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REVIEW

The clinical management in extremely severe COPD

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Summary
Chronic obstructive pulmonary disease (COPD) affects 6% of the general population and is the fourth-leading cause of death in the United States with severe and very severe disease accounting for 15% and 3% of physician diagnoses of COPD. Guidelines make few recommendations regarding providing the provision of care for the most severe stages of disease, namely Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages III and IV with chronic respiratory failure.
The effectiveness of inhaled drug therapy in very severe patients has not been assessed yet. Health care systems in many countries include public funding of long-term oxygen therapy for eligible candidates. Currently, there is little evidence for the use of mechanical ventilatory support in the routine management of hypercapnic patients. Pulmonary rehabilitation should be considered as a significant component of therapy, even in the most severe patients. Although Lung Volume Reduction Surgery has been shown to improve mortality, exercise capacity, and quality of life in selected patients, this modality is associated with significant morbidity and an early mortality rate in the most severe patients. Despite significant progress over the past 25 years, both short- and long-term outcomes remain significantly inferior for lung transplantation relative to other "solid" organ recipients.
Nutritional assessment and management is an important therapeutic option in patients with chronic respiratory diseases. Morphine may significantly reduce dyspnoea and does not significantly accelerate death. No consistent improvement in dyspnoea over placebo has been shown with anxiolytics. Supplemental oxygen during exercise reduces exertional breathlessness and improves exercise tolerance of the hypoxaemic patient. Non-invasive ventilation has been used as a palliative treatment to reduce dyspnoea.
Hypoxaemic COPD patients, on long-term oxygen therapy, may show reduced health-related quality of life, cognitive function, and depression. Only a small proportion of patients with severe COPD discuss end-of-life issues with their physicians.

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Introduction

Improving the quality of care for patients at the end of life has become a major goal of the medical community and the general public.[1] Current chronic obstructive pulmonary disease (COPD) guidelines make few recommendations on the care for the most severe patients i.e. those with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages III and IV with chronic respiratory failure.[2,3] Until recently, little attention was paid to the health care needs of the most severe COPD patients, despite the fact that as many patients with COPD die each year as those with lung cancer, and health decline occurs over a substantial period before that.[4]

Size of the problem: COPD affects 6% of the general population and is a leading cause of morbidity and mortality worldwide. Age-adjusted mortality continues to increase at difference with mortality from other leading causes of death, including cardiovascular disease and cancer.[2,5] In a Dutch study severe and very severe disease assessed by post-bronchodilator FEV_1 accounted for 15% and 3% of physician diagnoses of COPD.[6] The 0.13% of the population in O' Stersund, Sweden in 2004 had physician-diagnosed stage IV COPD.[7] In an Italian study of prevalence rate, GOLD stages III and IV were 4.5% and 0.4%, respectively, in males and 2.2% and 0.3% in females.[8] Similar prevalence is reported in five cities of South America.[9]

Mortality: GOLD stage III or IV patients are more likely to comprise the most rapidly declining lung function quartile with a modestly increased risk of death and time to a COPD-related hospitalisation.[10] Mannino et al.[11] classified subjects using a modification of the GOLD criteria for COPD (prebronchodilator FEV_1) stratification of disease severity, and added a ''restricted'' category ($FEV_1/FVC > 70\%$ and $FVC < 80\%$ predicted). They used Cox proportional hazard models to determine the risk of impaired lung function on subsequent mortality, after adjusting for age, race, sex and smoking status. The overall rate of death was 8.9 per 1000 person years, but varied from 5.4/1000 among normal subjects to 42.9/1000 among subjects with GOLD Stage III or IV COPD. After adjusting for covariates, all GOLD categories, along with the restricted category, predicted a higher risk of death: GOLD Stage III or IV, hazard ratio (HR) 5.7, 95% GOLD Stage II HR 2.4, 95%; GOLD Stage I HR 1.4, 95%; GOLD Stage 0 HR 1.5, 95%; and restricted HR 2.3, 95% CI 1.9, 2.8. Increased mortality has been observed in patients with older age, lower body mass index (BMI), need of oxygen utilisation and greater hyperinflation. Exercise capacity, as quantified by cardiopulmonary exercise testing, proves a powerful independent predictor of survival.[12] Even when properly adjusted for potential confounding factors, women with severe COPD on Long-Term Oxygen Therapy (LTOT) have a greater risk of death than men.[13]

Exacerbations. Almost one-fourth of the COPD patients had died within a year of first hospital admission for the disease. This group with a poor prognosis made abundant use of hospital services. The burden imposed on such services by severe COPD patients is U-shaped, with hospital use increasing towards the end of their lives.[14]

Patients admitted to Intensive Care Unit (ICU) with an acute exacerbation of COPD have a median survival of 2 years, and 50% of patients are readmitted to the hospital within 6 months.[15] Prediction of survival status may be enhanced by considering arterial oxygen tension, albumin, BMI, disease duration and time elapsed since the first hospitalisation.[16] In these patients hypercapnia at discharge is related to inspiratory work, respiratory muscle strength, and breathing pattern.[17] The mortality rate after an acute exacerbation is high, especially for older patients with chronic respiratory failure in whom the symptom burden in the last 6 months of life is significant.[18,19] The 6-year mortality of patients with COPD requiring ICU admission is substantial and is mainly influenced by pre-ICU admission quality of life (QOL). At 6 years, around 15% are alive; survivors have a worse QOL compared with pre-ICU admission, although three quarters are self-sufficient.[20]

Systemic effects: COPD affects many organ systems in addition to the lungs.[21] The risk of atherosclerosis, cardiovascular disease and mortality is further increased in COPD individuals who smoke.[22,23] Chaouat et al.[24] reported severe pulmonary hypertension in less than 5% of patients. Such patients had severe exertional dyspnoea, a short life expectancy, hypocapnia, very low DL_{CO}, and haemodynamic

alterations similar to those seen in idiopathic pulmonary hypertension.

There is emerging evidence that poor exercise capacity and peripheral muscle dysfunction may be linked by the presence of systemic inflammation. Patients with COPD have higher levels of C-reactive protein independent of coexisting cardiac or non-cardiac risks.[25,26] Those patients also show increased levels of peripheral muscle apoptosis[27] and local oxidative stress.[28] Patients with severe COPD become less mobile and reduce their activities of daily living (ADL). In a survey of patients with severe COPD (Medical Research Council dyspnoea grade 5) treated with LTOT, 50% did not leave the house and 78% were breathless walking around at home and performing ADL.[29] In one study,[30] patients with severe COPD with at least one hospital admission for hypercapnic respiratory failure were compared to patients who had been treated for unresectable non-small cell lung cancer (NSCLC). This study showed that COPD patients had significantly less ability to perform the ADL, and lower social and emotional functioning than patients with NSCLC.[30] These patients are more likely to die with aggressive, technological care to prolong life and are less likely to receive home nursing and palliative care services than patients with lung cancer, despite having similar preferences for palliation.[15,31]

Treatment perspectives for survival

Drug therapy: Only smoking cessation[32] and LTOT[33,34] improve survival in COPD.[2,3] Studies have shown an association between inhaled corticosteroids and a reduction in mortality and re-hospitalisation[35,36] and a recent meta-analysis of long-term trials with inhaled steroids reported a significant effect in reducing mortality from all causes in patients with COPD.[37] A large, randomised, controlled clinical trial has tested this hypothesis prospectively[38] and results seem to show an advantage in survival by using inhaled combination of long acting agonists with steroids. Nevertheless the real effectiveness of inhaled drug therapy in very severe patients has not been assessed yet. Furthermore oral corticosteroids as maintenance treatment in patients with end-stage respiratory disease are an independent risk factor for death, and should be avoided in most cases.[39]

Oxygen: It has been clearly established that selected patients with COPD with chronic hypoxaemia live longer when they receive LTOT,[33,34] an effect maybe also due to prevention of exercise induced oxidative stress.[40] As a result, health care systems in many countries include public funding of LTOT for eligible applicants. However, as some patients may no longer meet eligibility criteria at some time after the initial prescription, uncertainty remains as to the modalities of re-evaluation of these patients to maintain or withdraw this long-term treatment.[41] Reassessment of applicants for LTOT after a long period of stability will identify a significant proportion of patients who are no longer eligible, thus reducing costs and use of resources without affecting QOL or mortality in these patients.[42]

Long-term domiciliary non-invasive mechanical ventilation: Mechanical ventilation increases or substitutes for spontaneous respiration, as in the case of acute respiratory or ventilatory pump failure. Non-invasive positive pressure ventilation (nPPV), delivered by nasal mask, has recently re-emerged as an option that avoids the risks associated with invasive ventilation. nPPV is thought to assist ventilation, by improving inspiratory flow rate and correcting hypoventilation. Other possible mechanisms of action include unloading respiratory muscles and resetting the central respiratory drive.[43] In contrast to the evidence supporting the use of nPPV for other causes of chronic respiratory failure, there is conflicting evidence regarding the benefits of nPPV in COPD. One trial published as an abstract indicates that there is no overall survival benefit in patients receiving nPPV plus LTOT, although there may be a slight improvement in survival for patients over 65.[44] A 2-year multi-centre study also examined the effects of nPPV plus LTOT compared with LTOT alone. In this trial, nPPV plus LTOT improved $PaCO_2$ during breathing of the usual oxygen inspiratory fraction. Long-term improvements were also noted in dyspnoea and QOL in the nPPV plus LTOT group, but survival was similar between treatment groups.[45] Home nocturnal nPPV added to daytime exercise training has been found to significantly increase exercise capacity and QOL compared with exercise training alone.[46] Taken together all studies indicate that currently, there is little evidence for the use of mechanical ventilatory support in the routine management of hypercapnic COPD patients. However, further large studies may be able to identify subsets of patients able to take advantage from this therapy.[43]

Rehabilitation: COPD patients who perform regular exercise activity have reduced risk of both hospital admission and mortality.[47] Exercise training as part of pulmonary rehabilitation appears to counteract increased exercise-associated oxidative stress.[48] Several studies provide scientific evidence that rehabilitation improves several of the variables associated with poor outcomes, such as exercise capacity and dyspnoea,[49] as well as the multidimensional BODE index.[50,51] In the study[51] the changes in the BODE index induced by rehabilitation were predictive of final outcome. Recently studies have reported the beneficial effects of physiotherapy in COPD patients also in the ICU setting.[52,53] Patients receiving chronic ventilation are weak and deconditioned but respond to aggressive whole-body and respiratory muscle training with an improvement in strength, weaning outcome, and functional status.[54]

Pulmonary rehabilitation should be considered a significant component of therapy, even in most severe patients.[49] Nevertheless in these severe COPD patients extreme breathlessness and/or peripheral muscle fatigue may prevent patients from higher levels of exercise intensity. Increased inspiratory muscle work may contribute to dyspnoea and exercise limitation. Several studies have shown that continuous positive airway pressure (CPAP) and different modalities of *ventilatory assistance* delivered through nasal or facial mask during exercise, may reduce dyspnoea and work of breathing and enhance exercise tolerance in COPD patients. Inspiratory support provides symptomatic benefit by unloading and assisting such overburdened ventilatory muscles, whereas CPAP counterbalances the intrinsic positive end-expiratory pressure (PEEPi).[55,56] Nevertheless, the role of assisted ventilation in pulmonary rehabilitation is still controversial: additional benefit of assisted ventilation on exercise tolerance,

dyspnoea and health status was not unanimously demonstrated when compared with training alone. Larger prospective controlled studies should be undertaken to determine if assisted ventilation may eventually have routine applicability, and in particular subgroups of patients.[57]

Neuromuscular electrical low-voltage stimulation has been shown to induce an increase in the muscular oxidative capacities. Small controlled studies of this technique in severe COPD patients have been reported.[55]

Lung volume reduction surgery: Lung volume reduction surgery (LVRS) is used to treat patients with severe emphysema by removing the most damaged areas of the lung, thus reducing hyperinflation. Although LVRS has been shown to improve mortality, exercise capacity, and QOL in selected patients with upper lobe disease and poor exercise capacity compared with patients randomised to medical therapy, this modality is associated with significant morbidity and an early mortality rate of about 5% in the most severe patients.[59,60] For these reasons, and because of the high risk of the procedure for patients with the most severe disease, alternatives have been studied, including bronchoscopic lung volume reduction and endobronchial valve placement. These techniques have been shown to improve mean exercise capacity and reduce dynamic hyperinflation in a subgroup of patients with COPD.[61]

Lung transplantation: Lung transplantation is an option for a more limited number of patients. A COPD patient can be considered an appropriate candidate for transplantation when the FEV_1 is below 25% predicted and/or the $PaCO_2$ is $\geqslant = 55$ mmHg. Despite significant progress over the past 25 years, both short- and long-term outcomes remain significantly inferior for lung recipients relative to other ''solid'' organs.[62] Pulmonary function generally improves after lung transplantation, but exercise capacity remains below predicted values, primarily due to a peripheral muscle myopathy.[62] Pulmonary rehabilitation programs can improve the exercise tolerance and QOL in both short and long term after lung transplantation.[63] Long-term results of lung transplantation are limited by significant complications that impair survival; an approximately 80% 1-year, 50% 5-year, and 35% 10-year survival has been reported. Bronchiolitis obliterans is the most important long-term complication of lung transplantation resulting in decreased pulmonary function.[64]

Nutrition

Survival studies have consistently shown significantly greater mortality rates in underweight and normal-weight than in overweight and obese COPD patients.[65–67] Malnutrition is a common and underrecognised problem in hospitalised patients. Indeed hospitalisation is frequently associated with negative energy balance and further deterioration in nutritional status. A survey of admissions to a general hospital reported a prevalence of malnutrition of 27–46% across various hospital specialties.[68,69] In particular nutritional depletion is a common problem in COPD patients. It is caused, to a large extent, by an imbalance between low-energy intake and high-energy requirements,[70] leading to muscle wasting and dysfunction.[71] A compromised nutrition is associated with a poor prognosis in stable COPD patients with and without respiratory failure.[72,73]

In a study by Sivasothy et al.[74] chronically ventilated hypercapnic COPD patients with BMI value lower than 20 showed a worse survival. Other studies have confirmed that besides established prognosis factors such as FEV_1 and PaO_2, nutritional depletion as assessed by BMI and overall systemic inflammation as estimated by C-reactive protein appear as major determinants of hospitalisation and death risks whatever the end-stage respiratory disease. BMI and C-reactive protein should be included in the monitoring of chronic respiratory failure. Additionally, nutritional status has been recently studied in 744 patients with different underlying diseases on long-term respiratory treatments (oxygen and/or mechanical ventilation).[75] Authors have found that fat-free mass (FFM), BMI below 20 and low serum albumin were the most sensitive parameters detecting malnutrition. In these conditions BMI has been reported lower than 25, being more compromised in COPD than in other thoracic diseases.[76] Patients with COPD are at risk of a low FFM and a low FFM is prevalent even among subjects with normal BMI. Because FFM index is associated with prognosis, it seems that assessment of FFM provides important information in COPD and should be considered in the routine evaluation of patients with this condition.[77] Indeed in COPD patients semi-starvation and muscle atrophy are equally distributed among disease stages, but the highest prevalence of cachexia is reported in GOLD stage IV. In a follow-up study, 46% of the patient died during a maximum follow-up of 5 years. Cox regression models, with and without adjustment for disease severity, showed that FFM index was an independent predictor of survival. This supports the inclusion of body-composition assessment as a systemic marker of disease severity in COPD staging.[78]

Nutritional depletion is an independent risk factor for mortality and hospitalisation in patients with COPD receiving LTOT. The best prognosis was observed in overweight and obese patients.[65,79] Clinical research has confirmed the negative impact of muscle wasting on patients' survival. Gain in body weight, muscle mass and strength has been associated with better exercise tolerance and survival,[51,73] therefore, improving peripheral muscle function could be a reasonable therapeutic target in patients with COPD. Pharmacological approaches to this problem, for instance anabolic steroids[80] and growth hormone[81] supplementation has been disappointing so far.

Nutritional assessment and management is an important therapeutic option in patients with chronic respiratory diseases,[82] especially those dealing with prolonged/difficult weaning from mechanical ventilation in ICU.[83] Specific nutritional deficiency like hypophosphatemia[84] and impaired lipid synthesis[85] can also be associated with acute respiratory failure and with an abnormal increase in the fat mass of these patients, respectively. These patients often complain of dietary problems such as 'anorexia', 'dyspeptic symptoms other than diarrhoea', 'slimming', 'fear of gaining weight', 'dyspnoea', 'diarrhoea', 'depression, anxiety, solitude'. It has been observed that smoking habits and gender have impact on the kind of dietary problems reported. Reporting two dietary problems correlated to low FFM index, whereas reporting one or more dietary problems correlated to decreased energy intake.[86]

One of the most important problems occurring in patients needing prolonged mechanical ventilation is swallowing dysfunction. Although this dysfunction is usually induced by an underlying neuromuscular disease, many factors may also contribute including: acute illness and medications used to treat these conditions (steroids, neuromuscular blocking agents, general sedatives), prolonged inactivity of swallowing muscles, injury due to endotracheal intubation, tracheostomy tube.[76] Tracheostomy *per se* may limit swallowing function by either compressing the oesophagus or decreasing larynx elevation and anterior displacement thus increasing the chances of aspiration.[87] Recent studies both in acute and chronic setting suggested that swallowing dysfunction and pulmonary aspiration occur in patients receiving ventilatory support through a cuffed tracheostomy tube. Therefore, dietary intake through the mouth should be carefully evaluated. Recognition of swallowing dysfunction in these patients may identify patients at high risk of aspiration, and thereby help to avoid pulmonary related complications such as pneumonia and atelectasis.[88] In tracheostomised difficult-to-wean COPD patients under unassisted breathing, meals may induce increase in respiratory rate, end-tidal CO_2 and dyspnoea, in this condition inspiratory pressure support ventilation prevents dyspnoea from worsening during meals.[89]

Enteral nutrition by means of oral nutritional supplements (ONS) or tube feeding (TF) enables nutritional intake to be maintained or increased when normal intake is inadequate. In COPD patients, enteral nutrition in combination with exercise and anabolic pharmacotherapy has the potential to improve nutritional status and function. Frequent small amounts of ONS are preferred in order to avoid postprandial dyspnoea and satiety as well as to improve compliance.[90] However, a meta-analysis has provided no evidence that nutritional support has a significant effect on anthropometric measures, lung function, or exercise capacity in patients with stable COPD.[91,92] By contrast, repeated administration of ghrelin, a novel growth hormone-releasing peptide that is reduced in COPD[93] may improve body composition, muscle wasting, and functional capacity in cachectic patients with COPD, thus possibly reversing some of the systemic aspects of COPD.[94]

Supportive therapy

As in other chronic diseases when severity of disease increases along the natural history, therapy aimed to prolong life become less and less important in comparison to palliative therapy aimed to relieve symptoms (Fig. 1).

Drug therapy of dyspnoea

The symptomatic treatment of dyspnoea remains relatively ineffective and is often accompanied by significant adverse effects.[95] In patients with advanced emphysema, dyspnoea is an incapacitating symptom that commonly indicates the onset of the final stage of this illness. The most effective treatments for dyspnoea in COPD are bronchodilators[96] and LVRS[58] to improve the mechanical impairment, and pulmonary rehabilitation[49] to reduce ventilatory demand. These are useful at all stages of the illness, but in end-stage disease a range of other less well validated approaches have been tried.[97]

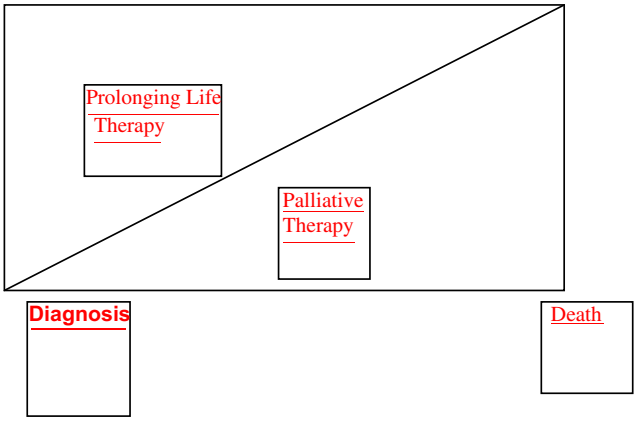

Figure 1 Diagram of main goals of care according to disease stage.

One possibility is to reduce *ventilatory demand* by decreasing the central drive by *opiates*.[98,99] Opiates have been shown to decrease minute ventilation at rest and during submaximal exercise. They can alter the central processing of neural signals within the Central Nervous System to reduce sensations associated with breathing. Also the drug's cardiovascular effects are thought to be responsible for relieving dyspnoea. Therapeutic doses of opioids induce peripheral vasodilation, reduce peripheral vascular resistances and inhibit baroreceptors response. Furthermore opioids reduce the anxiety associated with dyspnoea. There is also speculation that they may act directly on opioid receptors in the airways.[100] Despite safety concerns, these drugs do have place in the management of patients in the terminal phase of their disease.[101] Recent meta-analysis[102] has shown that morphine may significantly reduce dyspnoea, in patients with cancer, and does not significantly accelerate death in patients in whom mechanical ventilation was withdrawn. Epidural methadone perfusion at thoracic level can effectively palliate dyspnoea and improve exercise capacity and QOL in patients with advanced emphysema, without deterioration in respiratory control or lung function.[103] No consistent improvement in dyspnoea over placebo has been shown with *anxiolitics*.[104–106] Nonetheless the American Thoracic Society (ATS) statement ''recommend(s) a trial of anxiolitic therapy on an individual basis''.[95]

Decreasing central drive, that is *reducing ventilatory demand*, obtained by altering pulmonary afferent information to central controller potentially may reduce dyspnoea. However, there are many concerns about the real usefulness of such interventions in a clinical setting.[107] The following must be considered: (i) there is speculation that opioids may act directly on opioid receptors in the airways[100,108]; (ii) aerosolised topical anaesthesia has inconsistent effects on dyspnoea[109]; (iii) vagal blockade has highly variable effects on dyspnoea[110]; (iv) intact ventilatory response to exercise in post-transplantated vagally denervated subjects has been reported.[111] Inhalation of furosemide alleviated the sensation of dyspnoea induced by constant-load exercise testing in patients with COPD.[112]

Oxygen

Decreasing *ventilatory demands and/or gas density* have been recently shown to improve exercise tolerance, symptoms, and QOL.[113] A way to reduce metabolic load is oxygen supplementation. Hypoxia has no dyspnogenic effect *per se*, it causes dyspnoea by stimulating minute ventilation. Supplemental oxygen during exercise reduces exertional breathlessness and improves exercise tolerance of the hypoxaemic COPD patient by different mechanisms: reduction of hypoxic stimulation of the carotid bodies, pulmonary vasodilation, increase in arterial oxygen. The latter two mechanisms may potentially reduce carotid body stimulation at heavy levels of exercise by increasing oxygen delivery to the exercising muscles and reducing carotid body stimulation by lactic acidaemia. Recent studies indicate that also reduction in hyperinflation, that is decrease in *ventilatory impedance*, plays an important role in the oxygen-related relief of dyspnoea.[113,114] Early studies[115] failed to demonstrate benefits of supplemental oxygen during rehabilitation. Nevertheless, a recent double blind study of non-hypoxaemic patients with severe COPD showed that patients trained with oxygen supplementation increased training intensity and endurance more rapidly than patients trained without.[116]

Manipulating gas density using *heliox* breathing has also been shown to be beneficial in relieving symptoms and improving exercise capacity, for it facilitates gas emptying during expiration. As a result, the amount of expiratory flow limitation and operational lung volumes decreases, thus reducing *ventilatory impedance* and ultimately leading to greater exercise tolerance.[113,117–119]

Non-invasive mechanical ventilation

Non-invasive ventilation has been used increasingly as an alternative to invasive ventilation in patients with a 'do not intubate' order. In a recent study,[120] nPPV was applied to treat episodes of acute respiratory failure in 114 patients with 'do not intubate' orders. About half of the patients survived and were discharged from the ICU. Similar results have been recently obtained by Schettino et al.,[121] and Chan et al.[122] so that there is increasing recognition that nPPV may be an effective alternative to intubation especially in those patients in which an invasive approach is questionable because of the presence of a chronic disease or poor life expectancy. Interestingly, in 40% of the patients undergoing nPPV this was used solely as a palliative treatment, as it has been shown that nPPV may reduce dyspnoea shortly after initiation not only during an episode of hypercapnic respiratory failure[123] but also in terminally ill patients.[124]

Health status and psychological effects

Although the underlying pathology is initially confined to the lungs, the associated psychological responses to COPD contribute greatly to the resulting morbidity. The ability to function in ADL, as well as the QOL of a patient with COPD, may be further complicated by psychological complaints or even a concurrent mental disorder. Although the physical illness itself probably contributes to the occurrence and severity of the psychological complaints, this does not mean that these complaints will be resolved once the respiratory complaints are treated. Hypoxaemic COPD patients, in LTOT, may show reduced QOL, decreased ability to cope with ADL, cognitive function, and depression.[125,126]

As greater numbers of patients survive intensive care it is becoming increasingly evident that QOL after critical illness may be compromised. It has been found that nearly half of patients who survive ARDS manifest neurocognitive sequelae 2 year after their illness. Anxiety and depression were also common and QOL was poor.[127] Information on health status of patients after acute respiratory failure due to acute COPD exacerbations requiring ICU admission are scanty. COPD patients surviving acute on chronic respiratory failure and requiring mechanical ventilation suffer worsened perceived health status and cognitive function than stable COPD patients on LTOT who have never previously required ICU/RIICU admission. After discharge the health and cognitive status may improve to levels similar to those of stable COPD patients on LTOT.[128]

In daily practice, the presence of psychological complaints or mental disorders in patients with COPD is often regarded as a complication caused by the physical complaints.[129] As a result, they are regularly overlooked, often remain undiagnosed and are rarely treated. COPD patients experienced markedly more psychological distress than a random sample from the general Dutch population. The prevalence of depression in patients with severe or very severe COPD was 37% compared with 22% in patients with mild or moderate COPD.[130] Van Manen et al. also found that patients with severe airways obstruction were at an increased risk of depression in comparison with mild to moderate COPD (25 versus 20%).[131] Other results[132] show that less than 40% of anxiety or depressive disorders in COPD patients are recognised. It appears that only 30% of patients with depression or anxiety and only a slightly higher percentage of those with severe anxiety and/or depression are being treated. These data also suggest that despite treatment, many patients still meet criteria for a depressive and/or anxiety spectrum illness.

Few studies have examined the neuropsychological complications associated with end-stage pulmonary disease. Neuropsychological data were shown for 47 patients with end-stage COPD, candidates for lung transplantation. Patients exhibited a variety of neurocognitive deficits. Specifically, over 50% of the patients exhibited impaired immediate free recall and consistent long-term retrieval deficits, while more than 44% of these individuals displayed deficient long-term retrieval. Deficient long-term storage strategies, cued recall, and delayed recall were exhibited by between 26% and 35% of these patients, while more than 32% of this sample displayed elevated numbers of intrusion errors.[133] Separate and distinct personality styles that could affect QOL, the need for adjunct treatments, and medical compliance emerged from a sample of individuals with end-stage lung disease.[134] Furthermore the results of a small randomised trial indicated that patients with end-stage COPD may benefit from antidepressant drug therapy when significant depressive symptoms are present.[135]

Improving end-of-life decision-making

In recent times the simple principles of beneficence and non-maleficence have been augmented and sometimes challenged by a rising awareness of patient/consumer rights, and the public expectation of greater involvement in medical, social and scientific affairs which affect them. In a publicly funded health care system in which rationing (explicit or otherwise) is inevitable, the additional concepts of utility and distributive justice can easily come into conflict with the individual's right to autonomy. Possible treatment options for end-stage lung disease include transplantation and long-term invasive ventilation which are challenging in resource terms. Other interventions such as pulmonary rehabilitation and palliative care are relatively low cost but not uniformly accessible.[136]

Patients with COPD have a poor QOL and limited life expectancy. A study examined whether these patients were relatively disadvantaged in terms of medical and social care compared with a group with inoperable lung cancer.[30] An open two group comparison was made of 50 patients with severe COPD (forced expiratory volume in 1 s (FEV_1) <0.75 l and at least one admission for hypercapnic respiratory failure) and 50 patients with unresectable NSCLC. A multimethod design was used involving standardised QOL tools, semi-structured interviews, and review of documentation. The patients with COPD had significantly worse ADL and physical, social, and emotional functioning than the patients with NSCLC. Ninety percent of patients with COPD suffered clinically relevant anxiety or depression compared with 52% of patients with NSCLC. Patients were generally satisfied with the medical care received, but only 4% in each group were formally assessed or treated for mental health problems. With regard to social support, the main difference between the groups was that, while 30% of patients with NSCLC received help from specialist palliative care services, none of the patients with COPD had access to a similar system of specialist care. Finally, patients in both groups reported a lack of information from professionals regarding diagnosis, prognosis and social support, although patients' information needs were disparate and often conflicting. This study suggests that patients with end-stage COPD have significantly impaired QOL and emotional well being which may not be as well met as those of patients with lung cancer, nor do they receive holistic care appropriate to their needs. A palliative care approach, as used routinely in cancer, might be also valid for incurable chronic illnesses such as COPD. However, a London study recently reported that general practitioners, who provide most end-stage care for COPD patients, do not routinely discuss prognosis with these patients.[137]

Increased and equal participation of patients in decision-making about their care facilitates patient autonomy as a fundamental ethical principle, although most medical care systems recognise there are limits to care and physicians need not pursue futile therapy.[4] Despite widespread public acceptance of the central role of the patient, decision-making is based on the expectation that there are reliable prognostic indicators for most lung conditions, the choices available to patients are real, and that individuals can meaningfully take part in complex decision-making. All these assumptions are questionable. There are several major impediments to planning end-of-life care, especially in COPD patients. Prognosis may be hard to predict as a gradual decline punctuated by acute exacerbations is the usual course, but it is difficult to know which exacerbation will be the last. Perhaps as a consequence, difficult discussions and decision-making may be deferred, and patients may not realise their condition has reached a terminal phase. This makes end-stage planning problematical and may explain why relatively few patients complete advance directives. Of the main carers of COPD patients interviewed by Elkington et al.,[138] 40% were not aware the deceased might die. The carers felt that approximately 63% of the deceased realised definitely or probably they might die—but that leaves a substantial number who were unclear about their own prognosis. Clearly these individuals cannot plan adequately for death if they do not know it is imminent. Regarding the place of death, it is also important to note that significantly more carers of subjects who died at home felt this was the right place to die as opposed to informants of those who died in hospital. In England, for example, a current Department of Health initiative is aiming to improve end-of-life care by ensuring more patients die in the site of their choice (usually home).[4]

Determinants of end-of-life decision-making

The timing and content of discussion about mechanical ventilation in end-stage lung disease has been examined by McNeely and colleagues.[139] In this Canadian study respiratory medicine specialists were likely to embark on discussions when the patients dyspnoea was reported as severe (84.2%), or when FEV_1 was less than 30% predicted. In total 43% reported they discussed mechanical ventilation with 40% or less of their COPD patients before an exacerbation necessitated ventilatory support. The majority felt decision-making was collaborative, but over half often or always modified presentation of information provided to patients in order to influence their decision about mechanical ventilation.

Treatment preferences on life sustaining interventions have been assessed in a range of patients with limited life expectancy due to cancer, congestive cardiac failure or COPD.[140] Individuals of average age approximately 73 years were asked whether they would wish to receive a given treatment if the outcome was certain, or if there were differing likelihoods of an adverse outcome. Importantly participants were able to balance the outcome against the burden of treatment (e.g. length of hospital stay, invasiveness of procedure). For example, a low burden treatment that returned the individual to previous functioning level would be accepted by nearly all participants (98.7%), but 11.2% would not accept this option of the treatment had a high burden. Conversely, if the likely outcome was survival but with severe functional or cognitive impairment 74.4% and 88.8% would not want to receive low and high burden treatment, respectively. There was no difference between choices between the diagnostic groups, although there was a trend for COPD and cancer patients to reject high burden therapy. This work demonstrates that patients can evaluate the personal impact of varying outcomes, and that the impact on functional and cognitive performance play a

greater part in the decision-making process than survival itself. This should help inform discussion with patients. Clearly they also need to know the probable consequences of *non-intervention* to make a valid decision.

It is clear that the understanding of information by patients depends not only on content, but on how that information is framed. For example, patients are more likely to favour an intervention with a 90% survival rate rather than a 10% mortality rate. Relative risk reduction is often assimilated better than actual rate reductions. Risks should be set into context against every day risks. It is also likely that personal accounts and narratives can lead to increased identification of risk. Visual presentation e.g. in the form of a diagram or pie chart work better than a barrage of numbers or graphs.

Decision aids

Decision aids, if developed appropriately can be very effective. They can increase knowledge, improve the proportion of patients with a realistic perceptions of benefit and harm from an interventions, reduce decisional conflict, decrease the number of patients who remain undecided or passive about choices, and can improve agreement between the patient's reported values and the option that is chosen. An example is the instrument developed to elicit patient preferences for intubation and mechanical ventilation in COPD by Dales et al.[141] This scenario-based tool consists of an audiotape and booklet describing intubation, mechanical ventilation and possible outcomes. The authors found that use of the aid allowed 20 advanced COPD patients (10 male, 10 female) to reach a decision. Decisional conflict was low and these choices remained stable over a year of follow-up. The agreement between patients and their physicians regarding choices was 65%. Interestingly far more females chose to forego mechanical ventilation than males. Clearly one problem concerns the options presented. Since this tool was devised there has been increasing use of nPPV in acute exacerbations and this recent information needs to be incorporated in any up-to-date decision tool. In the decision aid described above Dales et al.[141] found no agreement between decisions made by patients and surrogate decision-maker. In a further study in end-stage renal patients on haemodialysis Pruchno et al.[142] found that decisions made by spouses (as proxy) about continued dialysis in hypothetical scenarios were completely in line with the spouses *own* preferences for their care rather than the patient's preferences.

Advance directives

Advance directives are widely encouraged in order to increase patient autonomy by allowing control over care by specifying treatment choices and indicating surrogate decision makers. Only around 30% of US citizens make advance statements and in some countries this rate is significantly lower.[143] They can work well in conditions where the disease trajectory is clearer than in COPD Such as Amyotrophic lateral sclerosis (ALS). The American Academy of Neurology have reported that around 90% of ALS patients have advance directives and these are followed in 97%. However, advance directives work less well in other circumstances, and this may be a particular problem in ICU. Instructions may be too vague to be of use or too medically specific to be applied in common situations. They tend to focus on the right to refuse treatment with little emphasis on the underlying goals or values of the patient. Once completed they are often not reviewed even when health declines. These directives are based on patient autonomy but in some cultures decisions are family or religious-based. There are concerns from some disability groups that directives deal predominantly with treatment refusal where some groups would like to emphasise their continued wish for treatment. Regardless of these comments advance directives can work well for COPD patients.

Improving communication

Opportunities to raise this end-of-life matters occur during pulmonary rehabilitation sessions, although in group meetings general topics rather than specific management plans are easier to address. For example, Heffner et al.[144] carried out a two-site prospective evaluation of advance directive education during a pulmonary rehabilitation course to assess the effects on completion of (i) Living Wills, (ii) durable powers of attorney (i.e. identifying a proxy decision-maker), (iii) patient–physician discussion about end-of-life issues, (iv) decisions about life support and (v) patient impression that their physician understood their end-of-life preferences. The group that received education on these topics was subsequently significantly more likely to discuss these issues, complete advance directives, and felt more assured their physicians understood their preferences. It has been demonstrated that COPD patients in particular want further information on their disease course and treatments from their doctors, but may not necessarily raise these topics without prompting.[145] They may not even be aware their condition is progressive. The way the topics are raised is also crucial. Most individuals welcome discussion but this is usefully directed to the symptom control approach throughout the remainder of the patient's life, rather than an exclusive focus on their death. Striking a realistic and kindly balance between maintaining hope and a pragmatic expectation of decline is part of the clinical judgement health care workers should exercise, and adapt to the individual.

Knauft and colleagues[146] have recently examined barriers to end-of-life discussions between patient and the care team. In a focus group analysis of oxygen dependent COPD patients and their physician, they found that only 32% of patients had taken part in such discussion with their physician. Frequently cited barriers were 'I'd rather concentrate on staying alive' and 'I'm not sure which doctor will be taking care of me'. Physicians ranked the most important barriers as 'There was too little time during our appointment to discuss everything we should', or 'I worry that discussing end-of-life care will take away his/her hope', and 'The patient is not ready to talk about the care he/she wants if he/she is sick'. It is evident that this topic is easier to defer on both sides. On the other hand, the authors found a number of facilitators which made effective communication more likely. These included the patient's experience of friends or family who had died, the fact they

trusted their physician, the feeling that their physician was good at caring for their lung disease, and that he/she viewed them as person, rather than focusing purely on their lung condition.

Finally and encouragingly, there is evidence that physician skills in discussing end-of-life care can be improved. The oncology world is ahead of respiratory medicine in these training initiatives which include video feedback sessions, but the area is gaining increasing attention. At the same there is every reason to foster a wider debate to raise public awareness on advance directives and treatment options, and increase the provision of palliative and supportive care for our COPD patients.

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