

Management of exacerbations of chronic obstructive pulmonary disease with a focus on comorbidities

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ABSTRACT

Exacerbations of chronic obstructive pulmonary disease (COPD) are episodes of worsening of lower respiratory symptoms, especially dyspnea, sputum purulence and cough. They are usually triggered by infective factors, especially respiratory viruses. COPD is associated with considerable co-morbidity and this will also affect the nature and severity of the exacerbations. There are key interactions between exacerbations and co-morbidities including issues of differential diagnosis and higher co-morbidity in patients with the frequent exacerbator phenotype. It is, therefore, essential that any studies of exacerbation prevention in COPD also set out to evaluate the effect on co-morbidity in COPD.

Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) are episodes of lower respiratory symptom worsening, especially the symptoms of dyspnea, sputum purulence and cough. They are usually triggered by infective factors, especially respiratory viruses¹ (Figure 1). There has been much recent interest in COPD exacerbations as they lead to considerable morbidity, hospital admission and readmission, and mortality. COPD exacerbations are the most important determinant of health status in COPD² and are also important outcomes of therapies. COPD is associated with considerable co-morbidity and this will also affect the nature and severity of exacerbations. COPD patients with co-morbidities are more likely to be hospitalized than those without.³

COPD exacerbations are associated with variable amounts of airway and systemic inflammation, and this inflammation is highest in the presence of both airway bacteria and viruses.⁴ Plasma fibrinogen has been shown to be an important cardiovascular risk factor, increasing exacerbations, especially in the presence of infective factors.⁵

Exacerbation frequency

Some patients with COPD across a range of severe conditions are particularly susceptible to exacerbations. Such patients are known as frequent exacerbators, usually defined as two or more treated exacerbations per year.^{2,6} Patients with a history of frequent exacerbations have a poorer quality of life, faster disease progression, increased hospitalization and chance of hospital readmission, and increased mortality. The frequent exacerbator phenotype has also been shown to be relatively stable from year to year, and the best way to predict whether a patient is becoming a frequent exacerbator is to determine the number of exacerbations in the previous year. A key finding from the *Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints* (ECLIPSE) cohort study was that even in the *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) Stage 2 [forced expiratory volume (FEV1) 50-80% predicted], 22% of patients are frequent exacerbators and the proportion of frequent exacerbators rises with disease severity.⁶

However, there are relationships between co-morbidity and exacerbation frequency. In an analysis of a UK primary care database, Donaldson and colleagues showed that patients with higher exacerbation frequencies had a higher chance of developing a myocardial infarction and this risk was highest in the first five days of the exacerbation.⁷ Donaldson and colleagues also

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showed that, over time, patients with a history of frequent exacerbations progressively develop higher plasma fibrinogen levels.⁸ Therefore, it seems that in COPD patients, cardiovascular risk develops further over time and along with disease severity.

In a recent study of COPD patients admitted to hospital with a diagnosis of COPD exacerbations, McAllister and colleagues have shown that 8.3% of the admitted patients had criteria fulfilling a diagnosis of myocardial infarction.⁹ The earlier that an exacerbation

is treated the better the outcome with faster recovery and reduced chance of hospital admission.¹⁰ Therefore, early intervention with exacerbation treatment may actually prevent cardiovascular co-morbidity, especially myocardial infarction, and studies to confirm this are required.

Other co-morbidities have been shown to interact with exacerbation frequency. Anxiety and depression are common in COPD and associated with a worse quality of life and reduced time outdoors.¹¹ Depression

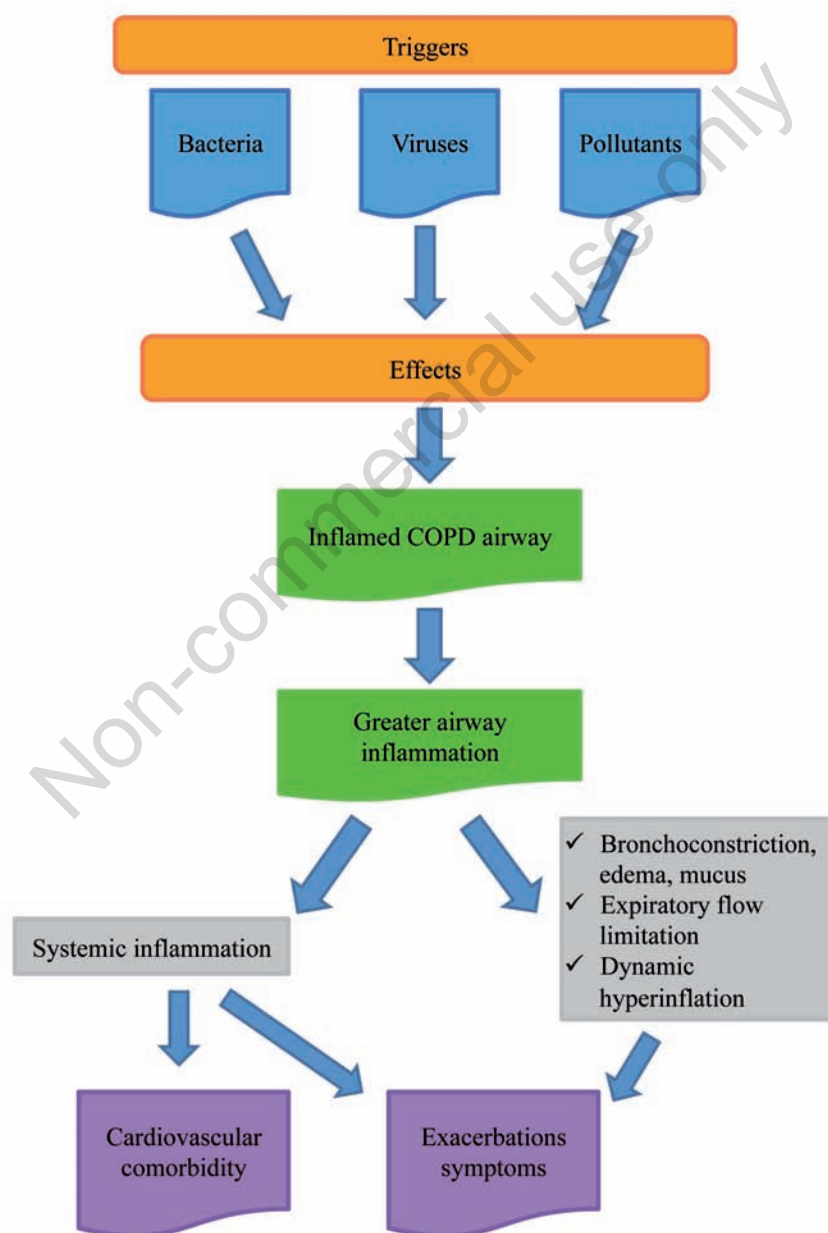


Figure 1. Pathogenesis of chronic obstructive pulmonary disease (COPD) exacerbations. Adapted from Wedzicha and Seemungal, 2007.¹

scores become worse when a patient develops an exacerbation, and patients with a history of frequent exacerbations show increased depression compared to patients with a history of infrequent exacerbations.¹¹

Gastroesophageal reflux has also been shown to relate to exacerbation frequency in the ECLIPSE observational study, though a formal questionnaire for reflux symptoms was not used.⁶ However, the mechanisms for such an effect on exacerbation frequency are not clear. Hyperinflation may be associated with gastroesophageal reflux or microaspiration may occur increasing airway irritation and thus inflammation. Reflux is common in elderly people and a significant prevalence would be expected in COPD. Further work is required to evaluate the true prevalence of reflux in COPD and potential mechanisms prior to designing specific targeted interventions.

Exacerbation severity and recovery

It is now recognized that exacerbations can last for a considerable period and a number of exacerbations do not return to normal baseline state. The longer the exacerbation, the more likely it is to be more severe.¹² The lack of complete recovery of exacerbations is likely to explain the relationship between exacerbations and lung function decline, with exacerbations contributing to around 25% of the decline.¹³ Thus any therapy that reduces COPD exacerbations may be expected to affect FEV1 decline.

A number of factors are associated with prolonged recovery of exacerbations including respiratory viral infection and seasonal changes with longer exacerbations in the winter months.¹⁴ Patients with heart failure also have longer exacerbations and especially the symptom of dyspnea may be prolonged.¹⁵ This may lead to issues of differential diagnosis of an exacerbation, especially when COPD is complicated by comorbidity.

There has been some interest in the role of pulmonary embolism at COPD exacerbations and the hypothesis that exacerbations may trigger pulmonary embolic events is plausible since acute infections are known to predispose to deep venous thrombosis and pulmonary embolism. COPD patients are often elderly, may be immobile, and often have systemic inflammation and co-morbid conditions, all of which increase susceptibility to venous thromboembolism. Both COPD exacerbations and pulmonary embolism may present solely with dyspnea and thus diagnostic difficulties may occur. Although initially a study suggested that pulmonary embolism may be rather common,¹⁶ further studies actually suggested a low prevalence of pulmonary embolism at exacerbations.¹⁷ It is, therefore, likely that community-treated exacerbations are rarely associated with pulmonary em-

bolism but that this is more common with hospitalized exacerbations or those events complicated by respiratory failure.

Implications of co-morbidity for the management of chronic obstructive pulmonary disease exacerbations

An important issue, as discussed above, is that patients with concomitant COPD and heart failure are more likely to have longer exacerbation events and thus the differential diagnosis of exacerbation and comorbidity is important. COPD patients with comorbidity are more likely to require hospital admission and should, therefore, be treated promptly on development of an exacerbation to avoid hospitalization. On development of an exacerbation, confirmation of the degree of co-morbidity is essential, referral to appropriate specialists may be required, and careful follow up is essential.

A number of interventions can reduce exacerbations, including long-acting bronchodilators alone or in combination with inhaled corticosteroids (ICS) and oral phosphodiesterase 4 (PDE4) inhibitors. One of the issues of large-scale clinical trials is that patients with comorbidities, especially cardiac problems, are generally excluded. However, in the *TOwards a Revolution in COPD Health* (TORCH) study, in which a combination of a long-acting β adrenergic agent (salmeterol) with fluticasone (ICS) was compared to placebo and its components,¹⁸ some reduction in cardiac events was found. Oral PDE4 inhibitors as anti-inflammatory agents that are effective in preventing exacerbations in patients with a predicted FEV1 below 50%¹⁹ may also potentially have effects on various comorbidities, including diabetes and cardiac events. Further large-scale studies are currently in place to evaluate the effect of COPD therapies on cardiac events.

Recently, interest has been shown in the effects of therapies that reduce cardiac risk of COPD patients. In an observational study, Mancini and colleagues showed that statins or combinations of cardioprotective therapies can reduce hospitalization due to COPD.²⁰ Similarly, COPD patients on β -blockers in observational studies have been shown to have a better outcome and reduced mortality with hospital admission, with suggestions that there may also be a direct effect on COPD exacerbations.^{21,22} Interventional controlled studies are now required with these therapies to confirm the epidemiological findings.

Conclusions

Exacerbations are important events in the natural history of COPD and an important outcome measure for interventions. However, there are key interactions

between exacerbations and co-morbidities including issues of differential diagnosis and higher co-morbidity in patients with the frequent exacerbator phenotype. It is, therefore, essential that any studies of exacerbation prevention in COPD also set out to evaluate the effect on co-morbidity in COPD.

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