Management of chronic obstructive pulmonary disease: the Swiss guidelines

Official Guidelines of the Swiss Respiratory Society

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Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a disorder characterised by expiratory airflow limitation that is not fully reversible [1]. The airflow limitation is usually slowly progressive and associated with an inflammatory response of the lungs to noxious particles or gases. The airflow obstruction may be caused by structural alterations and/or functional factors. COPD, related in most cases to extensive cigarette smoking, is a leading cause of chronic morbidity and mortality among patients over 55.

Over the past ten years several guidelines for the assessment and management of COPD have been published [2–5]. Our new guidelines are based on those published in 1997 [6], the GOLD report (*Global initiative on chronic Obstructive Lung Disease*), a collaborative project of the U.S. National Heart, Lung and Blood Institute and the World Health Organisation, and an extensive review of the pertinent literature. Following the requirements of evidence-based medicine, we used the system for assigning levels of evidence to the statements made throughout the present report (table 1) [7].

The goal of these guidelines is to advise pulmonary physicians, general practitioners and other health care workers on the early detection, diagnosis and prevention of COPD, the best symptomatic control of the disease, and the avoidance of complications and deterioration of COPD.

Definition

The terms chronic bronchitis and emphysema are no longer included in this working definition of COPD. Chronic bronchitis is a clinical and epidemiological term (i.e. cough and mucus produc-

Table 1	Evidence category	sources of evidence	definition
Description of levels of evidence.	A	Randomised controlled trials (RCT). Rich body of data.	Evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A therefore requires substantial numbers of studies involving substantial numbers of participants.
	B	Randomised controlled trials (RCT). Limited body of data.	Evidence is from endpoints of intervention studies that include only a limited number of RCTs, posthoc or subgroup analysis of RCTs, or metaanalysis of RCTs. Category B pertains when few randomised trials exist, they are small in size, the trial results are somewhat inconsistent, or the trials were undertaken in a population that differs from the target population of the recommendation.
	C	Nonrandomised trials. Observational studies	Evidence is from outcomes of uncontrolled or nonrandomised trials or from observational studies.
	D	Panel consensus judgment	This category is used only in cases where provision of some guidance was deemed valuable but an adequately compelling clinical literature addressing the subject of the recommendation was deemed insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.

tion on most days for at least three months a year during at least two successive years) but does not reflect the major impact of the airflow limitation in COPD on mortality and morbidity. Emphysema, the definition of which is based on pathology (abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of the alveolar walls and without obvious fibrosis) is often – but incorrectly – used clinically, since it represents only a part of the structural abnormalities present in COPD. A variable mixture of inflammatory changes of large and small airways and emphysema causes chronic airflow limitation, which is the major characteristic of COPD.

Pathophysiology

The major risk factors for the development of COPD are inhaled toxic substances – particularly the inhalation of tobacco smoke – which cause inflammation of the lungs. The inflammation can lead to tissue damage if the normal protective and/or repair mechanisms are overwhelmed or defective. The results of the lung tissue damage are mucus hypersecretion, airway narrowing and fibrosis, destruction of the parenchyma and vascular changes. These pathological changes lead to airflow limitation and the other physiological abnormalities [8–10].

COPD is characterised by persistent inflammation throughout the airways and parenchyma, intensity and cellular characteristics, which vary as the disease progresses. Activated inflammatory cells release products that are capable of damaging lung structures. These cell products include proteases, oxidants and toxic peptides. The inflammation in COPD is markedly different from that in asthma. However, some patients with COPD also have asthma, and the inflammation in their lungs may show characteristics of both diseases.

Since inflammation is a feature of COPD, anti-inflammatory therapies may have beneficial effects in controlling symptoms, preventing exacerbations, and slowing disease progression. However, the response of inflammation to corticosteroids is poor in COPD, contrary to their effectiveness in asthma [11]. The functional consequences and therapeutic outlook depend on the relative contribution of the following processes [12]:
– inflammatory narrowing and remodelling of the bronchi and bronchioli;
– impaired mucociliary clearance;
– proteolytic digestion of the connective-tissue framework of the lung, which results in decreased parenchymal tethering of the airways;
– loss of alveolar surface area and capillary bed;
– lung hyperinflation caused by loss of lung elastic recoil and air trapping;
– increased pulmonary vascular resistance caused by vasoconstriction and loss of capillary bed.

Risk factors

Risk factors for COPD include both host factors and environmental exposures, and the disease arises from an interaction between these two [13]. Much of the evidence concerning risk factors for COPD comes from cross-sectional epidemiological studies which identify associations rather than causal links. Cigarette smoking is the main identified risk factor for COPD, although non-smokers may occasionally be affected. It is important to note that currently no methods exist to predict which smoker will develop COPD. Heavy exposure to occupational dust (e.g. farming), indoor pollution, low socioeconomic status and inherited α-1 antitrypsin deficiency are recognised additional risk factors for COPD [14–16]. It is estimated that α-1 antitrypsin deficiency is responsible for approximately 2% of all cases of emphysema in the United States [17, 18]. Passive exposure to environmental tobacco smoke, respiratory infections and airway hyperresponsiveness may also contribute [19].

Epidemiology and burden of disease

COPD is a leading cause of morbidity and mortality worldwide [20–22]. COPD is underdiagnosed and its social and economic burden on patients and society are underestimated. Prevalence, morbidity, and mortality vary across countries, but in all regions, where data are available, COPD is a significant public health problem in both men and women. Prevalence data from the United States indicate that COPD has been increasing steadily over the past 20 years, with a higher rate of increase in women than in men. In the United Kingdom COPD affects 6% of men and 4% of women aged over 45. In Switzerland the prevalence of cough and chronic sputum is 3.1%, whereas cough or sputum production is reported in up to 16.7% of smokers, 7.5% of ex-smokers and 7.0% of never-smokers [23]. Today's high prevalence of smoking among young adults and adolescents in Switzerland is alarming and may increase the burden of COPD in the years to come [24]. It is estimated that at least 350 000 individuals in Switzerland have COPD.

COPD mortality is highest in east European countries, Ireland, Scotland, and England [25]. In the USA the age-adjusted mortality rate increased by 17% in men, from 96.3 per 100 000 in 1979 to 112.8 per 100 000 in 1993, whereas the rate increased by 126% in women, from 24.5 per 100 000 in 1979 to 55.4 in 1993 [20, 26].

COPD is usually diagnosed late in its course, because patients may be insensitive to airflow obstruction and lack symptoms even at low FEV_1 [21]. 5-year survival in patients with severe COPD (e.g. mean FEV_1 of 49% predicted, mean age 66 years) was 47%, while 10-year survival was 23% in spite of therapy [27]. The non-smoking population shows a decline in FEV_1 of approximately 20 ml/year compared with an annual FEV_1 decrease of 50–60 ml/year in smokers. The only proven way

Table 2

Classification of severity of COPD.

Stage	characteristics
Mild (Stage I)	• FEV_1/FVC <70% • FEV_1 >80% predicted
Moderate (Stage II)	• FEV_1/FVC <70% • 30% <FEV_1 <80% predicted (II A: 50% ≤FEV_1 <80% predicted) (II B: 30% ≤FEV_1 <50% predicted)
Severe (Stage III)	• FEV_1/FVC <70% • FEV_1 ≤30% predicted or FEV_1 <50% predicted with a PaO_2 <8 kPa or clinical signs of right heart failure

Table 3

Modified Medical Research Council Scale (mMRC).

0	No breathlessness except during strenuous exercise
1	Shortness of breath when hurrying on the level or up a slight rise
2	Walking more slowly than people of the same age on the level because of breathlessness or need to stop for breath when walking at own pace on the level
3	Stopping for breath after walking 100 metres or after a few minutes on the level
4	Too breathless to leave the house or breathlessness on dressing or undressing

to slow down this course is smoking cessation [28] (Evidence A).

Assessment

Clinical assessment

A complete history and physical examination should be performed in the initial assessment of each patient suspected of having COPD. Shortness of breath due to COPD cannot be reliably distinguished from dyspnoea due to other causes. It is frequently associated with cough, wheezes, sputum production, and recurrent respiratory infections. Physical examination may reveal signs of lung hyperinflation, increased respiratory muscle effort, altered breathing patterns (i.e. increased respiratory rate, prolonged expiration), and abnormal breath sounds. The accuracy of physical examination to detect or exclude moderately severe COPD is poor [3]. Since most patients with COPD are cigarette smokers and usually belong to an older age group, they often suffer from concomitant diseases such as coronary heart disease, peripheral vascular disease etc. This must be considered in the diagnostic workup and for treatment strategies.

Pulmonary function testing

In patients with symptoms of COPD or a history of exposure to risk factors, particularly cigarette smoking, lung function should be tested. Spirometry is the gold standard for assessment of the presence and degree of airflow obstruction. The abnormalities consist of a reduction in FEV_1 and in the ratio of FEV_1 to forced vital capacity (FVC). Small spirometers, fulfilling the usual qual-ity criteria are available at a reasonable cost. These handheld spirometers are convenient to use, have a graphic display, and store and print the numeric results and flow-volume curve, i.e. the patient's spirogram. Office spirometry with such a device is recommended for widespread use by primary care physicians, particularly in smokers ≥45 years [29]. If COPD is detected at an early stage, successful smoking cessation may prevent further disease progression. In COPD the correlation between peak expiratory flow (PEF) and FEV_1 is poor. Hence measurement of PEF, well established in the management of asthma, should not be used in patients with COPD. The severity of COPD is classified on the basis of clinical signs and symptoms and the degree of airflow obstruction (see table 2) [1]. This somewhat arbitrary staging system is intended to standardise the grading of disease severity.

COPD is frequently associated with an increase in total lung capacity and residual volume and with a reduction in diffusing capacity for carbon monoxide, which correlates with the degree of emphysema.

Arterial blood gas analysis should be performed in patients with an FEV_1 <50% predicted or clinical signs of right heart failure.

Chest x-ray and thoracic CT scan

A plain chest x-ray in posterior-anterior and lateral projection may demonstrate the presence of hyperlucency, vascular attenuation and hyperinflation, suggesting the presence of emphysema. A chest radiograph is indicated as part of the initial workup of patients with COPD to exclude concomitant pathologies. However, chest films are not sensitive enough to detect emphysema. Computed tomography (CT) in high-resolution technique is the most sensitive and specific *in vivo* technique for detection of pulmonary emphysema and grading of its severity. While CT scanning is not recommended for routine clinical assessment of COPD, it may be used to evaluate the feasibility of lung volume reduction surgery.

Additional tests

The detection of erythrocytosis arouses suspicion of chronic hypoxaemia. ECG changes suggestive of cor pulmonale are insensitive but indicate the need for arterial blood gas analysis. Measurement of serum α-1 antitrypsin is indicated in patients with early manifestations of emphysema. Other laboratory investigations are indicated in COPD patients in the presence of complications. Quality of life assessment by questionnaire is a validated method of evaluating the effects of COPD on everyday life and may be used to monitor the course of the disease [30–32]. Six-minute walking distance may be used to quantify global functional impairment. Shortness of breath in patients with COPD can be assessed by using the modified Medical Research Council (mMRC) dyspnoea scale [33, 34] (table 3).

Management of COPD

The objectives of COPD treatment are summarised in table 4.

Relief of symptoms
Improvement of exercise tolerance
Improvement in health status
Improvement in quality of life
Prevention of disease progression
Prevention and treatment of complications
Prevention and treatment of exacerbations
Reduction in mortality due to respiratory illness

Prevention

Identification, reduction, and control of risk factors to prevent the onset of COPD (primary prevention) are important steps towards developing strategies for secondary prevention of COPD. These factors include tobacco smoke, occupational exposure, indoor/outdoor pollution and irritants. In smokers, smoking cessation is the single most effective way of reducing the risk of COPD progression [35] (Evidence A). A brief advisory session from a general practitioner results in smoking cessation rates of 7.4%, i.e. an increase of 2.5% over the cessation rate in control groups, and 3–10 minutes' counselling achieves higher cessation rates of approx. 12%. With greater investment of time and complexity of interventions, including skills training, problem solving and psychosocial support, the quit rate may reach 20–30% [36] (Evidence A). In the Lung Health Study, a multicentre controlled clinical trial, a combination of physician advice, group support, skills training and nicotine replacement therapy achieved quit rates of 35% at one year and sustained quit rates of 22% at 5 years [37]. The following pharmacotherapies are effective in supporting smoking cessation attempts and at least one of these drugs should be prescribed in the absence of contraindications: bupropion SR, nicotine replacement in various galenic preparations [28, 38–42] (Evidence A).

Many occupational respiratory disorders (e.g. in farmers) can be reduced or controlled by a variety of strategies aimed at reducing the burden of inhaled particles and gases at the workplace [16] (Evidence B).

Patient education

Studies suggest that education is effective in accomplishing certain specific goals, including smoking cessation [37] (Evidence A), initiation of discussions and understanding of advanced directives and end-of-life issues [43] (Evidence B), and improvement of patients' responses to acute exacerbations [44] (Evidence B).

Pharmacological treatment

None of the available drugs for COPD are effective in modifying the long-term progression of airflow limitation that is the hallmark of this disease (Evidence A). Therefore, today's polypharmacy, overuse, and overdose of drugs are a significant burden on the cost of COPD management.

Bronchodilators

Bronchodilator drugs are central to the symptomatic management of COPD. However, they do not modify the decline of lung function or, by inference, the prognosis of the disease (Evidence B). They are given on an as-needed or regular basis to prevent or reduce shortness of breath.

Aerosol formulations are the preferred way of administration. Attention to effective drug delivery and training in inhalation technique is essential. The use of metered dose inhalers (MDI) with spacer devices, dry powder inhalers (DPI) or possibly nebulisers should be tailored to the patient's abilities.

The choice between β_2-agonists or anticholinergics, or a combination therapy, depends on individual symptomatic response. Long-acting inhaled bronchodilators may be the most convenient for continuous symptomatic relief. Slow-release xanthines are effective in COPD but are a second-line choice due to their potential toxicity. They may be added to regular inhaled bronchodilators in more severe COPD.

Combining drugs whose mechanisms and duration of action differ increases the degree of bronchodilatation and lessens the probability of side effects [45, 46].

Anticholinergics: Inhibition of vagal stimulation of the bronchial tree is associated with reduced smooth muscle tone and bronchial gland secretion. The bronchodilating effect of short-acting inhaled anticholinergics lasts up to 8 hours after administration [37, 47] (Evidence A). Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. When administered via metered dose inhaler (MDI), the recommended dose of ipratropium bromide is 2–4 puffs (40–80 µg) 4 times daily. For severe exacerbations, the dosage may be increased, e.g. MDI with spacer 6–8 puffs every 3–4 h or nebulised ipratropium 0.5 mg every 4–8 hours (0.5 mg corresponds to 40 gtts. of a 0.25% solution) [48]. More recently several studies have reported favourable effects with tiotropium, a new long-acting anticholinergic bronchodilator which must be inhaled only once daily [49, 50].

Beta-2-agonists: Beta-2-agonists are useful for patients with reversible airway obstruction and for patients with dyspnoea or cough, even under maximal anticholinergic inhalation therapy. Because of their rapid onset of action, beta-2-agonists (such as salbutamol, terbutaline or formoterol) can be

used as rescue medication in cases of bronchospasm. The bronchodilator effect of short-acting beta-agonists usually disappears within 4–6 hours. For severe exacerbations it is acceptable to increase the number of puffs and to shorten the interval between puffs from MDI or DPI by up to 3–4 hours, provided it is for short periods of time. Since sympathomimetic bronchodilators protect against bronchospasm induced by various stimuli and reduce dynamic hyperinflation during physical exercise, they may reduce dyspnoea even if they do not improve FEV_1 [51].

The effect of long-acting inhaled β_2-agonists (salmeterol and formoterol) in COPD patients is maintained over 12 hours with no loss of effectiveness overnight or during regular use [52, 53] (Evidence B). The effectiveness of long-acting inhaled β_2-agonists in COPD has not been studied enough to allow a general recommendation for their use in COPD patients. However, 50 µg salmeterol twice daily reduces breathlessness and improves quality of life [54]. Formoterol brings about long-lasting functional improvement in apparently poorly reversible chronic pulmonary disease [55] (Evidence B). The degree of improvement in airway function does not correlate with subjective symptomatic improvement [56].

Salmeterol has an effect on exercise-induced dyspnoea comparable to ipratropium for up to 6 hours after administration [57]. Furthermore, this long-acting beta-2-agonist was superior to theophylline alone with respect to lung function and symptom control [58, 59]. Cumulative use of multiple forms of beta-2-adrenergics does not enhance their effectiveness but increases the risk of side effects and should therefore be avoided. However, some patients with COPD may benefit from a combination of salmeterol or formoterol plus ipratropium or theophylline without a resultant increase in adverse effects [58, 60, 61].

Theophylline: Theophylline acts as a non-selective phosphodiesterase inhibitor. Besides bronchodilatation, theophylline shows various physiologic actions such as increased central respiratory drive, mucociliary clearance, respiratory muscle endurance, cardiac output, and dilatation of pulmonary arteries [62].

Theophylline is given orally at a low dose and in a sustained-release formulation for administration once or twice a day. Its use may be considered when inhaled therapy fails to produce adequate bronchodilatation or when patients have nocturnal respiratory symptoms. The therapeutic index of theophylline is narrow. Toxicity is characterised by wide individual differences due to variations in metabolism and drug interactions, which restrict its utility. Several studies have recently been started with cilomilast, a selective phosphodiesterase-4 inhibitor. Its potential therapeutic actions include bronchodilatation and effects on inflammation and neuromodulation without major adverse events [63].

Glucocorticosteroids

When considering the position of glucocorticosteroids in the management of COPD, their role during exacerbations and during stable phases of COPD (steroid trial) should be distinguished.

The effects of glucocorticosteroids on airway inflammation in COPD are much less pronounced than in asthma. Based on the lack of evidence of a long-term beneficial effect of chronic oral glucocorticoid therapy in subjects with confirmed COPD, and a large body of evidence on the long-term adverse effects of this treatment, including the contribution of steroid myopathy to respiratory failure in COPD, chronic treatment with oral glucocorticosteroids should not be used in COPD [64–68] (Evidence A). There is strong evidence that prolonged treatment with inhaled glucocorticosteroids does not modify the long-term decline in FEV_1 in patients with COPD.

Steroid trial: Many recent COPD guidelines recommend the use of a short course (two weeks) of oral glucocorticoids (e.g. 0.5 mg prednisone or prednisolone/kg body weight) to identify patients who respond favourably and hence may benefit from long-term treatment with inhaled glucocorticosteroids. However, a short course of oral glucocorticosteroids is not a very reliable predictor of the long-term response to inhaled glucocorticosteroids in COPD [69]. Nevertheless, patients with symptomatic obstruction to airflow qualify for a therapeutic trial with systemic glucocorticosteroids. The response to the trial should be assessed by spirometry to identify patients with significantly reversible airways obstruction (i.e. an increase in FEV_1 >200 ml and >12–15% from postbronchodilator baseline measurements), who should be identified in order to detect a component of associated bronchial asthma [70]. The results of a steroid trial can only be assessed in a stable phase of the disease, at least 6 weeks after an exacerbation and on the basis of repetitive and reproducible measurements of the patient's FEV_1.

Inhaled glucocorticosteroids: Recent studies on the long-term effects of inhaled corticosteroids in COPD have shown only minimal effect, despite relatively high dosages [71–74]. The annual decline of FEV_1 did not change in mild COPD (budesonide 1200 µg/d for 6 months followed by 800 µg for the remaining 30 months or triamcinolone 1200 µg/d for 40 months). In more severe COPD, inhaled steroids improved the FEV_1 during the first 3 months but the decline thereafter was not modified (budesonide 800 µg/d for three years, fluticasone 1000 µg/d for three years). Other outcome variables such as respiratory symptoms or number of annual exacerbations were positively modified in some studies. In the ISOLDE study, fluticasone treatment significantly reduced the number of exacerbations and slowed the loss of quality of life in patients with advanced COPD (FEV_1 <50% predicted).

The formulation of topical steroids (budesonide, fluticasone, triamcinolone) is probably not important. The dose-response relationship or the therapeutic effect of inhaled corticosteroids in COPD and their safety during long-term use are not known. Similar adverse effects to those in asthma can be expected in COPD, depending on the dose and type of glucocorticosteroid. There is a need for further documentation in this population. Some studies have shown an increased incidence of skin bruising [73, 74]. Bone demineralisation was observed in one study [75]. The economic consequences of regular use of inhaled steroids should be evaluated in future cost-benefit studies.

On the basis of these data, regular treatment with inhaled corticosteroids should only be considered for symptomatic patients with advanced COPD suffering from repeated exacerbations [76–78] (Evidence B).

Antibiotics

The use of antibiotics, other than to treat infectious exacerbations, is not recommended [79].

Mucolytics

The regular use of mucolytics in COPD has been evaluated in a number of long-term studies with controversial results. The majority showed no effect of mucolytics on lung function or symptoms, although some reported a reduction in the frequency of acute exacerbation [80]. Although a few patients with viscous sputum may benefit from mucolytics, the widespread use of these agents cannot be recommended [81] (Evidence D). Effects of beta-2-adrenergics or theophylline on mucociliary clearance are minor but welcome additional effects partly mediated by bronchodilatation.

N-acetylcysteine

Oral N-acetylcysteine (NAC) in a daily dose of 400–600 mg for 3–6 months reduces the risk of exacerbations and improves symptoms in patients with chronic bronchitis compared with placebo. NAC is well tolerated and has no relevant side effects [82] (Evidence B). An ongoing multicentre study will shortly provide additional data on NAC's effects on the decline in FEV_1, exacerbation rate, quality of life and cost-utility [83].

Immunoregulators

Immunostimulating agents made from bacterial extracts represent a class of medication whose potential benefit results from nonspecific stimulation of the immune system. OM-85 BV is an immunostimulating agent made from eight different species of bacteria that are frequently present in the lower respiratory tract. A study using OM-85 BV showed beneficial effects in patients with COPD by lessening the likelihood of severe respiratory events leading to *hospitalisation* [84, 85] (Evidence B).

Respiratory stimulants

Doxapram, a nonspecific respiratory stimulant available as an intravenous formulation, is not recommended in stable COPD (Evidence D). Due to its potential neurological side effects almitrine bismesylate is not recommended in the treatment of COPD patients [86] (Evidence B).

The carboanhydrase inhibitor acetazolamide should no longer be used in patients with hypercapnic respiratory failure.

Vaccination

Influenza vaccination

Influenza vaccination reduces serious illness and death in COPD patients by approximately 50% [87]. Most fatalities from influenza result from secondary bacterial pneumonia, which leads to respiratory failure [88]. Immunisation should be performed once in autumn of each year or twice autumn/winter (Evidence A).

Pneumococcal vaccine

A pneumococcal vaccine containing epitopes from 23 virulent strains has been proposed for COPD patients to prevent pneumococcal infection. It has been shown that about 50% of invasive pneumococcal infections could be prevented by the vaccination. Since 1997 the Advisory Committee on Immunisation Practices has recommended the vaccination in COPD patients, particularly those over 64 [89] (Evidence B).

Haemophilus influenzae vaccine

Oral vaccination, in the autumn, of patients with recurrent exacerbations of bronchitis reduces the number and severity of exacerbations over the winter months [90] (Evidence B). The whole cell non-typable *Haemophilus influenzae* (NTHi) vaccine is not yet available in Switzerland.

Oxygen therapy

It has been conclusively shown that the survival of patients with COPD-induced hypoxaemia is improved by long-term O_2 therapy, and that the benefit is greatest if the treatment is administered for at least 15–18 h/day [91–94] (Evidence A).

Long-term oxygen therapy [95] is indicated if the PaO_2 is:
– at or below 7.3 kPa (55 mm Hg) with or without hypercapnia
– between 7.3 kPa (55 mm Hg) and 8.0 kPa (59 mm Hg), if symptoms or signs of right heart failure and/or erythrocytosis are present.

The primary goal of oxygen therapy is to increase the baseline arterial partial pressure (PaO_2) to at least 8.0 kPa (60 mm Hg) or to achieve arterial oxygen saturation equal to or above 90%. Samples for arterial blood gas measurement should be obtained by arterial puncture.

In the absence of sleep apnoea symptoms there is no indication for specific sleep studies.

Prescription of oxygen should always include the source of supplemental oxygen (gas or liquid), the method of delivery (nasal cannula, transtracheal), duration of use (hours per day), and the flow rate at rest, during exercise and sleep. Oxygen given during exercise may increase walking distance and endurance, most probably by optimising oxygen delivery to tissues and its utilisation by muscles. However, there are no data to suggest that long term oxygen therapy changes exercise capacity *per se*. This treatment is usually restricted to patients who meet criteria for continuous oxygen or experience significant oxygen desaturation during exercise (Evidence C).

Alpha-1-antitrypsin replacement

Augmentation therapy with α_1-antitrypsin increases α_1-antitrypsin levels and anti-elastase activity in serum and bronchoalveolar lavage fluid. Patients with documented severe deficiency and established emphysema who have stopped smoking may be considered candidates for this therapy. However, intravenous substitution therapy is expensive and its benefits have not been confirmed in a prospective randomised trial [96–100] (Evidence D).

Ventilatory support

While several studies have confirmed the usefulness of non-invasive ventilation during acute exacerbations by avoiding intubation and decreasing short-term mortality [101, 102], the role of noninvasive ventilation in the long-term management of COPD patients at home is controversial [103, 104]. Uncontrolled studies suggest that it decreases the rate of hospital admissions in hypercapnic COPD patients with frequent exacerbations [105].

Pulmonary rehabilitation

The components of pulmonary rehabilitation vary widely from one institution to another but a comprehensive pulmonary rehabilitation programme should include exercise training, nutrition counselling and education. All patients, irrespective of their degree of disability, benefit from exercise training programmes (Evidence A). The type of exercise (stair climbing, walking, treadmill, or bicycle ergometer) may vary and is best determined by patient preference and cost. The exercises should aim at training all parts of the musculoskeletal system, especially the muscles of the back and the upper extremities. Whether pulmonary rehabilitation is carried out in an in- or outpatient programme depends on local availability and patients preference. After structured rehabilitation the patient should continue with regular exercises at home and preferably participate in a guided outpatient group [106–113].

Scientific evidence does not support the routine use of respiratory muscle training; it may be considered for individual patients [106, 114] (Evidence B).

Psychosocial support

By natural history COPD is a progressive disease which will eventually severely impair quality of life. Even with the best pharmacological care, shortness of breath, already occurring during daily activities, profoundly modifies family life, sexuality, and social interaction. The patient becomes more isolated, dependent, and full of grief. This complex burden of suffering can be overwhelming. The patient's coping mechanisms may be insufficient. This is a challenging disease for the physician in charge as well as for other health care workers.

As in other chronic diseases, the medical approach should be "patient-centred" and should leave enough time for the patient to express his or her subjective suffering [115]. Severe chronic illness such as advanced COPD requires all the caring physician's medical and human resources [116, 117]. The use of anxiolytic or antidepressive agents may be helpful. Participation in support groups should be encouraged.

Nutrition

Weight loss is a common feature in patients with advanced COPD. The clinical importance of weight loss, particularly of fat-free mass (FFM), and its adverse effects on physical performance and quality of life has been demonstrated [118]. Moreover, a low body mass index (BMI) is an independent predictor for increased mortality [119].

Although nutritional support in these patients seems logical, controlled trials have not shown significant effects of weight gain on lung function or exercise capacity in patients with stable COPD [120–125].

Anabolic steroids and growth hormones

Some studies using anabolic steroids such as nandrolone decanoate or stanozolol [126] as a component of a training programme [122] have shown an increase in free fat mass and improvement in respiratory muscle strength. However, there is insufficient evidence to support the use of these drugs in the treatment of COPD patients (Evidence B).

Preliminary reports suggest that nitrogen balance in COPD patients may be improved by growth hormone therapy [127, 128]. However, daily administration of recombinant growth hormone increases lean body mass but does not improve muscle strength or exercise tolerance in underweight patients with COPD [129].

Surgical approaches

Lung volume reduction surgery

Bullectomy i.e. the removal of large bulla compressing the adjacent lung structures is effective in reducing dyspnoea and improving lung function [130] (Evidence B). Lung volume reduction surgery (LVRS) is a palliative procedure which not only improves pulmonary function and exercise

capacity in selected patients with severe hyperinflation, but has a major positive impact on quality of life for several years [131–134]. Patients with heterogeneous types of emphysema show the greatest improvement in pulmonary function after LVRS [135–142].

Lung transplantation

In appropriately selected patients with very advanced COPD and an estimated life expectancy below 6–18 months (FEV$_1$ <25% predicted, PaO$_2$ <55–60 mm Hg, hypercapnia, secondary pulmonary hypertension, 6´ walking distance <250 m) unilateral or bilateral *lung transplantation* has the potential to improve quality of life and functional capacity [143, 144]. Contraindications for this treatment, which makes lifelong immunosuppression mandatory, are malignancies, generalised arteriosclerosis, renal failure or liver failure, drug abuse, and emotional instability.

Management of acute exacerbations

Exacerbations of respiratory symptoms requiring medical intervention are important clinical events in COPD. The most common causes of an exacerbation are viral and bacterial bronchial infections and peaks of air pollution [145–147], but in about one-third of severe exacerbations the cause cannot be identified.

There is no widely accepted definition of acute exacerbation in COPD, but most published definitions encompass a combination of three clinical findings: worsening of dyspnoea, increase in sputum purulence, and increase in sputum volume.

Bronchodilators

Home management of COPD exacerbation involves increasing the dose and/or frequency of already established bronchodilator therapy (Evidence A), particularly inhaled β$_2$-agonists or/and anticholinergics. Some patients experience additional benefit when a second inhaled bronchodilating agent is administered after the maximum dose of the initial agent is reached.

The efficacy of wet nebulisation and dry aerosol delivery systems (meter-dose inhaler plus spacer or powder) are probably clinically equivalent [148]. Hence the choice of a specific delivery method should be determined on an individual basis, depending on each patient's ability to use the various methods.

Corticosteroids

Systemic, preferably oral glucocorticosteroids are beneficial in the management of acute COPD exacerbations (Evidence A). They shorten recovery time, restore lung function more quickly, and may decrease the need for hospitalisations. Several studies have shown that treatment with oral or i.v. corticosteroids improves the rate of lung function more rapidly during the first 72 hours of an exacerbation. There is no evidence that this benefit is maintained beyond 72 hours, or that other outcomes, such as re-hospitalisation rate, are improved [149, 150]. Dosage and length of treatment vary greatly among studies. An oral dose of 40 mg prednisolone (or equivalent), for not more than 2 weeks, can be recommended [151] (Evidence D). Tapering of corticosteroids is not necessary following short-term administration. Hyperglycaemia is the most common adverse effect associated with systemic corticosteroids for acute exacerbation of COPD.

There is no data on the use of intramuscular depot steroids in the therapy of COPD exacerbations. Inhaled steroids are not appropriate in acute exacerbation of COPD.

Antibiotics

COPD exacerbations with clinical signs of airway infection benefit from antibiotic treatment [152, 153] (Evidence B). Because *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Branhamella catarrhalis* are most frequently associated with COPD exacerbation, the antibiotics used should be directed preferentially against these bacteria [154, 155]. Commonly used antibiotics include amoxicilline and clavulanic acid, trimethoprim-sulfamethoxazole, macrolides and quinolones. Because of the reported increase in resistant bacterial strains it has become common practice to use broader-spectrum antibiotics. However, to date no randomised, placebo-controlled trials have proved the superiority of the newer broad-spectrum antibiotics in this scenario.

Studies show that patients with more severe exacerbations are more likely to experience benefit from antibiotics. Typical administration periods ranged from 3 to 14 days.

Hospital admission

Although most acute exacerbations can be treated on an outpatient basis, some patients require hospitalisation or treatment in an emergency room.

Indications for hospitalisation for acute exacerbation of COPD:
– increase in symptom intensity
– failure to respond to initial medical management
– severe COPD
– respiratory failure
– significant co-morbidity
– older age
– mental confusion
– insufficient home support

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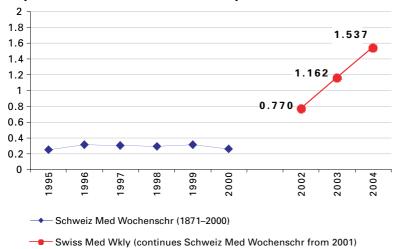
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