Review Article

Acute Exacerbations of Chronic Obstructive Pulmonary Disease: Causes and Impacts

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Abstract

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are recognised clinically as episodes of increased breathlessness and productive cough requiring a more intensive treatment. A subset of patients with this disease is especially prone to such exacerbations. These patients are labelled as 'frequent exacerbators'. Though yet poorly characterised in terms of host characteristics, including any genetic basis, these patients are believed to represent a distinct phenotype as they have a different natural history with a more progressive disease and a poorer prognosis than those who get exacerbations infrequently. Most exacerbations appear to be associated with infective triggers, either bacterial or viral, although 'non-infective' agents, such as air pollution and other irritants may also be important. Susceptibility to exacerbations is determined by multiple factors. Several risk factors have been identified, some of which are modifiable. Chronic obstructive pulmonary disease (COPD) exacerbations are major drivers of health status and patient-centered outcomes, and are a major reason for health care utilisation including hospitalisations and intensive care admissions. These are associated with considerable morbidity and mortality, both immediate and long-term. These episodes have a negative impact on the patient and the disease including high economic burden, increased mortality, worsening of health status, limitation of activity, and aggravation of comorbidities including cardiovascular disease, osteoporosis and neuro-psychiatric complications. Exacerbations also increase the rate of progression of disease, increasing the annual decline in lung function and leading to a poorer prognosis. Evaluation of risk of exacerbations is now included as a major component of the initial assessment of a patient with COPD in addition to the traditionally used lung function parameter, forced expiratory volume in one second (FEV_1). Decreasing the risk of exacerbations and their prevention is a major therapeutic goal of management in COPD. **[Indian J Chest Dis Allied Sci 2014;56:93-104]**

Key words: COPD, Exacerbations, Aetiology, Quality of life, Lung function, Mortality.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by a usually progressive decline in lung function and worsening of breathlessness, exercise capacity and impairment of quality of life (QoL) with time.[1,2] The rate of decline varies from patient to patient. In a subset of patients, this steady decline is punctuated in the natural course by episodes of increased symptoms, labelled as "acute exacerbations". These exacerbations apart from posing an immediate threat to survival and being a significant economic burden are also important because of their long-term negative effects on the health status, activity, symptoms and lung function and also aggravate related extra-pulmonary comorbidities. Recovery from an acute exacerbation is seldom complete and the patient's respiratory health status is reset at a lower level hastening the decline. These are major milestones in the natural history and more frequent exacerbations (FEs) portend a poor prognosis. Therefore, patients who have more FEs are now considered to represent a clinical phenotype that a distinct and probably have a more severe form of the disease. Prevention, early diagnosis and prompt institution of effective treatment of exacerbations are an essential part of best practices in COPD management.[1,2] The new Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for grading the severity of COPD has recognised the importance of acute exacerbations. A higher risk of exacerbations merits a more aggressive treatment.[1]

Definition

Exacerbations are episodes of acute worsening of clinical condition in patients with COPD. An episode of acute exacerbation of COPD (AECOPD) was defined at the Aspen workshop as "*a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD*".[3] Similar definitions have been adopted by several management guidelines on COPD.[1,2,4] The GOLD 2014 update[1] defines an acute exacerbation as "*an acute event characterised by worsening of the patient's*

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respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication". A diagnosis of AECOPD is essentially clinical and event-based.

The definition underscores that there is a range of day-to-day variations in a patients' symptoms. Such variations can usually be managed by increasing the use of rescue bronchodilators and cutting down on activities of daily living. These are not labelled as AECOPD. Disabling symptoms of very severe and end-stage disease are also excluded. Stepping-up of treatment by additional bronchodilators or inhaled steroids in patients not well-controlled at a particular step of therapeutic intervention is a strategy for chronic stable disease recommended in the COPD management guidelines and is also not considered as an AECOPD. A definite AECOPD is a substantial and sustained increase in symptoms occurring over a few days that interrupts activities of daily living and requires the patient to seek medical attention resulting in a short-term change in the regular medication, usually an addition of antibiotics and/or oral corticosteroids, and may necessitate emergency room treatment or hospitalisation. Distinction must be drawn from an episode of pneumonia that is a parenchymal infection of the lung, as distinct from AECOPD that is an airways complication although management of both conditions may overlap substantially. Other causes of an acute increase in breathlessness in a patient with COPD, such as a pneumothorax, acute pulmonary thromboembolism or acute left ventricular failure, constitute the differential diagnosis of AECOPD but may also complicate it.

Clinical Recognition

The cardinal symptoms of AECOPD are increased shortness of breath, increased cough and increased sputum volume or purulence. These symptoms were originally considered by Anthonisen *et al*[5] to categorise patients into three types with the purpose to prospectively analyse the effect of antibiotics on exacerbations. Type 1 exacerbations were defined by the presence of increased breathlessness, sputum volume and sputum purulence; type 2 by the presence of two of these symptoms, and type 3 by the presence of one of these symptoms. Use of antibiotics was recommended for type I exacerbations. These symptoms have since been used in most studies to identify patients with AECOPD and also form the basis of its recognition in clinical practice.

Patients may also present with additional symptoms, such as malaise, body aches, decreased exercise tolerance, fluid retention, increased fatigue and confusion depending upon the disease severity as well as the extent of physiological derangements. Presence of fever is not a defining criterion although patients may be febrile. Haemoptysis is distinctly rare unless associated with pneumonia or co-morbidity. Severe chest pain should lead to a search for a complication, such as a pneumothorax or pneumonia.

"Common colds", sore throat, runny nose and cough increase significantly during the prodrome, suggesting that respiratory viruses are important exacerbation triggers. These may serve as early warning signs, and therefore, patients should be educated about their recognition. However, the prodrome is relatively short. Usually, acute exacerbations do not develop as a "bolt out of the blue" and such an increase in dyspnoea is more likely to be due to an acute pulmonary embolism (PE), pneumothorax or an acute left ventricular failure.

The clinical severity of an AECOPD varies widely. It may be managed in the out-patient setting but may be severe enough to require hospitalisation. When complicated by respiratory failure, intensive care including ventilator support, non-invasive or invasive, may be required. Physiological derangements include increased airway resistance and static as well as dynamic hyperinflation causing respiratory distress and at times, hypoxaemia and hypercapnia. A decline in lung function can be demonstrated on spirometry. However, a lung function assessment is not usually carried out during an acute exacerbation as the performance of spirometry may not meet the acceptability criteria.

A more detailed discussion of the management of AECOPD including the diagnostic work-up and assessment, differential diagnosis, monitoring and treatment are beyond the scope of the present review. Comprehensive, standard and evidence-based guidelines for management are available.[1, 2]

Aetiology

A majority (up to three-fourths) of episodes of AECOPD are triggered by infections.[6] Environmental pollution is likely to be a trigger in a small proportion of patients (up to 10%)[7] while in almost a quarter of patients, no cause may be identified. Decreased air temperature and other meteorological factors may contribute to the occurrence of an AECOPD. A 1 °C decrease in air temperature was associated with a 0.8% increase in exacerbations in a recent study. Higher barometric pressure, more hours of sunshine, and lower humidity were also found to be associated with an increase in the risk of COPD exacerbation.[8] A strong seasonality is, therefore, evident in hospital and intensive care admission patterns with winters being the worst months for the patients.

The proof for a bacterial infection as the inciting event for AECOPD comes from isolation of pathogens in lower respiratory tract secretions obtained by different techniques, isolation of new strains in such patients, the development of a pathogen strain-specific immune response and association of neutrophilic airway inflammation with bacterial isolation during exacerbations. While pathogenic bacteria may be

isolated in a smaller proportion of patients in a stable state too, the frequency of isolation, the bacterial load and the degree of airway inflammation is much higher during exacerbations. Studies employing bronchoscopic sampling with a protected specimen brush (PSB) to obtain uncontaminated lower airways secretions have found approximately 30% of sputum cultures and 50% of bronchial secretion cultures associated with the presence of potential pathogenic bacteria (PPB).[9, 10] However, as no bacterial pathogen can be cultured in a majority of cases, the true incidence of AECOPD due to bacterial infections is difficult to establish. Such studies of course do not imply that those in whom no pathogens are isolated by conventional microbiological techniques do not have an infection. Cultures by standard techniques may fail to grow micro-organisms. This may be due to technical reasons as well as prior use of antibiotics. Interestingly, the initial severity of those in whom a pathogen is identified does not differ from those in whom no pathogen is found. The outcomes also do not differ when empirical antibiotic therapy is compared to guided therapy.[9] Therefore, empirical and evidence-based use of antibiotics is the standard of care rather than a microbiological-guided therapy for a majority of patients.

Emerging evidence from molecular epidemiology studies and presence of airway inflammation in lower respiratory tract specimens further supports the role of bacteria as the inciting agents in AECOPD. When properly defined, as high as 80% of episodes of AECOPD are likely to be infectious in origin.[11] Culture-independent techniques have been developed targeting bacterial genes, such as the 16S ribosomal ribonucleic acid (RNA) gene, that function as molecular chronometers. Application of these techniques in patients with COPD has suggested microbial diversity that varies with age, disease severity, and medication use.[12] Unless there are strong clinical pointers that infection is not the cause, use of antibiotics remains the cornerstone of therapy in AECOPD along with other supportive and symptomatic measures.

The diagnostic yield in microbiological studies is strongly dependent on the types of specimens that are investigated as well as any pre-treatment by the patient before presenting to the physician. In general, direct sampling of lower respiratory tract secretions is likely to yield a higher positivity of cultures compared to that obtained from expectorated or induced sputum. A large number of earlier studies on sputum microbiological flora during acute exacerbations showed that the three most common bacterial pathogens were *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*.[6] These are all community-acquired pathogens. Most of the information about the bacteriology of exacerbations in earlier studies came from studies in patients with chronic bronchitis rather than COPD. In a comprehensive study by Soler *et al*[13], quantitative cultures of tracheobronchial aspirates (TBAs), PSB specimens and bronchoalveolar lavage fluid yielded potential pathogens and/or a positive serology in 72% of cases, including 33% that were polymicrobial. *S. pneumoniae, H. influenzae,* and *M. catarrhalis* together constituted 56% of the yield while gram-negative pathogens accounted for 44% of the bacterial isolates. The presence of pathogens was clinically unpredictable.

Increasingly, recent studies have reported a higher yield of pseudomonas and enterobacteriaceae in sputum specimens from patients with AECOPD. *Pseudomonas aeruginosa* isolation has been reported to increase with increasing severity of disease, and especially in association with co-morbidities, such as bronchiectasis. Organisms belonging to enterobacteriaceae have been isolated less frequently and *Staphylococcus aureus* is uncommon except when the infections are hospital-acquired. Atypical organisms, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have rarely been isolated.[11,14,15] This is in contrast to their higher frequency as pathogens in community-acquired pneumonias.

In a retrospective review of records of nearly 500 episodes of AECOPD in hospitalised patients in Taiwan,[16] *Klebsiella pneumoniae* and *P. aeruginosa* were the most common sputum pathogens with the former being more commonly isolated from mild COPD and the latter associated with a poorer clinical outcome. In a prospective study in a small sample of patients with severe COPD followed up for one year, out of a total of 188 sputum samples, 128 episodes yielded a single pathogen while 42 episodes were polymicrobial. The most frequent pathogen isolated was *P. aeruginosa* followed by *H. influenzae, S. pneumoniae, M. catarrhalis* and *S. aureus. Pseudomonas aeruginosa* was the most frequent pathogen in patients with a single as well as multiple exacerbations.[17]

Following bacterial exacerbations, patients develop new strain-specific antibodies.[18,19] This provides support to the hypothesis that bacteria cause exacerbations. As the response is specific, it also explains the lack of immunity and recurrent exacerbations with infection by the same bacterial species but a different genetic strain.[14]

Pseudomonas aeruginosa has the ability to cause several different patterns of infection in patients with COPD. It may be a coloniser, cause acute exacerbations and also may cause chronic infection. Exacerbations caused by this organism are more likely to be observed in patients with more advanced COPD, those who have received recent antibiotic therapy and those who require mechanical ventilation for an exacerbation. A proportion of patients with COPD may become chronically colonised with *P. aeruginosa*, but whether such patients benefit from anti-microbial therapy is not yet known.[20] Recurrences of infection with *P. aeruginosa* are also well documented. Two distinct patterns of carriage have been observed: a short-term colonisation

followed by clearance in a majority of patients and a long-term persistence in about a quarter of patients. Mucoid strains are more likely to persist than non-mucoid strains. However, recurrences of exacerbation may occur due to the acquisition of a new strain rather than because of persisters.[21] In chronic carriers in a small study,[22] each clone of *P. aeruginosa* was found to diversify leading to the co-existence of isolates with different morphotypes and antibiotic susceptibility. There was increased mutation rate, increased antibiotic resistance, and reduced production of proteases.[22]

Approximately 20% to 30% of patients with COPD have positive sputum bacterial cultures when clinically stable. These organisms are often similar to those that are isolated from the lower respiratory tract during acute exacerbations. Monso *et al*[10] using PSB cultures obtained *H. influenzae* and *S. pneumoniae* in concentrations exceeding 10^3 colony-forming units / milliliter (CFU / mL) in 25% of patients with stable disease. In another study using PSB,[23] 16% patients in stable state yielded positive cultures, predominantly *S. pneumoniae* and alpha-haemolytic streptococci with coagulase-negative staphylococci and *Branhamella catarralis* in a few. Miravitlles *et al*[24] recently reported that almost half of the population of ambulatory moderate-to-very severe COPD patients were colonised with potential pathogens and presented with more severe dyspnoea and a darker color of sputum.

A contentious issue has been whether increased load of the colonising pathogens in the lower airways or acquisition of a new bacterial strain is responsible for AECOPD.[25, 26] Several studies have found bacterial concentrations to be higher during exacerbations than during stable disease. In a study by Pela *et al*,[23] 84% of patients with AECOPD had positive cultures on PSB specimens in contrast to 16% of stable patients. Bronchial colonisation of 10^2 CFU / mL or greater by pathogenic bacteria was found in another study in 29% patients with stable COPD but in 54% patients during an exacerbation with a predominance of *H. influenzae* and *P. aeruginosa*. Higher microbial loads were associated with exacerbations.[27]

The relationship between occurrence of exacerbations, sputum bacterial concentrations, and acquisition of new strain was examined in a large cohort of patients for seven years. Among pre-existing strains, sputum concentrations of non-typeable *H. influenzae* and *Haemophilus haemolyticus* were not different in exacerbations compared to stable disease. *Moraxella catarrhalis* and *S. pneumoniae* concentrations were lower during exacerbations than in the stable state. Concentrations of new strains of *H. influenzae* and *M. catarrhalis* were increased during exacerbations, though the differences were small. The authors concluded that a change in bacterial load was unlikely to be an important mechanism for exacerbations and these were more likely caused by acquisition of new strains.[28] Further, new strains were more often associated with an antibody response. An immune response to homologous *H. influenzae* occurred in 61.1% exacerbations with newly acquired strains compared to 21% exacerbations with pre-existing strains.[18] Exacerbations with new bacterial strains are also associated with a more intense local neutrophilic and systemic inflammatory response (C-reactive protein) compared to exacerbations not associated with a change in pre-existing bacterial strains or recovery of pathogenic bacteria. Clinical resolution was found to be accompanied by resolution of inflammation to pre-exacerbation levels, whereas persistent symptoms were paralleled by persistently elevated inflammation.[29]

It has also been suggested that lower airway bacterial colonisation in the stable state modulates the character and frequency of COPD exacerbations. Patients colonised by *H. influenzae* in the stable state reported more symptoms and increased sputum purulence at exacerbation than those not colonised. Sputum interleukin (IL)-8 levels correlated with the total bacterial count.[30]

Apart from the controversy over the role of colonising pathogens as the cause of exacerbations, another unresolved question revolves around whether the bacterial colonisation is a harmless phenomenon or whether it contributes to the progressive deterioration in COPD by producing a greater inflammatory burden, more FEs, and a faster decline in lung function independently of tobacco smoking. Elevated sputum IL-8 levels were associated with higher bacterial load and a faster FEV_1 decline.[31] In another study[32], 37% patients with stable COPD were found to have lower airway bacterial colonisation in their sputum specimens with *H. influenzae* being the predominant organism. This was associated with significantly increased frequencies of exacerbations and decline in FEV_1. These patients also had higher IL-8, IL-6, and tumour necrosis factor-alpha (TNF-a) in sputum compared to those without colonisation.[32]

Though less often reported because of lack of facilities to investigate and establish these, viral exacerbations may be responsible for a sizeable proportion of AECOPD. Rhinovirus, the organism most often responsible for causing the common cold, is also the most common infectious cause of exacerbations of COPD. Coronavirus, influenza, respiratory syncytial virus, parainfluenza, adenovirus, and metapneumovirus are other important viral causes of exacerbations.[33] Cell culture and serological studies suggest that viral infections are the likely cause of approximately 20% of exacerbations,[34,35] while polymerase chain reaction (PCR) studies have suggested that up to 40% of acute respiratory infections in COPD are associated with viruses.[36] These may be secondarily complicated by bacterial infections.

An evolving approach is biomarker expression in COPD exacerbations to identify biologic clusters and determine biomarkers that recognise clinical COPD exacerbation phenotypes, namely, those associated with bacteria, viruses, or eosinophilic airway inflammation.[37] Sputum IL-1b, serum CXCL10, and peripheral eosinophils have been shown to be biomarkers of bacteria-, virus-, or eosinophil-associated exacerbations of COPD. Whether phenotype-specific biomarkers can be applied to management is yet to be established.

Risk Factors

Several observational cross-sectional and a few prospective longitudinal studies[38-43] have identified host and disease characteristics that may help to predict which patients are at an increased risk of exacerbations including hospitalisations, and therefore, may require additional interventions and preventive efforts. These include FEV_1 percent predicted, chronic cough and mucous hypersecretion (chronic bronchitis phenotype), advanced age, longer duration of COPD, previous history of antibiotic therapy or systemic corticosteroid use and COPD-related hospitalisation within the previous year, theophylline therapy, presence of respiratory failure, presence of comorbidities and gastro-esophageal reflux disease.[38-43] Often multiple factors co-exist and the relative importance of these on multivariate analysis has varied among different studies.

Other factors that may increase the risk of future exacerbations include systemic inflammation and elevated white cell counts,[44] faster decline in FEV_1 and peak expiratory flows,[45] weight loss / underweight status following hospitalisation,[46] and higher symptom score and BODE (Body mass index, airflow obstruction, dyspnoea, and exercise capacity) index.[47] The severity of exacerbations requiring hospital admissions is associated with the presence of significant comorbidity.[39] As the disease progresses, exacerbations tend to to be more severe and resolve more slowly. Patients with chronic respiratory failure are particularly susceptible to exacerbations.[48]

In the prospective evaluation of COPD longitudinally to identify predictive surrogate endpoints, ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogates) in 2138 patients followed-up for three years, history of exacerbations was the best predictor of such events in future.[43] Exacerbations became more frequent (and more severe) as the severity of COPD increased. The frequent exacerbation (FE) phenotype appeared to be relatively stable over a period of three years and could be predicted on the basis of the patient's recall of previous treated events. However, the frequent exacerbators may change to infrequent exacerbators (IEs) and *vice-versa* in a small proportion of patients during the natural course of the disease.[49] No parameter clearly predicts an imminent change in exacerbation frequency category though a more severe disease was found to be associated with a change from IE to FE and less severe disease from FE to IE. Over the preceding year, small falls in FEV_1 and six-minute walking distance were associated with a change from IE to FE category, and small falls in platelet count were associated with a change from FE to IE category.

Prediction models for exacerbations in patients with COPD are few. Combining physiologic variables, dyspnoea, prior exacerbations and co-morbidity may be useful in identifying patients at high risk for COPD exacerbations.[50] Two models were developed by Miravitlles *et al*[39]: (i) the admission model contained comorbidity and FEV_1 percent predicted, and (ii) the model for frequent exacerbations included advancing age, FEV_1 percent predicted and chronic mucus hypersecretion. In a study comparing three multi-dimensional assessment systems, BODE index, DOSE (dyspnoea, obstruction, smoking, exacerbations) index, or ADO (age, dyspnoea, obstruction) index for predicting exacerbations, the DOSE index was a better predictor of exacerbations of COPD compared to the other two.[51] Bertens *et al*[52] have recently developed a prediction model for AECOPD. The final model included four easily assessable variables: exacerbations in the previous year, pack years of smoking, level of airways obstruction, and a history of vascular disease, with a C-statistic of 0.75. The C-statistic or concordance statistic is a unitless index denoting the probability that a randomly selected subject who experienced the outcome will have a higher predicted probability of having the outcome occur compared to a randomly selected subject who did not experience the event.

It needs to be emphasised that the propensity for acute exacerbations is highly variable. Some patients do not exhibit any exacerbations at all whereas others suffer frequently from such events.[53] Whether or not these FE represent a unique population of COPD patients with higher morbidity and mortality risks is an area of intensive investigation and debate.[54] The small group of such patients accounts for a major proportion of hospital visits for this disease. These patients requiring greater care generally have more a severe disease (older, more severe bronchial obstruction and hypoxaemia).[54] The standardisation of terminology seems to be necessary to further identify COPD phenotypes in patients who have an individual susceptibility to develop frequent exacerbations. The risk factors identified in the studies reviewed above are strongly influenced by sample sizes, the specific risk factors examined, the populations from which the patients have been drawn as well as the standard of care. There is a need for a clearer definition of frequent exacerbators in terms of genetic as well as phenotypical characterisation of these patients.

Impacts

Exacerbations of COPD are important events as these have a major impact on the natural history of the disease. An acute exacerbation may be mild and require only an unscheduled visit to the physician and out-patient management or may be severe enough to require emergency room, in-patient or even intensive care. This generates significant economic burden for the patient. The high socio-economic costs are further exaggerated by loss of work / productivity due to absenteeism and slow and often incomplete recovery. Even after an exacerbation resolves, recovery is often incomplete and respiratory, physical, social and emotional impairment may persist for a prolonged time. It leads to a worsening of disease course marked by a decline in the QoL, impaired activities of daily living, and an accelerated loss of lung function. [55, 56]

Economic Costs

Hospitalisations due to AECOPD are the main reason for use of health-care resources and these costs are attributed to the small proportion of patients with repeated exacerbations.[57] Exacerbations account for about 70% of the total costs of COPD management.[58] Data extracted from a large national health plan in the US with a predominantly insured population showed that COPD-related mean annual costs were increased by more than 50% in patients with two or more exacerbations.[59]

Similarly, a retrospective cost analysis of a cohort[60] of nearly 60000 COPD patients revealed that the average cost of management per patient, excluding medications, was nearly three times greater in patients with two or more moderate-to-severe exacerbations compared to those with none. A systematic search of the MEDLINE database from 1998-2008 identified 11 studies examining health-care costs associated with COPD exacerbations. The estimated costs of exacerbations varied widely across studies with the largest component of the total costs of COPD exacerbations being due to hospitalisation. Costs were highly correlated with severity of exacerbations. Indirect costs have rarely been measured. The wide variability in the cost estimates may be related to differences in geographic locations, treatment patterns, local health delivery systems and patient populations. Differences in definitions of exacerbations (symptom-*versus* event-based definitions), tools to identify and measure exacerbations, and classification systems used to define exacerbation severity also have an impact on total cost calculations. Unreported exacerbations are common and may influence the long-term costs of exacerbations.[61]

Health-related Quality of Life

Health status is now regarded as one of the major outcome measures in COPD. Majority of patients suffer a sharp decline in the QoL after an acute exacerbation. A prospective cohort[62] followed for six months showed that only 26% of the patients were both alive and able to report a good, very good, or excellent QoL. In another study, in 61 (87%) patients there were 190 exacerbations. The patients were classified as infrequent exacerbators (≤2) or frequent exacerbators (3 or more). The St George Respiratory Questionnaire (SGRQ) total and component scores— symptoms, activities and impacts, were significantly worse in the group that had FE.[63]

Recovery of QoL scores is often incomplete after IE.[64] In the ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe) study, FE were independently associated with a more rapid rate of deterioration in health status.[65] The decline in QoL is related to the frequency of exacerbations as well as the severity of the disease. The more frequent the exacerbations, the more rapid is the decline.[66] In a recent prospective, multi-centre study conducted in 79 hospitals and primary care centers in Spain, 476 COPD patients with an acute exacerbation completed the COPD assessment test (CAT) and Clinical COPD Questionnaire (CCQ) questionnaires during the 24 hours after presentation and also at weeks 4-6. The best predictor of the magnitude of improvement in the scores was the severity of each score at onset.[67] In the 4-year UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) trial, increasing frequency of exacerbations was found to worsen the health-related QoL in patients with COPD.[68]

Lung Function Decline and Disease Progression

Chronic obstructive pulmonary disease is usually characterised by a progressive decline in lung function. Individual rates of decline in FEV_1 have varied considerably in both observational cohorts and intervention trials from 150 mL to 200 mL per year and some patients may even show increases of upto approximately 150 mL per year, with mean rates of decline ranging from 33 mL to 69 mL per year. The frequency of exacerbations is one of the determinants of the rate of decline.[69]

Several but not all studies have shown a faster decline among patients who have FE. Sample sizes, duration of follow-up, severity of disease and whether the patients continued to smoke may explain the differences among these studies.

Recovery of lung function after an exacerbation is usually less than complete. In one study, the median time to recovery of peak flow was six days and time to recovery from symptoms was seven days. Further, at 35 days, the peak flow had returned to normal in only 75% of patients, whereas at 91 days, 7.1% of patients had not returned to baseline lung function.[70] The incomplete recovery may be related to inadequate or

incomplete treatment or persistence of the pathogens with continued inflammatory response or may reflect an increase in the irreversible component of airflow limitation. Incomplete recovery implies a sharp step downwards in the natural progression of the disease.

Smoking and exacerbations have an interactive effect on disease progression in COPD. In an epidemiological study with a follow-up spanning five years, smokers with FEs had an annual decline in FEV_1 of 69.4 mL compared to 55.4 mL in those with less frequent exacerbations or no exacerbations. However, there was no difference among those who had quit smoking.[71] Donaldson *et al*[45] reported an 8 mL per year greater decline in FEV_1 over four years in 32 patients with moderate-to-severe COPD who had FEs, compared to those with less frequent acute episodes. A retrospective analysis of data of 921 patients from two 1-year, placebo-controlled clinical trials[72] with tiotropium revealed that in the placebo group, FEV_1 declined by –3.4%, –3.4%, –5.7% and –6.7% for exacerbation frequencies of 0, 1, 2, >2, respectively. Data from the TORCH (Toward a Revolution in COPD Health) study[73] that investigated the effects of combined salmeterol plus fluticasone propionate, either component alone or placebo, on the rate of post-bronchodilator FEV_1 decline in patients with moderate or severe COPD also showed that patients who exacerbated more frequently had a faster decline.

In a three-year prospective study[74] in 102 patients with COPD, the average annual rate of FEV_1 decline adjusted for smoking was found significantly increased in FEs compared to IEs. The highest decline was observed in smokers with FEs; a significant interaction between exacerbation frequency and decline was also observed in ex-smokers. A retrospective analysis of data from the 4-year UPLIFT trial compared annualised rates of decline according to subgroups based on exacerbation frequency. In the placebo group, patients with no exacerbations lost 40mL FEV_1 per year while those with two or more events lost 48 mL. [68]

Effect on Mortality: In-hospital and Future

A prospective cohort of 1016 adult patients with AECOPD and acute respiratory failure from five hospitals was followed up for six months. While 11% of the patients died during the index hospital stay, the 60-day, 180-day, 1-year, and 2-year mortality was high (20%, 33%, 43%, and 49%, respectively). After discharge, 446 patients were re-admitted 754 times in the next six months. Survival time was independently related to severity of illness, body mass index (BMI), age, prior functional status, partial pressure of arterial oxygen / fraction of inspired oxygen (PaO_2/FiO_2) ratio, congestive heart failure, serum albumin, and the presence of cor-pulmonale.[62] An audit of records of patients admitted to UK hospitals with AECOPD showed that 14% of cases died within three months of admission with a variation between hospitals of 0 to 50%. Poor performance status, acidosis, and the presence of leg oedema were the best significant independent predictors of death.[75] Patients who are "frequent COPD exacerbators," (those who had "three severe exacerbations per year) had a four-fold increased risk of death compared to patients who did not have exacerbations at all, independent of other standard prognostic factors, such as age, FEV_1, BMI, arterial blood gases, or concomitant comorbidities.[76]

Severe exacerbations are independent risk predictors for mortality along with the more well established BODE index.[77] Each new severe exacerbation requiring hospitalisation increases the risk of a subsequent exacerbation, and every new severe exacerbation increases the risk of death. The risk of the subsequent severe exacerbation was observed to increase three-fold after the second severe exacerbation and 24-fold after the 10th, relative to the first hospitalisation.[78] Pseudomonas isolation in sputum in patients hospitalised for AECOPD is a prognostic marker of three-year mortality with a hazard ratio of 2.23 compared to non-pseudomonas population. The poor prognosis was independent of other significant predictors of mortality, such as BODE index, age and comorbidity.[79]

In the four-year UPLIFT trial[68] reviewed above, increasing rates of hospitalised exacerbations were associated with increasing risk of death. A retrospective, observational, cohort study including 260 consecutive patients showed that the in-hospital mortality rate was 5.8% and the one-year mortality rate was 27.7%. Age, male sex, prior hospitalisation for AECOPD in the last two years, prior recorded congestive heart failure, hypercapnia and elevated levels of urea at hospital admission were independent predictors of mortality within the first year after admission.[80] In a recent study, the frequent exacerbators, though only 13.6% of the total study population, accounted for 56.6% of exacerbation-related hospitalisations, which overall, were associated with a three-fold increase in mortality.[81]

In-hospital mortality of patients for acute exacerbations is relatively high, and clinical features seem to be the most reliable factors to predict this outcome. A retrospective cohort study of 972 patients gave an in-hospital mortality rate of 6.4%. In the univariate analysis, moderate-to-severe AECOPD, age older than 75 years, severe COPD, abnormal blood gas values, onset of complications during hospital stay, radiologic consolidation, a positive result in a microbiological respiratory sample, home oxygen therapy, admission to the intensive care unit, left ventricular ejection fraction, and department of admission were statistically significant factors. The multivariate analysis showed that moderate-to-severe AECOPD, age older than 75 years, severe COPD, abnormal blood gas values and complication during hospital stay were independently related to mortality.[82]

Autopsy results suggest that common contributing causes of early death in patients hospitalised with severe COPD exacerbation are concomitant complications including cardiac failure, pneumonia, and pulmonary tropical eosinophilia. Respiratory failure due to a progression of COPD was less common than these.[83]

Mortality rates one year after hospital discharge for patients requiring mechanical ventilation for respiratory failure have been reported to be as high as 59%, and the risk factors include hypercapnia, hypoxaemia, low BMI, older age, cardiac diseases, comorbidities, severity of illness, low serum albumin level, long-term use of oral corticosteroids, and functional status.[84]

Physical Activity

Chronic obstructive pulmonary disease exacerbations aggravate peripheral muscle weakness. Muscle force (quadriceps peak torque) was found to be lower at three days after admission for an exacerbation than 90 days later.[85] An acute fall in outdoor activity is also seen with exacerbations. Frequent exacerbations lead to a greater decline in time spent outdoors.[86] Patients with hospitalisation for an exacerbation in the previous year have a lower activity level when compared to those without a recent hospitalisation.[87,88]

Physical inactivity brings with it unfavourable prognostic factors including cardiorespiratory deconditioning leading to increased dyspnoea and fatiguability, increased risk of venous thromboembolism, worsening of osteoporosis and neuropsychiatric comorbidity.

Impact on Multi-dimensional Assessment Scores

The BODE index is a composite score based on BMI, degree of airflow obstruction, Medical Research Council grade of dyspnoea, and the six-minute walk distance and has been validated as a predictor of mortality in COPD. A one-year retrospective study in 76 patients with COPD observed that the exacerbation frequency was correlated significantly to BODE index score. Chronic obstructive pulmonary disease patients who experienced FEs in a previous year had significantly higher BODE score than those who experienced IEs.[89] Chronic obstructive pulmonary disease exacerbations negatively impact on the BODE index and its components, including the six-minute walk distance. In one study,[90] the BODE index score worsened by 1.38 points during the exacerbation, and remained 0.8 and 1.1 points above the baseline at one and two years, respectively, indicating an incomplete recovery in the patient-centered outcomes.

Cardiovascular Disease

Cardiovascular involvement is the most important and frequent extra-pulmonary comorbidity in patients with COPD and is believed to be a result of the systemic inflammation that complicates COPD. Exacerbations have an aggravating effect on cardiovascular disease that may be evident during the event or in future.

There is evidence of silent myocardial ischaemia during an acute exacerbation that may be overlooked. Using the Cardiac Infarction Injury Score (CIIS) to assess the prevalence of prior myocardial infarction (MI) in patients with COPD admitted previously for an acute exacerbation, Brekke *et al*[91] found that unrecognised MI was common in patients hospitalised with COPD exacerbation. Less than one-third of patients with electro-cardiogram (ECG) evidence of previous MI by the CIIS system actually had the diagnosis established during the episode of exacerbation.[91]

The period following an exacerbation appears to be a particularly high risk time. Evidence from a large observational database in the UK of 25857 patients with COPD followed-up over a two-year period suggests that exacerbations of COPD increase the risk of MI and stroke in the post-exacerbation period. There was a 2.27-fold increased risk of MI one to five days after the exacerbation that diminished progressively with time. There was a 1.26-fold increased risk of stroke 1 to 49 days after exacerbation.[92] In the four-year UPLIFT trial, non-lower respiratory serious adverse events (NRSAEs) including cardiac were calculated for the 30 and 180 days before and after the first exacerbation in 3960 patients. The relative risk for all NRSAEs at 30 days following an exacerbation was 3.22 and at 180 days was 2.36. The relative risks of cardiac failure, MI and stroke were 10.71, 3.20 and 2.31, respectively, for the 180 days after their first exacerbation compared to the 180 days preceding it.[93]

In a cohort of 242 patients hospitalised for a COPD exacerbation in Scotland,[94] raised troponin, chest pain and serial ECG changes were common. Overall, one in 12 patients met the criteria for MI. Recently, Patel *et al*[94] observed that frequent COPD exacerbators have greater arterial stiffness than infrequent exacerbators. Arterial stiffness was found to rise acutely during COPD exacerbations, particularly with airway infection. Increases in arterial stiffness were related to inflammation, and were slow to recover. Increases in cardiac biomarkers (troponin T and N-terminal pro-brain natriuretic peptide) at exacerbation were higher in those with ischaemic heart disease.[95]

The increased risk of acute vascular events may be related to increased systemic inflammation. It has been reported that COPD exacerbations increase serum IL-6 levels, leading to a rise in plasma fibrinogen.[96]

Chronic obstructive pulmonary disease is a recognised risk factor for deep venous thrombosis (DVT) and PE because of several reasons. Pulmonary embolism may be associated also with COPD exacerbations. A study of 211 consecutive patients with COPD admitted to the hospital for severe exacerbation of unknown origin and who did not require invasive mechanical ventilation showed a 25% prevalence of

PE.[97] A review of five cross-sectional or prospective studies[98] that used computed tomography (CT) scanning or pulmonary angiography for the diagnosis of PE showed that one in four patients with COPD who require hospitalisation for an acute exacerbation may have PE. Presenting symptoms and signs were similar between patients who did and did not have PE.[98] A diagnosis of PE should be considered in patients admitted with exacerbation, especially in those with an intermediate-to-high pre-test probability of PE and where an infectious aetiology appears unlikely.

Data from an international, multi-centre registry consisting of 2984 patients with COPD and 25936 non-COPD showed that the former presented more frequently with PE than DVT and had a higher risk of death, bleeding or venous thromboembolism recurrences as PE compared with non-COPD patients.[99]

Osteoporosis

Nearly two-thirds of patients with COPD have osteoporosis or osteopaenia.[100] It can be correlated with the extent of emphysema.[101] It is multi-factorial in origin and several factors, such as age, smoking, physical inactivity, corticosteroid usage and systemic inflammation may explain the association with COPD.

There is some evidence that osteoporosis is aggravated by FEs. The decrease in thoracic vertebral bone mineral density is greater in patients with FEs than in those without a history of exacerbations.[102]

Neuro-psychiatric Complications

Depression is common in patients with COPD. The ECLIPSE study found a prevalence of symptom-defined depression in 26% of patients compared to 12% of controls that increased with disease severity.[103] A study by Quint *et al*[104] showed a relationship between depression and exacerbation frequency in patients with COPD. Frequent exacerbators had a significantly higher median baseline depression score than infrequent exacerbators. Depression increased significantly in patients from baseline to exacerbation.[104]

Depression is a major factor contributing to decreased physical activity, deconditioning and worsening of symptoms, and also adversely impacts adherence, compliance and utilisation of health-care.

Changes in GOLD Classification of Severity

The GOLD classifications of severity of COPD, prior to 2011, were based only on spirometry. While a reduced FEV_1 has been identified as a risk factor for exacerbations, it is seldom the only determinant and the strength of association is modest. Not all patients with severe disease on spirometry are frequent exacerbators. In fact, one study showed that decreased FEV_1 was not significantly associated with frequent exacerbator status.[105]

The ECLIPSE study observations provide support for a frequent-exacerbation phenotype of COPD independent of spirometry-defined severity. This dissociation between the degree of airways obstruction and the frequency of exacerbations has been recognised under the new GOLD 2011 classification of severity.[1] A history of zero or one exacerbation suggests a low future risk of exacerbations, while two or more suggest a high future risk. The 2011 GOLD guidelines recommend using a combination of an individual's FEV_1 and history of exacerbations to assess the exacerbation risk as follows: (i) Low risk: GOLD 1 or 2 (mild to moderate airflow limitation) and/or 0 to 1 exacerbation per year; (ii) High risk: The GOLD 3 or 4 (severe or very severe airflow limitation) and/or 2 or more exacerbations/hospitalisation per year

Conclusions

Exacerbations are episodes of acute worsening of clinical condition in patients with COPD. Majority but not all exacerbations are infectious in origin, mostly bacterial or viral. Risk factors for the occurrence of acute exacerbations have been identified. Among others, a COPD-related hospitalisation within the previous year, previous history of antibiotic therapy or systemic corticosteroid use, more severe disease, presence of comorbidities, chronic bronchitis phenotype and chronic respiratory failure are the more important risk factors. A proportion of patients who have more frequent exacerbations likely constitute a clinical phenotype that represents a distinct and probably a more severe form of the disease. These exacerbations apart from posing an immediate threat to survival and being a significant economic burden are also important because of their long-term negative effects on the health status, symptoms, lung function, physical activity and associated comorbidities. Recovery from an acute exacerbation is seldom complete, and therefore, exacerbations represent important milestones in the natural history of COPD. The new GOLD criteria introduced in 2011 for grading the severity of COPD takes into account the risk of exacerbations in addition to the symptoms and FEV_1. Patients identified as having a higher risk of exacerbations merit a more aggressive treatment. Reduction in the risk and prevention of acute exacerbations is a major objective of management.

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