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ATS/ERS TASK FORCE

Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper

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Background

The Standards for the Diagnosis and Treatment of Patients with COPD document 2004 updates the position papers on chronic obstructive pulmonary disease (COPD) published by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 1995 [1, 2]. Both societies felt the need to update the previous documents due to the following. 1) The prevalence and overall importance of COPD as a health problem is increasing. 2) There have been enough advances in the field to require an update, especially adapted to the particular needs of the ATS/ERS constituency. 3) It allows for the creation of a "live" modular document based on the web; it should provide healthcare professionals and patients with a user friendly and reliable authoritative source of information. 4) The care of COPD should be comprehensive, is often multidisciplinary and rapidly changing. 5) Both the ATS and the ERS acknowledge the recent dissemination of the Global Initiative of Obstructive Lung Disease (GOLD) [3] as a major worldwide

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contribution to the battle against COPD. However, some specific requirements of the members of both societies require adaptation of the broad GOLD initiative. Those requirements include specific recommendations on oxygen therapy, pulmonary rehabilitation, noninvasive ventilation, surgery in and for COPD, sleep, air travel, and end-of-life. In addition, special emphasis has been placed on issues related to the habit of smoking and its control.

Goals and objectives

The main goals of the updated document are to improve the quality of care provided to patients with COPD and to develop the project using a disease-oriented approach. To achieve these goals, both organisations have developed a modular electronic web-based document with two components. 1) A component for health professionals that intends to: raise awareness of COPD; inform on the latest advances in the overall pathogenesis, diagnosis, monitoring and management of COPD; and promote the concept that COPD is a treatable disease. 2) A component for the patient that intends to: provide practical information on all aspects of COPD; and promote a healthy lifestyle to all patients afflicted with the disease.

Participants

The committee members who were involved in the production of this document are clinicians, nurses, respiratory therapists and educators interested in the field of COPD. The current Standards for the Diagnosis and Treatment of Patients with COPD document is unique in that it also had input from patients suffering from COPD. The committee members were proposed and approved by the ATS and ERS. The members were selected because of their expertise and willingness to participate in the generation of the document. A unique feature of this project was the development of a patient document that could serve as a formal source of information for the patients, thereby making them partners in the effort to decrease the burden of the disease.

Evidence, methodology and validation

Several well-accepted guidelines served as the blueprint for the document. Namely, the ATS and the ERS standards of 1995 [1, 2] and the GOLD initiative published in 2001 [3]. At the initial meeting, each member of the committee was assigned a specific section of the document and was asked to select a subcommittee to gather literature and review the existing evidence. The document was discussed in four group meetings, and the content and validity of each section was thoroughly reviewed. The final statement is the product of those discussions and has been approved by all the members of the committee. Several of the basic source documents reviewed have used an evidence-based approach, and the committee utilised those references as a source of evidence wherever appropriate.

The draft document was reviewed by a diverse group of experts whose input was also considered. Peer review was identified by the ATS and ERS, and the final document was submitted for review and approval by the Board of Directors of the ATS and the Executive Committee of the ERS.

Concept of a "live", modular document

Understanding that medicine and, in particular, the area of COPD is constantly undergoing changes, the ATS and the ERS considered that it was time to develop new instruments capable of adjusting to the changes. As such, this is the first statement conceived to be primarily based on the web and capable of being changed as needed. To achieve this goal, the organisations have developed a COPD task force composed of three members from each society whose office will last for 3 yrs. The main task of the members is to constantly review advances in the field of COPD and to propose changes to the modules of the document. As is customary in both organisations, the need to do so may arise from the membership through the current existing mechanisms. One of the members of the task force from each society will represent the society on the executive GOLD committee. The overall goal is to attempt to maintain a synchronous flow with the wider objectives of GOLD.

Organisation of the document

The document has two distinct components. The first, directed at patients and their needs, which can be accessed from the ATS/ERS website (www.copd-ats-ers.org) and from the website of each society (www.ersnet.org and www.thoracic.org), is not the subject of this summary. The second is directed at healthcare practitioners and all those interested in the professional issues related to COPD. This summary highlights the contents of the document for health practitioners, but the readers are encouraged to access the document *via* the website, where an easy navigational tool will allow you to explore its contents. The reader is also encouraged to access the patient document in order to familiarise themselves with its content. It was designed for and with patients so as to serve as a reliable resource for everyone.

Definition of COPD

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.

Diagnosis of COPD

The diagnosis of COPD should be considered in any patient who has the following: symptoms of cough; sputum production; or dyspnoea; or history of exposure to risk factors for the disease.

The diagnosis requires spirometry; a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) $\leqslant 0.7$ confirms the presence of airflow limitation that is not fully reversible (table 1). Spirometry should be obtained in all persons with the following history: exposure to cigarettes; and/or environmental or occupational pollutants; and/or presence of cough, sputum production or dyspnoea. Spirometric classification has proved useful in predicting health status [4], utilisation of healthcare resources [5], development of exacerbations [6, 7] and mortality [8] in

Table 1. – Spirometric classification of chronic obstructive pulmonary disease (COPD)

Severity	Postbronchodilator FEV1/FVC	FEV1 % pred
At risk#	>0.7	≥80
Mild COPD	≤0.7	≥80
Moderate COPD	≤0.7	50–80
Severe COPD	≤0.7	30–50
Very severe COPD	≤0.7	<30

FEV1: forced expiratory volume in one second; FVC: forced vital capacity. #: patients who smoke or have exposure to pollutants, have cough, sputum or dyspnoea.

COPD. It is intended to be applicable to populations [9] and not to substitute clinical judgment in the evaluation of the severity of disease in individual patients.

It is accepted that a single measurement of FEV1 incompletely represents the complex clinical consequences of COPD. A staging system that could offer a composite picture of disease severity is highly desirable, although it is currently unavailable. However, spirometric classification is useful in predicting outcomes such as health status and mortality, and should be evaluated. In addition to the FEV1, the body mass index (BMI) [10, 11] and dyspnoea [12] have proved useful in predicting outcomes such as survival, and this document recommends that they be evaluated in all patients.

BMI is easily obtained by dividing weight (in kg) over height (in m^2). Values <21 $kg \cdot m^{-2}$ are associated with increased mortality.

Functional dyspnoea can be assessed by the Medical Research Council dyspnoea scale as follows. 0: not troubled with breathlessness except with strenuous exercise. 1: troubled by shortness of breath when hurrying or walking up a slight hill. 2: walks slower than people of the same age due to breathlessness or has to stop for breath when walking at own pace on the level. 3: stops for breath after walking about 100 m or after a few minutes on the level. 4: too breathless to leave the house or breathless when dressing or undressing.

Poorly reversible airflow limitation associated with bronchiectasis, cystic fibrosis and fibrosis due to tuberculosis are not included in the definition of COPD, and should be considered in its differential diagnosis.

Patients presenting with airflow limitation at a relatively early age (4th or 5th decade) and particularly those with a family history of COPD should be tested for α_1-antitrypsin deficiency.

Epidemiology, risk factors and natural history of COPD

COPD is a leading cause of morbidity and mortality worldwide, and results in an economic and social burden that is both substantial and increasing. The prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced. In people aged 25–75 yrs in the USA, the estimated prevalence of mild COPD (defined as FEV1/FVC <70% and FEV1 ≥80% predicted) was 6.9% and of moderate COPD (defined as FEV1/FVC <70% and FEV1 ≤80% pred) was 6.6%, according to National Health and Nutrition Examination Survey (NHANES). COPD is the fourth-leading cause of death in the USA and Europe, and COPD mortality in females has more than doubled over the last 20 yrs [13]. Currently, COPD is a more costly disease than asthma and, depending on country, 50–75% of the costs are for services associated with exacerbations. Tobacco smoke is by far the most important risk factor for COPD worldwide. Other important risk factors are occupational exposures, socio-economic status and genetic predisposition.

COPD has a variable natural history and not all individuals follow the same course [14]. The often-quoted statistic that only 15–20% of smokers develop clinically significant COPD may underestimate the toll of COPD.

It is increasingly apparent that COPD often has its roots decades before the onset of symptoms [15]. Impaired growth of lung function during childhood and adolescence, caused by recurrent infections or tobacco smoking, may lead to lower maximally attained lung function in early adulthood [16, 17]. This abnormal growth will, often combined with a shortened plateau phase in teenage smokers, increase the risk of COPD.

The risk factors for COPD are shown in table 2 and they are separated into host factors and exposures.

Pathology and pathophysiology in COPD

COPD comprises pathological changes in four different compartments of the lungs (central airways, peripheral airways, lung parenchyma and pulmonary vasculature), which are variably present in individuals with the disease [18–22].

Tobacco smoking is the main risk factor for COPD, although other inhaled noxious particles and gases may contribute. This causes an inflammatory response in the lungs, which is exaggerated in some smokers, and leads to the characteristic pathological lesions of COPD. In addition to inflammation, an imbalance of proteinases and antiproteinases in the lungs, and oxidative stress are also important in the pathogenesis of COPD [23]. The different pathogenic mechanisms produce the pathological changes which, in turn, give rise to the following physiological abnormalities in COPD: mucous hypersecretion and cilliary dysfunction; airflow limitation and hyperinflation; gas exchange abnormalities; pulmonary hypertension; and systemic effects [24, 25].

Clinical assessment, testing and differential diagnosis of COPD

COPD runs an insidious course, measured over years, with an often undiagnosed initial phase. Its presence can be suspected after a directed clinical evaluation and then confirmed physiologically with simple spirometry. Chest radiography helps in differential diagnosis (table 3), and other tests may be useful to better determine the phenotype and physiological characteristics of individual patients.

Some patients with asthma cannot be distinguished from

Table 2. – Risk factors for chronic obstructive pulmonary disease

Host factors	Exposures
Genetic factors	Smoking
Sex	Socio-economic status
Airway hyperreactivity, IgE and asthma	Occupation
	Environmental pollution
	Perinatal events and childhood illness
	Recurrent bronchopulmonary infections
	Diet

Ig: immunoglobulin.

Table 3. – Differential diagnosis of chronic obstructive pulmonary disease (COPD)

Diagnosis	Suggestive features
COPD	Mid-life onset Slowly progressing symptoms Long history of smoking
Asthma	Early onset Varying symptoms Symptoms during the night/early morning Presence of allergy, rhinitis and/or eczema A family history Airflow limitation that is largely reversible
Congestive heart failure	Fine basilar crackles on auscultation Dilated heart on chest radiography Pulmonary oedema Volume restriction not airflow limitation on pulmonary function tests
Bronchiectasis	Large volume of purulent sputum Commonly associated with bacterial infection Coarse crackles/clubbing on auscultation Bronchial dilation and bronchial wall thickening on chest radiography/CT
Tuberculosis	Onset at all ages Lung infiltrate on chest radiography Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Younger onset and in nonsmokers History of rheumatoid arthritis/fume exposure Hypodense areas on expiration on CT suggestive of bronchiolitis
Diffuse panbronchiolitis	Effects mostly male nonsmokers Almost all have chronic sinusitis Diffuse small centrilobular nodular opacities and hyperinflation on chest radiography and HRCT

CT: computed tomography; HRCT: high resolution computed tomography.

COPD with the current diagnostic tests. The management of these patients should be similar to that of asthma.

Medical history

A directed medical history should assess the following issues: symptoms of cough, sputum production and dyspnoea; past medical history of asthma, allergies and other respiratory diseases; family history of COPD or other respiratory diseases; co-morbidities; any unexplained weight loss; and exposure history, smoking, and occupational and environmental exposures.

Physical signs

A normal physical examination is common in early COPD [13]. As the disease progresses, some signs become apparent and in advanced stages many are almost pathognomonic. Examination should aim at eliciting the presence of respiratory and systemic effects of COPD. All patients should have their respiratory rate, weight and height, and BMI measured.

Smoking cessation

Cigarette smoking is an addiction and a chronic relapsing disorder, and is regarded as a primary disorder by the Department of Health and Human Services Guidelines in the USA [26, 27] and by the World Health Organization (WHO). Therefore, treating tobacco use and dependence should be regarded as a primary and specific intervention. Smoking should be routinely evaluated whenever a patient presents to a healthcare facility and all smokers should be offered the best chance to treat this disorder.

The most comprehensive of the guidelines prepared on smoking cessation is "Treating Tobacco Use and Dependence", an evidence-based guideline sponsored by the US Department of Health and Human Services and released in 2000, which updates the previous evidence-based guideline "Smoking Cessation" released in 1996. The guideline and the meta-analyses on which it is based are available online [28]. The key findings of this report are summarised in table 4.

Brief intervention

The key steps in brief intervention are as follows. Ask: systematically, identify all tobacco users at every visit, implement an office-wide system that ensures that tobacco use is queried and documented for every patient at every clinic visit. Advise: strongly urge all tobacco users to quit, in a clear, strong and personalised manner. Assess: determine willingness to make a quit attempt. Assist: help the patient with a quit plan, provide practical counselling, provide treatment and social support, help the patient obtain extra treatment and social support, recommend the use of approved pharmacotherapy (except in special circumstances), and provide supplementary materials. Arrange: schedule follow-up contact, either in person or *via* the telephone.

Permanent remissions can be achieved in a substantial percentage of smokers with currently available treatments. Successful treatment of this disorder can have a substantial benefit in reducing many secondary complications of which COPD is one. All patients willing to make a serious attempt

Table 4. – Key points of the Treating Tobacco Use and Dependence guidelines

Tobacco dependence is a chronic condition that warrants repeated treatment until long-term or permanent abstinence is achieved
Effective treatments for tobacco dependence exist and all tobacco users should be offered these treatments
Clinicians and healthcare delivery systems must institutionalise the consistent identification, documentation and treatment of every tobacco user at every visit
Brief tobacco dependence intervention is effective and every tobacco user should be offered at least brief intervention
There is a strong dose-response relationship between the intensity of tobacco dependence counselling and its effectiveness
Three types of counselling were found to be especially effective: practical counselling, social support as part of treatment and social support arranged outside treatment
Five first-line pharmacotherapies for tobacco dependence are effective: bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray and nicotine patch, and at least one of these medications should be prescribed in the absence of contraindications
Tobacco-dependence treatments are cost effective relative to other medical and disease prevention interventions

to quit should be offered pharmacological support (nicotine replacement therapy and/or bupropion) [26, 27]. Smoking cessation activities and support for its implementation should be integrated into the healthcare system.

Management of stable COPD: pharmacological therapy

Effective medications for COPD are available and all patients who are symptomatic merit a trial of drug treatment [1–3]. The medications for COPD currently available can reduce or abolish symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status. At present, no treatment has modified the rate of decline in lung function. The inhaled route is preferred.

The change in lung function after brief treatment with any drug does not help in predicting other clinically related outcomes. Changes in FEV1 following bronchodilator therapy can be small but are often accompanied by larger changes in lung volumes, which contribute to a reduction in perceived breathlessness. Combining different agents produces a greater change in spirometry and symptoms than single agents alone.

Bronchodilators

Three types of bronchodilator are in common clinical use: β-agonists, anticholinergic drugs and methylxanthines. Despite substantial differences in their site of action within the cell and some evidence for nonbronchodilator activity with some classes of drug, the most important consequence of bronchodilator therapy appears to be airway smooth muscle relaxation and improved lung emptying during tidal breathing. The resultant increase in FEV1 may be relatively small but is often accompanied by larger changes in lung volumes [29], with a reduction in residual volume and/or a delay of the onset of dynamic hyperinflation during exercise. Both of these changes contribute to a reduction in perceived breathlessness [30, 31]. In general, the more advanced the COPD, the more important the changes in lung volume become relative to those in FEV1. The clinical use of bronchodilator drugs is illustrated in figure 1.

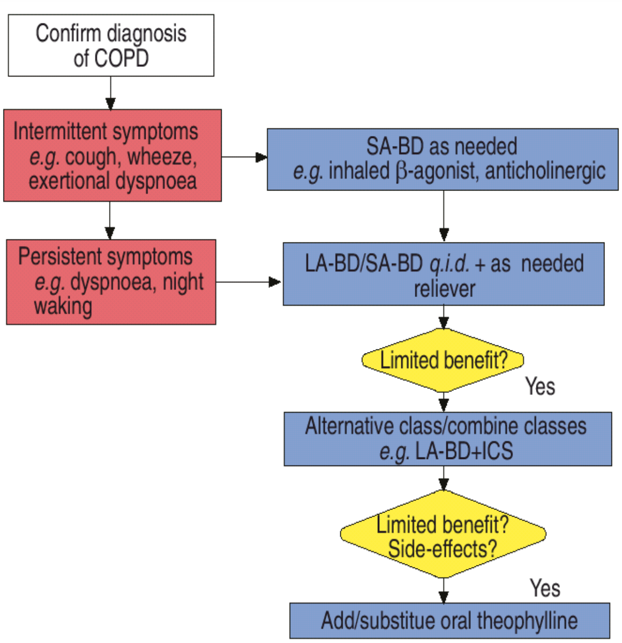

Fig. 1. – Algorithm for pharmacological treatment of chronic obstructive pulmonary disease (COPD). SA-BD: short-acting bronchodilator; LA-BD: long-acting bronchodilator; ICS: inhaled corticosteroid. Assess effectiveness by treatment response criteria. If forced expiratory volume <50% predicted and exacerbations of COPD requiring a course of oral corticosteroid or antibiotic occurred at least once within the last year, consider adding regular ICS. Always ensure the patient can use an inhaled device effectively and understands its purpose. If an ICS and a long-acting β-agonist are used, prescribe a combination inhaler.

Short-acting bronchodilators can increase exercise tolerance acutely [30, 31]. Long-acting inhaled β-agonists improve health status possibly to a greater extent than regular short-acting anticholinergics [32], reduce symptoms, rescue medication use and increase time between exacerbations compared with placebo [33–35]. Combining short-acting bronchodilator agents (salbutamol (albuterol)/ipratropium) produces a greater change in spirometry than either agent alone [34]. Combining long-acting β-agonists and ipratropium leads to fewer exacerbations than either drug alone. No good comparative data between different long-acting β-agonists are presently available, although it is likely that their effects will be similar. Combining long-acting β-agonists and theophylline appears to produce a greater spirometric change than either drug alone [35]. Tiotropium improves health status and reduces exacerbations and hospitalisations compared with both placebo and regular ipratropium [36, 37].

Theophylline is a weak bronchodilator, which may have some anti-inflammatory properties. Its narrow therapeutic index and complex pharmacokinetics make its use difficult, but modern slow-release preparations have improved this problem and lead to more stable plasma levels. Generally, therapeutic levels should be measured and patients should be kept on the lowest effective dose (recommended serum level 8–14 $\mu g \cdot dL^{-1}$).

Glucocorticoids

Glucocorticoids act at multiple points within the inflammatory cascade, although their effects in COPD are more modest as compared with bronchial asthma. Data from large patient studies suggest that inhaled corticosteroids can produce a small increase in postbronchodilator FEV1 and a small reduction in bronchial reactivity in stable COPD [38–40]. In patients with more advanced disease (usually classified as an FEV1 <50% pred) there is evidence that the number of exacerbations per year and the rate of deterioration in health status can be reduced by inhaled corticosteroids in COPD [38]. Evidence from four large prospective 3-yr studies has shown no effect of inhaled corticosteroids on rate of change of FEV1 in any severity of COPD [38–41].

When therapy is thought to be ineffective, a trial of withdrawing treatment is reasonable. Some patients will exacerbate when this occurs, which is a reason for re-instituting this therapy [42]. The results of forthcoming large randomised trials with mortality as an outcome will help clarify the role of inhaled glucocorticoids in COPD.

Outcomes of frequently used drugs

Table 5 summarises the effects of frequently used medications in patients with COPD. The evidence level was obtained from the GOLD document [3] using the same grade of evidence, as follows. Grade A: randomised clinical trial (RCT), rich body of data. Grade B: RCT, limited body of data. Grade C: nonrandomised trials, observational studies. Grade D: panel consensus.

Table 5. – Effect of commonly used medications on important clinical outcomes in chronic obstructive pulmonary disease

	FEV1	Lung volume	Dyspnoea	HRQoL	AE	Exercise endurance	Disease modifier by FEV1	Mortality	Side-effects
Short-acting β-agonists	Yes (A)	Yes (B)	Yes (A)	NA	NA	Yes (B)	NA	NA	Some
Ipratropium bromide	Yes (A)	Yes (B)	Yes (A)	No (B)	Yes (B)	Yes (B)	No	NA	Some
Long-acting β-agonists	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	No	NA	Minimal
Tiotropium	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	NA	NA	Minimal
Inhaled corticosteroids	Yes (A)	NA	Yes (B)	Yes (A)	Yes (A)	NA	No	NA	Some
Theophylline	Yes (A)	Yes (B)	Yes (A)	Yes (B)	NA	Yes (B)	NA	NA	Important

FEV1: forced expiratory volume in one second; HRQoL: health-related quality of life; AE: exacerbation of COPD; NA: evidence not available. GOLD grade levels are indicated in brackets (see text for explanation).

Combination therapy

Combining medications of different classes seems a convenient way of delivering treatment and obtaining better results. This includes better lung function and improved symptoms [43–45].

Data from trials combining long-acting inhaled β-agonists and inhaled corticosteroids show a significant additional effect on pulmonary function and a reduction in symptoms in those receiving combination therapy compared with its components [45]. The largest effects in terms of exacerbations and health status are seen in patients with an FEV1 <50% pred, where combining treatment is clearly better than either component drug used alone.

Management of stable COPD: long-term oxygen therapy

Supplemental long-term oxygen therapy (LTOT) improves survival, exercise, sleep and cognitive performance in hypoxaemic patients [1–3, 45–50]. Reversal of hypoxaemia supersedes concerns about carbon dioxide (CO_2) retention.

Arterial blood gas (ABG) assessment is the preferred method to determine oxygen need because it includes acid-base information. Arterial oxygen saturation as measured by pulse oximetry (S_{p,O_2}) is adequate for trending. Physiological indications for oxygen include a arterial oxygen tension (P_{a,O_2}) <7.3 kPa (55 mmHg). The therapeutic goal is to maintain S_{p,O_2} >90% during rest, sleep and exertion. If oxygen is prescribed during an exacerbation, ABG should be rechecked in 30–90 days. Withdrawal of oxygen because of improved P_{a,O_2} in patients whose need for oxygen was determined when in a stable state may be detrimental.

Active patients require portable oxygen. Oxygen sources include gas, liquid and concentrator; while oxygen delivery methods include nasal continuous flow, pulse demand, reservoir cannulae and transtracheal catheters [51]. Patient education improves compliance.

Figure 2 shows a flow chart for prescribing home oxygen therapy.

Management of stable COPD: pulmonary rehabilitation

Pulmonary rehabilitation is defined as "a multidisciplinary programme of care for patients with chronic respiratory impairment that is individually tailored and designed to optimise physical and social performance and autonomy" [52].

Pulmonary rehabilitation results in improvements in multiple outcome areas of considerable importance to the patient, including dyspnoea, exercise ability, health status and healthcare utilisation [53–57]. These positive effects occur despite the fact that it has a minimal effect on pulmonary function measurements. This reflects the fact that much of the morbidity from COPD results from secondary conditions, which are often treatable if recognised. Examples of these treatable conditions are cardiac deconditioning, peripheral muscle dysfunction, and a reduction in total and lean body mass, anxiety and poor coping skills. Elements of comprehensive pulmonary rehabilitation, including promoting a healthy lifestyle, stressing adherence to therapy and encouraging physical activity, should be incorporated into the care of all patients with COPD. Pulmonary rehabilitation is a multidisciplinary programme of care that is individually tailored and designed to optimise physical and social performance, and autonomy.

Pulmonary rehabilitation should be considered for patients with COPD who have dyspnoea or other respiratory symptoms, reduced exercise tolerance, a restriction in activities because of their disease, or impaired health status. There are

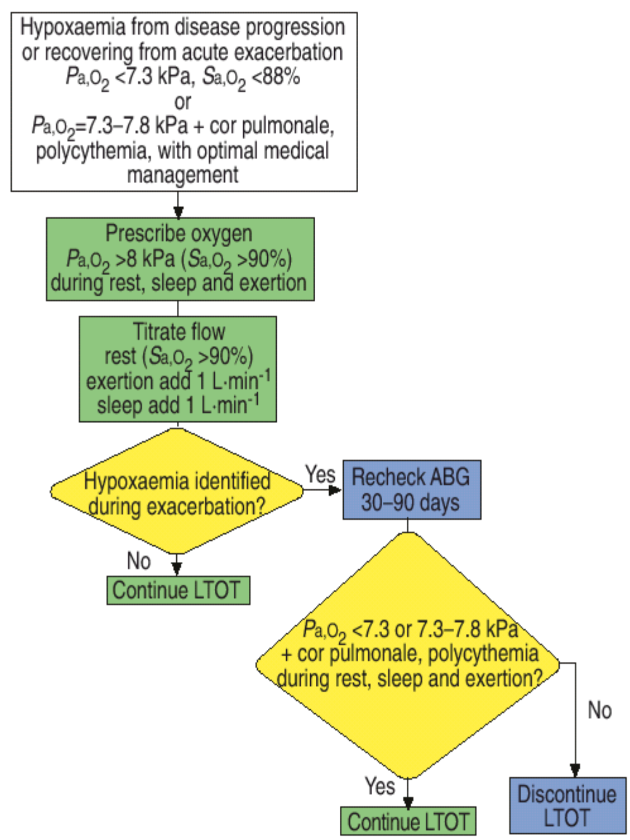

Fig. 2. – A flow chart for prescribing long-term oxygen therapy (LTOT). P_{a,O_2}: arterial oxygen tension; S_{a,O_2}: arterial oxygen saturation; ABG: arterial blood gases.

no specific pulmonary function inclusion criteria that indicate the need for pulmonary rehabilitation, since symptoms and functional limitations direct the need for pulmonary rehabilitation.

The pulmonary rehabilitation programme includes exercise training, education, psychosocial/behavioural intervention, nutritional therapy, outcome assessment and promotion of long-term adherence to the rehabilitation recommendations.

Management of stable COPD: nutrition

Weight loss, as well as a depletion of fat-free mass (FFM), may be observed in stable COPD patients, irrespective of the degree of airflow limitation, and being underweight is associated with an increased mortality risk [58].

Nutritional screening is recommended in the assessment of COPD. Simple screening can be based on measurements of BMI and weight change. Patients are considered underweight (BMI <21 kg·m^{-2}; age >50 yrs), normal weight (BMI 21–25 kg·m^{-2}), overweight (BMI 25–30 kg·m^{-2}) or obese (BMI $\geqslant$30 kg·m^{-2}). Criteria to define weight loss are weight loss >10% in the past 6 months or >5% in the past month.

Weight loss and particularly muscle wasting contribute significantly to morbidity, disability and handicap in COPD patients. Weight loss and loss in fat mass is primarily the result of a negative balance between dietary intake and energy expenditure, while muscle wasting is a consequence of an impaired balance between protein synthesis and protein breakdown. In advanced stages of COPD, both energy balance and protein balance are disturbed. Therefore, nutritional therapy may only be effective if combined with exercise or other anabolic stimuli [59, 60].

Management of stable COPD: surgery in and for COPD

Surgery in COPD

Patients with a diagnosis of COPD have a 2.7–4.7-fold increased risk of postoperative pulmonary complications [61–63]. However, COPD is not an absolute contraindication to any surgery. The most important concept determining the risk of surgery is that the further the procedure from the diaphragm, the lower the pulmonary complication rate. Although the value of pre-operative pulmonary function testing in general surgery is debatable, pre-operative pulmonary function studies have a well-documented role in the evaluation of patients undergoing lung surgery [64–67].

Smoking cessation at least 4–8 weeks pre-operatively and optimisation of lung function can decrease post-operative complications. In addition, early mobilisation, deep breathing, intermittent positive-pressure breathing, incentive spirometry and effective analgesia may decrease post-operative complications.

An algorithm for pre-operative evaluation of patients undergoing lung resection is shown in figure 3.

Surgery for COPD

Bullectomy, lung volume reduction surgery and lung transplantation may result in improved spirometry, lung volumes, exercise capacity, dyspnoea, health-related quality of life and possibly survival in highly selected patients [68–69]. Factors associated with a favourable or unfavourable outcome in bullectomy are shown in table 6.

The recently completed National Emphysema Therapy Trial (NETT) showed benefits for a subset of patients with nonhomogenous emphysema. Figure 4 summarises the stratification of the patients and the results of the trial for each of the groups. Group B is comprised of those patients with nonhomogenous emphysema of upper lobe predominance and limited exercise performance after pre-operative comprehensive rehabilitation. Group C corresponds to patients with predominant upper lobe emphysema and good post-rehabilitation exercise capacity. Group D corresponds to those patients with homogenous emphysema and low post-rehabilitation exercise capacity. Group E was characterised by homogeneous emphysema and good post-rehabilitation exercise capacity. Finally, group A corresponds to those patients with a very high risk for lung reduction surgery [70].

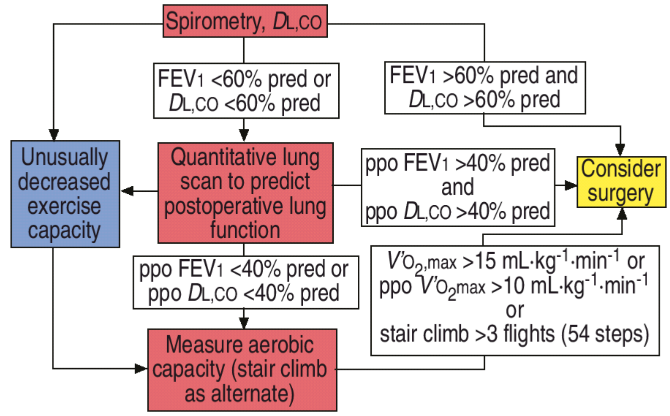

Fig. 3. – Algorithm for pre-operative testing for lung resection. $D_{L,CO}$: carbon dioxide diffusing capacity of the lung; FEV1: forced expiratory volume in one second; ppo: predicted postoperative; $V'_{O_2,max}$: maximum oxygen consumption.

The results of this trial showed that patients in group B who underwent surgery had a lower mortality, better exercise capacity and health status than patients randomised to medical therapy. The operated patients in groups C and D did not benefit from improved survival but had significant improvements in exercise capacity and health status compared to patients randomised to medical therapy. The patients in group E had higher mortality and would, therefore, not be candidates for LVRS. The results in this group are similar to those observed in the highest risk group (A) who should not be considered for surgery.

Lung transplantation results in improved pulmonary function, exercise capacity and quality of life, however, its effects on survival remain controversial [71]. Specific guidelines for lung transplantation in COPD are shown in table 7.

Management of stable COPD: sleep

Sleep in COPD is associated with oxygen desaturation, which is predominantly due to the disease itself rather than to sleep apnoea [72]. The desaturation during sleep may be greater than during maximum exercise [73]. In COPD, sleep quality is markedly impaired, both subjectively and objectively [74]. However, sleep apnoea syndrome is about as prevalent in COPD as in a general population of similar age, but oxygen desaturation during sleep is more pronounced when the two conditions co-exist [75].

The clinical assessment in all patients with COPD should include questions about sleep quality and possible co-existing sleep apnoea syndrome. Sleep studies are not indicated in COPD except in special circumstances. These include: a clinical

Table 6. – Factors associated with favourable or unfavourable outcome in classical bullectomy

Parameter	Favourable	Unfavourable
Clinical	Rapid progressive dyspnoea despite maximal medical therapy Ex-smoker	Older age Co-morbid illness Cardiac disease Pulmonary hypertension >10% weight loss Frequent respiratory infections Chronic bronchitis
Physiological	Normal FVC or slightly reduced FEV1 >40% pred Little reversibility High trapped lung volume Normal or near normal $D_{L,CO}$ Normal P_{a,O_2} and P_{a,CO_2}	FEV1 <35% pred Low trapped gas volume Decreased $D_{L,CO}$
Imaging		
CXR	Bulla >1/3 hemithorax	Vanishing lung syndrome Poorly defined bullae
CT	Large and localised bulla with vascular crowding and normal pulmonary parenchyma around bulla	Multiple ill-defined bullae in underlying lung
Angiography	Vascular crowding with preserved distal vascular branching	Vague bullae; disrupted vasculature elsewhere
Isotope scan	Well-localised matching defect with normal uptake and washout for underlying lung	Absence of target zones, poor washout in remaining lung

CXR: chest radiography; CT: computed tomography; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; $D_{L,CO}$: carbon monoxide diffusing capacity of the lung; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension. Table modified from [68].

suspicion of sleep apnoea or complications of hypoxaemia that are not explained by the awake arterial oxygen levels, and pulmonary hypertension out of proportion to the severity of pulmonary function derangement.

Management of sleep problems in COPD should particularly focus on minimising sleep disturbance by measures to limit cough and dyspnoea, and nocturnal oxygen therapy may be indicated for nocturnal hypoxaemia [76]. Hypnotics should be avoided, if possible, in patients with severe COPD.

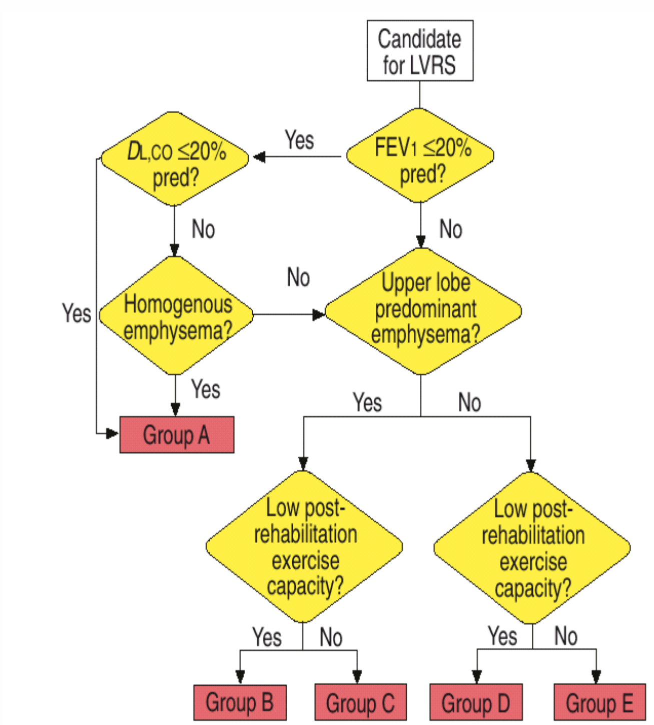

Fig. 4. – Schematic algorithm from the National Emphysema Therapy Trial for Lung Volume Reduction Surgery (LVRS) (see text). FEV1: forced expiratory volume in one second; $D_{L,CO}$: carbon dioxide diffusing capacity of the lung. Modified from [69].

Management of stable COPD: air-travel

Commercial airliners can cruise at >12,192 m (>40,000 feet), as long as the cabin is pressurised from 1,829–2,438 m (6,000–8,000 feet). This is equivalent to an inspired oxygen concentration at sea level of ~15% [77].

Patients with COPD can exhibit falls in P_{a,O_2} that average 3.3 kPa (25 mmHg) [78]. Pre-flight assessment can help determine oxygen needs and the presence of co-morbidities [79]. Oxygen needs can be estimated by using the hypoxia inhalation test or through the use of regression formulae. However, it is currently recommended that the P_{a,O_2} during air travel should be maintained above 6.7 kPa (50 mmHg) [80]. Treatment with 2–3 $L \cdot min^{-1}$ of oxygen by nasal cannula will replace the inspired oxygen partial pressure lost at 2,438 m (8,000 feet) compared to sea level [81]. For high-risk patients, the goal should be to maintain oxygen pressure during flight at the same level at which the patient is clinically stable at sea level. Most airlines will provide supplemental oxygen on request.

Exacerbation of COPD: definition, evaluation and treatment

Definition

An exacerbation of COPD is an event in the natural course of the disease characterised by a change in the patient's

Table 7. – Disease-specific guidelines for candidate selection for lung transplantation in chronic obstructive pulmonary disease patients

FEV1 ≤25% pred (without reversibility) and/or
Resting room air P_{a,CO_2} >7.3 kPa (55 mmHg) and/or
Elevated P_{a,CO_2} with progressive deterioration requiring long-term oxygen therapy
Elevated pulmonary arterial pressure with progressive deterioration

FEV1: forced expiratory volume in one second; P_{a,CO_2}: arterial carbon dioxide tension.

baseline dyspnoea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management.

There is no agreed classification of exacerbations. The following operational classification of severity can help rank the clinical relevance of the episode and its outcome. Level I: treated at home. Level II: requires hospitalisation. Level III: leads to respiratory failure.

Assessment

Several clinical elements must be considered when evaluating patients with exacerbations. These include the severity of the underlying COPD, the presence of co-morbidity and the history of previous exacerbations. The physical examination should evaluate the effect of the episode on the haemodynamic and respiratory systems. The diagnostic procedures to be performed depend on the setting of the evaluation [82, 83].

The pharmacological treatment of patients with an exacerbation of COPD is based on the same medications utilised in the management of the stable patient [1–3]. However, the evidence supports the use of systemic glucocorticosteroids [84–88].

Table 8 shows the elements of the clinical evaluation and diagnostic procedures that are usually informative in patients with exacerbations according to the severity of the episode.

Indication for hospitalisation

Table 9 provides reasonable guidelines for patient hospitalisation. Based on expert consensus, they consider the severity of the underlying respiratory dysfunction, progression of symptoms, response to outpatient therapy, existence of co-morbid conditions and the availability of adequate home care.

Indications for admission to specialised or intensive care unit

The severity of respiratory dysfunction dictates the need for admission to an intensive care unit (ICU). Depending on the resources available within an institution, admission of patients with severe exacerbations of COPD to intermediate or special respiratory care units may be appropriate if personnel, skills and equipment exist to identify and manage acute respiratory failure successfully.

Indications for ICU or special care unit admission include the following: impending or actual respiratory failure; presence of other end-organ dysfunction, *i.e.* shock, renal, liver or neurological disturbance; and/or haemodynamic instability.

Table 9. – Indications for hospitalisation of patients with a COPD exacerbation

The presence of high-risk co-morbid conditions, including pneumonia, cardiac arrhythmia, congestive heart failure, diabetes mellitus, renal or liver failure
Inadequate response of symptoms to outpatient management
Marked increase in dyspnoea
Inability to eat or sleep due to symptoms
Worsening hypoxaemia
Worsening hypercapnia
Changes in mental status
Inability of the patient to care for her/himself (lack of home support)
Uncertain diagnosis
Inadequate home care

Treatment of exacerbations

The treatment of exacerbations has to be based on the clinical presentation of the patient, as shown in tables 10, 11 and 12.

Exacerbation of COPD: inpatient oxygen therapy

During a severe exacerbation, ABGs should be monitored for P_{a,O_2}, arterial carbon dioxide tension (P_{a,CO_2}) and pH. The S_{p,O_2} should be monitored for trending and adjusting oxygen settings. The goal of inpatient oxygen therapy is to maintain P_{a,O_2} >8 kPa (60 mmHg) or S_{p,O_2} >90% in order to prevent tissue hypoxia and preserve cellular oxygenation. Due to the shape of the oxyhaemoglobin dissociation curve, increasing the P_{a,O_2} to values much greater than 8 kPa (60 mmHg) confers little added benefit (1–2 vol %) and may increase the risk of CO_2 retention, which may lead to respiratory acidosis

Table 8. – Clinical history, physical findings and diagnostic procedures in patients with exacerbation of chronic obstructive pulmonary disease (COPD)

	Level I	Level II	Level III
Clinical history			
Co-morbid conditions[#]	+	+++	+++
History of frequent exacerbations	+	+++	+++
Severity of COPD	Mild/moderate	Moderate/severe	Severe
Physical findings			
Haemodynamic evaluation	Stable	Stable	Stable/unstable
Use accessory respiratory muscles, tachypnoea	Not present	++	+++
Persistent symptoms after initial therapy	No	++	+++
Diagnostic procedures			
Oxygen saturation	Yes	Yes	Yes
Arterial blood gases	No	Yes	Yes
Chest radiograph	No	Yes	Yes
Blood tests[¶]	No	Yes	Yes
Serum drug concentrations[+]	If applicable	If applicable	If applicable
Sputum gram stain and culture	No[§]	Yes	Yes
Electrocardiogram	No	Yes	Yes

+: unlikely to be present; ++: likely to be present; +++: very likely to be present. [#]: the more common co-morbid conditions associated with poor prognosis in exacerbations are congestive heart failure, coronary artery disease, diabetes mellitus, renal and liver failure; [¶]: blood tests include cell blood count, serum electrolytes, renal and liver function; [+]: serum drug concentrations, consider if patients are using theophylline, warfarin, carbamezepine, digoxin; [§]: consider if patient has recently been on antibiotics.

Table 10. – Level I: outpatient treatment

- Patient education
  - Check inhalation technique
  - Consider use of spacer devices
- Bronchodilators
  - Short-acting β_2-agonist[#] and/or ipratropium MDI with spacer or hand-held nebuliser as needed
  - Consider adding long-acting bronchodilator if patient is not using one
- Corticosteroids (the actual dose may vary)
  - Prednisone 30–40 mg orally·day^{-1} for 10–14 days
  - Consider using an inhaled corticosteroid
- Antibiotics
  - May be initiated in patients with altered sputum characteristics[+]
  - Choice should be based on local bacterial resistance patterns
  - Amoxicillin/ampicillin[¶], cephalosporins
  - Doxycycline
  - Macrolides[§]
  - If the patient has failed prior antibiotic therapy consider:
    - Amoxicillin/clavulanate
    - Respiratory fluoroquinolones[ƒ]

MDI: metered-dose inhaler. #: salbutamol (albuterol), terbutaline; +: purulence and/or volume; ¶: depending on local prevalence of bacterial β-lactamases; §: azithromycin, clarithromycin, dirithromycin, roxithromycin; ƒ: gatifloxacin, levofloxacin, moxifloxacin.

[89, 90]. The main delivery devices include nasal cannula and venturi masks. Alternative delivery devices include nonrebreather masks, reservoir cannulae, nasal cannulae or transtracheal catheters.

As a general principle, prevention of tissue hypoxia supercedes CO_2 retention concerns. If CO_2 retention occurs, monitor for acidemia. If acidemia occurs, consider noninvasive or invasive mechanical ventilation.

Setting and adjusting oxygen flow

Figure 5 shows an algorithm for correcting hypoxaemia in the COPD patient.

Monitoring following hospital discharge

Patients may be started on oxygen for the first time during hospitalisation for an acute exacerbation and discharged before recovery is complete. Patients with hypoxaemia at discharge may require short-term oxygen therapy as the effects of the exacerbation are clearing. After 30–90 days, oxygen may no longer be required; thus re-evaluation of the patient's oxygen

Table 11. – Level II: treatment for hospitalised patient

- Bronchodilators
  - Short-acting β_2-agonist and/or
  - Ipratropium MDI with spacer or hand-held nebuliser as needed
- Supplemental oxygen (if saturation <90%)
- Corticosteroids
  - If patient tolerates, prednisone 30–40 mg orally·day^{-1} for 10–14 days
  - If patient can not tolerate oral intake, equivalent dose *i.v.* for up to 14 days
  - Consider using inhaled corticosteroids by MDI or hand-held nebuliser
- Antibiotics (based on local bacteria resistance patterns)
  - May be initiated in patients that have a change in their sputum characteristics[#]
  - Choice should be based on local bacteria resistance patterns
  - Amoxicillin/clavulanate
  - Respiratory fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin)
  - If *Pseudomonas* spp. and/or other *Enterobactereaces* spp. are suspected, consider combination therapy

MDI: metered-dose inhaler. #: purulence and/or volume.

Table 12. – Level III: treatment in patients requiring special or intensive care unit

- Supplemental oxygen
- Ventilatory support
- Bronchodilators
  - Short-acting β_2-agonist (salbutamol (albuterol)) and ipratropium MDI with spacer, two puffs every 2–4 h
  - If the patient is on the ventilator, consider MDI administration
  - Consider long-acting β-agonist
- Corticosteroids
  - If patient tolerates oral medications, prednisone 30–40 mg orally·day^{-1} for 10–14 days
  - If patient cannot tolerate, give the equivalent dose *i.v.* for up to 14 days
  - Consider using inhaled corticosteroids by MDI or hand-held nebuliser
- Antibiotics (based on local bacteria resistance patterns)
  - Choice should be based on local bacteria resistance patterns
  - Amoxicillin/clavulanate
  - Respiratory fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin)
  - If *Pseudomonas* spp. and/or other *Enterobactereaces* spp. are suspected, consider combination therapy

MDI: metered-dose inhaler.

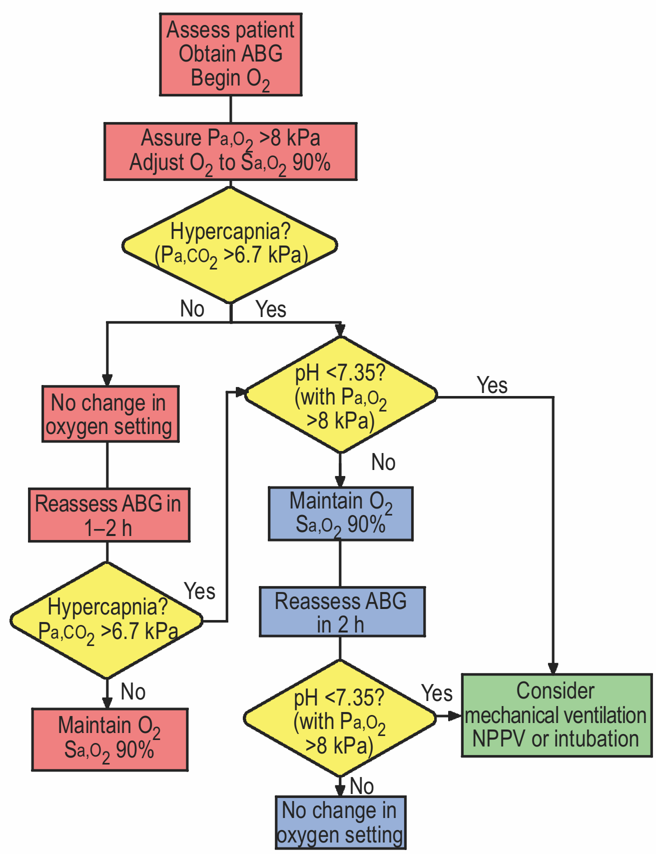

Fig. 5. – Algorithm to correct hypoxaemia in an acutely ill chronic obstructive pulmonary disease patient. ABG: arterial blood gas; P_{a,O_2}: arterial oxygen tension; O_2: oxygen; S_{a,O_2}: arterial oxygen saturation; P_{a,CO_2}: arterial carbon dioxide tension; NPPV: noninvasive positive pressure ventilation.

and medical status should be completed. If the patient no longer meets the prescribing criteria for LTOT, oxygen should be discontinued, as there is no proven survival benefit for patients with mild hypoxaemia [91]. Patients recovering from an exacerbation may benefit from pulmonary rehabilitation.

Some patients who needed oxygen prior to hospitalisation may, over time, increase their P_{a,O_2} to the point that they no longer qualify for oxygen. This phenomenon is thought to be due to a reparative effect of LTOT. Withdrawing oxygen from these patients may negate the reparative effect and cause the patient's status to deteriorate to the point of meeting the physiological requirement for oxygen. Consequently, these patients should continue their oxygen therapy without interruption, as withdrawing their oxygen might be detrimental [92, 93].

Exacerbation of COPD: assisted ventilation

Mechanical ventilation can be administered *via* noninvasive or invasive ventilation. Noninvasive is preferred whenever possible. Mechanical ventilation, either "invasive" or "noninvasive", is not a therapy but it is a form of life support until the cause underlying the acute respiratory failure is reversed with medical therapy [94–96]. Patients considered for mechanical ventilation should have a measurement of ABGs.

Indications for mechanical ventilation

The institution of mechanical ventilation should be considered when, despite optimal medical therapy and oxygen administration there is acidosis (pH<7.35) and hypercapnia (P_{a,CO_2} >6–8 kPa (45–60 mmHg)) and respiratory frequency >24 breaths·min^{-1}.

Modes of mechanical ventilation

Mechanical ventilation can be delivered as follows. 1) Through an endotracheal tube, by passing the upper airway, *i.e.* "conventional" or "invasive" mechanical ventilation. 2) Without the use of an endotracheal tube, *i.e.* "noninvasive" mechanical ventilation or NIMV, which can be instituted in two modes: noninvasive positive pressure ventilation (NPPV) (nasal or face masks); or negative pressure ventilation (*e.g.* iron lung, not recommended).

Noninvasive positive pressure ventilation. NPPV is by far the most popular mode of providing noninvasive ventilation. It is typically administered as a combination of continuous positive airway pressure (CPAP) plus pressure support ventilation (PSV) [94–98]. ABG improve because of an increase in alveolar ventilation without significant modifications in the alveolar ventilation/perfusion mismatching and gas exchange in the lungs [99].

ABGs are fundamental for the correct assessment and guidance of therapy. Once baseline ABGs are obtained, if the pH is <7.35 in the presence of hypercapnia, NPPV should be delivered in a controlled environment such as intermediate ICUs and/or high-dependency units. If the pH is <7.25, NPPV should be administered in the ICU and intubation should be readily available. The combination of some CPAP (*e.g.* 4–8 cmH_2O) and PSV (*e.g.* 10–15 cmH_2O) provides the most effective mode of NPPV.

Patients meeting exclusion criteria should be considered for immediate intubation and ICU admission. In the first hours, NPPV requires the same level of supervision as conventional mechanical ventilation.

Contraindications for NPPV include the following: respiratory arrest; cardiovascular instability (hypotension, arrhythmias, myocardial infarction); impaired mental status, somnolence, inability to cooperate; copious and/or viscous secretions with high aspiration risk; recent facial or gastro-oesophageal surgery; craniofacial trauma and/or fixed naso-pharyngeal abnormality; burns; and extreme obesity.

NPPV can be considered successful when ABGs and pH improve, dyspnoea is relieved, the acute episode resolves without the need of endotracheal intubation, mechanical ventilation can be discontinued and the patient is discharged from the hospital.

One-year mortality was reported to be lower in patients receiving NPPV for exacerbations of COPD, as compared to both conventional mechanical ventilation [100] and optimal medical therapy alone [101].

Figure 6 illustrates a useful flow-chart for the use of NPPV in exacerbation of COPD complicated by acute respiratory failure.

Invasive ventilation. Intubation should be considered in patients with the following. 1) NPPV failure: worsening of ABGs and or pH in 1–2 h; lack of improvement in ABGs and or pH after 4 h. 2) Severe acidosis (pH <7.25) and hypercapnia (P_{a,CO_2} >8 kPa (60 mmHg)). 3) Life-threatening hypoxaemia (arterial oxygen tension/inspiratory oxygen fraction <26.6 kPa (200 mmHg)). 4) Tachypnoea >35 breaths·min^{-1}.

Criteria for hospital discharge

As a general rule, patients hospitalised for an acute exacerbation can be considered for discharge once the reasons

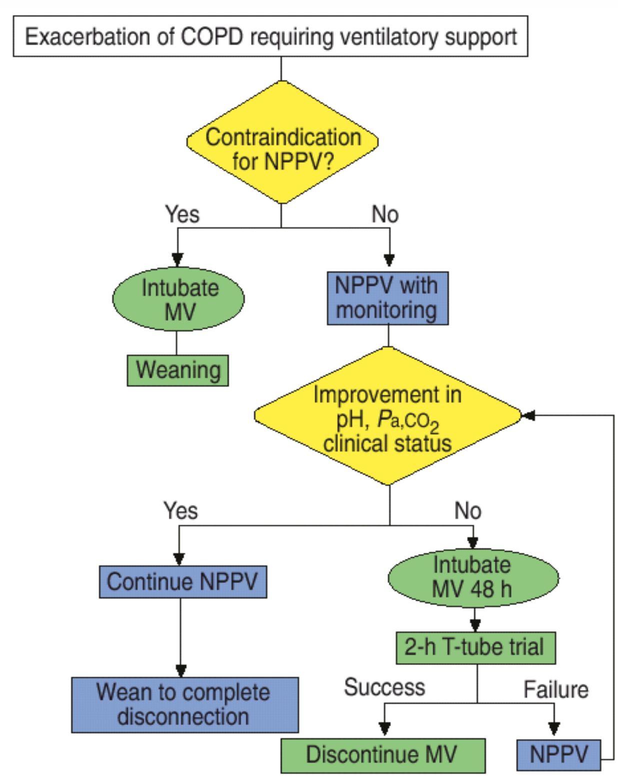

Fig. 6.—Flow-chart for the use of noninvasive positive pressure ventilation (NPPV) during exacerbation of chronic obstructive pulmonary disease (COPD) complicated by acute respiratory failure. MV: mechanical ventilation; P_{a,CO_2}: arterial carbon dioxide tension.

for admission are controlled and/or reversed. Based on consensus, conditions that need to be met when considering patients for discharge include: symptoms returning to baseline, including eating, sleeping, *etc.*; haemodynamic stability; oxygenation returning to baseline; inhaled β-agonist therapy required less frequently; ability to resume ambulation; ability to eat and sleep without frequent awakening by dyspnoea; off-parenteral therapy for 12–24 h; patient (or home caregiver) understands correct use of medications; follow-up and homecare arrangements have been completed (*e.g.* visiting nurse, oxygen delivery, meal provisions *etc.*).

Follow-up evaluation

Once discharged, the patient should be followed. There are no studies that have addressed the specific schedules more likely to result in a positive outcome, but patients with frequent exacerbations are more likely to relapse. Likewise, patients who have developed respiratory failure requiring admission to an ICU carry a very high mortality risk. Based on this, the guidelines for the re-evaluation of patients admitted for exacerbation of COPD should include: reassessment within 4 weeks; evaluation of improvement in symptoms and physical exam; assessment of need for supplemental oxygen; repeat examination if previous abnormalities were present; assessment of ability of the patient to cope with the environment; an understanding and re-adjustment of the treatment regimen.

Ethical and palliative care issues in COPD

Patients with COPD experience acute exacerbations of their disease, which may produce respiratory failure and a possible need for either ventilatory support or accepting death. No clinical features can identify patients with respiratory failure who will experience more burden than benefit from life supportive care.

If the patient has, or can have, clear preferences about treatment, respect for the patient's requires that care providers give effect to the patient's views. Autonomy of the patient is the predominant ethical principle that drives end-of-life decision-making in many societies.

All healthcare providers should assist patients during stable periods of health to think about their advance care planning by initiating discussions about end-of-life care. These discussions should prepare patients with advanced COPD for a life-threatening exacerbation of their chronic disease, while assisting them to go on living and enjoying life. Pulmonary rehabilitation provides an important opportunity to assist advance care planning for patients with moderate-to-severe COPD. Educational programmes on advance care planning within pulmonary rehabilitation increase the adoption rate for instruments of advance care planning and patient-physician discussion about end-of-life care [102]. Patients who choose to refuse life supportive care or have it withdrawn require expert delivery of palliative care.

Patients with COPD sometimes qualify for formal hospice services, especially when they are having repeated exacerbations and very poor measures on tests of pulmonary function. Nevertheless, many patients will have a fatal exacerbation within a short time of having fairly good function, so one cannot wait to consider using hospice until death is nearly certain. Opportunities for hospice care are frequently neglected for patients coming to the end of life with COPD [103, 104]. Neglect in offering patients and their families appropriate resources for supportive end-of-life care results in unnecessary admissions to acute care hospitals for worsening respiratory symptoms.

Integrated disease management for primary care in COPD

Disease management can be regarded as an integrated and systematic approach in which healthcare providers work together in a coordinated and cooperative manner to produce an optimal outcome for a particular patient with COPD, throughout the entire continuum of care [105]. The concept of the disease as a continuum is depicted in figure 7. This figure also represents the navigation tool for the web-based Standards for the Diagnosis and Treatment of Patients with COPD document 2004.

Integrated care for COPD involves the patient and a team of clinical professionals working in primary care, cooperating with secondary care and rehabilitation services. Optimal disease management involves redesigning standard medical care to integrate rehabilitative elements into a system of patient self-management and promotion of a healthy lifestyle.

The following aspects are important: smoking cessation for all patients who smoke; early diagnosis and secondary prevention (healthy lifestyle, vaccinations, exercise); education and self-management; pulmonary rehabilitation; monitoring and early recognition of exacerbation; implementation of rapid action plan; careful attention to end-of-life issues; palliative care.

Referral indications

Referral to specialist care is indicated for COPD patients with the following: disease onset at age <40 yrs; frequent exacerbations (two or more per year) despite adequate treatment; rapidly progressive course of disease (decline in FEV_1, progressive dyspnoea, decreased exercise tolerance, unintentional weight loss; severe COPD (FEV_1<50% pred) despite optimal treatment; need for LTOT; onset of co-morbid illness (osteoporosis, heart failure, bronchiectasis, lung cancer); evaluation for surgery.

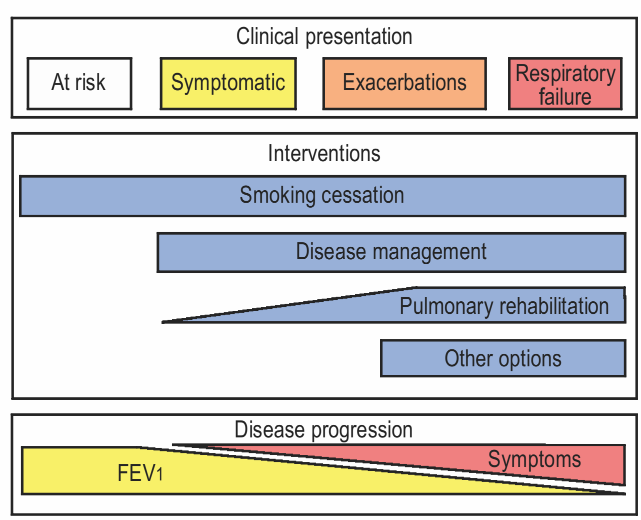

Fig. 7. – Continuum of care for chronic obstructive pulmonary disease (COPD). FEV_1: forced expiratory volume in one second.

Conclusions

This summary presents an overview of the entire document for the health practitioner, which is readily available online (www.copd-ats-ers, www.ersnet.org and www.thoracic.org). This summary does not include any reference to the patient document, which, due to its inherent characteristics, cannot be presented in a conventional format. The readers are encouraged to visit the website to access both full documents.

The committee that developed this document fully understands that the field is rapidly changing and that individual components of this document need to be updated periodically as the need arises. However, the modular and flexible design allows for this to occur easier than ever before. The challenge for the future is to develop mechanisms to permit the updated flow of valid scientific information to reach all who need it.

References

1. 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–S121.
2. Siafakas NM, Vermeire P, Pride NB, *et al.* Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. *Eur Respir J* 1995; 8: 1398–1420.
3. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, the GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001; 163: 1256–1276.
4. Ferrer M, Alonso J, Morera J, *et al.* Chronic obstructive pulmonary disease and health related quality of life. *Ann Int Med* 1997; 127: 1072–1079.
5. Friedman M, Serby C, Menjoge S, Wilson J, Hilleman D, Witek T. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. *Chest* 1999; 115: 635–641.
6. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297–1303.
7. Dewan N, Rafique S, Kanwar B, *et al.* Acute exacerbation of COPD. Factors associated with poor treatment outcome. *Chest* 2000; 117: 662–671.
8. Anthonisen NR, Wright EC, Hodgkin JE, the IPPB Trial Group. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 133: 14–20.
9. Celli B, Halbert R, Isonaka S, Schau B. Population impact of different definitions of airway obstruction. *Eur Respir J* 2003; 22: 268–273.
10. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1791–1797.
11. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 1856–1861.
12. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002; 121: 1434–1440.
13. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance – United States, 1971–2000. *MMWR* 2002; 51: 1–16.
14. Prescott E. Tobacco-related diseases: the role of gender. *Dan Med Bull* 2000; 47: 115–131.
15. Anto JM, Vermeire P, Vestbo J, Sunyer J. Epidemiology of chronic obstructive pulmonary disease. *Eur Respir J* 2001; 17: 982–994.
16. Fletcher CM, Tinker CM, Peto R, Speizer FE. The natural history of chronic bronchitis and emphysema. Oxford, Oxford University Press, 1976.
17. Gold DR, Wang X, Wipyj D, Speizer FE, Ware JH, Dockery DW. Effects of cigarette smoking on lung function in adolescent boys and girls. *N Engl J Med* 1996; 335: 931–937.
18. Saetta M, Di Stefano A, Turato G, *et al.* CD8+ T-lymphocytes in peripheral airways of smokers with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 822–826.
19. Rennard SI. Inflammation and repair processes in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: S12–S16.
20. Peinado VI, Barbera JA, Abate P, *et al.* Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159: 1605–1611.
21. Rodriguez-Roisin R, MacNee W. Pathophysiology of chronic obstructive pulmonary disease. *Eur Respir Mono* 1998; 3: 107–126.
22. O'Shaughnessy TC, Ansari TW, Barnes NC, Jeffery PK. Inflammation in bronchial biopsies of subjects with chronic bronchitis: inverse relationship of CD8+ T lymphocytes with FEV1. *Am J Respir Crit Care Med* 1997; 155: 852–857.
23. Repine JE, Bast A, Lankhorst I. Oxidative stress in chronic obstructive pulmonary disease. Oxidative Stress Study Group. *Am J Respir Crit Care Med* 1997; 156: 341–357.
24. Matsuba K, Wright JL, Wiggs BR, Pare PD, Hogg JC. The changes in airways structure associated with reduced forced expiratory volume in one second. *Eur Respir J* 1989; 2: 834–839.
25. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 770–777.
26. Fiore MC, Bailey WC, Cohen SJ. Smoking cessation. Guideline technical report no. 18. Publication No. AHCPR 97-Noo4. Rockville, MD, US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, October 1997.
27. Fiore MC. US public health service clinical practice guideline: treating tobacco use and dependence. *Respir Care* 2000; 45: 1200–1262.
28. Office of the Surgeon General. Tobacco Cessation Guideline www.surgeongeneral.gov/tobacco/default.htm. Data last updated: continuous.
29. Celli B, ZuWallack R, Wang S, Kesten S. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. *Chest* 2003; 124: 1743–1748.
30. O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 542–549.
31. Belman MJ, Botnick WC, Shin JW. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 153: 967–975.
32. Dahl R, Greefhorst LA, Nowak D, *et al.* Inhaled formoterol dry powder versus ipratropium in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 778–784.
33. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. *Am J Respir Crit Care Med* 1997; 155: 1283–1289.
34. Combivent trialists. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. COMBIVENT Inhalation Aerosol Study Group. *Chest* 1994; 105: 1411–1419.
35. Zuwallack RL, Mahler DA, Reilly D, *et al.* Salmeterol plus

theophylline combination therapy in the treatment of COPD. *Chest* 2001; 119: 1661–1670.
36. Casaburi R, Mahler DA, Jones PW, *et al.* A long-term evaluation of once daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002; 19: 217–224.
37. Vicken W, Van Noord JA, Greefhorst AP, *et al.*, on behalf of the Dutch/Belgian Tiotropium Study Group. Improved health outcomes in patients with COPD during 1 year treatment with tiotropium. *Eur Respir J* 2002; 19: 209–216.
38. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297–1303.
39. Pauwels RA, Lofdahl C-G, Laitinen LA, *et al.* Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. *New Engl J Med* 1999; 340: 1948–1953.
40. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *New Engl J Med* 2000; 343: 1902–1909.
41. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: A randomised controlled trial. *Lancet* 1999; 353: 1819–1823.
42. Jarad NA, Wedzicha JA, Burge PS, Calverley PMA. An observational study of inhaled corticosteroid withdrawal in stable chronic obstructive pulmonary disease. *Respir Med* 1999; 93: 161–168.
43. Calverley PM, Boonsawat W, Cseke Z, *et al.* Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 22: 912–919.
44. Szafranski W, Cukier A, Ramirez A, *et al.* Efficacy and safety of budesonide/formoterol in the management of COPD. *Eur Respir J* 2003; 21: 74–81.
45. Calverley P, Pauwels R, Vestbo J, *et al.* Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; 361: 449–456.
46. 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: 681–685.
47. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. *Ann Intern Med* 1980; 93: 391–398.
48. Weitzenblum E, Sautegeau A, Ehrhart M, Mammosser M, Pelletier A. Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1985; 131: 493–498.
49. Oswald-Mammosser M, Weitzenblum E, Quoix E, *et al.* Prognostic factors in COPD patients receiving long-term oxygen therapy: importance of pulmonary artery pressure. *Chest* 1995; 107: 1193–1198.
50. Zielinski J, Tobiasz M, Hawrylkiewicz I, Sliwinksi P, Palasiewicz G. Effects of long-term oxygen therapy on pulmonary hemodynamics in COPD patients: a 6-year prospective study. *Chest* 1998; 113: 65–70.
51. Tiep BL, Barnett J, Schiffman G, Sanchez O, Carter R. Maintaining oxygenation via demand oxygen delivery during rest and exercise. *Respir Care* 2002; 47: 887–892.
52. Pulmonary rehabilitation: official statement of the American Thoracic Society. *Am J Respir Crit Care Med* 1999; 159: 1666–1682.
53. Goldstein RS, Gort EH, Stubbing D, *et al.* Randomised controlled trial of respiratory rehabilitation. *Lancet* 1994; 344: 1394–1397.
54. Reardon J, Awad E, Normandin E, Vale F, Clark B, ZuWallack RL. The effect of comprehensive outpatient pulmonary rehabilitation on dyspnea. *Chest* 1994; 105: 1046–1052.
55. Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1995; 122: 823–832.
56. Wijkstra PJ, van der Mark TW, Kraan J, van Altena R, Koeter GH, Postma DS. Effects of home rehabilitation on physical performance in patients with chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1996; 9: 104–110.
57. Strijbos JH, Postma DS, van Altena R, Gimeno F, Koeter GH. A comparison between an outpatient hospital-based pulmonary rehabilitation program and a home-care pulmonary rehabilitation program in patients with COPD. A follow-up of 18 months. *Chest* 1996; 109: 366–372.
58. Schols AMWJ, Soeters PB, Dingemans AMC, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993; 147: 1151–1156.
59. Schols AM, Soeters PB, Mostert R, *et al.* Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease: A randomised controlled trial. *Am J Respir Crit Care Med* 1995; 152: 1248–1274.
60. Creutzberg EL, Wouters EFM, Mostert R, *et al.* Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease. *Nutrition* 2003; 19: 120–127.
61. Arozullah AM, Khuri SF, Henderson WG, Daley J. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. *Ann Intern Med* 2001; 135: 847–857.
62. Smetana GW. Preoperative pulmonary evaluation. *N Engl J Med* 1999; 340: 937–944.
63. Trayner E Jr, Celli BR. Postoperative pulmonary complications. *Med Clin North Am* 2001; 85: 1129–1139.
64. Weisman IM. Cardiopulmonary exercise testing in the preoperative assessment for lung resection surgery. *Semin Thorac Cardiovasc Surg* 2001; 13: 116–125.
65. Martinez FJ, Iannettoni M, Paine III R. Medical evaluation and management of the lung cancer patient prior to surgery, radiation or chemotherapy. *In*: Pass H, Mitchell J, Johnson D, Turrisi A, eds. Lung cancer: principles and practice. Philadelphia, PA, Lippincott Williams & Williams, 2000; pp. 649–681.
66. Bolliger CT, Jordan P, Soler M, *et al.* Pulmonary function and exercise capacity after lung resection. *Eur Respir J* 1996; 9: 415–421.
67. Bolliger CT, Perruchoud AP. Functional evaluation of the lung resection candidate. *Eur Respir J* 1998; 11: 198–212.
68. Martinez FJ. Surgical therapy for chronic obstructive pulmonary disease: conventional bullectomy and lung volume reduction surgery in the absence of giant bullae. *Semin Respir Crit Care Med* 1999; 20: 351–364.
69. Snider GL. Reduction pneumoplasty for giant bullous emphysema. Implications for surgical treatment of nonbullous emphysema. *Chest* 1996; 109: 540–548.
70. National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; 348: 2059–2073.
71. American Thoracic Society. International guidelines for the selection of lung transplant candidates. *Am J Respir Crit Care Med* 1998; 158: 335–339.
72. Hudgel DW, Martin RJ, Capehart M, Johnson B, Hill P. Contribution of hypoventilation to sleep oxygen desaturation in chronic obstructive pulmonary disease. *J Appl Physiol* 1983; 55: 669–677.
73. Mulloy E, McNicholas WT. Ventilation and gas exchange during sleep and exercise in patients with severe COPD. *Chest* 1996; 109: 387–394.

74. Klink M, Quan S. Prevalence of reported sleep disturbances in a general population and their relationship to obstructive airways diseases. *Chest* 1987; 91: 540–546.
75. Sanders MH, Newman AB, Haggerty CL, *et al.* Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. *Am J Respir Crit Care Med* 2003; 167: 7–14.
76. Fletcher EC, Luckett RA, Goodnight-White S, Miller CC, Qian W, Costarangos-Galarza C. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime Pa,O_2 above 60 mm Hg. *Am Rev Respir Dis* 1992; 145: 1070–1076.
77. Dillard TA, Berg BW, Rajagopal KR, Dooley JW, Mehm WJ. Hypoxemia during air travel in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1989; 111: 362–367.
78. Christensen CC, Ryg M, Refvem OK, *et al.* Development of severe hypoxaemia in chronic obstructive pulmonary disease patients at 2438 m (8000 ft) altitude. *Eur Respir J* 2000; 15: 635–639.
79. Gong H, Tashkin DP, Lee EY, Simmons MS. Hypoxia-altitude simulation test. *Am Rev Respir Dis* 1984; 130: 980–986.
80. AMA Commission on Emergency Medical Services. Medical aspects of transportation aboard commercial aircraft. *JAMA* 1982; 247: 1007–1011.
81. Berg BW, Dillard TA, Rajagopal KR, Mehm WJ. Oxygen supplementation during air travel in patients with chronic obstructive pulmonary disease. *Chest* 1992; 101: 638–641.
82. Emerman CL, Cydulka RAK. Evaluation of high-yield criteria for chest radiography in acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med* 1993; 22: 680–684.
83. O'Brien C, Guest PF. Physiological and radiological characterization of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000; 55: 631–632.
84. Albert RK, Martin TR, Lewis SW. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. *Ann Intern Med* 1980; 92: 753–758.
85. Niewhoehner DE, Erbland ML, Deupree RH, *et al.* Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med* 1999; 340: 1941–1947.
86. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomized controlled trial. *Lancet* 1999; 345: 456–460.
87. Thompson WH, Nielson CP, Carvalho P, *et al.* Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med* 1996; 154: 407–412.
88. Aaron S, Vandenheeur K, Hebert P, *et al.* Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med* 2003; 348: 2618–2625.
89. Aubier M, Murciano D, Milie-Emili M, *et al.* Effects of the administration of oxygen therapy on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. *Am Rev Respir Dis* 1980; 122: 747–754.
90. Dumont CP, Tiep BL. Using a reservoir nasal cannula in acute care. *Critical Care Nurse* 2002; 22: 41–46.
91. Górecka D, Gorzelak K, Śliwiński P, Tobiasz M, Zieliński J. Effect of long term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 1997; 52: 674–679.
92. O'Donohue WJ. Effect of arterial oxygen therapy on increasing arterial oxygen tension in hypoxemia patients with stable chronic obstructive pulmonary disease while breathing ambient air. *Chest* 1991; 100: 968–972.
93. Oba Y, Salzman GA, Willsie SK. Re-evaluation of continuous oxygen therapy after initial prescription in patients with chronic obstructive pulmonary disease. *Respir Care* 2000; 45: 401–406.
94. International Consensus Conferences in Intensive Care Medicine: noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 2001; 163: 283–291.
95. BTS Guideline. Non invasive ventilation in acute respiratory failure. British Thoracic Society Standards of Care Committee. *Thorax* 2002; 57: 192–211.
96. Mehta S, Hill NS. Non invasive ventilation. State of the Art. *Am J Respir Crit Care Med* 2001; 163: 540–577.
97. Lightowler JV, Wedzicha JA, Elliot M, Ram SF. Non invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *BMJ* 2003; 326: 185–189.
98. Rossi A, Appendini L, Roca J. Physiological aspects of noninvasive positive pressure ventilation. *Eur Respir Mon* 2001; 16: 1–10.
99. Diaz O, Iglesia R, Ferrer M, *et al.* Effects of non invasive ventilation on pulmonary gas exchange and hemodynamics duricng acute hypercapnic exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997; 156: 1840–1845.
100. Conti G, Antonelli M, Navalesi P, *et al.* Noninvaisve vs conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. *Intensive Care Med* 2002; 28: 1701–1707.
101. Plant PK, Owen JL, Elliott MW. Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome. *Thorax* 2001; 56: 708–712.
102. Heffner JE, Fahy B, Hilling L, Barbieri C. Outcomes of advance directive education of pulmonary rehabilitation patients. *Am J Respir Crit Care Med* 1997; 155: 1055–1059.
103. Emanuel EJ, Fairclough DL, Slutsman J, Alpert H, Baldwin D, Emanuel LL. Assistance from family members, friends, paid care givers, and volunteers in the care of terminally ill patients. *N Engl J Med* 1999; 341: 956–963.
104. Christakis NA, Escarce JJ. Survival of Medicare patients after enrollment in hospice programs. *N Engl J Med* 1996; 335: 172–178.
105. Epstein RS, Sherwood LM. From outcomes research to disease management: a guide for the perplexed. *Ann Intern Med* 1996; 124: 832–837.