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ERS - CONSENSUS STATEMENT

Optimal assessment and management of chronic obstructive pulmonary disease (COPD)

N.M. Siafakas, P. Vermeire, N.B. Pride, P. Paoletti, J. Gibson, P. Howard, J.C. Yernault, M. Decramer, T. Higenbottam, D.S. Postma, J. Rees, on behalf of the Task Force

A consensus statement of the European Respiratory Society (ERS)

Contents

Foreword

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. In the European Union, COPD and asthma, together with pneumonia, are the third most common cause of death. In North America, COPD is the fourth leading cause of death, and mortality rates and prevalence are increasing.

The major characteristic of COPD is the presence of chronic airflow limitation that progresses slowly over a period of years and is, by definition, largely irreversible. Most patients with COPD are, or were, cigarette smokers. Prevention by reducing the prevalence of smoking remains a priority. Although much of the damage is irreversible at the time of clinical presentation, treatments are available to improve the quality of life, the life expectancy, and perhaps the functional ability of patients with COPD.

Several national and international consensus statements on optimal assessment and management of asthma have been published in recent years. These consensus statements have led to international standardization of diagnosis and management and to better care. They also form a basis for clinical audits and suggest areas of future research. However, there have been few attempts to develop consensus guidelines on management of COPD [1, 2].

The European Respiratory Society (ERS) has taken the initiative of producing a consensus statement on COPD. A Task Force of scientists and clinicians was invited to provide this European consensus. The guidelines are intended for use by physicians involved in the care of patients with COPD, and their main goals are to inform health professionals and to reverse a widespread nihilistic approach to the management of these patients. This Task Force firmly believes that treatment can significantly improve the quality and length of life of patients suffering from this chronic, progressive condition.

Subcommittees of the Task Force focused on the five main sections of this project: Pathology/Pathophysiology, Epidemiology, Assessment, Treatment, and Management. Experts produced papers within each section, and these papers were brought together by the subcommittee heads. At a plenary meeting held in Wiesbaden, Germany on November 11–13, 1993, all contributions were extensively discussed, and additional working group meetings were arranged. Flowcharts for management in common clinical situations were produced. However, at all stages, members of the Task Force found themselves confronted by unresolved questions and regional differences in management across Europe. A practical approach was adopted, combining established scientific evidence and a consensus view when current data were inadequate. This approach identified more clearly those areas where further research is needed.

Comments on drafts of the consensus statement were invited from participants of the original meeting, which included colleagues from North America. The edited document was sent to independent experts for external review. All members had an opportunity to comment on the document at the ERS meeting in Nice on October 2, 1994.

As chairmen of the Task Force, we hope that the final document will promote better management of COPD in Europe. We would like to thank all who contributed to it. On behalf of the ERS, we also gratefully acknowledge a generous educational grant from Boehringer Ingelheim and the organizational assistance provided by M.T. Lopez-Vidriero.

N.M. Siafakas, P. Vermeire

Correspondence: N.M. Siafakas, University of Crete Medical School, Heraklion 711 10, Crete, Greece.
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Introduction

Definitions

Chronic obstructive pulmonary disease (COPD) is a disorder characterized by reduced maximum expiratory flow and slow forced emptying of the lungs; features which do not change markedly over several months [1]. Most of the airflow limitation is slowly progressive and irreversible. The airflow limitation is due to varying combinations of airway disease and emphysema; the relative contribution of the two processes is difficult to define *in vivo*. The airway component consists mainly of decreased luminal diameters due to various combinations of increased wall thickening, increased intraluminal mucus, and changes in the lining fluid of the small airways.

Emphysema is defined anatomically by permanent, destructive enlargement of airspaces distal to the terminal bronchioles without obvious fibrosis [2]. Loss of alveolar attachments to the airway perimeter contributes to airway stenosis. Pathological changes occurring in COPD are discussed more extensively in Appendix A.

Chronic bronchitis is defined by the presence of chronic or recurrent increases in bronchial secretions sufficient to cause expectoration. The secretions are present on most days for a minimum of 3 months a year, for at least two successive years, and cannot be attributed to other pulmonary or cardiac causes [3, 4]. This hypersecretion can occur in the absence of airflow limitation.

Patients with COPD often exhibit minimal reversibility of airflow limitation with bronchodilators. Airway hyperresponsiveness to a variety of constrictor stimuli is common. These patients often have recurrent or persistent productive cough.

Differential diagnosis

The most difficult diagnostic problem is distinguishing COPD from the persistent airflow limitation of chronic asthma in older subjects. Although the distinction may sometimes be impossible, the presence or absence of some clinical features may help in distinguishing between the two conditions. A history of heavy smoking, evidence of emphysema on imaging, decreased diffusing capacity, and chronic hypoxaemia favour the diagnosis of COPD. In contrast, atopy and marked improvement on spirometry with administration of bronchodilators or glucocorticosteroids favour the diagnosis of asthma.

A number of specific causes of chronic airflow limitation have, by convention, been excluded from COPD. These include cystic fibrosis, bronchiectasis, and bronchiolitis obliterans (associated with transplantation, chemical inhalation, severe viral infection, and other causes).

Pathophysiology

Aspects of the pathophysiology of COPD are presented in Appendix B. Changes occurring during the evolution of the disease, in either the presence or absence of emphysema, acute exacerbations and respiratory failure are discussed.

Epidemiology and natural history

The incidence, morbidity, and mortality from COPD are rising, but they vary widely between countries. The main risk factors are cigarette smoking and occupational exposure. There are, however, large variations in individual susceptibility.

This disease is often diagnosed late in its course, because patients may lack symptoms, even at low forced expiratory volume in one second (FEV_1). Frequent routine spirometry allows earlier detection of COPD. The main factor associated with rapid longitudinal decline in FEV_1 and poor prognosis is persistent smoking. Cessation of smoking reduces the rapid decline in FEV_1. Therefore, active intervention to help patients stop smoking is the primary tool for adequate management of COPD.

A more extensive overview of the epidemiology and natural history of COPD is presented in Appendix C.

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Assessment

Symptoms [1]

The two main symptoms that cause patients with COPD to consult a physician are breathlessness and

cough, sometimes accompanied by wheezing or sputum production. A history of repeated respiratory infections, especially during the winter, is common. Most patients are long-term cigarette smokers.

Breathlessness develops gradually over many years and eventually limits daily activities. By the time patients present with breathlessness, they are usually more than 40 yrs of age and have functional evidence of moderate or severe airflow limitation. Breathlessness and exercise capacity should be assessed by questions related to everyday activities, such as those found in standard questionnaires [2, 3].

Chronic cough, which is often productive and worse in the morning, is present in most patients, dominating the clinical picture in some cases. However, it bears no relationship to the severity of the functional deficit. The amount and character of sputum can provide useful information, especially when there is an increase in volume or purulence, which may indicate an exacerbation. Persistent large volumes of sputum (*e.g.* 30 mL·24 h^{-1}), especially if purulent, are suggestive of bronchiectasis. Haemoptysis is not uncommon during exacerbations, so that purulent sputum may be blood-streaked; however, the presence of blood should always alert the physician to the possibility of alternative diagnoses.

Obesity contributes to breathlessness in some individuals. In advanced COPD, however, anorexia and weight loss are common. Weight loss is associated with more severe impairment of lung function. Sleep-related symptoms, particularly daytime sleepiness and heavy snoring, should raise suspicion for coexisting obstructive sleep apnoea, which is particularly common in obese patients.

Physical findings [1]

The physical signs in patients with COPD depend on the degree of airflow limitation, the severity of pulmonary hyperinflation, and body build. The sensitivity of physical examination for detecting or excluding moderately severe COPD is poor, and reproducibility of physical signs is variable [4]. Among the classical physical signs, wheezing during tidal breathing and prolonged forced expiratory time (>5 s) are useful indicators of airflow limitation. These signs, however, are of no value as guides to severity, and their absence does not exclude COPD. Other signs, such as diminished breath sounds, reduced ribcage expansion and diaphragmatic excursion, and hyperresonance may be elicited; again, they are poor guides to the degree of airflow limitation. Visible activity of accessory muscles (*e.g.* the sternomastoid) or pursed-lip breathing usually imply severe airflow obstruction. Central cyanosis is seen with significant hypoxaemia, but its sensitivity is low, and it is influenced by other factors (*e.g.* haemoglobin concentration).

Peripheral oedema, raised jugular venous pressure, hepatic enlargement, and signs of pulmonary hypertension are seen with the development of cor pulmonale. Oedema may, however, be due to other causes, such as altered renal function, which is common in patients with hypoxaemia and hypercapnia [5].

During exacerbations, the clinical findings depend on the degree of additional airflow limitation, the severity of the underlying COPD, and the presence of coexisting conditions. The severity of an exacerbation is assessed crudely by tachypnoea, tachycardia, use of accessory respiratory muscles, cyanosis, and evidence of respiratory muscle dysfunction or fatigue (*e.g.* uncoordinated ribcage motion or paradoxical movement of the abdominal wall during inspiration). The classic signs of hypercapnia are inconsistent and unreliable. The poor sensitivity of symptoms and signs emphasizes the need for objective measurements. If the severity of an exacerbation is in doubt, it should always be assessed in hospital (see section on "Management").

Historically, patients with COPD have been classified as "pink puffers" and "blue bloaters". Many patients fall into neither group. Contrary to earlier thinking, these descriptive terms are not clearly related to specific functional or pathological features, and their use is not encouraged.

Investigations

Lung function tests

Lung function tests are used in the diagnosis of COPD as well as in the assessment of its severity, progression and prognosis. The presence of airflow limitation is recognized by a reduction in the ratio of FEV_1 to vital capacity (VC) or forced vital capacity (FVC). The FEV_1/VC ratio is a relatively sensitive index of mild COPD. In moderate to severe disease, the severity of airflow limtation is best assessed by the FEV_1 in relation to reference values [6].

A suggested, categorization of patients with COPD in terms of FEV_1 is shown in table 1. Any such grading is inevitably arbitrary, however.

Most studies of lung function in COPD are based on FEV_1, because it shows the least variability. Several other indices can be measured during forced expiration. An example is maximal mid-expiratory flow or maximal expiratory flow ($\dot{V}$max) at a given lung volume (*e.g.* maximal expiratory flow at 50% VC ($\dot{V}_{max50}$)). Because of greater intrasubject and intersubject variability, resulting in a larger range of predicted values, such indices

Table 1. – Severity of COPD based on FEV_1

Severity	FEV_1* % pred
Mild	≥70
Moderate	50–69
Severe	<50

*: in the presence of obstruction assessed as FEV_1/VC <88% predicted in men or <89% predicted in women (*i.e.* >1.64 residual standard deviation below predicted value). COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; VC: vital capacity; % pred: percentage of predicted value.

do not provide information that is more useful in clinical practice than that provided by FEV_1 and VC.

Peak expiratory flow (PEF) is more convenient for domiciliary monitoring of airway function. This measurement is sometimes used to assess response to treatment or to document diurnal variation. In advanced emphysema, however, the PEF should not be relied on, as it may be only moderately reduced, whilst the FEV_1 is severely affected.

Resistance measurements

Airways resistance can be measured by whole-body plethysmography, and respiratory resistance can be assessed by the forced oscillation technique. These measurements provide information about the calibre of the uncompressed airway as resistance is measured during quiet breathing or panting. The forced oscillation technique is less dependent on the co-operation of the subject. In most situations, resistance measurements have no clinical advantage over measurement of FEV_1.

Response to bronchodilators, corticosteroids and bronchoconstrictors

Most individuals with COPD show an increase of FEV_1 following inhalation of sympathomimetic or anticholinergic drugs. Different criteria of reversibility have been used [7]. Percentage increases from baseline are of limited value because of their dependence on the pretreatment level. Expression of reversibility as an absolute change or as a percentage of predicted value is more reproducible and independent of baseline FEV_1. However, symptomatic improvement may occur without a significant increase in FEV_1 [7, 8].

In stable COPD, an increase in FEV_1 following a therapeutic trial of corticosteroids for several days is often taken as an indication for regular use of these drugs, in either oral or inhaled form. An increase $\geq 10\%$ of the predicted value has been used to define a positive steroid response [9].

Many patients show airway hyperresponsiveness to inhaled histamine or methacholine. The response is largely dependent on prechallenge airway function. Testing of bronchoconstrictor response is of doubtful clinical value in patients with established airflow limitation.

Static lung volumes and distensibility

Functional residual capacity (FRC), residual volume (RV), and the ratio of RV to total lung capacity (TLC) are characteristically increased in COPD. In particular, TLC is increased in those patients with severe emphysema. An increase in static pulmonary compliance, a decrease in lung recoil pressure at a given lung volume, and a change in the shape of the static pressure-volume curve of the lung (defined by the shape factor, κ) are characteristic of pulmonary emphysema. Such measurements are not widely applied in clinical assessment.

Respiratory muscle function

Maximum inspiratory and expiratory pressures ($P_{I,max}$ and $P_{E,max}$, respectively) are reduced in many patients with COPD. Whereas $P_{I,max}$ is impaired by hyperinflation due to shortening of the inspiratory muscles, $P_{E,max}$ is less influenced by respiratory mechanics. Reduction in $P_{E,max}$ can be attributed to muscle weakness, which is common in advanced COPD [10]. Measurement of maximum respiratory pressures is indicated if poor nutrition or steroid myopathy is suspected, or if dyspnoea or hypercapnia are out of proportion to the FEV_1.

Transfer factor

A reduction in the single-breath carbon monoxide transfer factor ($T_{L,CO}$), is usually present in patients with symptomatic COPD. The transfer coefficient (K_{CO}) is the best functional indicator of the presence and severity of emphysema. Although nonspecific, the measurement is of clinical value in distinguishing patients with emphysema from those with asthma, in whom K_{CO} is generally not reduced.

Arterial blood gas tensions

The relationship between FEV_1 and arterial blood gas tensions is weak. However, measurement of blood gas tensions with the patient breathing room air is recommended in the assessment of patients with moderate or severe stable COPD. An alternative approach in patients with moderate COPD is to measure arterial oxygen saturation (S_{a,O_2}) using an oximeter. If the value is $\leq 92\%$, blood gas tensions should be measured.

Sequential measurements of blood gas tensions are necessary to follow the impairment of gas exchange, and are of paramount importance in the management of respiratory failure [11].

Exercise testing

Assessment of exercise performance is of particular value in patients whose breathlessness appears to be out of proportion to simple measurements, such as FEV_1. Exercise testing also helps select and follow patients in a pulmonary rehabilitation programme. The use of simple walking tests (*e.g.* a 6 min walk) is sometimes advocated for assessing and evaluating the response to treatment, but the reproducibility of such tests is generally poor [12].

Assessment of progression

Serial measurements of FEV_1 are used to monitor the progression of the disease. Longitudinal studies of the decline in FEV_1 yield varying results; however, a decrease of >50 mL·yr^{-1} suggests accelerated progression [13].

Because of the variability of the measurements, confident assessment of the rate of decline in an individual patient requires periodic measurements of FEV1 over at least 4 yrs [13].

Pulmonary circulation

Pulmonary hypertension is frequently present in advanced COPD, and its severity is related to the prognosis [14]. In recent years, noninvasive methods have been developed for assessing the presence and degree of pulmonary hypertension in patients with COPD. The best results have been obtained with Doppler echocardiography, but correlation with measured systolic pulmonary artery pressure is not sufficiently close for accurate estimation in an individual patient [15]. Right heart catheterization remains the only way to accurately measure pulmonary vascular pressures. However, because similar prognostic information can be obtained in COPD patients from simpler measurements, such as FEV1 and blood gases, routine catheterization is not recommended.

Investigation during sleep

Patients with COPD may have worsening hypoxaemia and hypercapnia during sleep, particularly during rapid eye movement (REM) sleep. The blood gas abnormalities during REM sleep are accompanied by a rise in pulmonary artery pressure. Although patients with nocturnal oxygen desaturation have significantly greater pulmonary artery pressure and pulmonary vascular resistance than those without nocturnal desaturation [16], the contribution of isolated nocturnal hypoxaemia to pulmonary hypertension is uncertain. In general, more severe nocturnal desaturation is associated with low daytime arterial oxygen pressure (P_{a,O_2}), although the correlation is not very close. Other possible consequences of oxygen desaturation during sleep include cardiac arrhythmias and polycythaemia.

The need for nocturnal studies in routine assessment of patients with COPD is controversial. Detailed sleep studies (polysomnography) are indicated if coexisting obstructive sleep apnoea (the so-called overlap syndrome) is suspected. Measurement of nocturnal oxygenation may also be helpful in the presence of other unexplained features, such as cor pulmonale or polycythaemia despite relatively mild airway obstruction. Further research is needed on the prognostic value of sleep measurements for assessing nocturnal desaturation in individuals with moderately severe daytime hypoxaemia (arterial oxygen tension (P_{a,O_2}) 7.3–8.7 kPa (55–65 mmHg)). With current criteria, such hypoxaemia is not generally regarded as an indication for long-term oxygen treatment.

Radiology

Plain chest radiography. Although a plain chest radiograph is not sensitive for the diagnosis of COPD, it is useful in the initial assessment. Depression and flattening of the diaphragm on the posteroanterior film and increase in the retrosternal airspace on the lateral chest radiograph are well-recognized signs of hyperinflation. Bullae and/or irregular radiolucency of the lung fields (absence of vasculature) may be obvious in severe cases of emphysema, but their recognition is subjective and dependent on the quality of the radiograph. The presence of such abnormalities is considered specific for emphysema in a patient with COPD [17]. However, the extent of emphysema diagnosed radiographically is poorly correlated with its severity at necropsy [18]. At presentation of patients with COPD, the plain chest radiograph can exclude other conditions, such as lung cancer. It may also suggest cor pulmonale and pulmonary hypertension; if the maximum diameter of the right descending pulmonary artery exceeds 16 mm, then pulmonary hypertension is likely [19]. In acute exacerbations of COPD, a chest radiograph is important to confirm or exclude complicating pneumonia or pneumothorax.

Computed tomography (CT). Computed tomography provides a means of measuring tissue density. Emphysema reduces lung density, and this can be visualized as low attenuation areas on the CT scan. The finding can be quantified by measuring the frequency distribution of density values from each picture element [20]. Recent evidence suggests that high-resolution CT scanning is sufficiently sensitive to diagnose emphysema in patients with normal chest radiographs and isolated low transfer factor [21]. It appears to be useful in identifying patterns of emphysema, such as centriacinar and panacinar emphysema [22]. The size and number of bullae can be quantified accurately by CT scanning. Knowledge of the extent of emphysema in the nonbullous lung may be useful in predicting the outcome of surgical treatment.

Despite these uses, CT scanning is not recommended for routine clinical assessment. Its role in patients with COPD is limited to evaluation of bullae and investigation of coexisting bronchiectasis.

Quality of life

Recently, questionnaires to assess quality of life have been introduced and evaluated in patients with COPD [3, 8, 23]. These tools are being used increasingly in studies of the effects of treatment, and may prove to be sensitive means of measuring the progression of the disease. However, none of the questionnaires is as yet generally accepted for use in everyday clinical practice.

Summary of initial assessment and follow-up

The investigations recommended for diagnosis and initial assessment of COPD are summarized in table 2. In follow-up assessment, spirometry is essential. If arterial blood gas tensions are abnormal at the initial assessment, they should be monitored. Otherwise, further investigations will usually depend on changes in spirometric volumes.

Table 2. – Investigations for diagnosis and initial assessment

Indication	Test
Routine	FEV_1
	VC or FVC
	Bronchodilator response
	Chest radiograph
	$T_{L,CO}/K_{CO}$
Specific indications	
Moderate or severe COPD	Lung volumes
	S_{a,O_2} and/or blood gases
	Electrocardiogram
	Haemoglobin
Persistent purulent sputum	Sputum culture and sensitivity
Emphysema in younger patients	α_1-antitrypsin level
Assessment of bullae	CT scan
Disproportionate breathlesssness	Exercise test
	Maximum respiratory pressures
Suspected asthma	Bronchoconstrictor response
	PEF monitoring
Suspected obstructive sleep apnoea	Nocturnal sleep study

FVC: forced vital capacity; $T_{L,CO}$: transfer factor of the lungs for carbon monoxide; K_{CO}: carbon monoxide transfer coefficient; S_{a,O_2}: arterial oxygen saturation; CT: computed tomography; PEF: peak expiratory flow.

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Treatment

Introduction

The goals of treatment in COPD are to prevent symptoms and recurrent exacerbations and to preserve optimal lung function both in the short- and long-term; thus, improving activities of daily living and enhancing the quality of life. However, few therapeutic options have been shown to prevent COPD or to stop the accelerated loss of lung function. The main preventive measure is smoking cessation.

Although COPD is largely an irreversible, progressive disease, a policy of minimal therapeutic intervention is not justified. Results of treatment should focus not only on changes in lung function but also on quality of life.

A reliable scientific basis in controlled clinical studies is lacking for many pharmacological and rehabilitation therapies. Therefore, an empirical approach based on current information is presented here and in the flowcharts that follow.

Cessation of smoking

A high priority should be given to the primary prevention of COPD by reducing the number of people who start to smoke. For patients who have already developed COPD, smoking cessation reduces the rate of lung function decline [1]. There is a small increase in FEV_1 initially in some patients. Approximately one third of patients are able to give up smoking with support; in the remainder, nicotine addiction and other factors make reduction or cessation difficult.

Most smokers have tried to stop at some time and repeated attempts are often needed to achieve success. Smoking cessation should be seen as a constant target and patients may need to be encouraged to go through the cycle of contemplation of cessation, positive action and relapse many times. Various degrees of support are possible from simple advice to pharmacological and behavioural therapy. Many interventions show impressive short-term results but poorer sustained cessation rates of up to 30%.

The most successful method of cessation is to quit abruptly, although the relapse rate is high. Gradual withdrawal may be successful in reducing total tobacco consumption but is generally unsuccessful in achieving cessation. Heavy smokers and those with multiple previous attempts are less likely to be successful.

The first stage is to provide an explanation of the effects of smoking, and the benefits of stopping, and to give encouragement to quit. A minority of patients will stop smoking after simple advice, which may be more successful at the time of presentation with respiratory or other symptoms. Advice should include helpful strategies in stopping and encouragement on other healthy life style changes. If such encouragement is not successful, then the second stage is more intensive support. This may include nicotine replacement, behavioural intervention, individual or group programmes. Temporary nicotine replacement by chewing gum or transcutaneous routes [2–4] and behavioural intervention [5] have been shown to increase success rates.

Encouragement to stop smoking is an important element in all professional consultations. Health-care professionals should not smoke. Advertising bans, smoke-free hospitals and public places, health warnings, and personal example are useful ways to discourage smoking.

Controlling occupational and atmospheric pollution

Occupational exposure to environmental pollution and to irritant dusts and fumes can trigger symptoms. Continued damage leads to accelerated decline in FEV_1 in patients with COPD. Protection of workers through masks and appropriate design of the workplace are essential where irritant dusts and fumes are released. Specific occupational risks need to be regulated carefully.

High levels of atmospheric pollution may exacerbate symptoms and impair function of patients with COPD [6, 7]. Indoor and outdoor air quality can be improved through adherence to air quality guidelines [8].

Antibiotics

Pathogens may be difficult to identify in exacerbations of COPD. The most common organisms are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and viruses [9]. When sputum becomes purulent, patients are treated on empirical grounds with a 7–14 day course of antibiotics [10]. Knowledge of local resistance patterns is helpful in directing empirical therapy.

Inexpensive antibiotics are sufficient in most cases. Commonly used antibiotics are amoxycillin, tetracycline derivatives, and amoxycillin/clavulanic acid. Alternative treatments include newer cephalosporins, macrolides, and quinolone antibiotics. Patients may have to keep a course of antibiotics in reserve and start treatment when symptoms suggest an infective exacerbation. There is no advantage to prophylactic or aerosolized therapy except in a few selected patients with frequently recurring infections, particularly in winter.

The incidences of Staphylococcus, resistant Haemophilus, and Streptococcus infections in exacerbations of COPD are increasing [9]. Culture of sputum in exacerbations helps determine appropriate second choices of therapy when response to initial therapy is poor.

Bronchodilator therapy

Bronchodilator drugs relax smooth muscles in the airways. Spirometric responses are not seen in all patients. Even without spirometric changes, however, improvement in symptoms and functional capacity can occur [11]. There are three groups of suitable drugs: β_2-agonists, anticholinergic drugs, and methylxanthines.

The inhaled route of drug delivery results in fewer adverse effects. It is available for β_2-agonists and anticholinergic drugs, as well as corticosteroids. Many devices are available, including metered-dose inhalers with or without large-volume spacer attachments, breath-actuated metered-dose inhalers, and dry-powder inhalers. Most patients can be taught to use the inhaled route. The technique should be taught at the first prescription and checked periodically [12]. During acute exacerbations, some breathless patients may find it easier to use a nebulizer. Otherwise a good response can be achieved with spacers and dry-powder devices.

β_2-agonists. β_2-agonists are best given by inhalation but may also be administered orally and parenterally. Short-acting agents produce bronchodilatation within minutes, reaching a peak at 15–30 min. The effect lasts 4–5 h.

β_2-agonists have been shown, in the laboratory, to protect against acute airway challenge [13]. This effect might be relevant clinically in certain situations, such as exposure to cold air. With prolonged use of β_2-agonists, there may be a small decrease in the acute bronchodilator effect [14].

Long-acting inhaled or oral β_2-agonists provide an alternative, especially for patients with night-time or early morning symptoms. However, adequate studies of long-acting inhaled β_2-agonists in COPD are not yet available.

In acute exacerbations, there is no consistent evidence of a difference between high doses of β_2-agonists and anticholinergics, or an additive effect from combining the two drug classes [15]. β_2-agonists may cause a fall in P_{a,O_2} due to pulmonary vascular effects, which do not occur with anticholinergic agents [16]. The intravenous route offers no advantage in most acute exacerbations.

Anticholinergic drugs. The onset of action of anticholinergic agents is slower than that of β_2-agonists, reaching a maximum in 30–90 min and lasting 4–6 h for ipratropium and 6–8 h for oxitropium. Anticholinergic agents are more effective in COPD than in asthma. Comparisons with β_2-agonists depend on the doses given. At submaximal doses combinations of anticholinergics and β_2-agonists will produce an additive effect [16, 17]. There are individual differences in response which mean that it is worth switching between β_2-agonists and anticholinergics, even if the response to the first drug is poor [18]. Results at higher doses, often with theophylline present, suggest that the maximal effects are probably equivalent [19, 20], although some studies have found further improvement with anticholinergic agents above the maximal β_2-agonist effect [21, 22].

No evidence has been found of tolerance to anticholinergic drugs during chronic therapy [13]. There are few adverse effects. Some patients find the taste unpleasant and the commonest reported side-effect is cough. Early concerns about a decrease in mucociliary clearance have not been substantiated. There are no effects on urine flow or pupil size at normal or high doses, except when an ill-fitting mask of a nebulizer allows direct administration into the eye.

Methylxanthines. Theophylline is given orally, and aminophylline can be administered either orally or intravenously. These drugs have comparable or less bronchodilator effect than β_2-agonists or anticholinergic agents [23, 24]. Methylxanthines have other effects, such as systemic and pulmonary vascular dilatation, increased salt and water excretion, and central nervous system stimulation. There is also an effect on respiratory muscles, but this is unlikely to be significant at usual therapeutic levels. Side-effects include gastric irritation, nausea, diarrhoea, headache, tremor, irritability, sleep disturbance, epileptic seizures, and cardiac arrhythmias.

Slow-release formulations can produce stable serum concentrations with once or twice-daily dosage. Therapeutic effects occur at blood levels >5 $\mu g \cdot mL^{-1}$, and side-effects increase considerably at levels >15 $\mu g \cdot mL^{-1}$. Smoking, alcohol, anticonvulsants, and rifampicin induce liver enzymes and reduce the half-life of methylxanthines. Old age, sustained fever, heart and liver failure, and drugs such as cimetidine, ciprofloxacin, and oral contraceptives increase blood levels. A change in the type of methylxanthine preparation may affect blood levels, even if the dose is unchanged. Peak blood levels should be monitored after methylxanthines are begun, every 6–12 months during therapy, after changes in dose or preparation, and with changes in the drugs or conditions mentioned above.

Corticosteroids

Corticosteroids are of great benefit in asthma, but their precise role in COPD has yet to be established. This section reflects current, common practice.

Corticosteroids can be administered intravenously, orally, and by inhalation. Oral or systemic drugs are used empirically during exacerbations and are often of benefit [25]. During an exacerbation-free period, a trial of corticosteroids, 0.4–0.6 $mg \cdot kg^{-1}$ for 2–4 weeks, may be used to test reversibility of the airflow limitation. About 10% of patients with stable COPD will achieve an improvement in FEV_1 [26].

The role of inhaled corticosteroids, which have the advantage of producing no or fewer systemic side-effects than oral corticosteroids, is much debated. Short-term studies show no or marginal beneficial effects on symptoms, lung function, and hyperresponsiveness. Three European studies are investigating the long term-effects on decline of FEV_1 in patients with COPD.

Long-term oral corticosteroids should be administered only when there is a clear functional benefit. An example is an increase in postbronchodilator FEV_1 of 10% predicted, and an absolute increase of at least 200 mL, in the absence of clear benefit from inhaled corticosteroids. The dose should be reduced to the lowest effective level.

Well-known side-effects of systemic corticosteroids are obesity, muscle weakness, hypertension, psychiatric disorders, diabetes mellitus, osteoporosis, skin thinning, and bruising. The risks of osteoporosis and skin thinning with inhaled corticosteroid doses >1,000 $\mu g \cdot day^{-1}$ are currently under investigation. Two other side-effects, oral candidiasis and hoarseness, can be minimized by using large-volume spacers and by rinsing the mouth.

Mucolytic and antioxidant agents

In COPD, mucus is generally copious and tenacious, properties thought to promote infection and lung damage. If this is so, improved sputum clearance might reduce symptoms and the loss of lung function. Two types of drugs are used: mucolytics, which contain substances that enhance breakdown of mucoproteins; and mucoregulators, which reduce viscosity by altering sialomucin synthesis. These drugs are given orally or parenterally; acetylcysteine and ambroxol can also be administered by nebulization.

There is no evidence to support prescription of these agents in acute exacerbations. A few long-term studies have suggested reduction in symptoms and the number of exacerbations. In a 6 month study, acetylcysteine was shown to reduce the frequency of acute exacerbations [27]. Appropriate assessment tools and prospective studies that include decay of FEV1, symptoms and quality of life as end parameters are needed. Widespread use of these agents cannot be recommended on the present evidence.

Respiratory stimulants

The use of respiratory stimulants varies markedly among European countries. Their role has not been established. Doxapram may have a positive effect during exacerbations of respiratory failure, but noninvasive supportive ventilation may prove to be a better alternative [28].

Oral almitrine bismesylate can improve oxygen tension to a similar degree as does a small increase in inspired oxygen. At the doses used originally, many side effects occurred, particularly peripheral neuropathy. There is no evidence of improved survival with almitrine, but there is with oxygen therapy. Other respiratory stimulants have not been shown to be effective, although theophylline can improve nocturnal dips in oxygen saturation [29]. On present evidence, respiratory stimulants are not recommended for patients with COPD.

Other unproven or research agents

Sodium cromoglycate, nedocromil sodium, and ketotifen have not been found to be effective in COPD. Calcium antagonists have some bronchodilator activity but have no clear therapeutic role. Antiprotease therapy is not recommended at present; it is under investigation as a replacement for α_1-antitrypsin deficiency.

Vaccination against pneumonia and influenza

Pneumococcal vaccination (containing polysaccharides of 23 of the most virulent serotypes) is used in many countries. To date, there is insufficient information for its general recommendation. If given, vaccination should be repeated every 5–10 yrs.

Killed influenza vaccines are recommended; they should be given parenterally once each autumn. Most vaccines are "split", with the envelope having been chemically disrupted. They are usually trivalent, containing two subtypes of influenza A and one of influenza B. The strains are adjusted each year for best effectiveness. The protective effect is less in the elderly than in younger individuals, but serious illness and death are probably reduced by approximately 50% [30]. Live vaccines have the same protective effect as inactivated vaccines when they are antigenically matched [31].

Other immunomodulators are under investigation for long-term use in COPD. No recommendations can be made at this time.

Treatment of cardiovascular sequelae

When cor pulmonale develops in patients with COPD, further treatment may be necessary. Only oxygen produces specific vasodilatation for the pulmonary hypertension induced by hypoxic vasoconstriction. Use of other vasodilators is usually limited by their effects on the systemic circulation. Diuretics can reduce oedema, but should be used carefully to avoid reducing cardiac output and renal perfusion and creating electrolyte imbalance. The hypoxic myocardium is especially sensitive to agents such as digoxin, aminophylline, *etc*.

Oxygen therapy

Oxygen supplementation has been proven to be lifesaving during exacerbations of COPD. In addition, it increases the life expectancy of patients with chronic respiratory failure [32–34].

Oxygen in the hospital. During an acute, severe exacerbation, oxygen is usually given through a Venturi mask or nasal cannulae, or by mechanical ventilation. The goal of therapy is to raise the S_{a,O_2} to ≥90% and/or the P_{a,O_2} to ≥8.0 kPa (60 mmHg) without elevating the arterial carbon dioxide tension (P_{a,CO_2}) by >1.3 kPa (10 mmHg) or lowering pH to <7.25. Oxygen administration should start at a low dose (24% by Venturi mask or 1–2 L·min^{-1} by nasal cannulae). Arterial blood gas tensions should be monitored regularly. Oxygen doses are adjusted until the goal is accomplished.

Long-term domiciliary oxygen treatment (LTOT). Studies have shown that LTOT improves survival in patients with COPD and chronic respiratory failure [33, 34]. Criteria for LTOT are respiratory failure during a stable 3–4 week period despite optimal therapy, with P_{a,O_2} ≤7.3 kPa (55 mmHg), with or without hypercapnia. In some countries, the criteria are broader: P_{a,O_2} of 7.3–7.9 kPa (55–59 mmHg) in the presence of pulmonary hypertension, cor pulmonale, polycythaemia, or severe nocturnal hypoxaemia. However, LTOT is generally not prescribed for patients who continue to smoke.

A flow of 1.5–2.5 L·min^{-1} through nasal cannulae is usually adequate to achieve P_{a,O_2} >8.0 kPa (60 mmHg). The flow should be adjusted according to arterial blood gas tensions or oximetry results. In some countries, night-time measurements are included in the determination of dosage. The dose should be assessed at least once each year. Because a greater survival benefit has been shown with continuous administration of oxygen, LTOT should be used for as many hours as possible; the minimum recommendation is 15 h·day^{-1}, including during sleep.

Nasal cannulae are usually used for LTOT. Venturi masks, however, deliver a more accurate oxygen concentration. Transtracheal oxygen through a fine percutaneous catheter should be considered for the few patients who have high oxygen demands or who prefer this route for cosmetic reasons [35].

Oxygen concentrators, cylinders, and liquid oxygen are available for delivering oxygen. Oxygen concentrators are the easiest mode of treatment, as they require only an electricity supply. Cylinders are too cumbersome and too expensive for LTOT. Liquid oxygen has one advantage: its additional small portable system can be used during travel and exercise. Oxygen-conserving devices (*e.g.* a moustache) extend the duration of cylinder and portable systems. A home oxygen care system requires careful monitoring by respiratory nurses or other domiciliary assistants. In subjects with exercise-induced hypoxaemia, oxygen supplementation may improve performance and reduces breathlessness. In end-stage COPD, short bursts of oxygen may ameliorate intractable dyspnoea, often *via* a placebo effect.

Home mechanical ventilation. Noninvasive ventilatory support, using either negative extrathoracic pressure or positive pressure techniques by nasal or facial mask, rests respiratory muscles and improves gas exchange. Positive pressure support is under investigation for its possible long-term beneficial effects in COPD [36]. Patients with severe nocturnal hypoxaemia or respiratory muscle weakness are the best candidates for this treatment.

Treatment of dyspnoea

In some cases, breathlessness is more severe than expected for the level of airflow limitation. Rehabilitation programmes can help achieve any reversibility of obstruction and improve muscle function. Cardiac dysfunction and anaemia may coexist, and depression and anxiety may aggravate the dyspnoea. Results regarding the effects of anxiolytic drugs are conflicting, and further studies are required.

In advanced disease, suppression of dyspnoea can be achieved only at the expense of depressed ventilation and at the risk of respiratory failure. Morphine is the most potent drug in this respect, but it carries the highest risk of respiratory depression and addiction; therefore, it should be used only in terminal stages.

Rehabilitation

Patients with advanced airflow limitation and severe dyspnoea become increasingly less mobile. Their skeletal muscles detrain, and dyspnoea and diminished exercise capacity are exacerbated. Rehabilitation programmes have been shown to increase exercise tolerance and to improve quality of life [37, 38]. An identifiable group of patients with muscle weakness may benefit from training specific muscles [39–41].

Rehabilitation uses a multidisciplinary programme of physiotherapy, muscle training, nutritional support, psychotherapy, and education.

Physiotherapy. Coughing and forced expiratory manoeuvres aid the clearance of secretions. Relaxation techniques, pursed-lip breathing, and control of breathing patterns to avoid rapid, shallow breaths may occasionally help patients to cope with acute dyspnoea.

Muscle training. General exercise reconditioning is the best mode of rehabilitation, even in patients with severe airflow limitation, if the programme is suitably modulated. Walking is generally preferred, but stair-climbing, treadmill, or cycling exercises can also be used. Patients with particularly severe muscle weakness benefit most. In those who can achieve the anaerobic threshold, physiological benefits have been demonstrated. Exercise programmes improve the quality of life through mechanisms that are not yet clear. The programme must be maintained, because benefits generally disappear rapidly if exercise is discontinued. Exercise training can be performed successfully at home [38].

The benefit of respiratory muscle training as an addition to general muscle conditioning or as an individual activity is not yet clear. Most studies indicate improved respiratory muscle function if the training load is adequately controlled. Whether the goal of training should be strength, endurance, or both is still under investigation.

Nutrition. Both obesity and loss of body mass are common features of COPD. Undernutrition is associated with respiratory muscle dysfunction and increased mortality. Nutritional intervention is important, but it is often unsuccessful. Until information is available on new avenues under investigation, it seems reasonable to recommend nutritional interventions aimed towards achieving an ideal body weight. High-carbohydrate diets and extremely high caloric intake should be avoided to reduce the risk of excess carbon dioxide production.

Psychotherapy and education. Psychosocial support and patient and family education are expected to improve quality of life. Those programmes focus on restoration of coping skills, management of stress and medical emergencies, use of medications, nutrition, general health, and social activities [42]. Patients who have a good understanding of their condition may be encouraged to discuss what they want to happen in the event that an episode of respiratory failure necessitates ventilation. Such a "living will" needs to be reviewed carefully if intensive care or ventilation is being considered.

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Management

Stable COPD

Aims of management. The aims of management of stable COPD are: 1) to improve symptoms and quality of life; 2) to reduce the decline of lung function; 3) to prevent and treat complications; 4) to increase survival with maintained quality of life; and 5) to avoid or minimize adverse effects of treatment.

The underlying damage in COPD is largely irreversible. Despite the irreversibility, clinicians should maintain a positive approach to the management of COPD, as symptoms and quality of life of the patient can be substantially improved. However, primary prevention of the condition is of utmost importance. The most important tactic, especially for younger subjects, is to stop smoking.

Some areas of management remain controversial and need further research. In particular, the role of inhaled corticosteroids in reducing the rate of decline of lung function, as well as the roles of antioxidants and mucolytics, need additional study. Monitoring of patients in early stages of the disease to detect a group having an accelerated decline in lung function is another important area for further research.

Algorithms. The following guidelines for the management of stable COPD assume that the correct diagnosis has been made. An alternative diagnosis may need to be considered at various points. A diagnosis of asthma necessitates consideration of the consensus guidelines for asthma [1–4]. Alternative diagnoses should be considered when the degree of breathlessness is out of proportion to the degree of airflow limitation.

Flow charts have been designed according to the severity of airflow limitation, based on the reduction in FEV_1. For convenience, two algorithms are proposed for use in stable COPD: one for mild disease (fig. 1) and the other for moderate to severe disease (fig. 2). The severity of airflow limitation has been divided into two categories: mild (fig 1) and moderate to severe (fig. 2). The distinction is based on the reduction in FEV_1.

The guidelines offer alternative therapies in some situations where multiple treatments having similar effects are available or scientific evidence is lacking. In these cases, preference of the patient or the doctor may influence the selection. Precise instructions on drug choice within a pharmacological group have not been included in the guidelines. Notes to the flowcharts, indicated by circled numbers, appear after figure 2.

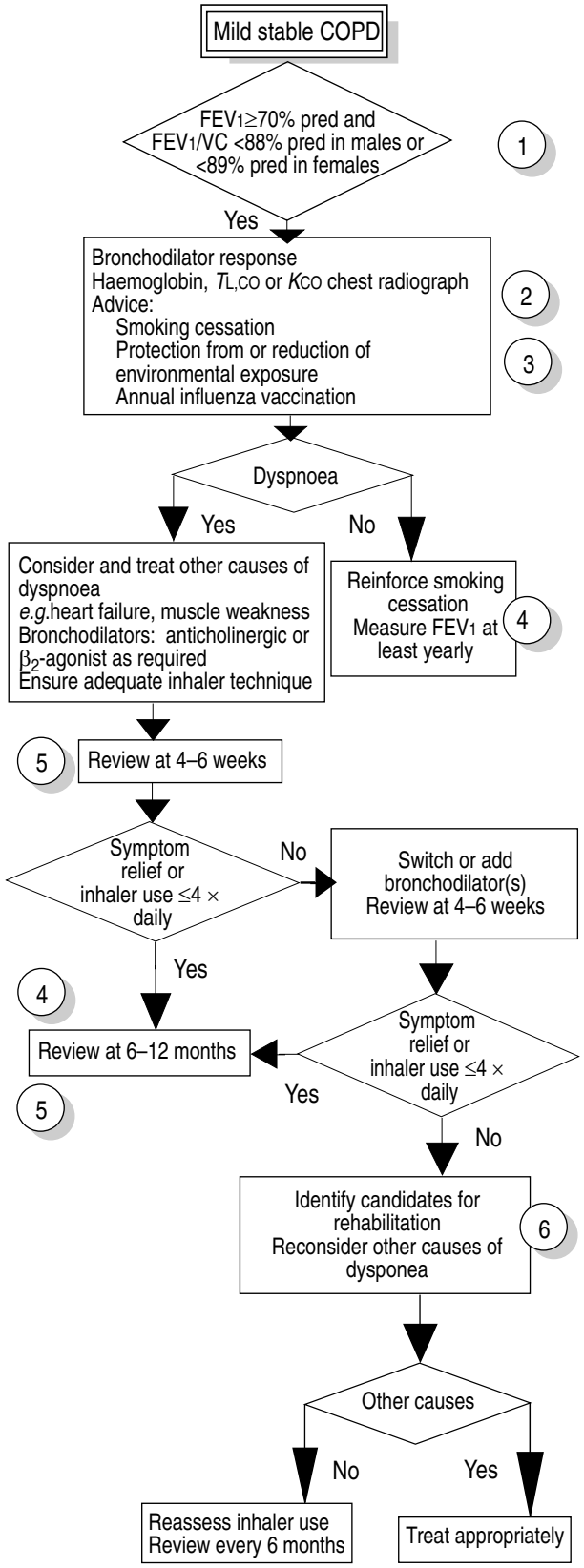

Fig. 1 – Flow chart designed for use in patients with mild, stable COPD. For explanation of circled number see notes after figure 2. COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; % pred: percentage of predicted value; VC: vital capacity; $T_{L,CO}$: transfer factor of the lungs for carbon monoxide; K_{CO}: carbon monoxide transfer coefficient.

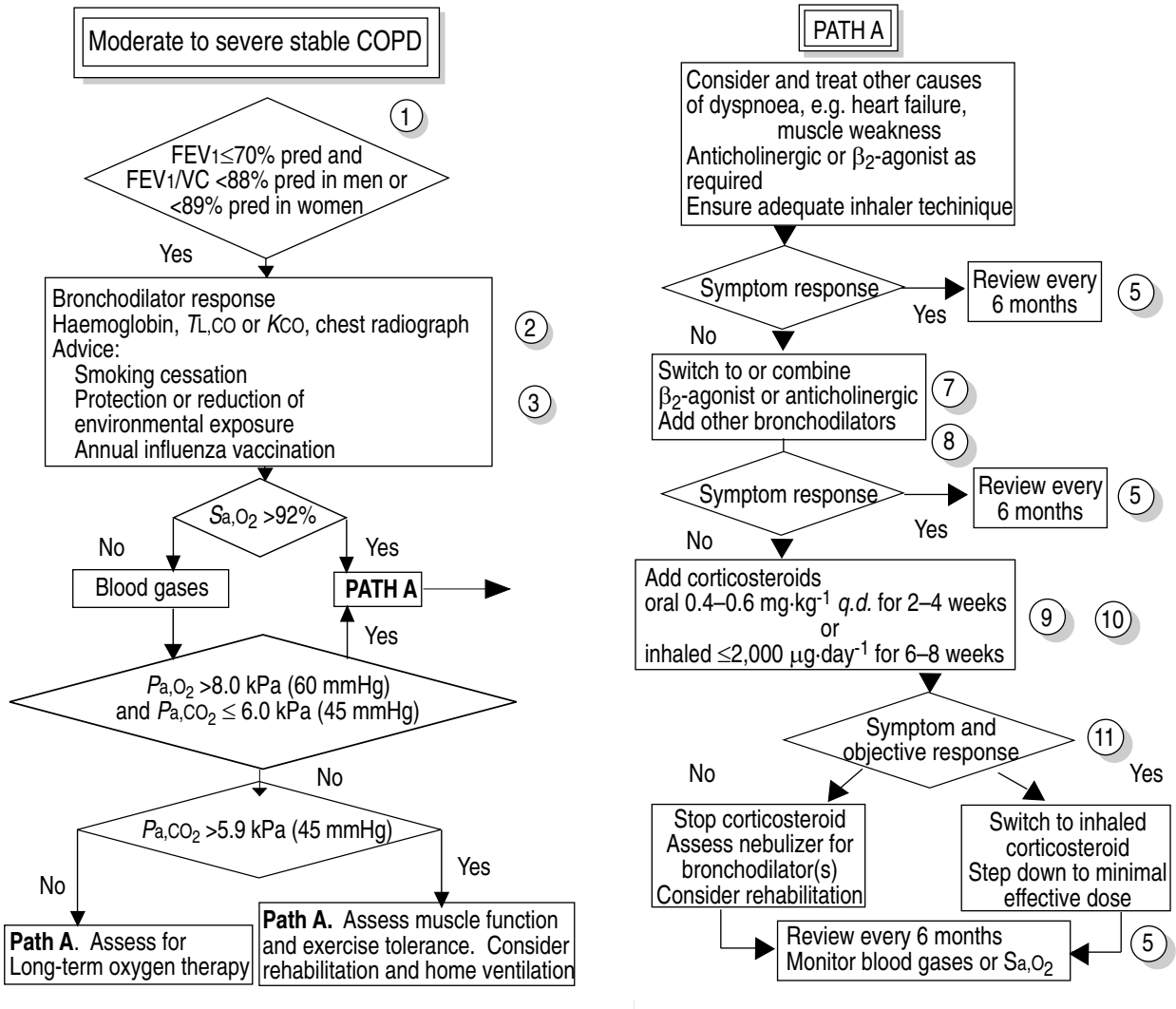

Fig. 2. – Flow chart designed for use in patients with moderate to severe, stable COPD. S_{a,O_2}: arterial oxygen saturation; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension. For explanation of circled numbers see notes below.

Notes

① FEV1/VC 11.7% below predicted in men and 10.7% below predicted in women are 1.64 residual standard deviations below predicted.

② If asthma is suspected (FEV1 reversibility >10% predicted after β_2-agonists and/or anticholinergic), then measure peak expiratory flow (PEF) and perform a bronchial challenge test to determine the concentration of histamine or methacholine needed to provoke a 20% reduction (PC20) in FEV1. Follow the asthma guidelines if: a) peak flow diurnal variation >15% over 2 weeks (PEF variation=highest PEF of the day-lowest PEF/mean of highest and lowest PEF; and b) PC20 <2 mg·mL^{-1} histamine or methacholine.

③ If emphysema is suspected, measure α_1-antitrypsin and consider computed tomography (CT) scanning.

④ A fast rate of decline in FEV1 (>50 mL·yr^{-1}) is an indication to consider inhaled corticosteroids.

⑤ At review, check dose and frequency of medications, symptom relief, inhaler technique, smoking status (reinforce cessation), FEV1, and VC.

⑥ Assess exercise capacity and respiratory muscle function to identify those patients who might benefit from general body or respiratory muscle training.

⑦ For some patients, the frequency of dosing may need to be increased; for others, the dose may need to be doubled.

⑧ Prescribe theophylline (adjusted doses to peak serum level of 5–15 μg·L^{-1}). If theophylline is not tolerated, consider long-acting oral or inhaled β_2-agonists.

⑨ If long-term oral corticosteroids are used, protection from osteoporosis should be considered (calcium and vitamin D, hormone replacement, diphosphonates). Inhaled corticosteroids should be used in addition to minimize the oral dose.

⑩ For high doses of inhaled corticosteroids (≥1,000 μg·day^{-1}), a large-volume spacer or dry-powder system should be used.

⑪ Objective response: FEV1 improvement ≥10% predicted and/or >200 ml.

Table 3. – Causes of acute exacerbation of COPD

Primary
Infection of the tracheobronchial tree (often viral)
Secondary
Pneumonia
Right or left heart failure or arrhythmias
Pulmonary embolism
Spontaneous pneumothorax
Inappropriate oxygen administration
Drugs (hypnotics, tranquillisers, diuretics, *etc*.)
Metabolic diseases (diabetes, electrolyte disturbances, *etc*.)
Poor nutritional stage
Other diseases (gastrointestinal bleeding, *etc*.)
End-stage respiratory disease (fatigue of respiratory muscles, *etc*.)

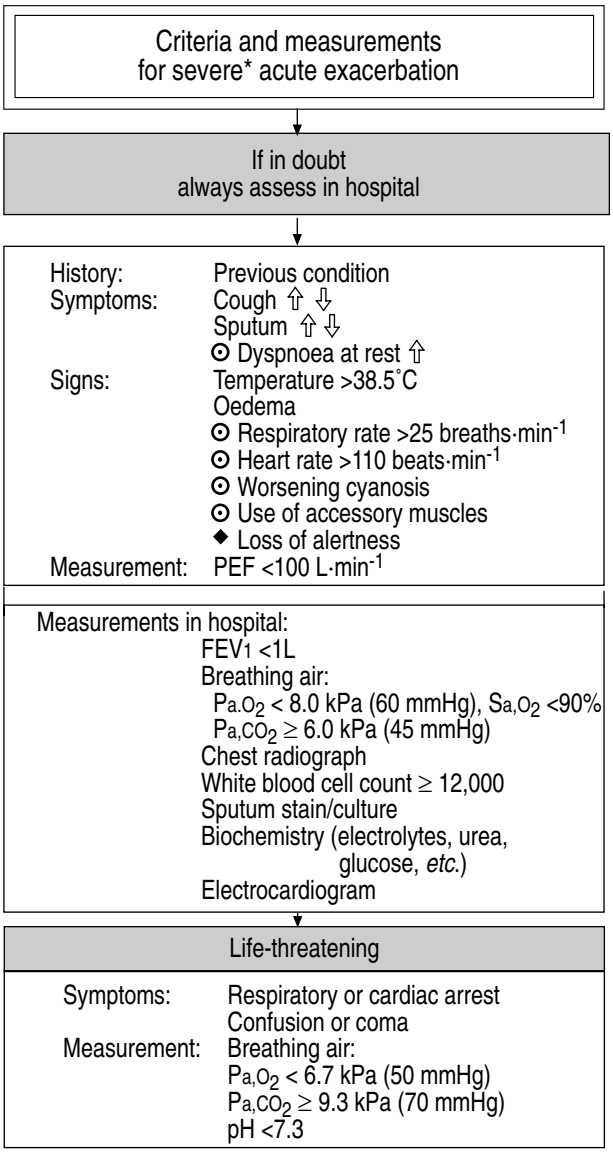

Fig. 3. – Criteria for management of severe, acute exacerbations of COPD. *: otherwise considered "Mild ⇒ Home management" (see fig. 4). Clinical judgement of the physician is important. Significant parameters are the loss of alertness (♦) and combination of conditions indicated by the symbol ⊙. PEF: peak expiratory flow. For further abbreviations see legends to figures 1 and 2.

Exacerbations

The proper management of an exacerbation of COPD requires knowledge of the usual causes of exacerbations (table 3). The previous condition of the patient must also be considered.

Although most exacerbations are mild and can be treated on an out-patient basis (home care), severe events should usually be evaluated in the Emergency Department of a hospital, so that the patient can be admitted if necessary. If the severity of an episode is in doubt, the assessment should take place in the hospital. In a very severe, life-threatening episode, direct admission into the Intensive Care Unit is indicated. Criteria for assessment of severity are presented in figure 3.

Home management. The usual cause of an exacerbation is infection, often viral. The goals of management are: 1) to treat bacterial infection if present; 2) to remove excess secretions; 3) to increase maximum airflow; and 4) to improve respiratory muscle strength.

Because of the broad range of clinical symptoms and signs, an individualized approach to treatment is needed. Figure 4 may be used as a guideline.

Hospital management. The main goals of hospital management of an exacerbation of COPD are: 1) to evaluate the severity, including life-threatening conditions; 2) to identify the cause of the exacerbation; 3) to provide controlled oxygenation; and 4) to return the patient to the best previous condition.

Figure 5 is a chart of hospital management. Because there are many causes of acute on chronic respiratory failure, this figure provides only guidelines for a general approach. Treatment depends on the degree of severity and should be adapted to the features of each individual case.

Special considerations

Air travel

Patients with COPD who have chronic hypoxaemia or borderline P_{a,O_2} (≤9.3 kPa (70 mmHg)) at rest, at sea level, may become more hypoxaemic during air travel. The clinical significance of short episodes of worsened hypoxaemia is largely unknown. When a long trip is planned, the risk may be estimated by simulating in the laboratory the partial pressure of inspired oxygen that will occur during the flight. Another approach is to try to predict the risk from the patient's blood gas tensions. These tests can also determine the amount of supplemental oxygen necessary.

Relative contraindications to air travel include current bronchospasm, severe dyspnoea, severe anaemia, unstable coexisting cardiac disorders, impaired pulmonary function, with P_{a,CO_2} ≥6.7 kPa (50 mmHg), P_{a,O_2} ≤6.7 kPa (50 mmHg), $T_{L,CO}$ ≤50% of predicted, and VC ≤50% of predicted. Conditions adversely affected by pressure changes (*e.g*. noncommunicating lung cysts, pneumothorax, or pneumomediastinum) may also contraindicate air travel [6, 7].

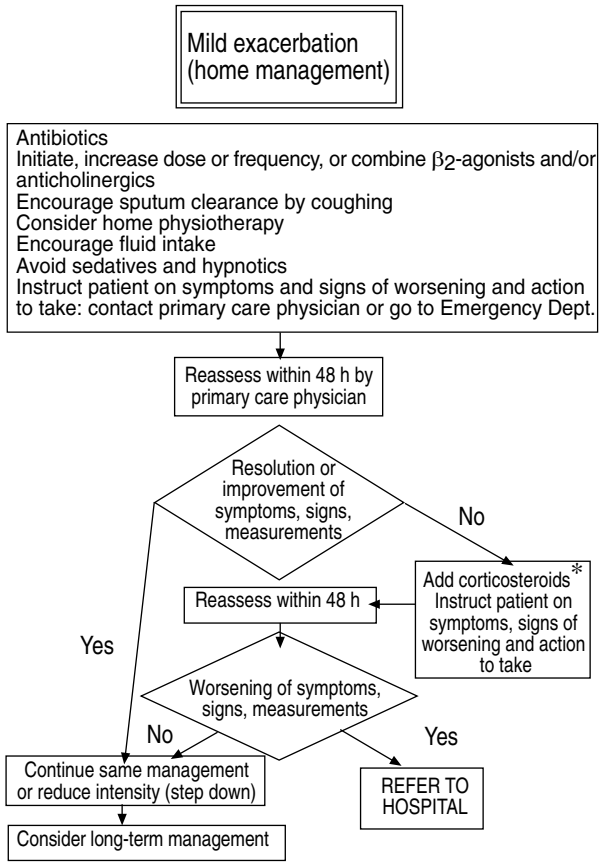

Fig. 4. – Guidelines for treatment of mild exacerbations of COPD. *: consider a short course of corticosteroids (0.4–0.6 mg·kg^{-1} daily), from the beginning if marked wheeze is present.

Surgical treatment

In selected patients with unilateral or even bilateral large air cysts, bullectomy *via* thoracostomy or sternotomy can result in improved lung function (*i.e.* an increase in VC) and exercise tolerance. Predictors of success include demonstration on CT of collapsed pulmonary parenchyma beneath the bullae and persistence of zones without or with only small amounts of emphysema, as well as the value of transfer factor and P_{a,CO_2}. Recent developments in thoracoscopic surgery, with use of a laser, if necessary, facilitate the operation. Thoracoscopic surgery may replace segmentectomy for resection of a peripheral carcinoma in patients with severely compromised lung function [8].

Patients <65 yrs of age who have very poor exercise tolerance and poor lung function (FEV_1 <25% predicted, P_{a,O_2} <7.5 kPa (56 mmHg) and P_{a,CO_2} >6.5 kPa (49 mmHg) will benefit from double or single lung transplantation. The latter is contraindicated in patients with chronic bronchial infection or bronchiectasis in the remaining lung. Long-term survival, which is approximately 50% at 5 yrs, has to be balanced with the individual's prognosis, a difficult task. Although posttransplantation exercise tolerance will improve, close follow-up is necessary [9–12].

Compliance and education

Compliance, or adherence to medical advice, has unfortunately been considered an unimportant aspect of clinical research in patients with chronic diseases, such as

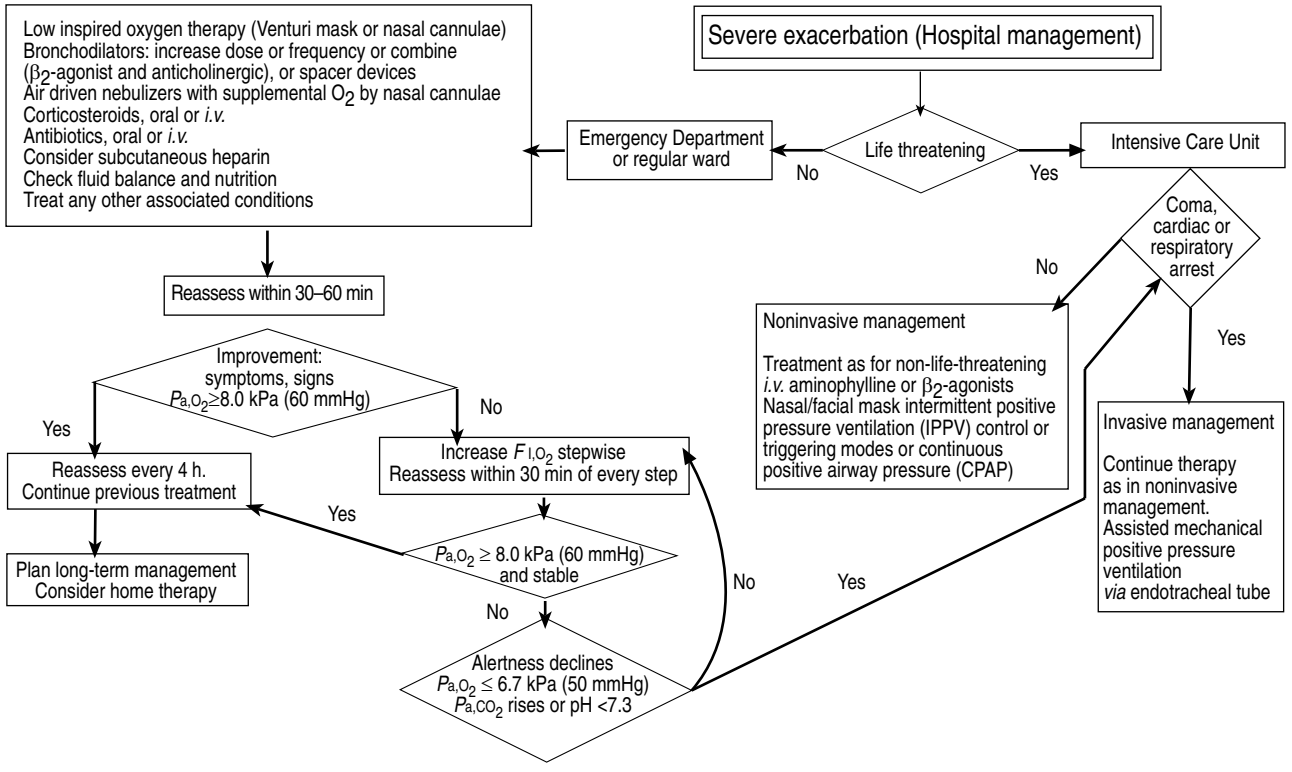

Fig. 5. – Guidelines for hospital management of severe exacerbations of COPD. F_{I,O_2}: fractional inspiratory oxygen. For further abbreviations see legend to figures 1 and 2.

COPD. Compliance assessments have relied mainly on self-reporting, and poor recall or a desire to please may affect the results. Some objective methods are available, however, including microprocessing devices attached to inhalers and measurement of theophylline plasma levels, carbon monoxide levels in expired air, or cotinine levels in saliva or urine.

Educational programmes for COPD patients have not been as actively promoted as programmes for asthma patients. Single-topic programmes are available (*e.g.* smoking cessation, long-term oxygen therapy, rehabilitation), but integrated educational materials incorporating all aspects of the management approach are lacking. Educational programmes should not aim solely to improve knowledge about the disease process and its treatment, but should also be directed at changing the patient's behaviour, which could improve the quality of life. A partnership approach should be developed, encouraging active involvement by patients, their families, and healthcare workers.

Future research

Pathophysiology. Cigarette smokers, especially those with airflow limitation, have more neutrophils, lymphocytes and activated macrophages in their airways and airspaces than nonsmokers. The inflammatory process in the small airways includes an increased number of lymphocytes and mononuclear cells, increased connective tissue deposition, epithelial metaplasia, and ulceration in the airway wall. Future research is expected to better delineate the role of cytokines, the mechanisms governing chemotaxis, adhesion, and diapedesis of neutrophils and lymphocytes in the airway, and the roles of oxidant-antioxidant and protease-antiprotease balances. New therapeutic modalities might follow. Genetic studies on COPD may also be helpful.

Epidemiology. Areas for future epidemiological research include: 1) standardized statistics for morbidity, mortality, and socioeconomic status in COPD for all of Europe; 2) promotion of routine use of lung function tests in symptomatic patients with lung disease; 3) surveillance of smokers and others with increased risks of COPD; 4) active involvement of chest physicians, general practitioners, and other health care workers in smoking cessation; 5) understanding of the relationship between air pollution and COPD; 6) correlation of occupational exposure and COPD, particularly the effect of cessation of exposure; 7) identification of biological markers of increased susceptibility to COPD; and 8) discovery of any genetic determinants of COPD.

Clinical benefits of treatment. Major ongoing studies (the United States National Institutes of Health Lung Health Study and European Respiratory Society Study on COPD (EUROSCOP)) are looking at the rate of change in FEV_1 as the major outcome. For the individual patient, however, improvement in the quality of life and decreases in symptoms and exacerbations are the desired outcomes. All interventions should focus not only on objective changes but also on quality-of-life changes, which have a major impact on everyday life. Further studies are needed to evaluate home mechanical ventilation, the various modes of rehabilitation, and, most importantly, education of the patient and family. In addition, governments need cost-benefit analyses.

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Appendix A: Pathology

Pathological changes in COPD can be found in the large (central) airways, the small (peripheral) bronchi and bronchioles, and the lung parenchyma [1–4]. Changes also occur in the pulmonary circulation and, in advanced disease, in the right heart.

Central airways

The site of most of the hypersecretion of mucus, expressed clinically as chronic bronchitis, are the large airways.

Histological studies show enlargement of tracheobronchial submucosal glands and hyperplasia of tracheobronchial surface mucous (goblet) cells. In the submucosal glands, a larger proportion of mucus is acidic [5]. Recent data indicate that airway wall inflammation is also present, even in the early stages; it consists predominantly of mononuclear cells in the mucosa [6–10], and neutrophils in airway fluid [11–13]. Recent reports indicate that eosinophils may also contribute [13–15]. Upregulation of vascular adhesion molecules may increase recruitment of inflammatory cells [16–18]. Atrophic changes in cartilage have been reported in advanced stages.

Peripheral airways

Small bronchi and bronchioles are the major sites of increased airflow resistance in COPD [19, 20]. Various terms have been used to describe these changes, for example, small or peripheral airway disease or chronic obstructive bronchiolitis. The changes are characterized histopathologically by the appearance and increase in number of goblet cells, increased intraluminal mucus, inflammation, increased wall muscle mass, fibrosis, obliteration and airway narrowing [21, 22]. There is also loss of alveolar attachments to bronchioles [22, 23].

Lung parenchyma

Emphysema is defined anatomically as a permanent destructive enlargement of airspaces distal to the terminal bronchioles, without obvious fibrosis; the last characteristic is much debated [24]. Tortuosity and stenosis of bronchioles may occur as a consequence of the loss of alveolar attachments, emphysema, or reduction of elastic recoil.

Two major patterns of emphysema, with distinct functional consequences, are recognized, panacinar and centriacinar [4, 25]. Panacinar emphysema involves destruction of the entire acinus. In centriacinar emphysema, respiratory bronchioles, alveolar ducts, and alveoli at the centre of the acinus are destroyed, but surrounding alveoli remain intact. An additional form is paraseptal emphysema, which affects areas adjacent to the connective tissue septa [4]. Widespread loss of alveolar wall surface area (per unit volume of lung) may be detected microscopically, even when emphysema cannot be detected macroscopically [26–28].

Other changes

In patients with more advanced COPD, changes also occur in pulmonary circulation, the right heart, and respiratory muscles. With alveolar hypoxia, the medial vascular smooth muscle extends distally to vessels that normally lack muscle and intimal thickening. Loss of the vascular bed occurs as a consequence of emphysema [4]. Right ventricular enlargement due to dilatation and/or hypertrophy is not uncommon. Atrophy of the diaphragm occurs in some cases [29].

Structure-function relationships

The pathological abnormalities in the airway can contribute to the increased resistance to flow by: 1) lumen obstruction by mucus; 2) changes in the properties of lining fluid; 3) increased wall thickening and decreased airway diameter; 4) smooth muscle contraction; 5) loss of alveolar attachments; and 6) obliteration of small airways.

Each of these changes may contribute to the airway hyperresponsiveness often found in patients with COPD. When these changes are mild and not accompanied by an obvious reduction in maximum expiratory flow, the increased resistance in the small airways may be detected by tests that assess the inhomogeneous functional behaviour of the lung.

Emphysema results in loss of lung recoil, which may appear early in the development of panacinar emphysema. In patients with mild to moderate airflow limitation, the decrease in maximum flow could be secondary to either loss of recoil or small airway abnormalities such as inflammation, deformity, narrowing, and obliteration. The predominant view favours emphysema as the most important factor in the limitation of airflow in severe COPD. Changes in the small airways play a greater role in mild to moderate COPD [30, 31].

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Appendix B: Pathophysiology

Evolution of the disease

The early stages of COPD are characterized by unevenly distributed narrowing of peripheral airways. As the disease progresses, FEV_1 and VC decrease and RV increases. The rate of decline in FEV_1 is greater than in normal subjects. Total airway resistance and inequality in ventilation/perfusion ratio (V'/Q') increase. When emphysema develops, lung elastic recoil and K_{CO}, the transfer of carbon monoxide per litre of alveolar volume, decrease, while static lung compliance and total lung capacity increase.

At all stages of COPD, irrespective of the presence or absence of emphysema, V'/Q' inequality is the major mechanism impairing gas exchange and leading to arterial hypoxaemia [1]. Limitation of alveolar end-capillary diffusion of oxygen is seen neither at rest nor during exercise. Any increased intrapulmonary shunt is negligible in the stable chronic condition.

In patients with severe, advanced COPD, a variety of abnormal V'/Q' distributions may be found. Some lung units have very high V'/Q', and most of the ventilation occurs in the zone of higher V'/Q'. In another pattern, a large proportion of blood flow perfuses lung units with very low V'/Q'. Another pattern combines both high and low V'/Q' areas [2, 3]. High V'/Q' units probably represent emphysematous regions with alveolar destruction and loss of pulmonary vasculature. Low V'/Q' units may represent areas with partially blocked airways. Most patients have mild to moderate increase in dead space. The absence of shunt suggests that collateral ventilation and hypoxic pulmonary vasoconstriction are very efficient, or that airway occlusion is not functionally complete.

Correlations between routine lung function tests and respiratory blood gases or patterns of V'/Q' distribution are poor. However, significant hypoxaemia or hypercapnia is rare with FEV_1 >1.0 L.

With increasing severity of airflow obstruction, expiration becomes flow-limited during tidal breathing. Initially, this occurs during exercise, but later it is also seen at rest. The increase in functional residual capacity (FRC) is due in part to static factors, such as loss of lung elastic recoil, and in part to dynamic factors at the end of expiration. The rate of lung emptying is slowed, and the interval between inspiratory efforts does not allow expiration to the relaxation volume of the respiratory system; this leads to dynamic pulmonary hyperinflation.

This end-expiratory recoil pressure of the total respiratory system has been termed intrinsic positive end-expiratory pressure (PEEPi) [4, 5]. PEEPi is an inspiratory threshold load that must be countered by the contracting inspiratory muscles to create negative alveolar pressure and to start inspiration. The increase in FRC can impair inspiratory muscle function and co-ordination, although the contractility of the diaphragm, when normalized for lung volume, seems to be preserved [6]. However, chronic hypercapnia is related to inspiratory muscle dysfunction [7]. Because of the increased mechanical workload, the energy consumption of the inspiratory muscles at any given level of minute ventilation is greater than in normal subjects. Respiratory drive is increased to maintain minute ventilation, which generally remains within normal limits [8].

Hypoxic pulmonary vasoconstriction may be present. This may result in pulmonary hypertension and right heart dysfunction.

Acute exacerbations and respiratory failure

Acute respiratory failure is characterized by significant deterioration of arterial blood gas tensions (hypoxaemia and hypercapnia). The severity of V'/Q' abnormalities increases during acute exacerbations and improves slowly over a few weeks. The V'/Q' abnormalities contribute to the increase in P_{a,CO_2}, which is enhanced by alveolar hypoventilation. Changes in cardiac output, overall ventilation, and oxygen consumption may affect arterial respiratory gases [3]. Patients needing mechanical ventilation have a mild to moderate intrapulmonary shunt, suggesting that some airways are completely occluded, possibly by bronchial secretions [3].

Airway resistance, end-expiratory lung volume, and PEEPi increase substantially during acute respiratory failure [9]. The increase in elastic load may exceed the increase in resistive load. Because of expiratory airflow limitation during tidal breathing, the compensatory mechanisms must be inspiratory: increased lung volume and increased inspiratory drive. Minute ventilation is normal or greater, but the breathing pattern is abnormal, with decreased tidal volume and increased ventilatory frequency. Mouth occlusion pressure, an index of overall neuromuscular drive, is markedly increased, compared with the pressure in the stable condition [10]. Whether the high level of inspiratory muscle activity causes respiratory muscle fatigue is still a matter of debate. Indirect measurements favour this hypothesis, both in spontaneously breathing patients and during weaning from mechanical ventilation.

The mechanisms controlling ventilation and breathing patterns are still uncertain. Both the hypoxic and hypercapnic drives to breathe play important roles. The influence of breathing pattern on arterial blood gas tensions remains uncertain. Administration of oxygen corrects hypoxaemia [11] but worsens V'/Q' balance, which contributes to the increase in P_{a,CO_2}. The clinical consequences of hypercapnia depend on the underlying acid-base status, because hypercapnia acts primarily through changes in hydrogen ion activity.

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Appendix C: Epidemiology

Mortality

Mortality rates from COPD and allied conditions vary widely between countries. Whilst the differences may be due to differences in exposure to risk factors, to a large extent methodological problems with death certification or coding [1] account for the high intercountry variation.

When International Classification of Diseases (ICD) codes 490–493 are used, mortality rates for males range from 41.4 per 100,000 in Hungary to 2.3 per 100,000 in Greece, but they may change appreciably when code 496 is considered (fig. 6). Because coding is not homogeneous in all European countries, mortality rates for COPD may also include deaths from asthma. In countries where asthma death rates can be separated, COPD is clearly associated with the highest burden of mortality. Furthermore, increases in COPD death rates in Europe are projected in the future [2].

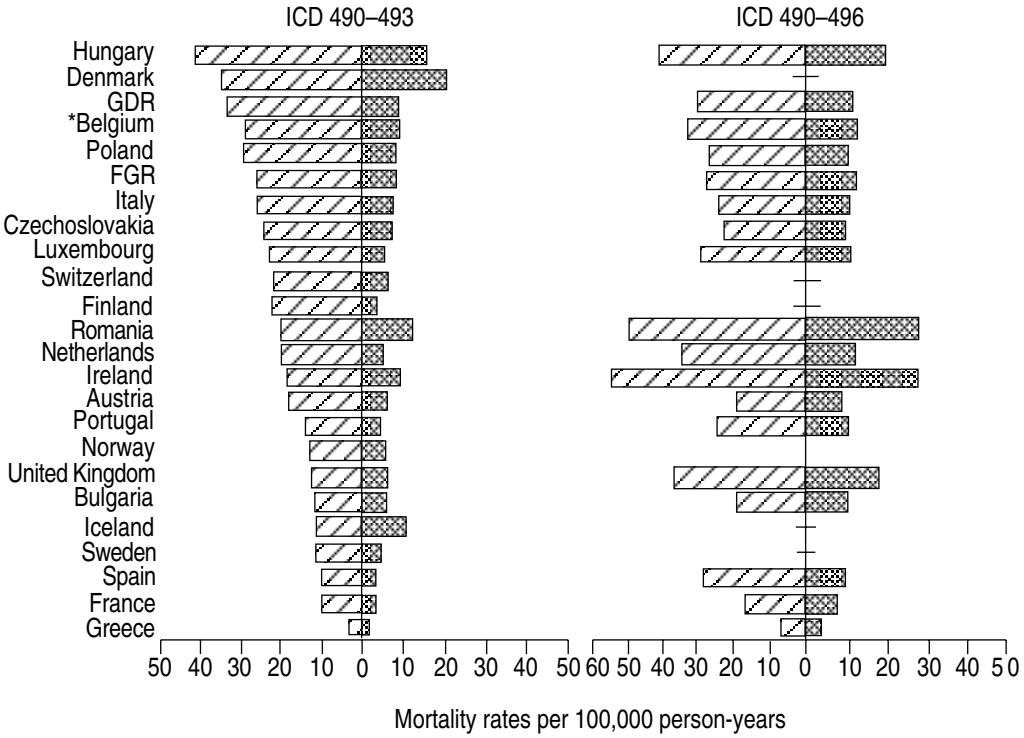

Fig. 6. – Chronic obstructive pulmonary disease (COPD) age standardized mortality rates in Europe, 1988–1991. ICD 490–496=COPD and similar conditions; ICD 490=non specified bronchitis (acute and chronic); ICD 491=chronic bronchitis; ICD 492=emphysema; ICD 493=asthma; ICD 494=bronchiectasis; ICD 495=extrinsic allergic alveolitis; ICD 496=chronic obstruction of the respiratory tract not classified anywhere: *: data from 1986. GDR: German Democratic Republic; FRG: Federal Republic of Germany; ICD: International Classification of Diseases. ▨ : male; ▩ : female.

Morbidity

There are no reliable government morbidity statistics for COPD across Europe. However, good evidence suggests underdiagnosis in the general population, with only about 25% of cases being diagnosed [3–5].

Morbidity from COPD is more common in men than in women, and it increases steeply with age [6, 7]. Gender differences may be due to the higher prevalence of cigarette smoking and occupational exposure to noxious agents in men. Recent data on young cohorts [8] show an increasing tendency to smoke among women, which might influence future figures for COPD morbidity; women may be more susceptible to develop COPD when exposed to risk factors (tobacco).

According to British data for 1982–1983, respiratory diseases rank as the third most common cause of days of certified incapacity; COPD accounted for 56% of days in males and 24% in females [9]. Without question, COPD leads to substantial disability, loss of productivity, and reduced quality of life, which worsen as the disease progresses. Its economic impact is substantial. Exacerbations and respiratory failure may necessitate hospital admission and prolonged, costly treatment. Long-term home oxygen therapy adds to the costs.

Risk factors

The main risk factors for COPD are inhaled agents, particularly cigarette smoke. The range of individual susceptibility is wide. Recognized risk factors are listed in table 4.

Table 4. – Risk factors for COPD

Degree of certainty	Environmental factors	Host factors
Established	Cigarette smoking	α_1-antitrypsin deficiency
	Some occupational exposures	
Good evidence	Air pollution (particularly SO_2 and particulates)	Low birth weight
		Childhood respiratory infection
	Poverty, low socioeconomic status	Atopy (high IgE)
	Alcohol	Bronchial hyperresponsiveness
	Environmental tobacco smoke in childhood	Family history
	Other occupational exposures	
Putative	Adenovirus infection	Genetic predisposition
	Dietary deficiency of vitamin C	Blood group A
		IgA nonsecretor

COPD: chronic obstructive pulmonary disease; IgE: immunoglobulin E; IgA: immunoglobulin A.

Among occupational risks, good evidence is available that cadmium and silica cause COPD. Workers at increased risk for COPD include coal miners, construction workers who handle cement, metal workers who are subject to heat exposure from furnaces, transport workers, grain handlers, cotton workers, and workers in paper mills. Population studies have also indicated increased risks from dust exposure and, to a lesser extent, exposure to fumes [10–14].

Early detection of COPD

COPD is usually diagnosed late in its course because patients often lack symptoms, even at low FEV1, and because simple spirometry is not routinely performed. The best method for early detection is serial measurement of FEV1 and FEV1/FVC [15].

In the 1960s and 1970s, various tests of small airway function were proposed as means to detect early COPD. Several tests showed differences between smokers and nonsmokers in cross-sectional studies, including the slope of phase 3 of the nitrogen washout curve ($\Delta N_2\%\cdot L^{-1}$), forced expiratory flow during the middle of FVC (FEF_{25-75}), V'_{max50}, and density-dependent flow rates [16]. With the exception of $\Delta N_2\%\cdot L^{-1}$, none of these tests has since been shown to predict decline in lung function reliably [17]. Biological markers, (*e.g.* deoxyribonucleic acid (DNA) adducts, products of elastin degradation, and products of inflammatory cells, are under investigation but cannot at present be used for early detection of COPD.

Natural history

Reliable estimation of the longitudinal decline in FEV1, needed to assess progression of COPD in an individual patient, requires spirometry of high quality. Because the accepted intraindividual variability of a single test is 5% [18], measurements over at least a 4 year span are usually required.

Several epidemiological studies have shown that FEV1 declines about 20–30 $mL\cdot yr^{-1}$ in healthy nonsmokers after 30 yrs of age. However, wide interindividual variability has been observed [19–22]. Among smokers, 10–20% show an accelerated decline in FEV1 [23]. Most studies in patients with COPD show a decline of 48–91 $mL\cdot yr^{-1}$ [24, 25]. The most important predictor of future decline is the current rate of decline, which can be estimated from the current FEV1 [22]. Except for α_1-antitrypsin deficiency, there are no laboratory tests to detect susceptible smokers. A positive family history [26] and childhood respiratory infections [27, 28] may indicate individual susceptibility.

There is no evidence that a persistent decline in FEV1 is related to acute exacerbations [29, 30]. As the disease progresses, the complications of acute exacerbations - respiratory failure, and cor pulmonale - may develop, as well as lung cancer [31].

Table 5. – Factors related to reduced survival in COPD

Advanced age
Continued smoking
Initial FEV1 <50% predicted
Accelerated FEV1 decline
Poor bronchodilator response
Severe untreated hypoxaemia
Cor pulmonale and poor overall functional capacity

For abbreviations see legend to table 1. (Modified from BURROWS [24]).

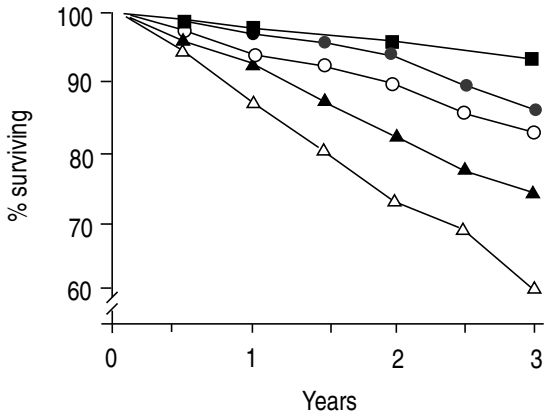

Fig. 7. – Survival in groups segregated according to baseline post-bronchodilator FEV1. FEV1: forced expiratory volume in one second. —■— : "normals:; —●— : FEV1 ≥50% predicted; —○— : FEV1 40–49% pred; —▲— : FEV1 30–39% pred; —△— : FEV1 <30% pred. (Modified from ANTHONISEN [40]).

Smoking cessation clearly reduces the decline in FEV1 and reduces mortality, especially in patients with mild to moderate disease [32–37]. The beneficial effect of long-term oxygen therapy has been clearly documented [38, 39].

Prognosis

Factors associated with reduced survival are listed in table 5. The FEV1 has been found to be a good predictor of mortality from COPD (fig. 7) [40], and assessment of prognosis is an important reason to measure FEV1. Prognosis is especially affected when FEV1 is <50% predicted. In severe COPD, with FEV1 around 1.0L, the 5 year survival is approximately 50% [41, 42].

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Task Force producing the statement

Chairs: N.M. Siafakas, P. Vermeire. **Definition/Pathology/Pathophysiology Subcommittee:** N.B. Pride (Head), J-P. Derenne, P.K. Jeffery, D. Lamb, R. Rodriguez-Roisin, A. Rossi, M. Saetta, P. Vermeire. **Epidemiology Subcommittee:** P. Paoletti (Head), S. Burge, U. Costabel, G. Viegi. **Clinical Assessment Subcommittee:** J. Gibson (Head), W. De Backer, D. Georgopoulos, W. McNee, E. Russi, D. Stanescu, E. Weitzenblum. **Treatment Subcommittee:** P. Howard (Head), M. Decramer, M. Del Donno, H. Donner, H. Lode, C-G. Lofdahl, D. Olivieri, D.S. Postma, J. Rees, D. Robert. **Management Subcommittee:** J.C. Yernault (Head), D. Bouros, M. Cochrane, T. Higenbottam, K. Moghissi, C. Roussos, N.M. Siafakas, S. Zakinthinos. **North American Advisers:** A.S. Buist, K.R. Chapman, M.G. Cosio. **Internal Reviewing Committee:** M. Decramer, T. Higenbottam, D.S. Postma, N.B. Pride, J. Rees, N.M. Siafakas, P. Vermeire, J.C. Yernault. **External Reviewers:** S. Spiro, C. Giuntini, A. Woodcock.