop respiratory rehabilitation and to provide assessments for long term oxygen treatment;
- a nebuliser service which includes patient assessment and equipment support;
- provision for terminal and respite care for patients with the most severe COPD.

In primary care

- if a practice does not have its own spirometer and the appropriately trained staff to use this an open access hospital referral service

should be established comparable to the general practice access to radiographic facilities;

- there will be a need for more practice nurses to cover the substantial unmet needs of COPD. These nurses will need formal training;
- "obstructive airway" clinics similar to asthma clinics may be worthwhile.

Justification for increased resources for COPD

FROM THE PATIENT'S VIEWPOINT

- The patient wants a definite diagnosis and a clear treatment plan that is consistent from all those involved in his/her health care.
- Many would like help with smoking cessation but cannot find such help at present.
- Patients would like to be informed about their condition and to be allowed to participate in the decisions leading to treatment choices.
- Patients would like to be cured but, as this is not possible, they want to maximise their quality of life.

POTENTIAL BENEFITS FOR THE PATIENT AND FOR THE HEALTH SERVICE

- Less smoking of cigarettes will result in less COPD in 10–15 years' time and also in fewer patients with mild/moderate disease reaching the severe stage at which most treatment and social support is needed. There would also be reductions in the incidence of lung cancer and coronary artery disease.
- Better hospital care combined with links with the community should reduce the number of readmissions for patients with severe COPD.
- Appropriate referral and hospital assessment should optimise the use of both domiciliary nebuliser and oxygen therapy.

References

- 1 Medical Research Council. Definition and classification of chronic bronchitis for clinical and epidemiological purposes. *Lancet* 1965;i:775-9.
- 2 Traver GA, Cline MG, Burrows B. Predictors of mortality in COPD. *Am Rev Respir Dis* 1979;119:895-902.
- 3 Thurlbeck WM. Chronic airflow obstruction in asthma. In: Bennington JL, ed. *Major problems in pathology* (Series No 5). Philadelphia: Saunders, 1976.
- 4 Nisar M, Walshaw MJ, Earis JE, Pearson MG, Calverley PMA. Assessment of airway reversibility of airway obstruction in patients with chronic obstructive airways disease. *Thorax* 1990;45:190-4.
- 5 Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years observations on male British doctors. *BMJ* 1994;309:901-10.
- 6 Burrows B, Knudson RJ, Cline MG, Lebowitz MD. Quantitative relationships between cigarette smoking and ventilatory function. *Am Rev Respir Dis* 1979;115:195-205.
- 7 Oxman AD, Muir DCF, Shannon HS, Stock SR, Hnizdo E, Lange HJ. Occupational dust exposure and chronic obstructive pulmonary disease. A systematic overview of the evidence. *Am Rev Respir Dis* 1993;148:38-48.
- 8 Korn RJ, Dockery DW, Speizer FE, Ware JH, Ferris BG Jr. Occupational exposures and chronic respiratory symptoms. A population-based study. *Am Rev Respir Dis* 1987;136:296-304.
- 9 Tashkin DP, Detels R, Simmons M, Liu H, Coulsen AH, Sayre J, et al. The UCLA population study of chronic obstructive respiratory disease: impact of air pollution and smoking on annual change in FEV₁. *Am J Respir Crit Care Med* 1994;149:1209-17.
- 10 Janus ED, Phillips NT, Carroll RW. Smoking, lung function and α_1 -antitrypsin deficiency. *Lancet* 1985;i:152-4.
- 11 Barker DJP, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive lung disease. *BMJ* 1991;303:671-5.
- 12 Postma DS, de Vries K, Koeter GK, Sluiter HJ. Independent influence of reversibility of airflow obstruction and non-specific bronchial hyperreactivity in chronic airflow obstruction. *Am Rev Respir Dis* 1986;134:276-80.
- 13 O'Connor GT, Sparrow D, Weiss ST. The role of allergy and non-specific airway hyper-responsiveness in the pathogenesis of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989;140:225-52.
- 14 Fletcher CM, Peto R, Tinker CM, Speizer FE. *The natural history of chronic bronchitis and emphysema*. Oxford: Oxford University Press, 1976.
- 15 Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977;1:1645-8.
- 16 Tashkin DP, Clark VA, Coulson AH, Simmons M, Bourque LB, Reems C, et al. The UCLA population studies of chronic obstructive respiratory disease. VIII. Effects of smoking cessation on lung function: a prospective study of a free-living population. *Am Rev Respir Dis* 1984;130:707-15.
- 17 Anthonisen NR. The Lung Health study: effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV₁. *JAMA* 1994;272:1497-505.
- 18 Burrows B. Predictors of cause and prognosis of obstructive lung diseases. *Eur Respir Rev* 1991;1:340-5.
- 19 Anthonisen NR, Wright EC, Hodgkin JE. IPPB Trial Group. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986;133:14-20.
- 20 Anthonisen NR. Prognosis in chronic obstructive pulmonary disease; results from multicenter clinical trials. *Am Rev Respir Dis* 1989;140:S95-9.
- 21 The Intermittent Positive Pressure Breathing Trial Group. Intermittent positive pressure breathing therapy of chronic obstructive pulmonary disease. *Ann Intern Med* 1983;99:612-20.
- 22 Burrows B. The course and prognosis of different types of chronic airflow limitation in a general population sample from Arizona: comparison with the Chicago "COPD" series. *Am Rev Respir Dis* 1989;140:S92-4.
- 23 Weitzblum E, Sautageau A, Ehrhart M, Mammosser M, Hirth C, Roegel E. Long term course of pulmonary arterial pressure in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1984;130:993-8.
- 24 Weitzblum E, Hirth C, Duclon A, Mirhom R, Rasaholjanahary J, Erhart M. Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. *Thorax* 1989;36:752-8.
- 25 Cooper CB, Waterhouse J, Howard P. Twelve year clinical study of patients with hypoxic cor pulmonale given long term domiciliary oxygen therapy. *Thorax* 1987;42:105-10.
- 26 Office of Population Censuses and Surveys. *Mortality statistics, cause: England and Wales 1992*. Series DH2 no. 19. London: HMSO, 1993.
- 27 Anderson HR, Esmail A, Hollowell J, et al. *Epidemiologically based needs assessment: lower respiratory disease*. London: Department of Health, 1994.
- 28 Pearson MG, Littler J, Davies PDO. An analysis of medical workload by speciality and diagnosis in Mersey: evidence of a specialist to patient mismatch. *J R Coll Phys* 1994;28:230-4.
- 29 Goldacre MJ, Ferguson JA. In-patient workload in medical specialities I. Demographic profiles and time trends from linked statistics. *Q J Med* 1995;88:649-60.
- 30 McCormick A, Fleming D, Charlton J. *Morbidity statistics from general practice: Fourth national study 1991-2*. London: Office of Population Censuses and Surveys, 1995.
- 31 Pearson MG, Calverley PMA. Clinical and laboratory assessment. In: Calverley PMA, Pride NB, eds. *Chronic obstructive pulmonary disease*. London: Chapman and Hall, 1994.
- 32 Wolkove N, Dajczman E, Colacone A, Kreisman H. The relationship between pulmonary function and dyspnoea in obstructive lung disease. *Chest* 1989;96:1247-51.
- 33 Connolly MJ, Crowley JJ, Charan NB, Neilson CP, Vestel RE. Reduced subjective awareness of bronchoconstriction by methacholine in elderly asthmatic and normal subjects as measured on a simple awareness scale. *Thorax* 1992;47:410-3.
- 34 Kesten S, Chapman KR. Physician perceptions and management of COPD. *Chest* 1993;104:254-8.
- 35 France AJ, Prescott RJ, Biernacki W, Muir AL, MacNee W. Does right ventricular function predict survival in patients with chronic obstructive pulmonary disease? *Thorax* 1988;43:621-6.
- 36 Thurlbeck WM, Simon G. Radiographic appearance of the chest in emphysema. *Am J Roentgenol* 1978;130:429-40.
- 37 Skillrid DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic pulmonary disease. A prospective matched case-controlled study. *Ann Intern Med* 1986;105:503-7.
- 38 Anthonisen NR, Wright EC, IPPB Trial Group. Bronchodilator response in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986;133:814-9.
- 39 Nisar M, Earis JE, Pearson MG, Calverley PMA. Acute bronchodilator trials in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992;146:555-9.
- 40 Quanjer PH. Standardised Lung Function Testing. Official Statement of the European Respiratory Society. *Eur Respir J* 1993;6(Suppl 16):5-40.
- 41 Tweeddale PM, Alexander F, McHardy GJR. Short term variability in FEV₁ and bronchodilator responsiveness in patients with obstructive ventilatory defects. *Thorax* 1987;42:87-90.
- 42 Anthonisen NR, Wright EC, IPPB Trial Group. Bronchodilator response in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986;133:814-9.
- 43 Callahan CM, Cittus RS, Katz BP. Oral corticosteroid therapy for patients with stable chronic obstructive pulmonary disease: a meta-analysis. *Ann Intern Med* 1991;114:216-23.
- 44 Rimmington LD, Spence DPS, Nisar M, Earis JE, Calverley PMA, Pearson MG. Predictors of 5 year mortality in COPD. *Am Rev Respir Dis* 1993;147:A323.
- 45 Weir DC, Gove RI, Robertson AS, Burge PS. Corticosteroid trials in non-asthmatic airflow obstruction: comparison of oral prednisolone and inhaled beclomethasone dipropionate. *Thorax* 1990;45:112-7.
- 46 Roberts CM, Bugler JR, Melchor R, Hetzel ML, Spiro SG. Value of pulse oximetry for long-term oxygen therapy requirement. *Eur Respir J* 1993;6:559-62.
- 47 Morgan MDL, Denison DM, Strickland B. Value of computed tomography for selecting patients with bullous emphysema. *Thorax* 1986;41:855-62.
- 48 Lehtonen J, Sutinen S, Ikaheimo M, Paakko P. Electrocardiographic criteria for the diagnosis of right ventricular hypertrophy verified at autopsy. *Chest* 1988;93:839-42.
- 49 Cooper CB. Domiciliary oxygen therapy. In: Calverley P, Pride N, eds. *Chronic obstructive pulmonary disease*. London: Chapman and Hall, 1995: 495-526.
- 50 Royal College of Physicians. *Health or smoking? Follow-up report*. London: Pitman, 1983.
- 51 US Department of Health and Human Services. *The health benefits of smoking cessation. A report of the Surgeon General*. Washington: US Government Printing Office, 1989.
- 52 Flaxman J. Quitting smoking now or later: gradual, abrupt, immediate, and delayed quitting. *Behav Ther* 1978;9:240-70.
- 53 Hajek P. Withdrawal-orientated therapy for smokers. *Br J Addict* 1989;84:591-8.
- 54 Lam W, Sze PC, Sacks HS, Chalmers TC. Meta-analysis of randomised controlled trials of nicotine chewing gum. *Lancet* 1987;ii:27-30.
- 55 Russell MAH, Stapleton JA, Feyerabend C, Wiseman SM, Gustavsson G, Sawe U, et al. Targeting heavy smokers in general practice: randomised controlled trial of transdermal nicotine patches. *BMJ* 1993;306:1308-12.
- 56 Jamrozik K, Vessey M, Fowler G, Wald N, Parker G, Van Vunakis H. Controlled trial of three different antismoking interventions in general practice. *BMJ* 1984;288:1499-503.
- 57 Gross NJ, Co E, Skorodin MS. Cholinergic bronchomotor tone in COPD: estimates of its amount in comparison with that in normal subjects. *Chest* 1989;96:984-7.
- 58 Gross NJ, Skorodin MS. Anti-cholinergic, anti-muscarinic bronchodilators. *Am Rev Respir Dis* 1984;139:1185-91.
- 59 Guyatt GH, Townsend M, Nogradi S, Pugsley SO, Keller JL, Newhouse MT. Acute response to bronchodilator.

- An imperfect guide for bronchodilator therapy in chronic airflow limitation. *Arch Intern Med* 1988;148:1949-52.
- 60 Berger R, Smith D. Effect of inhaled metaproterenol on exercise performance in patients with stable 'fixed' airway obstruction. *Am Rev Respir Dis* 1988;138:626-9.
- 61 Corris PA, Neville E, Nariman S, Gibson GJ. Dose-response study of inhaled salbutamol powder in chronic airflow obstruction. *Thorax* 1983;39:292-6.
- 62 Van Schayck CP, Dompeling E, van Herwaarden CLA, Folgering H, Verbeek AL, van Der Hoogen HJ. Bronchodilator treatment in moderate asthma or chronic bronchitis: continuous or on demand. A randomised controlled study. *BMJ* 1991;303:1426-31.
- 63 Nisar M, Earis JE, Pearson MG, Calverley PMA. Acute bronchodilator trials in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992;146:555-9.
- 64 Ulrik CS. Efficacy of inhaled salmeterol in the management of smokers with chronic obstructive pulmonary disease: a single centre randomised, double blind, placebo controlled cross-over study. *Thorax* 1995;50:750-4.
- 65 Grove A, Lipworth BJ, Reid P, Smith RP, Ramage L, Ingram CG, et al. Effects of regular salmeterol on lung function and exercise capacity in patients with chronic obstructive airways disease. *Thorax* 1996;51:689-93.
- 66 Braun SR, McKenzie WN, Copeland C, Knight L, Eilersieck M. A comparison of the effect of ipratropium and albuterol in the treatment of chronic airways disease. *Arch Intern Med* 1989;149:544-7.
- 67 Tashkin DP, Ashutosh K, Bleeker ER, Britt EJ, Cuzell DW, Cumiskey JM. Comparison of the anti-cholinergic bronchodilator ipratropium bromide with metaproterenol in chronic obstructive pulmonary disease: a multicentre study. *Am J Med* 1986;81(Suppl 5a):61-5.
- 68 The Combivent inhalation aerosol study. Combination of ipratropium and albuterol is more effective than either agent alone. *Chest* 1994;105:1411-9.
- 69 Leitch AG, Hopkin JM, Ellis DA, Merchant S, McHardy GJ. The effect of aerosol ipratropium bromide and salbutamol on exercise tolerance in chronic bronchitis. *Thorax* 1978;33:711-3.
- 70 Van der Palen J, Klein JJ, Kerckhoff AHM, van Herwaarden CLA. Evaluation of the effectiveness of four different inhalers in patients with chronic obstructive pulmonary disease. *Thorax* 1995;50:1183-7.
- 71 Newhouse M, Dolovich M. Aerosol therapy: nebuliser vs metered dose inhaler. *Chest* 1987;91:799-80.
- 72 Gross NJ, Petty TL, Friedman M, Skorodin MS, Silvers GW, Donoghue JF. Dose response to ipratropium as a nebulised solution in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989;139:1188-91.
- 73 Morrison JFJ, Jones PC, Muers MF. Assessing physiological benefit from domiciliary nebulised bronchodilators in severe airflow limitation. *Eur Respir J* 1992;5:424-9.
- 74 Jenkins SC, Heaton RW, Fulton TJ, Moxham J. Comparison of domiciliary nebulised salbutamol and salbutamol from a metered dose inhaler in stable chronic airflow limitation. *Chest* 1987;91:804-7.
- 75 O'Driscoll BR, Kay EA, Taylor RJ, Weatherby H, Chetty MCP, Bernstein A. A long-term prospective assessment of home nebuliser treatment. *Respir Med* 1992;86:317-25.
- 76 British Thoracic Society. Current best practice for nebuliser treatment. *Thorax* 1997;52(Suppl 2):S1-106.
- 77 Murciano D, Auclair M-H, Pariente R, Aubier M. A randomised controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease. *N Engl J Med* 1989;320:1521-5.
- 78 McKay SE, Howie CA, Thomson AH, Whiting B, Addis GJ. Value of theophylline treatment in patients handicapped by chronic obstructive pulmonary disease. *Thorax* 1993;48:227-32.
- 79 Mulloy E, McNicholas WT. Theophylline improves gas exchange during rest, exercise and sleep in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1993;148:1030-6.
- 80 Evans WW. Plasma theophylline concentrations, six minute walking distances and breathlessness in patients with chronic airflow obstruction. *BMJ* 1984;289:1649-51.
- 81 Cooper CB, Davidson AC, Cameron IR. Aminophylline, respiratory muscle strength and exercise tolerance in chronic obstructive airway disease. *Clin Respir Physiol* 1987;23:15-22.
- 82 Murciano D, Aubier M, Lecolguic Y, Pariente R. The effects of theophylline on diaphragmatic strength and exercise tolerance in patients with chronic obstructive pulmonary disease. *N Engl J Med* 1984;322:349-53.
- 83 Peake MD, Chrystyn J, Mulley BA. Response to oral theophylline in severe chronic obstructive airways disease. *BMJ* 1989;298:523-4.
- 84 Tsui SJ, Self TH, Burns R. Theophylline toxicity: update. *Ann Allergy* 1990;64:241-57.
- 85 Van Schayck CP, Folgering H, Harbers H, Maas KL, van Weel C. Effects of allergy and age on responses to salbutamol and ipratropium in moderate asthma and chronic bronchitis. *Thorax* 1991;46:355-9.
- 86 Saetta M, Di Stephano A, Maestrelli P, Ferraroso A, Drigo R, Potena A, et al. Activated T lymphocytes and macrophages in bronchial mucosa of subjects with chronic bronchitis. *Am Rev Respir Dis* 1993;147:301-6.
- 87 Nagai A, Thurlbeck W M, Konno K. Responsiveness and variability of airflow obstruction in chronic obstructive pulmonary disease: clinicopathologic correlative studies. *Am J Respir Crit Care Med* 1995;151:635-9.
- 88 Nagai A, West WW, Thurlbeck WM. The National Institutes of Health. Intermittent positive pressure breathing trial: pathology studies II. Correlation between morphologic findings, clinical findings and evidence of airflow obstruction. *Am Rev Respir Dis* 1985;132:946-53.
- 89 Postma DS, Steenhuis EJ, Weele Van der LTh, Sluiter HJ. Severe chronic airflow obstruction: can corticosteroids slow down progression? *Eur J Respir Dis* 1985;67:56-64.
- 90 Postma DS, Peters I, Steenhuis EJ, Sluiter HJ. Moderately severe chronic airflow obstruction. Can corticosteroids slow down progression? *Eur Respir J* 1988;1:22-6.
- 91 Dompeling E, van Schayck CP, Molema J, Folgering H, van Grunsven PM, van Weel C. Inhaled beclomethasone improves the course of asthma and COPD. *Eur Respir J* 1992;5:945-52.
- 92 British Thoracic Society, National Asthma Campaign, Royal College of Physicians of London, et al. The British guidelines on asthma management. *Thorax* 1997;52(Suppl 1):S1-21.
- 93 Petty TL. The national mucolytic study. Results of a randomised double blind placebo controlled study of iodinated glycerol in chronic obstructive bronchitis. *Chest* 1990;97:75-83.
- 94 Bowman R, Backer U, Larsson S, Melander B, Wahlandel L. Oral N-acetylcysteine reduces exacerbation rate in chronic bronchitis. *Eur Respir J* 1983;64:405-15.
- 95 British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airways obstruction. *Thorax* 1985;40:832-5.
- 96 Voisin C, Howard P, Ansquer JC. Almitrine and bismesylate: a long-term placebo controlled double blind study in chronic obstructive pulmonary disease. *Bull Eur Physiopathol Respir* 1987;239(Suppl 11):167-82.
- 97 Howard P, Empey D, Harrison B, et al. Lower dose almitrine bismesylate in hypoxaemic chronic bronchitis. *Eur Respir J* 1989;2(Suppl 8):774S.
- 98 MacNee W. State of the Art: Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994;150:part 1 833-52; part II 1158-68.
- 99 American Thoracic Society. Evaluation of impairment/disability secondary to respiratory disorders. *Am Rev Respir Dis* 1986;133:1205-9.
- 100 Hunter ABN, Carey MA, Larsh HW. The nutritional status of patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1981;124:376-81; 1985;132:1347-65.
- 101 Fitting JW. Nutritional support in chronic obstructive lung disease. *Thorax* 1992;47:141-3.
- 102 Calman KC. Influenza immunisation. Letter from the Chief Medical Officer, 8th October 1993. Department of Health PL/CMO(93):13.
- 103 Kilbourne ED. Inactivated influenza vaccines. In: Plotkin SA, Mortimer EA, eds. *Vaccines*. Philadelphia: WB Saunders, 1988: 420-34.
- 104 American College of Physicians Task Force on Adult Immunization. Infectious Diseases Society of America. *Guide for adult immunization*. 2nd ed. Philadelphia: American College of Physicians, 1990.
- 105 Shapiro ED, Berg AT, Austrian R, Schroeder D, Parcells V, Margolis A, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med* 1991;325:1453-60.
- 106 Jones PW, Baveystock CM, Little-Johns P. Relationship between general health measured with the sickness impact profile and respiratory symptoms, physiological measures and mood in patients with chronic airflow limitation. *Am Rev Respir Dis* 1989;140:1538-43.
- 107 Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure for chronic airflow limitation: the St George's respiratory questionnaire. *Am Rev Respir Dis* 1992;145:1321-7.
- 108 Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring the quality of life in asthma. *Am Rev Respir Dis* 1993;147:832-8.
- 109 Guyatt G. Measuring health status in chronic airflow limitation. *Eur Respir J* 1988;1:560-4.
- 110 Mahler FDA, Rosialto RA, Harmer A, Lantane T, McGovern JF, Daubenspek JA. Comparison of clinical dyspnoea ratings and psychophysical measurements of respiratory sensation in obstructive airways disease. *Am Rev Respir Dis* 1987;135:1229-33.
- 111 Hay JG, Stone P, Carter J, Church S, Eyre-Brook A, Pearson MG, et al. Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive airways disease. *Eur Respir J* 1993;5:659-64.
- 112 Woodcock AA, Gross ER, Gellert A, Shah S, Johnson M, Geddes DM. Effects of dihydrocodeine, alcohol and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. *N Engl J Med* 1981;305:1611-6.
- 113 Johnson MA, Woodcock AA, Geddes DM. Dihydrocodeine for breathlessness in 'pink puffers'. *BMJ* 1983;276:675-7.
- 114 Mitchell-Heggs P, Murphy K, Minty K, Guz A, Patterson SC, Minty PS, et al. Diazepam in the treatment of dyspnoea in the "pink puffer" syndrome. *Q J Med* 1980;193:9-20.
- 115 American Thoracic Society. Guidelines for pulmonary rehabilitation. *Am Rev Respir Dis* 1981;124:663-6.
- 116 Folgering H, DeKhuijzen R, Cox N, Van Herwaarden C. The rationale of pulmonary rehabilitation. *Eur Respir Rev* 1991;6:464-71.
- 117 Goldstein RS, Gort EH, Stubbings D, Arendano MA, Guyatt GH. Randomised controlled trial of respiratory rehabilitation. *Lancet* 1994;344:1394-7.
- 118 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
- 119 Lacasse Y, Wong E, Guyatt GH, King D, Cook DJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. *Lancet* 1996; 348:1115-9.
 - 120 Niderinan MS, Clements PH, Fein AM, Feinsilver SH, Robinson DA, Ilowite JS, et al. Benefits of a multidisciplinary pulmonary rehabilitation programme. *Chest* 1991;99:798-804.
 - 121 Morgan AD, Peck DF, Cannon DR, McHardy GJR. Psychological factors contributing to disproportionate disability in chronic bronchitis. *J Psychosomatic Res* 1983; 27:259-61.
 - 122 Clark CJ. Strategies for the evaluation of rehabilitation treatment. *Eur Respir Rev* 1991;6:475-81.
 - 123 Smith K, Hook D, Guyatt GH, Madhavan J, Oxman AD. Respiratory muscle training in chronic airflow limitation: meta-analysis. *Am Rev Respir Dis* 1992;145:533-9.
 - 124 Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxaemic chronic obstructive lung disease. A clinical trial. *Ann Intern Med* 1980;93:391-8.
 - 125 Medical Research Council Working Group. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis emphysema. *Lancet* 1981;i:681-6.
 - 126 Department of Health. *Domiciliary oxygen therapy service. Drug tariff Part X*. London: HMSO, 1990.
 - 127 Bloom BS, Daniel JM, Wiseman M, Knorr RS, Cebul R, Kissick WL. Transtracheal oxygen delivery and patients with chronic obstructive pulmonary disease. *Respir Med* 1989;83:281-8.
 - 128 Walshaw MJ, Lim R, Evans CC. Prescription of oxygen concentrators for long term oxygen treatment: reassessment in one district. *BMJ* 1988;297:1030-2.
 - 129 Morrison D, Skwarski K, MacNee W. A review of the prescription of domiciliary long-term oxygen in Scotland. *Thorax* 1995;50:1103-5.
 - 130 Restrick LJ, Paul EA, Braid GM, Cullinan P, Moore-Gillon J, Wedzicha JA. Assessment and follow-up of patients prescribed long term oxygen therapy. *Thorax* 1993;48:708-13.
 - 131 Lock SH, Paul EA, Rudd RM, Wedzicha JA. Portable oxygen therapy: assessment and usage. *Respir Med* 1991; 85:407-12.
 - 132 Corris P. Lung transplantation. In: Calverley PMA, Pride NB, eds. *Chronic obstructive pulmonary disease*. London: Chapman and Hall, 1995: 562-70.
 - 133 Scott JP, Higenbottam TW, Sharples L, Clelland CA, Smyth RL, Stewart S, et al. Risk factors for obliterative bronchiolitis in heart-lung transplant recipients. *Transplantation* 1991;51:813-7.
 - 134 Pearson MG, Ogilvie CMO. Surgical treatment of emphysematous bullae: late outcome. *Thorax* 1983;38:134-7.
 - 135 Davies L, Calverley PMA. Lung volume reduction surgery in chronic obstructive pulmonary disease. *Thorax* 1996; 51(Suppl 2):529-34.
 - 136 Light RW, Merrill EJ, Despars JA, et al. Prevalence of depression and anxiety in patients with COPD: relationship to functional capacity. *Chest* 1985;87:35-8.
 - 137 Schwartz JS, Bencowitz HZ, Moser KM. Air travel hypoxaemia with chronic obstructive pulmonary disease. *Ann Intern Med* 1984;10:473-7.
 - 138 Dennison DJ. Adverse environments. In: Brewis RAL, Gibson GJ, Geddes DM, eds. *Respiratory medicine*. London: Balliere Tynhall, 1990: 1503-4.
 - 139 Royal College of Physicians. *Disabling Chest Disease: Prevention and Care*. *J R Coll Phys Lond* 1981;15:69-87.
 - 140 Cockcroft A, Bagnall P, Heslop A, Andersson N, Heaton R, Batstone J, et al. Control trial of respiratory health worker visiting patients with chronic respiratory disability. *BMJ* 1987;294:225-8.
 - 141 Georgopoulos D, Anthonisen NR. Symptoms and signs of COPD. In Cherniak NS, ed. *Chronic obstructive pulmonary disease*. Philadelphia: Saunders, 1991: 357-63.
 - 142 Anthonisen NR, Manfreda J, Warren CPW, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106:196-204.
 - 143 Calverley PMA. Symptomatic bronchodilator treatment. In: Calverley PMA, Pride NB, eds. *Chronic obstructive pulmonary disease*. London: Chapman and Hall, 1994.
 - 144 Calverley PMA, Howatson R, Flenley DC, Lamb D. Clinico-pathological correlations in cor pulmonale. *Thorax* 1992;47:494-8.
 - 145 Jeffrey AA, Warren PM, Flenley DC. Acute hypercapnic respiratory failure in patients with chronic obstructive lung disease; risk factors and use of guidelines for management. *Thorax* 1992;47:34-40.
 - 146 Dunn WF, Nelson SB, Hubmayr RD. Oxygen induced hypercarbia in obstructive pulmonary disease. *Am Rev Respir Dis* 1991;144:526-30.
 - 147 Bazuaye EA, Stone TN, Corris PA, Gibson GJ. Variability in inspired oxygen concentrations with nasal cannulae. *Thorax* 1992;47:609-11.
 - 148 Costello RW, Liston R, McNicholas WT. Compliance at night with low flow oxygen therapy: a comparison of nasal cannulae and venturi face masks *Thorax* 1995;50:405-6.
 - 149 Shrestha M, O'Brian T, Maddox R, Gourley HR, Ried G. Decreased duration of emergency department treatment of chronic obstructive pulmonary disease exacerbations with the addition of ipratropium bromide to agonist therapy. *Ann Emerg Med* 1991;20:1206-9.
 - 150 O'Driscoll BR, Taylor RJ, Mosley MG, Chambers DJ, Beinstein A. Nebulized Salbutamol with or without ipratropium bromide in acute airflow obstruction. *Lancet* 1989;i:1418-20.
 - 151 Fernandez A, Munoz J, De la Calle B, Alia A, Izpeleta A, De laCalle MA, et al. Comparison of one versus two bronchodilator drugs in ventilated COPD patients. *Intensive Care Med* 1994;20:199-202.
 - 152 Moayyedi P, Congleton J, Page RL, Pearson SB, Muers MH. Comparison of nebulised salbutamol and ipratropium bromide with salbutamol alone in the treatment of chronic obstructive pulmonary disease. *Thorax* 1995; 50:834-7.
 - 153 Rice KL, Leatherman JW, Duane PG, Snyder LS, Harmon KR, Abel J, et al. Aminophylline for acute exacerbations of chronic obstructive pulmonary disease. A controlled trial. *Ann Intern Med* 1987;107:305-9.
 - 154 Blasi F, Legnani D, Lombardo VM, Negretto GG, Magliano E, Pozzoli R, et al. *Chlamydia pneumoniae* infection in acute exacerbations of COPD. *Eur Respir J* 1993;6: 19-22.
 - 155 Guidelines for the management of community acquired pneumonia in adults admitted to hospital. *Br J Hosp Med* 1993;49:346-50.
 - 156 Albert RK, Martin TR, Lewis SW. Controlled clinical trials of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. *Ann Intern Med* 1980; 92:753-8.
 - 157 Thromboembolic Risk Factors Consensus Group. Risk and prophylaxis for venous thrombo embolism in hospital patients. *BMJ* 1992;305:567-73.
 - 158 Sutton PP. Chest physiotherapy; time for reappraisal. *Br J Dis Chest* 1988;82:127-37.
 - 159 Bott J, Carroll MP, Conway J, Keilty SE, Ward EM, Brown AM, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993;341:1555-67.
 - 160 Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, et al. Non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995;338:817-22.
 - 161 Meecham-Jones DJ, Paul EA, Graham-Clark C, Wedzicha JA. Nasal ventilation in acute exacerbations of chronic obstructive pulmonary disease: effect on arterial blood gas tensions. *Thorax* 1994;49:1222-4.
 - 162 Vitacca M, Rubini F, Foglio K, Scalvini S, Nava S, Ambrosino N. Non-invasive modalities of positive pressure ventilation improve the outcome of acute exacerbations in COPD patients. *Intensive Care Med* 1993;19:450-5.
 - 163 Costello R, McNicholas WT. Five year follow-up of respiratory failure in COPD. *Thorax* 1993;48:419P.
 - 164 Kelly CA, Gibson GJ. Relation between FEV₁ and peak expiratory flow in patients with chronic obstructive pulmonary disease. *Thorax* 1988;43:335-6.
 - 165 American Thoracic Society. Standardisation of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152:1107-36.
 - 166 Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson GJ, Howard P, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995;8:1398-420.
 - 167 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;152:S77-121.
 - 168 Lamb D. Pathology. In: Calverley PMA, Pride NB. *Chronic obstructive pulmonary disease*. London: Chapman and Hall, 1995.
 - 169 Snider GL, Klenerman J, Thurlbeck WM, Bengali ZH. The definition of emphysema: Report of a National Heart and Blood Institute, Division of Lung Disease, Workshop. *Am Rev Respir Dis* 1985;132:182-5.
 - 170 Kim WD, Eidelman DH, Izquierdo JL, Ghezzi H, Saetta MP, Cosio MG. Centrilobular and panlobular emphysema in smokers; two distinct morphologic and functional entities. *Am Rev Respir Dis* 1981;141:385-90.
 - 171 Ollerenshaw SL, Woolcock AJ. Characteristics of the inflammation in biopsies from large airways of subjects with asthma and subjects with chronic airflow limitation. *Am Rev Respir Dis* 1992;145:922-7.