



Managing chronic obstructive pulmonary disease

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Summary

Chronic obstructive pulmonary disease is a common, burdensome and underdiagnosed condition in Australia. Spirometry is the basis of diagnosis and assessing severity in individual patients. Smoking cessation is the keystone for slowing the rate of decline in lung function. Pulmonary rehabilitation reduces breathlessness, anxiety and depression, and improves exercise capacity and quality of life. Multidisciplinary care plans and individual self-management plans may help to prevent or manage crises. Inhaled bronchodilators provide symptom relief and may increase exercise capacity. Systemic steroids reduce the severity and shorten recovery from acute exacerbations. Patients with chronic obstructive pulmonary disease should receive influenza and pneumococcal vaccination.

Key words: bronchodilators, corticosteroids, pulmonary rehabilitation.

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Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of disease burden in Australia. The Australian Lung Foundation has conservatively estimated the annual direct costs to exceed \$900 million. However, COPD was only the tenth most commonly managed chronic condition in general practice in 2003–04. There is substantial underdiagnosis and many patients are currently not receiving optimal medical care.

The Australian guidelines for COPD (COPD-X), first published in 2003¹, were based upon the Global initiative for Obstructive Lung Disease (GOLD).² They are now updated quarterly³ using the latest evidence from systematic reviews, particularly those published in the Cochrane Library.

C Confirm diagnosis and assess severity

Spirometry remains the basis for diagnosing and assessing the severity of COPD in individual patients¹, however this test

is underused in Australia. A recent systematic review found that spirometry, in addition to clinical examination, improved diagnostic accuracy compared to clinical examination alone. The diagnosis of COPD rests on the demonstration of airflow limitation which is not fully reversible. On the other hand, if the airflow limitation is fully or substantially reversible, the patient should be treated as for asthma.¹ Published studies do not support the diagnostic use of trials of therapy with either corticosteroids (both inhaled and oral), short- or long-acting bronchodilators or oral theophylline in COPD.⁴

O Optimise function

Bronchodilators

Inhaled bronchodilators provide symptom relief and may increase exercise capacity in patients with COPD. The dosage and frequency of short-acting beta₂ agonists (salbutamol, terbutaline) and anticholinergic drugs (ipratropium) can be titrated against the severity of the disease.¹ Long-acting bronchodilators can provide sustained symptom relief in patients with moderate to severe disease. They include the long-acting beta₂ agonists (salmeterol, eformoterol) which are inhaled twice daily and the long-acting inhaled anticholinergic drug tiotropium which is inhaled once daily.

Tiotropium has become first-line therapy in COPD. It has been shown to improve exercise capacity and quality of life. A Cochrane review found that 14 patients would need to be treated with tiotropium for a year to prevent one exacerbation and 30 to prevent one hospitalisation compared to placebo and ipratropium. Controversially, a recent meta-analysis suggested that tiotropium might also be associated with reduced mortality and estimated that 278 patients would need to be treated to prevent one death.⁵

Combination therapy

The combination of short-acting beta₂ agonists and anticholinergics may be more effective and better tolerated than higher doses of either drug used alone.¹ Fixed-dose combinations of a long-acting beta₂ agonist with a corticosteroid in a single inhaler (salmeterol/fluticasone, eformoterol/budesonide) are widely used in COPD, although this is not yet an approved indication in Australia. In a Cochrane review of six randomised controlled trials, combination therapy

led to clinically meaningful differences in quality of life and symptoms compared to placebo. However, a subsequent critique⁶ raised questions about the methodology used in those studies showing benefits in exacerbation rates. The Cochrane review found conflicting results when the different combination therapies were compared with their individual components alone. Firmer conclusions about the effects and optimal dosage of combination therapy require more data, including assessment of the comparative effects with separate administration of the two drugs in double-dummy trials.

Comorbidities and complications

Most patients with COPD have other comorbid conditions. Ischaemic heart disease and lung cancer share cigarette smoking as a common risk factor. There is increased mortality from respiratory failure, pneumonia, pulmonary vascular disease and heart failure. Anxiety and depression are also more common among patients with COPD. Corticosteroid treatment may contribute to the development of osteoporosis or diabetes.

The systemic effects of COPD include nutritional abnormalities and skeletal muscle wasting.⁷ Many patients lose fat free mass, due to an increased basal metabolic rate that is not compensated for by increased dietary intake, or to the adverse effects of drugs (including beta₂ agonists and theophylline). Nutritional supplementation has not been associated with any improvement in lung function or exercise capacity. Causes of muscle weakness include physical deconditioning, systemic inflammation, oxidative stress, corticosteroid adverse effects, hypoxia, electrolyte disturbances and many other factors. Physical deconditioning can be effectively reduced by pulmonary rehabilitation.

Pulmonary rehabilitation

Pulmonary rehabilitation reduces breathlessness, anxiety and depression, and improves exercise capacity and quality of life in COPD. Comprehensive integrated rehabilitation programs include exercise training, patient education and psychosocial support. Long recommended for patients with moderate to severe disease, there is now evidence that exercise training also benefits those with milder disease. An online toolkit is available to assist health professionals to implement pulmonary rehabilitation programs.⁸

Surgery

In patients with predominantly upper lobe emphysema and low baseline exercise capacity, who remain disabled following pulmonary rehabilitation, there may be a limited place for lung volume reduction surgery. However, high-risk patients with more widespread emphysema should not be referred for surgery because of increased mortality and negligible functional gain.⁹

P Prevent deterioration

Smoking cessation is the keystone for slowing the rate of decline of forced expiratory volume in one second (FEV₁) in COPD. The behavioural and pharmacological interventions available to promote complete cessation of smoking and maintain abstinence were reviewed in COPD-X.¹

Systemic corticosteroids have a very limited role in COPD other than in acute exacerbations. Inhaled corticosteroids are associated with a modest reduction in the rate of FEV₁ decline which is of uncertain clinical significance.³ A slightly greater effect was seen in trials that gave patients 800 microgram or more of budesonide or 1000 microgram of fluticasone per day. The longer-term adverse events associated with these high doses of inhaled corticosteroids are yet to be determined, so the

optimum dose is unknown. A recent systematic review which pooled individual patient data from seven clinical trials found a 25% reduction in mortality among patients treated with inhaled steroids compared to placebo.¹⁰ We estimate that 94 patients would need to be treated with inhaled steroids for two years to prevent one death. Patients with COPD should receive annual influenza and five-yearly pneumococcal vaccination.¹¹

Systemic corticosteroids have a very limited role in COPD

Domiciliary oxygen

Long-term continuous oxygen therapy

Long-term continuous oxygen therapy for at least 15 hours a day has been shown to reduce mortality in patients whose arterial oxygen (PaO₂) is consistently ≤ 55 mmHg, or 55–59 mmHg with evidence of hypoxic sequelae such as polycythaemia, pulmonary hypertension or cor pulmonale. Oxygen may also improve exercise capacity and mental state.

Intermittent oxygen therapy

A Cochrane review of 31 studies of patients with moderate to severe COPD found that compared to air, ambulatory oxygen improved endurance exercise capacity, dyspnoea and oxygen saturation. This benefit cannot be predicted by a resting test. A six-minute walking test with and without oxygen is required. The available evidence does not allow any firm conclusions to be made about the effectiveness of intermittent ambulatory oxygen therapy used in the **domiciliary** setting by patients who are not significantly hypoxaemic at rest.

D Develop a support network and self-management plan

Patients with COPD can be supported by their general practitioner, respiratory physician, respiratory nurse/educator, physiotherapist, social worker, pharmacist and many other health professionals. Multidisciplinary care plans and individual

self-management plans may help to prevent or manage crises. However, evidence for the beneficial effects of self-management is more convincing in asthma than in COPD. Effective support can help relieve anxiety and depression. If drug treatment is needed, consider using drugs which do not cause sedation. Support groups can provide ongoing education and psychosocial support for patients and their carers.*

X manage eXacerbations

Home management of acute exacerbations of COPD may relieve pressure on acute care facilities. Up to a quarter of carefully selected patients presenting to hospital emergency departments can be safely and successfully treated at home with support from respiratory nurses. A systematic review of seven randomised controlled trials found no significant differences in readmission rates or mortality, and patients preferred 'hospital at home' schemes.

Guidelines for the investigation and initial assessment of severity in acute exacerbations are detailed in COPD-X.¹ Frequent bronchodilators (beta₂ agonist with ipratropium) delivered via nebuliser or metered dose inhaler plus spacer are effective treatments for dyspnoea and airflow limitation. The routine use of intravenous aminophylline is no longer recommended because of the potential for severe toxicity. Patients who have acute exacerbations with signs of infection (increased volume and change of colour of sputum and/or fever, leucocytosis) benefit from antibiotic therapy.

Systemic corticosteroids (oral prednisolone, intravenous hydrocortisone) improve dyspnoea and lung function, reduce the severity and shorten recovery from acute exacerbations. A Cochrane review found that it would be necessary to treat nine patients with systemic corticosteroids to avoid one treatment failure. However, one additional acute adverse effect (such as hyperglycaemia) occurred for every six patients treated. Up to two weeks therapy is adequate and longer courses only increase the risk of adverse effects.¹

Non-invasive positive pressure ventilation with a face mask is effective in patients who develop acute hypercapnic ventilatory failure. It reduces mortality and the need for intubation, with all the attendant complications. Non-invasive positive pressure ventilation results in more rapid improvements in respiratory rate, dyspnoea and blood gas abnormalities and a shorter stay in hospital than conventional therapy alone. However, patients who are unable to protect their airways, who are not breathing spontaneously or who have severe facial injuries may still require endotracheal intubation.

Follow-up at home after discharge from hospital helps to continue the management begun within the acute environment.

* See Patient support organisation: The Australian Lung Foundation, page 79.

However, there is no current evidence to show a benefit from nurse-led chronic disease management for people with COPD.

Conclusion

The challenge remains to improve the recognition and management of COPD in Australia. A large multicentre trial of combination therapy is due to report shortly. However, there is a pressing need for more randomised controlled trials of non-drug therapies for COPD. The latest full version of the guidelines approved by the Australian Lung Foundation can be consulted at www.copdx.org.au.

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Self-test questions

The following statements are either true or false (answers on page 83)

1. Anticholinergic bronchodilators are ineffective in chronic obstructive airways disease.
2. Lung volume reduction surgery reduces mortality in patients with widespread emphysema.

Medicinal mishap

Interstitial nephritis associated with omeprazole

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Case

A 62-year-old man presented with acute renal failure. On examination, there were no allergic features such as rash, fever or eosinophilia. Urine examination was normal. Previous renal function was normal. His creatinine peaked at 470 micromol/L. Investigations included tests for anti-neutrophil cytoplasmic and antinuclear antibodies, antibodies against extractable nuclear antigens, double-stranded DNA, complement, hepatitis serology, serum paraprotein concentration and renal ultrasound, all of which were normal. Renal biopsy showed florid interstitial nephritis.

A few weeks earlier, he was diagnosed with Helicobacter gastritis and treated with triple therapy (omeprazole, amoxicillin, clarithromycin) followed by omeprazole 40 mg daily. He had previously been taking pantoprazole for dyspepsia. Other medical history included a knee injury six months earlier. This had been treated with diclofenac, which was associated with the development of a rash and was substituted with rofecoxib. The exact duration of treatment with rofecoxib was unclear.

Omeprazole was changed to ranitidine and the man was treated with tapering doses of prednisolone, commencing at 75 mg daily. On examination three years later, his creatinine had improved to 123 micromol/L.

Comment

Acute interstitial nephritis is due to a hypersensitivity reaction and is typically associated with reversible acute renal failure. Drugs account for 71% of cases of acute interstitial nephritis.¹ Medicines commonly implicated include non-steroidal anti-inflammatory drugs (NSAIDs), penicillins, cephalosporins, sulfonamides and proton pump inhibitors. Drug-induced interstitial nephritis is not dose dependent and can recur with

rechallenge. The classic triad for interstitial nephritis of fever, rash and eosinophilia occurs in less than 10% of cases.² Urine examination including microscopy may show haematuria, proteinuria, white cells, casts and eosinophiluria, but may be unremarkable.

Interstitial nephritis may occur with all of the proton pump inhibitors, although most reports to the Australian Adverse Drug Reactions Advisory Committee (ADRAC) have been with omeprazole.³ To date (14 May 2007) ADRAC have 82 reports associated with proton pump inhibitors. Of these cases, 50 were associated with omeprazole, 12 with esomeprazole, 6 with pantoprazole and 14 with rabeprazole. The duration of proton pump inhibitor treatment before presentation is usually between two weeks and nine months.⁴

The temporal relationship in this case suggests that omeprazole was the most likely cause of interstitial nephritis, although the possibility that amoxicillin, pantoprazole or the NSAID were implicated cannot be excluded.

Recommendation

Maintain a high index of suspicion for interstitial nephritis in patients who develop acute renal failure while on a proton pump inhibitor. The diagnosis can only be confirmed on renal biopsy. Management involves drug withdrawal and supportive treatment. The efficacy of corticosteroids has not been demonstrated in controlled trials.⁴

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