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# Natural history of successive COPD exacerbations

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Exacerbations of chronic obstructive pulmonary disease (COPD) are episodes of respiratory symptom worsening that are usually associated with infective triggers and variable amounts of airway and systemic inflammation.[1] There has been much interest in COPD exacerbations as they lead to considerable morbidity, hospital admission and readmission and mortality. COPD exacerbations are the most important determinants of health status in COPD[2] and are important targets for therapies both from the point of view of treating the event and prevention.

It is now known from a number of studies that COPD exacerbations affect disease progression[3 4] and have an effect on accelerating forced expiratory volume in 1 s decline independent of cigarette smoking. Some patients with COPD across disease severities are particularly susceptible to exacerbations and are known as frequent exacerbators[2 5] and these patients are at a greater risk of poor health status, faster disease progression and mortality. The best predictor of a subsequent exacerbation and hospital admission is a history of previous exacerbations.[2 5] Thus, it is important to understand the natural history of exacerbations and especially how severe exacerbations evolve as these are associated with significant healthcare cost.

Most studies of the epidemiology of COPD exacerbations to date have used either cross sectional data or prospective data over a relatively short follow-up. A study from the London COPD cohort in a relatively small number of patients but followed on a daily basis for around 3 years showed that over time exacerbations are associated with more symptoms of dyspnoea and sputum purulence, probably reflecting also the increased severity of the underlying disease.[6] Data from a recent 10 year study from two population cohorts recruited to study cardiovascular risk showed that hospitalisation in COPD is associated with an increase in both short and long term mortality.[7] Thus, there is a need to understand more clearly determinants of a first severe exacerbation or hospital admission in COPD patients and how this relates to subsequent admissions, but no studies have followed patients from the same time point in the natural history of the disease so that a first exacerbation can be identified.

This issue has now been explored in a study published by Suissa and colleagues.[8] Patients were recruited from a large comprehensive database in Quebec, Canada, and included in the analysis if they received a first prescription of a therapy to treat airways disease to form a unique inception COPD cohort. COPD patients were then followed to the first severe exacerbation requiring hospital admission and then followed on through successive exacerbations. The authors report that each successive exacerbation was associated with a decreased inter-exacerbation interval till death. The risk of severe exacerbations is estimated to be three times more likely after the second than after the first exacerbation and the risk increases progressively through successive exacerbations. This reflects the fact that exacerbations may not recover to the usual stable state[9] and may be associated with increased airway inflammation,[10] lung function decline, increased bacterial colonisation[11] and thus increased susceptibility to further exacerbations.

As this was a database study, there is no detailed lung function to substantiate these observations and severe exacerbations were recorded from hospital discharge records. The age of the COPD patients (mean 75 years in the entire cohort) and frequency of severe exacerbations suggest that some of these patients had already advanced disease even at entry to the cohort. A reassuring feature is that patients who entered the cohort at a later period in time after 2000 showed a longer time from the first to the second severe exacerbation suggesting improved management of COPD and awareness of exacerbations.

An interesting finding in this study is that the time between the first and second severe exacerbation in the cohort was relatively long at between 2 and 5 years depending if the inter-exacerbation interval was corrected for death. It is possible that the first hospital admission was related to deterioration of symptoms in patients with relatively untreated COPD and perhaps the addition of another comorbidity such as pneumonia or heart failure, especially as the average age at the time of the first exacerbation was 75 years. Optimisation of treatment of COPD on this occasion and education may be responsible for a period of relative stability and then disease progression may account for the increased susceptibility to exacerbations. The influence of comorbidity may also modulate exacerbation susceptibility and we know that patients with heart failure have longer and thus more severe exacerbations and more likely to be hospitalised.[12] However, there is no information in this study on the frequency of moderate exacerbations requiring oral corticosteroids and/or antibiotics after the first admission and thus it is not possible to define which patients had actually developed a true, frequent exacerbation phenotype during the early follow-up period.

It has been previously shown in the London COPD cohort that exacerbations cluster and that patients are more likely to develop another exacerbation within 8 weeks after an index event.[13] This has now been confirmed in the paper by Suissa and colleagues who also show that patients are more susceptible to another severe exacerbation peaking at a month and increased risk for a total of 3 months[8]. Clustering effects are also accentuated with successive exacerbations. The mechanisms for these observations are not totally clear, but may include suboptimal therapy of the exacerbations or secondary bacterial infection leading to upregulation of airway inflammation and receptors for human viruses that are major triggers. We now know that treatment of an exacerbation with antibiotics affects the time to the next exacerbation and subsequent exacerbations.[14] Thus, these observations emphasise the importance of early presentation and appropriate intervention at COPD exacerbation that shorten exacerbation recovery and chance of hospital admission.[15] In view of the

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postexacerbation susceptibility, careful follow-up of the exacerbation after therapy is required to detect incomplete resolution and recurrence.

Understanding the natural history and risk of COPD exacerbations is important as exacerbations are key outcomes and drivers of healthcare costs. The data in the paper by Suissa and colleagues provide useful data for planning strategies to reduce exacerbations and their severity that will lead to less hospital admission.[8] However, once the patient develops an exacerbation, optimal therapy and follow-up is essential to prevent successive events.

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