Acute COPD Exacerbations

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KEYWORDS

• COPD • Exacerbations • Respiratory viral infections • Bacterial infections

KEY POINTS

- Chronic obstructive pulmonary disease (COPD) exacerbations are important events in COPD and are major determinants of health status in COPD.
- The natural course of COPD is interrupted by episodes of respiratory symptom worsening, termed *exacerbations*.
- Optimal management of acute exacerbations not only increases the rate of exacerbation recovery but also affects exacerbation rates and prevents hospital admissions.
- There is a need for the development of novel antiinflammatory agents that are effective at COPD exacerbations.

IMPACT OF COPD EXACERBATIONS

The natural course of COPD is interrupted by episodes of respiratory symptom worsening, termed exacerbations.[1] COPD exacerbations are important events in COPD and are major determinants of health status in COPD. COPD exacerbations are also independent predictors of mortality in COPD and also drive disease progression, with approximately 25% of the lung function decline attributed to exacerbations.[2]

COPD is the second largest cause of emergency admissions in the United Kingdom, with 1 in 8 hospital emergency admissions resulting from COPD, accounting for more than £800 million ($1.3 billion) in direct health care costs.[3] COPD exacerbations are also associated with cardiovascular events, especially myocardial infarction,[4,5] and patients hospitalized with exacerbations of COPD are a particularly vulnerable group for ischemic events. Every new severe exacerbation requiring hospitalization increases the risk of a subsequent exacerbation, and every new severe exacerbation increases the risk of death, up to 5 times after the 10th compared with after a first COPD hospitalization.[6] COPD exacerbations are also more common and more severe in the winter months, when there are already pressures on numbers of admissions in hospitals.

Thus, the COPD strategy document developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) highlights the importance of avoiding future risk in COPD by preventing exacerbations.[7] In view of the wide impact of COPD exacerbations, any therapy that prevents exacerbations will also improve health status and prevent forced expiratory volume in the first second of expiration (FEV_1) decline.

DEFINITION OF EXACERBATIONS

The common symptoms of a COPD exacerbation are increase in dyspnea, sputum purulence, and cough, but other symptoms may include increased wheezing, chest discomfort, and symptoms of an upper airway cold. Physiologic changes at COPD exacerbations (eg, falls in peak flow or FEV_1) are

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generally small and not useful in predicting or monitoring exacerbations.[1]

An exacerbation of COPD is defined in the GOLD strategy in terms of health care utilization as "an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication." There is considerable evidence, however, that approximately half of all COPD exacerbations identified by symptom worsening are not reported to health care professionals for treatment.[8] Furthermore, these unreported exacerbations, although generally of lesser severity than reported or treated exacerbations, also have an impact on health status.[8]

For this reason, considerable interest exists in the potential of patient-reported outcomes in studies of exacerbation, and one of these is an instrument specifically designed for exacerbations, the Exacerbations of Chronic Pulmonary Disease Tool (EXACT). Although it may be useful in assessing the severity of exacerbations and the response to acute exacerbation therapy,[9] detection of an exacerbation probably still depends on patient report. Recently, a study in the London COPD cohort has shown that EXACT scores at the peak of the exacerbation were higher in treated than untreated events (Fig. 1), suggesting that the symptomatic burden of the exacerbation drives a patient's need for therapy. Further data from this study showed that the change in EXACT score to detect an exacerbation is smaller in severe COPD than in milder patients and highlights the difficulty in assigning scores to changes in exacerbations that occur across the disease spectrum. The scores on the COPD assessment test (CAT) also rise on exacerbation and reflect severity of the exacerbation, but the CAT has not been developed or validated for use at exacerbation.[10]

CAUSES AND PATHOGENESIS OF EXACERBATION

A majority of COPD exacerbations are triggered by respiratory viral infections, especially rhinovirus, the cause of the common cold. Using molecular techniques, respiratory viruses can be identified in up to 60% of exacerbations.[11] Exacerbations associated with viruses tend to have greater airway and systemic inflammatory effects than those without any evidence of viral infection and are more common in the winter months, with more chance of hospital admission. Airway pollutants may also be associated with precipitating exacerbations, especially by interacting with respiratory viruses, although significant effects of pollution are seen only in global areas of high urban pollution.[12]

Bacteria are present in the lower airway and are known to be present in the stable state and colonize the airway. Although airway bacterial load increases at exacerbation, it is now considered that bacteria are not often the primary infective cause of the exacerbation but are secondary invaders after a viral trigger. The effect of the infective triggers is to increase inflammation further in a chronically inflamed airway, leading to an

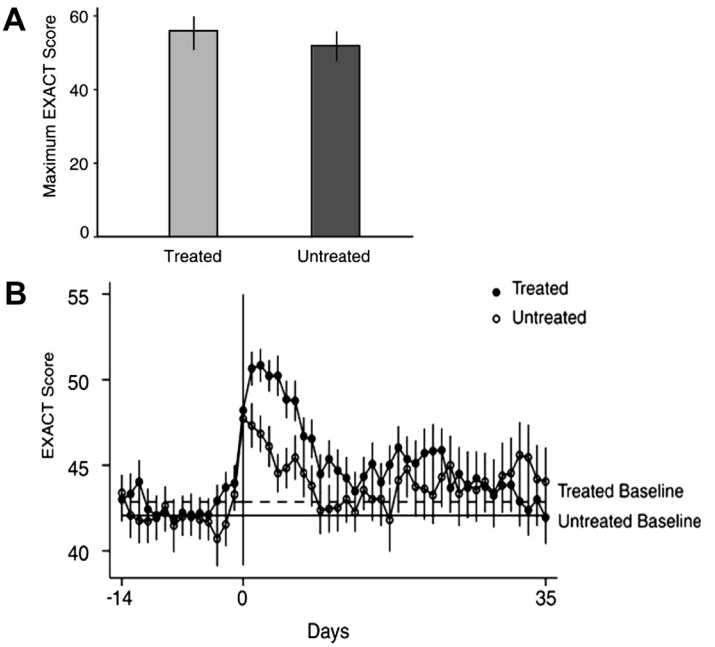

Fig. 1. (*A*) Maximum exacerbations of chronic pulmonary disease tool (EXACT) scores in chronic obstructive pulmonary disease patients treated and not treated with increased systemic therapy at exacerbation. Vertical lines represent standard errors. (*B*) Time course of EXACT scores during treated and untreated exacerbations. Vertical lines represent standard errors. (*From* Mackay AJ, Donaldson GC, Patel AR, et al. Detection and severity grading of COPD exacerbations using the exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT). Eur Respir J 2013 Aug 29. [Epub ahead of print]).

increase in bronchoconstriction, edema, and mucus production, resulting in an increase in dynamic hyperinflation and symptoms of increased dyspnea characteristic of an exacerbation Fig. 2.[1] Thus, any intervention that reduces inflammation in COPD reduces the number and severity of exacerbation, whereas bronchodilators have an impact on exacerbation by their effects on reducing dynamic hyperinflation.

THE FREQUENT EXACERBATOR PHENOTYPE

Exacerbations become more frequent and severe as COPD severity increases. One distinct group of patients seems susceptible to exacerbations, irrespective of disease severity. This COPD phenotype of frequent exacerbations is stable over time and the major determinant of developing frequent exacerbations is a history of prior exacerbations.[13] This phenomenon is seen across all GOLD stages, including patients with stage 2 disease, of whom 22% had frequent exacerbations in the first year of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study.[14]

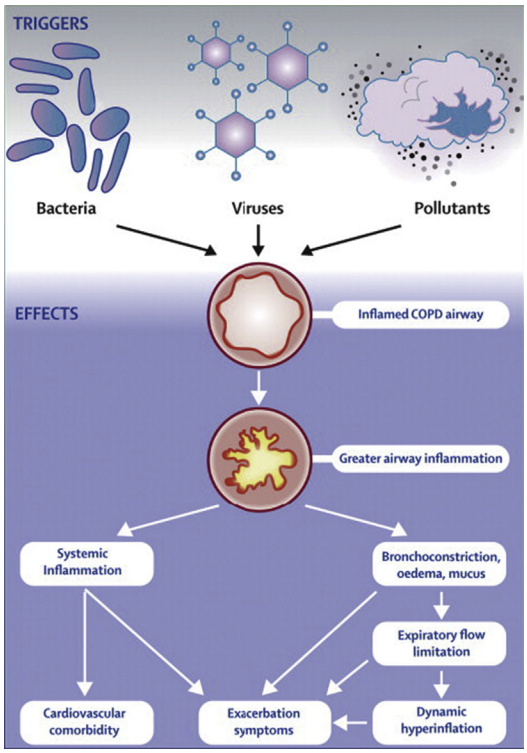

Fig. 2. Triggers of COPD exacerbations and associated pathophysiologic changes leading to increased exacerbation symptoms. (*From* Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. Lancet 2007;370:787; with permission.)

Patients with a history of frequent exacerbations are at particular future risk of further events and death Fig. 3.[15] Studies have shown that this group of patients has worse quality of life, increased risk of hospitalization, and a greater chance of recurrent exacerbations. Frequent exacerbators also exhibit faster decline in lung function and may have worse functional status. Thus, it is vital to identify patients at risk of frequent exacerbations and target this group for therapy (Table 1).

EXACERBATION PREVENTION

Vaccines

In retrospective cohort studies of community-dwelling elderly patients, influenza vaccination is associated with a 27% reduction in the risk of hospitalization for pneumonia or influenza and a 48% reduction in the risk of death.[16] Thus, influenza vaccines are recommended in a majority of patients with COPD. There is less evidence for the role of pneumococcal polysaccharide vaccine in preventing exacerbations and hospital admissions in COPD, but large studies are currently under way with vaccines with improved immunogenicity. Nevertheless, pneumococcal vaccines are commonly administered to COPD patients.

Inhaled Corticosteroids and Long-acting Bronchodilators

Both inhaled corticosteroids (ICSs) and long-acting β-agonists (LABAs) reduce exacerbation frequency. In the Towards a Revolution in COPD Health (TORCH) study, where patients were followed over 3 years, both inhaled fluticasone and salmeterol reduced exacerbation frequency when administered separately in comparison with placebo.[17] The combination of fluticasone and salmeterol reduced exacerbation frequency further, in addition to improving health status and lung function in comparison with placebo. The combination of ICSs and LABAs also resulted in fewer hospital admissions over the study period. Reduction in exacerbation frequency has been also found with other LABA/ICS combinations, such as formoterol and budesonide. Guidelines indicate a LABA/ICS combination for patients with an FEV_1 below 50% predicted (groups C and D) and where there is a history of 2 or more exacerbations.

Long-acting *muscarinic antagonists* (LAMAs) also reduce exacerbation frequency. In the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, patients were randomized to tiotropium or placebo for 4 years, with concomitant therapy allowed.[18] Although the primary endpoint of the trial (reduction in rate of decline in FEV_1) was negative, tiotropium was

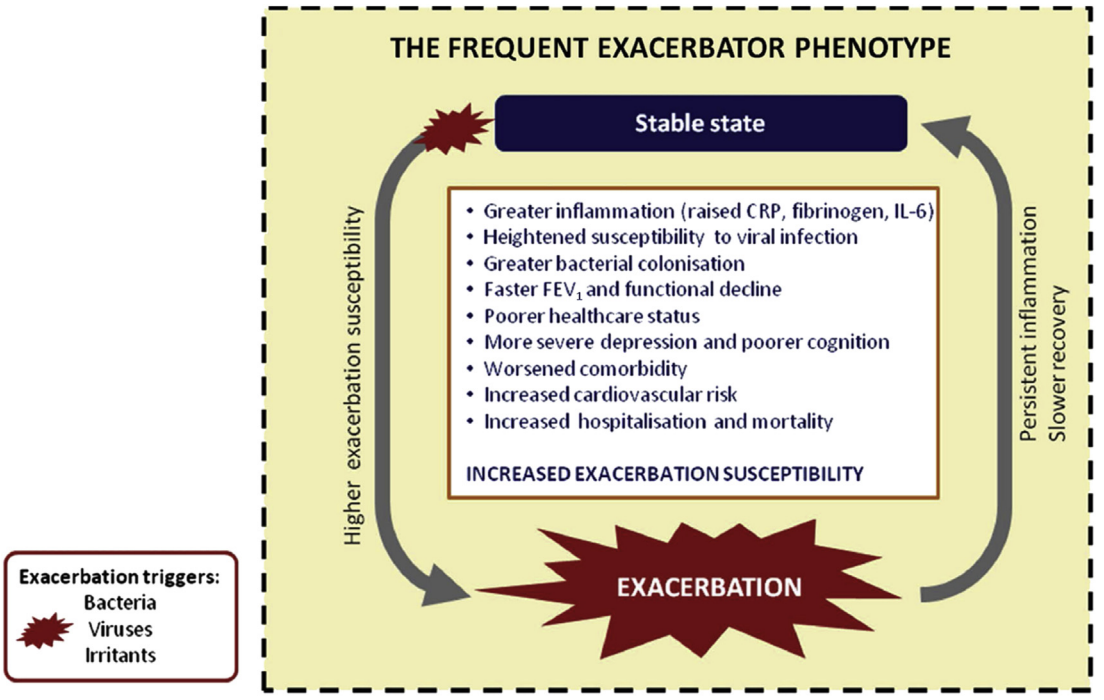

Fig. 3. Effect of COPD exacerbations in the group with frequent exacerbations. CRP, C-reactive protein; IL, interleukin. (*Adapted from* Wedzicha JA, Brill SE, Allinson JP, et al. Mechanisms and impact of the frequent exacerbator phenotype in chronic obstructive pulmonary disease. BMC Medicine 2013;11:181; with permission.)

associated with a reduction in exacerbation risk, related hospitalizations, and respiratory failure. The Prevention of Exacerbations with Tiotropium in COPD (POET-COPD) trial showed that, in patients with moderate to very severe COPD, tiotropium is more effective than salmeterol in preventing exacerbations.[19] In both the National Institute for Health and Clinical Excellence guidelines and GOLD strategy document, LAMAs can be used as an alternative to LABA/ICS to reduce exacerbations or in addition to the LABA/ICS combination as a triple therapy.[3]

Table 1
Strategies to prevent exacerbations

Pharmacologic Therapies for Exacerbation Prevention	Nonpharmacologic Therapies

• Antiviral therapy
• Vaccines
• Long-acting bronchodilators (LABAs/LAMAs)
• Combinations of LABA and ICS
• Dual bronchodilators (LABA + LAMA)
  ○ Phosphodiesterase-4 inhibitors
  ○ Mucolytics
  ○ Macrolide therapy
• Long-acting antibiotic therapy
	• Smoking cessation
	• Pollution control
	  ○ Pulmonary rehabilitation
	  ○ Home oxygen therapy
	  ○ Home ventilatory support

Dual Bronchodilators

Dual inhaled long-acting bronchodilators contained in one inhaler are being introduced and the first one, approved by European regulators, is QVA that is a combination of a LABA (indacaterolol) and a LAMA (glycopyrronium). QVA has been shown to produce increased bronchodilation compared with its components. In the SPARK study, where COPD patients were included with an FEV_1 of below 50% predicted and a history of COPD exacerbations, QVA reduced health care utilization exacerbation compared with glycopyrronium.[20] Diary cards were used in the SPARK study, however, to collect all exacerbation events and QVA was superior to both glycopyrronium and open-label tiotropium in the reduction of all exacerbations, that is, mild, moderate, and severe combined. Thus, future studies of dual bronchodilators must be designed to collect data on all exacerbation

events as in the SPARK study. Availability of the new dual bronchodilators will change treatment algorithms because these therapies reduce both symptoms and prevent exacerbations.

Phosphodiesterase Inhibitors

Phosphodiesterase-4 inhibitors have broad antiinflammatory activity, inhibiting the airway inflammation associated with COPD, especially by reducing airway neutrophils that are key cells in COPD. Evidence from a pooled analysis of 2 large placebo-controlled, double-blind multicenter trials revealed a significant reduction of 17% in the frequency of moderate (glucocorticoid-treated) or severe (hospitalization/death) exacerbations with Roflumilast.[21] Only patients with an FEV_1 less than 50% (GOLD stages 3 and 4), presence of bronchitic symptoms, and a history of exacerbations, however, were enrolled. There currently are no comparator studies with ICSs. Weight loss was also noted in the roflumilast group, with a mean reduction of 2.1 kg after 1 year, and was highest in obese patients. Therefore, after treatment with roflumilast, weight needs to be monitored carefully. Recent evidence also suggests that roflumilast may reduce the number of patients in the frequent exacerbator group after 12 months of therapy.[22]

Long-term Antibiotics

At present there is insufficient evidence to recommend routine prophylactic antibiotic therapy in the management of stable COPD, but some studies have shown promise. Erythromycin reduced the frequency of moderate and/or severe exacerbations (treated with systemic steroids, treated with antibiotics, or hospitalized) and shortened exacerbation length when taken twice daily over 12 months by patients with moderate to severe COPD.[23] The macrolide azithromycin has been used as prophylaxis in patients with cystic fibrosis and when added to usual treatment azithromycin has also been shown to decrease exacerbation frequency and improve quality of life in COPD patients.[24] The benefits were most significant, however, in treatment-naive patients with mild disease (GOLD stage 2), and significant rates of hearing decrement (as measured by audiometry) and antibiotic resistance were found. Also, a recent large epidemiologic study has suggested a small increase in cardiovascular deaths in patients receiving azithromycin, particularly in those with a high baseline risk of cardiovascular disease.

Furthermore, intermittent pulsed moxifloxacin when given to stable patients has been shown to significantly reduce exacerbation frequency in a per protocol population and in a post hoc subgroup of patients with bronchitis at baseline.[25] This reduction did not meet statistical significance, however, in the intention-to-treat analysis, and further studies are required on nonmacrolide antibiotics, including assessment of safety.

Thus, before prescription of long-term antibiotics in COPD, patients should be treated with an optimum combination inhaled therapy, show evidence of ongoing frequent exacerbations, and be carefully assessed for risk of potential cardiovascular and auditory side effects.

Pulmonary Rehabilitation, Home Oxygen, and Ventilatory Support

There is some evidence from clinical trials that pulmonary rehabilitation programs reduce hospital stay. There is some evidence from epidemiologic studies in COPD patients that long-term oxygen therapy and noninvasive ventilatory support may reduce hospital admissions and prevent exacerbations,[26] but controlled trials have not yet addressed these issues. Although it is difficult to perform controlled trials of long-term oxygen therapy, there are ongoing studies of the role of home noninvasive ventilation in COPD patients who are hypercapnic and at risk of further events.

MANAGEMENT OF THE ACUTE EXACERBATION

After the earlier studies of Anthonisen and colleagues,[27] the standard management of an acute exacerbation consists of oral antibiotics, such as amoxicillin or doxycycline, if there is evidence of increased sputum purulence or increased sputum volume. Oral corticosteroids in short courses are also added depending on individual exacerbation severity, and there is recent evidence suggesting that shorter courses (5 days) may be as beneficial as longer ones, such as more conventional 14-day courses.[28] There is evidence that the earlier therapy is started at onset of exacerbation, the shorter the recovery of the event and less chance of hospital admission.[8] COPD exacerbations may show early recurrence, especially in patients who are frequent exacerbators. There is evidence that exacerbation therapy may prolong the time to subsequent events.[29] Thus, prompt and appropriate management of an exacerbation event not only will have an effect on optimizing recovery but also delay the time to the next event.

The use of oral corticosteroids at exacerbations is currently essential but it is possible that steroids may exacerbate bacterial infection at exacerbation in patients whose airways are colonized with bacteria, such as *Haemophilus influenzae* and

Streptococcus pneumoniae. There is a high risk of recurrent exacerbations in COPD patients and this may be due to secondary infection.[30] Thus, there is a need for the development of novel anti-inflammatory agents that are effective at COPD exacerbations. Optimal management of acute exacerbations not only will increase the rate of exacerbation recovery but also affect exacerbation rates and prevent hospital admissions.

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