Chronic Lung Disease

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Background

Chronic obstructive pulmonary (lung) disease (COPD) is a major contributor to global and local morbidity and mortality. At a global level COPD is responsible for 4% of all deaths and over 80% of those due to respiratory disease.[1] In 1998 2.2 million people died as a direct result of COPD, a number equivalent to the number of deaths due to HIV.[1] COPD is, however, a chronic disease from which those afflicted do not usually die immediately. It is estimated that worldwide over 28 million people or 2.1% of the world's population suffer from COPD.[1] A World Bank/World Health Organization study estimated that COPD was the twelfth ranked burden of disease in 1990 and is expected to rise to fifth place by the year 2020. Thus, these deaths mask the far greater problem posed by COPD, namely its influence on quality of life, families and careers, economic productivity, and limited health resources.

COPD is, however, an even greater cause of morbidity and mortality for Indigenous Australians. A study of hospital admissions in Western Australia between 1983 and 1991 revealed that age-standardised hospital admission rates for COPD were 8.8 and 4.5 times greater for Aboriginal women and men respectively compared with non-Aboriginal Western Australians.[2] Similar overrepresentation was seen in a Northern Territory (NT) study by Plant and co-workers who showed that in 1988 age-standardised hospital admission rates for COPD were 4.2 and 1.7 times greater for Aboriginal women and men.[3] In addition, this over representation of respiratory morbidity, as represented by hospitalisations, became more marked over the period from 1979 to 1988, especially for women. This same over-burden of poor respiratory health was reflected in causes of mortality in Aboriginal adults in the NT. A study by Cunningham and others of causes of death of Aboriginal people in the NT between 1979 and 1991 showed that COPD accounted for 10% of excess mortality for women (the greatest contributor of any of the studied causes) and 7% of excess deaths for men (the third most important cause after motor vehicle accidents and pneumonia-influenza). Further, the standardised mortality ratio for COPD were 22.4 and 14.8 for Aboriginal women and men respectively compared with non-Aboriginal Northern Territorians.[4] A later review of Indigenous mortality in the NT by Dempsey and Condon[5] demonstrated that this health disparity had persisted until 1997. Thus, COPD is a major cause of global morbidity and mortality and is a significant factor in the hospitalisation of NT and WA Aboriginal adults and the premature death of NT Aboriginal adults.

The pathophysiology of COPD has undergone extensive study since the seminal work of Doll and Hall and the British Doctors Study, which demonstrated the association between tobacco consumption and death from

COPD.[6–10] This was followed by Fletchers' later study that illustrated the decline in lung function seen in 15% of tobacco smokers.[11,12] The demonstration of an association between tobacco smoking and COPD prompted the Lung Health Study which showed that smoking cessation was effective in reducing the decline in lung function seen in cigarette smokers with airflow obstruction.[13] Whilst tobacco consumption has been identified as the major aetiologic factor in COPD there is increasing evidence that environmental pollution[14,15,16] (especially wood/biomass fires), abnormalities in antiproteases (including α_1-antitrypsin deficiency), infections in early life[17,18,19] and intrauterine growth impairment/low birth weight[17,20] may all play a variable role in the development of this condition.

There is continuing potential confusion relating to the management of COPD in contrast to that of asthma. Asthma is predominantly a condition associated with Type 1 hypersensitivity, eosinophilic inflammation, airway smooth muscle hyperreactivity and hypertrophy, airway wall fibrosis, mucosal oedema and mucous plugging. In contrast, COPD is predominantly associated with an airway neutrophilia, mucosal oedema and a loss of airway support with premature airway closure on expiration. It is therefore not surprising that drugs which have been shown to be effective in asthma — including short- and long-acting bronchodilators, inhaled steroids, and leukotriene receptor antagonists — may not be similarly effective in COPD. Nevertheless, health providers are often provided with ambiguous messages particularly from pharmaceutical companies. These guidelines therefore aim to illustrate where agents typically utilised in asthma may be helpful in COPD whilst seeking to de-emphasise the importance of inhaled steroids and newer agents.

These guidelines for the management of COPD aim to provide a framework for the management of COPD and chronic lung disease, particularly for Indigenous Australians. They have been drafted with the recognition that delivery and access to health care in remote communities in Australia often poses unique and challenging issues to health providers, patients, and their carers. These guidelines do not aim to be a systematic review of all potential therapeutic interventions for COPD. Rather, they attempt to use evidence to most efficiently utilise limited health resources. Whilst we have outlined what we believe is best practice we are cognisant that it may not always be possible to provide everything that is suggested here. Nevertheless, we believe that these guidelines in turn may be useful in advocating for such resources when they are not available.

Finally, an important caveat is that guidelines such as this, whilst seeking to be comprehensive, do not aim to present all knowledge pertaining to COPD nor every possible therapeutic or preventive option. Thus, individual patients may sometimes be managed in ways that do not reflect what is outlined here. Such differences in clinical practice are legitimate as long as they are based on evidence gleaned from clinical trials or proven therapeutic response in individual patients.

Definition (including rationale for the inclusion of bronchiectasis)

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive airway disease that produces a decline in lung function that is not fully reversible. The loss of lung function (airflow limitation) is associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The characteristic symptoms of COPD — cough, sputum production and

shortness of breath (dyspnea) on exertion — often precede the development of COPD by many years, although not all individuals with cough and sputum production develop COPD.

The diagnosis of COPD is based on the patient having a history of exposure to risk factors and the presence of airflow limitation that is not fully reversible with treatment, with or without the presence of symptoms, such as chronic cough and sputum production. Whilst tobacco is the major risk factor for development of disease 5% of people with COPD in the developed world have no significant history of tobacco consumption. This may be even higher in the developing world populations and in Indigenous Australians. Thus, whilst a lack of a history of tobacco use should prompt a search for another cause of airflow obstruction it should not exclude the diagnosis.

The inclusion of bronchiectasis under the guise of COPD may surprise some readers. In remote communities the differentiation between COPD and bronchiectasis is often not possible and the evidence for any difference in management is minimal. Certainly there are rare congenital causes of bronchiectasis (e.g. cystic fibrosis and immune deficiencies) that may warrant different management. Such patients should be identified by an earlier onset of disease, especially in the setting of a limited history of tobacco consumption, and should be referred for specialist attention.

Existing guidelines

Existing guidelines for the management of COPD include those developed by the American[21] and British Thoracic Societies.[22] More recent initiatives have been the Global COPD guidelines developed as an international collaboration involving representatives from a broad range of countries, including Australia, with the National Heart, Lung, and Blood Institute and the World Health Organization[23] and the first draft of the Australian COPD management guidelines developed as an initiative of the Thoracic Society of Australia and New Zealand.[24] In general, these show a great deal of concordance and the general outline employed by the British, GOLD and Australian guidelines is utilised here.

Aims and principles of management

These are: (1) Assessment and monitoring of disease; (2) Reduction of risk factors/secondary prevention; (3) Managing chronic disease/long-term management; and (4) Managing acute exacerbations of chronic disease.

1. Assessment and monitoring of disease/grading of severity

COPD can be defined as mild, moderate or severe based on the degree of airflow obstruction determined by spirometry. The grading of severity in existing guidelines varies slightly, but all rely on the finding that Forced Expiratory Volume in one second (FEV1) as a percentage of the predicted value in a comparable well population – (see Spirometry, below) and the ratio of this with the Forced Vital Capacity (FVC) are an indicator of the risk of premature death, and correlate with functional impairment.[25–30]

Spirometry

Spirometry has three common uses in COPD. First, in diagnosing and grading the severity of COPD, second in monitoring progression and third in considering alternative diagnoses for airflow obstruction, particularly

asthma. The grading of severity is dependent on spirometry values. Values of FEV1 are compared to 'normal' values of lung function obtained from a 'healthy' population controlling for age, gender and height. The ratio of measured and predicted value is then calculated ([measured]/[predicted] x 100%). In the case of Aboriginal Australians in the NT the most representative values are those of Veale et al.[31] though other normal values for Indigenous Australians in Far North Queensland[32] and northern Western Australia[33] are available. These values were derived from populations of Aboriginal Australians in the Centre of the NT and in Far North Queensland. A similar study in the Top End of the NT[34] demonstrated close concordance with these results. For non-Indigenous Australians the values of Knudson[35] or Gore[36] are most commonly used, and values for Torres Strait Islanders are likely to be most consistent with those derived from coastal residents of PNG.[37]

An additional use of spirometry is to determine the rate of disease progression (indicated by the average annual decline in FEV1) and thus to predict subsequent morbidity. The average rate of decline in FEV1 with age is approximately 20 ml/year.[12] Cross-sectional studies in Indigenous[31,34] and non-Indigenous Australians[35,36] demonstrate a presumed rate of decline. In the setting of COPD this increases and is typically over 60 ml/year.[12] Taking into account acceptable intra-subject variability (<200 ml of FEV1[38]) it can be seen that spirometry should be repeated every two years in order to determine the rate of decline in those who are declining at a high rate and therefore most at risk of rapidly progressing to more severe disease and its associated morbidity.

The final benefit of spirometry is to identify individuals who have significant reversibility/increase in FEV1 after the administration of bronchodilator. Reversibility with bronchodilator is often used as a defacto measure of airway hyperreactivity, and thus asthma. Although it is not within the scope of this document to explore the complexities of this association it is nevertheless important to note that this is not the case. In reality asthma is a diagnosis made by a combination of symptoms, variability in lung function over time and a response to anti-asthma medication. Epidemiologic studies have utilised a definition of asthma as symptoms and underlying airway hyperreactivity and a lack of significant airway hyperreactivity (to histamine, methacholine or hypertonic saline) can be used to eliminate a diagnosis of asthma. Nevertheless, many patients with airway hyperreactivity will not have a clinical diagnosis of asthma and it is traditional dogma that advanced airflow obstruction associated with asthma may not be immediately reversible with bronchodilators. What this means is that you cannot necessarily exclude asthma if there is a lack of immediate reversibility with bronchodilators.

If spirometry is to be clinically useful it must be performed in a consistent and validated manner using a properly calibrated spirometer with strict adherence to protocols regarding reproducibility and patient technique.[38] In so doing individual patient results can be generalised to previous studies of treatment or prognosis. Put another way, inaccurate and unreliable spirometry is likely to be worse than no spirometry at all. Adequate spirometry is achievable in a community setting. A cross-sectional survey of respiratory health in a remote NT Aboriginal community demonstrated that 93% of adult residents could perform adequate spirometry.[39]

Peak expiratory flow rate (PEFR)

PEFR is an inferior method to diagnose COPD compared with spirometry. In general, it cannot be recommended that Wright peak flow meters be used as a diagnostic tool as they provide little information relating to patient technique or effort. Further, although PEFR is correlated with FEV1, intra-subject variability is greater even in the setting of close attention to technique. As a result normal values for PEFR are broader for any given gender, height and age. In a cross-sectional study of residents of a remote Aboriginal community in the NT only 52% of the variability in FEV1 was explained by PEFR, and in those without symptomatic respiratory disease age, gender and height explained only 40% of the variance in PEFR compared with 60% for FEV1.[34]

Nevertheless, in Aboriginal Australians a value of PEFR >400 l/min has a negative predictive value for a low FEV1 (<80% predicted) of 94% (95% CI 91–97%) irrespective of age, height or gender.[34] Thus, if spirometry were not readily available a PEFR of >400 l/min would reasonably exclude the diagnosis of COPD. Lower values would, however, require confirmatory testing with spirometry to make or exclude a diagnosis of COPD.

2. & 3. Reduction of risk factors/ Managing chronic disease

Monitoring frequency

There is no proven optimal frequency of review. In general, the frequency of review will be determined by health system resources, the severity of disease, perceived patient knowledge of disease and treatment, whether continuing to smoke, the number and complexity of interventions and the presence of co-morbid conditions.

A general recommendation would be that those with mild/moderate disease should be reviewed annually, and this could be timed with the annual influenza vaccination. Review should occur more frequently, especially if subjects have previously demonstrated a willingness to consider smoking cessation.

Subjects with severe disease, who are on long-term oxygen therapy or who are having therapeutic venesection, should be reviewed at least every six months to reemphasise smoking cessation if continuing to smoke, to review and address knowledge of and adherence to therapy and to monitor and address environmental issues — including the impact of their respiratory disease on self-caring and carers. If possible this group of patients should also have their long-term care plan discussed annually as part of a multidisciplinary review in association with local health providers, physiotherapy, occupational therapy and a specialist physician.

Care plans

The development of care plans for all patients with chronic diseases as part of multidisciplinary care involving patients and their carers should be encouraged. These would be particularly of benefit for patients with moderate or severe disease and for those with multiple additional chronic medical problems. Such care plans should seek to address long-term management, including monitoring frequency and an action plan for acute exacerbations.

Investigations

Spirometry

See above

CXR

A single plain PA chest X-ray should be performed at diagnosis. Although this may support a diagnosis of COPD/bronchiectasis (evidence of hyperexpansion, emphysema or airway dilatation/thickening) it is predominantly utilised to exclude conditions that may have similar clinical presentations. These include chronic infections (e.g. tuberculosis) and interstitial lung disease. Subsequent CXRs may be required if there is a sudden change in symptoms (especially haemoptysis), loss of weight (TB/malignancy), or chest pain (malignancy/pneumothorax) or if patients present with an acute exacerbation with atypical features (haemoptysis, chest pain). Patients who have a severe acute exacerbation necessitating hospitalisation will usually have a CXR on admission, particularly to exclude pneumonia. There is no current evidence or consensus to suggest that screening CXRs or CT scans are useful for the early detection of lung cancer in this setting or a population with a history of tobacco consumption.

ECG

An ECG should be performed at diagnosis to provide a baseline for later assessments and to specifically look for evidence of right ventricular hypertropy/cor pulmonale. Further, an ECG may provide evidence to support an alternative diagnosis including rheumatic/valvular heart disease or cardiac failure related to ischaemic heart disease. Patients with any such changes would require local doctor ± specialist review.

FBE/haemoglobin

In general, haemoglobin should be measured at first presentation. Anaemia may contribute to unexplained shortness of breath and chronic lung disease may be associated with polycythaemia, which may require treatment (therapeutic venesection) or be indicative of significant hypoxia suitable for long-term oxygen therapy. All haemoglobin concentrations greater than 16 g/dl should be confirmed with a full blood examination. Subjects with moderate and severe disease should further have a repeat haemoglobin estimation annually. (see therapeutic venesection and long-term oxygen therapy below).

BMI

Being underweight is associated with chronic lung disease and is most likely a sequale rather than a cause of this condition. This is also the case for Indigenous Australians.[40] Although good evidence to support nutritional supplementation/dietician review in those with wasting is lacking[41] it is reasonable to monitor BMI and to consider education ± nutritional supplementation if the BMI falls below 20 kg/m^2. Nevertheless, a recent systematic review of nine trials assessing the benefit of nutritional supplementation in patients with COPD and low body weight demonstrated no significant benefit on anthropometric measures, lung function or exercise capacity.[42]

Pulse oximetry/oxygen saturation

Pulse oximetry, when available, can provide useful additional information pertinent to the management of chronic lung disease. In long-term management it can be a useful screening test to determine if further assessment is required to consider suitability for long-term oxygen therapy (LTOT) or a requirement for supplemental oxygen for air transport; and in

the setting of an acute exacerbation can allow the titration of supplemental oxygen. Nevertheless, the limitations of pulse oximetry must be appreciated to facilitate its rational and safe use.

(Figure not shown)
Figure 1. Oxygen dissociation curve comparing haemoglobin saturation and tissue oxygen tension

It is perhaps most important to understand the association between oximetry readings and the measure that it is taken to approximate, namely tissue oxygenation. To do this it is necessary to be aware of the relationship between oxygen saturation (SO_2) and tissue oxygen partial pressure (pO_2). This relationship is summarised by the oxygen dissociation curve (figure 1). Because the curve becomes relatively flat above an arterial pO_2 of 60 mmHg (corresponding to an approximate saturation of 90%), pulse oximetry is relatively insensitive to changes in pO_2 above this level. Further, the position of the curve, and therefore the specific relationship between PO_2 and SO_2, may change depending on factors such as temperature, pH, and the erythrocyte concentration of 2,3-diphosphoglycerate (2,3-DPG). Increasing temperature, falling pH (more acidic environments) and increased levels of 2,3-DPG occur in metabolically active and hypoxic tissue, reduce the affinity of oxygen for haemoglobin and encourage the dissociation of oxygen from haemoglobin. This is reflected in shifting of the oxygen dissociation curve to the right (2 in figure 1) and facilitates oxygen delivery to metabolically active tissue. In contrast, falling temperature, and increasing pH increase the affinity of haemoglobin for oxygen and encourages the binding of oxygen as occurs in the pulmonary capillary (1 in figure 1).

When perfusion of the skin is decreased, as may occur with a low cardiac output, the oximeter signal may also be unreliable or even unobtainable. Finally, other forms of haemoglobin, such as carboxyhaemoglobin (carbon monoxide associated with haemoglobin) and methaemoglobin (a rare abnormality in haemoglobin usually associated with a sensitivity to sulphur-containing drugs) cannot be differentiated from oxygen-containing haemoglobin (oxyhaemoglobin) using standard oximetry. In these rare cases the result of the oximetry reading correlates even less accurately with the tissue oxygen tension.

With these factors in mind it can be seen that in general an oximetry reading over 94% is likely to reflect adequate tissue oxygen tension (i.e. pO_2 >60 mmHg) and usually obviates the need for further assessment for LTOT. The requirement for supplemental oxygen for air transportation raises an additional issue. Whilst the proportion of oxygen in the atmosphere (the fractional inspired oxygen, F_IO_2) remains largely unchanged at the higher altitudes encountered during air travel in unpressurised aircraft the ambient pressure falls as altitude increases. The net effect of this is a reduction in the partial pressure of inspired oxygen (p_IO_2) (p_IO_2 = F_IO_2 x ambient pressure) and as a result tissue oxygenation. Even in commercial pressurised aircraft the ambient pressure is typically maintained at 550 mmHg, or about 70% of that at sea level. In individuals without low tissue oxygenation on the ground the resulting reduction in tissue oxygenation is well tolerated without adverse effect. Individuals with low levels of tissue oxygenation at ground level, as can occur in chronic lung disease when stable and particularly during an exacerbation, may however become dangerously hypoxic during air travel.

These guidelines advocate the assessment of subjects with severe disease in a centre where blood gases can be performed. We are, however, cognisant that this may require air travel of people who may have significant hypoxia. If oximetry is available a reading less than 94% is likely to indicate a pO_2 that is sufficiently low to warrant supplemental oxygen for air transport. Issues relating to transport with oxygen must be addressed in liaison with the clinician the patient is referred to and the commercial carrier (if an RPT or charter service is used). It may also be possible to utilise medical evacuation (RFDS and AirMed) flights and this should be discussed with the relevant service.

Smoking cessation

The causative link between COPD and tobacco consumption has been well established.[6,8,9,10,12] As a result it is clear the most important primary preventive initiative for COPD is to prevent people commencing smoking and to stop those who do smoke before they develop COPD. Nevertheless, there are a small group of people who develop COPD and who do not have a history of tobacco consumption.[43] The second role for smoking cessation is as secondary prevention. The Lung Health Study demonstrated that in smokers with COPD that smoking cessation was associated with a reduction in the accelerated decline in FEV1.[13] Although the success in converting smokers to sustained quitters was reasonably low, it is likely the effect today is even more than that demonstrated in this earlier study with the advent of newer and more effective smoking cessation strategies.

A meta-analysis comparing low intensity counselling, high intensity counselling and specific pharmacotherapy for smoking cessation in subjects with COPD is currently in process and should provide further support and more contemporary direction for specific smoking cessation strategies in this population.[44]

Vaccination

Vaccination for Streptococcus pneumoniae and influenza is frequently advocated for those with COPD and is recommended as part of the national vaccination guidelines.[44] Certainly acute exacerbations of COPD are a significant cause of morbidity and mortality and these are associated with both these agents. A recent meta-analysis of influenza vaccination reviewed four studies in patients with COPD and five with patients belonging to high-risk groups, of which a proportion also had COPD.[46] Although the data were limited it suggested that influenza vaccine in COPD decreased exacerbations in the following year, although only in the three weeks after the vaccination. The authors concluded that influenza vaccination was associated with some early adverse effects, although these were not serious and were outweighed by the long-term benefit of vaccination.

The evidence for a beneficial effect of poly-valent pneumococcal vaccination for non-Indigenous patients with COPD is less persuasive. Observational studies have demonstrated superior vaccine efficacy for invasive disease in subjects with chronic diseases including chronic lung disease.[47] Nevertheless, a more recent meta-analysis of randomised-controlled trials has concluded that there is evidence only to support vaccination in reducing bacteremic pneumococcal pneumonia in low-risk adults.[48] A current protocol by the Cochrane Airways Group investigating the role of pneumococcal vaccination in COPD will provide more up-to-date information relating to this question.[49] Nevertheless, in the Northern Territory rates of invasive pneumococcal disease are high, and the current

recommendation is to provide the 23-valent vaccine to all Indigenous Australians aged 15 years or greater irrespective of the presence of chronic lung disease.[50]

Delivery system of inhalation therapy

In general, the choice of delivery system for inhalational therapy in stable COPD is dependent on patient preference. No method of delivery – be it pressurised metered dose inhaler (pMDI), dry powder inhaler or nebuliser – appears to be superior.[51] In general, dry powder inhalers, breath actuated inhalers and spacers may be useful if patients have difficulty coordinating inhalation with standard pMDIs. Spacers may be particularly useful if inspiratory flows are low as occurs in severe disease and if local side-effects due to propellants or inhaled steroids are encountered.

Bronchodilators

In general, bronchodilators and particularly ipratropium have been shown to not alter the rate of decline in FEV1 in COPD.[13] There is no evidence to suggest this would be different for subjects with bronchiectasis. Nevertheless, bronchodilators can result in a temporary increase in FEV1 that may, in those with severe disease, be clinically significant.[13] As a result we have suggested that whilst bronchodilators may be used in any level of severity of chronic lung disease they may be particularly beneficial in subjects with severe disease where the small average improvement may become clinically significant. Both β_2 agonists (e.g. salbutamol) and anticholinergics (ipratropium bromide) can produce this effect. Nevertheless, there is some evidence that their effect may be at least partially additive[52], and thus in severe disease the use of β_2 agonists (e.g. salbutamol) and anticholinergics may be beneficial

Long-acting β_2 agonists

Like bronchodilators in general, long-acting β_2 agonists are associated with an improvement in lung function. In general, this improvement is small and of minimal clinical significance. In a meta-analysis of four RCTs of salmeterol the average improvement in FEV1 after 4–16 weeks of treatment was 100ml.[53] Such an improvement is of doubtful clinical significance and no study demonstrated an improvement in functional performance as demonstrated by an improvement in the six minute walk test. Nevertheless, one study did demonstrate an improvement in QOL and a reduction in breathlessness. In general, these finding would indicate that there is little role for long-acting β_2 agonists in the routine management of COPD. Nevertheless, in patients with severe airflow obstruction – and particularly those with evidence of reversibility but not sufficient to warrant the diagnosis of asthma – a trial of salmeterol or eformoterol may be warranted.

Theophylline

Methylxanthines as exemplified by theophylline/ aminophylline are associated with a fixed improvement in FEV1 similar to β_2 agonists and anticholinergics. Nevertheless, like these there is no evidence that they alter the decline in FEV1 when used long-term. In general the use of oral theophylline for maintenance therapy has been discouraged due to potential toxicity, monitoring requirements and no evidence that they are superior in improving FEV1 as compared to inhaled bronchodilators. The authors, however, realise that oral bronchodilators may improve adherence to therapy compared with inhalation preparations due to a combination of patient

preference and an inability to properly use inhaled bronchodilators, even when supplemented with spacers or nebulisers. In this case theophylline use may be warranted.

Determination of theophylline levels is recommended soon after initiating therapy (within two weeks), before increasing the dose when a patient fails to have an expected response and when an adverse reaction or toxicity is suspected. Further levels should be monitored whenever drugs known to alter theophylline elimination are introduced or withdrawn and upon the addition of any new medication with an unknown effect on theophylline elimination. (Theophylline clearance increased by: carbamazepine; phenobarbital; phenytoin; rifampicin and tobacco consumption and reduced by: allopurinol, oestrogen containing contraceptives; fluoroquinolone antibiotics; macrolide antibiotics (though azithromycin appears to have no effect); methotrexate; propranolol; thiabendazole; ticlopidine and verapamil). In general, before the institution of theophylline all current medications should be reviewed in relation to their effect on theophylline clearance. If none of these events occur it is generally recommended that levels be performed at least every six to 12 months in stable patients.[54]

Inhaled steroids

In general, the utility of inhaled steroids in the management of COPD may be summarised by reviewing their effect on the rate of decline in lung function/FEV1, initial effect on lung function, effect on acute exacerbation frequency and effect on quality of life and its decline with disease progression. Large multicentre randomised-controlled trials — including the Lung Health Study, ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe) study[55] and the EuroSCOP (European Respiratory Society Study on Chronic Obstructive Pulmonary Disease) study[56] — all failed to demonstrate any reduction in the rate of decline in FEV1. Nevertheless, a meta-analysis of three earlier studies [57] did demonstrate such a reduction over two years of treatment with relatively high doses (generally 1 500 μg of beclomethasone diproprionate) of inhaled steroids. Whilst most recent studies and the specialist respiratory community in general conclude that inhaled steroids do not alter the rate of decline in FEV1 a Cochrane review currently being conducted may clarify this position.[58]

The above trials did, however, demonstrate an improvement in lung function with the addition of inhaled steroids, but this was an initial effect and, as noted above, was not associated with any difference in the ultimate decline in lung function. The size of this effect was generally small and ranged from 40[55]–98 ml.[56] Although such a difference is likely to be clinically insignificant an increase of 100 ml in FEV1 in those with severe disease may result in a significant symptomatic improvement. In light of this we have advocated the general use of inhaled steroid in those subjects with severe/stage three disease.

The evidence for the use of inhaled steroids in bronchiectasis is less substantial. A meta-analysis of trials in bronchiectasis was able to find only two suitable randomised double-blind controlled trials of inhaled steroid use in bronchiectasis and these were conducted for a maximum of six weeks.[59] Whilst such studies were too brief to determine any change in decline in lung function there was a non-significant trend for improvement in lung function measures. Certainly this would be consistent with the findings in COPD and would support a similar recommendation for inhaled steroid use in this sub-group of individuals with chronic lung disease.

Inhaled steroids have, however, been shown in occasional studies to reduce the frequency of exacerbations. In the ISOLDE study exacerbations, defined as an increase in symptoms necessitating the prescription of oral corticosteroids or antibiotics by a general practitioner, were less frequent in those on inhaled steroids (fluticasone proprionate 1 000 μg/d — a high dose comparable to approximately 2 000 μg of beclomethasone diproprionate) (0.99/year) compared to those on placebo (1.32/year). This represented a statistically significant reduction in exacerbation frequency of 25%. A similarly designed study comparing fluticasone proprionate 500 μg/d with placebo over six months demonstrated no significant difference in the number of exacerbation, but did show a significant reduction in the number of moderate or severe exacerbations.[60] In view of these findings we have suggested that subjects with frequent acute exacerbations of chronic lung disease (in this case we have chosen an arbitrary cut-off of three exacerbations) may benefit from the addition of inhaled steroids. Whilst data are lacking for Indigenous Australians our initial findings in a prospective cohort study would suggest that exacerbations (defined as two of increased sputum volume, change in sputum colour or increased dyspnoea) are likely to be more frequent in Indigenous compared with non-Indigenous population with chronic lung disease. Our initial estimates are that self-reported acute exacerbations of COPD in Indigenous Australians in the Top End of the NT occur on average once every two months.[61]

The final potential role for inhaled steroids that may be clinically relevant is the effect on quality of life. No well-validated measure of quality of life for Indigenous Australians is available and perceptions of health, disease and function are likely to be different in this population. Thus, caution should be used in generalising quality of life studies in non-Indigenous populations to Indigenous Australians. Nevertheless, there is evidence that inhaled steroids may at least be associated with an initial improvement in quality of life and a reduced decline in this measure over time in non-Indigenous developed world populations. Using the disease-specific St George Respiratory Questionnaire (SGRQ), the ISOLDE study demonstrated that inhaled steroids delayed a clinically significant reduction in respiratory health status from 15 to 24 months.[55] In turn the SGRQ has been shown to be a better predictor of hospitalisation and death within 12 months than FEV1.

At this time the high rate of subjects lost to follow-up (approximately 50% in each group), and the use of a quality of life questionnaire which is not validated for Indigenous Australians makes it difficult to advocate the routine use of inhaled steroids in the local practice setting based on a rationale of improved quality of life. Nevertheless, this is an area that requires further local investigation.

Oral steroids

Long term

There is no proven role for oral steroids in the long-term management of stable COPD or bronchiectasis. Like inhaled steroid they may be associated with a one-off increase in lung function even in stable disease but this has not been shown to reduce the rate of decline in lung function in the long term. Although a one-off improvement in lung function may be clinically significant in patients with severe disease the side effects of long-term systemic steroids would preclude their routine use. Nevertheless, the authors realise it may occasionally be difficult to wean systemic steroids in some patients as this can occasionally be associated with

further exacerbations of disease. In the minority of patients in whom this occurs the use of high doses of inhaled steroids may occasionally allow the weaning of systemic steroids, though no evidence from RCTs is available to support this. If weaning of systemic steroids is not possible it is important to consider alternative diagnoses, including asthma and interstitial lung disease, and specialist review is warranted as well as monitoring for adverse effects of long-term steroids (including diabetes, hypertension and osteoporosis). The risk of reactivation of latent tuberculosis in patients on long-term systemic steroids should be considered. Appropriate investigations and consideration for isoniazid prophylaxis should be discussed with the treating doctor (see section on TB).

Oral steroid trial

A trial of oral steroids is occasionally advocated to determine which subjects may benefit from longer term inhaled steroids.[22] A recent large randomised controlled trial of long-term fluticasone proprionate, however, demonstrated that the improvement in FEV1 associated with prednisolone 0.6 mg/kg/day for 14 days did not correlate with the subsequent decline in FEV1 in those assigned to inhaled steroids. Although short courses of oral corticosteroids are reasonably safe the use of steroid trials to plan future inhaled steroid use is not advocated here.

Long-term oxygen therapy

Long-term oxygen therapy (LTOT) refers to the use of supplemental oxygen in patients with significant hypoxia due to lung disease. In general the aim is to increase the tissue oxygen partial pressure (pO_2) to levels above 60 mmHg and to maintain these levels for at least 16 hours per day. In appropriately selected patients LTOT is associated with increased survival. People who benefit are those with lung disease and a p_aO_2 <60 mmHg whilst breathing room air. Several studies have supported the role of LTOT in patients with chronic lung disease (in this COPD) and significant hypoxaemia.[62-64] In general LTOT has improved survival in such patients at both two and five years. Of note the Nocturnal oxygen therapy trial (NOTT)[62] and a study by Fletcher et al[65] demonstrated no significant benefit from supplemental oxygen at night for patients who had isolated nocturnal (only) oxygen desaturation. A recent systematic review has also supported the role of LTOT in patients with chronic lung disease and a p_aO_2 <60 mmHg.[66]

The assessment for suitability for LTOT typically requires the collection of an arterial blood gas (ABG) sample. As a result this requires the referral of a patient to a centre where this can be performed (usually a hospital). An oximetry reading that is <90% on room air would correlate which such a low reading and would be a reasonable de facto measure. Nonetheless many patients with oximetry readings between 90 and 94% may still be appropriate for LTOT and should have ABGs performed. It is important that assessment occurs when the patient is stable and not having an acute exacerbation of their disease. ABGs performed whilst hospitalised should therefore not be used to assess the suitability for LTOT but can be useful in identifying those who require further assessment once stable. Since it can take over two weeks to return to baseline lung function after an acute exacerbation even ABGs on discharge from hospital can be misleading.

Current smoking is an absolute contraindication for LTOT as smoking and supplemental oxygen is an explosive combination and can be associated with

life threatening facial and airway burns. It is therefore important to confirm that patients are not currently smoking before considering LTOT. If there is any doubt abstinence can be determined by assessment with urinary/serum/salivary cotinine.

Typically LTOT is delivered using nasal prongs at a rate of 2–4 l/min. LTOT is usually delivered using an oxygen concentrator. This requires a reliable power supply and in turn is associated with increased home electricity costs. Backup cylinders of oxygen may be supplied if the electricity supply is unreliable. Although these can be kept at home it is often more convenient in remote communities for such cylinders to be stored at the local health centre. To encourage mobility and maximise quality of life it is possible to provide smaller cylinders for excursions outside the home.

It is important to realise that LTOT has only shown to be of benefit if used more than 12 hours per day, and particularly more than 16 hours. As such LTOT supplied by an oxygen concentrator alone can restrict mobility. It is important that patients on LTOT are encouraged to maintain their mobility and mobile small cylinders can therefore be useful. The details of delivery of LTOT should be discussed with the relevant respiratory nurse (Darwin and Alice Springs).

Supplemental oxygen is also occasionally used if exercise capacity is limited by hypoxia. The evidence for this is limited and the benefit of supplemental oxygen in improving exercise capacity should be objectively assessed before it is prescribed for this use. A planned systematic review of supplemental oxygen for exercise alone is planned and should help address this issue.[67] It is, however, important to draw a distinction between ambulatory oxygen as a method of improving adherence to LTOT, which is of proven benefit, and its use only for exercise, which remains controversial. Finally, supplemental oxygen is sometimes used in late stage disease as palliation. Its use in this setting should be discussed with the local palliative care service if available. In both cases it should be remembered that current smoking is an absolute contraindication for its use.

Therapeutic venesection

Long-standing tissue hypoxia due to severe chronic lung disease can be associated with an increase in the total red cell mass (polycythaemia). Whilst this can increase tissue oxygen delivery it can result in increased blood viscosity, worsening pulmonary hypertension and an increased risk of intravascular thrombosis, and particularly thrombotic stroke. The red cell mass is reflected in the standard full blood count by an increase in the haemoglobin and particularly the packed cell volume (PCV)/haematocrit (HCT). The risk of intravascular thrombosis increases when the PCV rises above 0.55 (i.e. 55% of the blood volume is made of cells, and particularly by erythrocytes). If the PCV is above 0.55 it should prompt an assessment for the suitability for LTOT if this has not been performed. If the polycythaemia fails to respond to maximal medical treatment (including LTOT if indicated) then regular slow therapeutic venesection may be indicated. This should be discussed with the caring doctor/specialist as some patients do not tolerate venesection well.

Mucolytics

Oral mucolytics include N-acetylcysteine (NAC), S-carboxymethylcysteine, bromhexine, ambroxol, sobrerol, cithiolone, letosteine and iodinated

glycerol, N-isobutyrylcysteine (NIC), and myrtol. N-acetylcysteine (NAC) is the most frequently used and studied agent. A systematic review of regular mucolytics (for at least two months) in COPD demonstrated a significant reduction in the frequency of exacerbations with their use.[68] The summary measure of effect of mucolytics was a small but significant reduction in the number of exacerbations per month of 0.07. The average exacerbation rate across these studies was 2.7 per year and extrapolated to a reduction in exacerbations of 0.8/patient/year. There is insufficient data for mucolytics in bronchiectasis specifically, nevertheless, it is likely a similar effect would be seen in this condition.

Hypertonic agents (hypertonic saline 3–14% and mannitol) are also frequently utilised in chronic respiratory disease. Unlike mucolytics these agents do not attempt to solubilise sputum, making it less viscous and easier to expectorate. Rather they attempt to correct the impaired mucociliary clearance that is a characteristic of bronchiectasis and COPD. Whilst hypertonic agents have been shown to improve markers of sputum clearance[69] controlled trials of their benefit in reducing exacerbation frequency or improving lung function are lacking. Nevertheless, current trials investigating such clinical efficacy of hypertonic saline are currently in process and should address this question.

Prophylactic antibiotics

Patients with chronic lung disease and frequent acute exacerbation or copious sputum production are occasionally prescribed long-term antibiotics. Dosing regimens include continuous use of a single antibiotic or rotating use of different antibiotics. Evidence to support such a practice as a way of reducing exacerbation frequency or decline in lung function or improving quality of life is confusing, with occasional studies demonstrating benefit and many showing no effect. The use of long-term antibiotics further raises questions of selecting for resistant bacteria in such patients. Two systematic reviews are currently in process which may help to address this area for both COPD[70] and bronchiectasis[71] and studies addressing the efficacy of prophylactic antibiotics in Indigenous Australians with chronic lung disease living in remote communities are planned.

Physiotherapy

The role of physiotherapy in the management of chronic lung disease covers a broad range of interventions. The role of physiotherapy, as part of a multidisciplinary approach to rehabilitation, has been shown to improve quality of life and mobility and will be explored below. Apart from rehabilitation physiotherapy is also occasionally advocated to encourage expectoration of sputum. Techniques utilised to achieve this, covered by the broad-term bronchopulmonary hygiene physical therapy (BHPT), include exhalation techniques, postural drainage and external percussion. BHPT is labour intensive and can place additional demands on health providers, patients and their families. Further, in some patients it is associated with adverse side effects including hypoxia[72] and a temporary reduction in lung function.[73] A systematic review of the use of BHPT in COPD and bronchiectasis demonstrated no significant clinical benefit on lung function or p_aO_2 in either condition.[74] Nevertheless, only seven trials with a total of 129 subjects were deemed to be of sufficient methodological quality for inclusion. This finding would nonetheless indicate that if there is a beneficial effect of BHPT it is likely to be small and that

further study is required to determine this with particular emphasis on quality of life and exacerbation frequency. The lack of conclusive benefit from BHPT, the demands it places on patients and their carers and the risk of adverse effect mean that we have not advocated the routine use of BHPT in chronic lung disease.

Pulmonary rehabilitation

Unlike BHPT (see above) there is an increasing body of evidence from randomised controlled trials to support the benefit of pulmonary rehabilitation in chronic lung disease. Evaluated pulmonary rehabilitation programs have utilised a multi-disciplinary approach in either an inpatient or outpatient setting. Whilst pulmonary rehabilitation programs do not appear to improve lung function they are associated with clinically significant improvement in exercise capacity as measured by a six minute walk test and maximal oxygen consumption, a measure of fitness.[75] Outpatient programs involving physiotherapy assessment, exercise training, dietary assessment and advice and occupational therapy assessment are also associated with a significant improvements in quality of life[76], and these improvement persist for at least 18 months[77] and up to two years.[78] Whilst such programs are resource intense their immediate efficacy and persisting clinically significant benefit would encourage the development and funding of similar programs for patients with COPD in the NT.

Surgery

Surgical options in COPD include bullectomy, lung volume reduction surgery (LVRS) and single or double lung transplantation. For bronchiectasis they include resection of focally diseased lung and lung transplantation. Such procedures are difficult to evaluate in the setting of a randomised controlled trial. Whilst there is currently little evidence to support long-term benefit for LVRS[79] this is, however, currently being evaluated as part of an RCT, the National Emphysema Treatment Trial. Nevertheless, it is already apparent that such interventions can be associated with substantial morbidity and mortality.[80] In general these procedures (except focal resection in bronchiectasis) are reserved for patients with advanced disease. Nevertheless, patients with advanced disease, especially when this is associated with an FEV1 <35% predicted, should be reviewed by a specialist physician where the suitability for such procedures can be determined.

The role of resection of focal bronchiectasis remains unclear and is informed largely by case series with an absence of controlled trials.[81] Many patients with presumed focal disease are often found on further investigation to have more generalised disease. If, however, bronchiectasis is confirmed on high resolution CT (HRCT) to be confined to one or two lobes it is reasonable to consider this option and to refer patients for specialist review irrespective of lung function.

4. Managing acute exacerbations of chronic respiratory disease

Background

Despite the prevalence of COPD and the frequency of exacerbations resulting in utilisation of increased medical resources there is no standard definition of an acute exacerbation (AE). A proposed working definition from the American Thoracic Society is a ‘sustained worsening of the patient’s condition, from the stable state and beyond normal day to day variations, that is acute in onset and necessitates a change in regular

medication in a patient with underlying COPD'.[82] There are further subclassifications of severity based on clinical need.

In the absence of a generally accepted definition, evaluation of the published literature has been problematic. However, most definitions include the three clinical findings of worsening dyspnoea, increased sputum production and sputum purulence. Most patients receive most available therapies and the presence of co-interventions has made analysis of any single therapy more difficult. Further, the majority of research studies are in an emergency department or in-patient setting while the majority of episodes of acute exacerbation are treated on an outpatient basis.

Inhaled bronchodilators, corticosteroids, antibiotics and non-invasive ventilatory support have all shown efficacy but methylxanthines, mucolytics and chest physiotherapy do not appear of benefit. While oxygen is frequently required, in an identifiable subgroup it increases the risk of respiratory failure and needs to be utilized with caution.[83]

Bronchodilating agents

Short-acting beta agonist type (e.g. salbutamol) and anticholinergic (e.g. ipratropium) inhaled bronchodilators appear to have comparable effects on spirometry, and the combined use of them has not been clearly demonstrated to confer advantage over larger doses of either alone. Patients receiving ipratropium alone had the lowest rate of side effects. Again, conclusions are limited by differences in inclusion and exclusion criteria and the small numbers of trials.[83]

A meta analysis of eight RCTs failed to find evidence supporting any delivery system conferring advantage over another, MDI use appearing equally efficacious as nebuliser and response being dose dependent.[83]

Antibiotics

The role of antibiotics in acute exacerbations has been controversial. While nine placebo controlled trials concluded there was significant improvements in outcomes for those treated with antibiotics, six studies were unable to find statistically significant differences. It would appear the overall benefit is related to the severity of the exacerbation, and antibiotics are recommended for all with increased dyspnoea, increased sputum volume and the development of purulent sputum.[84] While in one study those treated with antibiotics had significantly lower relapse rates (independent of the severity of their underlying disease or the severity of the exacerbation[85]) in other studies those identified as most likely to benefit were those with higher numbers of exacerbations per year and those with comorbid illness (diabetes, asthma and CHD).[83,86]

There is little evidence for recommending the most appropriate duration of treatment; trials typically ranged from 3–14 days.[83]

The agents used for the RCTs included amoxycillin, trimethoprim-sulfamethoxazole and tetracycline.

Corticosteroid drugs

The pathological features of AE of COPD share with exacerbations of asthma, as well as worsening of the inflammatory component of the disease during exacerbations, provide rationale for the use of corticosteroids. In a Cochrane review, use of systemic corticosteroids improved spirometry over the first 72 hours and reduced relapse rates but there was no evidence that their use reduced the likelihood of dying or decreased hospital stay.[87] The SCCOPE trial found FEV1 improvements with steroid use highest after the

first day of treatment, still statistically significant up to the third day but no longer significant at two weeks. There appeared no advantage in an eight-week course over a two-week course. Patients receiving steroids were 2.7 times more likely to have adverse reactions, and the recommendation was for further research into the risk benefit ratio.[83]

Oxygen therapy

While oxygen therapy does increase the risk of respiratory failure in an identifiable group of patients, (those with simultaneous hypercarbia and hypoxaemia), oxygen therapy is indicated for all patients with hypoxaemia. Oxygen relieves pulmonary vasoconstriction and right heart strain and lessens myocardial ischemia. Improved oxygen delivery to the lungs probably aids mucociliary transport. Oxygen administration in studies generally ranged from 24–28%.[83,88]

Mucolytic agents and percussion

While mucolytic agents may improve symptoms they have not been demonstrated to improve function or outcome.[89]

From three RCTs mechanical percussion is not only ineffective but may decrease FEV1 transiently in patients with acute exacerbations of COPD.[89]

Methylxanthines

Not only did most studies show little if any additional bronchodilator effect with aminophylline or theophylline if maximal doses of beta adrenergics or anticholinergics have been used, but these agents have numerous adverse effects and drug interactions, sometimes life threatening, and their use is generally not recommended, particularly in patients with co morbidities.[90]

Identifiable risk factors for relapse

From several studies there appear to be identifiable predictors for relapse. These include:

- lower baseline FEV1 levels;
- higher rates of previous relapse; and
- more bronchodilator treatments or corticosteroids during visit.

However, all have only moderate discriminatory power.[89]

Predictors of in-patient mortality

Physiological characteristics associated with higher rates of mortality have been identified, but inclusion criteria showed substantial variability and predictability of death was less than 90% for any model.

Rationale for referral

While COPD is a common condition and exacerbations frequent, because most studies are in-patient or emergency department-based, and because there has been no standard definition of exacerbation or inclusion/exclusion criteria, recommendations for when to refer are based on present practice. While factors related to risk of relapse and mortality have been identified, currently there are no reliable models for risk stratification.

References

1. Jamison, D., A. Cresse & T. Prentice. The world health report 1999: Making a difference. World Health Organization: Geneva, 1999; 121.
2. Unwin, E., N. Thomson & M. Gracey. The impact of tobacco smoking and alcohol consumption on Aboriginal mortality and hospitalisation in Western Australia: 1983–1991. 1st ed. Perth: Health Department of Western Australia, 1994; 12–31.
3. Plant, A., J. Condon & G. Durling. Northern Territory health outcomes: Morbidity and mortality 1979–91. Northern Territory Department of Health and Community Services, 1995; 133.
4. Cunningham, J. & J. Condon. Premature mortality in Aboriginal adults in the Northern Territory, 1979–1991. MJA 1996; 165:309–12.
5. Dempsey, K. & J. Condon. Mortality in the Northern Territory 1979–1997. Darwin: Territory Health Services, 1999; 186.
6. Doll, R. & A. Hill. The mortality of doctors in relation to their smoking habits: A preliminary report. Brit Med J 1954; 2(4877):1451–5.
7. Doll, R. & A. Hill. Lung cancer and other causes of death in relation to smoking: A second report on the mortality of British doctors. Brit Med J 1956; 2(5001):1072–81.
8. Doll, R. & A. Hill. Mortality in relation to smoking: Ten years' observation of British doctors. Brit Med J 1964; 1:1399–410, 1460–7.
9. Doll, R. & R. Peto. Mortality in relation to smoking: 20 years' observation on male British doctors. Brit Med J 1976; 2:1525–36.
10. Doll, R., et al. Mortality in relation to smoking: 22 years' observations on female British doctors. British Medical Journal 1980; 1:967–71.
11. Fletcher, C. & R. Peto. The natural history of chronic airflow obstruction. Brit Med J 1977; 1:1645–8.
12. Fletcher, C., et al. The natural history of chronic bronchitis and emphysema: An eight-year study of early chronic obstructive lung disease in working men in London. Oxford: Oxford University Press, 1976; 1–272.
13. Anthonisen, N.R., et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. JAMA 1994; 272(19):1497–505.
14. Dennis, R.J., et al. Wood smoke exposure and risk for obstructive airways disease among women. Chest 1996; 109(3 Suppl):55s–56s.
15. Døssing, M., J. Khan & F. al Rabiah. Risk factors for chronic obstructive lung disease in Saudi Arabia. Respir Med 1994; 88(7):519–22.
16. Smith, K., A. Aggarwal & R. Dave. Air pollution and rural biomass fuels in developing countries: A pilot village study in India and implications for research and policy. Atmospheric Environment 1983; 17(11):2343–62.
17. Barker, D., et al., Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. BMJ 1991; 303:671–5.
18. Shaheen, S.O., D.J. Barker & S.T. Holgate, Do lower respiratory tract infections in early childhood cause chronic obstructive pulmonary disease? Am J Respir Crit Care Med 1995; 151(5):1649–51; discussion 1651–2.
19. Shaheen, S.O., et al., The relationship between pneumonia in early childhood and impaired lung function in late adult life. Am J Respir Crit Care Med 1994; 149(3Pt 1):616–19.
20. Shaheen, S. & D.J. Barker, Early lung growth and chronic airflow obstruction [editorial]. Thorax 1994; 49(6):533–6.
21. American Thoracic Society, Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995; 152:S77–S120.

22. British Thoracic Society, British Thoracic Society COPD guidelines. Thorax, 1997. 52 (supp 5): p. S1–S32.
23. Global Initiative for Chronic Obstructive Lung Disease, GOLD, Phase III, Global Initiative for Chronic Obstructive Lung Disease, Editor. 2001, GOLD.
24. Thoracic Society of Australia and New Zealand, The Australian Lung Foundation first draft of a COPD management plan, Thoracic Society of Australia and New Zealand, Editor. Thoracic Society of Australia and New Zealand, 2001.
25. Bang, K.M., et al. The effect of pulmonary impairment on all-cause mortality in a national cohort. Chest 1993; 103(2):536–40.
26. Sorlie, P.D., W.B. Kannel & G. O'Connor, Mortality associated with respiratory function and symptoms in advanced age. The Framingham Study. American Review of Respiratory Disease 1989; 140(2):379–84.
27. Krzyzanowski, M. & M. Wysocki, The relation of thirteen-year mortality to ventilatory impairment and other respiratory symptoms: the Cracow Study. International Journal of Epidemiology 1986; 15(1):56–64.
28. Bishop, J.M. & K.W. Cross. Physiological variables and mortality in patients with various categories of chronic respiratory disease. Bull Eur Physiopathol Respir 1984; 20(6):495–500.
29. Engstrom, G., et al. Respiratory decline in smokers and ex-smokers: an independent risk factor for cardiovascular disease and death. J Cardiovasc Risk 2000; 7(4):267–72.
30. Meijers, J.M., G.M. Swaen & J.J. Slangen. Mortality of Dutch coal miners in relation to pneumoconiosis, chronic obstructive pulmonary disease, and lung function. Occup Environ Med 1997; 54(10):708–13.
31. Veale, A., et al. 'Normal' lung function in rural Australian Aborigines. Aust NZ J Med 1997; 27:543–9.
32. Thompson, J., et al. Venrtilatory standards for clinically well Aboriginal adults. Med J Aust 1992; 156:566–9.
33. Bremner, P., et al. Respiratory symptoms and lung function in Aborigines from Tropical Western Australia. Am J Respir Crit Care Med 1998; 158:1724–9.
34. Maguire, G., et al. Social advantage and 'normal' respiratory function in a Northern Australian remote Aboriginal community. Submitted Chest, 2001.
35. Knudson, R.J., et al. Changes in the normal maximal expiratory flow-volume curve with growth and aging. American Review Of Respiratory Disease 1983; 127(6):725–34.
36. Gore, C.J., et al. Spirometric standards for healthy adult lifetime nonsmokers in Australia. European Respiratory Journal 1995; 8(5):773–82.
37. Anderson, H., J. Anderson & J. Cotes. Lung function values in healthy children and adults from highland and coastal areas of Papua New Guinea: prediction nomograms for forced expiratory volume and forced vital capacity. Papua New Guinea Medical Journal 1974; 17:165–7.
38. American Thoracic Society, Standardization of Spirometry, 1994 Update. Am J Respir Crit Care Med 1995; 152(3):1107–36.
39. Maguire, G., et al. The assessment and burden of chronic respiratory disease in a remote northern Australian Aboriginal community. Submitted International Journal of Public Health, 2001.
40. Maguire, G., et al. Risk factors for chronic respiratory disease in an Indigenous Australian community. Submitted Thorax, 2001.
41. Ferreira, I.M., et al. Nutritional support for individuals with COPD: a meta-analysis. Chest 2000; 117(3):672–8.
42. Ferreira, I., et al. Nutritional supplementation for stable chronic obstructive pulmonary disease, Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
43. Stang, P., et al. The prevalence of COPD: using smoking rates to estimate disease frequency in the general population. Chest 2000; 117(5 Suppl 2):354S–9S.

44. van der Meer, R., et al. Smoking cessation for patients with chronic obstructive pulmonary disease, Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
45. National Health and Medical Research Council, National Indigenous Pnuemococcal and Influenza Immunisation Program, National Health and Medical Research Council, Editor. 2001. Canberra: National Health and Medical Research Council: .
46. Poole, P., et al. Influenza vaccine for patients with chronic obstructive pulmonary disease., Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
47. Butler, J.C., et al. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. JAMA 1993; 270(15):1826–31.
48. Fine, M.J., et al. Efficacy of pneumococcal vaccination in adults. A meta-analysis of randomized controlled trials. Archives of Internal Medicine 1994; 154(23):2666–77.
49. Wood-Baker, R. & P. Poole. Vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease [Protocol]. Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
50. Krause, V.L., S.J. Reid & A. Merianos. Invasive pneumococcal disease in the Northern Territory of Australia, 1994–1998. Med J Aust 2000; 173 Suppl:S27–31.
51. Ram, F., et al., Pressurised metered-dose inhalers versus all other hand-held inhalers devices to deliver bronchodilators for chronic obstructive pulmonary disease (Cochrane Review). 2002, The Cochrane Library.
52. Ikeda, A., et al. Bronchodilating effects of combined therapy with clinical dosages of ipratropium bromide and salbutamol for stable COPD: comparison with ipratropium bromide alone. Chest 1995; 107(2):401–5.
53. Appleton, S., et al. Long-acting beta2-agonists for chronic obstructive pulmonary disease (Cochrane Review). 2002, The Cochrane Library.
54. Honig, E. & R. Ingram. Harrison’s 14th Edition CD ROM, in Harrison’s principles of internal medicine. E. Braunwald, et al. (editors). New York: McGraw-Hill, 2001; 1491–9.
55. Burge, P.S., et al. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ (Clinical Research Ed.) 2000; 320(7245):1297–303.
56. Pauwels, R.A., et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. New England Journal of Medicine 1999; 340(25):1948–53.
57. van_Grunsven, P.M., et al. Long term effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a meta-analysis. Thorax 1999; 54(1):7–14.
58. Yang, I., et al. Inhaled corticosteroids for stable chronic obstructive pulmonary disease [Protocol], Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
59. Kolbe, J., A. Wells & F. Ram, Inhaled steroids for bronchiectasis, Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
60. Paggiaro, P.L., et al. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. Lancet 1998; 351(9105):773–80.
61. Maguire, G., R. Bailie & B. Currie, Optimising chronic lung disease care for Indigenous Australians. Unpublished document. Darwin: Menzies School of Health Research, 2001.
62. Timms, R., F. Khaja & G. Williams, Nocturnal oxygen therapy trial group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. Ann Intern Med 1980; 93:391–8.

63. Report of the Medical Research Council working party, Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 1981; 1:681–5.
64. Gorecka, D., et al., Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. Thorax 1997; 52(8):674–9.
65. Fletcher, E., et al., A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO2 above 60 mmHg. Am Rev Respir Dis 1992; 145(5):1070–6.
66. Crockett, A., et al. Domiciliary oxygen for chronic obstructive pulmonary disease, Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
67. Wedzicha, W., E. Paul & P. Jones, Ambulatory oxygen for chronic obstructive pulmonary disease [Protocol], Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
68. Poole, P. & P. Black, Mucolytic agents for chronic bronchitis, Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
69. Daviskas, E., et al., Inhalation of dry powder mannitol improves clearance of mucus in patients with bronchiectasis. J Respir Crit Care Med 1999; 159:1843–8.
70. Black, P. & P. Poole, Antibiotics for preventing exacerbations in chronic bronchitis [Protocol], Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
71. Greenstone, M., P. Sullivan & C. Brady, Prolonged high-dose antibiotics for purulent bronchiectasis [Protocol], Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
72. Connors, A., et al. Chest physical therapy: the immediate effect on oxygenation in acutely ill patients. Chest 1980; 78:559–64.
73. Campbell, A. & J. O'Connell. The effect of chest physiotherapy upon FEV. MJA 1975; 1:33–5.
74. Jones, A. & B. Rowe, Bronchopulmonary hygiene physical therapy for chronic obstructive pulmonary disease and bronchiectasis, Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
75. Criner, G.J., et al. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999; 160(6):2018–27.
76. Finnerty, J.P., et al. The effectiveness of outpatient pulmonary rehabilitation in chronic lung disease: a randomized controlled trial. Chest 2001; 119(6):1705–10.
77. Troosters, T., R. Gosselink & M. Decramer, Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Am J Med 2000; 109(3):207–12.
78. Guell, R., et al. Long-term effects of outpatient rehabilitation of COPD: A randomized trial. Chest 2000; 117(4):976–83.
79. Hensley, M.C., JL; Davies, HR; Gibson, P. Lung volume reduction surgery for diffuse emphysema, Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
80. The National Emphysema Treatment Trial. Patients at high risk of death after lung-volume-reduction surgery. New England Journal of Medicine 2001; 345(15):1075–83.
81. Corless, J. & C. Warburton. Surgery versus non-surgical treatment for bronchiectasis, Cochrane Database of Systematic Reviews. Issue 3, Editor. 2001.
82. Rodriguez Roisin, R. Toward a consensus definition for COPD exacerbations. Chest 2000; 117(5Suppl2): 398S–401S.
83. McCrory, D.C., et al. Management of acute exacerbations of COPD: a summary and appraisal of published evidence. Chest 2001; 119(4):1190–209.

84. Russo, R.L. & M. D'Aprile. Role of antimicrobial therapy in acute exacerbations of chronic obstructive pulmonary disease. Ann Pharmacother 2001; 35(5):576–81.
85. Adams, S.G., et al. Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. Chest 2000; 117(5):1345–52.
86. Allegra, L., et al. Antibiotic treatment and baseline severity of disease in acute exacerbations of chronic bronchitis: a re-evaluation of previously published data of a placebo-controlled randomized study. Pulm Pharmacol Ther 2001; 14(2):149–55.
87. Wood-Baker, R., E. Walters & P. Gibson. Oral corticosteroids for acute exacerbations of chronic obstructive pulmonary disease, Cochrane Database of Systematic Reviews. Issue 3, Editor. 2000.
88. Moloney, E.D., J.L. Kiely & W.T. McNicholas. Controlled oxygen therapy and carbon dioxide retention during exacerbations of chronic obstructive pulmonary disease. Lancet 2001; 357(9255):526–8.
89. Snow, V., S. Lascher & C. Mottur-Pilson. The evidence base for management of acute exacerbations of COPD: clinical practice guideline, part 1. Chest 2001; 119(4):1185–9.
90. Rice, K.L., et al. Aminophylline for acute exacerbations of chronic obstructive pulmonary disease. A controlled trial. Ann Intern Med 1987; 107(3):305–9.