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Acute Exacerbations of COPD

Chapter 68

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EPIDEMIOLOGY OF COPD EXACERBATIONS

There has been considerable recent interest into the causes and mechanisms of exacerbations of COPD, as COPD exacerbations are an important cause of the considerable morbidity and mortality found in COPD.[1] COPD exacerbations increase with increasing severity of COPD. Some patients are prone to frequent exacerbations that are an important cause of hospital admission and readmission and these frequent exacerbations may have considerable impact on quality of life and activities of daily living.[2] COPD exacerbations are also associated with considerable physiological deterioration and increased airway inflammatory changes[3] that are caused by a variety of factors such as viruses, bacteria and possibly common pollutants (**Fig. 68.1**). COPD exacerbations are more common in the winter months and there may be important interactions between cold temperatures and exacerbations caused by viruses or pollutants.[4]

Earlier descriptions of COPD exacerbations have concentrated mainly on studies of hospital admission, though most COPD exacerbations are treated in the community and not associated with hospital admission. A cohort of moderate to severe COPD patients was followed in East London, UK (East London COPD Study) with daily diary cards and peak flow readings. The patients were asked to report exacerbations as soon as possible after symptomatic onset.[2] The diagnosis of COPD exacerbation was based on criteria modified from those described by Anthonisen and colleagues,[5] that require two symptoms for diagnosis, one of which must be a major symptom of increased dyspnea, sputum volume or sputum purulence. Minor exacerbation symptoms included cough, wheeze, sore throat, nasal discharge or fever (**Table 68.1**). The study found that about 50% of exacerbations were unreported to the research team, despite the considerable encouragement provided and only diagnosed from diary cards, though there were no differences in major symptoms or physiological parameters between reported and unreported exacerbations.[2] Patients with COPD are accustomed to frequent symptom changes and thus may tend to underreport exacerbations to physicians. These patients have high levels of anxiety and depression and may accept their situation.[6,7] The tendency of patients to underreport exacerbations may explain the higher total rate of exacerbations at 2.7 per patient per year, which is higher than previously reported by Anthonisen and co-workers[5] at 1.1 per patient per year. However, in the latter study, exacerbations were unreported and diagnosed from patients' recall of symptoms.

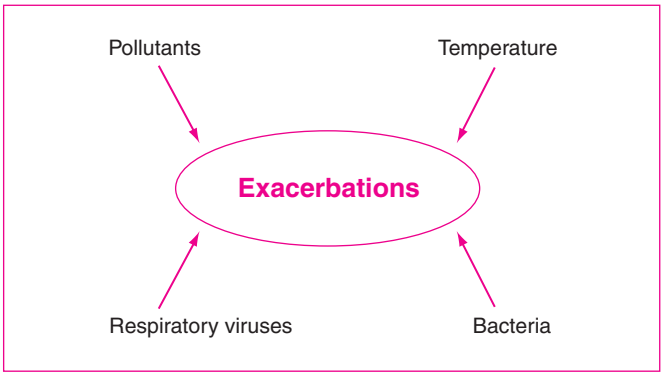

Fig. 68.1. Etiology of COPD exacerbations.

Table 68.1. Diagnosis of exacerbation

Major symptoms	Dyspnea
	Increase in sputum volume
	Sputum purulence
Minor symptoms	Cough
	Wheeze
	Sore throat
	Common cold symptoms (nasal congestion/discharge)

Definition requires 2 symptoms, one of which at least must be a major symptom. Symptoms must be present for 2 consecutive days. Adapted from Refs 2 and 3.

Using the median number of exacerbations as a cut-off point, COPD patients in the East London Study were classified as frequent and infrequent exacerbators. Quality of life scores measured using a validated disease-specific scale – the St George's Respiratory Questionnaire (SGRQ) – were significantly worse in all of its three component scores (symptoms, activities and impacts) in the frequent, compared with the infrequent exacerbators. This suggests that exacerbation frequency is an important determinant of health status in COPD and is thus one of the important outcome measures in COPD. Factors predictive of frequent exacerbations included daily cough and sputum and frequent exacerbations in the previous year. A previous study of acute infective exacerbations of chronic bronchitis found that one of the factors predicting exacerbation was also the number in the previous year,[8] though this study was limited to exacerbations presenting with purulent sputum and no physiological data were available during the study.

In a further prospective analysis of 504 exacerbations, where daily monitoring was performed, there was some deterioration in symptoms, though no significant peak flow changes.[9] Falls in peak flow and FEV_1 at exacerbation were generally small and not useful in predicting exacerbations, but larger falls in peak flow were associated with symptoms of dyspnea, presence of colds and related to longer recovery time from exacerbations. Symptoms of dyspnea, common colds, sore throat and cough increased significantly during the prodromal phase and this suggests that respiratory viruses may have early effects at exacerbations. The median time to recovery of peak flow was 6 days and 7 days for symptoms, but at 35 days peak flow had returned to normal in only 75% of exacerbations, while at 91 days, 7.1% of exacerbations had not returned to baseline lung function. Recovery was longer in the presence of increased dyspnea or symptoms of a common cold at exacerbation. The changes observed in lung function at exacerbation were smaller than those observed at asthmatic exacerbations, though the average duration of an asthmatic exacerbation was longer at 9.6 days.[10,11]

The reasons for the incomplete recovery of symptoms and lung function are not clear, but may involve inadequate treatment or persistence of the causative agent. The incomplete physiological recovery after an exacerbation could contribute to the decline in lung function with time in patients with COPD. However to date there is no evidence that patients with incomplete recovery of their exacerbation have a greater decline in lung function and further studies on the natural history of COPD exacerbations are required. The association of the symptoms of increased dyspnea and of the common cold at exacerbation with a prolonged recovery suggests that viral infections may lead to more prolonged exacerbations. As colds are associated with longer exacerbations, COPD patients who develop a cold may be prone to more severe exacerbations and should be considered for therapy early at onset of symptoms.

AIRWAY INFLAMMATION AT EXACERBATION

Although it has been assumed that exacerbations are associated with increased airway inflammation, there has been little information available on the nature of inflammatory markers especially when studied close to an exacerbation, as performing bronchial biopsies at exacerbation is difficult in patients with moderate to severe COPD. The relation of any airway inflammatory changes to symptoms and physiological changes at exacerbations of COPD is also an important factor to consider.

In one study, where biopsies were performed at exacerbation in patients with chronic bronchitis, increased airway eosinophilia was found, though the patients studied had only mild COPD.[12] With exacerbation, there were more modest increases observed in neutrophils, T-lymphocytes (CD3) and tumor necrosis factor-α (TNF-α) positive cells, while there were no changes in CD4 or CD8 T cells, macrophages or mast cells. However the technique of sputum induction allows study of these patients at exacerbation and it has been shown that it is a safe and well-tolerated technique in COPD patients.[13] Levels of inflammatory cytokines have been shown to be elevated in induced sputum in COPD patients when stable, though changes at exacerbation had not been previously studied.[14]

In a prospectively followed cohort of patients from the East London COPD Study, inflammatory markers in induced sputum were related to symptoms and physiological parameters both at baseline and at exacerbation.[3] There was a relation between exacerbation frequency and sputum cytokines, in that there was increased sputum IL-6 and IL-8 found in patients at baseline when stable with frequent exacerbations, compared with those with infrequent exacerbations (**Fig. 68.2**), although there was no relation between cytokines and baseline lung function. Sputum cell counts were not increased at baseline in patients with more frequent exacerbations suggesting that the increased cytokine production comes from the bronchial epithelium in COPD. As discussed below, exacerbations are triggered by viral infections, especially by rhinovirus that is the cause of the common cold. Rhinovirus has been shown to increase cytokine production in an epithelial cell line[15] and thus repeated viral infection may lead to up-regulation of cytokine airway expression.

At exacerbation, increases were found in induced sputum interleukin (IL)-6 levels and the levels of IL-6 were higher when exacerbations were associated with symptoms of the common cold (**Fig. 68.3**). Experimental rhinovirus infection has been shown to increase sputum IL-6 in normal subjects and asthmatics.[16–18] However, rises in cell counts and IL-8 were more variable with exacerbation and not reaching statistical significance, suggesting marked heterogeneity in the degree of the inflammatory response at exacerbation. The exacerbation IL-8 levels were related to sputum neutrophil and total cell counts, indicating that neutrophil recruitment is the major source of airway IL-8 at exacerbation. Lower

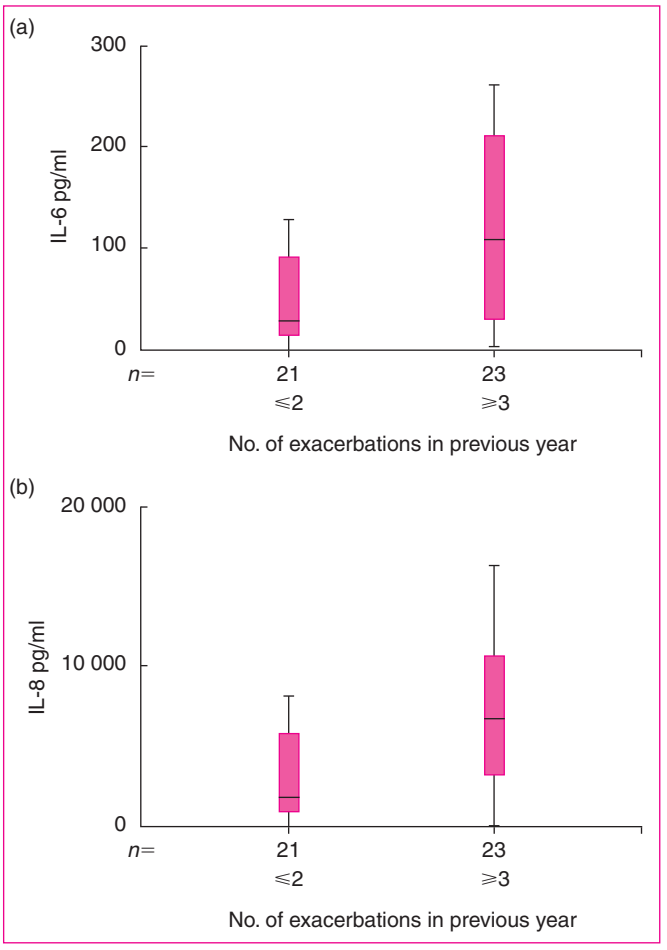

Fig. 68.2. (a) Induced sputum levels of IL-6 in patients who are categorized as frequent exacerbators (more than three exacerbations in the previous year) and those who are infrequent exacerbators (less than two exacerbations in previous year). Data is expressed as medians (IQR) (reproduced from Bhowmik et al.[3]). **(b)** Induced sputum levels of IL-8 in patients with frequent exacerbations and infrequent exacerbations. Data are expressed as medians (IQR) (reproduced with permission from Bhwomik et al.[3]).

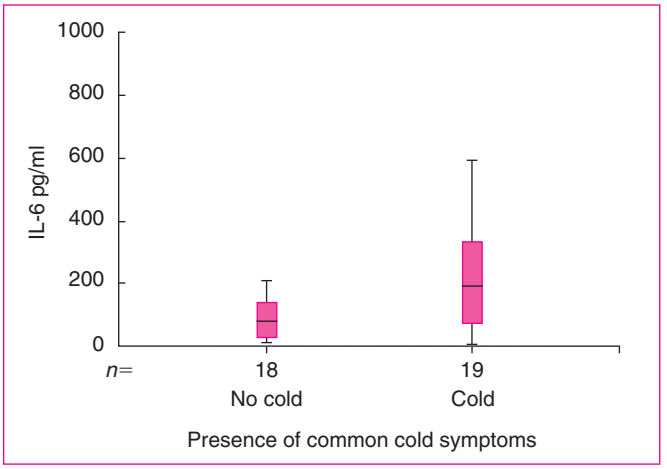

Fig. 68.3. Induced sputum IL-6 levels in the absence and presence of a natural cold. Data are expressed as medians (IQR) (reproduced with permission from Bhwomik et al.[3]).

airway IL-8 has been shown to increase with experimental rhinovirus infection in normal and asthmatic patients in some studies,[17] but not in others.[18] However, COPD patients already have up-regulated airway IL-8 levels when stable due to their high sputum neutrophil load[14] and further increases in IL-8 would be unlikely. COPD exacerbations are associated with a less pronounced airway inflammatory response than asthmatic exacerbations,[19] and this may explain the relatively reduced response to steroids seen at exacerbation in COPD patients, relative to asthma.[20–26]

In the study performed by Bhowmik and colleagues,[3] there was no increase seen in the eosinophil count at exacerbation, even though the patients in that study were sampled early at exacerbation with onset of symptoms. Compared with the study by Saetta and colleagues,[12] where patients had mild COPD, the patients had more severe and irreversible airflow obstruction with an FEV_1 at 39% predicted. Thus it is possible that the inflammatory response at exacerbation is different in nature in patients with moderate to severe COPD than in patients with milder COPD.

Patients were followed with daily diary cards in the study by Bhowmik and colleagues[3] and thus the inflammatory response could be related to exacerbation recovery. There was no relation between the degree of inflammatory cell response with exacerbation and duration of symptoms and lung function changes. Induced sputum markers taken 3 to 6 weeks after exacerbation showed no relation to exacerbation changes. Thus levels of induced sputum markers at exacerbation do not predict the subsequent course of the exacerbation and will not be useful in the prediction of exacerbation severity.

ETIOLOGY

COPD exacerbations have been associated with a number of etiological factors, including infection and pollution episodes (**Table 68.2**). COPD exacerbations are frequently triggered by upper respiratory tract infections and these are more common in the winter months, when there are more respiratory viral infections in the community. Patients may also be more prone to exacerbations in the winter months, as lung function in COPD patients shows small but significant falls with reduction in outdoor temperature during the winter months.[4] COPD patients have been found to have increased hospital admissions, suggesting increased exacerbation when increasing environmental pollution occurs. During the December 1991 pollution episode in the UK, COPD mortality was increased together with an increase in hospital admission in elderly COPD patients.[27] However, common pollutants especially oxides of nitrogen and particulates may interact with viral infection to precipitate exacerbation rather than acting alone.[28]

Viral infections

Viral infections are an important trigger for COPD exacerbations. Studies in childhood asthma have shown that

Table 68.2. Causes of COPD exacerbations

Viruses	Rhinovirus (common cold)
	Influenza
	Parainfluenza
	Coronavirus
	Adenovirus
	RSV
	Chlamydia pneumoniae
Bacteria	*Haemophilus influenzae*
	Streptococcus penumoniae
	Branhamella cattarhalis
	Staphylococcus aureus
	Pseudomonas aeruginosa
Common pollutants	Nitrogen dioxide
	Particulates
	Sulfur dioxide
	Ozone

viruses, especially rhinovirus (the cause of the common cold) can be detected by polymerase chain reaction from a large number of these exacerbations.[29] Rhinovirus has not hitherto been considered to be of much significance during exacerbations of COPD. In a study of 44 chronic bronchitics over 2 years, Stott and colleagues[30] found rhinovirus in 13 (14.9%) of 87 exacerbations of chronic bronchitis. In a more detailed study of 25 chronic bronchitics with 116 exacerbations over 4 years, Gump et al.[31] found that only 3.4% of exacerbations could be attributed to rhinoviruses. In a more recent study of 35 episodes of COPD exacerbation using serological methods and nasal samples for viral culture, little evidence was found for a rhinovirus etiology of COPD exacerbation.[32]

Two recent studies showed that at least one-third of COPD exacerbations was associated with viral infections, and that the majority of these were due to rhinovirus.[33,34] Viral exacerbations were associated with symptomatic colds and prolonged recovery.[9] However Seemungal and colleagues[34] showed that rhinovirus can be recovered from induced sputum more frequently than from nasal aspirates at exacerbation, suggesting that wild-type rhinovirus can infect the lower airway and contribute to inflammatory changes at exacerbation. They also found that exacerbations associated with the presence of rhinovirus in induced sputum had larger increases in airway IL-6 levels,[34] suggesting that viruses increase the severity of airway inflammation at exacerbation. This finding is in agreement with the data that respiratory viruses produce longer and more severe exacerbations and have a major impact on health care utilization.[9,33] Other viruses may trigger COPD exacerbation, though coronavirus was associated with only a small proportion of asthmatic exacerbations and is unlikely to play a major role in COPD.[29,35]

Bacterial colonization

Airway bacterial colonization has been found in approximately 30% of COPD patients, and this colonization has been shown to be related to the degree of airflow obstruction and current cigarette smoking status.[36] Although bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae* have been associated with COPD exacerbation, some studies have shown increasing bacterial counts during exacerbation, while others have not confirmed these findings.[37,38] Soler and colleagues[39] showed that the presence of potentially pathogenic organisms in bronchoalveolar lavage from COPD patients at bronchoscopy was associated with a greater degree of neutrophilia and higher TNF-α levels. Hill and colleagues[40] in a larger study showed that the airway bacterial load was related to inflammatory markers. They also found that the bacterial species was related to the degree of inflammation, with *Pseudomonas aeruginosa* colonization showing greater myeloperoxidase activity (an indirect measure of neutrophil activation).

Thus bacterial colonization in COPD may be an important determinant of airway inflammation and thus further long-term studies are required as to whether bacterial colonization predisposes to decline in lung function, characteristic of COPD. There is no evidence that patients with frequent exacerbations have increased sputum bacterial colonization to explain the higher cytokine levels observed in the frequent exacerbator patient group.[3] However, it is also possible that there may be interactions between viral and bacterial infection at COPD exacerbation. Other organisms such as *Chlamydia pneumoniae*, that have been associated with asthmatic exacerbation, may also play a role in COPD exacerbation.

PATHOPHYSIOLOGICAL CHANGES

Relatively little information is available on pathological changes in the airway during COPD exacerbation. In patients with moderate and severe COPD, the mechanical performance of the respiratory muscles is reduced. The airflow obstruction leads to hyperinflation, with the respiratory muscles acting at a mechanical disadvantage and generating reduced inspiratory pressures. The load on the respiratory muscles is also increased in patients with airflow obstruction by the presence of intrinsic positive end-expiratory pressure (PEEP). With an exacerbation of COPD, the increase in airflow obstruction will further increase the load on the respiratory muscles and increase the work of breathing, precipitating respiratory failure in more severe cases. The minute ventilation may be normal, but the respiratory pattern will be irregular with increased frequency and decreased tidal volume. The resultant hypercapnia and acidosis will then reduce inspiratory muscle function, contributing to further deterioration of the respiratory failure.

Hypoxemia in COPD usually occurs due to a combination of ventilation-perfusion mismatch and hypoventilation,

although arterio-venous shunting can also contribute in the acute setting. This causes increase in pulmonary artery pressure, which can lead to salt and water retention and the development of edema. The degree of the ventilation perfusion abnormalities increases during acute exacerbations and then resolves over the following few weeks. Acidosis is an important prognostic factor in survival from respiratory failure during a COPD exacerbation and thus early correction of acidosis is an essential goal of therapy.

TREATMENT

Inhaled bronchodilator therapy

Beta-2-agonists and anti-cholinergic agents are the inhaled bronchodilators most frequently used in the treatment of acute exacerbations of COPD. In patients with stable COPD, symptomatic benefit can be obtained with bronchodilator therapy in COPD, even without significant changes in spirometry. This is probably due to a reduction in dynamic hyperinflation that is characteristic of COPD and hence leads to a decrease in the sensation of dyspnea especially during exertion.[41] In stable COPD, greater bronchodilatation has been demonstrated with anti-cholinergic agents than with β_2-agonists, which may be due to the excessive cholinergic neuronal bronchoconstrictor tone.[42] However, studies investigating bronchodilator responses in acute exacerbations of COPD have shown no differences between agents used and no significant additive effect of the combination therapy, even though the combination of an anticholinergic and bronchodilator has benefits in the stable state.[43,44] This difference in effect between the acute and stable states may be due to the fact that the larger doses of drug delivered in the acute setting produce maximal bronchodilatation, whereas the smaller doses administered in the stable condition may be having a submaximal effect.

Methylxanthines, such as theophylline, are sometimes used in the management of acute exacerbations of COPD. There is some evidence that theophyllines are useful in COPD, though the main limiting factor is the frequency of toxic side-effects. The therapeutic action of theophylline is thought to be due to its inhibition of phosphodiesterase which breaks down cyclic AMP, an intracellular messenger, thus facilitating bronchodilatation. However, studies of intravenous aminophylline therapy in acute exacerbations of COPD have shown no significant beneficial effect over and above conventional therapy.[45] There are some reports of beneficial effects of methylxanthines upon diaphragmatic and cardiac function, though these mechanisms require further study in patients with COPD exacerbations.

Corticosteroids

Only about 10 to 15% of patients with stable COPD show a spirometric response to oral corticosteroids[46] and, unlike the situation in asthma, steroids have little effect on airway inflammatory markers in patients with COPD.[47,48] Although corticosteroids have traditionally been used in the management of acute exacerbations of COPD, there is only recently evidence of their beneficial role in the acute situation.[20–26]

A number of early studies have investigated the effects of corticosteroid therapy on COPD exacerbation. In an early controlled trial in patients with COPD exacerbations and acute respiratory failure, Albert and co-workers[20] found that there were larger improvements in pre- and post-bronchodilator FEV_1 when patients were treated for the first 3 days of the hospital admission with intravenous methylprednislone than those treated with placebo. Another trial found that a single dose of methylprednisolone given within 30 minutes of arrival in the accident and emergency department produced no improvement after 5 hours in spirometry, and also had no effect on hospital admission, though another study reduced readmission.[21,22] A retrospective study of patients treated with steroids at exacerbation compared with those not treated showed that the steroid group had a reduced chance of relapse after therapy.[23]

Thompson and colleagues[24] gave a 9-day course of prednisolone or placebo in a randomized manner to out-patients presenting with acute exacerbations of COPD. Unlike the previous studies, these patients were either recruited from out-patients or from a group that were pre-enrolled and self-reported the exacerbation to the study team. In this study, patients with exacerbations associated with acidosis or pneumonia were excluded, so exacerbations of moderate severity were generally included. Patients in the steroid-treated group showed a more rapid improvement in P_aO_2, alveolar-arterial oxygen gradient, FEV_1, peak expiratory flow rate and a trend towards a more rapid improvement in dyspnea.

In a recent cohort study by Seemungal and colleagues,[9] the effect of therapy with prednisolone on COPD exacerbations diagnosed and treated in the community was studied. Exacerbations treated with steroids were more severe and associated with larger falls in peak flow rate. The treated exacerbations also had a longer recovery time to baseline for symptoms and peak flow rate. However, the rate of peak flow rate recovery was faster in the prednisolone-treated group, though not the rate of symptom score recovery. An interesting finding in this study was that steroids significantly prolonged the median time from the day of onset of the initial exacerbation to the next exacerbation from 60 days in the group not treated with prednisolone, to 84 days in the patients treated with prednisolone. In contrast, antibiotic therapy had no effect on the time to the next exacerbation. If short course oral steroid therapy at exacerbation does prolong the time to the next exacerbation, then this could be an important way to reduce exacerbation frequency in COPD patients, which is an important determinant of health status.[2]

Davies and colleagues[25] studied patients admitted to hospital with COPD exacerbations who were randomized to prednisolone or placebo. In the prednisolone group, the FEV_1 rose faster until day 5, when a plateau was observed in the steroid-treated group. Changes in the pre-bronchodilator and post-bronchodilator FEV_1 were similar suggesting that

this is not just an effect on bronchomotor tone, but involves faster resolution of airway inflammatory changes or airway wall edema with exacerbation. Length of hospital stay analysis showed that patients treated with prednisolone had a significantly shorter length of stay. Six weeks later, there were no differences in spirometry between the patient groups and health status was similar to that measured at 5 days after admission. Thus the benefits of steroid therapy at exacerbation are most obvious in the early course of the exacerbation. A similar proportion of the patients, approximately 32% in both study groups required further treatment for exacerbations within 6 weeks of follow-up, emphasizing the high exacerbation frequency in these patients.

Niewoehner and colleagues[26] performed a randomized controlled trial of either a 2-week or 8-week prednisolone course at exacerbation compared with placebo, in addition to other exacerbation therapy. The primary end point was a first treatment failure, including death, need for intubation, readmission or intensification of therapy. There was no difference in the results using the 2- or 8-week treatment protocol. The rates of treatment failure were higher in the placebo group at 30 days, compared with the combined 2- and 8-week prednisolone groups. As in the study by Davies and colleagues, the FEV_1 improved faster in the prednisolone-treated group, though there were no differences by 2 weeks. In contrast, Niewoehner and colleagues performed a detailed evaluation of steroid complications and found considerable evidence of hyperglycemia in the steroid-treated patients. Thus steroids should be used at COPD exacerbation in short courses of no more than 2 weeks duration to avoid risk of complications.

Antibiotics

Acute exacerbations of COPD often present with increased sputum purulence and volume and antibiotics have traditionally been used as first-line therapy in such exacerbations. However, viral infections may be the triggers in a significant proportion of acute infective exacerbations in COPD and antibiotics used for the consequences of secondary infection. A study investigating the benefit of antibiotics in over 300 acute exacerbations demonstrated a greater treatment success rate in patients treated with antibiotics, especially if their initial presentation was with the symptoms of increased dyspnea, sputum volume and purulence.[5] Patients with mild COPD obtained less benefit from antibiotic therapy. A randomized placebo-controlled study investigating the value of antibiotics in patients with mild obstructive lung disease in the community concluded that antibiotic therapy did not accelerate recovery or reduce the number of relapses.[49] A meta-analysis of trials of antibiotic therapy in COPD identified only nine studies of significant duration and concluded that antibiotic therapy offered a small but significant benefit in outcome in acute exacerbations.[50]

Management of respiratory failure

Hypoxemia occurs with more severe exacerbations and usually requires hospital admission. Caution should always be taken in providing supplemental oxygen to patients with COPD, particularly during acute exacerbations, when respiratory drive and muscle strength can be impaired leading to significant increases in carbon dioxide tension at relatively modest oxygen flow rates. However, in the vast majority of cases, the administration of supplemental oxygen increases arterial oxygen tension sufficiently without clinically significant rises in carbon dioxide. It is suggested that supplemental oxygen is delivered at an initial flow rate of 1–2 L/minute via nasal cannulae or 24–28% inspired oxygen via Venturi mask, with repeat blood gas analysis after 30–45 minutes of oxygen therapy.

Hypercapnia during COPD exacerbations may be managed initially with the use of respiratory stimulants. The most commonly used is doxapram, which acts centrally to increase respiratory drive and respiratory muscle activity. The effect is probably only appreciable for 24 to 48 hours, the main factor limiting its use being side-effects which can lead to agitation and are often not tolerated by the patient. There are only a few studies of the clinical efficacy of doxapram and short-term investigations suggest that improvements in acidosis and arterial carbon dioxide tension can be attained.[51] A small study comparing doxapram with noninvasive ventilation (NIPPV) in acute exacerbations of COPD, suggested that NIPPV was superior with regard to correction of blood gases during the initial treatment phase.[52] Increases in pulmonary artery pressure during acute exacerbations of COPD can result in right-sided cardiac dysfunction and development of peripheral edema. Diuretic therapy may thus be necessary if there is edema or a rise in jugular venous pressure.

Ventilatory support

Noninvasive ventilation

The introduction of noninvasive positive pressure ventilation (NIPPV) using nasal or face masks, has had a major impact on the management of acute exacerbations and has enabled acidosis to be corrected at an early stage. Studies have shown that NIPPV can produce improvements in pH relatively rapidly, at 1 hour after instituting ventilation.[53,54] This will allow time for other conventional therapy to work, such as oxygen therapy, bronchodilators, steroids and antibiotics and thus reverse the progression of respiratory failure and reduce mortality. With NIPPV, there are improvements in minute ventilation, reductions in respiratory rate and in transdiaphragmatic activity. Thus NIPPV can improve gas exchange and allows respiratory muscle rest in respiratory failure.

With the use of NIPPV patient comfort is improved. There is also no requirement for sedation with preservation of speech and swallowing. The technique can be applied in a general ward, though a high dependency area is preferable and intensive care is unnecessary. Patient cooperation is important in application of NIPPV. The main advantage of the use of NIPPV is avoidance of tracheal intubation and the ability to offer ventilatory support to patients with respiratory failure due to severe

COPD, who would be considered unsuitable for intubation. A lower incidence of nosocomial penumonia has also been reported with the use of NIPPV compared with conventional intubation and ventilation.

Following a number of uncontrolled studies, randomized controlled trials have shown benefit of NIPPV in acute COPD exacerbations. A UK study showed that with the use of NIPPV in exacerbations of respiratory failure, earlier correction of pH can be achieved, together with reduction in breathlessness over the initial 3 days of ventilation, compared with a control standard therapy group.[53] A study from the USA showed a significant reduction in intubation rates with NIPPV from 67% in a group receiving conventional therapy to 9% in the NIPPV group.[55] A third study showed convincingly that in patients with exacerbations of respiratory failure, the use of NIPPV with pressure support ventilation, reduces the need for intubation and mortality was significantly reduced from 29% in the conventionally treated group to 9% in the NIPPV group.[54] Complications, which were specifically associated with the use of mechanical ventilation, were also reduced. The difference in mortality disappeared after adjustment for intubation, suggesting that the benefits with NIPPV are due to fewer patients requiring intubation. This was also the first study to show that hospital length of stay can be reduced with use of NIPPV. A recent study showed that NIPPV can be applied on general wards, though patients with more severe acidosis had a worse outcome.[56]

These studies have treated patients where the pH was below 7.35, rather than just below 7.26, when the prognosis of COPD worsens. A number of these patients may have improved without NIPPV, though it seems that the major effect of NIPPV is the earlier correction of acidosis and thus avoidance of tracheal intubation, with all its associated complications. Studies have shown that NIPPV can be successfully implemented in up to 80% of cases.[57,58] NIPPV is less successful in patients who have worse blood gases at baseline before ventilation, are underweight, have a higher incidence of pneumonia, have a greater level of neurological deterioration and where compliance with the ventilation is poor.[57] Moretti and colleagues[59] have recently shown that "late treatment failure" (after an initial 48 hours of therapy with NIPPV) is up to 20% and that patients with late failure were more likely to have severe functional and clinical disease with more complications at the time of admission. Identification of patients with a potentially poor outcome is important as delay in intubation can have serious consequences for the patient.

Indications for invasive ventilation

If NIPPV fails, or is unavailable in the hospital, invasive ventilation may be required in the presence of increasing acidosis (Chapter 58). It may be considered in any patient when the pH falls below 7.26. Decisions to ventilate these patients may be difficult, though with improved modes of invasive ventilatory support and better weaning techniques, the outlook for the COPD patient is better.

Patients will be suitable for tracheal intubation if this is the first presentation of COPD exacerbation or respiratory failure, or there is a treatable cause of respiratory failure, such as pneumonia. Information will be required on the past history and quality of life, especially the ability to perform daily activities. Patients with severe disabling and progressive COPD may be less suitable, but it is important that adequate and appropriate therapy has been used in these patients, with documented disease progression. The patient's wishes and those of any close relatives should be considered in any decision to institute or withhold life-supporting therapy.

Supported discharge

Many hospital admissions are related to exacerbations of COPD and thus reductions of admissions, especially during the winter months when they are most frequent, is particularly desirable. Over the last few years, a number of different models of supported discharge have been developed and some evaluated.[60–62] Patients have been discharged early with an appropriate package of care organized, including domiciliary visits made to these patients after discharge by trained respiratory nurses.

Cotton and colleagues[61] randomized patients either to discharge on the next day or to usual management and found that there were no differences in mortality or re-admission rates between the two groups. There was a reduction in hospital stay from a mean of 6.1 days to 3.2 days. In another larger study by Skwarska and colleagues,[62] patients were randomized either to discharge on the day of assessment or to conventional management. Again there were no differences in readmission rates, no differences in visits to primary care physicians, and health status measured 8 weeks after discharge was similar in the two groups. The authors also demonstrated that there were significant cost savings of around 50% for the home support group, compared with the admitted group. However, other considerations need to be taken into account in organizing an assisted discharge service, in that resources have to be released for the nurses to follow the patients and the benefits may be seasonal, as COPD admissions are a particular problem in the winter months. Further work is required on the different models of supported discharge available and the cost-effectiveness of these programs.

Prevention of COPD exacerbation

There has been relatively little attention paid to aspects of prevention of exacerbations in patients with COPD. As respiratory tract infections are common factors in causing exacerbation, influenza and pneumococcal vaccinations are recommended for all patients with significant COPD. A study that reviewed the outcome of influenza vaccination in a cohort of elderly patients with chronic lung disease found that influenza vaccination is associated with significant health benefits with fewer outpatient visits, fewer hospitalizations and a reduced mortality.[63] Long-term antibiotic therapy has been used in patients with very frequent exacerbations,

though there is little evidence of effectiveness. Recently there has been a report of the effects of an immunostimulatory agent in patients with COPD exacerbations, with reduction in severe complications and hospital admissions in the actively treated group.[64] Further studies on the effects of these agents in the prevention of COPD exacerbation are required.

In the recent ISOLDE study of long-term inhaled steroids in patients with moderate to severe COPD, a small reduction in exacerbation frequency was demonstrated. However, the overall exacerbation frequency was relatively low in that study and this was probably due to a retrospective assessment of exacerbation.[65] Another earlier study suggested that the severity of exacerbations may be reduced with inhaled steroid therapy.[66] An observational study showed that exacerbations were increased following withdrawal of inhaled steroids, though this study was not placebo-controlled.[67] Two recent studies have also shown that small reductions in exacerbations can be achieved with bronchodilator therapy, though both studies involved relatively short periods of therapy at 12 weeks.[68,69] Mahler and colleagues[68] found that the time to the first exacerbation was longer with therapy with the long-acting beta-agonist, salmeterol, though the overall number of exacerbations during the study was relatively small. Van Noord and colleagues[69] in a similar study suggested that the combination of salmeterol and ipratropium was most effective in reduction of exacerbation. Longer-term studies of the effects of bronchodilators on COPD exacerbation are now required.

PATIENT EDUCATION

There is a need for increased patient education about detecting and treating exacerbations early in the natural history (Chapter 69). More specific written treatment plans for COPD patients at risk may be useful, as are produced for asthmatics, though such an approach requires formal testing. Following an exacerbation, the COPD patient's condition should be reviewed and attention given to risk factors and compliance with therapy. Strategies to reduce exacerbation frequency need to be urgently developed. We will then be in a better position to reduce significantly the morbidity associated with COPD exacerbation and improve the health-related quality of life of our patients in this disabling condition.

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