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REVIEW

Exacerbations of chronic obstructive pulmonary disease

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ABSTRACT: Exacerbations of chronic obstructive pulmonary disease are of major importance in terms of their prolonged detrimental effects on patients, the acceleration in disease progression and high healthcare costs.

There is still debate about how exacerbations should be defined and graded, and their mechanisms are poorly understood. The major causal agents are either bacteria or viral infections, or a combination of the two. Noninfective causes include air pollution and pulmonary embolus but, in some patients, no cause is identified.

Exacerbations represent an increase in the inflammation that is present in the stable state, with increased numbers of inflammatory cells (particularly neutrophils), cytokines, chemokines and proteases in the airways, and increased concentrations of certain cytokines and C-reactive protein in the blood. There are presently no reliable biomarkers with which to predict exacerbations.

Exacerbations have a long-lasting adverse influence on health status. High doses of bronchodilators are the mainstay of treatment and systemic corticosteroids have some benefit. The routine use of antibiotics remains controversial but they are of benefit with exacerbations of a bacterial origin. Noninvasive ventilation is beneficial in preventing the need for intubation and its important complications but it is not certain whether its use in stable patients prevents exacerbations. Although important advances have been made, more effective treatments are needed in the future for prevention and treatment of exacerbations.

KEYWORDS: Bacterial infection, exacerbation, health status, inflammation, viral infection

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The present review article is a summary of a meeting on the Exacerbations of COPD held in Como, Italy, in April 2005. The meeting was the fourth in the series entitled COPD: the Important Questions. The chairs of the meeting and its participants are listed in the Appendix. The aim of the meeting was to identify important questions related to the exacerbations of chronic obstructive pulmonary disease (COPD) and to discuss future approaches based on recent and evolving research. The present article contains the results of those discussions.

Exacerbations of COPD are of major global importance. They have a profound and long-lasting effect on patients, resulting in poor health status; they may accelerate the progression of the disease; and they account for a large proportion of the increasing healthcare spending on COPD. Yet controversies remain over the definition of exacerbations, how they should be monitored and their underlying mechanisms. Exacerbations of COPD are now recognised as important events in the natural course of COPD and this fact is underlined in major international guidelines [1, 2]. Exacerbations are an important outcome, not only because they pose a considerable economic burden but more importantly because repeated exacerbations of COPD lead to deteriorating health-related quality of life [3, 4] and, when associated with ventilatory failure, to premature death [5]. There is gathering evidence that exacerbations accelerate the progressive decline in lung function in COPD patients, making their prevention even more important [4]. In general, exacerbation frequency increases with disease severity, as represented by airflow obstruction [6], but the relationship between exacerbation frequency and forced expiratory volume in one second (FEV_1) is not particularly close and new evidence indicates a possible role for extrapulmonary factors in the genesis of

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exacerbation. Indeed, the BODE index, which includes the body mass index (B), obstruction (O), dyspnoea (D) and exercise endurance measured by the 6-min walk distance (E), is a better predictor of hospitalisation from COPD in a cohort of patients than FEV_1 [7].

Over time COPD exacerbations become more frequent and more severe, and this is associated with increasing functional impairment. Thus it is the patients with more severe COPD who are prone to more severe exacerbations and are more likely to need hospital admission, especially in the winter months when respiratory viral infections are common [8]. Risk factors for exacerbation relapses include low pre-treatment FEV_1, a need to increase bronchodilator or corticosteroid use, previous exacerbations (more than three in the last 2 yrs), prior use of antibiotics and the presence of comorbid conditions (congestive heart failure, coronary artery disease, chronic renal or liver failure) [9–12]. Patients with exacerbations are at increased risk of dying compared with patients who do not exacerbate or those who do so but do not require hospital admission [13].

CAUSAL AGENTS

Bacteria, viruses and environmental agents account for the vast majority of episodes of exacerbation (table 1). In a recent study of patients admitted to hospital with severe exacerbations, 78% of patients had evidence of viral or bacterial infection (fig. 1) [14]. However, many patients suffer from exacerbations where no specific causes can be identified.

Bacteria

Several lines of evidence now implicate bacteria as an important cause of exacerbation of COPD [15, 16]. Bronchoscopic sampling of the distal airways of the lung has demonstrated the presence of pathogenic bacteria in 50% of exacerbations. Acquisition of new strains of bacterial pathogens has been associated with a more than two-fold increase in the risk of exacerbation [17]. Systemic and mucosal immune responses to nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* develop in the majority of exacerbations associated with isolation of these bacteria from sputum. Bacterial exacerbations are associated with increased numbers of activated neutrophils in sputum that decline with treatment of the exacerbations using antibiotics [18]. Antibiotic treatment of exacerbations appears to be beneficial, especially in patients with more severe underlying obstructive disease and multisymptom exacerbations [19].

The host–pathogen interaction that determines the consequence of acquisition of strains of bacterial pathogens in a patient with COPD is complex. Increased understanding of this interaction is required to develop an effective means of treatment and prevention of bacterial exacerbations. Pathogen factors that may determine the outcome of the host–pathogen interaction include the ability of bacterial strains to elicit cytokines from and to invade airway epithelial cells. Bacterial colonisation is frequently found in patients with COPD but not in matched normal smokers, and this is associated with an increase in inflammatory markers in induced sputum, suggesting that bacterial colonisation may be a factor increasing airway inflammation [20]. There is an association between bacterial colonisation and increased markers of inflammation in sputum [18] and with the frequency of exacerbations [12].

Host factors that may be important include the development of a mucosal antibody response, as well as cellular immunity to bacterial pathogens. Alterations in innate immunity are likely to be of substantial importance, although these have not been investigated. There is evidence to suggest a defect in macrophage phagocytosis in COPD patients that may result in defective clearance of infectious agents from the lower respiratory tract [21].

Inflammation is recognised as an important pathological feature of COPD and exacerbations are now thought to represent the clinical manifestations of increased inflammation. Little information is available about the patterns of inflammation and spectrum of mediators in exacerbations due to different causal mechanisms.

Viruses

There is considerable evidence that upper respiratory tract viruses may precipitate exacerbations of COPD. Approximately 50% of exacerbations are associated with upper respiratory tract virus infections and infection with rhinovirus, respiratory syncytial virus and influenza have been associated with exacerbations [14, 22]. The presence of an upper respiratory

TABLE 1 Causes of chronic obstructive pulmonary disease

Causal mechanism	Common	Less common
Bacteria	*Haemophilus influenzae*	Pseudomonas
	Streptococcus pneumoniaie	
	Moraxella catarrhalis	
Virus	Rhinovirus	Influenza A and B
	Respiratory syncytial virus	Parainfluenza virus
		Coronavirus
		Adenovirus
Atypical organisms		*Mycoplasma pneumoniae*
		Chlamydia pneumoniae
Noninfective	Air pollution (particulates, ozone)	Pulmonary embolus
	Cold temperatures	Congestive cardiac failure

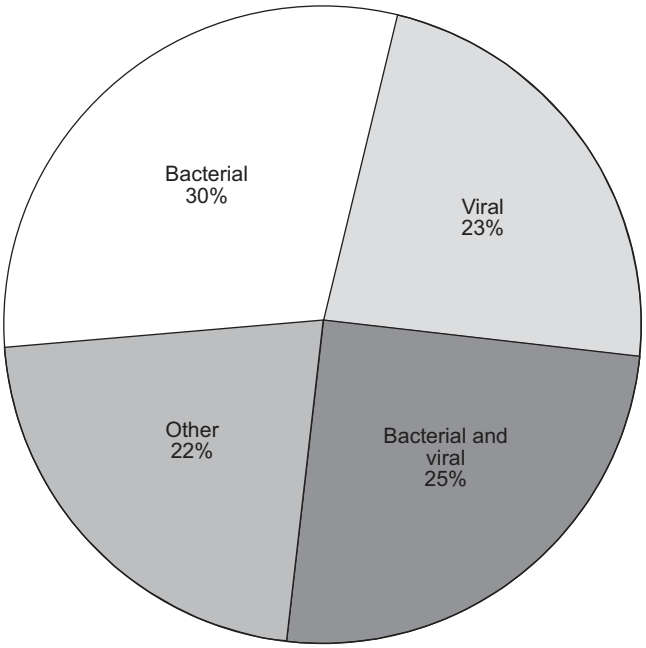

FIGURE 1. Causal mechanisms in chronic obstructive pulmonary disease. Data are derived from [14].

tract infection leads to a more severe exacerbation and a longer symptom recovery time at exacerbation [23]. Increased symptoms induced by virus-associated exacerbations appear to last longer than bacterial exacerbations [8]. More than 60% of exacerbations in COPD are associated with the symptoms of a common cold [23]. At least one virus is detected by PCR in 64% of exacerbations of COPD patients and these patients have a higher exacerbation frequency than patients in whom viruses are not detected [8]. COPD patients with a history of frequent exacerbations may be more susceptible to respiratory viral infections, although the nature of this susceptibility has not yet been defined. It is possible that upregulation of the intercellular adhesion molecule-1, which acts as a receptor for rhinoviruses, in airway epithelial cells is important [24] and is upregulated by rhinovirus infection *via* the activation of the transcription factor, nuclear factor (NF)-κB [25]. Rhinovirus can be recovered from the sputum more easily than from the upper airways, indicating that these viruses directly infect the lower respiratory tract [26, 27]. Virus infections, like bacterial infections, are associated with increased numbers of neutrophils in the sputum, and also with an increase in the numbers of eosinophils, suggesting that different inflammatory mediators are involved [14].

There is increasing recognition that many patients with exacerbations have concomitant viral and bacterial infection. Approximately 25% of patients admitted to hospital with an exacerbation of COPD had co-infection with bacteria and viruses, and these patients had more severe exacerbations, as measured by length of hospitalisation [14]. In a recent survey, ~70% of exacerbations were associated with an increase in *H. influenzae* and those patients who had concomitant rhinovirus infection (detected by PCR) had a greater fall in FEV_1 and rise in serum interleukin (IL)-6 and sputum CXCL8 (IL-8) [28]. This suggests that patients co-infected with a virus and bacteria may have more severe exacerbations.

Noninfective mechanisms

Epidemiological studies have shown that hospital admissions with COPD exacerbations increase slightly with a rise in atmospheric levels of sulphur dioxide, ozone, nitrogen dioxide and particulates [29]. There is convincing evidence that exposure to particulates with a 50% cut-off aerodynamic diameter of 10 μm is associated with increased hospital admissions in COPD patients [30]. Particulates induce oxidative stress and, *in vitro*, this leads to activation of NF-κB, histone acetylation and increased expression of CXCL8 [31]. This is enhanced by adenoviral early region 1A, suggesting that there may be an interaction between virus infection and air pollution in triggering exacerbations [32].

Low temperatures may also be associated with exacerbations of COPD. Reduced temperatures in the bedroom and outside air have been associated with falls in the lung function of COPD patients and an increased frequency of exacerbations [33]. The mechanisms are not yet understood but may relate in part to increased susceptibility to upper respiratory tract virus infections in cold weather. In patients admitted to hospital with severe COPD exacerbations of unknown cause, 25% had pulmonary embolism confirmed by spiral computerised tomography [34]. Heart failure may also lead to a symptomatic exacerbation of COPD, although it may be difficult to differentiate the symptoms of increased heart failure from those of a COPD exacerbation [35].

MECHANISMS

Pathological and cellular changes

There is an increase in sputum neutrophil numbers in exacerbations of COPD and a recent biopsy study demonstrated an increase in neutrophils in bronchial biopsies, although they are rarely seen in the stable state [36]. In bronchial biopsies of patients with mild exacerbation of chronic bronchitis, an eosinophilia exists that is associated with increased expression of CCL5 (also known as RANTES) [37–39]. Virally induced exacerbations are also associated with increased levels of eosinophils in sputum, as discussed previously [14]. Viral infections induce the expression of CCL5 in airway epithelial cells [40]. CCL5 may act synergistically with CD8+ cells to enhance the apoptosis of virally infected cells, thus leading to increased tissue destruction [41]. There is also an increase in the concentration of the elastolytic enzyme matrix metalloproteinase-9 and a decrease in its major inhibitor, tissue inhibitor of metalloproteinase-1, in sputum during exacerbations [42]. This is consistent with an increase in urinary desmosine, which is an indicator of elastolysis [43]. This may provide a causal link between exacerbations and accelerated decline in lung function.

Molecular mechanisms

The cellular and molecular mechanisms of exacerbations are still not well understood but most evidence suggests that they are due to a further amplification of the inflammatory process triggered by bacteria, viruses and noninfective stimuli, such as air pollution (fig. 2). There is a marked increase in neutrophil numbers (accounting for the change in sputum colour) and cytokines that are increased in stable COPD (tumour necrosis

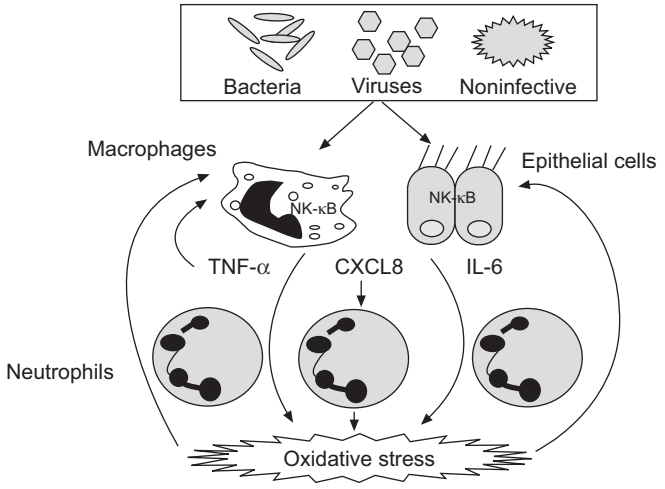

FIGURE 2. Pathogenic mechanisms in chronic obstructive pulmonary disease. Bacteria, viruses and other factors, such as air pollution, may activate the transcription factor nuclear factor (NF)-κB in airway epithelial cells and macrophages, which then release inflammatory cytokines, including interleukin (IL)-8 (CXCL8), which in turn attracts neutrophils, tumour necrosis factor (TNF)-α and IL-6, both of which amplify inflammation. Increased numbers of neutrophils generate oxidative stress, which further amplifies the inflammatory process.

factor (TNF)-α and IL-8) are further increased during the exacerbation [44, 45]. There is also increased expression of the chemokine CCL5, which attracts T-cells and eosinophils, and CXCL5 (previously known as epithelial neutrophil-activating peptide (ENA)-78), which attracts neutrophils [36, 46]. IL-6 is increased in sputum, breath and plasma of COPD patients during exacerbations [8, 47, 48]. These mediators are regulated primarily by NF-κB and there is evidence for its activation in macrophages in COPD exacerbations [49]. Rhinoviruses and bacteria, such as *H. influenzae*, may activate NF-κB through Toll-like receptors (TLR), which recognise surface pathogens (predominantly TLR2, TLR3 and TLR4) [50]. Nontypeable *H. influenzae* activates NF-κB synergistically with TNF-α through the activating enzyme inhibitor of NF-κB kinase-2 (IKK2) and activation of a p38 mitogen-activated protein kinase (MAPK) pathway [51]. There is an increase in leukotriene (LT)B_4 (chemotactic for neutrophils and involved in T-lymphocyte activation) in the sputum and exhaled breath [52, 53]. Oxidative stress is also increased, as evidenced by an increase in exhaled 8-isoprostane and hydrogen peroxide and this persists over several weeks [53–55]. Nitrative stress may also be increased in exacerbations, as exhaled nitric oxide (NO) levels are higher during exacerbations [56–58]. The increased formation of peroxynitrite may be important in amplifying inflammation during an exacerbation. The prolonged increase in COPD exacerbations may reflect the perpetuation of inflammation through an interaction between oxidative stress and NF-κB activation, and the establishment of amplification loops. COPD exacerbations respond relatively poorly to corticosteroids indicating a degree of steroid resistance, which may reflect a reduction in histone deacetylase (HDAC)-2 activity in the airways [59, 60]. The reduction in HDAC in COPD provides a molecular mechanism for amplification of inflammatory gene expression in COPD [61] and may be further reduced by the increased oxidative stress and NO production during an exacerbation [62]. This may explain why high doses of corticosteroids have relatively low efficacy in the treatment of COPD exacerbations [63].

BIOMARKERS OF EXACERBATIONS

A biomarker refers to the measurement of any molecule or material (cells and tissue) that reflects the disease process. In COPD, several types of biomarker have been measured that are related to disease pathophysiology and the inflammatory and destructive process in the lung, but there are few measurements during exacerbations [64]. Biomarkers have been measured in blood, urine, sputum, bronchoalveolar lavage and exhaled breath. So far there is little information about whether biomarkers can predict exacerbations or distinguish between different causal mechanisms for exacerbations, thus providing a means of guiding the therapy.

Blood

Various inflammatory biomarkers, including TNF-α, IL-6 and C-reactive protein (CRP) are increased in the plasma of patients with stable COPD, but it is uncertain whether or not they predict exacerbations. There is an increase in plasma concentrations of inflammatory markers during acute exacerbations, including TNF-α and IL-6, and this may represent overspill from the lung [65, 66]. A recent study measured 36 plasma biomarkers during acute exacerbations in 90 patients with COPD and compared concentrations with the baseline state [67]. The most selective biomarker turned out to be CRP, although it was not specific for an exacerbation. The interrelationships between the various biomarkers suggested that there was an increase in monocyte and lymphocyte activation during an exacerbation. None of the biomarkers proved to be useful in predicting the clinical severity of an exacerbation. Plasma leptin concentrations are increased during an exacerbation and this may indicate negative energy balance during an acute exacerbation [65, 68]. Systemic oxidative stress is also increased during exacerbations, with increased concentrations of markers of oxidative stress and reduced antioxidants [69].

Sputum

Several inflammatory markers are increased in induced sputum of COPD patients during acute exacerbations and fall during recovery. Increased sputum concentrations of TNF-α, IL-6, CXCL8, LTB_4 and endothelin-1 have been reported [45, 47, 70–72]. The increased purulence and colour change of sputum during exacerbations reflects the increased numbers of neutrophils containing the green pigment myeloperoxidase [73]. The colour may be useful in guiding whether antibiotic therapy is likely to be effective [18].

Exhaled NO

The levels of exhaled NO measured at the mouth are usually normal in patients with COPD [74] but when exhaled NO is partitioned by the multiple flow technique, peripheral NO (including small airways and lung parenchyma) is increased, whereas bronchial NO is normal [75]. However, exhaled NO is increased during exacerbations of COPD [56–58]. This may reflect increased nitrative stress during exacerbations and this hypothesis is supported by the demonstration of increased

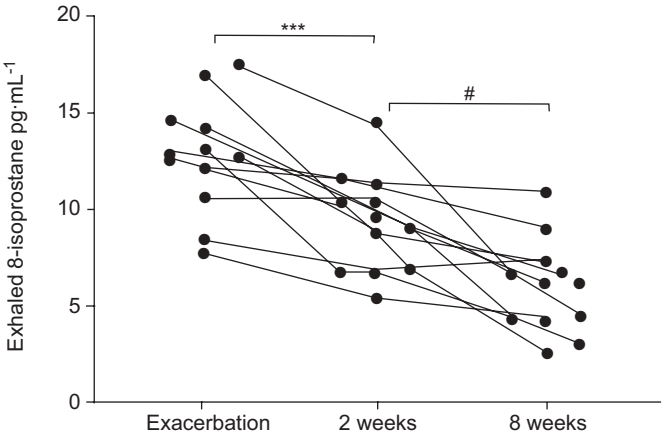

FIGURE 3. Increased oxidative stress in a chronic obstructive pulmonary disease (COPD) exacerbation results in increased 8-isoprostane in exhaled breath condensate of COPD patients treated with antibiotics. 8-Isoprotane concentrations fall to stable levels over 8 weeks. ***: $p<0.001$; #: $p=0.001$.

numbers of nitrotyrosine-positive cells (as a result of increased nitrite and peroxynitrite formation) in induced sputum during an exacerbation compared to the stable state [72].

Exhaled breath condensate

Several inflammatory mediators and markers of oxidative stress have been measured in exhaled breath condensate. There is a high variability in the measurement and dilution results in very low concentrations of many mediators, making this a difficult measurement [76]. However, this is a non-invasive measurement and is suited to serial measurements during an exacerbation of COPD. An increased concentration of hydrogen peroxide in exhaled breath condensate has been reported during exacerbations of COPD, suggesting increased oxidative stress [54, 55]. In a general practice-based study, an increase in LTB_4 and 8-isoprostane, a marker of oxidative stress, were found in exacerbations of COPD and these abnormalities took several weeks to normalise (fig. 3) [53]. Acute exacerbations of COPD are associated with an increase in several cytokines in exhaled breath condensate, including TNF-α, IL-1β, IL-6 and CXCL8 [77].

CLINICAL CONSEQUENCE OF EXACERBATIONS

Health status

Although it is recognised that exacerbations are associated with considerable symptomatic and physiological deterioration, the burden imposed on patients may be underestimated. Interestingly, patients are not familiar with the term ''exacerbation'' as used by healthcare professionals and, if given a choice, they may use their own words to describe the worsening of symptoms. The terminology used by patients is extremely varied but consistent for each patient. The way in which patients perceive exacerbations and how exacerbations affect patients have been greatly helped by the systematic scoring of health status questionnaires. The application of such tools to study exacerbations has provided major new insights, although it still remains a hypothesis-generating exercise. It has been shown that the frequency of exacerbations accounts for some of the differences in health status between patients [3] and for some of the deterioration in health status scores within patients over time [78]. Reducing exacerbation rate appears to reduce this deterioration. The mechanism for this is not clear but is likely to be associated with the large and sustained effect of a single exacerbation on health [78]. Even if the patient fails to improve by a very small degree following each exacerbation, the accumulated effect could account for the progressive deterioration attributable to COPD exacerbations [4]. During an exacerbation, poorer health status is associated with an increased likelihood of further exacerbations within 6 months [78]. Thus, the composite data from patient-centred studies and, mostly, pharmacological trials indicate an important role for repeated exacerbations on the health status of patients with COPD. Furthermore, in one long-term randomised trial comparing inhaled corticosteroids with placebo, there was no significant change in the rate of decline of FEV1 whereas, in the group receiving active medication, there was a slower deterioration in the rate of worsening of the health status scores over time that appeared to be related to a decrease in exacerbation frequency [79].

Physiological consequences

There is limited information describing the physiological changes that occur during exacerbations of COPD that do not require mechanical ventilation. The data from patients requiring mechanical ventilation indicates the presence of increased central drive, dyspnoea, tachypnoea, reduced tidal volume and development of hypercapnoeic respiratory failure, while ventilation/perfusion matching seems to be relatively preserved [80, 81]. Two recent studies have increased present knowledge about the changes in lung mechanics and its relation to dyspnoea during exacerbation of COPD [82, 83]. In both studies, lung mechanics, including spirometry, inspiratory capacity and dyspnoea, were recorded during recovery from an exacerbation. Consistent reduction in dyspnoea was seen as resolution of the exacerbation. In both studies, the FEV1/forced vital capacity (FVC) ratio and expiratory flow limitation changed relatively little throughout the study period. In contrast, both studies demonstrated that changes in lung volume rather than airflow resistance predominated. During hospitalisation in one of the studies, there was rapid and significant improvement in dyspnoea, respiratory rate, inspiratory capacity, pulse and FVC, and fewer changes in FEV1. The FEV1 and lung volume improved over time. An exacerbation of COPD appears to be characterised by increased central drive, decreased inspiratory capacity and decreased inspiratory muscle force, perhaps secondary to dynamic hyperinflation. Few studies have attempted to relate the changes in physiology to changes in the inflammatory process that are thought to occur during the episodes. There is an association between increased serum levels of IL-6 and LTB_4 and the magnitude of dyspnoea, respiratory rate and inspiratory capacity [84], suggesting that it may be possible to detect serum changes that reflect the inflammatory burden of the exacerbation. This finding has been confirmed in sputum where changes in concentrations of IL-6, CXCL8, TNF-α, myeloperoxidase, neutrophil elastase and LTB_4 suggest an inflammatory burst [45, 47, 70]. Once patients develop ventilatory insufficiency, the prognosis is very poor, with ~50% mortality at 2 yrs [5].

Economic consequences

Some studies have determined that hospitalisation costs represent 40–57% of total direct costs generated by patients with COPD, and this percentage may be as high as 63% in severe patients [85]. The average cost of hospitalisation for COPD in a cohort of severe patients was estimated to be ~US$7,000. Since acute exacerbations are the main cause of hospitalisation among COPD patients, it is evident that the economic burden of acute exacerbations is considerable. Observational studies performed in primary care centres observed that 16–22% of patients having exacerbations were admitted during 1 yr [86]. The costs of exacerbations that require hospitalisation increase dramatically compared with those that can be treated in an ambulatory setting. An analysis derived from a clinical trial in patients with COPD demonstrated that the 15% of exacerbations requiring hospital admission generated 90% of the costs associated with exacerbations [87]. In a recent study in primary care in Spain, the mean total cost of an acute exacerbation of COPD was estimated to be US$159, with the main part being due to hospitalisations, which represented 58% of the total cost, followed by the drug costs amounting to 32% of the total [88]. However, these costs may not be applicable to other countries because of the differences in reference prices, management practices and healthcare systems. Failure implies a cost that is three times higher than the cost of management of the exacerbation, particularly due to the high cost of hospitalisation. If the percentage of relapses could be reduced, especially in severe cases, or if switching a patient from parenteral to oral therapy could reduce the length of hospital stay, valuable resources could be saved. This is particularly important considering that a recent study demonstrated that patients with stage IV COPD (FEV_1 <35% predicted) had a significantly greater percentage of failures than successful exacerbations, with 52% of failures requiring hospitalisation [87]. The costs of managing acute exacerbations of chronic bronchitis are high, particularly because of the high costs associated with relapse [89, 90]. Strategies to improve the outcome of ambulatory treatment of exacerbations should be very cost-effective, especially in more severe patients who are at increased risk of being admitted to hospital as a consequence of therapeutic failure.

COPD comorbidities and exacerbations

COPD is a condition that becomes clinically apparent in mid-to-late life. Comorbidity is relatively common in patients with COPD and this raises the issue as to whether such a comorbidity is age-related, related to a common factor, such as smoking and cardiovascular disease, due to the effect of drugs like corticosteroids and the development of diabetes, or a reflection of the increase in systemic inflammatory cytokine concentrations, which are a feature of COPD with systemic involvement. Data are emerging that the same inflammatory mediators are central to the pathogenesis of other diseases and, to illustrate this, focus was directed towards type 2 diabetes and cardiovascular diseases. Comorbidities are relevant to exacerbations of COPD as there may be an interaction between the comorbid condition and the severity of the exacerbation. For example, exacerbations may worsen heart failure, whereas heart failure may in turn increase the clinical severity of an exacerbation by increasing the degree of dyspnoea.

There is increasing evidence that the cytokines systemically released in COPD, such as CRP, IL-6 and TNF-α, play a key role in the pathogenesis of insulin resistance and type 2 diabetes [91]. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict development of type 2 diabetes [92]. Indeed, the odds ratio for developing type 2 diabetes in females with COPD is 1.8 [93]. The mechanism may occur *via* a common pathway. For example, in COPD, there is a general metabolic shift toward catabolism and an increase in resting energy expenditure [94]. The plasma concentration of TNF-α in patients with COPD and malnutrition is increased [95] and TNF-α decreases peripheral insulin action [96]. In addition, oxidative stress is increased in COPD, particularly during exacerbations, and has also been implicated in insulin resistance [97].

Cardiovascular disease

Recent studies have shown that there is a 3.14 and 2.57 incidence ratio of myocardial infarction or first stroke during the first 3 days after a systemic respiratory infection, suggesting a close association [98]. Systemic respiratory infections are associated with peripheral acute-phase responses, including the production and release of TNF-α, IL-6 and CRP. A subsequent study indicated that the concentrations of IL-6 and CRP in plasma were significantly related to an increased risk of coronary heart disease in males and females, and that an increase in soluble TNF-α receptors was associated with an increased risk in females [99]. Cardiac troponin-1 is often raised during acute exacerbations that require hospitalisation but are without other evidence of an acute coronary syndrome, indicating that an acute exacerbation has detrimental effects on cardiac muscle [100].

Elevation of the CRP is an independent predictor of myocardial infarction. The relative risk for subjects with CRP concentrations >3 $mg \cdot L^{-1}$ is 1.79 compared with those in whom the CRP is <1 $mg \cdot L^{-1}$ [101]. CRP increases the expression of intercellular adhesion molecules, induces monocyte chemoattractant production, activates complement and mediates low density lipoprotein uptake by macrophages. In addition, CRP may deposit directly into the arterial wall during atherogenesis to create foam cells, which are the building blocks of atherosclerotic plaques. Furthermore, there is an increased pro-thrombotic state in patients with COPD, as shown by increased circulating fibrinogen levels during acute exacerbations [66].

The interaction between comorbidities and COPD is only just beginning to be explored but it is clear that survival in COPD is better predicted by variables other than simply the degree of airflow limitation [102]. How these factors relate to the development and perpetuation of exacerbations remains to be elucidated but they are likely to be very important in patients with COPD.

THERAPY

Bronchodilators

Bronchodilators have important roles in both the prevention and treatment of acute exacerbations of COPD. In exacerbations, bronchodilators are the primary treatment modality designed to alleviate patient symptoms, improve physiological state and prevent or reverse respiratory failure. Unlike noninvasive ventilation, the use of bronchodilators has not

been shown to prolong survival. Nevertheless, several important questions remain about bronchodilators in the setting of acute exacerbations. There is no difference in outcome between nebulised short-acting β_2-agonists and ipratropium bromide in acute exacerbations and no evidence that the combination of these two drugs is any more effective [103]. This contrasts with the greater efficacy of these combinations in stable disease [104]; it is not known whether sequential administration differs from concurrent delivery. Patients admitted for acute exacerbations are usually already taking chronic bronchodilator treatment but there is no convincing evidence for the development of tolerance. The question of how effective rapid-acting bronchodilators are when added to long-acting agents needs to be evaluated in future studies.

Several studies suggest that β-agonists and anticholinergic bronchodilators can prevent exacerbations [105–109]. These studies show that long-acting agents appear to be more effective than shorter-acting agents in reducing exacerbation frequency [110]. The mechanism by which this benefit is achieved has not yet been fully delineated. It is possible that bronchodilators reduce exacerbation frequency by a common physiological effect through deflating the lungs and reducing dynamic hyperinflation. Why short-acting agents are less effective, however, is not clear, although this may be due to less effective bronchodilatation and fluctuating airway function as the drug effects wear off. An effect mediated through nonbronchodilator mechanisms, such as an anti-inflammatory effect, is also plausible for long-acting β_2-agonists [111] and possibly for tiotropium [112].

Corticosteroids

The inflammation in COPD is largely resistant to the anti-inflammatory effects of corticosteroids and this appears to be due to a reduction in HDAC-2, which is required for corticosteroids to switch off inflammatory genes [62]. However, systemic corticosteroids reduce both systemic inflammation and certain types of airway inflammation. Prednisolone (30 mg for 2 weeks) reduces sputum eosinophil counts by six-fold in patients diagnosed as having COPD but does not have a significant effect on other inflammatory cells [113]. A similar treatment protocol reduces plasma CRP levels by >60% in COPD patients [114]. A very high dose of corticosteroids (prednisone 50–75 mg *q.d.*) reduced plasma CRP by 80% during an acute exacerbation after 24 h of therapy and this effect was maintained for a week [115]. Oral corticosteroids have beneficial, albeit small, effects in the management of acute exacerbations. In one trial, prednisolone (30 mg *q.d. p.o.* for 14 days) shortened the length of hospitalisation by 2 days (29% reduction compared with placebo), improved FEV_1 by 60 mL per day (or 7% pred overall) and accelerated recovery from symptoms [116]. In another study, systemic corticosteroids improved oxygenation and dyspnoea during acute exacerbations [117]. Treatment with systemic corticosteroids for 2 weeks resulted in higher FEV_1 values and lower treatment failures than placebo over 6 months in patients admitted to hospital with COPD exacerbations [118]. Therapy for 8 weeks produced no incremental benefits above those achieved by a 2-week course. These data are consistent with the observation that 60–80% of COPD patients recover from their exacerbation by day 15 [23]. The majority of patients with COPD probably only require 2 weeks of oral corticosteroids, but a few with more severe exacerbations may require a longer duration of exposure. Systemic corticosteroids are also useful in preventing hospitalisations and relapses in those who visit emergency departments only during flare-ups. Prednisone (40 mg *q.d. p.o.* for 10 days) reduced relapses (either an unscheduled physician visit or repeat emergency visit) by 37% and the risk for hospitalisation by 47% (although the latter did not reach statistical significance due to insufficient power of the study) [119]. Interestingly, the only subgroup in which prednisone reduced relapses was the group of patients that were also receiving inhaled corticosteroids (relative risk of 0.44). In one study, nebulised budesonide (2 mg, 6 hourly) had a similar clinical effect to oral prednisone (30 mg *q.d.*) in the management of more acute exacerbations [120].

One concern about the use of systemic corticosteroids in exacerbations is the possibility of diagnostic confusion with community-acquired pneumonia. However, there is no evidence that systemic corticosteroids worsen health outcomes in community-acquired pneumonia if appropriate antibiotics are used. Indeed, a recent study has suggested that systemic corticosteroids may even reduce morbidity and mortality in community-acquired pneumonia [121]. In summary, there is convincing evidence that systemic corticosteroids improve health outcomes during COPD exacerbations. Their use improves health status, reduces dyspnoea, accelerates recovery of lung function, reduces length of hospitalisations and prevents relapses, which are very common in moderate-to-severe COPD. Whether the addition of inhaled corticosteroids at the time of hospital or emergency department discharge can provide incremental benefits is unknown.

Several recently reported large multicentre trials evaluated the role of inhaled corticosteroids in preventing or slowing the progressive course of symptomatic COPD [79, 122–124]. In all of these trials, while there was no evidence for any reduction in disease progression, exacerbations were reduced by 12–25% depending on the severity and the definition used. These findings have been confirmed in studies of fixed combination inhalers containing acorticosteroids and a long-acting β_2-agonist. Both fluticasone/salmeterol and budesonide/formoterol combinations reduce exacerbation frequency to a greater extent than using a corticosteroid or long-acting β_2-agonist alone [125–127]. Retrospective analyses of large databases suggest a possible effect of inhaled corticosteroids on reducing all-cause mortality in COPD patients and, by implication, some effect in reducing exacerbations [128–130]. This prompted the initiation of a large prospective trial to explore the effect of inhaled corticosteroids and a combination inhaler on mortality. Preliminary results of this trial indicate a 17.5% reduction in death over 3 yrs in patients receiving the fluticasone/salmeterol combination compared with placebo, although this did not quite reach significance ($p=0.52$) [131]. Patients treated with inhaled fluticasone alone showed no such reduction in mortality. In the same trial, there was a 25% decrease in moderate-to-severe exacerbations compared with fluticasone/salmeterol with placebo regardless of the airflow severity. Interestingly, there were more investigator-reported pneumonias in the two arms of treatment with inhaled corticosteroids. This finding deserves further study to establish the nature of the relationship.

Antibiotics

The debate about whether or not to give an antibiotic has been driven by studies of the bacteriology of COPD both during and between exacerbations [12, 132–135] and by several placebo-controlled antibiotic trials. The results of these trials are not concordant so there is continuing uncertainty on this topic [136–139]. The recent available data support the prescription of antibiotics in the presence of purulent sputum, although a proportion of the latter will not benefit [140–142]. Specific properties of new antimicrobials, the demonstration of different bacterial isolates in those with different lung function, identification of a subgroup of patients who are more likely to fail with conventional antibiotic therapy and the results of comparative antibiotic studies have been used to support different antibiotic strategies [135, 143, 144]. The guiding principle for the use of antibiotics remain that of knowledge of the local prevalence of bacteria in the population of patients being evaluated, as has been suggested by the American Thoracic Society (ATS)/European Respiratory Society (ERS) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1, 2].

Mechanical ventilation

Noninvasive or invasive (*via* endotracheal intubation) mechanical ventilation is a form of life support to be instituted until the cause underlying the acute respiratory failure is reversed with medical therapy [145]. Noninvasive ventilation should be used whenever possible as it has been shown to be an effective treatment for respiratory failure during acute exacerbations of COPD [146, 147]. Indeed, 1-yr mortality is lower in patients receiving noninvasive ventilation for exacerbations of COPD compared with both conventional mechanical ventilation and optimal medical therapy alone [148, 149]. The institution of mechanical ventilation should be considered when, despite optimal medical therapy and oxygen administration, one of the following persists: 1) moderate-to-severe dyspnoea with evident use of accessory muscles and abdominal paradox; 2) moderate-to-severe acidosis (pH<7.36) and hypercapnia (carbon dioxide arterial tension (P_{a,CO_2}) >6–8 kPa); and 3) respiratory frequency >24 breaths·min^{-1}. Compared with invasive mechanical ventilation, noninvasive ventilation lowers infectious complications and reduces hospitalisation time, resulting in considerable reductions in healthcare costs [150, 151]. It is not yet certain whether the use of noninvasive ventilation at home may prevent exacerbations.

FUTURE THERAPIES

Current pharmacological treatments have a modest effect in treating and preventing exacerbations, indicating the need for new therapies. Since exacerbations, from whatever cause, appear to represent an increase in ongoing inflammation, more effective anti-inflammatory treatments may not only treat exacerbations but may also prevent them, which would be very cost-effective. Several potential anti-inflammatory treatments are now in clinical development [152]. Targeting the causal mechanisms of COPD is a logical approach but it is difficult to differentiate between viral and bacterial infections based on clinical features alone. More rapid diagnostic approaches are therefore needed; for example, the use of PCR to diagnose specific viruses and bacteria in sputum samples, thus allowing more logical treatment. This may then guide the use of appropriate antibiotics and, in the future, antiviral treatments. The future use of biomarkers in the blood or breath to predict the evolution of an exacerbation may allow earlier intervention to prevent the development of a severe exacerbation.

Although several new classes of drug are in development for COPD, there are few clinical trials and little information about whether they prevent exacerbations. Unfortunately, no animal models of COPD exacerbations exist that could be used to explore this in pre-clinical studies and this is an area for future research using acute infections in addition to cigarette smoke exposure. The most clinically advanced new anti-inflammatory treatments are phosphodiesterase (PDE)4 inhibitors; these have a broad spectrum of anti-inflammatory effects that are relevant to COPD [153] and reduce emphysema in an animal model of COPD [154]. Although the dose of PDE4 inhibitor that can be used is limited by side-effects, such as nausea, vomiting and diarrhoea, PDE4 inhibitors not only improve lung function but also reduce the frequency of exacerbations in COPD patients. One such PDE4 inhibitor, roflumilast (500 mg *q.d. p.o.*), was found to significantly decrease the frequency of exacerbations by 34% over a 6-month period [155]. This effect was largely due to a reduction in mild exacerbations, defined by increased rescue bronchodilator use over 2 days, without any change in the use of oral steroids or hospitalisation. Another study using a different PDE4 inhibitor, cilomilast (15 mg *b.i.d. p.o.*) showed that a significantly greater percentage of patients were free of exacerbations over a 6-month period in the cilomilast (74%) compared with the placebo group (62%) [156]. Additional studies are now needed over longer periods of time in more severe patients who have frequent exacerbations.

There is a striking increase in sputum neutrophils during acute exacerbations, suggesting that any drug that inhibits neutrophil recruitment or activation may be of clinical benefit. Chemotactic factors for neutrophils include LTB_4 and CXCL8, and the levels of both of these were increased during exacerbations [45, 52]. Specific LTB_4 inhibitors and anti-IL-8 antibodies reduce the neutrophil chemotactic activity of COPD sputum in the stable state [157]. LTB_4 antagonists may therefore be used to prevent and treat exacerbations but no clinical studies have been reported. CXCL8 and related CXC chemokines, including CXCL1 and CXCL5, which are elevated in COPD, act through a common receptor, CXCR2, for which small molecule inhibitors have now been developed [158]. CXCR2 antagonists are currently entering into clinical trials in COPD patients and it is predicted that they may be useful in reducing and treating exacerbations.

Oxidative stress is increased during COPD exacerbations and acts as an amplifying mechanism for inflammation. This suggests that antioxidants may be useful in preventing and treating exacerbations. Although a meta-analysis of clinical studies with *N*-acetylcysteine, which has antioxidant properties, showed a significant reduction in exacerbation frequency of ~25% [159], a large placebo-controlled trial did not show any significant reduction in the number of exacerbations [160]. However, when patients not treated with inhaled corticosteroids were analysed, a significant reduction was noted. It is clear that more potent antioxidants are needed in the future.

Other approaches that are currently being explored are the use of inhibitors of NF-κB (IKK2 inhibitors) and p38 MAPK inhibitors; both these kinases may mediate the increased inflammation during exacerbations.

TOWARDS A NEW DEFINITION OF EXACERBATIONS

There is currently no general agreement on the definition of a COPD exacerbation. A standardised definition could provide benefits to patients, physicians, researchers and other healthcare payers (*e.g.* Primary Care Trusts, insurance companies, *etc.*) and decision-makers. It would also help patients to optimise their primary and emergency management and would guide physicians in selecting appropriate pharmacological and nonpharmacological therapeutic interventions. An agreed definition would help in the design of randomised clinical trials and allow the results to be accurately evaluated and compared with other trials.

COPD exacerbations have been defined according to the presence of specific signs and symptoms, changes in symptoms and the need for medical intervention, and each of these approaches has positive and negative connotations. Possibly the most seminal definition of COPD exacerbation is the one provided by ANTHONISEN *et al.* [136], based on the presence of three specific symptoms in a patient with COPD, namely increased shortness of breath, increased sputum volume and increased purulence. Moreover, three subtypes were also proposed (types 1, 2, and 3) according to the occurrence of all or some of the symptoms [136]. In the year 2000, an international panel of chest physicians proposed a second definition: ''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 treatment in patients with underlying COPD'' [161]. Exacerbations were defined in terms of mild, moderate and severe according to the use of healthcare resources. The first definition is essentially symptom based and was designed for the study of the effectiveness of therapies, such as antibiotics. The second definition is ''action or event-driven'', which dictates a specific medical intervention. Here, instead of specifying particular symptom criteria, the definition includes a deterioration of respiratory symptoms that requires the use of systemic corticosteroids either with or without antibiotics and/or hospitalisation due to symptoms. These action-driven definitions may vary among regions and countries, and are heavily dependent on the local availability of healthcare. In addition, they are of little value to the clinician seeing an individual patient.

It may be time to learn from the advances provided by the cumulative experience seen in the evaluation and classification of the natural history of coronary artery disease; a parallel approach is summarised in table 2. Coronary artery disease is similar to COPD in that it has a long asymptomatic phase where preventive therapy is highly effective. Once detected, the disease may be stable and treated as such. In patients with COPD, at a certain point in time the disease may become more symptomatic and unstable; this clinical syndrome could be named ''unstable COPD'' akin to the similar picture in the patient with coronary artery disease where the diagnosis of ''unstable angina'' prompts modifications in therapy and more careful follow-up. If the decompensation is associated with refractory dyspnoea (>4 on a 0–10 scale), worse cough and sputum, manifestations of systemic involvement, such as tachypnoea (>24 breaths·min^{-1}), fever, elevated white cell count (>9,000 cells·dL^{-1}) and CRP (>10 mg·dL^{-1}), without evidence of

TABLE 2 Proposed clinical definitions of chronic obstructive pulmonary disease (COPD) syndromes by analogy to syndromes in coronary artery disease

Syndrome	Elements
COPD	
Unstable COPD	Worsening of dyspnoea cough or sputum
	RR <24
	Dyspnoea <4 on 0–10 scale
	Normal laboratory investigations
Exacerbation	Worsening of dyspnoea, cough or sputum
	Dyspnoea ⩾4 on a 0–10 scale
	Normal chest radiograph
	WBC count >9000 cells·dL^{-1} or CRP >10 mg·dL^{-1}
Ventilatory insufficiency	Same plus elevation of P_{a,CO_2} in arterial blood gases
Coronary artery disease	
Unstable angina	Worsening of chest pain
	No ECG changes
	Normal laboratory results
Myocardial infarction	Chest pain
	Abnormal ECG
	Abnormal serum enzyme pattern
Cardiogenic shock	Same syndrome plus shock

RR: relative risk; WBC: white blood cell; CRP: C-reactive protein; P_{a,CO_2}: carbon dioxide arterial tension.

infiltrates in the chest radiograph, the syndrome could be defined as ''exacerbation'' or ''chest attack'', akin to the myocardial infarction or ''heart attack'' of coronary artery disease. Finally, if the same syndrome is accompanied by hypoxaemia and elevation of P_{a,CO_2} in the arterial blood, the syndrome is defined as ''ventilatory failure'', akin to the cardiogenic shock in coronary artery disease. These definitions have the advantage of being practical and of providing clear guidance to clinicians, and would also help to classify the episodes, thus providing a valuable tool to prospectively evaluate the effect of therapy on either the episode itself or its prevention.

CONCLUSIONS

Exacerbations of chronic obstructive pulmonary disease have rightly become an important outcome to define, prevent and treat during the natural course of the disease in patients. The present article has reviewed recent advances in the causes, mechanisms and pathophysiological and clinical consequences of exacerbations. Evidence has also been presented that supports the use of pharmacological and nonpharmacological therapies in the prevention and treatment of the exacerbations *per se*. Central to the development of exacerbation is the role of inflammation and, as such, the potential development of new anti-inflammatory therapy is also reviewed. Finally, a new definition and classification is proposed as a way to add objective elements to the now-subjective definition of exacerbations of chronic obstructive pulmonary disease. It is hoped that current and future research will result in an even more significant impact on exacerbations of chronic obstructive pulmonary disease.

APPENDIX

The meeting summarised in the present review was chaired by P. Barnes (National Heart and Lung Institute, Imperial College, London, UK) and B. Celli (Caritas St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA, USA). The following people also participated in the meeting: P. Calverley (University Hospital Aintree, Liverpool, UK), M. Elliot (St James's University Hospital, Leeds, UK), S. Johnston (National Heart and Lung Institute), T. Hansel (Royal Brompton Hospital, London, UK), P. Jones (University of London, London, UK), S. Kharitonov (National Heart and Lung Institute), W. MacNee (The Queen's Medical Research Institute, Edinburgh, UK), R. Stockley (The Queen Elisabeth Hospital, Birmingham, UK), W. Wedzicha (Royal Free Hospital, London, UK), M. Woodhead (Manchester Royal Infirmary, Manchester, UK), A. Young (AstraZeneca, Charnwood, UK), T. Larsson (AstraZeneca, Lund, Sweden), M. Miravitlles (Servicio de Neumologia, UVIR, Barcelona, Spain), J. Roca (Hospital Clinic, Villarroel, Barcelona, Spain), R. Rodriguez Roisin (Hospital Clinic, Barcelona, Spain), D. Niewoehner (University of Minnesota, Minneapolis, MN, USA), S. Rennard (University of Nebraska Medical Centre, Nebraska Medical Centre, Omaha, NE, USA), S. Sethi (University of Buffalo, Buffalo, NY, USA), M. Saetta (Universite degli Studi di padova, Padova, Italy), D. Sin (University of British Colombia, Vancouver, BC, Canada). E. Stahl (IVAX Research Institute, Pulmonary Clinic of Research, Miami, FL, Sweden).

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