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REVIEW

Impact of exacerbations on COPD

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ABSTRACT: Exacerbations of chronic obstructive pulmonary disease (COPD) determine disease-associated morbidity, mortality, resource burden and healthcare costs. Acute exacerbation care requirements range from unscheduled primary care visits to emergency room, inpatient or intensive care, generating significant costs in COPD. Even after an exacerbation resolves, respiratory, physical, social and emotional impairment may persist for prolonged time. Frequent exacerbations, mainly in patients with severe COPD, accelerate disease progression and mortality. Thus, patients with frequent exacerbations have a more rapid decline in lung function, worse quality of life and decreased exercise performance. Management of COPD directed to reduce incidence and severity of exacerbations improves long-term health status and conserves health care resources and costs.

KEYWORDS: Acute exacerbations, chronic obstructive pulmonary disease, pulmonary function, quality of life

Chronic obstructive pulmonary disease (COPD) affects a large number of patients and is associated with significant morbidity, disability and mortality [1, 2]. COPD is complicated by frequent and recurrent acute exacerbations, which result in enormous healthcare expenditures and high morbidity. An exacerbation of COPD is defined as ''an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum and beyond normal day-to-day variations, that is acute in onset and may warrant a change in regular medication in a patient with underlying COPD'' [3, 4]. Exacerbations are categorised in terms of either clinical presentation (number of symptoms) or utilisation of heathcare resources [3, 4].

Exacerbations of COPD are estimated to result in ~110,000 deaths and more than 500,000 hospitalisations per year, with over $18 billion spent in direct costs annually [1, 2]. In addition to the financial burden required to care for these patients, other ''costs'', such as days missed from work and severe limitations in quality of life, are important features of this condition [5, 6].

Exacerbations are a significant component of the clinical course in COPD [7]. Furthermore, as COPD progresses, exacerbations become more frequent [3, 8–14]. DONALDSON *et al.* [11] reported that patients with severe COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) category III) had an annual exacerbation frequency of 3.43 events per year compared with 2.68 per year for those with moderate COPD (GOLD category II; $p=0.029$). PAGGIARO *et al.* [10] reported, in patients with forced expiratory volume (FEV_1) >60% predicted, 1.6 ± 1.5 exacerbations per year (mean$\pm$SD), compared with 1.9 ± 1.8 exacerbations in patients with FEV_1 59%–40% pred, and 2.3 ± 1.9 exacerbations in patients with FEV_1 <40% pred [10, 11]. Other studies showed that patients who suffer a high number of exacerbations will continue to have frequent episodes [14]. Recent large prospective clinical studies have shown that COPD patients in GOLD category II (FEV_1 50–80% pred) also have a significant number of exacerbations that can be reduced with pharmacotherapy [15, 16]. Thus, patients with more severe COPD are going to have frequent exacerbations, but it is also important to point out that patients with more moderate disease also develop a significant number of these events (table 1).

IMPACT OF EXACERBATIONS ON SYSTEMIC INFLAMMATION AND COMORBIDITIES

Although respiratory infections are assumed to be the main risk factors for exacerbation of COPD, other conditions, including industrial pollutants, allergens, sedatives, congestive heart failure and pulmonary embolism, have been identified [3, 4, 19, 20]. The cause of an exacerbation of COPD may be multifactorial, so that viral infection or levels of air pollution may exacerbate the existing inflammation in the

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TABLE 1 Risk factors for frequent exacerbations (more than two per year) in patients with chronic obstructive pulmonary disease

Risk factors
Increased age
Severity of FEV1 impairment
Chronic bronchial mucus hypersecretion
Frequent past exacerbations
Daily cough and wheeze
Persistent symptoms of chronic bronchitis
Comorbid conditions: mainly cardiovascular disease

FEV1: forced expiratory volume in 1 s. Adapted from [11–14, 17, 18].

airways, which in turn may predispose to secondary bacterial infections. COPD patients have frequent comorbid conditions, particularly coexistent cardiac disease, hypertension, diabetes, *etc.* [3]. Coexistent cardiac disease has been shown to be a risk factor for increased hospital admission [21, 22] and mortality in patients with COPD exacerbation [23, 24]. Furthermore, ischaemic heart disease and/or congestive heart failure were reported to increase the rate of treatment failure, thus contributing to the worsening of the patients' condition [21, 22]. However, in a hospital-based study, very severe COPD patients (FEV1 <35% pred and use of supplemental oxygen therapy) no association between cardiac comorbidity and outcome was found [24]. The results suggest that cardiac comorbidity is a risk factor of poor outcome, particularly in moderate–severe COPD patients; however, when lung disease is severe, impairment in pulmonary function prevails over cardiac disease. Additionally, older patients who also have more severe comorbid conditions appear to be at risk for severe life-threatening exacerbations that may result in hospital admission and even death [8, 24, 25].

Several studies have shown that COPD patients have higher levels of some inflammatory markers in blood, mainly C-reactive protein (CRP) [26], fibrinogen [27] and inflammatory cytokines [28]. EAGAN *et al.* [29] assessed the systemic levels of six inflammatory mediators in a large cohort of COPD patients and controls. These investigators confirmed that certain circulating inflammatory mediators are affected in COPD. COPD confounded variables, such as sex, age, smoking status, disease severity, comorbid conditions, *etc.*, were controlled. These investigators demonstrated that COPD patients were more likely to have significantly decreased blood levels of osteoprotegrin and higher levels of CRP. They were also able to identify that soluble tumour necrosis factor receptor-1 and osteoprotegrin changes were related to disease severity, based on GOLD stage and frequency of exacerbations. Furthermore, recent reports have shown that using anti-inflammatory medications, such as statins, significantly impact the rate of lung function decline, and their use prior to exacerbations is associated with significant decreases in mortality [30]. Therefore, exacerbations are likely to be present in patients with comorbid conditions and result in a significant inflammatory burden. Further prospective studies are needed to validate these clinical studies.

IMPACT OF EXACERBATIONS ON LUNG FUNCTION

Some investigators believe that more frequent exacerbations are associated with more rapid decline of FEV1 [31]. DONALDSON *et al.* [11] reported a mean of 2.92 exacerbations per year in COPD patients with moderate to very severe disease (mean FEV1 38% pred). The mean rate of decline in FEV1 in the total cohort was 36 $mL \cdot yr^{-1}$, but was greater in patients with more exacerbations (40.1 $mL \cdot yr^{-1}$ *versus* 32.1 $mL \cdot yr^{-1}$, respectively; $p<0.05$). Frequent exacerbations (more than two per year) have been associated with increased dyspnoea and reduced exercise capacity [11, 16], greater decline in health status [32, 33] and increased likelihood of becoming housebound [11, 34]. More recently, CELLI *et al.* [35] reported the impact of frequent exacerbations on the decline in FEV1 in data from the Toward a Revolution in COPD Health (TORCH) study, in which patients experiencing greater frequency of exacerbations during the 3-yr study period had a faster decline in FEV1.

It seems logical that repeated episodes of COPD exacerbations may potentially impair lung tissues and lead to an accelerated rate of decline in pulmonary function. This concept is supported by a number of experimental observations. 1) Exacerbations are associated with transient decreases in pulmonary function that, in some cases, take weeks to return to baseline levels [36, 37]. 2) Patients suffering from recurrent exacerbations have been shown to have increased concentrations of inflammatory markers in sputum, even in stable phase, which suggests persistent inflammation and potential lung damage [38]. 3) Neutrophils are attracted into the airway lumen during exacerbations [39]. In fact, increased levels of neutrophils in sputum correlated with rapid decline in FEV1 in a 15-yr follow-up study [40]. There are recent reports that have identified a significantly increased number of eosinophils in patients with COPD exacerbation [41, 42]. The significance of these findings is not fully understood. 4) In cross-sectional studies, higher bacterial load in respiratory secretions have been associated with increased inflammation and decreased lung function [43]. 5) The urinary excretion of desmosine and isodesmosine, products of degradation of lung elastine, are significantly increased during exacerbations of COPD compared with stable phase [44], coinciding with an increase in free elastase during exacerbations [38, 45]; furthermore, higher urinary concentrations of desmosine have been associated with faster decline in FEV1 in COPD [46]. 6) A correlation has been found between the number of previous exacerbations and the extent of emphysematous changes seen by computed tomography scan [17].

IMPACT OF EXACERBATIONS ON HEALTH-RELATED QUALITY OF LIFE

Exacerbations have been shown to dramatically impair the feeling of wellbeing in COPD patients. Differences in scores in health-related quality of life (HRQoL) questionnaires between the stable phase and the exacerbation are very important in magnitude. A group of patients with COPD exacerbation showed a moderate-to-large improvement in all four domains of the Chronic Respiratory Disease Questionnaire after 10 days of treatment [18]. This improvement was not observed in patients who relapsed after treatment of exacerbation.

A study by CONNORS JR *et al.* [36] reported the quality of life outcomes in patients hospitalised with acute exacerbations of COPD. At 6 months, 54% of patients required assistance with at least one activity of daily living and 49% considered their health status to be fair or poor. No analysis was conducted on the relationship between readmissions and perceived quality of life. The recovery of HRQoL parameters after an acute COPD exacerbation may be determined by several factors. SPENCER *et al.* [33] in exacerbated patients who did not relapse during follow-up experienced an improvement in the St George's Respiratory Questionnaire (SGRQ) of 11.8 units at 1 month and 17 units after 5 months of the onset of the exacerbation. These results indicate that the recovery of health status after an exacerbation may take longer than previously expected. In contrast, median recovery time for lung function after an exacerbation is 6 days and for symptoms is 7 days [33]. However, this recovery may be influenced by the severity of the exacerbation. The more severe the exacerbation, the longer it takes to recover. SEEMUNGAL *et al.* [37] showed that only 75% of patients return to their baseline peak flow values 35 days after the episode. The SGRQ and Medical Research Council questionnaire were completed by patients at the end of the study. Exacerbations were more frequent in patients with frequent previous exacerbations (OR 5.5, $p=0.001$). Using the median number of exacerbations, patients were classified as infrequent exacerbators (0–2) or frequent exacerbators (3–8). SGRQ total score was significantly worse in frequent exacerbators (mean difference 14.8; $p<0.001$) (fig. 1).

In multiple regression analyses, exacerbation frequency was strongly correlated with SGRQ total score and component scores. MIRAVITLLES *et al.* [6] confirmed the impact of exacerbations on health status. Thus, these studies showed that patients who suffered more exacerbations had significantly worse SGRQ scores compared with infrequent exacerbators, and HRQoL-related questionnaires offer complementary information to lung function and respiratory symptoms to monitor the course of recovery of an exacerbation. The slow recovery of HRQoL after an exacerbation suggests that these patients will not return to their baseline condition and will experience further deterioration of their quality of life over time.

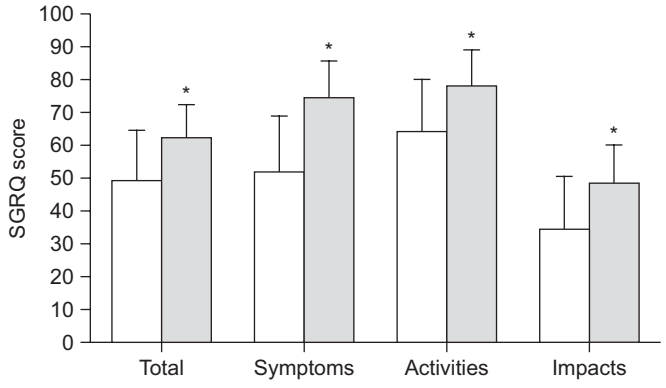

FIGURE 1. Relationship between exacerbation frequency and quality of life parameters. □: 0–2 exacerbations per year; ■: 3–8 exacerbations per year. SGRQ: St George's Respiratory Questionnaire. *: $p<0.05$. Reproduced from [37] with permission from the publisher.

Furthermore, a patient's therapy during the exacerbation may influence outcome. ANDERSSON *et al.* [47] showed that patients who received long-term oxygen therapy had an improvement of the SGRQ scores by a mean of 14 units after 3 months; in contrast, those who did not receive oxygen showed a change of 9 units.

Unreported exacerbations are common and their long-term impact on HRQoL has been identified. Previous studies have shown that at least half of all COPD exacerbations identified by symptom worsening were not medically reported and therefore left untreated. SEEMUNGAL *et al.* [48] demonstrated that unreported exacerbations had similar characteristics to the reported ones. These exacerbations are associated with worsening symptoms worsening when they remain untreated. The short- and long-term impacts of unreported exacerbations on HRLQ were recently reported by XU *et al.* [49]. In a multicentre prospective cohort of 491 COPD patients, these investigators demonstrated that more than one unreported exacerbation was associated with significant worsening of the SGRQ score, and HRQoL at 1 yr after adjusting for known confounders. These data suggest that unreported exacerbations may have important long-term impact on patients, and there is an urgent need to develop tools that emphasise early recognition of exacerbations.

IMPACT OF EXACERBATIONS ON EXERCISE PERFORMANCE

COPD exacerbations not only impair both the short- and long-term quality of life, but also produce significant reduction in physical activity [50]. In order to understand how exacerbations actual impaired patients, HAUGHNEY *et al.* [51] reported a study that used actual patients' relative value judgment with discrete choice modelling techniques. These investigators demonstrated that exacerbations significant impact daily activities and level of medical care. For patients, the main impact of exacerbation on daily life is being housebound, more so than the actual symptoms. Other studies have also shown that exacerbations will not only impact physical activity but also physiological wellbeing [52]. These and future studies are needed to develop strategies in the prevention and management of COPD.

Loss of skeletal muscle has long been established as a feature of stable COPD. COPD patients have decreased quadriceps strength and fat-free mass [53]. These effects are worse after acute exacerbations. These effects may be more pronounced if we take into consideration that these patients received high doses of corticosteroids during an exacerbation. Further data related to the impact of exacerbation on exercise activity is the work by DONALDSON *et al.* [34]. In a longitudinal study, these investigators quantified time spent outdoors, and found that frequent exacerbators had spent less time. These investigators identified decreased activity a few days prior to exacerbations, which remained decreased for up to 5 weeks. More recent studies have utilised ambulatory activity monitoring. PITTA *et al.* [54] confirmed prior reports, and also described decreased activity level in patients that have exacerbations compared with those who did not. Furthermore, a decreased activity level 1 month after an exacerbation was associated with increased risk for hospitalisation. Thus, the investigators concluded that exacerbations decreased the overall exercise tolerance.

More recently, the effect of exacerbations on the body mass, obstruction, dyspnoea and exercise capacity (BODE) index were reported [55]. The BODE index significantly decreases with an exacerbation and these effects remain over time. Most of the effect is due to significantly decreased exercise tolerance, manifested as decreased distance in 6-min walk test. Thus, exacerbations also impact upon exercise tolerance.

ECONOMIC IMPACT OF EXACERBATIONS

A further consequence of acute exacerbations of COPD is the great economic burden associated with the medical care required for these patients. Exacerbations are the largest direct cost for the treatment of COPD [5, 6, 56, 57]. The major component was hospitalisations, which represented 58% of the total cost, followed by the medication acquisition cost of 32.2% [5].

IMPACT OF EXACERBATIONS ON MORTALITY

Clinical studies have reported a high mortality rate in patients admitted to the hospital with an acute exacerbation of COPD [36, 58–61]. Several studies have identified the risk factors associated with increased mortality. The Study to Understand Prognosis and Preferences for Outcomes and Rates of Treatment (SUPPORT) [36], which enrolled patients who had severe acute exacerbation of COPD, reported an in-hospital mortality rate of 11% in patients with acute hypercapnic respiratory failure. The 180-day mortality rate was 33% and the 2-yr mortality rate was 49% (fig. 2). Predictors of mortality include acute physiology and chronic health evaluation (APACHE) III score, body mass index, age, functional status 2 weeks prior to admission, lower ratio of partial pressure (tension) of oxygen (P_{O_2}) to fraction of inspired oxygen (F_{I,O_2}), congestive heart failure, level of serum albumin, cor pulmonale, lower activities of daily living scores and lower scores on the Duke Activity Status Index. This study also reported that only 25% of patients were both alive and able to report a good, very good, or excellent quality of life 6 months after discharge [36].

Several studies reported in-hospital mortality rate of 11–24% [38] and 22–35.6% after 1 and 2 yrs, respectively [58, 59]. None of these studies have specifically examined the prognostic influence of acute exacerbation by itself. SOLER-CATALUNA *et al.* [61] were the first to report that severe exacerbations of COPD have an independent negative prognostic impact, with mortality increasing with the frequency of severe exacerbations and those requiring hospitalisation. Patients with frequent exacerbations had the highest mortality rate ($p<0.001$) with a risk of death 4.3 times greater (95% CI 2.62–7.02) than for patients requiring no hospital management. Thus, exacerbation itself may be a significant factor associated with increased mortality in COPD, but the severity of the underlying disease may influence patient's outcome.

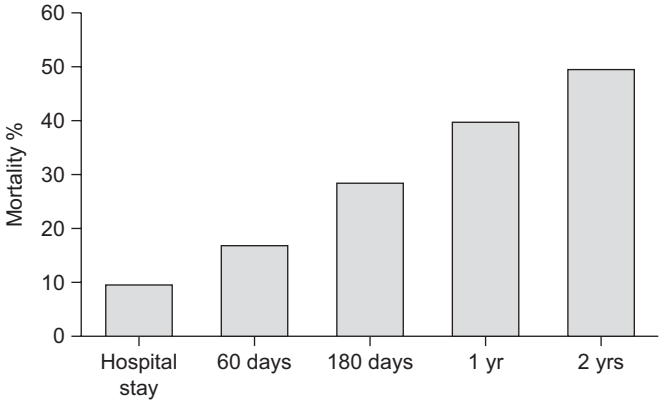

FIGURE 2. Mortality after chronic obstructive pulmonary disease exacerbation. Reproduced from [36] with permission from the publisher.

PREVENTION/REDUCTION OF EXACERBATIONS

The two most important preventive measures of COPD exacerbation are active immunisations, including influenza and pneumococcal vaccinations, and chronic maintenance pharmacotherapy [3, 4]. Currently, both annual influenza vaccination and polyvalent pneumococcal vaccine are recommended in patients with COPD [3, 4].

Recent clinical studies have demonstrated that chronic maintenance therapy in patients with COPD can significantly decrease the frequency of exacerbations. These studies show that long-active bronchodilators, including long-acting β-agonists (LABAs) (*e.g.* salmeterol and formoterol) [62]; and long-acting anticholinergics (*e.g.* tiotropium) reduce the mean rate of COPD exacerbation [15, 63–65]. These effects have also been reported with combination therapy of inhaled corticosteroids and LABAs [66–69]. Furthermore, these studies have demonstrated that the reduction in exacerbations results in a significant decrease in hospitalisations and healthcare utilisation [63–69]. Other chronic therapies, such as carbocisteine and *N*-acetylcysteine, showed a decrease in COPD exacerbations [70–73], while other studies failed to show these effects [74]. These findings could be explained by severity of patients enrolled in these studies and the use of concomitant medications. More detailed discussion is presented elsewhere in the present issue of the *European Respiratory Review* [75, 76].

CONCLUSIONS

Together, these studies demonstrate that exacerbations represent an important event in the natural history of COPD patients and are associated with significant morbidity and mortality. Though substantial progress has been made in the understanding of the aetiology of exacerbations in COPD, much still needs to be learned. The complexity of the host–pathogen interaction that determines the onset and course of exacerbations needs further exploration, including examination of host cellular and molecular mechanisms, and the determinants of pathogen virulence and their interaction with airway epithelial cells and macrophages. Exacerbations have a significant impact on patients' lung function, quality of life and exercise performance. Exacerbations are associated with increased morbidity and mortality and have a significant socioeconomic impact. Patients with frequent exacerbations often experience impaired quality of life and faster decline in lung function over time. In addition, exacerbations, including those requiring hospitalisation, are the largest item associated with the direct cost in the treatment of COPD.

STATEMENT OF INTEREST

A. Anzueto has been a consultant and paid speaker for the following companies: Boehringer-Ingelheim, GlaxoSmithKline, Dompé, Dey Pharmaceutical, Pfizer and Seprracor, and has been the principal

investigator in clinical studies for which the University of Texas Health Science Center at San Antonio received funding from GlaxoSmithKline, Pfizer and Lilly.

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