

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

CM Roberts, I Ryland, D Lowe, Y Kelly, CE Bucknall, MG Pearson 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

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 estimate⁵), 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 Questionnaire⁹ 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 dysrhythmia.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 changes²⁰ of this inflammatory process are shown schematically in fig 1.

Diagnosis and assessment

The definition of an exacerbation of COPD is variable. The BTS guidelines² 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 FEV₁ 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.

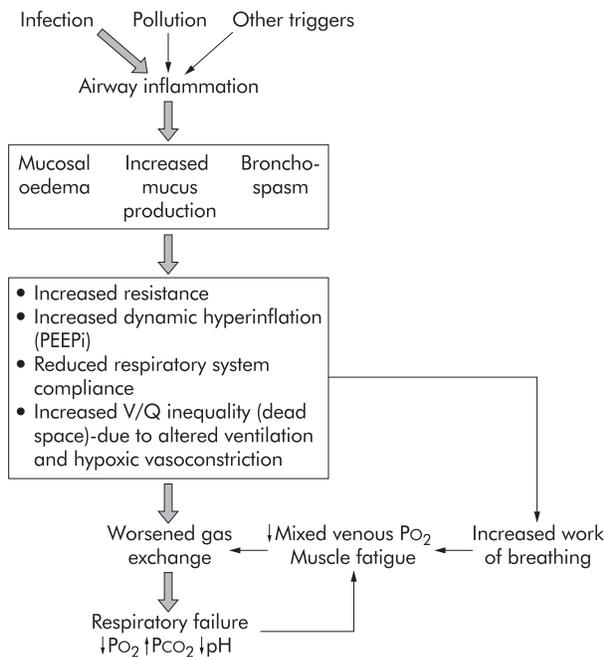


Figure 1 Pathophysiology of acute respiratory failure in COPD: increased load and reduced capacity.

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 (CO₂) 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 radiography²⁵ 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 review²⁷ 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 FEV₁ of 150–250 ml at 90 minutes with no difference detectable between them. However, one study²⁹ did show a significant improvement in arterial oxygen tension (Pao₂) 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 FEV₁ 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-analysis³⁵ 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 FEV₁. This unexpected result needs further confirmation as numbers were small (48 patients in three studies) and FEV₁ may not be the optimal outcome measure.

Roberts *et al*¹ did not audit the use of methylxanthines. These are mentioned in the BTS guidelines² 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 review³⁶ 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 FEV₁, 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 Pao₂ 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 FEV₁ 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 study³⁹ systemic steroids accelerated the rate of recovery of FEV₁ (90 ml/day *v* 30 ml/day) and shortened the median hospital stay (by 2 days). The accelerated improvement in FEV₁ 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 PEF_R (10.75 l/min) compared with placebo⁴⁷ 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*⁵¹ 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 (FiO₂).

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 PaO₂ 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 FiO₂ until the PaO₂ is above 7.5 kPa. Repeat arterial blood gas analysis 1 hour after every change in FiO₂.
- (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 CO₂ retention after oxygen supplementation. In the largest study looking at this problem⁵² the authors derived an equation which required only the pH and PaO₂ values while breathing 24% oxygen and could predict with 81% sensitivity who would develop acidotic hypercapnic respiratory failure on controlled oxygen therapy:

$$\text{pH} = 7.66 - 0.0675 \times \text{PaO}_2 \text{ (kPa)}$$

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 setting⁶¹ 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 PaCO₂ without major hypoxaemia—that is, those with a low (A–a)O₂ 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 NIV⁶⁵ 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 FEV₁ 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 study⁷⁰ 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*⁶⁶ 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 FEV₁ 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 FEV₁.

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 study⁸⁵ 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 Liverpool⁸⁸ 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 FEV₁ was also higher in the Glasgow patients (0.941 *v* 0.681 in Edinburgh and 0.741 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 units⁸⁹ 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 status⁹ 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 FEV₁.^{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 study⁹⁷ the number of patients having moderate or severe exacerbations was reduced by 26%. A further observational study in 22 620 elderly COPD patients⁹⁸ 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 FEV₁ but may reflect the adverse effect of increased frequency of exacerbations on quality of life.

Bronchodilators

A drug company sponsored trial¹⁰³ 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 placebo¹⁰⁵ and ipratropium¹⁰⁶ 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 review¹⁰⁷ 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 carbocysteine 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 review¹⁰⁹ 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 mortality¹¹¹; 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 disease¹²⁰ 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.

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