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MANAGEMENT OF AN ACUTE EXACERBATION OF COPD: ARE WE IGNORING THE EVIDENCE?

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Introductory article

Audit of acute admissions of COPD: standards of care and management in the hospital setting

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*Despite publication of several management guidelines for COPD, relatively little is known about standards of care in clinical practice. Data were collected on the management of 1400 cases of acute admission with chronic obstructive pulmonary disease in 38 UK hospitals to compare clinical practice against the recommended British Thoracic Society standards. Variation in the process of care between the different centres was analysed and a comparison of the management by respiratory specialists and nonrespiratory specialists made. There were large variations between centres for many of the variables studied. A forced expiratory volume in one second measurement was found in only 53% of cases. Of the investigations recommended in the acute management arterial blood gases were performed in 79% (interhospital range 40–100%) of admissions and oxygen was formally prescribed in only 64% (range 9–94%). Of those cases with acidosis and hypercapnia 35% had no further blood gas analysis and only 13% received ventilatory support. Long term management was also deficient with 246 cases known to be severely hypoxic on admission yet two thirds had no confirmation that oxygen levels had returned to levels above the requirements for long term oxygen therapy. Only 30% of current smokers had cessation advice documented. To conclude, the median standards of care observed fell below those recommended by the guidelines. The lowest levels of performance were for patients not under the respiratory specialists, but specialists also have room for improvement. The substantial variation in the process of care between hospitals is strong evidence that it is possible for other centres with poorer performance to improve their levels of care. (**Eur Respir J** 2000;17:343–9)*

We first become exposed to patients with an exacerbation of chronic obstructive pulmonary disease (COPD) as junior doctors. It does not take many days in the medical admissions ward to become confident and then complacent in managing this common problem for a variety of reasons. The condition is chronic, self-inflicted and largely irreversible, the treatment is cheap and stereotyped ("oxygen, nebuliser, antibiotics, steroids"), and the patients are for the most part not candidates for the intensive care unit (ICU) in the UK.

It is salutary therefore to have a snapshot taken of our management of this condition in the form of the audit results described by Roberts *et al* in the Introductory article.[1] They highlight not only differences in management between specialists and non-specialists but also between hospitals and compare the results with the practice advocated in the British Thoracic Society (BTS) guidelines for the management of COPD.[2]

This audit is well timed. Over the last few years there have been major developments in the treatment options for patients with exacerbations of COPD. For the sickest patients, non-invasive ventilation has emerged as an effective treatment modality, avoiding intubation in some patients and providing a real treatment option in others who would not be considered for invasive ventilation. For milder cases, "Hospital at Home" for acute COPD has been adopted widely throughout the country, demonstrating that it is safe to manage exacerbations in a domiciliary setting with respiratory outreach nurses to the satisfaction of both the patients and the hospital managers.

In this review we have taken the opportunity both to highlight changes in acute COPD management that have arisen since the BTS guidelines were published and to explore the evidence base behind current management strategy for exacerbations of COPD.

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AN INTRODUCTION TO THE PROBLEM

COPD is a common and important problem in the UK. The prevalence in 1997 of clinically significant COPD was estimated to be 1.7% of the population in men and 1.4% in women.[3] Although the figures have probably reached their plateau for men, there is still a marked trend upwards for women with the prevalence in this group having increased by 69% between 1990 and 1997. Exacerbations of COPD are the largest single cause of emergency respiratory admissions, accounting for 21% of this group with a mean hospital stay of 10.3 days.[4]

Exacerbations that require admission to hospital may only affect a small proportion of the COPD population (probably less than 2% by one estimate[5]), but they make a disproportionate demand on the expenditure on this condition. Hospital episode statistics showed that COPD resulted in approximately 100 000 admissions and 1.2 million bed days in England in 1992/3.[6] Based on these figures, it has been estimated that hospital admissions account for 35% of the annual health care costs of managing COPD. Expressed in terms of 1996/7 prices, inpatient costs were £3000 per admission, amounting to £285.3 million out of a total annual expenditure on COPD of £817.5 million.[5]

Exacerbations have both short and long term consequences for the health of the individual concerned. There may be permanent impairment of lung function, functional ability, and health status. Seemungal *et al*[7] showed that 35 days after an exacerbation only 75% of patients had regained their original peak expiratory flow rate (PEFR) and 7.1% had not returned to baseline lung function at 3 months. It has been known for some time that functional ability measured by activities of daily living may be permanently impaired in elderly patients with COPD.[8] In this study approximately 30% of patients had still not regained their previous mobility 3 months after discharge and 65% were unable to do housework that they could previously manage. Patients with frequent exacerbations (3 or more per year) have a worse quality of life when assessed by the St George's Respiratory Questionnaire[9] than those with less frequent exacerbations.

After an exacerbation readmission is common with estimated figures of 34% at 3 months,[10] 44% at 6 months,[11] and 70% at 1 year.[12] Estimates of in-hospital mortality from a single episode of exacerbation range from 4% to 11%.[11–13] Mortality from the BTS audit study population was 14% at 3 months.[10] Hypercapnia is associated with a worse outcome with mortality in hospital, at 60 days, 180 days, 1 year, and 2 years recorded as 11%, 20%, 33%, 43%, and 49%, respectively.[11] Unsurprisingly, ICU admission is also associated with a worse outcome; in-hospital mortality following ICU admission is estimated as 21–24% with 1 year mortality of 49%, although these were obtained in ICUs outside the UK.[14 15]

Aetiology and pathophysiology

Infection, either viral or bacterial, is the most common cause of an exacerbation of COPD. In one large American study of 1016 patients 38% of exacerbations requiring admission to hospital resulted from non-infective causes such as cardiac failure, pneumothorax, pulmonary embolism, lung cancer, or dysrrhythmia.[11] Air pollution is also associated with increased numbers of exacerbations,[16] suggesting that this too is a cause.

An infective exacerbation leads to increased inflammation in the airways which is detectable as an increase in inflammatory cells,[17] an increase in cytokines,[18] and possibly a reduction in protective proteins.[19] The pathophysiological changes[20] of this inflammatory process are shown schematically in fig 1.

Diagnosis and assessment

The definition of an exacerbation of COPD is variable. The BTS guidelines[2] define it as "a worsening of the previous stable situation" which may include increased breathlessness, sputum volume, sputum purulence, wheeze, chest tightness, or fluid retention. A similar broad description has been used in a recent consensus statement which defined an exacerbation as "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication".[21]

One problem facing the clinician when assessing breathless patients in an emergency situation is knowing whether they have significant underlying COPD. In the audit by Roberts *et al*[1] a definitive diagnosis of COPD (by measurement of FEV_1 in the period 5 years before or 3 months after the exacerbation) was made in only half of the 1400 cases. Consequently, a clinical diagnosis of COPD often needs to be made at the time of presentation as an emergency. Clinical features that increase the likelihood of underlying significant COPD have been established[22 23] and include:

- smoking history (especially >70 pack years);
- chronic cough, wheeze, exertional dyspnoea, sputum production;
- hyperresonance or decreased cardiac dullness on percussion;
- decreased breath sounds;
- wheezing;
- prolonged expiratory time.

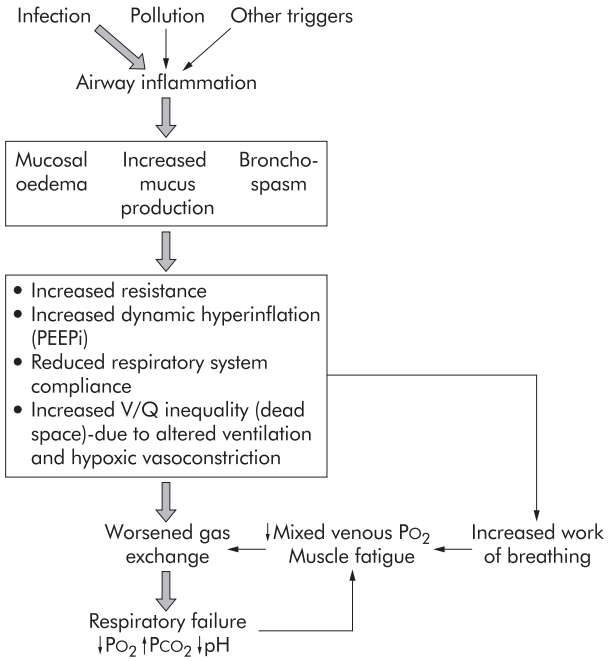

Figure 1 Pathophysiology of acute respiratory failure in COPD: increased load and reduced capacity.

Roberts *et al*[1] found that the appropriate history, examination, and initial investigations were performed in two thirds to three quarters of cases. Arterial blood gas analysis should be carried out as 20–47% of patients will have carbon dioxide (CO_2) retention at presentation[12 24] and one in five will be acidotic,[24] both of which affect oxygen prescription. Chest radiography is also necessary as careful clinical examination fails to predict a quarter of the abnormalities found on radiography[25] and one in five cases has a chest radiograph that alters management.[26]

Treatment

There is a perception that the appropriate treatment in an acute exacerbation of COPD is a standard package of nebulised bronchodilators (usually a β_2 agonist and anticholinergic in combination), antibiotics, systemic steroids, and controlled oxygen therapy. Roberts *et al*[1] have shown that this is indeed common practice. They found that nebulised bronchodilators were documented as prescribed in 91% of cases and presumably were also given to most of the remainder. In most cases (77%) a combination of a β_2 agonist and anticholinergic was given. Anticholinergic agents were rarely used on their own (2%). They found that 85% of patients were documented as receiving systemic steroids and 80% were given antibiotics.

From the studies of treatment in an acute exacerbation, it is possible to discriminate clinically between exacerbations in order to tailor the treatment package to the individual case. This might avoid unpleasant side effects in a group of patients who need several courses of treatment yearly.

Bronchodilators

Despite the complete absence of placebo controlled trials, few people would question the efficacy of bronchodilators in an acute exacerbation of COPD. There are, however, data comparing bronchodilators either singly or in combination and on the effectiveness of the nebulised route.

A Cochrane systematic review[27] identified three studies[28–30] with a total of 103 patients comparing β_2 agonists (fenoterol, metaproterenol) with an anticholinergic agent (ipratropium). Both agents produced an improvement in FEV_1 of 150–250 ml at 90 minutes with no difference detectable between them. However, one study[29] did show a significant improvement in arterial oxygen tension (Pa_{O_2}) at 30 minutes in those treated with ipratropium (+0.79 kPa) compared with metaproterenol (–0.84 kPa).

Several studies[30–33] have looked at the addition of ipratropium to a β_2 agonist (salbutamol, fenoterol); all were unable to show any further improvement in FEV_1 resulting from the addition of the anticholinergic. The only positive support for an additive effect comes from an American study of patients in the emergency room which found that ipratropium added to isoetharine led to shorter stays in the emergency room but no difference in hospital admission rates.[34]

Patients with an acute exacerbation of COPD often say that their inhalers had stopped having a useful effect and their symptoms were only relieved by nebulised therapy on arriving at the hospital. Surprisingly, this is not reflected by clinical trial evidence. A meta-analysis[35] of the effectiveness of nebuliser versus metered dose inhaler as mode of delivery for bronchodilators in exacerbations found no significant difference in their effect on FEV_1. This unexpected result needs further confirmation as numbers were small (48 patients in three studies) and FEV_1 may not be the optimal outcome measure.

Roberts *et al*[1] did not audit the use of methylxanthines. These are mentioned in the BTS guidelines[2] as a second line treatment via the intravenous route if nebulised bronchodilators fail to work, although the authors state that there is no evidence to support this practice. A recent Cochrane systematic review[36] has reinforced this point. Four randomised controlled trials were identified with 172 patients randomised either to methylxanthine or placebo. Methylxanthine failed to produce an improvement in FEV_1, to reduce hospital admission rates, or to improve symptoms relative to placebo but did increase nausea and vomiting. With the caveat that the numbers on which this conclusion is based are small and the study outcomes heterogeneous, methylxanthines cannot be recommended for routine use on current evidence.

In summary, there is little evidence to support the current UK pattern of use of bronchodilators in acute COPD. Nebulised ipratropium as a single agent may be just as effective as salbutamol or combined bronchodilators. Indeed, it could be argued that this should be the first line treatment as β_2 agonists may lower Pa_{O_2} and are associated with more side effects.[30] However, it is possible that the studies have failed to detect the superiority of β_2 agonists or combined bronchodilators. Many of the studies used older β_2 agonists such as fenoterol which are no longer in widespread use. Also, the evidence base in this area has relied on FEV_1 as its outcome measure. This has proved of limited value in detecting benefit in studies of stable COPD.[37] More relevant information on the role of nebulised bronchodilators in acute COPD might be obtained from studies using clinical end points such as symptoms, length of hospital stay, or mortality or by including a measurement of hyperinflation such as inspiratory capacity.

Systemic steroids

There have been a number of recent trials of systemic steroids in exacerbations of COPD.[38–40] Despite the large variation in steroid dose (from 125 mg methylprednisolone 6

hourly to 30 mg prednisolone daily) and treatment duration (8 weeks to 2 weeks), the trial outcomes have been remarkably consistent. In a UK study[39] systemic steroids accelerated the rate of recovery of FEV_1 (90 ml/day *v* 30 ml/day) and shortened the median hospital stay (by 2 days). The accelerated improvement in FEV_1 has only been shown for the first 5 days with measurements performed at later time points failing to show a significant difference between steroid and placebo.

The benefits found in the clinical trials are minor, particularly compared with other interventions. For example, early supported discharge has a much larger effect on reducing hospital stay. Given the side effects of steroid therapy and the uncertain hazards of intermittent courses of high dose treatment,[41 42] the blanket prescribing of oral steroids in most cases of acute COPD as currently practised in the UK may not be justifiable.

Antibiotics

The proportion of exacerbations of COPD with a bacterial aetiology is unknown as sputum cultures from stable COPD patients grow pathogenic bacteria in a significant proportion of cases (25–41%).[43 44] In an exacerbation the proportion of patients with a positive sputum culture increases—for example, in a group of patients with chronic bronchitis, positive sputum cultures were found in 71% of cases.[44] A further study found the following distribution of organisms: *Haemophilus influenzae* (22%), *Pseudomonas aeruginosa* (15%), *Streptococcus pneumoniae* (10%), and *Moraxella catarrhalis* (9%).[45]

Viruses undoubtedly play a significant role. Rhinovirus has recently been implicated as a major cause of exacerbations, being found in both nasopharyngeal aspirates and induced sputum.[46] It has been claimed that one third of COPD exacerbations are viral in aetiology and, of these, rhinovirus accounts for 75%.

Studies looking at the blanket prescription of antibiotics for COPD have found them to be beneficial on the whole.[47–49] Patients on antibiotics had a larger improvement in PEFR (10.75 l/min) compared with placebo[47] and fewer treatment failures (68% *v* 55%).[50] The studies also attempted to subdivide exacerbations by severity of symptoms in the hope of identifying patients who would benefit from antibiotics. In general, they found that greater severity was associated with increased response to antibiotic.

In the best of these studies Anthonisen *et al*[50] classified exacerbations into mild, moderate and severe according to the presence of one, two, or three of the characteristic symptoms of an acute exacerbation—namely, worsening breathlessness, increased sputum purulence, and increased sputum volume. They found that statistically significant benefit from antibiotics was seen only in exacerbations classed as severe, where all three major symptoms were present. This requirement for increased sputum volume and purulence in order to detect a definite response to an antibiotic has been supported indirectly by a more recent study by Stockley *et al*[44] in which patients with an exacerbation of COPD were divided into those with purulent and those with mucoid sputum. In the former group sputum cultures were positive in 84% in the acute state and 38% in the stable state, whereas in the latter there was no difference in the proportion of positive cultures in acute (38%) and stable (41%) specimens.

Supplemental oxygen

Roberts *et al*[1] found that arterial blood gas tensions were measured in most patients (79%) with 71% having simultaneous documentation of the inspired fraction (Fio_2). However, only 34% underwent repeat arterial blood gas analysis to check for worsening hypercapnia and acidosis.

Supplemental oxygen is of value in acute respiratory failure because it improves oxygen delivery to critical organs such as the heart and brain and reduces pulmonary vasoconstriction and right heart strain.[20] Swinburn *et al*[51] reported that oxygen administered to hypoxaemic COPD patients (mean PaO_2 6.8 kPa) also improved dyspnoea, albeit in stable patients.

However, oxygen therapy is not without its dangers. Several studies[52–56] have shown that oxygen therapy, even when controlled, can induce severe hypercapnia in a proportion of patients with COPD. In some cases it is impossible to achieve a satisfactory balance between life threatening hypoxaemia and respiratory acidosis secondary to oxygen induced hypercapnia.

The BTS guidelines adopt a simple approach to the problem of managing supplemental oxygen in COPD, namely:

(1) Give 28% (or less) oxygen via Venturi mask.
(2) Measure arterial blood gas tensions within 1 hour.
(3) If the pH is satisfactory, increase the Fio_2 until the Pao_2 is above 7.5 kPa. Repeat arterial blood gas analysis 1 hour after every change in Fio_2.
(4) If this fails, consider other strategies (assisted ventilation or respiratory stimulants).

There are no controlled studies validating this strategy, although data from a similar approach applied in an uncontrolled manner do suggest that it is an acceptable one.[57]

It may be possible in a proportion of cases to use the arterial blood gas results to predict those who will develop dangerous CO_2 retention after oxygen supplementation. In the largest study looking at this problem[52] the authors derived an equation which required only the pH and Pao_2 values while breathing 24% oxygen and could predict with 81% sensitivity who would develop acidotic hypercapnic respiratory failure on controlled oxygen therapy:

$$pH = 7.66 - 0.0675 \times Pao_2 \text{ (kPa)}$$

If the patient's measured pH is greater than the calculated pH, then dangerous respiratory acidosis is unlikely. This, or a similar equation, could be used to identify those at particular risk of decompensation.

Non-invasive ventilation

Roberts *et al*[1] found that 3% of cases of acute exacerbation of COPD received assisted ventilation. Current use of non-invasive ventilation (NIV) is likely to have increased this figure as it was not widely available at the time of the audit. In a study in Leeds Plant *et al*[24] found that NIV is indicated for approximately 16% of cases of acute COPD.

The benefits of NIV in acute COPD have been established by several trials in the ICU setting which show reduced rates of intubation.[58–60] The best trial in a general medicine setting[61] established a clear reduction in both treatment failure (from 27% to 15% compared with standard treatment) and in-hospital mortality (from 20% to 10%). The indication for NIV used in this trial was a pH of 7.25–7.35 after initial treatment had been instigated which therefore avoided the group of patients who may have been given too much oxygen in transit to hospital.

Patients who respond to NIV are those with a high $Paco_2$ without major hypoxaemia—that is, those with a low $(A–a)o_2$ gradient.[62] Such patients usually show an increase in pH and a reduction in respiratory rate after 1–4 hours of NIV.[58 61 63 64] Patients predicted to have poor outcomes are more sick

initially (assessed by Acute Physiology and Chronic Health Evaluation II score), have excessive respiratory secretions, no teeth, or are those in a poor nutritional state.[65 66] COPD patients with pneumonia have been thought to do badly with NIV[65] but a more recent study has challenged this view.[67]

Invasive ventilation

The acute mortality of patients with an exacerbation of COPD who are invasively ventilated is no greater than patients ventilated for other conditions. As mentioned earlier, the in-hospital death rate in this group is in the range of 21–24%. However, the long term outlook is poor with a 1 year mortality of 49%. Markers of good prognosis are thought to be absence of previous diagnosis of respiratory disease, presence of an obvious reversible cause for the respiratory failure such as infection, and good mobility. If hypercapnic patients become normocapnic, the mean survival is 2.9 years.[68] Conversely, mortality is particularly high when FEV_1 is less than 30% predicted, where there is multiple co-morbidity, or the patient is housebound or on long term oxygen therapy.[69]

NIV may have a role in the weaning of patients with COPD from invasive ventilation. In one study[70] 50 invasively ventilated patients with COPD who had failed a T-piece trial after 48 hours of ventilation were randomised to extubation followed by NIV or continued invasive ventilation. NIV appeared more successful in several outcome measures including ICU stay and survival. However, no significant differences were found in a further study of very similar design.[71] Two studies[72 73] comparing NIV with oxygen therapy or continuous positive airway pressure (CPAP) after extubation showed no benefit for the NIV arm. None of the negative weaning studies exclusively looked at patients with COPD.

Respiratory stimulants

The only respiratory stimulant in use in the UK today is doxapram. The prescription of this drug is becoming less popular with the wider availability of NIV. There is little conclusive evidence that it is effective in an acute exacerbation of COPD, but what evidence there is[74–76] has been summarised in a Cochrane review.[77]

Two of these studies[74 75] showed that doxapram has a short term benefit in improving arterial blood gas tensions but they were not designed to demonstrate its effectiveness as a treatment for respiratory failure. The study by Angus *et al*[76] compared doxapram with NIV and showed superiority of the latter treatment in terms of sustained improvement in arterial blood gases and perhaps also in survival, although the numbers were too small (n=17) to prove this. Although the difference between doxapram and NIV in this study may have resulted from the doxapram infusion regime giving an insufficient dose of this drug, an alternative and persuasive argument is that doxapram simply accelerated respiratory muscle fatigue whereas NIV alleviated it.

It is now unlikely that any further placebo controlled trials for doxapram will be performed. Its use will therefore be as a temporary bridging treatment before initiating NIV, as an adjunct to NIV where respiratory effort is reduced, or in sites where NIV is not available and invasive ventilation is not indicated.

Mucolytics

Several trials have studied the use of mucolytics in patients with an acute exacerbation of COPD.[78–82] These treatments consistently failed to accelerate FEV_1 recovery in an exacerbation although two of the five trials showed that the mucolytic improved symptoms.[80 82]

Physiotherapy

Three randomised controlled trials[78 83 84] have failed to show any benefit for chest physiotherapy (mechanical percussion) and one trial showed a significant reduction in FEV_1.

Hospital at home

Some patients with exacerbations of COPD are suitable for home treatment because sophisticated monitoring is unnecessary, sudden deterioration is unlikely, and once daily observation is usually sufficient. Initial hospital assessment is important to confirm the diagnosis and exclude uncompensated respiratory acidosis. Suitable patients can then be sent home with a treatment package and their progress monitored by respiratory nurses. An uncontrolled study[85] showed that this development was safe, effective, and popular with patients and GPs. Three randomised controlled studies were then carried out in Glasgow,[86] Edinburgh,[87] and Liverpool[88] and all showed a reduction in hospital admissions or bed-days with no increase in morbidity, mortality, or readmission rate.

The studies in the three sites differed in design. In Liverpool and Edinburgh the subjects were recruited in A&E whereas in Glasgow patients were admitted and allowed to stay up to 3 days in hospital. This difference was reflected in the proportion of patients assessed for the study who were eligible for home care (33% in Liverpool and Edinburgh, 42% in Glasgow). The FEV_1 was also higher in the Glasgow patients (0.94 l *v* 0.68 l in Edinburgh and 0.74 l in Liverpool), suggesting that delayed assessment had allowed some recovery from the acute event. Direct GP referral achieves higher eligibility rates (70%) but it is not known how many of these patients would actually have been admitted to hospital.

Of the various approaches, we think that the early supported discharge model is the simplest and most efficient. It targets patients who are using hospital resources, eligibility is acceptable, and it is very economical of nurses' time since they do not need to be immediately available for prompt patient assessment in A&E. A postal survey of British respiratory units[89] showed that the proportion of the UK's respiratory departments offering a "Hospital at Home" service for acute COPD had increased from 16% in 1999 to 28% in 2001. Most of these (65%) had established services using the early supported discharge model. Of those with no service, 76% stated that funding was the major barrier.

Prevention of further exacerbations

Since frequent exacerbations of COPD worsen health status[9] and may accelerate decline in pulmonary function,[7 90] treatment to reduce the frequency of exacerbations is highly relevant.

Smoking cessation and prescription of long term oxygen therapy (LTOT) are both actively pursued following an exacerbation as these interventions affect mortality. Smoking cessation reduces the rate of fall in FEV_1.[91 92] In addition there is evidence from the Lung Health Study to suggest that stopping smoking reduces exacerbation frequency, albeit in a population of mild COPD patients.[90] The main evidence for LTOT comes from two randomised controlled trials[93 94] which showed a reduced mortality when oxygen supplementation was used for at least 15 hours per day. However, as far as is known, LTOT does not alter exacerbation rate.

It is becoming increasingly apparent that we can make an impact on exacerbation frequency in COPD as a number of interventions have been shown to have this effect.

Inhaled steroids

Several of the trials of inhaled steroids in stable COPD used exacerbation rate as a primary or secondary outcome measure. In the ISOLDE trial[95 96] a significant reduction of approximately 25% was found in frequency of exacerbations. In another study[97] the number of patients having moderate or severe exacerbations was reduced by 26%. A further observational study in 22 620 elderly COPD patients[98] suggested that inhaled corticosteroids reduced hospital admission rates by 24%. The studies that failed to show a reduction[99–102] were possibly underpowered due to small numbers of subjects or lower exacerbation rates in subjects with milder disease.

This effect of inhaled steroids on exacerbation rate is mirrored by its effect on quality of life. In the ISOLDE trial[95 96] the rate of worsening of quality of life scores (measured by St George's Respiratory Questionnaire) was significantly reduced in the inhaled steroid group and the gap between the two groups widened over time. This cannot be explained by a difference in FEV_1 but may reflect the adverse effect of increased frequency of exacerbations on quality of life.

Bronchodilators

A drug company sponsored trial[103] in 1067 patients found that ipratropium bromide reduced exacerbation rates in COPD compared with salbutamol. By contrast, a study comparing salmeterol with ipratropium bromide and placebo in 411 patients failed to show a reduction in exacerbation rates for ipratropium compared with placebo but did show a reduction for salmeterol.[104] Two further large studies comparing tiotropium (a new long acting anticholinergic agent soon to be released) with placebo[105] and ipratropium[106] have shown a 20–24% reduction in exacerbation rate. It is therefore possible that anticholinergics and long acting β_2 agonists do reduce exacerbation rates but more data are required to test this claim and to determine the size of the effect.

Mucolytic agents

A Cochrane review[107] which included 22 trials showed that oral mucolytic agents produced a 29% reduction in exacerbation rate as well as a reduction in the number of days of sickness and an increase in the number of patients who remained free of exacerbations. With the exacerbation rates seen in the trials, this translated to one fewer exacerbation and six fewer days of acute disability per year. Of the mucolytic agents used, only carbocisteine is available in the UK but cannot currently be prescribed by GPs for this indication.

Antioxidants

Oral N-acetylcysteine has been proposed as an antioxidant therapy in COPD. A number of trials performed between 1976 and 1994 have assessed its effect and their results have recently been amalgamated in a systematic review.[108] The authors concluded that oral N-acetylcysteine can increase the proportion of patients with COPD who are free of exacerbations from 31% to 49% over a treatment period of 12–24 weeks.

Influenza and pneumococcal vaccination (see further information in clinical evidence)

A Cochrane review[109] identified four small trials (n=29–55) performed exclusively in patients with COPD and five trials in elderly patients (n=27–1838) which included a proportion with chronic lung disease. Influenza vaccination appeared to reduce the number of late exacerbations—that is, those occurring more than 3 weeks after vaccination—by 0.45 exacerbations per person over the study period of 3–4 months. There was no increase in early exacerbations, contrary to many patients' experience. The evidence of benefit is stronger for a general population of elderly patients in whom the vaccination reduces pneumonia, hospitalisation, and death.[110]

There is as yet no evidence that pneumococcal vaccination has a specific benefit on COPD exacerbations. In a meta-analysis of 40 431 subjects pneumococcal vaccination reduced the incidence of pneumococcal pneumonia but not mortality[111]; this reduction in pneumonia only occurred in young healthy adults. Two subsequent studies have suggested benefit in an old frail population. Pneumococcal vaccination given in a randomised controlled trial of 2837 nursing home residents resulted in a reduction in pneumonia only in those with significant co-morbidities, one of which was lung disease.[112] In a cohort study of 1898 members of a healthcare organisation, pneumococcal vaccination reduced both hospital admission for pneumonia and death.[113]

Pulmonary rehabilitation

It is widely accepted that pulmonary rehabilitation improves functional status and quality of life in patients with COPD. Several observational studies have suggested that both outpatient and inpatient rehabilitation reduce the frequency of exacerbations.[114–117] A randomised controlled trial in Barcelona showed that outpatient rehabilitation reduced the frequency of exacerbations but not the number of hospital admissions over a 2 year period.[118] In a second randomised controlled study performed in Wales the number of days in hospital was reduced in the rehabilitation group during a 1 year follow up period although there was no difference in the numbers admitted.[119] Further studies are therefore required to confirm whether this treatment modality has a real effect on exacerbation frequency or severity.

Conclusions

Guideline fatigue is an iatrogenic ailment which afflicts doctors. Nevertheless, we should welcome the guideline culture if it results in better practice which can be demonstrated by audit. The paper by Roberts *et al*[1] serves as a useful starting point from which to build an audit process for acute COPD. Standards of care were considered to have fallen below guideline recommendations, but the criticisms were mainly related to process of care and were based on the assumption that doctors faithfully document their activities in the case records. Some of the variation between centres may well have been clerical rather than clinical. It is not known if suboptimal process of care during the acute illness significantly affected outcome, with the exception that few patients received ventilatory support. Obviously, NIV was not widely available at that time. Assessment of recovery from respiratory failure seems to have been neglected in many cases, but a decision on long term oxygen therapy is best made at outpatient review. It is to be hoped that in the future a repeat of this audit will show that we have embraced new developments. For this purpose, it is likely that we will need new guidelines, more solidly evidence-based, to use as the yardstick.

In this review we suggest that good practice should include tailoring of care in relation to individual clinical features. Antibiotics should be offered only to patients with an increased volume of purulent sputum; steroids should be restricted to patients with severe exacerbations to minimise myopathy and osteopathy; and NIV should be considered for

Learning points

- Exacerbations of COPD are the most common cause of emergency respiratory admissions accounting for at least one fifth of cases
- It is likely that they accelerate decline of pulmonary function and health status
- The majority of patients admitted to hospital for an exacerbation are readmitted within a year
- Evidence suggests that we can tailor our treatment of an exacerbation using clinical and arterial blood gas criteria rather than the blanket prescribing which is widespread practice at present
- Frequency of future exacerbations can be reduced by pharmacological and physical means and should be pursued in a more systematic manner

acidotic hypercapnic respiratory failure. In the absence of uncompensated respiratory failure, early supported discharge with hospital at home is now accepted practice.

Attempts to reduce exacerbation frequency and declining lung function are clearly important and should be pursued more vigorously. Non-pharmacological measures include smoking cessation and pulmonary rehabilitation, although both of these are likely to be most beneficial if implemented before an exacerbation requires admission to hospital. Opinion on the use of inhaled steroids is polarised. Evidence is adduced by antagonists that COPD is not a steroid sensitive disease[120] and the minor improvements claimed by protagonists would not have been discovered without major financial investment by the pharmaceutical industry. However, it seems reasonable to recommend inhaled steroids to established exacerbators but we must decide on the appropriate threshold of exacerbation frequency. It is likely that the newer bronchodilators may also affect exacerbation frequency. There is some evidence specific to COPD that influenza vaccination is of value. Finally, it seems that simple mucolytic and antioxidant therapy may have been unjustifiably ignored by respiratory physicians.

References

1 **Roberts CM**, Ryland I, Lowe D, *et al* on behalf of the Audit Subcommittee of the Standards of Care Committee of the British Thoracic Society and the Clinical Effectiveness and Evaluation Unit at the Royal College of Physicians. Audit of acute admissions of COPD: standards of care and management in the hospital setting. *Eur Respir J* 2000;**17**:343–9.

2 **COPD Guidelines Group of the Standards of Care Committee of the BTS**. BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997;**52**(Suppl 5):S1–28.

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

4 **Department of Health**. *Hospital in-patient data based on hospital episode statistics 2000/01.* www doh gov uk/hes, 2001.

5 **Guest JF**. The annual cost of chronic obstructive pulmonary disease to the UK's National Health Service. *Dis Manage Health Outcomes* 1999;**5**:93–100.

6 **Department of Health**. *Hospital in-patient data based on hospital episode statistics 1992/93.* London: HMSO, 1993.

7 **Seemungal TA**, Donaldson GC, Bhowmik A, *et al.* Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;**161**:1608–13.

8 **Peach H**, Pathy MS. Follow-up study of disability among elderly patients discharged from hospital with exacerbations of chronic bronchitis. *Thorax* 1981;**36**:585–9.

9 **Seemungal TA**, Donaldson GC, Paul EA, *et al.* Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**157**:1418–22.

10 **Roberts CM**, Lowe D, Bucknall CE, *et al.* Clinical audit indicators of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease. *Thorax* 2002;**57**:137–41.

11 **Connors AF**, Dawson NV, Thomas C, *et al.* Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med* 1996;**154**:959–67.

12 **Gibson PG**, Wlodarczyk JH, Wilson AJ, *et al.* Severe exacerbation of chronic obstructive airways disease: health resource use in general practice and hospital. *J Qual Clin Pract* 1998;**18**:125–33.

13 **Mushlin AI**, Black ER, Connolly CA, *et al.* The necessary length of hospital stay for chronic pulmonary disease. *JAMA* 1991;**266**:80–3.

14 **Seneff MG**, Wagner DP, Wagner RP, *et al.* Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *JAMA* 1995;**274**:1852–7.

15 **Breen D**, Churches T, Hawker F, *et al.* Acute respiratory failure secondary to chronic obstructive pulmonary disease treated in the intensive care unit: a long term follow up study. *Thorax* 2002;**57**:29–33.

16 **Schwartz J**. Air pollution and hospital admissions for the elderly in Detroit, Michigan. *Am J Respir Crit Care Med* 1994;**150**:648–55.

17 **Saetta M**, Di Stefano A, Maestrelli P, *et al.* Airway eosinophilia in chronic bronchitis during exacerbations. *Am J Respir Crit Care Med* 1994;**150**:1646–52.

18 **Bhowmik A**, Seemungal TA, Sapsford RJ, *et al.* Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax* 2000;**55**:114–20.

19 **Gompertz S**, Bayley DL, Hill SL, *et al.* Relationship between airway inflammation and the frequency of exacerbations in patients with smoking related COPD. *Thorax* 2001;**56**:36–41.

20 **Derenne JP**, Whitelaw WA, Similowski T. *Acute respiratory failure in chronic obstructive pulmonary disease.* Lung Biology in Health and Disease. Volume 92. New York: Marcel Dekker, 1996.

21 **Rodriguez-Roisin R**. Toward a consensus definition for COPD exacerbations. *Chest* 2000;**117**(5 Suppl 2):398–401S.

22 **Holleman DR**, Simel DL, Goldberg JS. Diagnosis of obstructive airways disease from the clinical examination. *J Gen Intern Med* 1993;**8**:63–8.

23 **Holleman DR**, Simel DL. Does the clinical examination predict airflow limitation? *JAMA* 1995;**273**:313–9.

24 **Plant PK**, Owen JL, Elliott MW. One year period prevalence study of respiratory acidosis in acute exacerbations of COPD: implications for the provision of non-invasive ventilation and oxygen administration. *Thorax* 2000;**55**:550–4.

25 **Emerman CL**, Cydulka RK. Evaluation of high-yield criteria for chest radiography in acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med* 1993;**22**:680–4.

26 **Tsai TW**, Gallagher EJ, Lombardi G, *et al.* Guidelines for the selective ordering of admission chest radiography in adult obstructive airway disease. *Ann Emerg Med* 1993;**22**:1854–8.

27 **Brown CD**, McCrory DC, White J. Inhaled short-acting beta2-agonists versus ipratropium for acute exacerbations of chronic obstructive pulmonary disease. In: *Cochrane Database of Systematic Reviews.* Oxford: Update Software, 2002.

28 **Backman R**, Hellstrom P-E. Femoterol and ipratropium bromide in respiratory treatment of patients with chronic bronchitis. *Curr Ther Res* 1985;**38**:135–40.

29 **Karpel JP**, Pesin J, Greenberg D, *et al.* A comparison of the effects of ipratropium bromide and metaproterenol sulfate in acute exacerbations of COPD. *Chest* 1990;**98**:835–9.
30 **Rebuck AS**, Chapman KR, Abboud R, *et al.* Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. *Am J Med* 1987;**82**:59–64.
31 **Moayyedi P**, Congleton J, Page RL, *et al.* Comparison of nebulised salbutamol and ipratropium bromide with salbutamol alone in the treatment of chronic obstructive pulmonary disease. *Thorax* 1995;**50**:834–7.
32 **Patrick DM**, Dales RE, Stark RM, *et al.* Severe exacerbations of COPD and asthma. Incremental benefit of adding ipratropium to usual therapy. *Chest* 1990;**98**:295–7.
33 **O'Driscoll BR**, Taylor RJ, Horsley MG, *et al.* Nebulised salbutamol with and without ipratropium bromide in acute airflow obstruction. *Lancet* 1989;i:1418–20.
34 **Shrestha M**, O'Brien T, Haddox R, *et al.* Decreased duration of emergency department treatment of chronic obstructive pulmonary disease exacerbations with the addition of ipratropium bromide to beta-agonist therapy. *Ann Emerg Med* 1991;**20**:1206–9.
35 **Turner MO**, Patel A, Ginsburg S, *et al.* Bronchodilator delivery in acute airflow obstruction. A meta-analysis. *Arch Intern Med* 1997;**157**:1736–44.
36 **Barr RG**, Rowe BH, Camargo CA Jr. Methyl-xanthines for exacerbations of chronic obstructive pulmonary disease. In: *Cochrane Database of Systematic Reviews*. Oxford: Update Software, 2000.
37 **O'Donnell DE**. Assessment of bronchodilator efficacy in symptomatic COPD: is spirometry useful? *Chest* 2000;**117**(2 Suppl):42–7S.
38 **Thompson WH**, Nielson CP, Carvalho P, *et al.* Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med* 1996;**154**:407–12.
39 **Davies L**, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet* 1999;**354**:456–60.
40 **Niewoehner DE**, Erbland ML, Deupree RH, *et al.* Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med* 1999;**340**:1941–7.
41 **McEvoy CE**, Niewoehner DE. Corticosteroids in chronic obstructive pulmonary disease. Clinical benefits and risks. *Clin Chest Med* 2000;**21**:739–52.
42 **McEvoy CE**, Niewoehner DE. Adverse effects of corticosteroid therapy for COPD. A critical review. *Chest* 1997;**111**:732–43.
43 **Monso E**, Ruiz J, Rosell A, *et al.* Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med* 1995;**152**:1316–20.
44 **Stockley RA**, O'Brien C, Pye A, *et al.* Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest* 2000;**117**:1638–45.
45 **Miravitlles M**, Espinosa C, Fernandez-Laso E, *et al.* Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. Study Group of Bacterial Infection in COPD. *Chest* 1999;**116**:40–6.
46 **Seemungal TA**, Harper-Owen R, Bhowmik A, *et al.* Detection of rhinovirus in induced sputum at exacerbation of chronic obstructive pulmonary disease. *Eur Respir J* 2000;**16**:677–83.
47 **Saint S**, Bent S, Vittinghoff E, *et al.* Antibiotics in chronic obstructive pulmonary disease exacerbations. A meta-analysis. *JAMA* 1995;**273**:957–60.
48 **Pines A**, Raafat H, Plucinski K, *et al.* Antibiotic regimens in severe and acute purulent exacerbations of chronic bronchitis. *BMJ* 1968;2:735–8.
49 **Sachs AP**, Koeter GH, Groenier KH, *et al.* Changes in symptoms, peak expiratory flow, and sputum flora during treatment with antibiotics of exacerbations in patients with chronic obstructive pulmonary disease in general practice. *Thorax* 1995;**50**:758–63.
50 **Anthonisen NR**, Manfreda J, Warren CP, *et al.* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;**106**:196–204.
51 **Swinburn CR**, Mould H, Stone TN, *et al.* Symptomatic benefit of supplemental oxygen in hypoxemic patients with chronic lung disease. *Am Rev Respir Dis* 1991;**143**:913–5.
52 **Bone RC**, Pierce AK, Johnson RL Jr. Controlled oxygen administration in acute respiratory failure in chronic obstructive pulmonary disease: a reappraisal. *Am J Med* 1978;**65**:896–902.
53 **Bedon GA**, Block AJ, Ball WC. The "28 percent" Venturi mask in obstructive airway disease. *Arch Intern Med* 1970;**125**:106–13.
54 **Eldridge F**, Gherman C. Studies of oxygen administration in respiratory failure. *Ann Intern Med* 1968;**68**:569–78.
55 **Warrell DA**, Edwards RH, Godfrey S, *et al.* Effect of controlled oxygen therapy on arterial blood gases in acute respiratory failure. *BMJ* 1970;1:452–5.
56 **Dunn WF**, Nelson SB, Hubmayr RD. Oxygen-induced hypercarbia in obstructive pulmonary disease. *Am Rev Respir Dis* 1991;**144**:526–30.
57 **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.
58 **Brochard L**, Mancebo J, Wysocki M, *et al.* Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995;**333**:817–22.
59 **Kramer N**, Meyer TJ, Meharg J, *et al.* Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 1995;**151**:1799–806.
60 **Martin TJ**, Hovis JD, Costantino JP, *et al.* A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure. *Am J Respir Crit Care Med* 2000;**161**:807–13.
61 **Plant PK**, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet* 2000;**355**:1931–5.
62 **Wysocki M**, Tric L, Wolff MA, *et al.* Noninvasive pressure support ventilation in patients with acute respiratory failure. *Chest* 1993;**103**:907–13.
63 **Bott J**, Carroll MP, Conway JH, *et al.* Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993;**341**:1555–7.
64 **Plant PK**, Owen JL, Elliott MW. Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome. *Thorax* 2001;**56**:708–12.
65 **Soo Hoo GW**, Santiago S, Williams AJ. Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease: determinants of success and failure. *Crit Care Med* 1994;**22**:1253–61.
66 **Ambrosino N**, Foglio K, Rubini F, *et al.* Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. *Thorax* 1995;**50**:755–7.
67 **Confalonieri M**, Potena A, Carbone G, *et al.* Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med* 1999;**160**:1585–91.
68 **Costello R**, Deegan P, Fitzpatrick M, *et al.* Reversible hypercapnia in chronic obstructive pulmonary disease: a distinct pattern of respiratory failure with a favorable prognosis. *Am J Med* 1997;**102**:239–44.
69 **NHLBI/WHO**. *Global initiative for chronic obstructive lung disease.* NHLBI/WHO Workshop Report, 2001.
70 **Nava S**, Ambrosino N, Clini E, *et al.* Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. *Ann Intern Med* 1998;**128**:721–8.
71 **Girault C**, Daudenthun I, Chevron V, *et al.* Noninvasive ventilation as a systematic extubation and weaning technique in acute-on-chronic respiratory failure: a prospective, randomized controlled study. *Am J Respir Crit Care Med* 1999;**160**:86–92.
72 **Gust R**, Gottschalk A, Schmidt H, *et al.* Effects of continuous (CPAP) and bi-level positive airway pressure (BiPAP) on extravascular lung water after extubation of the trachea in patients following coronary artery bypass grafting. *Intens Care Med* 1996;**22**:1345–50.
73 **Jiang JS**, Kao SJ, Wang SN. Effect of early application of biphasic positive airway pressure on the outcome of extubation in ventilator weaning. *Respirology* 1999;**4**:161–5.
74 **Edwards G**, Leszczynski SO. A double-blind trial of five respiratory stimulants in patients in acute ventilatory failure. *Lancet* 1967;226–9.
75 **Moser KM**, Luchsinger PC, Adamson JS, *et al.* Respiratory stimulation with intravenous doxapram in respiratory failure. A double-blind co-operative study. *N Engl J Med* 1973;**288**:427–31.
76 **Angus RM**, Ahmed AA, Fenwick LJ, *et al.* Comparison of the acute effects on gas exchange of nasal ventilation and doxapram in exacerbations of chronic obstructive pulmonary disease. *Thorax* 1996;**51**:1048–50.
77 **Greenstone M**. Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease. In: *Cochrane Database of Systematic Reviews*. Oxford: Update Software, 1997.
78 **Petersen ES**, Esmann V, Honcke P, *et al.* A controlled study of the effect of treatment on chronic bronchitis. An evaluation using pulmonary function tests. *Acta Med Scand* 1967;**182**:293–305.
79 **Langlands JH**. Double-blind clinical trial of bromhexine as a mucolytic drug in chronic bronchitis. *Lancet* 1970;i:448–50.
80 **Peralta J**, Poderoso JJ, Corazza C, *et al.* Ambroxol plus amoxicillin in the treatment of exacerbations of chronic bronchitis. *Arzneimittel-Forschung* 1987;**37**:969–71.

81 **Aylward M**. A between-patient, double-blind comparison of S-carboxymethylcysteine and bromhexine in chronic obstructive bronchitis. *Curr Med Res Opin* 1973;**1**:219–27.
82 **Finiguerra M**, Conti P, Figura I. Clinical study of the effects of an antibiotic and mucolytic association (amoxycillin and domiodol) in hypersecretory chronic bronchopulmonary diseases. *Curr Ther Res* 1982;**31**:895–905.
83 **Newton DA**, Stephenson A. Effect of physiotherapy on pulmonary function. A laboratory study. *Lancet* 1978;ii:228–9.
84 **Wollmer P**, Ursing K, Midgren B, *et al.* Inefficiency of chest percussion in the physical therapy of chronic bronchitis. *Eur J Respir Dis* 1985;**66**:233–9.
85 **Gravil JH**, Al Rawas OA, Cotton MM, *et al.* Home treatment of exacerbations of chronic obstructive pulmonary disease by an acute respiratory assessment service. *Lancet* 1998;**351**:1853–5.
86 **Cotton MM**, Bucknall CE, Dagg KD, *et al.* Early discharge for patients with exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Thorax* 2000;**55**:902–6.
87 **Skwarska E**, Cohen G, Skwarski KM, *et al.* Randomized controlled trial of supported discharge in patients with exacerbations of chronic obstructive pulmonary disease. *Thorax* 2000;**55**:907–12.
88 **Davies L**, Wilkinson M, Bonner S, *et al.* "Hospital at home" versus hospital care in patients with exacerbations of chronic obstructive pulmonary disease: prospective randomised controlled trial. *BMJ* 2000;**321**:1265–8.
89 **Johnson MK**, Choo-Kang BSW, Sarvesvaran JS, *et al.* Growth in hospital at home services for acute exacerbation of chronic obstructive pulmonary disease. *Thorax* 2001;**56**(Suppl III):iii11.
90 **Kanner RE**, Anthonisen NR, Connett JE. Lower respiratory illnesses promote FEV_1 decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease. Results from the Lung Health Study. *Am J Respir Crit Care Med* 2001;**164**:358–64.
91 **Fletcher C**, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977;1:1645–8.
92 **Scanlon PD**, Connett JE, Waller LA, *et al.* Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. *Am J Respir Crit Care Med* 2000;**161**:381–90.
93 **Medical Research Council Working Party**. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* 1981;i:681–6.
94 **Nocturnal Oxygen Therapy Trial Group**. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980;**93**:391–8.
95 **Burge PS**, Calverley PM, Jones PW, *et al.* Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000;**320**:1297–303.
96 **Spencer S**, Calverley PM, Sherwood BP, *et al*, ISOLDE Study Group. Health status deterioration in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**163**:122–8.
97 **Paggiaro PL**, Dahle R, Bakran I, *et al.* Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. *Lancet* 1998;**351**:773–80.
98 **Sin DD**, Tu JV. Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**164**:580–4.
99 **Weir DC**, Bale GA, Bright P, *et al.* A double-blind placebo-controlled study of the effect of inhaled beclomethasone dipropionate for 2 years in patients with nonasthmatic chronic obstructive pulmonary disease. *Clin Exp Allergy* 1999;**29**(Suppl 2):125–8.
100 **van Grunsven PM**, van Schayck CP, Derenne JP, *et al.* Long term effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a meta-analysis. *Thorax* 1999;**54**:7–14.
101 **Pauwels RA**, Lofdahl CG, Laitinen LA, *et al.* Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society study on chronic obstructive pulmonary disease. *N Engl J Med* 1999;**340**:1948–53.
102 **Vestbo J**, Sorensen T, Lange P, *et al.* Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999;**353**:1819–23.
103 **Friedman M**, Serby CW, Menjoge SS, *et al.* Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. *Chest* 1999;**115**:635–41.
104 **Mahler DA**, Donohue JF, Barbee RA, *et al.* Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest* 1999;**115**:957–65.
105 **Casaburi R**, Mahler DA, Jones PW, *et al.* A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;**19**:217–24.
106 **Vincken W**, Van Noord JA, Greefhorst APM, *et al.* Improved health outcomes in patients with COPD during 1 year's treatment with tiotropium. *Eur Respir J* 2002;**19**:209–16.
107 **Poole PJ**, Black PN. Oral mucolytic drugs for exacerbations of chronic obstructive pulmonary disease: systematic review. *BMJ* 2001;**322**:1271–4.
108 **Stey C**, Steurer J, Bachmann S, *et al.* The effect of oral N-acetylcysteine in chronic bronchitis: a quantitative systematic review. *Eur Respir J* 2000;**16**:253–62.
109 **Poole PJ**, Chacko E, Wood-Baker RW, *et al.* Influenza vaccine for patients with chronic obstructive pulmonary disease. In: *Cochrane Database of Systematic Reviews*. Issue 4. Oxford: Update Software, 2000: CD002733.
110 **Gross PA**, Hermogenes AW, Sacks HS, *et al.* The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. *Ann Intern Med* 1995;**123**:518–27.
111 **Fine MJ**, Smith MA, Carson CA, *et al.* Efficacy of pneumococcal vaccination in adults. A meta-analysis of randomized controlled trials. *Arch Intern Med* 1994;**154**:2666–77.
112 **Koivula I**, Sten M, Leinonen M, *et al.* Clinical efficacy of pneumococcal vaccine in the elderly: a randomized, single-blind population-based trial. *Am J Med* 1997;**103**:281–90.
113 **Nichol KL**, Baken L, Wuorenma J, *et al.* The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. *Arch Intern Med* 1999;**159**:2437–42.
114 **Foglio K**, Bianchi L, Bruletti G, *et al.* Long-term effectiveness of pulmonary rehabilitation in patients with chronic airway obstruction. *Eur Respir J* 1999;**13**:125–32.
115 **Stewart DG**, Drake DF, Robertson C, *et al.* Benefits of an inpatient pulmonary rehabilitation program: a prospective analysis. *Arch Phys Med Rehabil* 2001;**82**:347–52.
116 **Young P**, Dewse M, Fergusson W, *et al.* Improvements in outcomes for chronic obstructive pulmonary disease (COPD) attributable to a hospital-based respiratory rehabilitation programme. *Aust NZ J Med* 1999;**29**:59–65.
117 **Bowen JB**, Thrall RS, ZuWallack RL, *et al.* Long-term benefits of short-stay inpatient pulmonary rehabilitation in severe chronic obstructive pulmonary disease. *Monaldi Arch Chest Dis* 1999;**54**:189–92.
118 **Guell R**, Casan P, Belda J, *et al.* Long-term effects of outpatient rehabilitation of COPD: a randomized trial. *Chest* 2000;**117**:976–83.
119 **Griffiths TL**, Burr ML, Campbell IA, *et al.* Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000;**355**:362–8.
120 **Barnes PJ**. Mechanisms in COPD: differences from asthma. *Chest* 2000;**117**(2 Suppl):10–4S.