MedicineToday 2013; 14(4): 42-48

PEER REVIEWED FEATURE
POINTS: 2 CPD/2 PDP

COPD exacerbations
Improving outcomes

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Early diagnosis and treatment of exacerbations of chronic obstructive pulmonary disease (COPD) may improve outcomes and avoid the need for hospital admission.

Key points

- **An exacerbation of COPD is characterised by a change in the patient's baseline symptoms of dyspnoea, cough and/or sputum production that is acute in onset and may warrant a change in medication.**
- **An increased respiratory rate and/or airway inflammation may result in dynamic hyperinflation and gas trapping.**
- **Appropriate management of exacerbations includes the use of bronchodilators, systemic corticosteroids, antibiotics and, in severe exacerbations, noninvasive positive pressure ventilation.**
- **Patients who have had one exacerbation are highly likely to have a recurrence. An appropriate follow-up management plan and early initiation of therapy may improve outcomes.**

An exacerbation of COPD is an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough and/or sputum production that:

- is beyond normal day-to-day variations
- is acute in onset
- may warrant a change in regular medications in a patient with underlying COPD.[1]

As such, exacerbations vary markedly in their severity and clinical features. They are the main reason for treatment and hospitalisation of patients with COPD, and are closely associated with functional decline and mortality.

Exacerbations also become more frequent as COPD worsens. A recent major study found that the main predictor of exacerbations was previous exacerbations. There is, therefore, a proportion of patients who have the frequent exacerbator phenotype.[2]

The topic of COPD exacerbations has been comprehensively reviewed in the COPD-X guidelines, which are available from Lung Foundation Australia (http://lungfoundation.com.au) and directly from the COPD-X website (http://www.copdx.org.au).[3,4]

PATHOPHYSIOLOGY

By definition, COPD is characterised by airflow limitation that is not fully reversible. This results in a longer period required to exhale gas from the lung because of reduced diameter of the airways. Any factor that increases the respiratory rate results in a decreased time period available for expiration (as typically occurs in exercise). In patients with airway obstruction, an increased respiratory rate may not allow enough time to exhale fully before another breath needs to be taken, and this can cause air-trapping and dynamic hyperinflation. When patients stop exercising, the respiratory rate typically reduces and the increased period available for exhalation allows deflation of the lung.

In exacerbations there is often increased airway inflammation and obstruction and an

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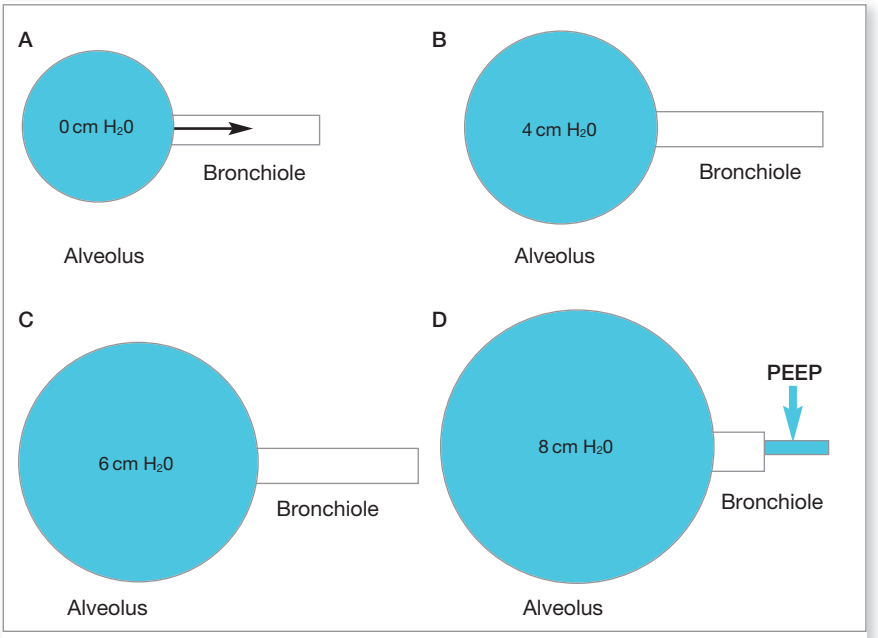
increased respiratory rate. As shown in work by O'Donnell and colleagues, and illustrated in Figure 1, this can result in a progressive increase in end-expiratory pressure and high intrathoracic pressures during exhalation (positive end expiratory pressure; PEEP).[5] This has two key functional effects:

- as alveolar pressures are positive at the end of expiration, a significant respiratory effort is required to expand the lungs enough to create a flow of air into the lungs
- the significant expiratory effort required to breathe out compresses the airways, further exacerbating the airflow obstruction.

In severe cases this results in progressive dynamic lung hyperinflation and patient exhaustion with consequent respiratory failure.



Figures 1a to d. Dynamic hyperinflation in COPD. a (top left). At the end of expiration (i.e. just before inspiration) pressure in the alveolus should normally be close to 0 cm H_2O. b to d (top right, bottom left and right). In an exacerbation of COPD there is air trapping, which leads to progressive dynamic hyperinflation of the alveolus and a positive pressure at the end of expiration. In addition, the strong effort to exhale causes positive end expiratory pressure (PEEP), which collapses the bronchiole, worsening obstruction (d; bottom right).

PRECIPITATING FACTORS

Exacerbations of COPD may be precipitated by various factors, particularly infections and airway pollutants. The most common cause is bacterial infection, responsible for about half of all exacerbations of COPD.[6] The main bacterial pathogens are *Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis*. Viral infections may also cause exacerbations.[7] A recently recognised entity is viral and bacterial co-infection, which may result in worse exacerbations.[8]

DIAGNOSIS AND ASSESSMENT OF SEVERITY

The diagnosis of an exacerbation of COPD may not be straightforward. Most cigarette smokers do not have severe COPD, and COPD may also occur in nonsmokers. In addition, there is considerable overlap in the symptoms with other conditions such as pneumonia and chronic congestive heart failure.

Lung function testing that has confirmed airflow obstruction previously with minimal or no reversibility is very helpful, as is a history of exacerbations. Increased sputum production and a change in sputum colour (e.g. white to green) are important symptoms (Figure 2) and correlate with airway inflammation.[9]

A key decision to make is whether patients can be managed at home or should be referred and admitted to hospital. Those who have documented previous severe exacerbations with respiratory failure or have clinical evidence of significant respiratory distress should generally be referred to hospital. The box on page 44 lists factors that may indicate the need for admission of patients attending the emergency department.

Assessment of all patients with COPD exacerbations who attend an emergency department should include measurement of urea, electrolytes and arterial blood gases and a chest x-ray. Patients who have acute respiratory failure with a low pH and elevated pCO_2 are likely to be candidates for assisted ventilation.

Shorr and colleagues have described the BAP-65 score, which uses age, blood urea, acute confusion/delirium and pulse rate (greater than 100 beats/min) to stratify the risk of exacerbations of COPD;[10] however, this is not widely used.

Figure 2. A key symptom of an exacerbation is a change in sputum colour (typically from white to yellow/green).

FACTORS INDICATING THE NEED FOR HOSPITAL ADMISSION

- Previous severe exacerbation
- Failure to improve on outpatient therapy
- Significant respiratory distress
- Major comorbidities
- Altered mental status
- Tachycardia
- Respiratory failure
- Abnormalities in blood gases, blood urea
- Lack of social support

KEY STEPS IN ACUTE TREATMENT

Regular bronchodilators
Inhaled short-acting beta-agonist and/or anticholinergic agents via spacer/nebuliser 1–6 hourly

Systemic glucocorticoids
Oral prednisolone 30–50 mg daily (not tapered), typically for 1 week

Antibiotics
Amoxycillin/doxycycline for 7–10 days. Parenteral or broader spectrum antibiotic if required

Oxygen
Low-dose to maintain saturation at 88–92%

Noninvasive positive pressure ventilation
For those with severe exacerbations and ventilatory failure

ACUTE MANAGEMENT

The acute management of exacerbations of COPD usually involves the use of a combination of bronchodilators, antibiotics and glucocorticoids and, for those with acute respiratory failure, the use of oxygen and/or noninvasive ventilation (see the box on this page).

Inhaled bronchodilators

Short-acting inhaled beta-agonists (e.g. salbutamol and terbutaline) and anticholinergic agents (e.g. ipratropium) can be given effectively by metered-dose inhaler with a spacer or by a jet nebuliser. The frequency of administration is governed by clinical response but typically ranges from hourly to six hourly. Dry powder inhalation of the long-acting beta-agonist eformoterol may also be helpful, given typically from hourly to six hourly, but patients may have difficulty inhaling dry powders during exacerbations.

The bronchodilator effect of these medications is usually small (in contrast to their effect in asthma) but may produce significant clinical improvement, particularly in terms of dyspnoea.

Systemic glucocorticoids

Systemic glucocorticoids are typically given orally at a daily dose of 30 to 50 mg, for a maximum of two weeks. There is no clear benefit in giving a tapering dose, nor in giving this medication parenterally.[11] Systemic glucocorticoids have been shown to reduce 30-day treatment failure, hospital stay and severity of symptoms.[12] Long-term use is associated with side effects, particularly osteoporosis, and should be avoided.

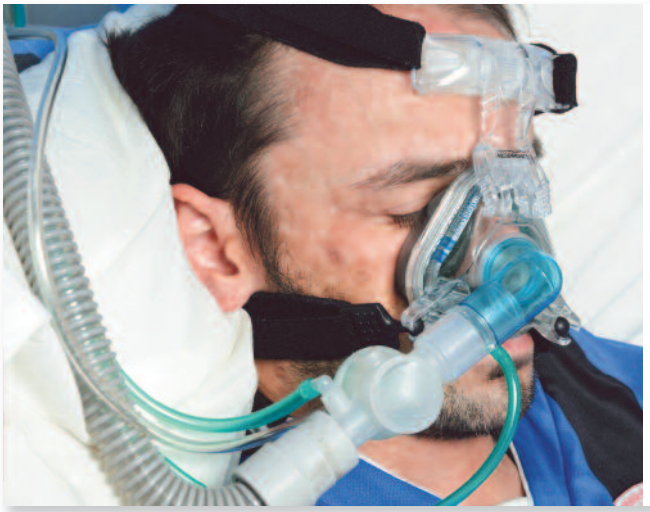
Antibiotics

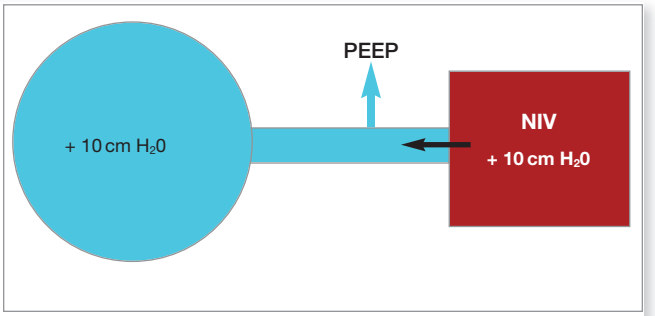
Bacterial infections have a role in about half of all COPD exacerbations. Patients with exacerbations with at least two out of three features of increased dyspnoea, increased sputum and change in sputum characteristics are the most likely to benefit from antibiotics.[13] Antibiotics have been shown clearly to improve outcomes in patients hospitalised for acute exacerbations.[14,15]

Randomised controlled trials have found that short duration of antibiotics (up to five days) were as effective as longer courses. There may also be a lower incidence of side effects with shorter dose therapy.[16]

Therapeutic Guidelines: Respiratory recommends initial oral use of antibiotics such as amoxycillin or doxycycline.[17] Patients should respond within three to five days. If there is failure to respond then broader spectrum antibiotics such as amoxycillin–clavulanic acid can be used or if specific resistant pathogens such as *Pseudomonas* spp. are present then appropriate therapy directed at the pathogen should be given. Generally most inpatients are initially treated with parenteral antibiotics and within 72 hours switched to oral therapy. Antibiotics are most commonly given for a course of seven to 10 days.

Combined therapy with systemic





Figures 3a and b. a (left). The use of noninvasive positive pressure ventilation (NIV) for COPD exacerbations. b (above). NIV reverses the effect of PEEP, holds the airways open in expiration and facilitates inspiration by reducing the gradient between mouth and alveolar pressure.

glucocorticoids and antibiotics produces a significantly higher rate of clinical cure than glucocorticoids alone.[18]

Some patients have a persistent fever, which may indicate of a resistant pathogen such as *Pseudomonas aeruginosa* or a complication, particularly an infected parapneumonic effusion or empyema. Appropriate therapy should be given.

Clearance of secretions

Patients with significant sputum production may benefit from sputum clearance techniques. Mechanical vibration or positive expiratory pressure therapy may be helpful for hospitalised patients.

Oxygen therapy

Oxygen therapy is given to maintain a PaO_2 above 55 to 60 mmHg (corresponding to an oxygen saturation of greater than 88 to 92%). Oxygen therapy does not reverse the primary pathophysiological process of dynamic hyperinflation in COPD. It is also very important not to give patients too much oxygen and risk suppressing hypoxic drive, further suppressing ventilation (with the potential for respiratory arrest). Nasal cannula-administrated oxygen, given at a flow rate of 0.5 to 2 L/min to maintain an oxygen saturation of 88 to 92%, is generally sufficient.

Noninvasive ventilation

The advent of noninvasive ventilation (NIV) has dramatically improved the treatment of severe exacerbations of COPD with acute ventilatory failure.[19] NIV is typically used when patients have an acute respiratory acidosis (pH less than 7.35 and elevated pCO_2 levels on arterial blood gas measurements) with tachypnoea.

A full-face mask is put on the patient and NIV is given using either continuous positive airway pressure (CPAP) or bi-level airway pressure (BiPAP). A significant clinical improvement usually occurs within an hour. NIV has an immediate effect on reversing the underlying pathophysiology of exacerbations of COPD, the with improvement in both the expiratory and inspiratory phases of ventilation.

The effect of NIV is shown in Figure 3b. Not all patients can tolerate NIV; some may panic, have increased respiratory effort or vomit into the mask. As such, the implementation of this treatment requires expert and, ideally, continuous nursing care.

Invasive ventilation

Invasive ventilation may be considered for patients who fail to improve with NIV, have respiratory arrest or are unable to protect their airways. Mechanical ventilation for COPD is associated with a high inpatient mortality of 39%.[20] Follow-up studies of patients treated with invasive ventilation have shown a mild decrease in quality of life, but most patients would elect to receive this treatment again.[20] If possible, the need for ventilation should be discussed with the patient and/or family before an acute severe deterioration occurs.

FOLLOW-UP MANAGEMENT

A key component of the management of exacerbations of COPD is organising appropriate follow up.

Hospital discharge planning

Features that indicate a patient who has been hospitalised for an exacerbation can be discharged include:

- no longer requiring parenteral therapy
- not requiring bronchodilators more often than four hourly
- being independent with activities of daily living and ambulation
- having an appropriate level of social support.

Patients should be given general information about COPD, use of medications and the importance of maintaining and increasing activity levels, as well as a plan for the management of future exacerbations. The GP should be informed of the

IMPORTANT STEPS IN FOLLOW-UP MANAGEMENT

- Appropriate hospital discharge planning
- Oxygen therapy for those who meet criteria
- Referral to pulmonary rehabilitation
- Lung function testing (to confirm COPD)
- Assessment of appropriate use of medications (including education about inhaler technique) and compliance
- Assurance of smoking cessation
- Regular influenza and pneumococcal vaccination
- Development of a management plan for future exacerbations
- Early institution of acute treatment
- Baseline assessment of risk of osteoporosis and nutritional status
- Specific treatment, if required, for anxiety, a prominent feature of severe COPD
- Management, as appropriate, of other important comorbidities, including depression, right-heart failure and obstructive sleep apnoea

admission and ideally patients should have at least one review in a hospital-based clinic. For patients who continue smoking, appropriate management to optimise smoking cessation should be undertaken.

Use of oxygen

A significant proportion of patients who come into hospital have hypoxia that persists throughout the admission, and they are discharged home on oxygen therapy. Domiciliary oxygen can be given as continuous oxygen for those with low oxygen saturation levels at rest (i.e. PaO_2 less than 56 mmHg) or ambulatory oxygen for those who significantly desaturate on walking (although the use of ambulatory oxygen is controversial). To qualify for ongoing oxygen therapy, patients need to be reassessed one to two months after discharge (at this time many do not require ongoing oxygen owing to clinical recovery).

Continuous oxygen therapy is the only treatment that has been shown to prolong life in patients with COPD. It needs to be taken for more than 16 hours a day so patients need to use this when they are sleeping.[21,22] It is imperative that patients do not smoke while on oxygen.

Lung function testing

For all patients who have not had lung function testing, this should be performed in a formal laboratory to confirm the presence of COPD and categorise severity. Lung volumes, bronchodilator effect and lung diffusing capacity should be measured.

Referral for pulmonary rehabilitation

Pulmonary rehabilitation has been shown to be associated with a variety of benefits including improved exercise capacity and reduced admissions and mortality.[23] All patients who have been hospitalised for an exacerbation should be referred to a pulmonary rehabilitation service. This will generally involve attendance for half a day a week for several months with a multidisciplinary team to improve patient understanding, self-management and fitness.

General management

Several issues need to be followed up after an exacerbation and are summarised in the box on this page.

Management of future exacerbations

Patients who have had previous COPD exacerbations are highly likely to have further exacerbations. Early diagnosis and treatment of exacerbations may improve outcome and avoid the need for hospital admission. Patients should be educated to recognise the symptoms and signs of an exacerbation and should have a plan to institute appropriate management. This would typically involve seeking medical attention within 24 hours and may also involve self-initiation of medications (e.g. glucocorticoids and antibiotics).

SUMMARY

Exacerbations of COPD are extremely common, but in the absence of previous lung function testing the diagnosis may not be straightforward. Increased airway inflammation and/or increased respiratory rate results in air trapping and dynamic lung hyperinflation and may lead to respiratory failure. Early initiation of appropriate therapy and follow-up management is vital to patient outcome. MT

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COMPETING INTERESTS. None.

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