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End stage chronic obstructive pulmonary disease

Postępowanie w ciężkiej postaci przewlekłej obturacyjnej choroby płuc

Abstract

Many patients with chronic obstructive pulmonary disease (COPD) die each year as those with lung cancer but current 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.

Only smoking cessation and long term oxygen therapy (LTOT) improve survival in COPD. Although non invasive positive pressure ventilation (NPPV) may have an adjunctive role in the management of chronic respiratory insufficiency there is little evidence for its use in the routine management of stable hypercapnic COPD patients. At difference, several prospective, randomised, controlled studies, systematic reviews and meta-analyses show good level of evidence for clinical efficacy of NPPV in the treatment of acute on chronic respiratory failure due to acute exacerbations of COPD. NPPV is also alternative to invasive ventilation for symptom relief in end stage COPD.

Surgical interventions for end stage COPD like bullectomy, different modalities of lung volume reduction surgery and lung transplantation are likely to be of value to only a small percentage of patients. Nevertheless, there are specific indications, which, when added to pulmonary rehabilitation will further advance exercise capacity and quality of life.

As in other chronic diseases when severity of disease increases along the natural history, therapy aimed to prolong life becomes less and less important in comparison to palliative therapy aimed to relieve symptoms. The most effective treatments for dyspnoea are bronchodilators, although also opiates may improve dyspnoea. Supplemental oxygen reduce exertional breathlessness and improve exercise tolerance in hypoxaemic COPD patients. There are difficulties in treating with antidepressant the frail and elderly COPD patients.

Good clinical care can prevent or alleviate suffering by assessing symptoms and providing psychological and social support to the patients and their families.

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Introduction

Many patients with chronic obstructive pulmonary disease (COPD) die each year as those with lung cancer, and health decline occurs over a substantial period before that. Until recently, little attention was paid to the healthcare needs of the most severe COPD patients. Indeed current 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 [1, 2].

COPD affects 6% of the general population and is a leading cause of morbidity and mortality worldwide, GOLD stages III–IV accounting for 4.5 and 0.4% respectively in males and 2.2 and 0.3% in females [3]. Age-adjusted mortality continues to increase at difference with mortality from other leading causes of death, including cardiovascular disease and cancer [2].

Exacerbations. Patients admitted to Intensive Care Unit (ICU) with an acute exacerbation of COPD (AECOPD) have a median survival of 2 years, and 50% of patients are readmitted to the hospital within 6 months [4]. In these patients hypercap-

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nia at discharge is related to inspiratory work, respiratory muscle strength, and breathing pattern [5]. The mortality rate after an AECOPD is high, especially for older patients with chronic respiratory failure in whom the symptom burden in the last six months of life is significant [6]. The 6-year mortality of patients with AECOPD requiring ICU admission is substantial (at 6 yrs, around 15% are alive) and is mainly influenced by pre-ICU admission quality of life (QoL) [7].

Systemic effects. COPD affects many organ systems in addition to the lungs [8]. 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 [9]. The risk of atherosclerosis, cardiovascular disease and mortality is further increased in COPD individuals who smoke [10, 11]. 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 [12].

Nutrition. Survival studies have consistently shown significantly greater mortality rates in underweight and normal-weight than in overweight and obese COPD patients. Malnutrition is a common and underrecognized problem in hospitalised patients. Indeed hospitalization 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% to 46% across various hospital specialities. 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 leading to muscle wasting and dysfunction [13]. A compromised nutrition is associated with a poor prognosis in stable COPD patients with and without respiratory failure [14].

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 [15].

As greater numbers of patients survive intensive care it is becoming increasingly evident that QOL after critical illness may be compromised. 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/RICU admission. After discharge the health and cognitive status may improve to levels similar to those of stable COPD patients on LTOT [16]. 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. As a result, they are regularly overlooked, often remain undiagnosed and are rarely treated [15].

Treatment perspectives for survival

Drug therapy. Only smoking cessation and LTOT improve survival in COPD [17]. Recent studies of inhaled corticosteroid therapy for managing stable COPD have yielded conflicting results regarding survival and risk of adverse events [18]. Studies have shown an association between inhaled corticosteroids and a reduction in mortality and rehospitalisation, with some caveats, an effect maybe associated with anti-inflammatory action [19, 20]. A large, randomised, controlled clinical trial has tested this hypothesis prospectively [21] and results seems to show an advantage in survival by using inhaled combination of beta2 long acting agonists with steroids. The real effectiveness of inhaled steroids 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 [22]. The effects of inhaled anticholinergics are even more discussed [23, 24]. Beta-blockers are often withheld from patients with COPD because of fear of pulmonary worsening. However, cardioselective β-blockers are demonstrated to be safe and beneficial in patients with COPD and are beneficial in the reduction of mortality in patients with COPD undergoing vascular surgery, with an intensified dosage being most effective [25].

Oxygen

Long-Term Oxygen Therapy is the main treatment for patients with chronic respiratory insuf-

ficiency due to advanced COPD. LTOT administered continuously (> 18 hours per day) to hypoxaemic COPD patients increases survival [26]. It is generally implemented according to international recommendations [27]. The prescription of LTOT should always include the source of supplemental oxygen (gas or liquid), method of delivery, duration of use, and flow rate at rest, during exercise, and during sleep. Oxygen therapy during exercise improves exercise endurance and dyspnoea [28]. A randomised study, failed to find an advantage in QoL of ambulatory oxygen over placebo in COPD patients who did not meet criteria for mortality reduction with LTOT, thus not supporting the general "off label" application of this treatment for patients not meeting recognised criteria for LTOT [29].

Non invasive positive pressure ventilation

Non invasive positive pressure ventilation (NPPV), delivered by nasal or face mask, avoids the risks associated with invasive ventilation. It assists ventilation by improving inspiratory flow rate, correcting hypoventilation, resting respiratory muscles and resetting the central respiratory drive [30]. The benefits of NPPV in stable patients are equivocal, with little evidence to support NPPV in addition to LTOT in the treatment of chronic hypercapnic COPD. One trial published as an abstract [31], indicated that there was no overall survival benefit from NPPV plus LTOT, despite a slight improvement in survival for patients over 65 years. An Italian 2-year multi-centre trial showed that NPPV plus LTOT improved daytime $PaCO_2$, dyspnoea and QoL, although survival was similar to the control (LTOT alone) group [32]. In a systematic review of short and long-term NPPV in stable hypercapnic COPD patients, 15 studies met the inclusion criteria: 6 randomised trials and 9 non randomised controlled trials, with no improvements identified in the former. Hyperinflation and diaphragmatic work of breathing were reduced in a subset of patients [33]. Therefore, although NPPV may have an adjunctive role in the management of chronic respiratory insufficiency there is little evidence for its use in the routine management of stable hypercapnic COPD patients [34].

NPPV in acute exacerbations of COPD. Acute exacerbations of COPD are important events in the natural course of disease leading to deteriorating in lung function and in QoL and, when associated with acute ventilatory failure, to severe short-and long-term prognosis. Frequency of AECOPD increases with disease severity, as represented by airflow obstruction, although the relationship between AECOPD frequency and severity of airflow obstruction is not particularly close and new evidence indicates a possible role for extrapulmonary factors in the genesis of exacerbation. Indeed the most severe COPD patients, especially those with several comorbidities are prone to more severe exacerbations and are likely to need hospital admission, especially in the winter months when respiratory viral infections are common [35, 36]. A stepwise drug therapy is recommended for both home and hospital management. Hospital management includes proper assessment of severity, diagnosis of the cause, controlled O2 therapy and/or mechanical ventilation with an early non-invasive approach as first line of intervention [37]. A very severe life threatening episode requires direct admission into the ICU. Several prospective, randomised, controlled studies, systematic reviews and meta-analyses show good level of evidence for clinical efficacy of NPPV in the treatment of acute on chronic respiratory failure due to AECOPD. Compared to standard medical therapy alone, NPPV improved survival, reduced the need for endotracheal intubation and the rate of complications, and shortened the hospital and ICU length of stay [38].

NPPV in palliative care. NPPV is alternative to invasive ventilation for symptom relief in end stage COPD [39] and a recent European survey of respiratory intermediate care units has reported a frequency of use and its role in almost a third of the patients among patients with poor life expectancy [40]. The Society of Critical Care Medicine has recently charged a Task Force with developing an approach for considering use of NPPV for patients who choose to forego endotracheal intubation. In acute respiratory failure it can be classified as follows: 1) NPPV as life support with no preset limitations on life-sustaining treatments, 2) NPPV as life support when patients and families have decided to forego endotracheal intubation, and 3) NPPV as a palliative measure when patients and families have chosen to forego all life support and receive only comfort measures. The goals of using NPPV and the parameters for success and failure, should be discussed by experienced personnel, in appropriate healthcare settings [41].

Rehabilitation

Patients with COPD demonstrate reduced levels of spontaneous physical activity compared with healthy controls. Furthermore, patients receiving LTOT have an even lower level of domestic

activity compared with that of those not on LTOT but with COPD of similar severity [42]. Pulmonary rehabilitation is an evidence based, multidisciplinary intervention comprising exercise training, education and psychological support and aimed at reducing disability and improving QoL [43]. In a multi-centre study of 1047 COPD patients pulmonary rehabilitation improved outcomes in patients both with and without chronic respiratory failure [44]. Also COPD patients in the ICU benefit from pulmonary rehabilitation, and guidelines have been developed [45–47]. In the frame of pulmonary rehabilitation, neuromuscular transcutaneous electrical stimulation (NMES) of the lower limb muscles increased muscular oxidative capacities. Small controlled studies with this technique in severe and even bed-bound COPD patients have been reported [48].

Surgery

Surgical interventions for end stage COPD are likely to be of value to only a small percentage of patients. Nevertheless, there are specific indications, which, when added to pulmonary rehabilitation will further advance exercise capacity and QoL.

Bullectomy is an established surgical procedure for bullous emphysema. In carefully selected patients, this procedure is effective in reducing dyspnoea and improving lung function. In considering the possible benefit of surgery it is important to estimate the effect of the bulla on the lung and the function of the remaining (non-bullous) lung. Some investigators have recommended that the bulla must occupy 50% or more of the hemithorax and produce definite displacement of the adjacent lung before surgery can be recommended [49].

Lung Volume Reduction Surgery (LVRS) is a surgical procedure in which parts of the lung are removed, to reduce hyperinflation, making respiratory muscles more effective by improving their mechanical efficiency, and improving overall gas exchange. Nevertheless LVRS in an unselected population with severe COPD had no effect on mortality, and in patients with FEV_1 and DLCO levels < 20% predicted, there was an increased risk of death whereas in selected patients with upper lobe disease and a low exercise capacity, LVRS improved mortality, exercise capacity, and QoL [50–53].

Given the increased risk of such procedures among patients with the most severe disease, alternatives have been studied. These include bronchoscopic LVRS and endobronchial valve placement which show improvements in exercise capacity and dynamic hyperinflation have been reported. Given the cost-effectiveness of LVRS, it is still considered a palliative surgical procedure for patients with advanced COPD [54]. Experimental studies of *biological lung volume reduction* using biological reagents to remodel and shrink damaged regions of the lung, are encouraging for patients with advanced heterogeneous emphysema [55]. All these techniques are promising, but have to date not been firmly studied.

Lung Transplantation (LTx) (single or double) is an option for a more limited number of patients, with highly impaired lung function, hypercapnia and secondary pulmonary hypertension. Despite the progress over the past 25 years, short and long-term outcomes of lung recipients are not as good as those for other *solid* organs [56, 57]. Pulmonary function improves, but exercise capacity may still be limited due to a peripheral muscle dysfunction [58]. Pulmonary rehabilitation further improves exercise and QoL, after LTx [59]. According to the International Society for Heart and Lung Transplantation's registry the survival for emphysema on 1 year is 85% and on three years is 68%, significant complications still impairing survival [60].

Supportive therapy

As in other chronic diseases when severity of disease increases along the natural history, therapy aimed to prolong life becomes less and less important in comparison to palliative therapy aimed to relieve symptoms [61].

Dyspnoea

Dyspnoea is the most important complaint in severe COPD. It is mainly evoked by exercise but may also be present at rest, especially during AECOPD of end-stage disease and can be incapacitating. Several strategies, may be considered and have been recently described elsewhere [62].

Drug therapy. The most effective treatments for dyspnoea are bronchodilators, although also a non pharmacological approach like LVRS may also improve dyspnoea. In end-stage disease one option may be also to reduce the ventilatory demand by decreasing the central drive with *opiates*. These have been shown to decrease minute ventilation at rest and during submaximal exercise thus reducing the sensation of breathing and its associated anxiety. Therapeutic doses of *opioids* induce collateral effects such as peripheral vasodilation and baroreceptor response inhibition which need to be carefully evaluated. Despite safety concerns, these drugs do have place in the management of pa-

tients in the terminal phase of their disease [63]. No consistent improvement in dyspnoea over placebo has been shown with anxiolitics. Nonetheless the American Thoracic Society statement recommends a trial of anxiolitic therapy on an individual basis [64]. Despite recent findings [65] do not support a beneficial effect from *nebulised furosemide* in patients with cancer related breathlessness, relief of exertional dyspnoea after single-dose furosemide inhalation in COPD is multifactorial but improvements in dynamic ventilatory mechanics are contributory in some individuals [66].

Breathed mixtures. Hypoxia contributes to dyspnoea by stimulating minute ventilation. Supplemental oxygen during exercise reduces exertional breathlessness and improves exercise tolerance in hypoxaemic COPD patients by: reduced hypoxic stimulation of the carotid bodies, pulmonary vasodilation, increase in arterial oxygen tension. Also reduced hyperinflation plays an important role in the oxygen-related relief of dyspnoea [67]. Reducing the gas density with *heliox* has also been shown to reduce ventilation and improve exercise capacity. The reduction in ventilation improves expiratory flow and reduces dynamic hyperinflation, thereby decreasing the operational lung volume and reducing the work of breathing [68].

Psychological consequences and cognitive status

Severe COPD patients experience a greater prevalence of depression compared with patients with mild or moderate disease. a possible causal association between depression and AECOPD and hospitalisation. Interventional trials appear to be warranted to evaluate the effectiveness of antidepressants and psychotherapies on reducing exacerbations [69]. There are difficulties in treating with antidepressant the frail and elderly COPD patients. Furthermore clinicians, care-givers and patients should be careful in prescription and assumption of benzodiazephines due to the risk of precipitating a severe episode of hypercapnia [15]. Pulmonary rehabilitation improves depression and anxiety in some COPD patients, although all pulmonary rehabilitation programmes include psychological therapy for those patients with high levels of depression and anxiety symptoms [70].

Conclusion

Good clinical care can prevent or alleviate suffering by assessing symptoms and providing psychological and social support to the patients and their families. There are recommendations based on systematic evidence review. The recommendations are:

In patients with serious illness at the end of life, clinicians should regularly assess patients for pain, dyspnoea, and depression, manage with therapies of proven effectiveness for pain, dyspnoea (including opioids and oxygen) and depression. They should ensure that advance care planning, including completion of advance directives, (in countries where available and/or legal) occurs for all patients with serious illness. Providing patients and their families with information about treatment options and anticipating possible future needs are crucial steps to appropriately tailor the management of the respiratory issues. These patients must be involved in the decision-making process on treatment escalation, such as endotracheal intubation, tracheotomy and eventually the option of palliative care [71–74]. As expected there are differences in attitudes toward end-of life decisions in different European countries. A survey promoted by the European Respiratory Society [40] has shown that in European respiratory intermediate care and high dependency units, an end of-life decision is taken for 30% of the patients admitted. The most common practices were withholding treatment, the use of non-invasive ventilation [39] as a ceiling therapy and provision of a do-not-resuscitate/do-not-intubate order, the latter occurring significantly more frequently in North compared with South Europe. Patients, when competent, and their families are often involved, together with nurses, in reaching these key decisions [40].

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