

## Key points

- ▶ Diagnosis of exacerbations of COPD is based largely on key symptoms (increasing sputum purulence and volume, and breathlessness) and the severity depends on the level of healthcare resource utilisation.
- ▶ Aetiology is varied, although infection is the major causative factor. Neutrophilic inflammation is a major pathological event, but eosinophils are also implicated, suggesting an "asthmatic" aetiology.
- ▶ Airflow limitation and dynamic hyperinflation are the physiological changes, which can result in deterioration in gas exchange and respiratory failure.
- ▶ Antibiotics are reserved for purulent exacerbations, with the exception of the presence of pneumonia and prophylaxis during ventilation.
- ▶ Steroids are recommended for all hospitalised patients and outpatients with a significant increase in breathlessness.
- ▶ Controlled oxygen therapy is central to management and is guided by arterial blood gas measurements.
- ▶ Noninvasive ventilation is the preferred management for patients with acidotic respiratory failure when the arterial pH is 7.25–7.35 despite the standard initial therapy.
- ▶ Prevention of exacerbations is aided by influenza vaccination and the institution of regular inhaled long-acting bronchodilators and inhaled corticosteroids.

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# Causes and management of exacerbations of COPD

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## Educational aims

- › To understand the definition and burden of exacerbations.
- › To understand the aetiology and varied pathophysiology.
- › To understand the treatment and prevention of exacerbations.

## Summary

Exacerbation of COPD is a common problem, which causes a considerable burden to the patient and the healthcare system. This article aims to give a structured overview of the different aspects of COPD exacerbations, including their classification, aetiology, pathophysiology, differential diagnosis, management and prevention.

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Exacerbation of chronic obstructive pulmonary disease (COPD) is a common clinical entity. However, constructing a definition is complex because of the heterogeneity of the condition. It has been defined in a consensus statement [1] as "a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD".

In reality, this is a patient-centred definition based on a change in baseline symptoms beyond normal day-to-day variability. Up to 10% of acute hospital admissions in the UK are the result of exacerbations of COPD [2], and the mortality rate of these cases is around 11% during in-hospital stay, 43–46% within 1 year [3]. Mortality is much higher for patients needing treatment in the intensive care unit [4]. In a recent statement published

by the British Thoracic Society [5], it was reported that 20% of annual deaths are due to respiratory diseases and almost 25% of respiratory deaths are due to COPD. Furthermore, the frequency of exacerbations is now known to have a major influence on the health status of patients [6] and probably the decline in lung function [7].

## Classification

In 1987, ANTHONISEN *et al.* [8] classified three types of exacerbations based on symptoms. These can be seen in the box on the following page.

This symptom-based definition is complemented by a severity classification based on healthcare utilisation. While SEEMUNGAL *et al.* [6] noted that up to 50% of symptom-based exacerbations were unreported and hence untreated, the rest were classified as follows:

**Exacerbation classification by symptoms**

- Type I:** characterised by new or increased sputum purulence and volume, together with increased breathlessness
- Type II:** any two of the three type I symptoms
- Type III:** any one of the type I symptoms with at least one additional feature (sore throat or nasal discharge within the previous 5 days; unexplained fever; increased wheeze; increased cough; or a 20% increase in respiratory or heart rate compared with baseline)

**Mild:** those requiring an increase in usual therapy.

**Moderate:** those requiring the introduction of antibiotics and/or steroids.

**Severe:** those needing hospital admissions.

Whereas this classification probably reflects the perceived risk to the patient or necessity for increasingly complex interventions, it probably does not reflect the pathophysiology of the problem. For instance, many symptomatic changes recorded on a daily diary card do not necessarily lead to a need to report the episodes or for change in medication. This suggests, from a patient's viewpoint, that the episode is felt to be mild. Conversely, episodes that cause a major change in symptoms or airflow obstruction in mildly obstructed patients (Global Initiative for COPD (GOLD) stage II) may be insufficient to require hospital admission (*i.e.* mild or moderate exacerbation), whereas an episode inducing small changes in symptoms in patients with severe airflow obstruction (GOLD stage IV) may tip the patient into a critical state requiring

hospitalisation (severe episode). Nevertheless, requirement for healthcare resources remains the gold standard in classification of the episodes.

## Aetiology

The aetiology of exacerbations of COPD is complex (table 1, figure 1). Bacteria and viruses have been implicated, although fluctuations in airflow obstruction in the absence of these organisms could also precipitate symptoms. In addition, although many studies implicate neutrophils as the predominant cells involved in exacerbations, some studies have found a distinct increase in eosinophils, suggesting an "asthmatic" aetiology.

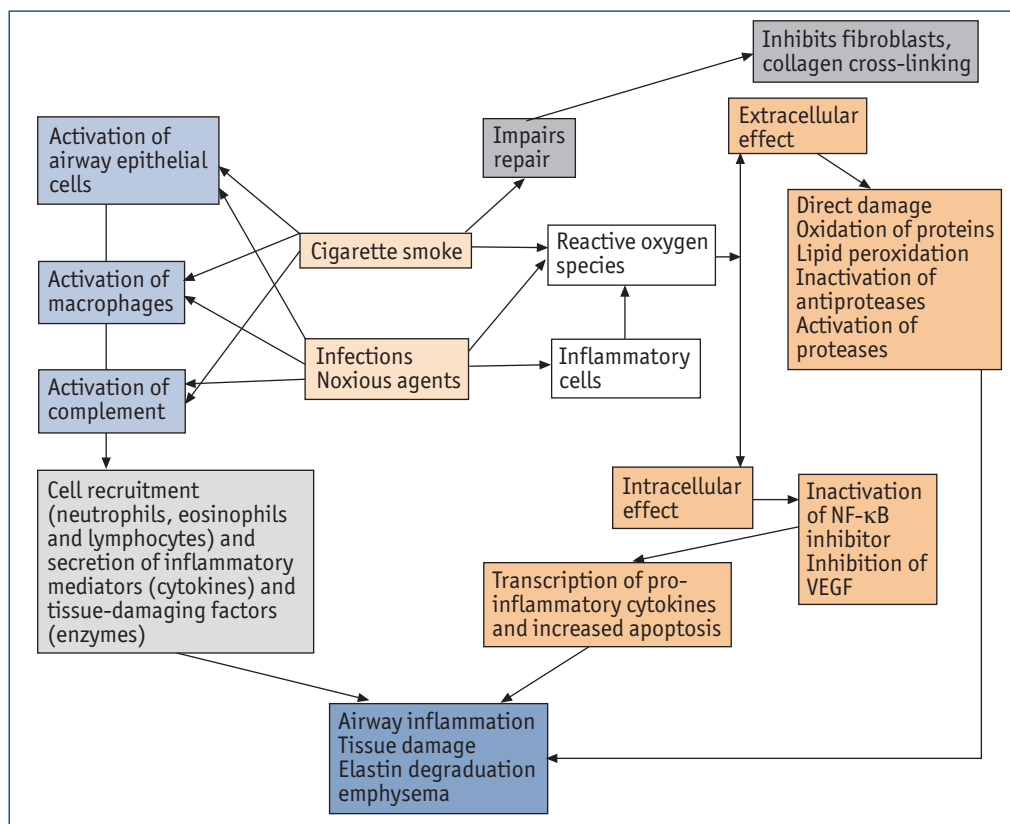
## Bacteria

Although there is a general belief that bacteria play a role in exacerbations of COPD, the relationship is somewhat complex. Bacteria are present in the cultured secretions of 30–40% of patients with chronic sputum expectoration and COPD even in the stable state. During exacerbations, the isolation rate increases to 50% [9]. This increase is not related to oral contaminations, as direct sampling has shown similar changes in bacterial isolation. These data indicate that antibiotics should have an effect on the management of COPD exacerbations in at least some patients. Indeed, meta-analysis does indicate a positive benefit [10]. Furthermore, the only well-designed controlled trial does suggest that antibiotics have a positive benefit, but only in those subjects with type I exacerbations featuring increased breathlessness, increased sputum volume and notably increased sputum purulence [8].

This issue was clarified by a series of studies published in 2001. Bacterial load in airway secretions does not influence inflammation until the load rises above  $10^6$  colony forming units per mL, at which stage a variety of inflammatory cytokines are released in increasing amounts and neutrophilic influx occurs. This neutrophil influx is associated with a very clear change in sputum

**Table 1** Causes of COPD exacerbations

Infections	Bacterial	<i>Haemophilus influenzae</i>
		<i>Streptococcus pneumoniae</i>
		<i>Moraxella catarrhalis</i>
		<i>Pseudomonas aeruginosa</i>
		<i>Staphylococcus aureus</i>
	Viral	Enterobacteriae
		<i>Rhinovirus</i>
		Influenza
		Parainfluenza
		Adenoviruses
Atypical	Respiratory syncytial virus	
	<i>Mycoplasma pneumoniae</i>	
	<i>Chlamydia pneumoniae</i>	
Air pollution	Nitrogen dioxide	
	Sulphur dioxide	
	Particulate matter (PM <sub>10</sub> )	
	Ozone	
Predisposing host factors	Severe disease	
	Current smoking	
	Bacterial colonisation in the stable state	

**Mediators of inflammation**

Interleukin-6  
 Interleukin-8  
 Leukotriene B<sub>4</sub>  
 Tumour necrosis factor-α  
 Matrix metalloproteinase-9  
 Cathepsin K,L,S  
 Neutrophil elastase  
 Matrix metalloproteinase-12  
 Cathepsin G

**Figure 1**

The inflammatory mechanisms involved in exacerbations of COPD in a simplified form. Cigarette smoke, infections and other noxious agents (light orange) activate epithelial cells, macrophages and complement pathway (light blue), which results in the recruitment of a variety of inflammatory cells (light grey). These cells secrete a number of inflammatory mediators (cytokines) and tissue-damaging enzymes. In addition, the same factors trigger the generation of reactive oxygen species directly or indirectly (white; by way of activating the inflammatory cells), which in turn cause oxidant-related tissue damage by intra- and extracellular mechanisms (dark orange). All these ultimately result in significant airway inflammation, tissue damage and elastin degradation leading to emphysema (dark blue). Smoking also inhibits tissue repair (dark grey) by inhibiting fibroblasts and collagen cross-linking, which will increase the effects of damage. NF-κB: nuclear factor-κB; VEGF: vascular endothelial growth factor.

purulence [11]. Indeed, if exacerbations are classified by sputum colour alone, studies have shown that the colour relates to an increased isolation rate of bacteria and an increase in bacterial load [12]. This concept was used to determine antibiotic prescription, which was limited to those with overtly purulent sputum. Following treatment and resolution of the symptoms, the bacterial load was decreased and in many cases the secretions were sterilised. This was associated with a decrease in inflammation. Conversely, in those with mucoid sputum who did not receive antibiotic therapy, there was no increased isolation rate of bacteria, no increase in bacterial numbers or inflammation and, following resolution, these factors remained stable [12].

The reason for the increase in bacterial numbers is not certain, although studies have suggested that a change in surface epitopes occurs at exacerbations when bacterial numbers rise [13]. It

was hypothesised that this enables the bacteria temporarily to evade immune surveillance.

**Viruses**

The role of viruses is also contentious, although clinically many exacerbations are preceded by upper respiratory tract symptoms suggestive of a viral infection. A variety of viruses have been isolated, but many are also present in the stable state. It seems likely that respiratory syncytial viruses are the most relevant. Recently, a comprehensive study suggested that a significant viral isolation occurs, especially in hospitalised patients [14]. In a proportion of cases, this was associated with bacterial isolation from the airways. Whether virus infections alone are the cause of the episode or whether they precipitate a secondary bacterial cause remains unknown. However, viruses alone may be implicated by the inflammatory profile that they potentially

generate [15, 16]. Nevertheless, the true role of viruses may only be identified when specific antiviral therapies become available.

### Atypical organisms

The detection of atypical organisms is difficult and is mostly implied by changes in serology (the immune response) following resolution of an episode. However, immunity to the organisms is often present as a legacy of acquired infections at a younger age. Evidence suggests that up to 14% of episodes are associated with mycoplasmal infection and 24–34% suggestive of a chlamydial infection [17, 18]. Again, evidence that these organisms play a central role remains contentious and may only be resolved with the development of specific therapies.

### Non-pathogen-associated exacerbations

As indicated above, there is evidence that COPD exacerbations are associated with an increase in eosinophil numbers in the airways and tissues. Although this may represent a subset of episodes, it may also explain the benefits of steroid therapy in the treatment and prevention of exacerbations, as these are largely considered "anti-asthma" therapies and eosinophils are the key cells implicated in asthma.

Irritable airways, particularly on the background of severely impaired lung function, are likely to be associated with fluctuating bronchospasm, reflected in laboured breathing and hence breathlessness. Short-term fluctuations in ambient pollution are known to relate to increased hospital admission rates [19] and this is likely to reflect the induction of increased airflow obstruction.

## Pathophysiology

COPD is a group of conditions characterised by airflow obstruction. It is largely irreversible. Many

studies in the stable clinical state have indicated that COPD is associated with increased inflammation and elevated numbers of airway inflammatory cells including neutrophils, monocytes/macrophages and T-lymphocytes [20, 21].

In addition, many studies have also indicated that a variety of proinflammatory cytokines are also increased in COPD, as is the presence of an oxidant burden. Oxidants and proteases that are side-effects of the inflammatory process are thought to play a key role in the pathophysiology of COPD [22, 23].

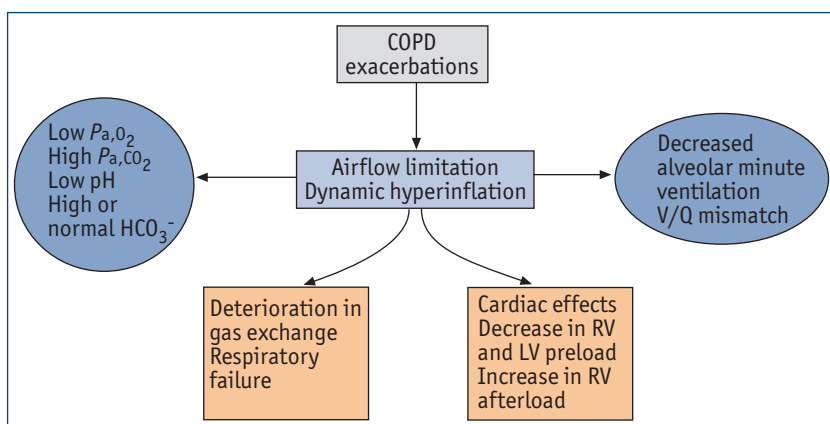
Exacerbations not only affect the health status of patients, but also have been shown to influence the deterioration of lung function [7] and hence to play a role in pathophysiology. This relationship is not unexpected, since at least some exacerbations are known to be associated with increased neutrophilic infiltration, increased proteinase release and an increase in the oxidant burden. This offers the possibility that anti-inflammatory therapy may not only improve the natural history of COPD, but may also reduce the severity and/or consequences of exacerbations.

### Physiological changes

Acute exacerbations of COPD are associated with an increase in airflow obstruction, air trapping, changes to ventilation-perfusion matching (hence gas exchange) and increased work of breathing (which may lead to mechanical failure of respiration), resulting in increasing respiratory failure. In some instances, these changes may be related to an increase in airflow limitation induced by smooth muscle contraction. Hence, the role of  $\beta_2$ -agonists and anticholinergic agents in preventing a proportion of exacerbations. Other episodes associated with increased airway inflammation may also increase airway wall oedema, mucus production and mucus plugging. These phenomena may all become critical, particularly in the small airways, also resulting in an increase in airflow obstruction and air trapping. The exact contributions of all these factors remain uncertain and may often be additive.

Tachypnoea, caused by increased expiratory flow limitation during exacerbations, means patients have less time to empty their lungs. The resulting dynamic hyperinflation increases workload on the respiratory muscles increasing the sensation of dyspnoea and causing other cardiovascular effects, such as a rise in pulmonary arterial pressures, which may precipitate right heart failure.

**Figure 2**  
Physiology of exacerbations.  $P_{a,O_2}$ : arterial oxygen tension;  $P_{a,CO_2}$ : arterial carbon dioxide tension;  $V/Q$ : ventilation/pulmonary perfusion; RV: right ventricular; LV: left ventricular.



As a result of dynamic hyperinflation, tidal breathing shifts to the less steep part of the pressure/volume compliance curve, where a further increase in pressure generates only a small volume change. There is shortening of the respiratory muscles (particularly the diaphragm) due to dynamic hyperinflation, resulting in inspiratory muscle dysfunction and fatigue. Treatment reverses this process, leading to an improvement in dynamic hyperinflation and an increase in inspiratory capacity [24]. This reduces the work of breathing and sensation of dyspnoea.

An exacerbation may be compounded by any increase in central drive due to hypoxia, hypercapnia and acidosis. When compensatory mechanisms fail to correct the impaired gas exchange, respiratory failure results. Acute or acute on chronic type-2 respiratory failure presents with raised bicarbonate, as a result. However, varying degrees of hypercapnia and acidosis, chronic or acute-on-chronic type-2 respiratory failure presents with raised serum bicarbonate, as a result of chronic renal compensation. Acidosis may not occur despite a rising arterial carbon dioxide tension.

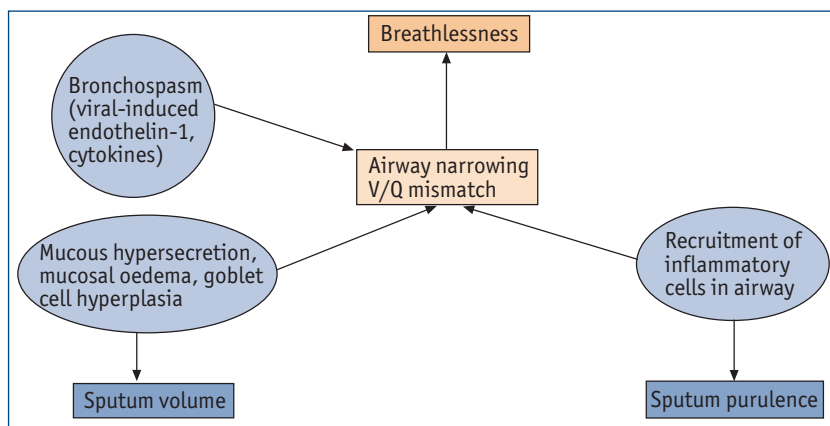
### Cardiac dysfunction

While left ventricular systolic function is usually preserved in COPD exacerbations, there is an increase in right ventricular afterload, the result of pulmonary vasoconstriction and a decrease in preload (owing to impaired venous return as a result of dynamic hyperinflation). Left ventricular preload is decreased, leading to impaired left ventricular filling (figure 2).

### Clinical features

Patients have increased symptoms compared with their stable state and are best classified into three types, based on the criteria of ANTHONISEN *et al.* [8]. Although it is not difficult to diagnose an exacerbation, this is largely a symptom-based (and hence subjective) diagnosis (figure 3). In a superficial study [6], nearly half of the episodes of symptom change remained unreported by the patients. However, it is unknown whether these were "milder" episodes.

Clinical features include: increased respiratory and heart rate; central cyanosis; signs of hypercapnia (warm peripheries, bounding pulse, flapping tremor and confusion); recruitment of accessory muscles of respiration; reduced breath sounds in the lung fields (with or without associated crackles or wheeze); and signs of right-heart failure. Measurements of vital signs and the clinical picture may help to determine the



**Figure 3** Symptoms of COPD exacerbations. V/Q: ventilation/pulmonary perfusion.

severity of the illness and hence the need for relevant interventions. Features pointing to impending respiratory failure include: respiratory rate >30 breaths per minute; heart rate >120 beats per minute; decreased level of consciousness; and inability of the patient to talk in sentences. The decision to treat patients at home or refer to hospital depends on the severity. In the UK, published guidelines are available to help with the decisions (table 2).

## Differential diagnoses

Pulmonary oedema and cardiac failure, pulmonary embolism, pneumothorax, upper airway obstruction, respiratory muscle weakness and other causes of dyspnoea should be borne in mind as differential diagnoses when treating an exacerbation.

**Table 2** Treating patients at home or in hospital

Factor	Treat at home	Treat in hospital
Able to cope at home	Yes	No
Breathlessness	Mild	Severe
General condition	Good	Poor/deteriorating
Level of activity	Good	Poor/confined to bed
Cyanosis	No	Yes
Worsening peripheral oedema	No	Yes
Level of consciousness	Normal	Impaired
Already receiving LTOT	No	Yes
Social circumstances	Good	Living alone/not coping
Acute confusion	No	Yes
Rapid rate of onset	No	Yes
Significant comorbidity (particularly cardiac disease and insulin-dependent diabetes)	No	Yes
Sa <sub>a</sub> O <sub>2</sub> < 90%	No	Yes
Changes on the CXR	No	Present
Arterial pH	≥7.35	<7.35
Arterial Pa <sub>a</sub> O <sub>2</sub> kPa	≥7	<7

LTOT: long-term oxygen therapy; Sa<sub>a</sub>O<sub>2</sub>: arterial oxygen saturation; CXR: chest radiography; Pa<sub>a</sub>O<sub>2</sub>: arterial oxygen tension. Reproduced from [24], with permission from the publisher.

## Investigations

Chest radiography during exacerbations is valuable if it shows a pneumothorax or consolidation, but other than hyperinflation it may be unremarkable in many cases. It is difficult to measure lung function during exacerbations and, in contrast to asthma, the usefulness of measuring peak expiratory flow (PEF) and forced expiratory volume in one second (FEV<sub>1</sub>) has not been validated in the management and monitoring of COPD exacerbations. Although one study found that in an emergency department, PEF and FEV<sub>1</sub> were significantly correlated [26], another study [27] found that PEF and FEV<sub>1</sub> did not decrease before the onset of exacerbations, rendering them ineffective as a predictive tool. PEF and FEV<sub>1</sub> were low during exacerbations and improved with treatment over many weeks, returning to baseline in most but not in all patients. Patients with severe disease with low baseline FEV<sub>1</sub> tend to fare worse during an exacerbation and have higher rates of mortality, intubations and readmission as well as more prolonged treatment. Although there have been studies relating spirometric findings at the time of exacerbations and the severity of exacerbations based on blood gas measurements, spirometry is generally not useful.

The measurement of arterial blood gases is mandatory in the management of exacerbations, as it helps to identify patients needing controlled oxygen therapy (patients with chronic type-2 respiratory failure) and patients who might need noninvasive or invasive ventilation (patients with acute or acute-on-chronic acidotic type-2 respiratory failure, or worsening type-2 respiratory failure).

## Management

Management of exacerbations is broadly based on clinical features and severity [1], although some aspects are subjective (table 3). The goals of treatment of acute exacerbations of COPD are to achieve symptom resolution and prevent treatment failures. Treatment can be discussed under three main headings: medical therapy; noninvasive ventilation (NIV); and invasive ventilation.

### Medical therapy

#### Bronchodilators

Inhaled or nebulised shortacting bronchodilators,  $\beta_2$ -agonists and anticholinergic agents remain the main treatment modalities during a COPD exacerbation. Although they are usually given together, there is no evidence that their effects are additive during exacerbations. Bronchodilators open the small airways to promote better emptying of the lung, thereby reducing dynamic hyperinflation and residual volume, and improving inspiratory capacity, the work of breathing and exercise endurance. There is no pharmacological benefit in using a nebuliser compared with a metered-dose inhaler, although the former is preferred when patients are unwell (it requires no coordination) and is easier for the administration of higher doses. When prescribing nebulised therapy, the driving gas (air or oxygen) must be stipulated, as this will be critical in chronic type-2 respiratory failure. The dosage of shortacting bronchodilators is usually higher and given more frequently (up to three times per hour) for the treatment of exacerbations. However, the cardiovascular adverse events associated with the use of higher doses of shortacting bronchodilators have to be borne in mind especially if the patient is already prescribed a long-acting  $\beta_2$ -agonist. The decision to continue or interrupt existing long-acting  $\beta_2$ -agonist treatment depends on the particular patient. However, it is conventional to withhold the long-acting antimuscarinic agent temporarily if the patient is receiving regular shortacting agents, in order to avoid precipitating side-effects, such as dryness of mouth, urinary retention and glaucoma.

#### Steroids

Steroid use is supported by several controlled clinical trials. In contrast to that in asthma, the inflammation associated with COPD exacerbations is not obviously suppressed by steroids unless it is predominantly eosinophilic [28]. It has, however, been reported that steroids reduce

**Table 3** Management of exacerbation based on the severity

Mild	Increased inhaled bronchodilators Increased inhaled corticosteroids
Moderate	Antibiotics (if purulent sputum) Oral steroids Increased inhaled bronchodilators and inhaled steroids
Severe	Admission to hospital Antibiotics Systemic steroids Oxygen therapy (if hypoxic and controlled if chronic type-2 respiratory failure) Nebulised bronchodilators Management of respiratory failure Non-invasive ventilation Invasive ventilation Treatment of complications Recognition and treatment of any drug toxicity (such as tremors, tachycardia from over use of $\beta_2$ -agonist, antibiotic side-effects, drug interactions, especially theophylline and quinolones)

airway inflammatory markers and C-reactive protein after 2 weeks of treatment in patients with COPD [29]. Treatment of an exacerbation with steroids reduces treatment failures (defined as death from any cause, need for intubation and mechanical ventilation, readmission or intensification of pharmacological treatment) [30]. Finally, steroids reduce duration of stay in hospital [31], speed up the rate of recovery of PEF and improve FEV<sub>1</sub> significantly within 72 hours [32]. Outpatient treatment of COPD exacerbations with oral steroids results in an increase in inter-exacerbation period [33]. For these reasons, National Institute of Health and Clinical Excellence guidelines in the UK recommend that steroids should be given to all hospitalised patients with COPD exacerbations unless there are contraindications and to outpatients with significant (undefined) increase in breathlessness. To obtain maximum benefits, steroid treatment must commence early in the exacerbation. A dose of 30–40 mg per day, for 7–14 days (at which time the course can be stopped abruptly, provided the patient has recovered), has been recommended for exacerbations. As a general rule the patient should be back to normal for several days before steroid treatment is withdrawn. If longer courses are needed, gradual withdrawal is advisable. Intravenous therapy should be reserved for patients who are unable to take oral therapy and/or have potential malabsorption problems. It is important to monitor glucose levels in hospitalised patients, as hyperglycaemia is a significant side-effect. A recent study has shown that hyperglycaemia significantly worsens outcomes [34]. Osteoporosis is a potential problem in COPD, but more so in patients taking recurrent courses of steroids for exacerbations. These patients may require osteoporosis prophylaxis.

### Antibiotics

The most frequent cause of an exacerbation is infection, and it is believed that about 50% are associated with bacterial isolation. The association is influenced by the underlying severity of the disease and the presence of colonisation in the stable state [9]. In a hospital-based study, treating patients mechanically ventilated for exacerbations of COPD prophylactically with oral ofloxacin reduced mortality, shortened ventilator days and cut length of stay when compared with placebo [35]. It is therefore reasonable to treat all exacerbations needing mechanical ventilation with antibiotics.



However, in other patients, there is a clear relationship between sputum purulence, bacterial isolation and increased bacterial load [12]. Thus, antibiotics are indicated if the sputum becomes purulent, especially in the presence of at least one more key symptom (dyspnoea, increased sputum volume) and/or chest radiology features of consolidation. Careful assessment of sputum colour is effective in identifying samples that are likely to have a positive bacterial culture (84% of samples). The presence of green (purulent) sputum is highly sensitive (94.4%) and specific (77.0%) for the yield of a high bacterial load [12]. This is supported by the presence of increased C-reactive protein and indicates a clear subset of patient episodes, identified simply at presentation, likely to benefit most from antibiotic therapy. In the same study, the remaining patients with mucoïd sputum recovered without antibiotic therapy. The need for antibiotic therapy is reduced by 50% based on observed sputum colour alone. This was accompanied by clear differences in biochemical measures. Purulent samples were inflammatory, with increased cytokines that settled with antibiotic therapy, whereas mucoïd samples were not inflammatory and did not change after resolution. More recently, studies have suggested that procalcitonin can be used to guide antibiotic therapy in lower respiratory tract infections, enabling antibiotic usage to be reduced with no adverse outcome [36]. However, in the absence of comparison with complete data (positive culture, purulent sputum and high bacterial load) the value of this technique cannot be determined. Indeed, the relative absence of positive sputum microbiological data (as opposed to lavage positivity) in the procalcitonin-directed antibiotic group suggests peripheral rather than



central infection. Thus, the role of procalcitonin measurement in therapeutic guidance needs further study and validation. Furthermore, even if validated, there may be problems translating such markers into primary care management, where simple sputum observation would appear to have an advantage.

The choice of antibiotic should depend on the local antibiotic policies, guidelines and resistance pattern. Patient factors, such as episode severity and known bacterial colonisation and sensitivity in the stable state, should be taken into consideration. Ideally, culture of the purulent sample should be undertaken before the initiation of treatment, particularly in hospitalised patients, in order that the presence of unusual resistant organisms can be identified before treatment failure becomes a major problem.

### Oxygen therapy

Oxygen therapy is vital to the management of exacerbations where patients are hypoxic. In the event that arterial gases are not available, controlled therapy (24% oxygen) should be given in the first instance. The risk of aggravating hypercapnia is minimal with controlled oxygen therapy [37]. Oxygen therapy reverses hypoxic pulmonary vasoconstriction, relieves right-heart strain, lessens myocardial ischaemia and improves cardiac output, thereby improving blood and oxygen supply to the vital organs. However, oxygen "overdose" may result in worsening hypercapnia and acidosis in a proportion of patients (those with chronic type-2 respiratory failure) [38]. This is due mainly to the suppression of the central hypoxic respiratory drive with oxygen therapy, thereby reducing ventilation. CO<sub>2</sub> exhalation, therefore, rises but in the presence of compensated retained bicarbonate does not reduce pH to maintain respiratory drive. This is less of a problem in acute type-2 respiratory failure, where the associated acidosis maintains respiratory drive. In summary, in acute COPD exacerbations, oxygen therapy is indicated in the presence of hypoxia (arterial carbon dioxide tension <8.0 kPa), it should be controlled (especially in the presence of chronic type-2 respiratory failure) and the arterial oxygen tension should be maintained at 7.3–10 kPa (a saturation of 85–92%) [38].

Controlled oxygen therapy is achieved with the use of venturi masks, delivering the required fraction of inspired oxygen and thus reducing the complications of inadequate oxygenation and/or hypercapnia. If masks are not tolerated, nasal prongs at fixed flow-rates (1 L = 24%,

2 L = 28%) are an alternative. Arterial blood gases need to be repeated soon (30 minutes) after the administration of oxygen to ensure reversal of hypoxia and, particularly, no worsening in CO<sub>2</sub> retention. Additional diagnoses, such as pulmonary embolism and pneumonia, should be considered if oxygenation does not improve despite supplementation.

### Theophyllines

Methylxanthines (theophyllines) are phosphodiesterase inhibitors and cause bronchodilation by increasing cyclic AMP and GMP levels. Their use in stable COPD is usually for severe patients after optimisation of all other medical therapy. It has been shown that withdrawing theophyllines from these patients can cause worsening of their symptoms. There is evidence that theophyllines have significant anti-inflammatory properties at subtherapeutic levels. The mechanism behind this is activation of histone deacetylases, which are nuclear enzymes involved in the "switching off" of inflammatory genes. Whether this reflects a mechanism of action in patients with COPD remains unknown.

There is no evidence supporting a role for theophyllines in exacerbations of COPD. It is possible (when used intravenously) that the concentrations achieved at the small airways may lead to some bronchodilation, but the narrow therapeutic index usually results in side-effects rather than bronchodilation. A recent study concluded that intravenous theophylline use in nonacidotic exacerbations of COPD does not alter the outcome [39]. Thus, routine use of intravenous theophyllines in the management of an exacerbation would be inappropriate. If the patient is already taking theophylline on admission, it may need to be continued, but the level should be monitored, as it interacts with many of the other drugs (antibiotics) that may be used.

### Noninvasive ventilation

Respiratory failure may be amplified by an inability to maintain the work of breathing and increasing fatigue. Effective treatments should reduce the work of breathing, but when ventilation is compromised critically, artificial support will be needed to maintain oxygenation and particularly to prevent increasing CO<sub>2</sub> retention.

The traditional way to achieve this has been invasive ventilation *via* an endotracheal tube. However, in recent years this has been accomplished by the use of NIV. This technique provides positive-pressure ventilation to a conscious patient with the use of a simple ventilator

machine and a tight-fitting facemask (figure 4). The ventilators are pressure-targeted and deliver the required tidal volume, thus leading to a reduction in patient effort while improving gas exchange.

Several randomised controlled clinical trials support the use of NIV in the management of selected cases of acute exacerbations of COPD, demonstrating decreased need for mechanical ventilation and improved survival. A key study from the UK (multicentre randomised controlled trial) showed that NIV used early in the admission reduced the need for intubation (using *a priori* criteria) from 27 to 15%, real intubation rates from 10 to 6%, and in-hospital mortality from 20 to 10% [40]. Furthermore, BROCHARD *et al.* [41] showed that in the intensive care unit environment, use of NIV reduced the need for intubation from 74 to 25% and mortality from 29 to 9%. A recent Cochrane systematic review [42] of good-quality randomised controlled trials on the use of NIV in the management of acute respiratory failure in exacerbations of COPD confirms that NIV is an effective treatment intervention and should be used as the first-line intervention when standard management fails. NIV should be commenced early before severe acidosis ensues, to avoid the need for endotracheal intubation and reduce mortality and treatment failures. One-year survival following NIV for exacerbations of COPD is better than in an untreated group [43]. Indications and contra-indications for the use of NIV are shown in table 4.

When commencing a patient on NIV, clear decisions must be taken and documented with regard to subsequent further escalation of treatment (invasive ventilation). Follow-up blood gases are mandatory 1 and 4–6 hours after initiation of NIV in order that the ventilator settings can be adjusted. Oxygen can be administered through the port in the NIV mask in order to maintain arterial oxygen saturations. Transcutaneous CO<sub>2</sub> measurements are a convenient way of monitoring without having to obtain multiple arterial gases, but the instrument requires regular calibration to ensure accurate data. Reduction in respiratory rate and resolution of acidaemia are the main therapeutic aims. Invasive ventilation has to be considered if there is no improvement in the initial 4–6 hours. It is generally recommended that NIV be used as much as possible in the first 24 hours. Although it has been shown that NIV can be administered safely and effectively on general medical wards, a lead respiratory consultant and trained staff nurses are mandatory to provide the service.



**Figure 4**  
Bi-level noninvasive ventilator and nasal mask.

## Invasive ventilation

Mechanical ventilation through an endotracheal tube is considered when patients have contra-indications to the use of NIV or fail to improve on NIV. Although patients with an arterial pH <7.25 after standard initial management usually need invasive ventilation, they may warrant a brief trial period of NIV in the intensive care unit if there is no major haemodynamic compromise. Weaning patients from a ventilator can prove to be difficult, particularly if those with chronic type-2 respiratory failure are ventilated to a normal CO<sub>2</sub>. (They should be ventilated to a normal pH.) NIV is increasingly used to wean these patients from ventilator and shorten their intensive care stay [44].

## Mucolytic therapy

Most COPD exacerbations are associated with excess production of mucus in the airways and mucus plugging, which will disturb ventilation and perfusion. Strategies aiming to reduce mucus viscosity and thus facilitate mucus clearance would seem to be beneficial. However, although there is some evidence that mucolytic therapy can reduce exacerbations, there is no data to support its routine use in exacerbations of COPD [45].

## Chest physiotherapy

Chest physiotherapy is ineffective and may prove to be detrimental in the treatment of exacerbations of COPD. Some studies show a slight decrease in FEV<sub>1</sub> after chest percussion therapy [46].

**Table 4** Indications and contraindications for the use of NIV

Indications	Acute hypercapnic acidotic respiratory failure with pH <7.35 and >7.25, Pa <sub>a</sub> CO <sub>2</sub> >6 kPa in a patient presenting with exacerbation of COPD despite maximum medical treatment on controlled oxygen therapy
Contra-indications	Inability to protect airways Confusion Severe hypoxaemia Haemodynamic instability Recent upper airway surgery Facial trauma Copious upper airway secretions Intolerant of mask Vomiting

## Respiratory stimulants

In the pre-NIV era, intravenous doxapram was used as a respiratory stimulant to treat patients with type-2 respiratory failure. It has been shown that NIV is more effective than doxapram in improving gas exchange [47]. The effect of doxapram is short-lived and its use is limited by the side-effects of agitation or fitting. However, there may still be a role for doxapram in patients who do not tolerate NIV or during transfer to an area where NIV can be started. In some patients who remain drowsy on NIV or who are particularly prone to CO<sub>2</sub> retention, it may be necessary to combine NIV and doxapram [48].

## Supportive measures

The fluid and electrolyte balance of patients admitted with exacerbations of COPD should be optimised. Prophylaxis against venous thromboembolism should be instituted unless there are clear contraindications.

## Palliative care for the terminally ill

For patients who are terminally ill with severe underlying lung disease (not suitable for further escalation of treatment), palliative measures should be taken to relieve breathlessness and anxiety (opiates and benzodiazepines). Patient and family participation in such decisions is essential. The ethical considerations in making such decisions are complex and beyond the scope of this article.

## Discharging a patient

The median length of hospital stay for exacerbations of COPD is 9 days (5–15 days) [3]. Some hospitals operate assisted discharge services with the help of respiratory specialist nurses. While these "hospital at home" services may not decrease mortality, they do reduce length of hospital stay, although their cost-effectiveness is unclear. Patients should remain stable and have acceptable arterial blood gases on the day of discharge. Patients may need supplemental oxygen therapy at this stage if their arterial oxygen saturation remains <90%. This should be reassessed at the first clinical visit (4–6 weeks) and continuation long-term (15 hours per day) or cessation should be determined.

## Predictors of poor outcome in patients admitted to hospital

Poor outcome relates to: the severity of underlying disease; severity of illness at presentation; age; presence of comorbidities; nutrition; chronic ill health; and quality of life. The combination of

quality of life, hospitalisation for COPD in the previous year and hypercapnia on discharge are predictors of readmission at 1 year [49]. Home oxygen use and the frequency of exacerbations significantly influence treatment failure within 4 weeks in outpatient-managed exacerbations of COPD [50]. Other factors influencing the outcome are: severity of lung disease; history of previous pneumonia; use of maintenance steroids; and history of sinusitis. However, in this study undertaken in outpatients, age, comorbidity and the choice of antibiotic did not alter treatment outcome.

## Preventive measures

Because of healthcare burden, effect on mortality and health status, there is increasing activity in developing strategies to prevent COPD exacerbations. Inhaled corticosteroids, long-acting  $\beta_2$ -agonists and long-acting antimuscarinic agents all reduce the overall frequency of episodes [51]. Steroids may have an effect on the eosinophilic episodes, whereas long-acting  $\beta_2$ -agonists and long-acting antimuscarinic agents may maintain airway patency, especially in episodes where bronchoconstriction would be a feature. Pulmonary rehabilitation has also been shown to have a benefit in preventing some episodes and to cause a significant reduction in frequency and duration of hospitalisations [52]. Influenza vaccination has been reported to be beneficial [53], but there is no data to support the use of pneumococcal vaccination, although this is recommended in the GOLD guidelines.

Prophylactic antibiotic therapy showed minimal benefit in some of the earlier studies [54], but this should be weighed against the risks of adverse drug events and antibiotic resistance. It may be of benefit to target patients with lower airway colonisation and increased frequency of exacerbations for trials of antibiotic prophylaxis.

Self-management of an exacerbation at home can be recommended for suitable patients with a pre-held supply of antibiotics (providing the patient understands the requirements of purulent sputum) and steroids to be started at the beginning of an exacerbation, thereby aiming to shorten or reduce the severity of the episode.

## Conclusion

Exacerbations of COPD cause a considerable burden to the patient and the healthcare system. Diagnosis is often made on clinical grounds and

treatment is based on the perceived severity of the episode and risk to the patient. The immediate treatment includes regular inhaled short-acting bronchodilators with or without corticosteroids, whereas antibiotics should be limited to patients with purulent sputum (in the absence of pneumonia or ventilation). The use of controlled oxygen therapy and NIV helps to optimise gas

exchange and decrease muscle fatigue but failure to improve is an indication for invasive ventilation. Preventive measures such as inhaled long-acting bronchodilator and inhaled corticosteroids are indicated in those with recurrent exacerbations, particularly if hospitalisation has occurred. Pulmonary rehabilitation and influenza vaccination will play a role in some patients.

### Educational questions

1. State whether the following statements are true or false:
  - a) Nearly 50% of symptom-based exacerbations are unreported and hence untreated.
  - b) Studies show that the bacterial isolation rate increases to 50% during exacerbations.
  - c) Severity depends on the need for healthcare resources and underlying disease severity.
  - d) Antibiotics are indicated if there is clearly purulent sputum.
  - e) Antibiotics are not needed in case of non-purulent sputum, despite the severity of the episode needing artificial ventilation.
  - f) Steroids are recommended for all hospitalised patients with COPD exacerbation.
  - g) Steroids shorten the interexacerbation period.
  - h) Steroids mainly have an effect on the neutrophilic episodes.
  - i) Steroids do not speed up the rate of recovery of peak flows.
  - j) High-flow oxygen therapy should not be given to patients who have chronic type-2 respiratory failure.
  - k) In COPD exacerbations, controlled oxygen therapy is indicated to maintain arterial oxygen tension at 10–12 kPa.
  - l) NIV should be commenced on exacerbations of COPD even if there is no respiratory acidosis.
  - m) There is evidence that short-acting bronchodilators are additive in action when given during exacerbations.
  - n) Patients on home long-term oxygen treatment are preferably treated in hospitals in the event of exacerbation of COPD.
  - o) Severity of underlying lung disease and severity of illness at presentation are predictors of poor outcome of COPD exacerbations in hospitalised patients.
  - p) The combination of quality of life, hospitalisation for COPD in the previous year and hypercapnia on discharge are predictors of readmission at 1 year.
  - q) Inhaled corticosteroids, long-acting  $\beta_2$ -agonists and long-acting antimuscarinic agents all reduce the overall frequency of episodes.
  - r) Prophylactic antibiotic therapy is useful to reduce the number of exacerbations.
  - s) Influenza vaccination is useful as a preventive measure to reduce the number and severity of COPD exacerbations.
  - t) Physiotherapy is one of the important treatment options for acute COPD exacerbations.
2. What is the next step in treating a patient presenting with exacerbation of COPD after the initial standard therapy? Arterial blood gas measurements now show pH 7.18, oxygen tension 7.2, carbon dioxide tension 11.2,  $\text{HCO}_3^-$  24. Chest radiography is normal.
  - a) Invasive ventilation and antibiotics.
  - b) Invasive ventilation only.
  - c) NIV and antibiotics.
  - d) Intravenous aminophylline and doxapram.
3. All of the following are true regarding exacerbations of COPD except:
  - a) Intravenous theophylline use in nonacidotic exacerbations of COPD does not alter the outcome.
  - b) NIV is not more effective than doxapram in improving gas exchange.
  - c) Patients with an arterial pH <7.25 after standard initial management usually need invasive ventilation.
  - d) The median length of hospital stay for exacerbation of COPD is 9 days.
4. Which one of the following is true regarding exacerbations of COPD?
  - a) PEF and FEV<sub>1</sub> are good predictive tools for identifying exacerbations at an early stage.
  - b) Chest radiography is often unremarkable.
  - c) The measurement of arterial blood gases is not mandatory in the management of exacerbations.
  - d) The severity of the disease does not correlate with rates of mortality, intubations or readmission.
5. Factors predicting admission to hospital for exacerbations of COPD are all of the following except:
  - a) Patients on long-term oxygen therapy.
  - b) Impaired level of consciousness.
  - c) Oxygen saturations <90% on air.
  - d) The presence of fever.

6. The clinical signs of hypercapnia include all of the following except:
- Warm peripheries.
  - Confusion and flapping tremor.
  - Bounding pulse.
  - Cyanosis.
7. Interpret the radiographical findings below.



Rightsided pneumothorax-complicating exacerbation of COPD  
 Case report: A 50-year-old female was admitted with exacerbation of COPD. A few days later in the admission she developed sudden rightsided pleuritic chest pain and went into acute type-2 respiratory failure. Chest radiography showed pneumothorax on the right side, which was drained, and she was ventilated noninvasively. Note that in such patients classical signs (reduced breath sounds and vocal resonance and hyperresonance) may be features of COPD alone, highlighting the importance of radiography.

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## Suggested answers

1. a) True  
b) True  
c) True  
d) True  
e) False  
f) True  
g) False  
h) False  
i) False  
j) True  
k) False  
l) False  
m) False  
n) True  
o) True  
p) True  
q) True  
r) False  
s) True  
t) False
2. a
3. b
4. b
5. d
6. d
7. Right lower lobe pneumonia. Subcutaneous emphysema. Chest drains 2 *in situ*.

For additional information on COPD exacerbations, visit [www.ersnet.org/copd](http://www.ersnet.org/copd). This interactive presentation of the ERS/ATS standards for the diagnosis and treatment of patients with COPD includes direct access to most references in PDF, and questionnaires for self-evaluation. Information for patients is also provided in English, German, French, Italian and Spanish on the European Lung Foundation website at [www.european-lung-foundation.org/COPD](http://www.european-lung-foundation.org/COPD).

Lectures on COPD exacerbations are also available from the ERS learning resources at [www.ers-education.org](http://www.ers-education.org). Discover the symposium on "Infection and acute exacerbation of COPD: what do we know?" (Session 401) organised at the Copenhagen 2005 Annual Congress, or the symposium on "Exacerbation of COPD" (Session 409) organised in Munich 2006.