Advances in chronic obstructive pulmonary disease (COPD): exacerbation management

Abstract

Exacerbations of chronic obstructive pulmonary disease (COPD) are important events to people living with COPD 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 is a new focus both on management of co-morbidities, and of optimising future care to reduce the risk of further events. This review summarises advances in managing COPD exacerbations, focusing on hospitalised exacerbations.

Key Points

1. Consider and exclude differential diagnoses in a patient with COPD presenting with a new deterioration in symptoms.

2. 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.

3. Always use a COPD exacerbation as an opportunity to optimise care to reduce the risk of future events.

Main Text

Exacerbations of chronic obstructive pulmonary disease (COPD) are a common acute presentation to hospital. In this review we provide an update on management, focusing on recent developments and areas of uncertainty which will be of relevance to those working in acute and general medicine, emergency departments and respiratory units.

What is an exacerbation of COPD?

COPD 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*" [1]. Conceptually, COPD is the end result of a genetically susceptible individual being exposed to sufficient environmental toxin. People living with COPD 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*" [1]. There are many reasons why a person living with COPD may have worsening symptoms, and thus the differential diagnosis of an exacerbation includes alternative diagnoses such as pneumonia, pneumothorax, pulmonary embolism and heart failure. There alternative diagnoses require specific treatment and whilst causing a deterioration in symptoms in someone living with COPD, they are not an exacerbation of the COPD itself [2]. Differential diagnoses should be considered and where necessary excluded with investigations (such as a chest radiograph). Recent data examining the prevalence of pulmonary emboli in unselected patients with COPD presenting with change in symptoms suggested a prevalence of 6%, and used a strategy of clinical risk score and d-dimer to guide the need for CT pulmonary angiography [3]. However, it is not clear that a strategy of active searching for PE is associated with improved clinical outcomes [4].

Reflecting dissatisfaction with the existing definition of COPD, and also with the classification of COPD exacerbation severity, there has been a recent approach to combine the change in symptoms with change in physiology and inflammation, and to consider both the timing of the event and the likely cause [5]. The new proposal is to define an exacerbation as "*an event characterized by dyspnoea and/or cough and sputum that worsen over ⩽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*." [5].

The Biology of a COPD Exacerbation

The cardinal symptoms of a COPD exacerbation 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. Our understanding of the airway microbiome is evolving rapidly [6] and the most important bacterial pathogen is non-typable *Haemophilus influenzae*. The importance of respiratory viruses has been highlighted by the 50% reduction in hospitalised exacerbations seen during the COVID-19 pandemic [7]: people shielding from coronavirus were also at less risk of acquiring rhinovirus. Airway infection drives airway inflammation and recent data suggest an important role for airway mucins [8] in the immunopathology of a COPD exacerbation. 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 at a COPD exacerbation [9]. There is generally a systemic inflammatory response during a COPD exacerbation [5]. From this description of the biology of a COPD exacerbation, the rationale for the bronchodilator, anti-inflammatory and anti-infective therapies described below becomes clear.

The Scale of the Problem

COPD contributes significantly to global deaths and is the third-leading cause of mortality accounting for 3.23 million deaths in 2019 [10]. Hospitalised exacerbations of COPD are one of the commonest 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 [11]. This is much greater than for asthma. Hospital treated events, representing the most severe presentations, are greatly out-numbered by community treated exacerbations. Outcomes during and after a hospitalised exacerbation are poor. Whilst length-of stay had fallen from 8 days in 1997 to a median of 4 days by 2014, and in patient mortality reduced from 7.8% in 2008 to 4.3% in 2014, this was at the expense of increasing risk of re-admission (from 33% to 43% at 90 days) and no overall improvement in three month mortality [12].

Current Management of a COPD Exacerbation

There have been no new interventions to treat a COPD exacerbation in more than thirty years. The management of a COPD exacerbation is outlined in the international GOLD strategy document [1] and, for the UK, in guidance by the National Institute of Health and Care Excellence [13]. 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 (SABA) 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 not responding to an increase in SABA alone, guidelines recommend short-course oral corticosteroids, for example prednisone at a dose of 30mg once daily for five 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 on-going 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*. The best indicator of a likely bacterial causes remains a change in sputum characteristics, but biomarkers such as C-reactive protein (CRP) 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 [14].

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 hypercapnoiec respiratory failure is generally non-invasive ventilation (NIV), unless there is severe acidosis or contra-indications, and usually delivered as bi-level positive airway pressure (BiPAP). It is good practice to have a clearly documented escalation plan when initiating NIV, considering whether invasive ventilation would be offered. The latter decision should consider the severity both of the underlying COPD and the exacerbation insult, co-morbidities 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 NIV has rendered use of the respiratory stimulant doxapram obsolete.

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

The remains unexplained variation in care for COPD exacerbations, and national audit programmes such as the UK National Asthma and COPD Audit Programme can be used to benchmark care [15]. There is evidence that care is improved when patients with COPD are reviewed by a COPD specialist from the multi-disciplinary team during their admission [16].

With high risk of re-admission, a major unmet need [17], transition from hospital to community-based care is a period of high-risk which may involved clinicians working across organisational structures. One approach to ensuring smooth transition of care and sharing of information is through the use of multi-disciplinary meetings.

There are two further areas in the management of a COPD exacerbation that warrant specific consideration: assessment and management of co-morbidities, and the importance of using an exacerbation event to optimise future care.

Impact of Co-Morbidities

People living with COPD often have COPD as just one component of multi-morbidity. Assessment and management of co-morbidities is therefore important in the context of a COPD exacerbation with the aim of providing holistic care. Co-morbidities are important drivers of re-admission risk [18] and track with underlying risk of exacerbation. Exacerbations are themselves associated with increased cardiovascular events [19]. Mental health co-morbidity, principally anxiety and depression, is common in COPD and also associated with poor outcomes.

Optimisation of Future Care

Patients report exacerbations, especially hospitalised exacerbations, as the most disruptive aspect of living with COPD [20]. Thus, whilst managing an exacerbation, the opportunity should be taken to mitigate the risk of future events. Given that COPD exacerbation is a clinical diagnosis of exclusion, if the diagnosis of COPD is not secure it is good practice to conduct spirometry prior to 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 COPD exacerbations 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), respiratory virus infection control measures [21]. Exposure reduction, such as support to quit smoking, is crucial.

The mainstay of drug therapy to reduce exacerbations are combination long-acting bronchodilators using long-acting beta agonists (LABA) and long-acting muscarinic antagonists (LAMA), 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 (ICS) are the backbone of maintenance therapy, use of ICS in COPD should be restricted to those most likely to benefit, in part because of an increased risk of pneumonia with ICS in COPD. Guidelines now indicate that the greatest benefit in reducing exacerbations with ICS in COPD is seen in those with feature of asthma-overlap, or reversibility, and in those a higher blood eosinophil count. Note that the

eosinophil count cannot be used in this way in people who are using inhaled corticosteroids. Inhalers are now available that combine ICS with LABA and LAMA in one device.

There are additional therapeutic option 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 NIV for the management of chronic respiratory failure.

Future Developments

Given the high prevalence and burden of COPD exacerbations, there is much unmet need in reducing the incidence of these events, and treating them more effectively. Being able to objectively confirm a COPD exacerbation using biomarkers would be an important step, and thoracic imaging is one potential route to achieve this [22]. The near future is likely to see the development of novel anti-viral 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' [23]. Existing and on-going research to more effectively target corticosteroids and antibiotics, using blood biomarkers such as eosinophils and CRP respectively, are an initial attempt to translate this theory into clinical practice. Underpinning the need to better prevent and treat exacerbations are the need to better identify and prevent COPD itself. This is a global challenge, with the burden of disease falling disproportionately in low- and middle-income countries where most COPD remains undiagnosed and untreated [24]. Further detail on new developments in COPD have been summarised in this 2022 review [25].

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

Figure Legends

FIGURE 1: Step wise treatment of a COPD exacerbation according to the severity of the presentation.

FIGURE 2: Approaches to preventing COPD exacerbations.

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