Strategies for improving outcomes of COPD exacerbations

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Abstract: COPD is uniquely situated as a chronic disease at the beginning of the 21st century; it is not only an established major cause of mortality and morbidity but is increasing in prevalence despite current medical interventions. In addition COPD is not a stable disease but its natural history is punctuated by periods of acute deterioration or exacerbations. Exacerbations generate considerable additional morbidity and mortality, and directly affect patients' quality of life. However, despite significant advances in understanding and treating this disease, exacerbations continue to be the major cause of COPD-associated hospitalization, and provision for their management incurs considerable health care costs. This review will consider the current management of COPD exacerbations and how new clinical strategies may improve outcome of these important clinical events.
Keywords: COPD, exacerbation therapy

Introduction

There can be little doubt that COPD is currently one of the most important chronic diseases worldwide. Whether the burden of disease is measured by mortality, estimates of morbidity, or associated health care burden and costs, it is consistently ranked at or near the top in the hierarchy of global diseases (Murray and Lopez 1996). However, unlike other diseases of comparable importance both its prevalence and consequent health care burden are increasing (Murray and Lopez 1996). Furthermore the emergence of COPD as a significant disease outside its established focus in the industrialized nations suggests growth in the international impact of this disease will continue (WHO 2000).

The natural history of COPD is of progressive deterioration in lung function as a result of persisting lung inflammation in response to inhaled pollutants, chiefly tobacco smoke (Pauwels et al 2001). This process results in the eventual development of chronic symptoms which may eventually become disabling (Celli et al 2004). The course of the disease is punctuated by episodes of acute deterioration in symptoms termed exacerbations. COPD exacerbations are associated with heightened levels of airway and systemic inflammation (Bhowmik et al 2000; Wedzicha et al 2000) and consequently contribute to disease progression (Kanner et al 2001; Donaldson et al 2002), and have prolonged effects on functional ability (Donaldson et al 2005) and health status (Seemungal et al 1998). There is currently no universally accepted definition of exacerbation, which may in part be due to the heterogeneity of these events but also due to the lack of an objective diagnostic measure or "gold standard" for the symptom-based diagnostic criteria that are in common usage (Seemungal et al 1998; Celli et al 2004). The median annual frequency of exacerbations using a symptom based diagnostic system is between two and three (Seemungal et al 1998); however, certain individuals suffer a greater number of exacerbations per year. These frequent exacerbators are at particular risk of the adverse consequences of

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exacerbations, with faster decline in FEV_1 (Donaldson et al 2002), worse health status (Seemungal et al 1998), and greater risk of hospitalization (Garcia-Aymerich et al 2001) than their counterparts with infrequent exacerbations.

The etiology of exacerbations is complex, with a number of environmental agents identified as playing a role in their genesis. The most commonly detected trigger for exacerbations is airway infection, and a role for respiratory viral (Seemungal et al 2000b, 2001; Rohde et al 2003) and bacterial (Sethi et al 2000; White et al 2003) infection has been shown not only in initiating but also in modulating the severity of these events. However, not all exacerbations are associated with an identifiable pathogen, and a role for environmental pollution (Yang et al 2005) and changes in temperature (Koskela et al 1996) have been suggested.

Considering the spectrum of disease and the array of etiologies that may trigger exacerbations or modulate their natural history, it is no surprise that there is marked heterogeneity both in the clinical severity and time course of these events (Seemungal et al 2000a). Hence, predicting responses to prescribed therapy can be difficult. Whilst current pharmacological therapies target the inflammation, infection and bronchoconstriction associated with exacerbations, their efficacy even in combination is limited, and targeting therapies to presumed etiologies of particular exacerbations remains largely a matter of clinical judgment. Furthermore, the prescription of pharmacological treatments alone does not address the deleterious effects on functional performance, and psychological and social factors caused by exacerbation.

Predicting outcome of exacerbations is therefore problematic; however, patients with more severe disease at baseline are less likely to do well (Garcia-Aymerich 2001; Wouters 2004), particularly those with poor baseline functional capacity (Garcia-Aymerich et al 2003). Indeed, following severe, hypercapnic, exacerbations requiring hospital admission, over a third of patients may require mechanical ventilation, with in-hospital mortality more than 10% (Connors et al 2004). Furthermore, the outcomes following admission remain poor, with 80% of patients requiring inpatient management of a severe exacerbation re-admitted within a year (Chu et al 2004). The outcome of less severe exacerbations managed in primary care is less well described. However, observational studies have revealed that a significant proportion of patients experiencing exacerbation symptoms fail to recover back to baseline levels (Seemungal et al 2000a) and that poor outcomes are often related to failure to seek appropriate therapy (Wilkinson et al 2004).

Despite recognition of the poor prognosis associated with COPD exacerbations requiring hospitalization and attempts to summarise the evidence base in management guidelines there are indications that appropriate standards of care for acute exacerbations are not met and simple assessments to identify at risk patients not completed (Roberts et al 2001). There is obviously considerable scope to improve management of COPD exacerbations, and thus to improve outcomes. This article will review potential strategies that may improve delivery of currently available therapies and hence improve exacerbation outcomes, whilst the pursuit of novel more efficacious pharmacotherapy continues.

Prevention is better than cure

Prevention of exacerbations will have obvious benefits for patients and health care providers alike. There are a number of interventions that have been shown to reduce the incidence of exacerbations; however, their use is currently far from systematic (Johnson and Stevenson 2002). It is of course difficult to target potentially effective preventive therapies if the appropriate diagnosis of COPD is not initially established. The findings of the confronting COPD study show that under-diagnosis of COPD and lack of public awareness of the disease remain significant problems which may impact on outcomes of the disease (Rennard et al 2002). Improving diagnosis rates particularly with the provision of access to spirometry in primary care is fundamental to the appropriate provision of preventive therapy.

Tobacco smoking is the key etiological factor in the development of COPD and smoking cessation therefore should be central to any management strategy for the condition. Smoking cessation has established beneficial effects on the rate of decline in lung function (Fletcher and Peto 1997), chronic symptoms (Willemse et al 2004), and the development of co-morbidities. In addition, beneficial effects of stopping smoking on exacerbation frequency have been described (Kanner et al 2001), and furthermore the impacts of exacerbations in terms of FEV_1 decline (Kanner et al 2001) and hospitalization (Gotfredsen et al 2002) are ameliorated and response to therapy improved (Chang et al 1995; Burge et al 2003). The importance of smoking cessation early in the disease state is highlighted by the observation that the impact of exacerbations on FEV_1 decline is apparent in smokers but not ex-smokers in mild disease (Kanner et al 2001), but the beneficial effect of smoking

cessation on this effect of exacerbations is no longer apparent in patients with more established airway obstruction (Donaldson et al 2002).

Respiratory infections are important triggers to exacerbations and hence are an appropriate target for preventive therapy. Influenza vaccination has been shown to reduce the need for out-patient and in-patient care and to benefit mortality in elderly patients with lung disease (Nichol et al 1999). The evidence that pneumococcal vaccination is of similar benefit in this patient group is lacking; however, influenza and pneumococcal vaccination are widely recommended to all patients with established COPD, and improving compliance is an important target in primary care.

There is now an evidence base suggesting that although inhaled corticosteroid therapy does not impact on the rate of lung function decline, it may have beneficial effects on exacerbation frequency and decline in health status (Burge et al 2000). The beneficial effects of inhaled corticosteroids when used in combination with long acting β_2-agonists are more pronounced (Calverley et al 2003). Inhaled long-acting anti-cholinergics have also been shown to have beneficial effects on exacerbation frequency and hospitalization for exacerbations, with effects more pronounced with greater severity of disease (Niewohner et al 2005).

Recent guidelines have tried to simplify the algorithms for prescription of these medications (Celli et al 2004; NICE 2004), but the data and therefore guidance are lacking on whether the beneficial effects of inhaled therapy are additive if multiple therapies of different classes are used. Furthermore, prescription practice remains primarily focused on controlling stable symptoms rather than preventing or modulating the severity of exacerbations. Particularly in patients with a history of frequent exacerbations, the prescriber should not ignore the goal of preventing exacerbations, as well as managing day-to-day symptoms.

Issues of poor compliance with inhaled medication have not been fully addressed in COPD, nor have potential difficulties with use of inhaler devices. Improving compliance with inhaled therapy can have tangible benefits for patients and practitioners alike (Worth and Dhein 2004); however, understanding of this problem, particularly in a population of elderly patients with COPD and significant co-morbidities, is incomplete.

Use of oral therapies, particularly mucolytic agents, currently varies greatly from country to country. The evidence for their efficacy in preventing exacerbations has been until recently based upon a number of smaller studies. However a meta-analysis (Cochrane review) demonstrated that a significant reduction in exacerbation frequency could be gained by regular use of mucolytics such as N-acetyl cysteine (Poole and Black 2001). However, the mechanism of action, whether mucolytic or antioxidant, remains uncertain. These findings are somewhat at odds with the recent results of the BRONCUS study. This large multi-centred study of the effects of NAC over 3 years failed to show an overall benefit on exacerbation frequency. However, a sub-group analysis suggested a benefit in patients not receiving inhaled corticosteroids (Decramer et al 2005). Use of long-term oral corticosteroids has been associated with adverse outcomes with high levels of systemic side-effects; therefore long-term use is not recommended (Walters et al 2005). The role of novel anti-inflammatory oral therapies such as selective phosphodiesterase inhibitors or long-term antibiotic therapy in exacerbation prevention needs to be determined.

Whilst pharmacotherapies clearly have a role to play in preventing exacerbations, there remains a need for additional physical therapies in reducing the impact of these events on patients and carers. Pulmonary rehabilitation is a multi-disciplinary strategy to optimize symptom control, physical capacity, and health-related quality of life and to limit the psychological impact of disease and to prevent complications and exacerbations (Pauwels et al 2001). It has become established as a useful strategy for improving exercise tolerance and functional ability in subjects with COPD, with associated benefits on health status (Goldstein et al 1994; Ries et al 1995; Troosters et al 2000). Despite these benefits, results from trials that examined effects on exacerbation frequency are at best mixed. One such study, in a large group of patients with mixed respiratory disease, largely COPD, found that a 6-week course of pulmonary rehabilitation had no effect on numbers of hospital admissions but did considerably reduce the length of stay and requirement for home visits by general practitioners (Griffiths 2000). It is perhaps surprising when poor functional status is a risk factor for hospital admission (Garcia-Aymerich et al 2003) that methods to improve functional status have not affected hospital admissions.

A study of a new approach to pulmonary rehabilitation investigated the benefit of initiating rehabilitation immediately after discharge following admission for an acute exacerbation. Despite few patients, with this approach the treatment group had fewer visits to accident and emergency, with trends towards fewer hospital admissions and bed days in the 3-month follow up period (Man et al

2004). Clearly, pulmonary rehabilitation can play a major role in the management of COPD and in improving exacerbation outcome; however, further studies are required to determine the optimal timing of this intervention with respect to improving exacerbation outcomes and preventing recurrence.

Health care delivery and exacerbation outcomes

There is considerable evidence that currently available therapies such as antibiotics (Anthonisen et al 1987), and oral corticosteroids (Thompson et al 1996; Davies et al 1999; Niewoehner et al 1999; Aaron et al 2003) improve exacerbation outcomes; however, debate continues whether these therapies are indicated across the spectrum of disease severity and heterogeneity of exacerbation phenotypes. If we accept that the administration of additional therapies at exacerbation benefits recovery then in the absence of established self-management protocols the patient must consult their physician before therapy can be administered and the benefits obtained. Using a symptom-based definition of exacerbation with daily data collection, it has been demonstrated that a significant proportion of exacerbations are not reported to a physician for therapy (Wilkinson et al 2004). Importantly these "unreported exacerbations" were associated with worse health status and patients with persistently poor reporting behavior were those most likely to be hospitalized for emergency management of exacerbations (Wilkinson et al 2004).

The causes of poor health utilization behavior are likely to be complex, but may be affected by poor patient understanding of their condition (Rennard et al 2002), high levels of anxiety and depression common in patients with COPD (Okubadejo et al 1996), social isolation and poor access to health care. Even if health care access is optimized this inadequate exacerbation reporting behavior persists (Wilkinson et al 2004), suggesting that patients' perception of their condition and attitudes to therapy may be paramount in modulating health-seeking behavior at exacerbation.

When patients do seek therapy for exacerbations they often delay presentation for several days after the onset of symptoms (Wilkinson et al 2004). Those individuals who present for therapy early have better outcomes than those who delay presentation after the onset of symptoms (Wilkinson et al 2004). This suggests that improving patient reporting behavior will improve the beneficial effects that standard exacerbation therapy has on outcomes. Interventional studies using an early treatment intervention are required.

One model of therapy that may improve patients' symptom perception and reduce time taken to initiate therapy is self-management. Those studies that have been undertaken suggest that self-management plans improve health related quality of life (Howland et al 1986; Littlejohns et al 1991; Bourbeau et al 2003) and may reduce hospitalization (Bourbeau et al 2003). However, such studies have, quite appropriately, used models of self-management that have affected all aspects of patients' disease; both stable and exacerbation, and have thus shown improvements in indicators of overall health such as quality of life measures. Whether self-management of exacerbations of COPD is appropriate, safe, and efficacious requires further study.

The burden associated with hospital admission for COPD exacerbations is extremely high: in the UK acute exacerbations account for 10% of all acute medical admissions (Kendrick et al 1994) and age-adjusted admission rates have risen greatly in recent years (Guest 1999). Alternatives to traditional inpatient care have been sought to reduce this burden on secondary care. A number of intervention studies using a "hospital at home" service have now been evaluated. These innovations aim to provide a complete and effective care package in the patients' home as an alternative to admission or as a way of facilitating early discharge from hospital. A systematic review of the key studies, involving 754 patients in 7 studies, concluded that these schemes were as safe and as effective as current in-patient care (Ram et al 2004). Accepting the inherent flaws of such analyses; differing inclusion and exclusion criteria, and variation in models of care used and primary outcomes measured, the data would suggest the safety of such schemes is at least equivalent to inpatient care. However, audit of UK in-patient exacerbation care reveals that the level of in-patient care given is often suboptimal (Roberts 2001), and therefore objective comparative standards for new models of care should be established for future studies. It is important that while these studies are performed to determine which patients and which components of care should be included in hospital-at-home schemes, the overall delivery of care for these events begins to approach the standards set out in current guidelines more closely (NICE 2004).

Preventing hospital admissions and re-admissions

The majority of health care costs associated with exacerbations are incurred by the management of severe events requiring hospitalization (Oostenbrink et al 2004). Therefore it is important that the modifiable risk factors associated with hospital admission are identified and where possible addressed. The EFRAM study performed in Spain has investigated the common features associated with hospitalization for exacerbation. The authors identified high incidence of a number of modifiable risk factors in a population of patients admitted for management of acute exacerbations. These included active smoking, low rates of involvement in rehabilitation programmes, inappropriate use of oxygen therapy, and poor inhaler technique (Garcia-Aymerich et al 2000). However, a further analysis of case control data revealed that only previous frequent admissions, disease severity as determined by the FEV_1, active smoking, and under-prescription of long-term oxygen therapy were associated with increased risk of hospitalization (Garcia-Aymerich et al 2000). These data suggest scope for interventions to prevent admission, with this evidence underlining the role of established measures such as smoking cessation and adequate provision of oxygen therapy.

It is becoming increasingly recognized that hospital admission for a COPD exacerbation is not only an important, expensive, and potentially preventable event, but may also signify that a particular individual is at risk of further exacerbations, hospitalization, and early mortality. A follow up to the EFRAM study examined risk factors for re-admission to hospital after in-patient management of an index exacerbation. During the 1.1-year follow up more than 60% of subjects were re-admitted and 29% died (Garcia-Aymerich et al 2003). In addition to the risk factors identified in the previous studies (Garcia-Aymerich et al 2000, 2001) the finding that high levels of "usual physical activity" were associated with reduced risk of re-admission suggests a potentially beneficial effect of pulmonary rehabilitation in preventing hospitalization as discussed previously, with the timing of rehabilitation early in the recovery phase important in preventing re-admission (Man 2004). A similar model of early rehabilitation as an adjunct to a hospital-at-home scheme suggests a benefit in preventing re-admission by improving functional status early in the recovery phase of an exacerbation (Murphy et al 2005). As highlighted previously, patients requiring acute non-invasive ventilation do very badly following discharge: approximately 80% were re-admitted and half died within a year (Chu et al 2004). While there is now an established role for acute non-invasive ventilation in the management of exacerbations (Brochard et al 1995; NICE 2004), the role of long-term non-invasive ventilation (NIV) in improving outcomes in these severe patients is not fully proven. While a definitive study has not been performed, current data would suggest that long-term NIV in stable COPD may reduce hospital admissions, length of stay, and importantly prove to be cost-effective compared with usual care (Tuggey et al 2003).

Health care utilization at the time of an exacerbation can also provide an opportunity to address the prevalent psychological as well as physical morbidity associated with COPD (Howland et al 1986). Recent guidelines highlight the importance of addressing these issues in the management of patients with COPD; however, there is little evidence to guide interventions or to determine their benefit (NICE 2004).

Optimizing therapy for acute exacerbations

There is now an expanding evidence base to demonstrate a beneficial effect on exacerbation outcomes for a number of existing therapies. There is for example established evidence for the use of oral corticosteroids in the management of exacerbations: they have been shown to reduce the length of hospital stay, and they can accelerate the rate of improvement in lung function (Thompson et al 1996; Davies et al 1999; Niewoehner et al 1999; Aaron et al 2003). However, the size of effect in randomized controlled trials is relatively small. There is no observable additional benefit from administration of longer courses (Niewoehner et al 1999) and current guidelines recommend a 7- to 10-day regime for hospital inpatients. The data available on the role of oral corticosteroids in the treatment of milder exacerbations, for example those seen in a primary care setting, are less substantial.

The role of antibiotics in the management of exacerbations remains controversial. Whilst analysis of studies examining the effect of antibiotics on exacerbations as a whole suggest a benefit on outcomes (Saint et al 1995), the seminal study on this topic found an outcome advantage in only treating patients with oral antibiotics who presented with symptoms of sputum volume, purulence, and dyspnea (Anthonisen et al 1987). This suggests that clinical symptoms may predict which patients will benefit from antibiotic therapy. This is confirmed by indirect evidence

that sputum purulent exacerbations are more likely to demonstrate a response to antibiotics, as they have a higher rate of isolation of bacterial airway pathogens (Stockley et al 2000). It would seem that targeting antibiotic use to more severe exacerbations associated with sputum purulence may seem an appropriate way of maximizing benefit while limiting their over-prescription.

A recent study examined the benefits of intravenous aminophylline in the acute management of exacerbations in in-patients' therapy and found no benefit in addition to standard therapy (Duffy et al 2005). Despite this evidence and the risks of serious side-effects, use of parental methylxanthines in this context remains widespread..

Clinicians are aware of the potential benefits and complications associated with the use of supplemental oxygen for patients with severe disease. The guidelines on the use of supplemental oxygen are explicit although the evidence base is weak. It is important that patients at risk of developing hypercapnic respiratory failure in response to supplemental oxygen are identified early and appropriate assessment of arterial blood gases is necessary in doing this (Plant et al 2000). The use of NIV for the management of hypercapnic exacerbations can greatly improve outcomes for the patients with severe COPD (Plant et al 2000) and there are well-established parameters encompassed in the guidelines covering appropriate indications for this treatment.

Despite guidelines on their administration, delivery of treatment in the acute stage may be sub-optimal, and evidence that specialist respiratory care is associated with better outcomes than non-specialist care suggests that appropriate use of available treatments is an important process in improving outcomes (Roberts et al 2003). Clearly there is a role for expanding specialist care, multidisciplinary teamwork, and evidence-based care pathways in the management of exacerbations.

Conclusion

Despite a wealth of new evidence from basic science and clinical research to improve our understanding of COPD exacerbations, coupled with tangible improvements in health service provision, exacerbations remain an important cause of morbidity and mortality. The natural history and consequences of these events, particularly in patients with more severe disease, has only recently been recognized. However, there are at the clinician's disposal a number of existing therapies which, if used effectively, can improve the poor outcome of COPD exacerbations. While we await the development of novel and more efficacious pharmacological therapies, the great should not become the enemy of the good. By improving the delivery of care, identifying and targeting high-risk patients and adopting a multi-disciplinary approach we can improve the outlook for patients with this prevalent and disabling disease.

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