Diagnosis and management of acute exacerbations of chronic obstructive pulmonary disease (COPD)

Acute exacerbations of COPD have serious consequences for the patient and for the economy.

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Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are characterised by sustained worsening of symptoms from the stable state. These are acute in onset with worsening of symptoms beyond the day-to-day variation of symptoms experienced by patients.

The **symptoms** include increased breathlessness, sputum purulence or increased sputum volume and in some patients these are accompanied by other problems such as increasing cough, wheeze, chest tightness or fatigue.[1]

Some authorities define AECOPD using definitive criteria with at least two of the following major symptoms:

- increased dyspnoea
- increased sputum purulence
- increased sputum volume

or one major and one minor symptom:

- nasal discharge/congestion
- wheeze
- sore throat
- cough

for at least 2 consecutive days.[2,3]

However, the severity of exacerbations can be extremely heterogeneous, ranging from a mild increase in symptoms to more serious manifestations and severe respiratory failure.

The magnitude of the problem is substantial for the patient, as well as economically. In the USA alone, in 2000, there were approximately 1.5 million emergency department visits related to COPD, 726 000 hospitalisations and 120 000 deaths with an annual cost of 32 billion dollars.[4,5]

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Precipitants

Infectious agents are recognised as a major pathogenic factor in AECOPD, accounting for an estimated 50 - 60% of exacerbations (mostly bacterial and viral).[6,7] Other contributing factors include environmental pollution, low temperature and interruption of regular treatment. In approximately 30% of cases a specific precipitant is not identified.

Initial evaluation

Initial evaluation of a suspected patient with AECOPD encompasses a thorough medical history, clinical examination, chest radiograph and appropriate blood and sputum laboratory investigations. Ideally, an arterial blood gas analysis should be performed in most patients to assess the severity of the exacerbation, as well as to establish a baseline from which improvement or deterioration can be measured.

Patients with mild acute exacerbations can be managed as outpatients, with more severe cases requiring hospitalisation. Indications for hospitalisation include:[8]

- inadequate response of symptoms to outpatient management
- marked increase in dyspnoea
- inability to eat or sleep due to symptoms
- worsening hypoxaemia
- worsening hypercapnia and acute respiratory acidosis
- changes in mental status
- inability to care for oneself or lack of home support
- uncertain diagnosis
- high-risk co-morbidities include pneumonia, cardiac arrhythmia, congestive heart failure, diabetes mellitus, renal failure or liver failure.

Management

Treatment goals

Successful management of AECOPD in either the inpatient or outpatient setting requires attention to several key issues, which include:[9,10]

- identifying and ameliorating the cause of the acute exacerbation, if possible

- optimising lung function by administering bronchodilator and other pharmacological agents
- ensuring adequate oxygenation and secretion clearance
- preventing the complications of immobility such as venous thromboembolism and deconditioning
- addressing nutritional needs.

Pharmacologically, the major components in managing AECOPD include the use of short-acting bronchodilators (beta-2-adrenergic agonists and anticholinergic agents), systemic corticosteroids and antibiotics.[11] Controlled oxygen therapy is generally employed and in some patients non-invasive positive-pressure ventilation (NPPV) may be beneficial. More severe exacerbations may require invasive ventilation.

Bronchodilators provide relief of lung hyperinflation with improvement of shortness of breath, chest tightness and wheeze. **Inhaled beta-2-agonists** (e.g. salbutamol 400 – 800 µg; terbutaline 500 – 1 000 µg; fenoterol 200 - 400 µg) and **anticholinergic agents** (ipratropium bromide 80 µg) may be given by pressured metered dose inhaler and spacer, or by jet nebulisation (salbutamol 2.5 - 5 mg; fenoterol 0.5 mg; ipratropium 500 µg). Combination formulations of these agents are available for use. Meta-analyses have shown no difference in the efficacy of delivering the bronchodilator therapy via a nebuliser over inhalation via a spacer device for patients with AECOPD.[12]

The dose interval is titrated to the response and can range from hourly to 6-hourly. There is currently no strong evidence to support the use of long-acting bronchodilators in the treatment of exacerbations.

The role of **methylxanthines** (**aminophylline** and **theophylline**) in the treatment of AECOPD remains controversial and in general, these agents are not recommended.[13] Randomised controlled trials of intravenous aminophylline in this setting have failed to demonstrate efficacy beyond that induced by accepted other therapies. In addition to lack of efficacy, methylxanthines have been associated with more nausea and vomiting than placebo and tended towards more frequent tremor, palpitations and arrhythmias. However, recent studies have suggested that low-dose theophylline (at plasma concentrations below 10 mg/l) has some anti-inflammatory effect on the COPD airway.[14,15] The proposed mechanism of its anti-inflammatory effect includes reversal of corticosteroid resistance of the airway by restoring the activity of histone deacetylase to normal levels.

Systemic corticosteroid therapy administered orally or intravenously is recommended for treating AECOPD, as this significantly reduces treatment failure and the need for additional medical treatment.[16,17] Use of systemic corticosteroid therapy for hospitalised AECOPD patients accelerates the rate of lung function improvement and improves the sensation of dyspnoea over the first 72 hours of treatment. A recent systematic review and meta-analysis revealed that compared with placebo, systemic corticosteroids reduced treatment failure by 46%, length of hospital stay by 1.4 days and improved FEV_1 by 0.13 l after 3 days of therapy.[18] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommends a 10 - 14-day course of 30 - 40 mg/day of oral prednisone for treatment of AECOPD.[19]

Patients experiencing AECOPD with clinical signs of airway infection (such as increased sputum volume and change of colour of sputum and/or fever) may benefit from **antibiotic treatment.** The choice of antibiotic should reflect the local patterns of antibiotic sensitivity to micro-organisms such as *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* (see Table I). Agents such as amoxicillin-clavulanate, second- and third-generation cephalosporins and newer anti-Gram-positive fluoroquinolones are most frequently used.

A recent Cochrane review has also supported the use of antibiotic therapy for patients who are moderately or severely ill with AECOPD with increased cough and sputum purulence. Antibiotic treatment is associated with reductions in mortality, treatment failure and sputum purulence.[20] These findings have been further confirmed in a recent meta-analysis which revealed that appropriate antibiotic therapy reduced treatment failure by 46% and in-hospital mortality by 78%.[18]

Controlled oxygen therapy

This is indicated in patients with hypoxia, with the aim of improving oxygen saturation to at least 90% (PaO_2 >50 mmHg or 6.7 kPa). Initiation of therapy can begin with nasal prongs/cannulae at 0.5 - 2.0 l/min or a Venturi mask at 24% or 28%. The patient should be monitored for worsening hypercapnia.

Mucoactive agents

There is little evidence supporting the use of mucoactive agents such as N-acetylcysteine in AECOPD.[21,22] Similarly, there is limited evidence to support the use of mechanical techniques to augment sputum clearance, although this is frequently employed.

Non-invasive ventilation

This refers to assisted ventilation delivered through a non-invasive interface, such as a facemask, nasal mask or nasal prongs.

In patients with decompensated hypercapnic respiratory failure, the use of NPPV can decrease mortality and the need for intubation. NPPV has led to a reduction in treatment failure and a more rapid improvement within the first hour in both respiratory rate and pH in blood gas measurement. Furthermore, length of hospital stay and complications associated with the treatment of AECOPD are reduced in the NPPV treatment group compared with medical treatment alone.[23]

Invasive ventilation

Invasive mechanical ventilation should be administered when patients fail NPPV, do not tolerate NPPV, or have contraindications to NPPV.

Prognosis

It is estimated that approximately 15% of patients admitted for AECOPD will die within 3 months of admission.[24,25] For those patients whose COPD exacerbations were severe enough to warrant application of NPPV respiratory support, the 1-year mortality rate approaches 50%.[26]

Prevention and new advances

Once the patient begins to improve, measures should be taken to prevent further exacerbations. This includes annual influenza vaccination, smoking

Table I. Infectious causes of acute COPD exacerbations

Bacteria	Viruses
Non-typeable *Haemophilus influenzae*	Rhinovirus
Moraxella catarrhalis	Influenza
Streptococcus pneumoniae	Parainfluenza
Pseudomonas aeruginosa	Coronavirus
Enterobacteriaceae	Adenovirus
Haemophilus parainfluenzae	Respiratory syncitial virus
'Atypical bacteria'	Human metapneumovirus

cessation, pulmonary rehabilitation and proper use of medications. The use of inhaled corticosteroids and long-acting beta-agonists should be considered[27] and more recent evidence suggests that therapy with tiotropium is associated with fewer exacerbations, hospitalisations, respiratory failure and improved quality of life.[28] Finally, treatment with statins is associated with improved survival after COPD exacerbation, and inhaled corticosteroids appear to increase the survival benefit associated with statins.[29,30]

References

1. Hurst JR, Wedzicha JA. Chronic obstructive pulmonary disease: the clinical management of an acute exacerbation. *Post Grad Med J* 2004; 80: 497-505.
2. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1418-1422.
3. Patel IS, Seemungal TA, Wilks M, Lloyd-Owen SJ, Donaldson GC, Wedzicha JA. Relationship between bacterial colonization and frequency, character, and severity of COPD exacerbations. *Thorax* 2002; 57: 759-764.
4. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance – United States, 1971-2000. *Resp Care* 2002; 47: 1184-1199.
5. Sinn DD, Stafinski T, Ng YC, Bell NR, Jacobs P. The impact of chronic obstructive pulmonary disease on work loss in the United States. *Am J Resp Crit Care Med* 2002; 165: 704-707.
6. Barnes PJ. Chronic obstructive pulmonary disease. *N Engl J Med* 2000; 343: 269-280.
7. Sapey E, Stockley RA. COPD exacerbations. 2: Aetiology. *Thorax* 2006; 61:250-258.
8. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Resp J* 2004; 23: 932-946.
9. Choi PP, Day A, Etchells E. Gaps in the care of patients admitted to hospital with an exacerbation of chronic obstructive pulmonary disease. *CMAJ* 2004; 170: 1409-1413.
10. Saudny-Unterberger H, Martyin JG, Gray-Donald K. Impact of nutritional support on functional status during an acute exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997; 156: 794-799.
11. Stoller JK. Clinical practice. Acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002; 346: 988-994.
12. Dolovich MB, Ahrens RC, Hess DR, *et al.* Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy and Immunology. *Chest* 2005; 127: 335-371.
13. Snow V, Lascher S, Mottur-Pilson C. Evidence base for management of acute exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 2001; 134: 595-599.
14. Barnes PJ. Theophylline for COPD. *Thorax* 2006; 61: 742-744.
15. Hirano T, Yamagata T, Gohda M, *et al.* Inhibition of reactive nitrogen species production in COPD airways: comparison of inhaled corticosteroid and oral theophylline. *Thorax* 2006; 61: 761-766.
16. Aaron SD, Vandemheen KL, Herbert P, *et al.* Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med* 2003; 348: 2618-2625.
17. Wood-Baker RR, Gibson PG, Hannay M, Walters EH, Walters JA. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005: CD001288.
18. Quon BS, Gan WQ, Sinn DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. *Chest* 2008; 133: 756-766.
19. National Heart, Lung and Blood Institute, World Health Organization Global Initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Updated 2005.
20. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006: CD004403.
21. Bach PB, Brown C, Gelfand SE, McCrory DC. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. *Ann Intern Med* 2001; 134: 600-620.
22. Black PN, Morgan-Day A, McMillan TE, *et al.* Randomised controlled trial of N-acetylcysteine for treatment of acute exacerbations of chronic obstructive pulmonary disease (ISRCTN21676344). *BMC Pulm Med* 2004; 4: 13.
23. Ram FS, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2004: CD004104.
24. Roberts CM, Lowe D, Bucknall CE, *et al.* Clinical audit indicators of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease. *Thorax* 2002; 57: 137-141.
25. Donaldson GC, Wedzicha JA. COPD exacerbations.1: Epidemiology. *Thorax* 2006; 61: 164-168.
26. Chu CM, Chan VL, Lin AW, Wong IW, Leung WS, Lai CK. Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. *Thorax* 2004; 59: 1020-1025.
27. Calverly PM, Anderson JA, Celli B, *et al.* TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775-789.
28. Tashkin DP, Celli B, Senn S, *et al.* For the UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359:1543-1554.
29. Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin converting enzyme inhibitors and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease *J Am Coll Cardiol* 2006; 47: 2554-2560.
30. Soyseth V, Brekke PH, Smith P, Omland T. Statin use is associated with reduced mortality in COPD. *Eur Respir J* 2007; 29: 279-283 .

In a nutshell

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- Symptoms include increased breathlessness, sputum purulence or increased sputum volume and in some patients these are accompanied by other problems such as increasing cough, wheeze, chest tightness or fatigue.
- Infectious agents are recognised as a major pathogenic factor in AECOPD, accounting for an estimated 50 - 60% of exacerbations (mostly bacterial and viral).
- Initial evaluation of a suspected patient with AECOPD encompasses a thorough medical history, clinical examination, chest radiograph and appropriate blood and sputum laboratory investigations.
- An arterial blood gas analysis should be performed in most patients to assess the severity of the exacerbation, as well as to establish a baseline from which improvement or deterioration can be measured.
- Pharmacologically, the major components in managing AECOPD include the use of short-acting bronchodilators (beta-2-adrenergic agonists and anticholinergic agents), systemic corticosteroids and antibiotics.
- Controlled oxygen therapy is indicated in patients with hypoxia.
- There is little evidence supporting the use of mucoactive agents such as N-acetylcysteine in AECOPD.
- In patients with decompensated hypercapnic respiratory failure, the use of NPPV can decrease mortality and the need for intubation.
- Invasive mechanical ventilation should be administered when patients fail NPPV, do not tolerate NPPV, or have contraindications to NPPV.
- It is estimated that approximately 15% of patients admitted for AECOPD will die within 3 months of admission.