Exacerbations of chronic obstructive pulmonary disease: definition, aetiology and management

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Chronic obstructive pulmonary disease (COPD) is preventable and treatable. It is characterised by airflow limitation which is not fully reversible and is progressive. The pathophysiological basis is an abnormal inflammatory response by the lung to inhaled noxious particles or gases, particularly cigarette smoke.[1] In the developing world exposure to indoor air pollution, such as fumes from biomass fuels for cooking and heating, is a major cause of COPD.

What defines an exacerbation?

Exacerbations of COPD are heterogeneous, ranging from self-limiting worsening of symptoms in mild disease to overwhelming respiratory failure in advanced COPD. The World Health Organization and the US National Heart Lung and Blood Institute Global Initiative for Chronic Obstructive Lung Disease (GOLD) define an exacerbation as:

> *an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough and or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.*[1]

Airway and systemic inflammatory mediators increase at exacerbation, including tumour necrosis factor-α, interleukin-6 (IL-6), IL-8 (CXCL-8) and markers of oxidative stress (Fig 1).[2] C-reactive protein (CRP) is the most selective biomarker of an exacerbation to date though it has low specificity.[3] A higher serum CRP level 14 days after a given exacerbation is associated with a shorter time to the next exacerbation. Persistent systemic inflammation following an event is seen in patients with frequent exacerbations.[4]

Why do exacerbations matter?

COPD exacerbations are the most common cause of medical hospital admission in the UK, accounting for 15.9% of acute admissions. Most of the increasing healthcare spending on COPD is attributable to exacerbations which cost the NHS over £253 million per year.[5] Severe exacerbations and those associated with treatment failure or hospitalisation are the most expensive.

Exacerbations can be protracted and recurrent, profoundly affecting patients' functional status, morbidity and mortality. In 25% of community treated cases lung function/symptoms have not returned to baseline after five weeks and some do not recover at three months.[5] Of those with moderate to severe disease, 22% experience a recurrent event within 50 days of an index exacerbation.[4] A single exacerbation causes sustained impairment of health status, with delayed recovery if a second event occurs within six months. Thus, repeated exacerbations are a major determinant of poor health-related quality of life.[6]

Exacerbation frequency

The frequency and severity of exacerbations increase as the severity of under-

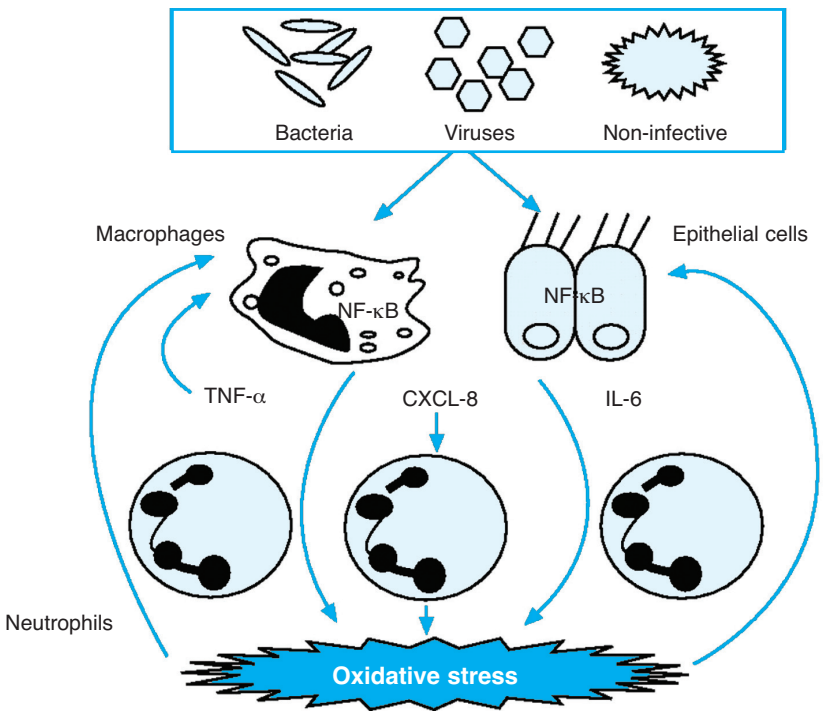

Fig 1. Inflammatory mechanisms at chronic obstructive pulmonary disease exacerbation. Bacteria, viruses and other factors such as ambient pollutants activate the transcription factor NF-κB in airway epithelial cells and macrophages. These cells release inflammatory cytokines, including the neutrophil chemoattractant interleukin (IL)-8 (CXCL-8), tumour necrosis factor-α (TNF-α) and IL-6, which further amplify airway inflammation. Increased numbers of neutrophils also generate oxidative stress. Reproduced, with permission, from Reference 2.

lying COPD progresses.[5] Frequent exacerbators are more breathless, more likely to become housebound and have reduced exercise capacity; they are also at increased risk of hospital admission and greater mortality. Importantly, in current smokers and those with frequent episodes, exacerbations contribute to lung function decline and accelerate disease progression over time.[7,8] In a number of multi-centre randomised controlled trials, treatment with inhaled corticosteroids, long-acting β_2-agonists and the long-acting anticholinergic tiotropium have all been shown to reduce exacerbation frequency in selected patients with COPD.[9,10]

Causes

Most COPD exacerbations are triggered by tracheobronchial infection by respiratory viruses or airway bacteria (Table 1). There is also an epidemiological association with environmental pollution. Complex interactions between these agents and host immune responses drive heightened inflammation, of which exacerbations are likely to be the clinical manifestation.

Viral infections

Molecular diagnostic techniques have indicated that up to 50% of COPD exacerbations are associated with viral pathogens, in particular human rhinovirus, the cause of most common colds. Viral exacerbations result in more symptoms, longer recovery, greater falls in lung function, higher airway inflammation and greater likelihood of hospitalisation.[11]

Bacterial infections

Until recently the role of bacterial infection in the pathophysiology of COPD exacerbations was unclear. There is now robust evidence that bacteria are an important cause of these events. Pathogenic bacteria are found in the distal airways at bronchoscopy in 30–50% of exacerbations. Molecular typing has shown that acquisition of new bacterial strains and strain-specific immune responses are associated with exacerbations.[12] Sputum purulence is a useful surrogate marker of bacterial infection.[13]

Table 2. Features of a severe chronic obstructive pulmonary disease exacerbation.

- Marked dyspnoea
- Tachypnoea
- Pursed lip breathing
- Use of accessory muscles at rest
- Acute confusion
- New-onset cyanosis
- New-onset peripheral oedema
- Marked reduction in activities of daily living

Up to 25% of patients may have co-infection by bacteria and viruses.[5] This can be associated with more severe exacerbations which, on a background of variable disease burden, could explain some of the heterogeneity of these episodes.

Management

Assessment of exacerbation severity is important and guides decisions on how and where to treat patients. Many COPD exacerbations can be managed in the community, and mechanisms for delivering this are a growing area of interest. During assessment, specific information is needed on the frequency of exacerbations, cough, sputum volume and colour, and functional limitation. Signs of a severe exacerbation and indications for hospital assessment are shown in Tables 2 and 3. This article focuses on acute hospital management strategies.

Controlled oxygen therapy

In severe COPD, hypercapnia and acidosis due to suppression of respiratory drive can result from uncontrolled oxygen therapy, which is often administered during the acute transfer of patients to hospital. Prior to the availability of arterial blood gases, controlled oxygen should be administered via a 28% Venturi mask at 4 l/min aiming for oxygen saturations

Table 1. Causes of chronic obstructive pulmonary disease exacerbations.

Cause	Type
Viruses	Rhinovirus Coronavirus Influenza Parainfluenza Adenovirus Respiratory syncytial virus
Bacteria	*Haemophilus influenzae* *Streptococcus pneumoniae* *Moraxella catarrhalis* *Pseudomonas aeruginosa* *Chlamydia pneumoniae*
Pollutants	Ozone Particulates Sulphur dioxide Nitrogen dioxide

Table 3. Indications for hospital assessment or admission at chronic obstructive pulmonary disease (COPD) exacerbation.

- Rapid onset/sudden change in symptom intensity
- Onset of new physical signs (eg cyanosis, peripheral oedema)
- Failure to respond to initial medical management
- Reduced conscious level
- Severe underlying COPD
- Long-term oxygen therapy
- Frequent exacerbations
- Significant comorbidity, especially cardiac disease and diabetes
- Abnormal chest X-ray findings
- pH <7.35 kPa
- PaO_2 <7 kPa
- Cardiac arrhythmias
- Diagnostic uncertainty
- Older age
- Insufficient home support

of 88–92% in patients at risk of hypercapnia. If the $PaCO_2$ is normal, the target range can be adjusted to 94–98% in patients without a history of previous respiratory acidosis or ventilation. Arterial blood gases should be measured 30 min after commencing oxygen, even if the initial $PaCO_2$ was in the normal range, and at regular intervals according to response to treatment.[14]

Bronchodilators

Short-acting β_2-agonist bronchodilators improve breathlessness in acute exacerbations. In severe episodes anticholinergic agents are also added, although evidence for the effectiveness of this combination is uncertain. Hand-held inhalers used with a spacer device are as effective as nebulisers at achieving bronchodilatation. In hypercapnic or acidotic patients nebulisers should be driven by air, not oxygen.[15]

Intravenous methylxanthines (theophyllines) are currently considered second-line therapy due to limited evidence of efficacy and the risk of drug interactions and adverse effects.

Antibiotics

Meta-analyses indicate that antibiotics given at exacerbation offer a small but significant benefit in terms of treatment failure and mortality.[16] Current evidence[1] suggests that antibiotics are indicated in patients presenting with:

- all three major symptoms of increased dyspnoea, increased sputum volume and sputum purulence (so-called Anthonisen Type 1 exacerbations[17])
- two of the three major symptoms, of which sputum purulence is one
- exacerbations requiring invasive or non-invasive (mechanical) ventilation (NIV).

Benefit from antibiotics is greatest in patients with more severe disease. Data on which antibiotic is most appropriate are conflicting, and empirical treatment requires knowledge of local bacterial prevalence and microbiological guidance. Patients with purulent sputum should have samples sent for culture, with antimicrobial therapy tailored to laboratory sensitivities.[15]

Key Points

Chronic obstructive pulmonary disease exacerbations are episodes of worsening symptoms, usually involving one or more of increased dyspnoea, cough and sputum production, and account for a steadily increasing burden of morbidity, mortality and health economic costs

Exacerbations are triggered by infection with respiratory viruses and bacteria, and levels of ambient air pollution

These events are associated with increased airway and systemic inflammation, of which C-reactive protein is a useful biomarker

Frequent exacerbations are associated with poorer health status and more rapid lung function decline. Strategies to reduce exacerbation frequency include appropriate pharmacotherapy with inhaled corticosteroids, long-acting β2-agonists, and tiotropium, as well as smoking cessation, vaccination and pulmonary rehabilitation

Management of exacerbations involves the administration of controlled oxygen therapy, bronchodilators, systemic corticosteroids and non-invasive or invasive ventilatory support. Antibiotics are indicated when sputum is purulent

KEY WORDS: antibiotics, chronic obstructive pulmonary disease exacerbation, C-reactive protein, exacerbation frequency, respiratory infection

Systemic corticosteroids

Treatment with oral steroids improves health outcomes during COPD exacerbations. They improve dyspnoea, FEV_1, oxygenation and health status, and accelerate recovery of symptoms and lung function.[18] Patients treated with steroids also exhibit fewer treatment failures and reduced length of hospital stay.[19] Both the optimal dose and length of treatment remain under debate. However, prednisolone 30 mg daily for 14 days is effective and safe, with longer courses conferring no greater benefit and increasing the potential side effects.[20]

Ventilatory support

Non-invasive. Mechanical ventilation essentially supports physiological processes until the underlying cause of respiratory failure responds to medical management. NIV is the treatment of choice for exacerbating patients with acute acidotic, hypercapnic respiratory failure and is cost-effective.[21] It corrects arterial blood gas abnormalities, improves breathlessness and reduces infective complications, hospital stay, intubation rates and mortality.[22] NIV can also be used to shorten the length of ventilation and to aid weaning.[15] Institution of NIV should always be accompanied by a decision about the next therapeutic step in the event of deterioration.

Invasive. Some patients require intubation and invasive ventilation because of failure to respond to NIV. In other cases it is because of adverse indicators such as impaired conscious level, life-threatening acidosis or multi-organ dysfunction. Factors to be taken into account in decisions to proceed to invasive ventilation include the presence of a potentially reversible precipitant, prior functional and health status, body mass index, long-term oxygen therapy and comorbidities. Contrary to some perceptions, duration of ventilation, intensive care unit stay and acute mortality in patients admitted to intensive care with decompensation due to COPD are lower than among patients with acute respiratory failure due to many other causes.[23]

Other measures

Other important hospital interventions include attention to nutrition, thromboprophylaxis and sputum clearance, where appropriate. On discharge, patients and carers need to be educated about the natural history of COPD and strategies for recognising and managing exacerbations. Opportunities for the prevention of future exacerbations should be reviewed by checking inhaler technique, offering smoking cessation advice, planning vaccination, organising pulmonary rehabilitation and addressing social isolation.

Comorbidities and exacerbations

COPD manifests itself in mid- to late life, and is associated with comorbid conditions such as ischaemic heart disease, pneumonia, pulmonary embolism and diabetes. Cytokines implicated in COPD pathogenesis also play a key role in insulin resistance, type 2 diabetes, thromboembolism and cardiovascular disease. There may be important associations between comorbidities, the severity of exacerbations and survival – an important focus of future research.

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