Exacerbation of Chronic Obstructive Pulmonary Disease

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SUMMARY

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are important events in COPD patients and place a large burden on healthcare resources. COPD patients with frequent exacerbations have accelerated decline in lung function, poorer health status and are at higher risk of mortality. The mainstay of treatment includes increasing short acting bronchodilator therapy and systemic glucocorticosteroids with or without antibiotics. Non invasive ventilation is indicated in those with respiratory failure with acidosis or hypercapnia. Preventive strategies to reduce exacerbations include smoking cessation, immunisation against influenza and *S. pneumonia*, chronic maintenance inhaled pharmacotherapy, pulmonary rehabilitation and self management education.

KEY WORDS:
Chronic obstructive pulmonary disease, Acute exacerbations, Management

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality throughout the world and the incidence will continue to rise especially in the developing countries as the prevalence of smoking increases. By 2020 COPD is expected to be the 3rd commonest cause of death and ranked 5th as the cause of loss of disability adjusted life years (DALYs) according to the baseline projections made in the Global Burden of Disease Study[1]. Based on model projections the prevalence of moderate to severe COPD in Malaysia is 4.7% which translates to 448,000 cases[2].

COPD is defined as "A preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases"[3].

COPD remains a disease which is often neglected and many doctors feel little can be done or indeed need to be done for the COPD patient. The disease is grossly undiagnosed as the availability of spirometry in Malaysia is limited to the major hospitals. Doctors may also miss the opportunity to make the diagnosis when the smoking individual with a "smokers cough" presents with other illnesses such as chest infection. Patients with mild COPD may already have symptoms such as cough with sputum production and by making the diagnosis early, steps can be taken to prevent further accelerated decline in lung function which is the characteristic hallmark of the disease. Without intervention, patients typically seek medical care when the disease is advanced and they are already disabled.

Exacerbation of COPD is defined as *"An event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day to day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD"*[3].

The most common cause of exacerbations are infection of the tracheobronchial tree and air pollution, but in one third the cause of severe exacerbations cannot be identified[4]. The cause of an exacerbation may be multifactorial, so that viral infection or air pollution may amplify the existing inflammation of the airways and in turn may predispose to secondary bacterial infections.

Guidelines for the diagnosis, management and prevention of COPD have been published by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[3] and various regional bodies such as the American Thoracic Society and the European Respiratory Society (ATS/ERS)[5], the British Thoracic Society (BTS)[6] and the Canadian Thoracic Society [7]. The Malaysian Clinical Practice Guidelines (CPG) on Management of COPD was published in 1998[8] and is currently being updated to include many new developments in COPD. This article will address the impact, management and prevention of exacerbations based on the current available evidence.

Impact of Exacerbations

COPD exacerbation is one of the greatest burdens associated with this condition. It is associated with significant economic burden as exacerbations account for two thirds of the direct cost of COPD care[9]. Patients with frequent exacerbations have significantly worse exercise capacity and greater decline in health status compared than those with infrequent exacerbations[10,11]. Exacerbations are also associated with an accelerated rate of decline in lung function[12]. Patients with poorer lung function are more likely to have exacerbations as there is a positive correlation between the severity of lung function and the frequency of exacerbations [13].

Severe exacerbations have a direct and independent effect on mortality[14]. Mortality is increased when COPD exacerbation is associated with hospitalisation. Connors *et al*[15] showed that patients hospitalised with an acute exacerbation of severe

This article was accepted: 10 September 2009
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Table I: Indications for hospital assessment or admission for acute exacerbations of COPD

- Marked increase in intensity of symptoms such as sudden development of dyspnoea
- Underlying severe COPD
- Development of new physical signs e.g. cyanosis, peripheral oedema
- Failure of exacerbation to respond to initial medical management
- Significant co-morbidities
- Newly occurring arrhythmias
- Older age
- Insufficient home support

Table II: Indications for invasive mechanical ventilation

- Life threatening hypoxaemia despite maximal therapy (P_aO_2 < 5.3kPa, 40mmHg)
- Severe acidosis despite maximal treatment (pH < 7.25 and/or hypercapnia (P_aO_2 > 8 kPa, 60mmHg)
- Respiratory arrest
- Severe breathlessness with use of accessory muscles
- Respiratory rate > 35 breaths per minute
- Impaired mental status
- Inability to protect airways
- Haemodynamic instability (hypotension, shock)

Table III: Management of severe but not life threatening exacerbations of COPD in the emergency department or the hospital

- Assess severity of symptoms, blood gases, chest X-ray
- Administer controlled oxygen therapy- repeat arterial blood gas measurements after 30 minutes
- Bronchodilators
  Increase dose frequency
  Combine β_2-agonists and anticholinergics
  Use spacers or air-driven nebulisers
  Consider adding intravenous aminophylline, if needed
- Oral or intravenous glucocorticosteroids
- Antibiotics
  When signs of bacterial infection
- Consider non invasive mechanical ventilation if condition deteriorating
- At all times
  Monitor fluid balance and nutrition
  Consider subcutaneous heparin
  Identify and treat associated conditions (e.g. heart failure, arrhythmias)
  Closely monitor condition of the patient

COPD had an inpatient mortality of 11% and the 60 day, 180 days, 1 year and 2 year mortality was high at 20%, 33%, 43% and 49% respectively. This is comparable to myocardial infarction and the prognosis is poorer than many other cancers.

Management of Exacerbations

The aims of management in exacerbations of COPD are to relieve symptoms and airflow obstruction, maintaining adequate oxygenation, treat any co-morbid conditions that may contribute to respiratory deterioration or any precipitating factors such as infection.

Table IV: Discharge criteria for patients with exacerbations of COPD

- Inhaled β_2-agonist therapy is required no more frequently than every 4 hours
- If previously ambulatory, able to walk across room
- Able to eat and sleep without frequent awakening by dyspnoea.
- Clinically stable for 24 hours
- Oxygen saturation has been stable for 24 hours
- Able to use medications correctly
- Follow up arranged at hospital or clinic
- Patient, family and doctor are confident patient can manage successfully at home

Table V: Indications for long term oxygen therapy

- PaO_2 at or below 7.3 kPa (55mmHg) or SaO_2 at or below 88%
  OR
- PaO_2 between 7.3kPa (55mmHg) and 8.0 kPa (60mmHg), or SaO_2 of 88%, if there is evidence of pulmonary hypertension, peripheral oedema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%)

The majority of patients with acute exacerbations of COPD are treated in primary care. However, a minority of patients will require hospital admissions to treat the exacerbations. The GOLD guidelines[3] have suggested indicators for hospital assessment or admission for acute exacerbations of COPD (Table I).

Home Management

Bronchodilator therapy

The dosage and frequency of existing short acting β_2-agonists therapy should be increased, e.g. salbutamol 2-4 puffs every 3-4 hours. Short acting anticholinergic therapy (ipratropium bromide) may be added until the symptoms improved. If the inhalers are inadequate to relieve the acute symptoms, nebulisers can be given on as 'needed basis' for several days if a nebuliser is available e.g. short acting β_2-agonists (salbutamol 2.5mg or terbutaline 5mg) or combination of short acting β_2-agonists and short acting anticholinergics (combivent 2.5mls or duovent 4mls). There is evidence that the use of spacer device with metered dose inhaler has a similar effect as nebulised bronchodilators for exacerbations of COPD [16].

Glucocorticosteroids

Systemic glucocorticosteroids should be used in an acute exacerbation of COPD with significant increase in breathlessness as it has been shown to shorten recovery time, improve oxygenation and lung function and reduce treatment failure [17,18]. A dose of 30-40mg prednisolone per day for 7-10 days is appropriate for most patients. The beneficial short term effects of glucocorticosteroids should be balanced against the potential risk of short term and long term side effects in the individual patients as many are often elderly with associated co-morbid conditions.

Antibiotics

The use of antibiotics in exacerbations of COPD is discussed in the hospital management section.

Hospital Management

The initial action in treating a patient with an exacerbation of COPD in emergency department is to provide controlled oxygen therapy and assessing the patient to determine if the exacerbation is life threatening requiring admission to high dependency unit or ICU. Guidelines have suggested indications for invasive mechanical ventilation in patients admitted with severe acute exacerbations of COPD (Table II). Otherwise, the patient may be managed in the emergency department or general wards (Table III).

Controlled oxygen therapy

Oxygen is considered the cornerstone of hospital treatment for an acute exacerbation of COPD. The aim of oxygen therapy during an acute exacerbation of COPD is to correct or prevent life threatening hypoxaemia. The potential benefits of oxygen are reduction of pulmonary vasoconstriction, decrease in right heart strain and improvement of cardiac output and oxygen delivery to the vital organs. Oxygen therapy is given to maintain adequate oxygenation (PaO_2 > 8kPa, 60mmHg or saturations > 90%) without worsening hypercapnia.

Controlled oxygen therapy is given in the form of 24-28% oxygen via venturi mask in the first instance, delivering the required fraction of inspired oxygen and reducing the complications of inadequate oxygenation and/or hypercapnia. If venturi masks are not available or tolerated, nasal prongs with 1-2 litres oxygen are an alternative. Arterial blood gases should be checked 30-60 minutes later to ensure adequate oxygenation without CO_2 retention or acidosis.

Bronchodilator therapy

The relief of airflow obstruction by bronchodilator therapy is the major goal in the treatment of acute exacerbation of COPD. Short acting inhaled β_2-agonists are the preferred initial bronchodilator for the treatment of acute exacerbations of COPD [3,5]. It is usually given in the nebulised form although there is evidence that administration of short acting inhaled β_2-agonists via metered dose inhaler and spacer device has equal efficacy to nebulised treatment [16]. If there is no prompt response to these drugs or if the patient has a very severe exacerbation, short acting anticholinergic (ipratropium bromide) treatment is recommended, although the evidence concerning the combination of these two drugs is controversial. When prescribing nebulised therapy, the driving gas (air or oxygen) must be stipulated, as some COPD patients may have background chronic type 2 respiratory failure.

Despite the widespread use, the role of methylxanthines (theophylline or aminophylline), in the treatment of acute exacerbations of COPD remains controversial[19]. In severe exacerbations, intravenous methylxanthines can be considered with close monitoring if there is inadequate response to short acting inhaled β_2-agonists and anticholinergics. Patients not previously treated with theophylline can be given a loading dose of slow intravenous aminophylline 250-500 mg (5mg/kg) over at least 20 minutes with close monitoring followed by maintenance dose of 0.5mg/kg/hour.

Glucocorticosteroids

Oral or intravenous corticosteroids are effective treatment for acute exacerbations of COPD and are recommended as an addition to other forms of therapy in hospital management of exacerbations of all COPD patients in the absence of significant contraindications. The use of oral or intravenous corticosteroids improves lung function over the first 72 hours, shortens hospital stay and reduces treatment failure over the subsequent 30 days [17,18]. Additional studies are required to determine the optimal dose and duration of corticosteroid therapy during acute exacerbations of COPD but a dose of 30-40mg of oral prednisolone daily for 7-10 days appears to be safe and effective. A study has shown that nebulised corticosteroids may also be beneficial during acute exacerbations of COPD as an alternative to oral prednisolone in the treatment of non acidotic exacerbations of COPD [20]. Intravenous corticosteroids should be reserved for patients who are unable to take oral therapy or have potential malabsorption problems. Systemic corticosteroids should be discontinued after the acute episode as it is associated with significant side effects such as hyperglycaemia and osteoporosis.

Antibiotics

Primary bacterial infection is the commonest cause in the development of exacerbations of COPD or represents a secondary infection following an initial viral infection. However, bacteria are present in the cultured secretions of 30-40% of patients with chronic sputum expectoration and COPD even in the stable state [21]. Meta analysis indicates the benefits of using antibiotics during acute exacerbations of COPD, but no benefit is derived if used to prevent exacerbations [22]. There is a clear relationship between sputum purulence, bacterial isolation and increased bacterial load[23], therefore antibiotics should be given to patients with purulent sputum with one more cardinal symptoms of dyspnoea or increased sputum [24]. Patients with a severe exacerbation of COPD that requires mechanical ventilation should also be covered with antibiotics as it has been shown to reduce mortality, shortened ventilator days and hospital days compared to placebo[25]. Simple first line antibiotics should be used and the choice of antibiotics should depend on local antibiotic policy and the pattern of local pathogens. The common pathogens isolated in patients hospitalised for pneumonia in Malaysia are *Klebsiella pneumoniae, Streptococcus pneumoniae, Haemophilus influenza, Mycoplasma pneumoniae and Pseudomonas aeruginosa* [26].

Assisted Ventilation

Some patients may show deterioration despite aggressive pharmacological and controlled oxygen therapy. These patients will require some form of ventilator support during this phase to maintain oxygenation. Ventilatory support can be instituted non invasively via facial mask (NIV) or invasively via an endotracheal tube.

Non invasive ventilation (NIV)

Many studies have shown the benefits of NIV in acute COPD exacerbations with early correction of acidosis and respiratory rate, reducing the intubation rates and mortality compared to those on conventional therapy [27]. Complications associated with endotracheal intubation and mechanical ventilation such as nosocomial pneumonia and length of hospital stay were also reduced. Another advantage of NIV is that it can be applied outside the intensive care unit such as high dependency ward or in a general ward with experienced staff using NIV. Clinical practice guidelines for the use of NIV in acute exacerbations of COPD have been published [28,29]. Generally, patients admitted with an acute exacerbation of COPD with the following features should be considered for NIV:

- Respiratory distress with moderate or severe dyspnoea with use of accessory muscles
- pH < 7.35 or pCO_2 > 6kPa or 45mmHg
- Respiratory rate of >25 breaths per minute

NIV may not be appropriate for all patients and there are several contraindications such as the presence of respiratory arrest, haemodynamic instability, inability to protect airways, uncooperative patient and inability to clear secretions. Currently NIV is only available in some hospitals in Malaysia with specialist facilities such as ICU, HDU and wards with trained nurses to handle NIV.

Other therapies

There is no convincing evidence to support the routine use of pharmacological mucus clearance strategies in acute exacerbations of COPD [30]. Chest physiotherapy has no proven value during exacerbations unless a large amount of sputum is produced (>25mls per day) or there is mucus plugging with lobar atelectasis. Fluid balance and nutrition should be monitored. Diuretics are indicated if there is evidence of peripheral oedema or increased jugular venous pressure. Prophylactic subcutaneous heparin should be used in immobile patients and those with acute on chronic respiratory failure if there are no contraindications [31].

Hospital discharge and follow up

The median length of hospital stay for an exacerbation of COPD is 9 days (5-15 days) [15]. Patients should be clinically stable with acceptable oxygen saturation prior to discharge. Discharge criteria have been suggested by the GOLD guidelines (Table IV). Follow up clinic visit is recommended 4-6 weeks after discharge from hospital. If the patient remains hypoxemic on air (oxygen saturation <90%), supplemental oxygen therapy at this stage may be required and this should be reassessed at the first follow up clinical visit (4-6 weeks) and a decision is made on whether the patient requires long term oxygen therapy (Table V) with an oxygen concentrator. Long term oxygen therapy has been shown to improve survival in patients whom fit the criteria when used more than 15 hours per day [32].

Prevention of Exacerbations

In view of the significant impact of exacerbations on the patient and the healthcare system, efforts should also be directed in preventing exacerbations. Several risk factors for frequent exacerbations (>2 exacerbations/year) have been identified which includes increased age, severity of forced expiratory volume in one second (FEV1) impairment, chronic bronchial mucus hypersecretion, frequent exacerbations, daily cough and wheeze and persistent symptoms of chronic bronchitis [33,34].

Smoking cessation has been shown to reduce the rate of decline in lung function in patients with COPD and may reduce the risk of acute exacerbations of COPD [35]. Since tracheobronchial infection is the commonest cause of exacerbation of COPD, improving the immune system may reduce the rate of exacerbation. Although there is little data available in COPD patients per se, influenza vaccination have been shown to reduce pneumonia and cardiac hospitalisations in the elderly population. Since most COPD patients are elderly with cardiac co-morbidities, influenza vaccination should be given to most COPD patients. The use of pneumococcal vaccination is recommended in the guidelines since *Streptococcus pneumoniae* is one of the most frequently identified bacterial pathogens in COPD exacerbations [36-38].

Chronic maintenance pharmacotherapy has been shown to reduce the exacerbation rates of COPD. There is evidence that inhaled corticosteroid[13], long acting β_2-agonists (salmeterol, formoterol) [39-41], long acting anticholinergics (tiotropium) [42,43] and combination inhaled therapy (symbicort, seretide) [39-41,44] reduces the rate of exacerbations. In the ISOLDE study [13], the inhaled corticosteroid fluticasone group had a 25% reduction in exacerbation rate (1.32 v 0.99/year) and slower decline in health status compared to placebo. The long acting β_2 agonist salmeterol treatment limb of the TRISTAN study[39] was associated with reduction in exacerbation rate of around 20% compared to those randomised to placebo. Trials with the long acting anticholinergic, tiotropium have shown a significant reduction in exacerbations of approximately 20-25% when tiotropium is added to the usual therapy [42,43]. Combination therapy of inhaled corticosteroids and long acting β_2-agonists have been known to produce greater improvement in lung function compared to either drug alone and studies now have shown that both combination inhalers reduces exacerbation rates by approximately 25% [39-41,44]. These studies demonstrated that the reductions in exacerbations results in decreased hospitalisations and health care utilisations.

Some of these medications are not available at many health centers in the country or only accessible by respiratory physicians, therefore patients who experiences recurrent exacerbations of COPD should be referred to the nearby centers with respiratory services as these patients are most likely to benefit from these medications.

Pulmonary rehabilitation is an effective non pharmacological treatment in stable COPD. Unfortunately only a few centers in Malaysia provide this service because of the lack of physiotherapist support although there is overwhelming evidence of its benefits in improving patients' quality of life, exercise tolerance and symptoms. Pulmonary rehabilitation has also been shown to reduce exacerbation rates and duration of hospitalisations [45,46]. If pulmonary rehabilitation is not available, patients should be encouraged to exercise at

home and maintain an active lifestyle as much as possible. Self management education including managing an exacerbation can be recommended for suitable patients by providing a supply of antibiotics and steroids (providing patient understands when to take them) to be started at the beginning of an exacerbation. This may shorten and reduce the severity of the exacerbation, reducing unscheduled doctor visits and hospital admissions [47].

CONCLUSIONS

Exacerbations of COPD are important events for the patient and expensive for the healthcare system. Patients with frequent exacerbations have poorer health status, greater decline in lung function and higher mortality compared to those spared the events. The immediate management is assessing the patient whether the exacerbation can be treated at home or requires hospital admission and if life threatening, high dependency unit or ICU admission.

The initial treatment includes regular inhaled short acting bronchodilators and corticosteroids. Antibiotics are indicated if purulent sputum is present with increased breathlessness or increased sputum volume and in severe exacerbations requiring mechanical ventilation.

Controlled oxygen therapy and non invasive ventilation improves gas exchange and decrease muscle fatigue. Failure to improve with treatment is an indication for invasive ventilation. Preventive strategies including smoking cessation, vaccinations, pulmonary rehabilitation, chronic maintenance pharmacotherapy and self management education may prevent exacerbations but the optimum combination remains to be established.

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MCQs for CME Article

1. The following statements regarding COPD exacerbations are true:
a. It is associated with a rapid decline in lung function
b. The mean average length of stay in hospital is 3-5 days
c. Patients with frequent exacerbations are at increased risk of mortality
d. Patients usually make a rapid recovery from the exacerbation
e. Steroids are recommended in all hospitalised patients with COPD exacerbation

2. The following are indications for non invasive ventilation in patients with COPD exacerbations:
a. Respiratory rate 30/min
b. pH $\leq$ 7.35
c. Partial pressure CO_2 - 4kPa
d. Consolidation on chest radiograph
e. Respiratory distress with use of accessory muscles

3. The following treatment have been shown to reduce COPD exacerbations:
a. Inhaled glucocorticosteroid
b. Smoking cessation
c. Influenza vaccination
d. Pulmonary rehabilitation
e. Self postural drainage

4. The benefits of systemic glucocorticosteroids in COPD exacerbations include:
a. Reduce treatment failure
b. Improves lung function
c. Prevents frequent exacerbations in the long term
d. Improves respiratory muscle strength
e. Shortens the duration of hospital stay

5. The following are true regarding antibiotics in COPD exacerbations:
a. Indicated if increasing purulent sputum
b. Broad spectrum antibiotics should be given
c. Antibiotics should be given intravenously
d. Indicated if patient requires invasive ventilation
e. Prophylactic antibiotics prevents future exacerbations