

# Advances in chronic obstructive pulmonary disease: management of exacerbations

## Abstract

Exacerbations of chronic obstructive pulmonary disease are important events to people living with this condition and a common cause of emergency hospital admission. In the absence of a confirmatory biomarker, an exacerbation remains a clinical diagnosis of exclusion and clinicians must be alert to alternative diagnoses. Most exacerbations are caused by airway infection, particularly with respiratory viruses. The mainstay of exacerbation treatment is an increase in the dose and/or frequency of short-acting beta-agonists, with short-course oral corticosteroids and/or antibiotics. Although there have been no new interventions to treat exacerbations in many years, there is still much variation in care and opportunity to improve outcomes. There has been a new focus on both the management of comorbidities and the optimisation of future care to reduce the risk of further events. This review summarises advances in managing exacerbations of chronic obstructive pulmonary disease, focusing on hospitalised patients.

**Key words:** Chronic obstructive pulmonary disease; COPD; Exacerbation

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Exacerbations of chronic obstructive pulmonary disease are a common acute presentation to hospital. This article provides an update on management, focusing on recent developments and areas of uncertainty, which will be relevant to those working in acute and general medicine, emergency departments and respiratory units.

## What is an exacerbation of chronic obstructive pulmonary disease?

Chronic obstructive pulmonary disease is defined as:

**‘A common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases’ (Global Initiative for Chronic Obstructive Lung Disease, 2022).**

Conceptually, chronic obstructive pulmonary disease is the end result of a genetically susceptible individual being exposed to sufficient environmental toxins. People living with chronic obstructive pulmonary disease experience day-to-day symptoms, principally breathlessness, and are also predisposed to acute deteriorations in their respiratory health called ‘exacerbations’. An exacerbation has been defined as ‘an acute worsening of respiratory symptoms that results in additional therapy’ (Global Initiative for Chronic Obstructive Lung Disease, 2022).

There are many reasons why a person living with chronic obstructive pulmonary disease may have worsening symptoms, and thus the differential diagnosis of an exacerbation includes alternative diagnoses such as pneumonia, pneumothorax, pulmonary embolism or heart failure. These alternative diagnoses require specific treatment and, while causing a deterioration in symptoms in someone living with chronic obstructive pulmonary disease, they are not an exacerbation of the chronic obstructive pulmonary disease itself (Hurst and Wedzicha, 2007a). Differential diagnoses should be considered and, where necessary, excluded with investigations (such as a chest X-ray). Data examining the prevalence of pulmonary emboli in unselected patients with chronic obstructive pulmonary disease

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presenting with change in symptoms suggested a prevalence of 6%, and used a strategy of clinical risk score and D-dimer levels to guide the need for computed tomography pulmonary angiography (Couturaud et al, 2021). However, it is not clear that a strategy of active searching for pulmonary emboli is associated with improved clinical outcomes (Jiménez et al, 2021).

Reflecting dissatisfaction with the existing definition of chronic obstructive pulmonary disease, and also with the classification of the severity of exacerbations of chronic obstructive pulmonary disease, Celli et al (2021) combined the change in symptoms with change in physiology and inflammation, and considered both the timing of the event and the likely cause. The new proposal is to define an exacerbation as:

**‘An event characterised by dyspnoea and/or cough and sputum that worsen over  $\leq 14$  d, which may be accompanied by tachypnoea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways.’ (Celli et al, 2021).**

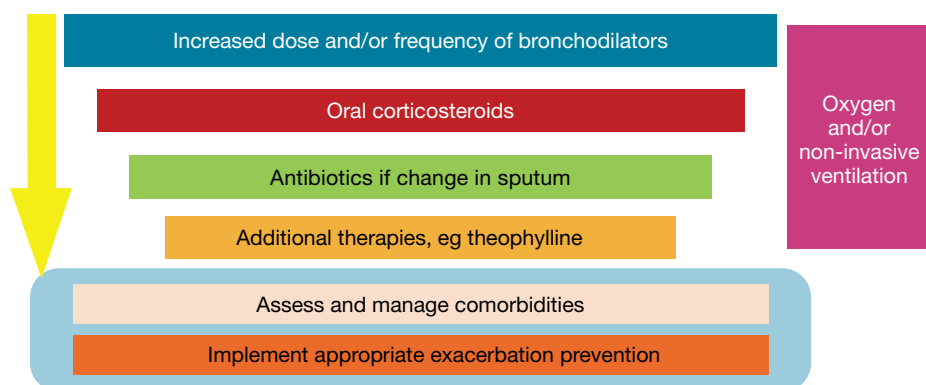
## The biology of an exacerbation of chronic obstructive pulmonary disease

The cardinal symptoms of an exacerbation of chronic obstructive pulmonary disease are an increase in breathlessness and change in sputum characteristics such as volume, viscosity and colour. It is believed that most exacerbations are driven by airway infection, with respiratory viruses (most commonly rhinovirus) and alterations in the airway bacterial microbiome – a ‘dysbiosis’ – responsible for these events. Understanding of the airway microbiome is evolving rapidly (Tiew et al, 2022) and the most important bacterial pathogen is non-typeable *Haemophilus influenzae*. The importance of respiratory viruses has been highlighted by the 50% reduction in hospitalised patients with exacerbations seen during the COVID-19 pandemic (Alqahtani et al, 2021): people shielding from coronavirus were also at lower risk of acquiring rhinovirus.

Airway infection drives airway inflammation and recent data suggest an important role for airway mucins (Singanayagam et al, 2022) in the immunopathology of an exacerbation of chronic obstructive pulmonary disease. Accumulation of mucus and airway wall inflammation with associated bronchoconstriction increases the rate and work of breathing and leads to dynamic hyperinflation – a key mechanism driving breathlessness during an exacerbation of chronic obstructive pulmonary disease (Hurst and Wedzicha, 2007b). There is generally a systemic inflammatory response during an exacerbation of chronic obstructive pulmonary disease (Celli et al, 2021). From this description of the biology of an exacerbation, the rationale for the bronchodilator, anti-inflammatory and anti-infective therapies described below becomes clear.

## The scale of the problem

Chronic obstructive pulmonary disease contributes significantly to global deaths and is the third-leading cause of mortality, accounting for 3.23 million deaths worldwide in 2019 (World Health Organization, 2020). Hospitalisation of patients with an exacerbation of chronic obstructive pulmonary disease is one of the most common reasons for emergency hospital admission in the UK, with emergency admissions in England rising steadily from 121 746 in 2014–15 to 133 103 in 2019–20, before a reduction during the COVID-19 pandemic (Office for Health Improvement and Disparities, 2022). This is much greater than hospitalisations for asthma. Hospital-treated events, representing the most severe presentations, are greatly outnumbered by community-treated exacerbations. Outcomes during and after a hospitalised exacerbation are poor. While length of stay had fallen from 8 days in 1997 to a median of 4 days by 2014, and inpatient mortality reduced from 7.8% in 2008 to 4.3% in 2014, this was at the expense of an increasing risk of re-admission (from 33% to 43% at 90 days) and no overall improvement in 3-month mortality (Hurst et al, 2020).



**Figure 1.** Stepwise treatment of an exacerbation of chronic obstructive pulmonary disease according to the severity of the presentation.

## Current management of an exacerbation of chronic obstructive pulmonary disease

There have been no new interventions to treat exacerbations in more than 30 years. The management of an exacerbation of chronic obstructive pulmonary disease is outlined in the international Global Initiative for Chronic Obstructive Lung Disease (2022) strategy document and, for the UK, in guidance by the National Institute of Health and Care Excellence (2019). The summary below and in [Figure 1](#) draws from both guidelines, and the reader is referred to the original documents for more detailed information and specific references.

The least severe presentations can be managed with an increase in the dose of short-acting bronchodilators alone. In practice, this generally means short-acting beta-agonists such as salbutamol, as there is no additional benefit of short-acting anti-muscarinic drugs (such as ipratropium) when patients are already using long-acting muscarinic antagonists. There is no intrinsic benefit of a nebuliser over an inhaler with spacer and, if using a nebuliser, the driving gas should be prescribed and would usually be air (to avoid the risk of inducing hypercapnoeic respiratory failure, described further below).

For exacerbations that are not responding to an increase in short-acting beta-agonists alone, guidelines recommend short-course oral corticosteroids, for example prednisone 30 mg once daily for 5 days (there is no benefit from longer courses). Oral corticosteroids increase the rate of recovery of lung function and measures of clinical success. There is ongoing work to evaluate whether the blood eosinophil count can be used to guide the need for systemic corticosteroid therapy.

The absence of specific interventions to treat most respiratory viruses is notable. When a bacterial cause is suspected, short course (5 days) oral antibiotics are indicated, based on local recommendations but typically an aminopenicillin, tetracycline or macrolide. There is generally no indication for parenteral antibiotics. Note that sputum culture is not usually recommended (the result will take too long), but antibiotic choice should be guided by previous results, particularly in patients who have previously grown *Pseudomonas* spp. The best indicator of a likely bacterial causes remains a change in sputum characteristics, but biomarkers such as C-reactive protein and procalcitonin have been used to guide the need for antibiotics, suggesting that, in selected patients in community settings, antibiotics can be withheld without additional clinical risk (Butler et al, 2019).

Oxygen should be used to treat respiratory failure, suspected using pulse oximetry and confirmed using blood–gas analysis. Oxygen should be prescribed and used carefully to avoid causing or decompensating hypercapnoeic respiratory failure in a proportion of patients. The treatment of choice for decompensated hypercapnoeic respiratory failure is generally non-invasive ventilation, unless there is severe acidosis or contraindications, and usually delivered as bi-level positive airway pressure. It is good practice to have a clearly documented escalation plan when initiating non-invasive ventilation, considering whether invasive ventilation would be offered. The latter decision should consider the severity both of the underlying chronic obstructive pulmonary disease and the exacerbation insult, comorbidities and baseline functional status, in addition to the wishes of the patient.

Respiratory physiotherapy techniques can be valuable in assisting with sputum clearance. Methylxanthine drugs are no longer recommended. The use of non-invasive ventilation has rendered use of the respiratory stimulant doxapram obsolete.

In patients who are not responding to treatment and for whom treatment escalation is not considered appropriate, there should be access to palliative care interventions to manage symptoms.

There remains unexplained variation in care for patients with exacerbations of chronic obstructive pulmonary disease, and national audit programmes such as the UK National Asthma and COPD Audit Programme can be used to benchmark care (Hurst et al, 2019). There is evidence that care is improved when patients with chronic obstructive pulmonary disease are reviewed by a chronic obstructive pulmonary disease specialist from the multidisciplinary team during their admission (Stone et al, 2022).

With high risk of re-admission, reduction of which is a major unmet need (Alqahtani et al, 2022), transition from hospital to community-based care is a period of high risk which may involve clinicians working across organisational structures. One approach to ensuring smooth transition of care and sharing of information is through the use of multidisciplinary meetings.

There are two further areas in the management of a patient with an exacerbation of chronic obstructive pulmonary disease that warrant specific consideration: assessment and management of comorbidities, and the importance of using an exacerbation event to optimise future care.

### Impact of comorbidities

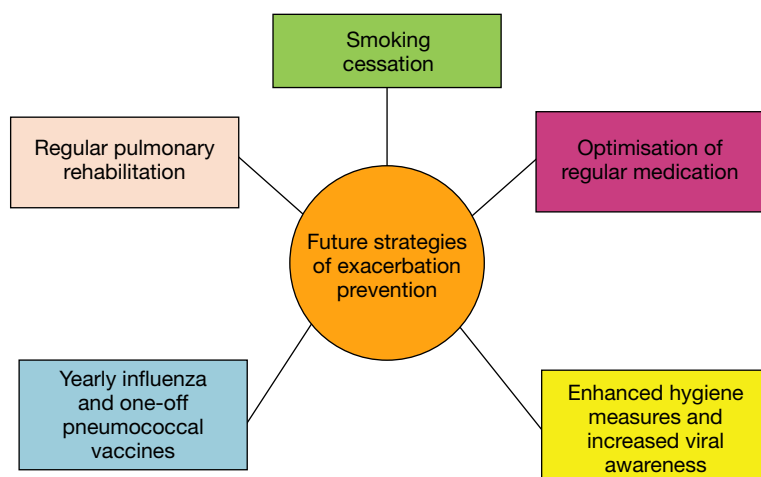
People living with chronic obstructive pulmonary disease often have this condition as just one component of multimorbidity. Therefore, assessment and management of comorbidities is important in the context of an exacerbation of chronic obstructive pulmonary disease with the aim of providing holistic care. Comorbidities are important drivers of the risk of re-admission (Alqahtani et al, 2020) and track with the underlying risk of exacerbation. Exacerbations are themselves associated with increased cardiovascular events (Rabe et al, 2018). Mental health comorbidity, principally anxiety and depression, is common in people with chronic obstructive pulmonary disease and is also associated with poor outcomes.

### Optimisation of future care

Patients report exacerbations, especially those for which they are hospitalised, as the most disruptive aspect of living with chronic obstructive pulmonary disease (Zhang et al, 2018). Thus, while managing an exacerbation, the opportunity should be taken to mitigate the risk of future events. Given that an exacerbation of chronic obstructive pulmonary disease is a clinical diagnosis of exclusion, if the diagnosis of chronic obstructive pulmonary disease is not secure, it is good practice to conduct spirometry before discharge to demonstrate (or exclude) airflow obstruction, accepting that the patient will not have fully recovered and will need spirometry again when well to understand the severity of their background disease.

In contrast to the absence of interventions to treat exacerbations, there have been many developments in the prevention of exacerbations of chronic obstructive pulmonary disease such that the challenge now is one of personalised medicine – deploying the optimal combination of interventions in the right patient at the right time (Figure 2). Non-pharmacological approaches include vaccinations against influenza and coronavirus (and pneumococcal vaccination is recommended too), pulmonary rehabilitation (including early ‘post-exacerbation’ pulmonary rehabilitation) and respiratory virus infection control measures (Hurst et al, 2022). Exposure reduction, such as support to quit smoking, is crucial.

The mainstay of drug therapy to reduce exacerbations is combination long-acting bronchodilators using long-acting beta agonists and long-acting muscarinic antagonists, which are now available in single-inhaler devices. As always with inhaled medicines, it is imperative that a patient can demonstrably use their device correctly. Patients must have sufficient inspiratory flow to activate dry powder devices. Pressurised metered dose inhalers should usually be used with a spacer. In contrast to asthma, where inhaled corticosteroids are the backbone of maintenance therapy, use of inhaled corticosteroids in people with chronic obstructive pulmonary disease should be restricted to those most likely to benefit,



**Figure 2.** Approaches to preventing exacerbations of chronic obstructive pulmonary disease.

in part because of an increased risk of pneumonia. Guidelines now indicate that the greatest benefit in reducing exacerbations by using inhaled corticosteroids in people with chronic obstructive pulmonary disease is seen in those with feature of asthma-overlap, or reversibility, and in those a higher blood eosinophil count (National Institute of Health and Care Excellence, 2019; Global Initiative for Chronic Obstructive Lung Disease, 2022). Note that the eosinophil count cannot be used in this way in people who are using oral corticosteroids. Inhalers are now available that combine inhaled corticosteroids with long-acting beta agonists and long-acting muscarinic antagonists in one device.

There are additional therapeutic options for people experiencing frequent exacerbations despite the interventions described above. These include prophylactic antibiotics in selected patients, usually using azithromycin, and long-term oxygen and home non-invasive ventilation for the management of chronic respiratory failure.

## Future developments

Given the high prevalence and burden of exacerbations of chronic obstructive pulmonary disease, there is a substantial unmet need to reduce the incidence of these events and treat them more effectively. Being able to objectively confirm an exacerbation of chronic obstructive pulmonary disease using biomarkers would be an important step, and thoracic imaging is one potential route to confirming an exacerbation (Rangelov et al, 2020). The near future is likely to see the development of novel antiviral and anti-inflammatory agents to treat and prevent exacerbations. In addition, and as alluded to above, there is increasing recognition that exacerbations are not all the same, and that they can be ‘phenotyped’ (Mathioudakis et al, 2020). Existing and ongoing research to more effectively target corticosteroids and antibiotics, using blood biomarkers such as eosinophils and C-reactive protein respectively, is an initial attempt to translate this theory into clinical practice. Underpinning the need to better prevent and treat exacerbations is the need to better identify and prevent chronic obstructive pulmonary disease itself. This is a global challenge, with the burden of disease falling disproportionately in low- and middle-income countries where most chronic obstructive pulmonary disease remains undiagnosed and untreated (Siddharthan et al, 2022). Further detail on new developments in chronic obstructive pulmonary disease has been summarised by Christenson et al (2022).

## Conclusions

For now, it is imperative that all clinicians managing patients with exacerbations of chronic obstructive pulmonary disease understand the principles of differential diagnosis, treatment and the need to optimise future care. By doing this now, we can start to address the burden of these exacerbations and improve the lives of people living with chronic obstructive pulmonary disease.

## Key points

- Consider and exclude differential diagnoses in a patient with chronic obstructive pulmonary disease presenting with a new deterioration in symptoms.
- The mainstay of exacerbation treatment is an increase in the dose and or frequency of short-acting beta-agonists, with short-course oral corticosteroids and/or antibiotics.
- Always use an exacerbation of chronic obstructive pulmonary disease as an opportunity to optimise care and reduce the risk of future events.

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### Conflicts of interest

JR Hurst has received personal payment and payment to his institution, for educational and advisory work, and support to attend meetings from pharmaceutical companies that make medicines to treat chronic obstructive pulmonary disease; V Jeyachandran has no conflicts of interest to declare.

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