

Management of Exacerbation of COPD

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Abstract

COPD is a progressive debilitating lung condition the clinical course of which is punctuated by acute severe increases in symptoms (exacerbations). These can be life threatening and are a considerable cause of morbidity and mortality as well as frequently requiring hospital admission. The aims of treatment are to prevent attacks through vaccination, smoking cessation, appropriate medication, the provision of pulmonary rehabilitation and also patient education. During an attack treatment should be provided in the most suitable place for the individual (home or hospital) and consists of an accurate diagnosis, clinical assessment and the provision of bronchodilators, corticosteroids and antibiotics where appropriate. More severe attacks necessitating hospital assessment and admission may require ventilatory support and even intensive care. Where possible patients should be involved in decision making, particularly with regard to treatment and a possible ceiling of care.

Keywords

COPD, Exacerbation, bronchodilators, antibiotics, corticosteroids.

Introduction

COPD (Chronic Obstructive Pulmonary Disease) is a chronic respiratory illness and has been defined by NICE as “airflow obstruction that is progressive, not fully reversible, remains predominantly unchanged over several months and predominantly caused by smoking”.¹

COPD is characterised by episodic exacerbations and these episodes:

- Have a deleterious effect on patient's condition,
- Accelerate disease progression¹
- Contribute to the burden of healthcare costs²

Exacerbations of COPD are one of the most common conditions that require hospital admission and optimal management is crucial to minimise the impact on disease progression and subsequent morbidity and mortality.

Epidemiology and Mortality

Exacerbations of COPD account for up to 10% of medical admissions in the UK, around 100,000

each year.³ The average hospital stay for such admissions is over a week. Thus the cost to the health service of each exacerbation is considerable. Moreover the mortality and morbidity associated with attacks are significant for each patient. There is a clear decline in quality of life with a mortality rate of up to greater than 10%.⁴

Patients who are experiencing an increased frequency of exacerbation have an increased loss of lung function, reduced quality of life and a restricted level of activity. An inexorable vicious cycle of decline can occur.

Furthermore inflammation is increasingly recognised as an important feature of COPD. Increased levels of inflammatory cytokines have been found in sputum, blood and broncho-alveolar lavage during exacerbations.⁵ Thus exacerbations may be the result in part of the increased inflammation and also themselves further increase inflammation.⁶

Exacerbations of COPD

Exacerbations of COPD are defined by the Global initiative for Obstructive Lung Disease (GOLD) as *an event in the natural course of the disease characterised by change in patient's baseline breathlessness, cough and/or sputum that is beyond normal day to day variations.*⁷ An exacerbation is acute in onset, symptoms occur and increase within a few hours, and may need an increase in medication.

Commonly reported symptoms include worsening breathlessness, cough, increased sputum and change in sputum colour.⁸ These changes will usually necessitate changes in medication.

Exacerbations are important events in the natural course of COPD. Patients with severe COPD are more prone to severe exacerbations and are likely to need hospital admissions.

Risk factors for exacerbation include⁹

- Low pre-treatment FEV1
- Increased bronchodilator/corticosteroid use
- Previous exacerbations (>3 in last 2 years.)
- Presence of co-morbid conditions such as congestive cardiac failure, ischaemic heart disease or renal disease.

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Management of Exacerbation of COPD

Causes of Exacerbations

Exacerbations are most often caused by viral or bacterial infections. However no definite cause is found in a majority of cases.¹⁰

1. Bacteria

Bronchoalveolar sampling of distal airways reveal pathogenic bacteria in up to 50% of cases.⁹ Common bacteria include

- *Haemophilus influenzae*
- *Streptococcus pneumoniae*
- *Moraxella catarrhalis*
- *Haemophilus parainfluenzae*
- *Pseudomonas aeruginosa*

The sputum of patients with COPD often contains bacteria and during an exacerbation the bacterial count increases by a factor of 2 or 3 logs.⁵

2. Viruses

50% of exacerbations are associated with upper respiratory tract virus infections.¹¹ Virus associated symptoms last longer and lead to more severe exacerbations. Patients with concomitant bacterial and viral infections have more severe symptoms. The common viruses implicated are

- Rhinovirus (most often)
- Influenza virus
- Para influenza virus
- Respiratory syncytial virus
- Corona virus

3. Non-infective causes

These may include:

- Airborne pollutants such as ozone, sulphur and nitrogen dioxide and particulates (PM10). Increased levels of these compounds and particles are found in cities especially in areas of high traffic pollution.^{9,12}
- Low temperature and temperature changes.¹³

Management of exacerbations of COPD

Diagnosis

Diagnosis of an exacerbation is based on an accurate history and clinical assessment. The key symptoms are

a history of increased breathlessness, wheezing, chest tightness, increased cough, increased sputum volume and/or change in sputum colour. If the diagnosis of COPD is well established and the patient has had frequent previous admissions, the history may be clearcut. Information on the patient's previous lung function, old X-ray and blood gas results should be sought to build up a picture of the severity of the current presentation. It is also important to consider alternative explanations for breathlessness, such as heart failure, pneumothorax and pulmonary embolism. In some cases there may be doubt about the patient's underlying diagnosis of COPD, or the patient may not have undergone formal assessment of lung function in the past. Sometimes uncertainty arises as to whether the patient has COPD or asthma: although there are some similarities in the initial management of these conditions, it is important to make the distinction as this will influence treatment choices if the patient fails to respond to therapy. Table 1 shows the main history and symptom differences between COPD and asthma.

The history should also take careful account of co-morbidities and also the patient's social circumstances, which will have an important influence on their need for and duration of hospital stay.

Important physical signs include tachypnoea, tachycardia, fever, hypoxia, and confusion. Formal assessment of mental state using an Abbreviated Mental Test Score should always be considered if the patient appears confused.

Initial Assessment

When an exacerbation of COPD is suspected, immediate assessment should include:

- Pulse oximetry to measure O₂ saturation and need for supplemental O₂
- Arterial blood gas measurement, with record of inspired O₂ concentration
- Electrocardiogram (ECG) to diagnose arrhythmias, ischaemia or right heart hypertrophy
- Chest x-ray (CXR) to identify alternative diagnoses and look for consolidation or pneumothorax
- Full Blood Count (to look for polycythaemia or neutrophilia)
- Urea and electrolytes (potassium excretion is increased by beta agonists and corticosteroids and hypokalaemia will increase the risk of arrhythmia)
- Theophylline level should be measured if patient is taking xanthines

	COPD	Asthma
Smoker or ex-smoker	Nearly all	Variable
Symptoms under 45	Uncommon	Often
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Spirometry	Always abnormal	May be normal
Serial PEF	Minimal variation	Day-to-day and diurnal variation
Reversibility	Usually <15%	Usually >15%

Table 1. Main differences between COPD and Asthma from history and initial clinical examination

Management of Exacerbation of COPD

- Sputum microscopy and culture when purulent
 - Blood culture if patient pyrexial.
- Addition of a long-acting bronchodilator.
 - Provision of a nebuliser if required

Key pharmacological interventions:

The approach to drug therapy in exacerbation of COPD can be summarised in using the ABC approach:

- A: Antibiotics (where appropriate),
- B: maximise Bronchodilation,
- C: Corticosteroid therapy.

Antibiotics⁸

- Should be initiated in patients with altered sputum characteristics
- Choice should be based on local resistance pattern and microbiology advice
- Choices include: amoxicillin, macrolides, tetracycline
- If patient has failed prior antibiotic therapy, consider amoxycillin/clavunate or respiratory fluoroquinolones such as moxifloxacin

Antibiotics should be prescribed according to local guidance and take into account local patterns of resistance and susceptibility. Penicillin resistance may be found in *Haemophilus influenzae*, the most commonly cultured organism in COPD exacerbations.

Antibiotics are generally overprescribed and should be reserved for those with severe exacerbations and the sputum characteristics as outlined above. It must be remembered that COPD patients are often in a weakened physical and nutritional state and thus antibiotic related complications such as *C.difficile* can be extremely hazardous.

Bronchodilators

- Increase frequency of β_2 agonists and/or ipratropium (with spacer if needed)

Corticosteroids

Steroids are the mainstay of the management of exacerbations of COPD. They should be given to all patients as they shorten the duration of each exacerbation and also increase the time to the next.^{14,15} A short course of 5 days may be sufficient.

- Prednisolone 30–40mg for 5–14 days depending upon clinical picture.
- Consider adding inhaled corticosteroid

Patients being discharged from hospital should be given clear instruction as to how to reduce their steroids. They may receive a relatively short course of therapy (<14 days) that can be stopped rapidly. However if they are on long term steroids or have had repeated courses a dose reduction will have to occur over several days or weeks. There is some evidence that a reduction in steroids following exacerbation can lead to a re-exacerbation.¹⁶ This may be difficult to avoid and an evidence based guidance is lacking.¹⁷

Other Drug therapies

Mucolytic medications may be used in exacerbations of COPD. Carbocysteine (Mucodyne), mecysteine (Visclair) and erdosteine (Erdotin) are all available and break up sputum and reduce its viscosity. There is some evidence that they reduce attack duration and time to next exacerbation.¹⁴

Home or Hospital Treatment?

Over recent years there has been considerable interest in home management of COPD exacerbations.^{18,19} Selection of patients for home management, requires careful evaluation (see Table 2) and may depend on local service provision. The facility to undertake assessment of

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 on LTOT	No	Yes
Social circumstances	Good	Living alone/not coping
Acute confusion	No	Yes
Rapid rate of onset	No	Yes
Significant comorbidities		
(cardiac disease and diabetes)	No	Yes
Sao ₂ <90%	No	Yes
New changes on CXR	No	Yes
Arterial pH	> 7.35	< 7.35
Arterial Pao ₂	> 7kPa	< 7kPa.

Table 2. Factors in determining appropriate place of treatment (adapted from BTS/NICE guidelines on management of COPD)¹⁵ (ref)

Management of Exacerbation of COPD

the patient in an 'ambulatory' hospital setting, may prove helpful in reducing the impact on in-patient beds. Some hospitals have developed specialist ambulatory respiratory units to meet this need, while in other cases such units are centred around the Acute Medical Unit.²⁰ It is important that staff working in such units have the expertise to identify and manage patients with exacerbation of COPD, and develop close links with community teams.

Home management of exacerbations of COPD combine both the medical input and prescription of medications with benefits of multi-professional working, self management and education.

The key components of home management that are distinct from hospital based care can be summarised as follows:

Patient education/support

This is a key component of home management and should include:

- Teaching of inhaler technique, including use of spacer devices
- Education in how to recognise early symptoms of deterioration
- Strategies to deal with worsening symptoms, including availability of telephone support if required.
- Psychological support for the patient and their family.

Patients being managed at home should have regular and frequent clinical reviews by trained clinical staff. This may include general practitioners, community matrons, hospital outreach teams and rapid response teams, depending on local resources.

Hospital Management

Treatment in the hospital setting may be necessary for patients with more severe exacerbations of COPD. Indications for in-patient treatment are summarised in Table 1.

In-patient treatment

As well as the core drug therapies outlined above the treatment of patients requiring hospital admission can be summarised as follows:

1. Oxygen Therapy

Controlled oxygen therapy is mandatory in the management of exacerbations of COPD. Oxygen should be prescribed where a patient is significantly hypoxic. The goal of oxygen therapy should be to maintain oxygen saturation $>90\%$ while avoiding CO_2 retention and respiratory acidosis. Arterial blood gas sampling should be undertaken 30–60 minutes after initiating oxygen therapy to ensure that this goal has been achieved.

A known concentration of oxygen should be given. This is most often achieved via a venturi mask which offers precise control of oxygen delivery. Nasal cannulae

can also be used but lead to less precise delivered oxygen concentrations. An inspired concentration of 24 or 28% is the usual starting concentration, although this may need to be varied in the light of arterial blood gas results. Nasal cannulae are often more comfortable for the patient to tolerate, and have the added advantage of allowing the patient to eat and drink while continuing oxygen treatment. If the mode of delivery is changed from a mask to nasal cannulae, repeat arterial blood gas measurement should be undertaken to confirm that pO_2 and pCO_2 are maintained.

Non-Invasive Ventilation (NIV)

NIV is the provision of bi-level (inspiratory and expiratory) ventilatory support without the need for intubation or tracheostomy. This is usually achieved with the use of either a face mask or nasal mask.

This is the treatment of choice in exacerbations of COPD when after optimum medical therapy and controlled O_2 therapy patients are not clinically improving. Blood gases should be checked and if the patient is acidotic and hypercapnoeic then NIV should be considered (pH of <7.35 and PaCO_2 of $>6\text{--}8\text{ kPa}$).¹⁴

There are several randomised controlled trials which show that NIV improves respiratory acidosis, decreases respiratory rate, breathlessness and length of hospital stay.^{21–23} Intubation rates are also reduced. NIV also has been shown to be a very effective strategy to use in the weaning of patients from invasive ventilation. This is both clinically and cost effective and shortens intensive care stays as well as improving survival rates.

NIV should be provided by dedicated, adequately trained staff and in a specialised setting. Before commencing NIV a clear plan should be made about what to do in the event of deterioration and the ceiling of therapy agreed. Contraindications to NIV include respiratory arrest, cardiovascular instability, impaired mental status, uncooperative patient and facial trauma or surgery.

Invasive Ventilation

Invasive ventilation should be provided in COPD exacerbations when necessary.

Indications include NIV failure, severe acidosis (pH <7.25 and PCO_2 $>8\text{ kPa}$), life threatening hypoxaemia and complications such as pneumonia and sepsis. The use of invasive ventilation is guided by functional status, BMI, comorbidities, previous ITU admissions, FEV1, age, requirement for O_2 when stable and patient's wishes. Neither age nor FEV1 should be used in isolation to make decisions on management. Patients may have expressed their views on future management at previous meetings or in advanced directives. These should be respected if available.

There is a prognostic pessimism in UK intensive care units which has been challenged following the publication of the CAOS study.²⁴ The outcome of invasively ventilated COPD patients are no worse and may be better than other groups of patients admitted to ITU's. Clearly some require

Management of Exacerbation of COPD

prolonged periods of ventilation, tracheostomy, weaning protocols, NIV and even long term domiciliary support. These interventions have been shown to be effective and worthwhile and it is thought that some patients are being denied ITU care unreasonably.^{24,25}

Other Measures

These include appropriate fluid management, DVT prophylaxis, nutrition and physiotherapy to help clear sputum and begin the rehabilitation process.

Monitoring Recovery

Regular clinical assessment including that of symptoms and observation of a patient's functional capacity is necessary to ascertain improvement. Oxygen saturation should be satisfactory on pulse oximetry along with improved and stable ABGs.

Discharge Criteria for Patients with Exacerbation

Prior to discharge patients should be established on their normal maintenance bronchodilator therapy. It is helpful to measure spirometry in hospital before discharge in all patients. Patients should be clinically stable for 24 hours and ambulatory patients should have reasonable mobility. Patients (or home carers) should fully understand the correct use of medications including oxygen. Prior to discharge the patient, family and physician should be confident that he or she can manage successfully. Arrangement for follow up and home care should also be made. Opportunities for prevention of future exacerbations should be reviewed prior to discharge with emphasis on smoking cessation, vaccination (influenza and pneumococcal), knowledge of therapy including inhaler technique and how to recognise symptoms of exacerbations.¹⁴

Hospital at Home (HaH)/Early Supported Discharge Scheme

These treatment schemes aim to bridge the interface between hospital and community care. They involve cooperation between hospital doctors, GPs, nurses, physiotherapists and other healthcare professionals. Hospital at home includes active treatment provided by healthcare professionals at home for a condition that would otherwise require inpatient care. Early supported discharge (ESD) schemes include a short initial hospital admission for assessment and the initiation of treatment followed by home care.

This approach to management has been the subject of a Cochrane review and many trials.^{26–33}

NICE have recommended HaH and ESD as a safe and effective alternative way of managing exacerbations.¹⁴ The multiprofessional team involved should be experienced in managing patients with COPD.

There are currently insufficient data to make firm recommendations but patient selection should depend on available resources and absence of factors associated with a worse prognosis. Patient preference should also be considered. The lead clinician should be a consultant respiratory physician and the homecare team should be lead by an appropriately trained healthcare professional.

Chest X-ray and pulse oximetry should be performed on all patients considered for home treatment. Ideally, arterial blood gases should be measured with the patient breathing room air. After suitability is confirmed by assessment, a treatment package is prescribed, comprising antibiotics, steroids, nebulised bronchodilators and oxygen if necessary. Regular assessment for improvement in the patient's condition is carried out with home visits and weekly team meetings. Patients who fail to improve should be referred for hospital treatment, although some may elect for home based symptom control and the involvement of community palliative care teams for terminal care.

Outpatient Follow Up

An appointment should be made for all patients discharged from hospital 4–6 weeks after exacerbation onset.¹⁴ This is an opportunity to check inhaler technique, provide help with smoking cessation and review all medications. There is also a need to discuss future treatment options and patient choice in how they would like to receive care in the future. Spirometry can be checked and patients educated in what to look out for in future exacerbations and where to get prompt definitive help if it occurs again.

Future Exacerbation Avoidance

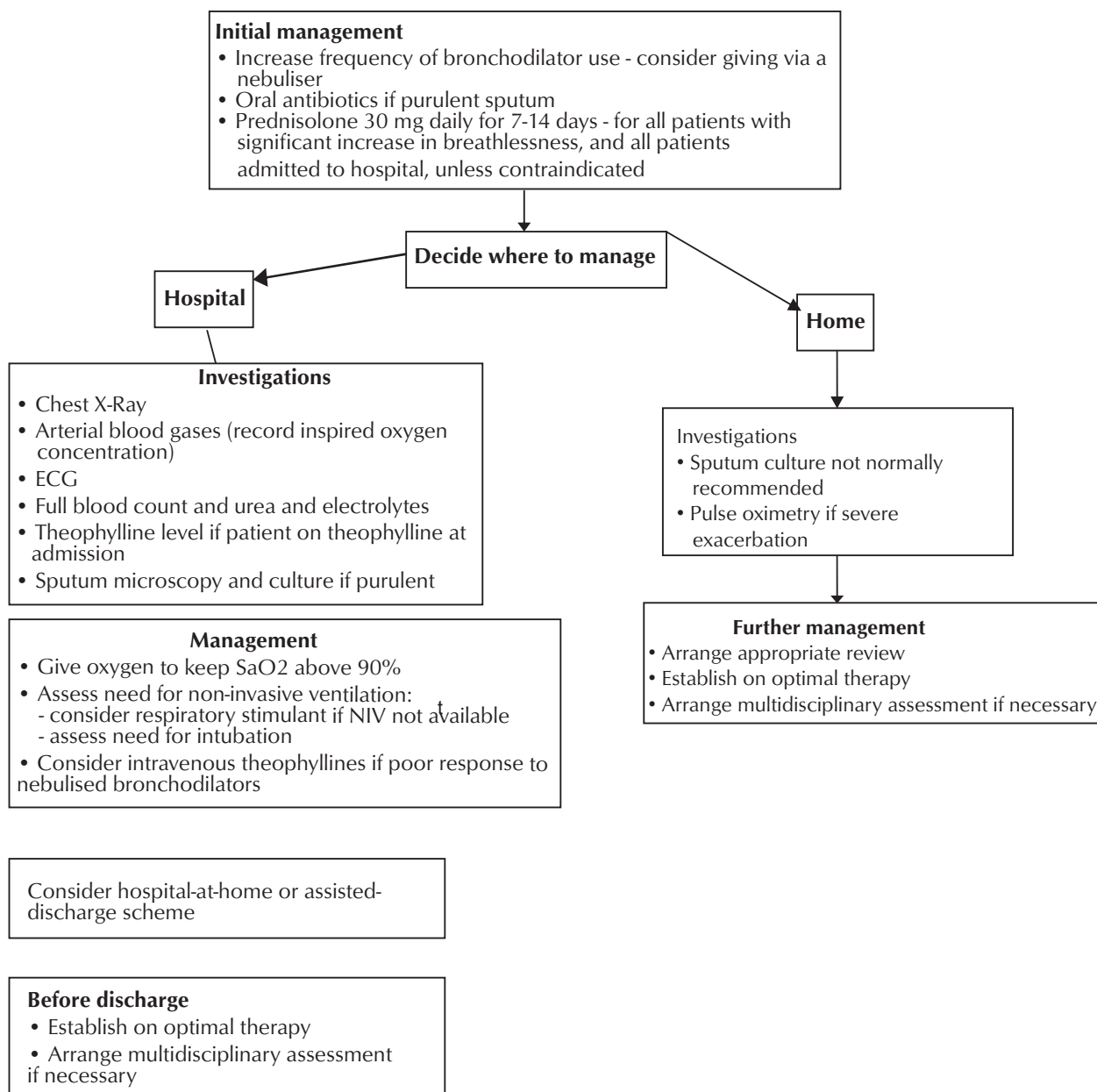
The provision of appropriate follow-up care for COPD after an exacerbation is vital. Patients should be provided with the medication, advice and ongoing support that will help them to reduce the likelihood of further attacks. The most effective approach includes both drug and non-drug related interventions.

Key Points:

1. Patients with exacerbations of COPD can be managed at home or in hospital
2. Clinically assess severity and decide upon best place for management.
3. Patients should receive bronchodilators, oral corticosteroid and often require antibiotic.
4. Monitor closely for deterioration and take patients wishes into account when deciding upon need for escalated care.
5. Non-invasive ventilators are often successful in the treatment of severe cases who are found on blood gas testing to be in acidotic, hyperapnoeic respiratory failure.
6. After exacerbation patients should be taught to manage their own disease, to watch for exacerbations and inhaler technique should be checked.
7. Drug therapy should be optimised in order to reduce future exacerbation rate.

Management of Exacerbation of COPD

Algorithm adapted from the NICE/BST guidance in the management of COPD¹⁴



Inhaled medications including corticosteroids and long acting bronchodilators are the mainstay of current therapy and have been shown to reduce exacerbation rate.^{34,35} Influenza and pneumococcal vaccination are also effective in this patient group.³⁶

Pulmonary rehabilitation should be offered to all patients after an exacerbation as this has been shown to be effective at reducing exacerbations and improving quality of life in a cost-effective manner.¹⁰

References

- 1 Silverman EK. Exacerbations in chronic obstructive pulmonary disease: do they contribute to disease progression? *Proc Am Thorac Soc* 2007; **4**(8): 586–590.
- 2 Schermer TR, Saris CG, van den Bosch WJ, *et al.* Exacerbations and associated healthcare cost in patients with COPD in general practice. *Monaldi Arch Chest Dis* 2006; **65**(3): 133–140.
- 3 Price LC, Lowe D, Hosker HS, *et al.* UK National COPD Audit 2003: Impact of hospital resources and organisation of care on patient outcome following admission for acute COPD exacerbation. *Thorax* 2006; **61**(10): 837–842.
- 4 O'Reilly JF, Williams AE, Rice L. Health status impairment and costs associated with COPD exacerbation managed in hospital. *Int J Clin Pract* 2007; **61**(7): 1112–1120.

Management of Exacerbation of COPD

- 5 Hurst JR, Wedzicha JA. The biology of a chronic obstructive pulmonary disease exacerbation. *Clin Chest Med* 2007; **28**(3): 525–36, v.
- 6 Hurst JR, Perera WR, Wilkinson TM, *et al.* Systemic and upper and lower airway inflammation at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; **173**(1): 71–78.
- 7 Rabe KF, Hurd S, Anzueto A, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; **176**(6): 532–555.
- 8 Anthonisen NR, Manfreda J, Warren CP, *et al.* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; **106**(2): 196–204.
- 9 Sapely E, Stockley RA. COPD exacerbations . 2: aetiology. *Thorax* 2006; **61**(3): 250–258.
- 10 Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet* 2007; **370**(9589): 786–796.
- 11 Wedzicha JA. Role of viruses in exacerbations of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2004; **1**(2): 115–120.
- 12 Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. *Eur Respir J* 2007; **29**(6): 1224–1238.
- 13 Donaldson GC, Seemungal T, Jeffries DJ, *et al.* Effect of temperature on lung function and symptoms in chronic obstructive pulmonary disease. *Eur Respir J* 1999; **13**(4): 844–849.
- 14 British Thoracic Society/NICE Guidelines for Chronic Obstructive Pulmonary Disease. 1-2-2004. Ref Type: Internet Communication
- 15 Halpin D. NICE guidance for COPD. *Thorax* 2004; **59**(3): 181–182.
- 16 van der Valk P, Monninkhof E, van der Palen J, *et al.* Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. *Am J Respir Crit Care Med* 2002; **166**(10): 1358–1363.
- 17 Aaron SD, Vandemheen KL, Hebert P, *et al.* Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med* 2003; **348**(26): 2618–2625.
- 18 Chetty M, MacKenzie M, Douglas G, *et al.* Immediate and early discharge for patients with exacerbations of chronic obstructive pulmonary disease: is there a role in “real life”? *Int J Chron Obstruct Pulmon Dis* 2006; **1**(4): 401–407.
- 19 Cotton MM, Bucknall CE, Dagg KD, *et al.* Early discharge for patients with exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Thorax* 2000; **55**(11): 902–906.
- 20 Ram FS, Wedzicha JA, Wright J, *et al.* Hospital at home for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2003; **(4)**: CD003573.
- 21 Brochard L, Mancebo J, Elliott MW. Noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2002; **19**(4): 712–721.
- 22 Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet* 2000; **355**(9219): 1931–1935.
- 23 Bott J, Carroll MP, Conway JH, *et al.* Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993; **341**(8860): 1555–1557.
- 24 Wildman MJ, Sanderson C, Groves J, *et al.* Implications of prognostic pessimism in patients with chronic obstructive pulmonary disease (COPD) or asthma admitted to intensive care in the UK within the COPD and asthma outcome study (CAOS): multicentre observational cohort study. *BMJ* 2007; **335**(7630): 1132.
- 25 Tuggey JM, Plant PK, Elliott MW. Domiciliary non-invasive ventilation for recurrent acidotic exacerbations of COPD: an economic analysis. *Thorax* 2003; **58**(10): 867–871.
- 26 Intermediate care--Hospital-at-Home in chronic obstructive pulmonary disease: British Thoracic Society guideline *Thorax* 2007; **62**(3): 200–210.
- 27 Shepperd S, Iliffe S. Hospital at home versus in-patient hospital care. *Cochrane Database Syst Rev* 2005; **(3)**: CD000356.
- 28 Quantrill SJ, Lowe D, Hosker HS, *et al.* Survey of early discharge schemes from the 2003 UK National COPD Audit. *Respir Med* 2007; **101**(5): 1026–1031.
- 29 Davies L, Wilkinson M, Bonner S, *et al.* “Hospital at home” versus hospital care in patients with exacerbations of chronic obstructive pulmonary disease: prospective randomised controlled trial. *BMJ* 2000; **321**(7271): 1265–1268.
- 30 Skwarska E, Cohen G, Skwarski KM, *et al.* Randomized controlled trial of supported discharge in patients with exacerbations of chronic obstructive pulmonary disease. *Thorax* 2000; **55**(11): 907–912.
- 31 Cotton MM, Bucknall CE, Dagg KD, *et al.* Early discharge for patients with exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Thorax* 2000; **55**(11): 902–906.
- 32 Ram FS, Wedzicha JA, Wright J, *et al.* Hospital at home for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2003; **(4)**: CD003573.
- 33 Gravit JH, Al Rawas OA, Cotton MM, *et al.* Home treatment of exacerbations of chronic obstructive pulmonary disease by an acute respiratory assessment service. *Lancet* 1998; **351**(9119): 1853–1855.
- 34 Nannini LJ, Cates CJ, Lasserson TJ, *et al.* Combined corticosteroid and long-acting beta-agonist in one inhaler versus inhaled steroids for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007; **(4)**: CD006826.
- 35 Nannini L, Cates CJ, Lasserson TJ, *et al.* Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007; **(4)**: CD003794.
- 36 Mallia P, Johnston SL. Influenza infection and COPD. *Int J Chron Obstruct Pulmon Dis* 2007; **2**(1): 55–64.
- 37 Burge PS. Prevention of exacerbations: how are we doing and can we do better? *Proc Am Thorac Soc* 2006; **3**(3): 257–261.