

Acute exacerbations of COPD

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Summary

Acute exacerbations of COPD (AECOPD) are a common cause of morbidity and mortality. There is a need for a standardised definition of an exacerbation of COPD. The common aetiological factors are bacterial, viral infection and air pollutants. Exacerbations of COPD may adversely affect the natural history of COPD. Several strategies are available now to prevent or reduce exacerbations of COPD including immunisation against influenza and inhaled corticosteroids in patients with moderate/severe disease. The mainstay of treatment involves increasing bronchodilator therapy, systemic glucocorticoids which have now been

shown to have a beneficial effect. The circumstances for the use of antibiotic therapy is now established in patients with increased breathlessness, increased sputum production and/or sputum purulence. In those with respiratory failure, non-invasive ventilation has been shown to reduce intubation rates, shorten lengths of hospitalisation, and improve mortality. Early or immediate supported discharge for selected patients has been shown to be effective in the management of patients with COPD.

Key words: COPD; acute exacerbation

Introduction

Acute exacerbations in chronic obstructive pulmonary disease (AECOPD) are a common cause of morbidity [1, 2] and mortality [3, 4] in COPD patients and place a large burden on health care resources. In the United States AECOPD annually account for 16 000 367 office visits, 500 000 hospitalisations, and 18 billion in direct health care cost [4]. In an average UK Health Authority, with a population of 250 000, there will be 14, 200 GP consultations and 680 hospital admissions for AECOPD per year [5]. In UK hospitals respiratory admissions make up around 25% of all acute med-

ical emergency admissions and AECOPD account for more than half of these [6] – 203, 193 hospital admissions in 1994 [7]. A regional UK survey of medical admissions found that in the age range 65–74 years, 73% of male and 32% of female admissions were due to COPD [5]. Recent studies have suggested that GP consultations for AECOPD underestimate the true number of exacerbations that are not reported. Additionally death often occurs during exacerbations. Hence the burden on health care resources for AECOPD is enormous.

Definition

There is currently no general agreement on the definition of an exacerbation in COPD. Definitions of exacerbations in COPD have been based on increasing symptoms and/or increased health care utilisation. In some studies exacerbations have been defined in operative terms according to the type and number of symptoms. One of the earliest and most quoted definitions is that of Anthonisen [10], which is based on an increase in symptoms of dyspnoea, sputum volume and sputum purulence with or without symptoms of upper respiratory infection and then subdivided depending on the number of symptoms. Other studies have defined an exacerbation as worsening of symptoms, requiring changes in normal treatment, including

antibiotic therapy, short courses of oral corticosteroids and increasing bronchodilator therapy [11, 12]. The severity of an exacerbation can also be defined in terms of increasing healthcare utilisation as mild – self managed by the patient at home; moderate – requiring treatment by a family physician and/or hospital out-patient attendance; and severe – resulting in admission to hospital. Others have defined an exacerbation in terms of its aetiology – infective or non-infective [13]. Clearly the severity of exacerbations and the extent of the healthcare utilisation may depend on the severity of the underlying COPD and co-existing conditions. Recently an AECOPD has been defined as “a sustained worsening of the patients condition,

from the stable state and beyond normal day to day variations, that is acute in onset and necessitates change in regular medication in a patient with underlying COPD" [14]. Although AECOPD clearly worsen health status [15], there is no definition of a COPD exacerbation using health status as defining a criterion. It may also be more precise to talk of an exacerbation *in* COPD rather than an exacerbation *of* COPD.

Some studies have used daily [8, 15] or twice

weekly [16] diary cards of symptoms that are completed by the patient and which can be used to assess the onset and duration of exacerbations. Peak expiratory flows have been shown to alter during exacerbations. However, the changes here are small and are not useful in individual patients [4]. National and International guidelines for the management of COPD have produced rather vague definitions of exacerbations [17–20].

Pathology

Studies of the pathology of exacerbations of COPD have been performed on post mortem material, on bronchial biopsies and most recently inflammation has been assessed by non-invasive surrogate markers. These studies have been carried out in relatively few patients and no large population studies have been undertaken. The largest post mortem studies from the NIH Intermittent Positive Pressure Breathing Trial showed that those patients dying of COPD had both emphysema and small airways inflammation [21, 22]. There is however a paucity of published pathological data illustrating the features of AECOPD, in spite of the fact that AECOPD are a common occurrence and often precipitate death in these patients.

It is assumed that increased inflammation in the airways is a characteristic feature of AECOPD. However, the presence of increased inflammation and the type of inflammatory response is inconsistent and depends on whether the inflammation is assessed in sputum, bronchoalveolar lavage or bronchial biopsies.

There have been relatively few bronchial biopsy studies in patients with AECOPD. The available studies have usually been in mild exacerbations, in patients with very mild or no airflow limitation i.e. in chronic bronchitis rather than in COPD [23]. In some of these studies (in patients with FEV₁ >60% predicted) increased numbers of eosinophils were present in induced sputum and bronchial biopsies in AECOPD [24]. However, neutrophils were also present in increased numbers in the bronchial walls and in bronchoalveolar lavage in exacerbations of COPD [25]. Neutrophils have also been shown to sequester in the pulmonary microcirculation in AECOPD prior to their migration into the airspaces [26]. It is perhaps because dynamic trafficking of neutrophils occurs from the blood to the airspace in AECOPD that

bronchial biopsy studies have not shown dramatic increases in neutrophil numbers in bronchial walls.

In a more general population of COPD patients during exacerbations an increase in eosinophil and neutrophil numbers in induced sputum has not been confirmed [27]. Thus, the type and number of inflammatory cells in the airspaces in AECOPD depends both on the severity of the disease and on the origin of the sample, whether this is from induced or spontaneous sputum, bronchoalveolar lavage or bronchial biopsy [28].

Surrogate markers of inflammation have been shown to be elevated in AECOPD. TNF α levels were elevated in sputum in AECOPD in some studies [29] but not in others [30]. IL-8 and IL-6 levels were elevated in induced sputum [27] and IL-6 in plasma [30] in AECOPD. The levels of IL-6 in sputum at the time of clinical stability were also higher in those with recurrent exacerbations [27].

Oxidative stress is a major factor in the airway inflammation in COPD [31]. Surrogate markers of oxidative stress have been measured in blood, exhaled breath and breath condensate in COPD and have been shown to be elevated in patients with COPD and to be further elevated in exacerbations. Products of lipid peroxidation, particularly isoprostane-F₂ α , a lipid peroxidation product of arachidonic acid, have also been shown to be increased in exhaled breath in patients with AECOPD [32]. Oxidised proteins are also present in the bronchoalveolar lavage in acute exacerbations of bronchitis [33]. This local increase in oxidative stress in the lungs is reflected by the presence of systemic oxidative stress, as shown by a decrease in antioxidant capacity in the plasma in AECOPD [34]. Oxidative stress is an important process in the inflammatory response, since it may activate transcription factors such as nuclear factor kappa β , which enhance the transcription of pro-inflammatory genes such as those for cytokines [35].

Aetiology

The main aetiological factors in exacerbations of COPD are thought to be viral and bacterial infections and air pollutants. Between 30–50% of pa-

tients with AECOPD have a positive sputum culture for bacteria, largely *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*

[31]. However, around 20–30% patients studied when clinically stable also have positive bacterial cultures in sputum [36–38]. Studies using the protected-specimen brush technique have established that bacteria are present in the lower airways during exacerbations at thresholds normally used to define pneumonia ($>10^3$ colony forming units) [39–43]. However a proportion of patients (25%) in a stable condition also have significant concentrations of bacteria ($>10^3$ cfu/ml) using the protected brush specimen technique, while 52% of patients had this amount of bacteria present during an exacerbation [39]. In some studies *Haemophilus parainfluenzae* or *Pseudomonas aeruginosa* were also present in exacerbations of COPD [40–44], particularly in patients with more severe airflow lim-

itation [45]. In one study these organisms were present in 63% of patients whose baseline FEV₁ was $\leq 35\%$ predicted [45]. It is also increasingly recognised that a subgroup of patients with COPD may also have bronchiectasis as assessed by CT scanning [46]. Immunoassays with homologous strains of bacteria show that a specific immune response to the infecting bacterial strain is observed following exacerbations of COPD, which is further proof of infection [47, 48].

There has been increasing recognition of the role of atypical bacterial pathogens in acute bronchitis. *Chlamydia pneumoniae* has been shown to be present in 5–10% of mild to moderate exacerbations [49, 50] but in 18% of severe exacerbations requiring intensive care [42].

Respiratory viruses

Studies in the 1970s, using serology and occasionally culture, detected viruses, commonly the influenzae virus, in around 30% of episodes of AECOPD [36]. More recent studies using PCR to detect virus mRNA have shown viruses in around

30% of patients, with AECOPD, rhinoviruses predominating [51]. There is some preliminary data [51] suggesting that these viruses are also present in stable disease but more data is necessary to confirm this association.

Air pollution

Air pollution as a cause of exacerbations in patients with COPD has been recognised over the last 40 years. AECOPD are especially associated with levels of particulate air pollution, measured either as black smoke or PM₁₀ [52]. The APHEA study [53] showed a relationship between temporal trends in air pollution and emergency admissions for COPD in European cities. A reduction of about 50 $\mu\text{g}/\text{m}^3$ in sulphur dioxide was accompanied by reductions of 6% in emergency admissions for COPD. Ozone levels were also associated with emergency room visits for COPD, a reduction in ozone of 50 $\mu\text{g}/\text{m}^3$ being associated with a 4% re-

duction in emergency room visits for COPD [53]. In the APHEA study which examined admissions for COPD in 6 European cities [54], the relative risks of admission to hospital for COPD for a 50 $\mu\text{g}/\text{m}^3$ increase in the daily level of any air pollutant were 1.02 for sulphur dioxide, 1.04 for black smoke, 1.02 for nitrogen dioxide and 1.04 for ozone. In Birmingham, UK, Wordley and co-workers [55] reported a 2.4% increase in respiratory admissions, many of whom had COPD. Thus there is now overwhelming evidence that the levels of air pollution, especially particulate air pollution are associated with AECOPD [56].

Natural history

Studies in the 1960s in the UK suggested that although AECOPD are associated with a small transient decrease in respiratory function, exacerbations did not alter the natural history of the disease [57]. This has recently been challenged in studies that suggested that in patients with airways obstruction, exacerbations might accelerate the decline in FEV₁ [58, 59].

There have now been several large population studies in COPD [12, 60, 61], which show a trivial number of exacerbations in those with mild disease (FEV₁ $>50\%$ predicted), whereas in moderate to severe disease exacerbation rates range from 1.5–2.5 per year. There is however a wide varia-

tion, with some individuals having recurrent (>3) exacerbations per year. In a prospective study of a cohort of 101 patients with moderate to severe COPD followed up over 2.5 years, the median number of exacerbations was 2.4 (interquartile range 1.3–3.84) exacerbations per patient per year [8]. Using recovery times from exacerbations measured by change in peak expiratory flow and daily symptom score, increased dyspnoea and the presence of symptoms of an upper respiratory tract infection at the onset of the exacerbation indicated prolonged recovery times [8].

Follow up of patients with AECOPD has shown a high re-admission rate and a mortality of

20% at 60 days, 47% at one year and 49% at 2 years [62].

The commonest circumstance of death in patients with COPD is respiratory failure, occurring in 35% of deaths [63]. Although respiratory failure is a common cause of death, co-morbidity also plays a role. Several studies have investigated which variables predict death after admission for an AECOPD and therefore identify at risk subjects. A cohort study of 270 patients, followed over 3 years from the index admission for an AECOPD, found that the predictors of mortality were age, signs of right ventricular hypertrophy, chronic renal failure, ischaemic heart disease and FEV₁ [62, 64]. In a further study of a prospective cohort of 1016 adult patients from 5 hospitals who were ad-

mitted for an AECOPD with a PCO₂ >50 mm Hg, survival was independently related to severity of the illness, body mass index, age, prior functional status, PaO₂, inspiratory oxygen fraction (FiO₂), congestive cardiac failure, serum albumin and the presence of cor pulmonale [65, 66]. Poor treatment outcome, as assessed by a return visit four weeks following an exacerbation with a respiratory problem requiring further treatment, was also related to the severity of the airways obstruction. Other factors associated with poor treatment outcome following an exacerbation were the use of home oxygen therapy, frequency of exacerbations, history of previous pneumonia and the use of maintenance oral corticosteroids [66].

Prevention of acute exacerbations in COPD

Prevention or reduction in the severity or duration of exacerbations is an important goal in the management of COPD. Influenza vaccination is recommended in the prevention of AECOPD since it reduces hospitalisation for pneumonia in elderly patients with COPD during epidemic periods [67]. Vaccination against *S. pneumonia* is available and is effective in preventing infective complications of *S. pneumonia* [68]. There is evidence that inhaled corticosteroids may prevent exacerbations and reduce their severity. A six months trial of inhaled fluticasone showed no decrease in the exacerbation rate, but did show a reduction in the number of moderate to severe exacerbations with inhaled fluticasone [11]. A larger study in patients with moderate to severe COPD (FEV₁ <50% predicted) showed a reduction in exacerbation rate by 25% from 1.32 per year on placebo to 0.99 a year ($p = 0.026$) in patients treated with fluticasone 500 µg/twice daily [12]. In the same study health status, measured by the St Georges Respiratory Questionnaire, deteriorated in those on

placebo by 3.2 units per year and by 2 units per year in those treated with fluticasone ($p = 0.004$). This improvement in health status may relate to a reduction in exacerbation rates, which have been shown to affect quality of life [15]. The threshold dose of inhaled corticosteroids for this effect has not been studied. However, there have been further studies, which have shown no definite effect of inhaled corticosteroids on exacerbations [60, 61] possibly due to the fact that relatively mild COPD patients were studied in these trials, in whom exacerbations were few.

Reduction in mucus production is also a target to prevent or attenuate exacerbations. A six month trial showed that once daily treatment with a carbocysteine lysine salt significantly decreased the frequency of exacerbations [69]. A meta-analysis of randomised controlled trial of the antioxidant and mucolytic drug N-acetylcysteine also showed it to have value in decreasing the frequency of exacerbations by around the same extent as inhaled corticosteroids [70].

Assessment

Patients with acute exacerbations in COPD typically present with increased cough, changes in

sputum volume and purulence and increased breathlessness, wheezing and chest tightness.

A number of factors obtained from the clinical history, examination and arterial blood gases are used to assess the severity of exacerbations and to judge whether the patients require admission to hospital (table 1). Particular attention should be paid to changes in mental status, which might indicate the presence of respiratory failure. Arterial blood gas measurements are important in the assessment of patients with exacerbations of COPD. However, interpretation of these results will depend on previous baseline values. Generally an arterial PaO₂ <55 mm Hg or a PaCO₂ >53 mm Hg, with accompanying acute or acute on chronic res-

Table 1

Indications for hospital assessment or admission for acute exacerbation of COPD.

Marked increase in intensity of symptoms, such as sudden development of resting dyspnoea
Severe background COPD
Onset of new physical signs (e.g. cyanosis, peripheral oedema)
Failure of exacerbation to respond to initial medical management
Significant comorbidities
Newly occurring arrhythmias
Diagnostic uncertainty
Older age
Insufficient home support

piratory acidosis indicate acute respiratory failure and are an indication for hospital admission. In the absence of respiratory failure the indications for hospital admission are judged on the ability to manage daily activity at home, the speed of worsening of symptoms or gas exchange abnormalities and the response to initial therapy in the patients' home setting [18–20]. Peak flow measurements are not as useful in COPD as they are in asthma in determining the need for hospital admission [71]. The lack of clear criteria for admission is one factor that results in the high re-admission rate (between 17–28% of patients) in patients discharged from emergency departments.

Supported discharge has now been shown to be effective in patients with mild to moderate ex-

acerbations of COPD [72–74]. However, re-admission rates are high, up to 30%. A recent study in a cohort of 33,384 elderly patients with COPD, aged 65 years or older, in Ontario, Canada showed that although patients with hospital stays of less than 4 days were younger and had fewer co-morbidities, they were 39% more likely to be admitted and 45% more likely to die within 15 days post-discharge, compared with those who stayed 4–6 days in hospital [75]. This study suggests that some elderly patients with COPD are being prematurely discharged. However, this study was conducted in a setting without supported discharge and mortality is much lower when supported discharge is employed [72–74].

Management

The aims of management in exacerbations of COPD are to relieve airway obstruction, correct hypoxaemia, address any co-morbid disorder that may contribute to the respiratory deterioration and also to treat any precipitating factors such as infection.

Management at home

Most exacerbations in COPD are treated in primary care. A minority of patients are sent for admission to hospital. The British Thoracic Society has suggested guidelines [19] to help determine which patients might be more suitably sent to hospital. However these guidelines have never been fully tested.

Bronchodilator therapy

Home management of exacerbations of COPD involves increasing the dose and frequency of existing bronchodilator therapy. If not already used, anticholinergic therapy may be added until symptoms improve. There is evidence that the use of a metered dose inhaler and spacer device has a similar effect as nebulised bronchodilators for exacerbations of COPD [76]. In exacerbations of COPD it is probably safer to use air as the driving gas for nebulisers, rather than oxygen and continue with oxygen by nasal prongs. Long-term use of the

nebuliser therapy after the acute episode is not routinely recommended.

There is still controversy over the use of antibiotics in AECOPD (see below). If antibiotics are given they should be simple antibiotics, modified according to local bacterial resistance patterns. Amoxicillin can be given as a first line treatment or Co-amoxiclav in those that fail to respond or who are known to have a beta-lactamase producing organism [17–19]. Clarithromycin is an alternative in patients who are hypersensitive to penicillin.

The use of corticosteroids in acute exacerbations of COPD is now well established, with at least four controlled trials showing benefit. In a study of 27 patients with exacerbations of COPD treated as an out patient, oral corticosteroid showed a greater rate of improvement in oxygenation, spirometry and a decrease in treatment failures, compared with placebo [77]. The lowest dose used in these trials was 30 mg of prednisolone for 2 weeks, but the threshold dose that will produce improvement is not known. Corticosteroids have been shown to be effective in exacerbations in COPD in both primary and secondary care [77–80].

Hospital treatment

The decision to treat at home or in hospital can be difficult. Measurement of FEV₁ is difficult

Table 2

Indications for invasive mechanical ventilation.

Persistent hypoxaemia (PaO₂ <5.3 kPa, 40 mm Hg) despite maximum therapy

Worsening acute respiratory acidosis despite maximum therapy (pH <7.25, H⁺ >55 nmol/l).

Other relative indications are:

severe breathlessness

respiratory frequency higher than 25 breaths/min in association with severe dyspnoea

somnolence, impaired mental status

inability to protect airway

inability to clear copious secretions

respiratory arrest

Table 3

Management of severe but not life-threatening exacerbations of COPD in hospital.

Assess severity of symptoms, blood gases, chest x-ray
Administer controlled oxygen therapy – repeat arterial blood gas measurements after 30 minutes
Bronchodilators
increase dose frequency
combine β_2 -agonists and anticholinergics
use spacers or air-driven nebulizers
consider adding intravenous aminophylline, if needed
Glucocorticosteroids
oral or intravenous
Antibiotics
when signs of bacterial infection, oral or occasionally intravenous
consider mechanical ventilation
At all times
monitor fluid balance and nutrition
consider subcutaneous heparin
identify and treat associated conditions (e.g. heart failure, arrhythmias)
closely monitor condition of the patient

in sick patients but in general a peak expiratory flow of <100 l/min and an FEV₁ <1 litre indicates a severe exacerbation [81, 82], but these values clearly depend on the severity of the underlying disease.

Recent guidelines suggest management of patients with AECOPD admitted to hospital and for those with severe exacerbations admitted to the ICU (table 2) [20]. A PaO₂ of <6.7 kPa (50 mm Hg), a PaCO₂ of >9.3 kPa (70 mm Hg) and a pH of <7.3 suggest a life threatening episode that needs close monitoring or ICU management [83]. Chest radiographs are useful in identifying alternative diagnoses that can mimic symptoms of an exacerbation. An ECG may help in the diagnosis of right ventricular hypertrophy, arrhythmias or ischaemic episodes. The presence of pulmonary embolism can be very difficult to diagnose especially in COPD. Spiral CT pulmonary angiography is the best tool available for the diagnosis of pulmonary embolism. Ventilation/perfusion scanning is of no value. A low diastolic blood pressure, an inability to increase PaO₂ >8 kPa (60 mm Hg) despite oxygen therapy also suggest pulmonary embolism. Measurement of whole blood count may identify polycythaemia (haematocrit >55%). White blood cell counts are not usually informative.

The first action in treating patients with exacerbations of COPD in the Accident & Emergency Department is to provide controlled oxygen therapy and to determine if the exacerbation is life threatening in which case admission to the HDU or ICU is indicated. The management of acute exacerbations of COPD is summarised in table 3.

Oxygen therapy

The aim of oxygen therapy is to maintain adequate oxygenation (PaO₂ >8 kPa (60 mm Hg or saturation >90%) without worsening hypercapnea. In many patients who have chronic hypoxaemia, a target PaO₂ of >60 mm Hg can be accepted after

administration of oxygen. Oxygen is given in the form of 24–28% oxygen by Venturi mask or 1–2 litres through nasal prongs. Oxygen masks provide more accurate inspired oxygen concentrations but are less well tolerated by patients than nasal prongs. Arterial blood gases should be reassessed to ensure satisfactory oxygenation without added CO₂ retention and acidosis.

Bronchodilator therapy

Increased airways obstruction in patients with exacerbations in COPD results in increased respiratory work, hyperinflation, respiratory muscle mechanical disadvantage and impaired ventilation/perfusion matching causing hypoxaemia. The relief of airflow obstruction by bronchodilator therapy is a major goal in the treatment of exacerbations in COPD.

Short-acting inhaled β_2 -agonists are the preferred initial bronchodilator for the treatment of acute exacerbations of COPD [17–20]. Although usually given in nebulised form there is evidence that administration of β_2 -agonists via a metered dose inhaler and a spacer device has equal efficacy to nebulised therapy [76]. Nebulisers should be powered by compressed air rather than oxygen if the PaCO₂ is raised in order to prevent worsening hypercapnia and acidosis. Oxygen can continue to be administered by nasal prongs 1–2 l/minute during nebulisation. If there is not a prompt response to a beta-agonist or if the patient has a very severe exacerbation, the anticholinergic drug ipratropium bromide can be added, although the evidence supporting the combination of these two bronchodilators is controversial [84–86].

The role of intravenous aminophylline treatment for exacerbations of COPD is also controversial. A recent meta-analysis of its use has not shown any benefit [87].

Glucocorticosteroids

Several studies have now shown that glucocorticosteroids given to patients with acute exacerbations are effective in reducing symptoms and improving lung function [77–80]. In patients admitted to hospital for acute exacerbations in COPD, a randomised controlled trial showed that patients treated with oral systemic corticosteroids had fewer treatment failures, better spirometry and a shorter hospital stay [80]. Furthermore, the risk of treatment failures was reduced by 10% and the FEV₁ improvement averaged 100 mls in the first three days of treatment, compared with placebo. This trial also showed that a two week and an eight week course of systemic corticosteroids were similar with respect to the clinical outcome. Therefore a shorter course of treatment, which should reduce adverse side effects, is preferred. This is supported by a further randomised controlled trial of 30mg of prednisolone given for two weeks to hospital patients with exacerbations of COPD, which showed a small improvement in FEV₁ and a reduction in hospital stay of around one day, compared with placebo [79]. Additional studies are required to determine the optimal dose and duration of corticosteroid therapy during acute exacerbations in COPD. A recent study has shown that nebulised corticosteroids may also be beneficial in AECOPD [88]. Currently systemic corticosteroids are recommended for all patients presenting with acute exacerbations in the absence of significant contraindications. Corticosteroids should be discontinued after the acute episode, since clinical improvement during an exacerbation with corticosteroids does not necessarily indicate the need for long-term oral or inhaled corticosteroids.

Antibiotic therapy

Bacteria play either a primary role in the development of exacerbations of COPD or represent a secondary infection following an initial viral process [89]. The role of bacteria in exacerbations of COPD remains controversial, since bacterial species are present in the airways of between 25–50% of patients with COPD even when in a stable condition [36–38]. A number of randomised placebo controlled trials have shown some benefits of the use of antibiotics during acute exacerbations of COPD, but no benefit if used to prevent exacerbations [90, 91]. A recent meta-analysis evaluated 9 randomised, placebo controlled trials of antibiotic therapy in AECOPD between 1957 and 1992 [90]. This established a small but significant benefit from antibiotic therapy in AECOPD, which was supported by a similar analysis of placebo controlled trials [91]. The largest and probably the best study of antibiotics in acute ex-

acerbations of COPD is that of Anthonisen and co-workers who studied a total of 362 exacerbations in 173 patients in a placebo controlled randomised double-blind study design [10]. Compared with placebo, the rate of symptom resolution and improvement in peak expiratory flow during the exacerbation was slightly, but significantly faster for patients who were treated with antibiotics. The benefit from antibiotics was most evident for patients with the most symptoms. This has led to the use of antibiotics in patients who have at least two of the three cardinal symptoms – increasing breathlessness, increasing sputum volume, increasing sputum purulence [19].

In most cases sputum gram stain and cultures are not necessary because of evidence of bacterial contamination in clinically stable patients [92]. The choice of antibiotics depends on the local antibiotic policy and the pattern of local pathogens. Oral rather than intravenous antibiotics and simple antibiotics, such as amoxycillin, should be used. In recent years there has been an increase in the frequency of beta-lactamase production by *Haemophilus influenzae* and *Moraxella catarrhalis* and more recently strains of penicillin-resistant pneumococci have emerged [93]. Failure to respond to simple antibiotics or a knowledge of previous beta-lactamase producing organisms in the sputum or in severe exacerbations indicates the need for co-amoxiclav, a 2nd or 3rd generation cephalosporin, a fluroquinolone or a newer macrolide.

The hypothesis that recurrent bacterial infections have a role in the progression of COPD is unproven and remains controversial [94].

Sputum clearance

There is no convincing data to support the use of pharmacological measures, such as N-acetylcysteine, iodides and DNase, to improve mucokinetics in exacerbations [17–19]. The use of mechanical techniques, such as physiotherapy [95], has no proven value during exacerbations of COPD, unless a large amount of sputum is produced (>25 ml sputum produced per day) or there is mucus plugging with lobar atelectasis [96]. Physiotherapy is not recommended in acute or chronic respiratory failure.

Diuretics

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

Anticoagulants

Prophylactic subcutaneous heparin should be used for patients with exacerbations of COPD, particularly those who are immobile and those with acute or chronic respiratory failure [97].

Respiratory failure

Ventilatory support should be considered in those patients with severe acidosis (pH <7.26) and/or a rising PaCO₂, who fail to respond to supportive treatment and controlled oxygen therapy [98]. There is considerable debate over the appropriateness of invasive ventilation in end-stage COPD patients. Mortality amongst COPD patients with respiratory failure is no greater than mortality among patients ventilated for non-COPD causes. However, duration of ICU stay may be longer in patients with COPD than in uncomplicated post-operative cases.

Factors which encourage the use of invasive ventilators include:

- A demonstrable remedial reason for recurrent decline. For example radiographic evidence of pneumonia or drug overdosing.
- The first episode of respiratory failure.
- Acceptable quality of life, habitual level of activity.

Factors which are likely to discourage the use of invasive ventilators include:

- Previously documented severe COPD that has been assessed and found to be unresponsive to the relevant therapy.

- Poor quality of life – for example being house bound despite the maximum appropriate therapy.
- Severe co-morbidities – for example pulmonary oedema or neoplasm.

Neither age nor the level of PaCO₂ are a guide to the outcome of assisted ventilation in hypercapnic respiratory failure due to COPD [19]. A pH of >7.26 is a better predictor of survival during an acute episode [98]. The patient's own wishes, if known, should be considered when making the decision regarding ventilation.

Other therapy has been used to try and avoid the need for intubation and IPPV. This includes the use of the respiratory stimulant Doxapram to increase alveolar ventilation. There have been no controlled trials of Doxapram, although one study showed that patients treated with Doxapram had less increase in PaCO₂ during the first two hours after admission to hospital [99]. However, no study has shown that Doxapram decreases the need for assisted ventilation.

Noninvasive ventilation (NIV)

Randomised controlled trials have shown benefit of NIV in acute COPD exacerbations with early correction of pH, together with reduction in breathlessness, compared with a control standard therapy group [100, 101]. Significant reductions in intubation rates and mortality have been shown with NIV, together with a shorter length of hospital stay, compared to those receiving conventional therapy [100–103]. Complications, which were specifically associated with the use of mechanical ventilation, such as nosocomial pneumonia, were also reduced. The technique can be applied in a general ward and, although a high dependency area is preferable, intensive care is unnecessary, thus reducing costs. A recent study showed that NIV could be applied on general wards, though patients with more severe acidosis had a worse outcome [104]. Factors affecting outcome are severe

functional and clinical disease, severe acidosis, pneumonia, neurological deterioration and underweight [105, 106].

The best time to start non-invasive ventilation is not established. However, a recent consensus statement from the American Associations of Respiratory Care [107] endorses the early use of NIPPV in acute exacerbations of COPD in the following conditions:

- Respiratory distress with moderate/severe dyspnoea
- pH <7.35 or PaCO₂ above 45 mm Hg
- Respiratory rate of 25/minute or greater

NIPPV is contra-indicated in the presence of cardiovascular instability, craniofacial trauma or an inability to protect the airways.

Table 4

Discharge criteria for patients with acute exacerbations of COPD.

Inhaled β₂-agonist therapy is required no more frequently than every 4 hrs

Patient, if previously ambulatory, is able to walk across room

Patient is able to eat and sleep without frequent awakening by dyspnoea

Patients has been clinically stable for 12–24 hrs

Arterial blood gases have been stable for 12–24 hrs

Patient (or home caregiver) fully understands correct use of medications

Follow-up and home care arrangements have been completed (e.g. visiting nurse, oxygen delivery, meal provisions)

Patient, family, and physician are confident patient can manage successfully

Hospital discharge and follow-up

There are no data indicating the optimal duration of hospitalisation for acute exacerbation of COPD [108–112]. Discharge criteria have been suggested (table 4). Follow-up assessment is recommended 4–6 weeks after discharge from hospital (table 5). The presence of hypoxaemia during the exacerbation should prompt re-checking of blood gases at discharge. If the patient remains hypoxaemic, the need for long term out-patient oxygen therapy should be considered and should be assessed when clinical stability has been established.

Recent randomised controlled trials have shown that 20–30% of acute exacerbations of COPD sent to hospital can be safely discharged home with supported discharge without adverse outcome, compared with hospital admission [72, 73]. Supported discharge following admission to hospital has been shown to be effective in a randomised controlled trial [74].

Table 5

Follow-up assessment 4–6 weeks after discharge from hospital for an acute exacerbation of COPD.

Ability to cope in usual environment
Measurement of FEV ₁
Reassessment of inhaler technique
Understanding of recommended treatment regimen
Need for long-term oxygen therapy and/or home nebulizer (for patients with severe COPD)

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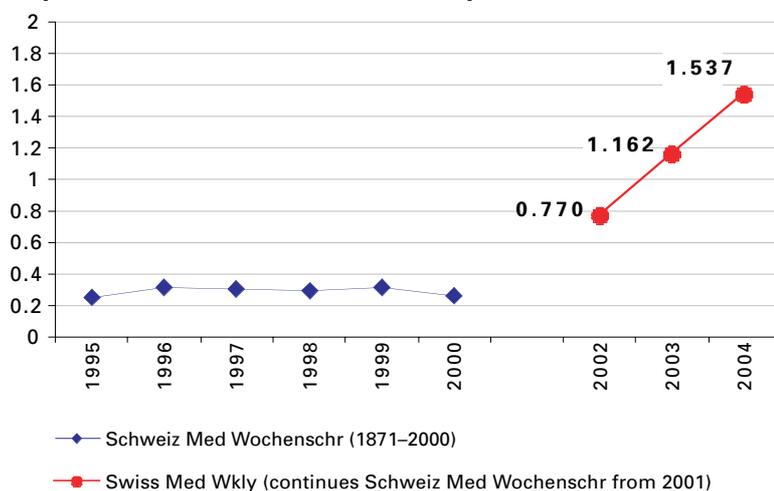
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