National Medicines Information Centre

VOLUME 10
NUMBER 3
2004

ST. JAMES'S HOSPITAL • DUBLIN 8
TEL 01-4730589 or 1850-727-727 • FAX 01-4730596 • e-mail: nmic@stjames.ie

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

SUMMARY

- **After pneumonia, COPD is the number one cause of respiratory death in Ireland**
- **Smoking accounts for over 90% of cases in developed countries**
- **Inhaled bronchodilators, taken appropriately, are the most effective pharmacological therapy for symptomatic relief, albeit of limited value**
- **Long term oxygen therapy is associated with a survival benefit, but its use is often inappropriate**

INTRODUCTION

COPD is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is in most cases both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[1] It is a heterogeneous condition which is underdiagnosed and is commonly mistreated.[2,3] The Global Burden of Disease Studies have predicted that by 2020 it will be the fifth commonest cause of disease morbidity, and the third commonest cause of death worldwide, outpacing that of lung cancer, heart disease and stroke.[4,5,6] The increasing disease burden is due to an increase in tobacco consumption in underdeveloped countries and an ageing population in developed countries.[3,7] In Ireland, in 1999, COPD was the number two cause of respiratory death, accounting for 26% of the total respiratory related mortality, and accounting for 20% of the respiratory hospital in-patient bed days.[8] Given the prevalence of smoking among young adults it does seem unlikely that mortality from COPD will fall dramatically in the medium term, and therefore Ireland is likely to continue to have one of the highest mortality rates from this disease.[8]

PATHOLOGY

COPD is the result of a chronic inflammatory response in the large airways (chronic bronchitis), the small airways (bronchiolitis which may progress to fibrosis) and the lung parenchyma (emphysema). Airflow obstruction arises as a result of progressive thickening, fibrosis and smooth muscle hypertrophy of the small airways, along with the loss of elastic recoil pressure due to pulmonary emphysema.[7,9,10] Pathological changes that occur include mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation and gas exchange abnormalities. Unlike other chronic diseases: rheumatoid arthritis and interstitial lung disease, which tend to "burn out", the inflammatory response in COPD appears to increase with the severity of the disease.[7] In advanced disease, pulmonary hypertension, right ventricular hypertrophy and right ventricular failure may occur. Systemic changes that may occur in advanced disease include osteoporosis, low body-mass index, and abnormal skeletal muscles with reduced muscle strength.[9]

RISK FACTORS AND NATURAL HISTORY

Cigarette smoke is the most important risk factor for COPD in developed countries.[3,7] In general, the greater the exposure to cigarettes (younger age at commencement, total pack-years smoked and current smoking status), the greater the risk of developing COPD. While not all smokers develop clinically significant COPD, recent epidemiological studies show that most smokers, if they live long enough and smoke enough, will develop airflow limitation.[11] Worldwide, up to 20% of COPD patients are lifelong nonsmokers.[12] Other risk factors include: recurrent bronchopulmonary infections, exposure to occupational dusts and chemicals, indoor and outdoor pollution, low socio-economic status, genetic factors, allergy and airway hyper-responsiveness and alpha-1-antitrypsin deficiency.[1,10] Continued exposure to the causative noxious agents promotes a more rapid decline in lung function and increases the risk of repeated exacerbations.[11] Five-year survival for men with mild disease is 78% and with severe disease it is 32%, with corresponding figures for women being 72% and 24%.[2]

DIAGNOSIS

The diagnosis of COPD is made on a combination of the presence of chronic progressive symptoms and signs on a background of exposure to potential risk factors, and spirometric evidence of airflow obstruction. Common symptoms include dyspnoea (persistent and progressive), cough, sputum (variable volume and purulence), wheeze (particularly early morning) and exercise intolerance. Common signs are chest hyperinflation, quiet breath sounds or rhonchi on forced expiration, use of accessory muscles of respiration and peripheral oedema.

Spirometry is used to measure airflow obstruction. The necessary measurements are (i) forced vital capacity (FVC) - the maximal volume of air forcibly exhaled from the point of maximal inhalation, (ii) forced expiratory volume in one second (FEV_1) - the volume of air exhaled during the first second of this manoeuvre, and (iii) the ratio of these two measurements (FEV_1 / FVC). Normal ageing results in an average decrease in FEV_1 of 20 ml/year, which is increased in smokers to 45 ml/year. Those who are susceptible to COPD have an accelerated decline of 50-70 ml/year.[10] **An FEV_1 of < 80% of the predicted value and an FEV_1 / FVC ratio < 70% confirms airflow limitation.**[1,2] The main differential diagnoses are chronic bronchitis, chronic asthma or congestive cardiac failure. These may be difficult to differentiate and frequently co-exist. Table 1 outlines some clinical features that differentiate COPD from asthma. Rarer differential diagnoses include: bronchiectasis, lung cancer, bronchopulmonary obliterans and chronic sarcoidosis.[2,3,10]

Table 1. Clinical features differentiating COPD and asthma [3,11]

	COPD	Asthma
Onset	Midlife	Early in life
Smoker or ex-smoker	Nearly all	Possibly
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent, progressive	Variable
Nighttime waking with breathlessness +/- wheeze	Uncommon	Common
Significant diurnal or day-to-day variability of symptoms	Uncommon	Common

A classification of disease severity according to FEV_1 measurements along with appropriate therapy per stage is outlined in Table 2.[1]

MANAGEMENT

Management is divided into three areas: prevention of disease progression, management of stable (but inevitably progressive) disease and management of acute exacerbations.[9] The majority of patients have established moderate or even severe airflow obstruction at the time of diagnosis.[3]

Prevention of disease progression

Evidence: Smoking cessation has been proven to reduce morbidity (cough and sputum production), slow the accelerated decline in lung function and reduce mortality (particularly in early stage disease). [9] Setting a definite date for cessation, offering advice (written and oral), and the judicious use of nicotine replacement products (patch, gum, nasal spray) or bupropion all increase cessation rates.[9] Advice on smoking cessation is available in a previous NMIC bulletin (Vol 7 (2) 2001).

Practical Advice: Enquiries regarding smoking status and / or advice on cessation should be part of every consultation with any smoker. Keenness to discontinue is the most important determinant of success. All COPD patients who smoke should be encouraged at every opportunity to stop.

Management of stable disease

As drug therapy does not alter the natural history of COPD, the management goals are to control symptoms, improve exercise capacity and reduce the frequency of exacerbations. With any therapy, if no benefit is apparent after an appropriate trial (usually 4 weeks), it should be discontinued. A stepwise approach per stage is outlined in Table 2.

Table 2. Characteristics and recommended treatments for each stage of COPD[1]

Stage	Characteristics (FEV_1/FVC <70%,+/- Symptoms applies to all stages)	Recommended treatment
Mild / I	FEV_1 >80%,	Avoid risk factors; annual influenza vaccination *Add* Short-acting bronchodilator prn
Moderate / II	FEV_1 50-80%	*Add* Regular long-acting bronchodilators *Add* Rehabilitation
Severe / III	FEV_1 30-50%	*Add* Inhaled steroids if repeated exacerbations
Very Severe / IV	FEV_1<30% +/- Chronic respiratory failure +/- Right heart failure	*Add* Oxygen therapy* Consider surgical options

*Indications for oxygen therapy listed over

1) Bronchodilators

Evidence: As airflow obstruction is the predominant feature of COPD, bronchodilation is the first line of management. The available agents are divided into three categories: **ß$_2$ agonists** (short- and long-acting), **anticholinergics** (short- and long-acting) and **methylxanthines**. Short-acting inhaled ß$_2$ agonists (salbutamol, terbutaline) and anticholinergics (ipratropium), as single agents or in combination, relieve symptoms, decrease exacerbations and improve exercise tolerance.[1,2,14] Long-acting inhaled drugs (ß$_2$ agonists - salmeterol, formoterol, and the anticholinergic - tiotropium) produce more sustained bronchodilation of between 8 to 24 hours and are associated with fewer disease exacerbations.[9,13,14] Methylxanthines (theophylline, aminophylline) have been used both orally and intravenously for many years. While effective, their usefulness is limited by the need for plasma level monitoring, their adverse reactions and the potential for interactions with other medications.[2,13]

Practical Advice: A stepwise approach to the use of bronchodilators is outlined in Table 2. Care is necessary with the combination of short- and long-acting anticholinergic agents, as they may be associated with an increased risk of anticholinergic side effects, e.g. dry mouth, constipation. The ***technique involved in using the prescribed delivery device*** should be assessed at every opportunity. Acquiring the proper technique as well as **retention** of the technique requires time and patience (of prescriber, pharmacist and user!).

2) Corticosteroids

Evidence: **Inhaled corticosteroids** (beclomethasone, budesonide, fluticasone) reduce the number of exacerbations and the decline in health status in patients with severe disease (FEV_1 < 50% predicted, with a minimum of two exacerbations a year), but do not modify the rate of decline of lung function.[1,2] They are of most benefit in those with persistent symptoms despite optimal bronchodilator therapy.[13] The combination of inhaled corticosteroids and long-acting inhaled ß$_2$ agonists has been shown to lead to fewer exacerbations, better health status, fewer symptoms, and improved lung function than either treatment used alone.[2,9,13] Inhaled steroids are associated with oral candidiasis and easy bruising. Use of maintenance **oral corticosteroids** is not recommended in the routine management of stable COPD.[1,2,13] Some patients require maintenance oral steroids when they cannot be discontinued following an exacerbation. In these patients, the maintenance dose should be kept as low as possible.[2]

Practical Advice: Patients taking inhaled steroids should be advised on appropriate oral hygiene, e.g. brush teeth or rinse well after each inhalation. Patients should be monitored for potential complications of steroid use, which include proximal myopathy, osteoporosis, hypertension and abnormal glucose tolerance.[2]

3) Oxygen therapy

Evidence: Hypoxic patients (PaO_2 < 7.8 kPa) with evidence of cor pulmonale have a 5-year survival of less than 50%.[2] Long-term oxygen therapy (LTOT), used for in excess of 15 hours a day (up to 20 hours) in patients with persistent daytime hypoxaemia (PaO_2 < 7.3 kPa) has been shown to increase survival.[15,16,17] **The only patients for whom LTOT is indicated are a) those with stable disease on full medical regimen, with PaO_2 < 7.3 kPa (corresponding to SaO_2 < 88%) and b) patients with stable disease on full therapy and PaO_2 7.3-7.8 kPa in association with documented cor pulmonale.**[1,2] There is no survival benefit in patients with lesser degrees of hypoxaemia.[18] The cost of LTOT is outlined in Table 3.

Practical Advice: LTOT should be initiated by specialists. Short-term oxygen therapy may be necessary for some patients during acute exacerbations, but LTOT should only be prescribed when there is evidence of hypoxaemia in a clinically stable patient on maximum medical therapy. Oxygen concentrators are the most convenient method of providing LTOT. Users and their carers should be warned about the risks of fire and explosion if they smoke in the same environs as oxygen therapy.

Table 3. The monthly cost of LTOT[19]

Device	GMS cost in ERHA
Concentrator	€60.95 + VAT
Portable Unit	€69.84 + VAT

4) Pulmonary rehabilitation

Evidence: Pulmonary rehabilitation is a co-ordinated programme of non-pharmacological treatment and support, including exercise training and education (regarding the benefits of smoking cessation, nutrition, appropriate use of inhaler devices and COPD itself). Benefits in quality of life, exercise capacity and patients' attitude to their illness, together with a reduction in hospitalisation have been noted for up to a year after completion of programmes.[13,20] There is no data on the impact of rehabilitation on exacerbation rate or survival.[1,2]

Practical Advice: Ideally this should be offered to all patients, but availability is extremely limited!

5) Surgery

Evidence: The roles of bullectomy, lung-volume-reduction surgery and lung transplantation have been studied. Survival benefits have not been documented to date.[13,14]

Practical Advice: The majority of patients are unsuitable for these therapies.

6) Additional Therapies:

Mucolytic therapy, such as carbocisteine, should be considered for those with persistent productive cough.[2] Anxiety and depression are common co-morbidities, which can be successfully treated once recognised.

Management of exacerbations

Definition: An acute worsening of the patient's condition from the stable state, beyond the normal day-to-day variation, which necessitates a change in regular medication.[1,2]

Causes: Acute bacterial infections account for 30-50% of episodes (common pathogens: *Haemophilus influenza, Moraxella catarrhalis* and *Strep pneumonie*), and 30% are viral (common pathogens: *rhino-, influenza, parainfluenza, corona-, adeno-* and *respiratory syncytial virus*). In up to 30% of cases the cause may be unidentifiable. Differential diagnoses include pneumonia, pneumothorax and pulmonary embolism. [1,2,21]

Management: Optimal management includes prompt maximisation of bronchodilator therapy, short courses of broad-spectrum antibiotics (if there is a change in the volume and purulence of the sputum) and the addition of oral corticosteroids. Steroids (30mg prednisolone for 7-10 days) are of most benefit when the FEV_1 is <50% predicted and if the patient has had two or more exacerbations in the previous year.[2,9,22,23] Following an exacerbation, some patients require maintenance oral steroids when they cannot be discontinued. In these patients, the dose should be kept as low as possible.[2] The majority of exacerbations are managed at home. The decision to refer a patient to hospital involves an assessment of the severity of symptoms, presence of co-morbidities, the level of physical functioning and the patient's ability to cope. Other factors that may need to be taken into account are listed in Table 4.

Table 4. Factors to consider when deciding where to manage a patient with an exacerbation[2]

Factor	Favours home management	Consider hospitalisation
Ability to cope at home	Yes	No
Social circumstances	Good	Living alone/not coping
General condition	Good	Poor/deteriorating
Already receiving LTOT	No	Yes
Significant co-morbidity	No	Yes
Rapid rate of onset	No	Yes
Breathlessness	Mild	Severe
Cyanosis	No	Yes
Acute confusion	No	Yes
Worsening peripheral oedema	No	Yes

Non-invasive positive-pressure ventilation (NIPPV) may be used during an acute exacerbation, and is associated with a reduction in nosocomial pneumonia and in-hospital stay.[1,2,24] The most appropriate use is in a patient with moderate to severe dyspnoea who is acidotic (pH 7.25-7.35), hypercapnic ($PaCO_2$ > 6.5 kPa) and tachypnoeic (respiratory rate > 25 breaths / minute). It may also improve quality of life when added to LTOT in carefully selected patients. Successful discharge from hospital requires close liaison between hospital and community teams.

Prevention: Prophylactic antibiotic treatment does not reduce exacerbation frequency.[2] Influenza vaccination during the appropriate season, and pneumococcal vaccination are beneficial and should be offered to all patients.[1,2]

CONCLUSIONS

COPD is a major cause of mortality and morbidity and the disease burden is increasing. Cigarette smoking is the root cause of COPD in the vast majority of affected persons and therefore smoking cessation is the cornerstone of management of the disease. The current medications used in the management of COPD ($ß_2$ agonists, anticholinergics or corticosteroids) do not slow disease progression, therefore prevention of lung damage by implementation of effective strategies for smoking cessation and early diagnosis are the current priorities.

New therapies under investigation include: inflammatory mediator antagonists, protease inhibitors, anti-inflammatory agents, immunostimulatory agents and oral vaccination with whole killed haemophilus influenza.

References available on request. Date prepared: August 2004

References for NMIC Bulletin 2004;10(3) "Chronic Obstructive Pulmonary Disease (COPD)":

1. Global initiative for Chronic Obstructive Lung Disease
   Updated 2003
   www.goldcopd.com

2. NICE Guidelines on management of COPD
   Thorax 2004; 59(Supp 1): 1-232
   Clinical guideline 12, developed by the National Collaborating Centre for Chronic Conditions

3. White J, Winter R, Chilvers E
   COPD: recent advances
   Horizons in Medicine 2003; 14: 373-82

4. Murray CJ, Lopez AD
   Mortality by cause for eight regions of the world: Global Burden of Disease Study
   Lancet 1997; 349: 1269-76

5. Murray CJ, Lopez AD
   Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study
   Lancet 1997; 349: 1436-42

6. Murray CJ, Lopez AD
   Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study
   Lancet 1997; 349: 1498-504

7. Barnes PJ
   Small airways in COPD
   NEJM 2004; 350: 2635-2635

8. Brennan N, O'Connor T
   Ireland Needs Healthier Airways and Lungs – the evidence
   June 2003

9. Calverley PMA, Walker P
   Seminar : Chronic obstructive pulmonary disease
   Lancet 2003; 362: 1053-61

10. MacNee William
    COPD: causes and pathology
    Medicine 2003; 71-75

11. Pauwels RA, Rabe KF
    Burden and clinical features of chronic obstructive pulmonary disease (COPD)

Lancet 2004; 364: 613-20

11b MacNee William
Guidelines for chronic obstructive pulmonary disease
BMJ 2004; 329: 361-3

11c Rennard Stephen I
Treatment of stable chronic obstructive pulmonary disease
Lancet 2004; 364: 791-802

12. Rennard S
Looking at the patient – approaching the problem of COPD
NEJM 2004; 350:965-66

13. Sutherland Er, Cherniack RM
Management of COPD – Current concepts
NEJM 2004; 350: 2689-97

14. Sin DD, McAlister FA, Paul Man SF, Anthonisen NR
Contemporary management of COPD – Scientific review
JAMA 2003; 290: 2301-2312

15. Continuous or nocturnal oxygen therapy in hypoxaemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group
Ann Intern Med 1980; 93: 391

16. Long term domicillary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema
Report of the Medical Research Council Working Party
Lancet 1981; 1: 681

16b Tarpy SP, Celli BR
Long term Oxygen therapy
NEJM 1995; 333: 710-4

17. Cochrane Database system – Domiciliary oxygen for COPD
Cochrane Database Syst Rev 2000;(2):CD001744

18. Gorecka D, Gorzelak K, Sliwinske P et al
Effect of long term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia
Thorax 1997; 52: 674

19. Phone call to Airproducts 01 8326184 and ERHA Aids and Appliances 01 6486500 for costs of LTOT July 2004-07-29

20. Griffiths TL, Burr M et al
Results at 1 year of out patient multidisciplinary pulmonary rehabilitation: a randomised controlled trial
Lancet 2000; 355: 362-68

21. Seemungal T, Wedzicha JA
Management of exacerbations of COPD
Medicine 2003; 82-83

22. Hall CS, Kyprianou A, Fein AM
Acute exacerbations in COPD – Current strategies with pharmacological therapy
Drugs 2003; 63 (14): 1481-1488

23. Stoller JK
Acute exacerbations of COPD – Clinical practice
NEJM 2002; 346: 988-994

24. Plant PK, Owen JL, Elliott MW
Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome
Thorax 2001; 56: 708-71