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Diagnosis and Management of Chronic Obstructive Pulmonary Disease: The Swiss Guidelines

Official Guidelines of the Swiss Respiratory Society

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Abstract
The new Swiss Chronic Obstructive Pulmonary Disease (COPD) Guidelines are based on a previous version, which was published 10 years ago. The Swiss Respiratory Society felt the need to update the previous document due to new knowledge and novel therapeutic developments about this prevalent and important disease. The recommendations and statements are based on the available literature, on other national guidelines and, in particular, on the GOLD (Global Initiative for Chronic Obstructive Lung Disease) report. Our aim is to advise pulmonary physicians, general practitioners and other health care workers on the early detection and diagnosis, prevention, best symptomatic control, and avoidance of COPD as well as its complications and deterioration.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of chronic morbidity and mortality throughout the world. Its prevalence and its social as well as economic burden are increasing, due, in part, to the aging of the population. According to the global BOLD (Burden of Obstructive Lung Disease) study, COPD is projected to rank fifth worldwide as cause of death in the year 2020 [1]. COPD is related, in many cases but not exclusively, to cigarette smoking, and in some areas of the world with large populations, air pollution resulting from the burning of biomass fuels has been identified as a relevant risk factor [2, 3].

Over the past years, the COPD guidelines of various national and professional associations have been revised [4–7] and in December 2011, 10 years after its first release, the third and updated version of the GOLD (Global Initiative for Chronic Obstructive Lung Disease) report became available [8]. Our current guidelines are based on a

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previous version, 2002 [9], and consider new knowledge and novel developments. They aim to advise pulmonary physicians, general practitioners and other healthcare workers on early detection and diagnosis, prevention, best symptomatic control, avoidance of complications and deterioration of COPD.

Definition

COPD is characterized by chronic airflow limitation and a range of pathological changes in the lung, significant extrapulmonary effects and important comorbidities, which may contribute to the severity of the disease in individual patients (GOLD, updated 2011) [8]. The chronic airflow limitation is caused by an individual mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). Chronic bronchitis is a clinical and epidemiological term and is defined by a history of cough and mucus production on most days for at least 3 months a year over at least 2 successive years. Not all patients with chronic bronchitis have COPD, and not all patients with COPD suffer from the symptoms of chronic bronchitis.

Pathophysiology

The major risk factors for the development of COPD are inhaled toxic substances, particularly tobacco smoke and the products from the burning of biomass fuels that 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, fibrosis, destruction of the parenchyma and vascular changes. These pathological changes lead to airflow limitation, loss of elastic recoil and other physiological abnormalities. 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 the characteristics of both diseases. Since inflammation is a feature of COPD, specific anti-inflammatory therapies may have beneficial effects in controlling symptoms, preventing exacerbations and slowing disease progression. However, the response of inflammation to corticosteroids in COPD is poor, contrary to their effectiveness in asthma.

Risk Factors

COPD arises from an interaction of both host factors and environmental exposures. Smoking remains a leading cause for COPD. It is estimated that in industrialized countries, in men about 80% and in women around 60% of the COPD mortality is attributable to smoking, whereas in developing countries smoking contributes to only about 45% in men and 20% in women [10, 11]. In unindustrialized countries biomass fuel utilization for cooking and heating at home is an important environmental factor. Other factors may include occupational exposures, passive smoking and outdoor air pollution. The population-attributable fraction for the workplace contribution to COPD risk has been estimated to be 15–20% in Europe and North America [10]. The risk in less-regulated areas of the world is likely to be much higher. In the SAPALDIA study (Swiss study on Air Pollution And Lung Disease in Adults), high levels of occupational exposure to biological dusts, mineral dusts, gases or fumes, as determined from self-reports, were found to be associated with an increased incidence of COPD of GOLD stage II or higher [12].

Host factors include genetics, epigenetics and other characteristics of the host such as bronchial hyperreactivity and a history of asthma [13] as well as a history of severe respiratory infection in childhood. Inherited α-1-antitrypsin deficiency is a single-gene autosomal recessive disease that predisposes to COPD, but this accounts for less than 1% of all cases of COPD [14, 15]. Apart from this particular gene, genetic predisposition to COPD is very complex and is incompletely understood at present. COPD has been associated with the polymorphisms of various genes, but very few of these associations have been replicated in more than 2 or 3 independent population samples [16]. Other factors may also predispose to the development of COPD. Bronchial hyperreactivity is a risk factor, even after exclusion of asthmatics [17, 18], and chronic bronchitis symptoms seem to increase the risk for the later development of COPD [19, 20].

Epidemiology and Burden of Disease

COPD prevalence data show remarkable variation due to differences in survey methods and diagnostic criteria. The BOLD study reports a variability between countries in the prevalence of GOLD stage II–IV COPD [21], ranging from 9% in Iceland to 19% in the Philippines for male subjects of more than 40 years of age.

Country-specific age distributions, smoking prevalence rates and other important environmental factors may contribute to most of these disparities. In Switzerland, in a sample of 6,126 subjects (SAPALDIA), the prevalence of COPD of GOLD stage II or higher was 5.1% in the population aged 30–73 years, and the prevalence of GOLD stage I or higher was 10% [22]. Prevalence was strongly dependent on age. Consequently, extrapolated to a resident population of 7.8 million in Switzerland (2010 census), the estimated number of stage II or higher ranges between 200,000 and 300,000, and that for stage I or higher is about 400,000.

Table 1. mMRC scale

0	No breathlessness, except during strenuous exercise.
1	Shortness of breath when hurrying on the level or walking up a slight hill.
2	Walk slower than people of the same age on the level because of breathlessness, or have to stop for breath when walking at own pace on the level.
3	Stop for breath after walking 100 m or after a few minutes on the level.
4	Too breathless to leave the house or breathlessness from dressing or undressing.

Assessment

Clinical Assessment

Although it is an important part of patient care, physical examination has a low sensitivity and specificity for the detection or exclusion of mild to moderately severe forms of COPD. If the physical signs of airflow obstruction and pulmonary hyperinflation are present, the patient usually suffers from an advanced stage of the disease. The leading symptoms of COPD are shortness of breath during exercise, exercise limitation and chronic cough [23]. The degree of dyspnea can be assessed by the Modified Medical Research Council (mMRC) questionnaire [24] (table 1). The COPD Assessment Test [25] has a broader coverage of the impact of COPD on the patient's daily life and well-being and correlates closely with health status measured using the St. Georges Respiratory questionnaire. The test has been translated into several languages, contains 8 items and can be easily performed on the internet www.catestonline.org (table 2). Another important element of a patient's history is the occurrence and frequency of exacerbations. An exacerbation of COPD is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication. The exacerbation rate varies greatly between patients. The best predictor of frequent exacerbations ($\geq$2 per year) is a history of previous exacerbations and the severity of COPD [26]. Since COPD often develops in middle-aged long-time smokers, patients frequently have a variety of other diseases related to either smoking or aging. Comorbidities that occur frequently in COPD patients include cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, lung cancer and depression [27]. The comprehensive assessment of a patient with COPD forms the basis for therapy and combines the symptomatic assessment with the patient's spirometric classification and/or the risk of exacerbations.

The degree of airflow obstruction, as assessed by the FEV_1, is but one of the essential prognostic features of COPD. Several studies have shown that, in addition, the severity of dyspnea, walking distance and body mass index (BMI; see BODE index, table 3) correlate best with life expectancy in COPD [28].

Pulmonary Function Testing

Lung function should be tested in patients with symptoms of COPD such as chronic cough, wheezing, shortness of breath and limitation on exertion. Clinicians should, however, be alert to the fact that some patients may deny exercise limitation because they have spontaneously reduced their habitual level of activity [29]. Spirometry is the gold standard to assess the presence and degree of airflow obstruction. The abnormalities consist of a reduction in FEV_1 and in the ratio of FEV_1 to the forced vital capacity (FVC). Small, handheld spirometers are convenient to use, have a graphic display, and store and print the numeric results as well as the flow-volume curve or the spirogram of the patient. Office spirometry should be performed in primary care by well-trained personnel [30, 31]. In COPD, the correlation between peak expiratory flow (PEF) and FEV_1 is poor. Therefore, the measurement of PEF, well established in the management of asthma, should not be used in patients with COPD. The degree of airflow obstruction in COPD is classified as proposed by the GOLD (table 4). This arbitrary international staging system is intended to standardize the diagnosis of COPD by using a fixed threshold of $FEV_1/FVC < 0.70$ for airflow obstruction and to grade its severity based on FEV_1 as percent of predicted (% pred.). However, since the FEV_1/

Table 2. COPD Assessment Test

							Score
I never cough	1	2	3	4	5	I cough all the time	□
I have no phlegm (mucus) in my chest at all	1	2	3	4	5	My chest is completely full of phlegm (mucus)	□
My chest does not feel tight at all	1	2	3	4	5	My chest feels very tight	□
When I walk up a hill or one flight of stairs I am not breathless	1	2	3	4	5	When I walk up a hill or one flight of stairs I am very breathless	□
I am not limited doing any activities at home	1	2	3	4	5	I am very limited doing activities at home	□
I am confident leaving my home despite my lung condition	1	2	3	4	5	I am not at all confident leaving my home because of my lung condition	□
I sleep soundly	1	2	3	4	5	I don't sleep soundly because of my lung condition	□
I have lots of energy	1	2	3	4	5	I have no energy at all	□
						Total score	□

Scores and resulting impact levels: <10 = low; 10–20 = medium; 21–30 = high.

FVC ratio declines physiologically with age, using a fixed ratio of 0.70 instead of the lower limit of normal (LLN), leads to COPD overdiagnosis in older subjects, particularly for GOLD stage I. In Switzerland, the SAPALDIA study showed that among individuals classified as GOLD stage I COPD, only the subjects manifesting cough, phlegm or dyspnea had a faster decline in FEV_1, increased respiratory care utilization and impaired quality of life. In contrast, asymptomatic individuals classified as having stage I COPD did not differ from subjects with normal lung function [20]. Thus, for subjects with lung function corresponding to GOLD stage I, a cautious approach would consider the diagnosis of COPD only in those manifesting symptoms of the disease. When provided by the spirometer, the use of LLN for FEV_1/FVC is a physiologically sound alternative which reduces the misclassification of airway obstruction [32–34]. Since in COPD no strong correlation exists between the degree of airflow obstruction and quality of life, the revised version of GOLD emphasizes considering also the severity of shortness of breath and the frequency of exacerbations in the assessment of an individual patient [8].

Bodyplethysmography is used to measure intrathoracic gas volume for the calculation of residual volume and total lung capacity, parameters that reflect pulmonary hyperinflation. Diffusing capacity for carbon monoxide is measured by the single breath technique. These parameters correlate with the degree of emphysema and it is therefore recommended that plethysmography is performed on a regular basis for follow-up in patients with severe COPD that may benefit from a lung volume reduction procedure.

Table 3. BODE index

Variable	BODE index points			
	0	1	2	3
FEV_1, % pred.	≥65	50–64	36–49	≤35
Distance walked in 6 min, m	≥350	250–349	150–249	≤149
mMRC dyspnea scale	0–1	2	3	4
BMI, kg/m^2	>21	≤21		

Approximate 4-year survival interpretation: 0–2 = 80%; 3–4 = 67%; 5–9 = 57%; 7–10 = 18%.

Table 4. GOLD classification of COPD according to the degree of airflow limitation based on FEV_1 after bronchodilator

GOLD I: mild	FEV_1 >80% pred.
GOLD II: moderate	50%≤ FEV_1 <80% pred.
GOLD III: severe	30%≤ FEV_1 <50% pred.
GOLD IV: very severe	FEV_1 ≤30% pred.

Table 5. Description of levels of evidence

Evidence category	Sources of evidence	Definition
A	Randomized controlled trials (RCTs). Rich body of data.	Evidence is from end points of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A therefore requires a substantial number of studies involving substantial numbers of participants.
B	RCTs. Limited body of data.	Evidence is from end points of intervention studies that include only a limited number of RCTs, and post hoc, subgroup or meta-analysis of RCTs. Category B applies when few randomized trials exist, they are small in size and the results are somewhat inconsistent, or they were undertaken in a population that differs from the target population of the recommendation.
C	Nonrandomized trials, observational studies	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D	Panel consensus judgment	This category is used only in case the 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.

Chest X-Ray and Thoracic CT Scan

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 for the detection of mild to moderate emphysema. High resolution computed tomography (HRCT) is the most sensitive and specific in vivo technique for the detection, grading and morphological characterizing of pulmonary emphysema. While CT scanning is not recommended for routine clinical assessment of COPD, it may be used to evaluate alternative diagnosis and to assess the feasibility of lung volume reduction surgery.

Further Assessment

Hypoxemia is an important problem in COPD, accentuates intolerance to physical exercise and adds to its morbidity. Exercise tests such as the 6-minute walk test or, in selected cases, spiroegometry should be performed with continuous oxygen saturation measurements. If pulsoxymetry at rest shows a saturation of <92%, an arterial blood gas analysis should be performed. If erythrocytosis is present, chronic hypoxemia should be suspected. Measurement of the α-1 antitrypsin serum concentrations is indicated in rapidly deteriorating COPD, in COPD patients of below 45 years of age and in cases with emphysema of basal predominance. In the case of increased daytime sleepiness, oximetry at night or respiratory polygraphy may be indicated to rule out hypoxemia during sleep or an overlap syndrome (COPD and obstructive sleep apnea).

Our Methodology – A Comment

The recommendations and statements in these guidelines are based on the available literature, in particular the GOLD report [8]. A level of evidence, i.e. A, B, C or D, is indicated when available; these are listed in table 5. When evidence was lacking or international guidelines were conflicting, the authors, elected by the board of the Swiss Respiratory Society and representing chest physicians working in private practice, in hospitals and in academic medicine, reached consensus after appropriate discussion.

Management of COPD

Prevention

Identification, reduction and control of risk factors such as tobacco smoke, occupational exposure and in- and outdoor pollution are important steps for preventing the development of COPD. Smoking cessation is the single most effective intervention with the greatest impact on the natural history of COPD [35, 36] (Evidence A). Brief advice by a general practitioner results in smoking cessation rates of 7.4%, i.e. an increase of 2.5% over the cessation rate in a control group, and counseling of 3–10 minutes duration achieves higher cessation rates of around 12%. With greater investment of time and com-

plexity of interventions, including skills training, problem-solving and psychosocial support, the quit rate can reach 20–30% (Evidence A) [37]. In the Lung Health Study, a multicenter, controlled clinical trial, a combination of advice by a physician, group support, skills training and nicotine replacement therapy achieved quit rates of 35% at 1 year and sustained quit rates of 22% at 5 years [38]. Pharmacotherapy is effective in supporting smoking cessation attempts and at least one of these substances should be prescribed in the absence of contraindications: varenicline, bupropion SR and nicotine in various galenic preparations (Evidence A) [39–44]. Occupationally induced respiratory disorders, e.g. in farmers, can be reduced or controlled by strategies aimed at reducing the burden of inhaled particles and gases at the workplace (Evidence B) [45].

Patient Education and Self-Management

Patient education is effective in accomplishing specific goals, including smoking cessation [38] (Evidence A), initiating discussion and understanding of advanced directives and end-of-life-issues (Evidence B) [46] and improving patients' responses to exacerbations (Evidence B) [47]. In addition, elderly patients can benefit from interdisciplinary education programs. Individualized, written action plans for patients' self-management improve quality of life and decrease exacerbation recovery time by reducing patients' delay. Patient education accompanied by instruction for self-management and individualized, written action plans can improve the outcome of exacerbations [48]. Although there are studies that show a beneficial effect of disease self-management in COPD [48], a study with negative results concerning patient's self-management and COPD-related hospitalizations was recently published [49]. Quality assessment in patient instruction and survey by specially trained medical staff is therefore crucial.

Pharmacologic Treatment

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

Bronchodilators

Bronchodilator medications are given on either an as-needed basis or a regular basis to prevent or reduce symptoms of COPD (Evidence A). They have the potential to improve exhalation, to reduce dynamic hyperinflation, to improve exercise performance and to decrease shortness of breath. 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 depending on the COPD severity. Inhalation is the preferred means 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 nebulizers should be tailored to the patient's ability. The choice between β_2 agonists or anticholinergics or a combination therapy depends on the individual patient response in terms of symptom relief and side effects. Long-acting inhaled bronchodilators are convenient and more effective in maintaining symptom relief than short-acting bronchodilators.

Anticholinergics

The 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 h after administration (Evidence A). Tiotropium is a long-acting anticholinergic bronchodilator, which has to be inhaled only once daily [50]. It reduces exacerbations and related hospitalizations, and improves symptoms and health status (Evidence A) [51]. In a large, long-term clinical trial (UPLIFT) [52], there was no effect of tiotropium added to other standard therapies on the rate of lung function decline and no reduction in mortality. In another large trial, tiotropium was superior to salmeterol in reducing exacerbations, but the difference was small (Evidence A) [53].

In 2008, a meta-analysis of 17 randomized trials reported an increased risk of cardiovascular events from using anticholinergics [54]. In contrast, the UPLIFT trial [52] did not show an increased risk. An FDA-expert panel discussed these contradictory findings and concluded, based on methodological considerations, that the current data do not support the supposition that the use of tiotropium is accompanied by an increased risk of cardiovascular events [55].

β_2 Agonists

Sympathomimetic bronchodilators protect against bronchospasm induced by various stimuli, reduce static

and dynamic hyperinflation and improve dyspnea, even if FEV_1 remains unchanged. The effects of short-acting β_2 agonists (SABA: salbutamol, terbutaline or formoterol) disappear within 4–6 h. SABAs are used as rescue medication and patients are allowed to increase the number of puffs and to shorten the interval between puffs from MDI or DPI, provided it is for a short period of time (3–4 h).

The effects of long-acting inhaled β_2 agonists (LABA: salmeterol and formoterol) are maintained over 12 h or even for up to 24 h by the ultralong-acting bronchodilator, indacaterol, which needs to be administered only once daily [56, 57].

In the TORCH trial studying the combined effect of salmeterol and fluticasone [58], the lung functions, number of exacerbations and average change in clinical scores over 3 years was significantly better in the combination-therapy group than in the group treated with salmeterol only, fluticasone only or placebo. The side effects of β_2 agonists are proportional to their dosage and consist mostly of tremor, some degree of tachycardia and hypokalemia especially when prescribed with diuretics.

Phosphodiesterase Inhibitors

Theophylline is a xanthine derivate and acts as a non-selective phosphodiesterase inhibitor. It has a modest bronchodilator effect in stable COPD (Evidence A) [59] and shows various physiological actions, the significance of which is disputed. Theophylline is metabolized by cytochrome P450-dependent mixed-function oxidases and many physiological variables and drugs modify its metabolism. It is less effective than and not as well tolerated as inhaled long-acting bronchodilators, and is therefore not recommended as a first-line drug.

Roflumilast is a phosphodiesterase-4 inhibitor and has recently been approved for use in GOLD stage III and IV COPD. Its principal action is to reduce inflammation by inhibiting the breakdown of intracellular cyclic adenosine monophosphate. Roflumilast reduces moderate and severe exacerbations by 15–20% in patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations (Evidence A) [60, 61]. It is a once-daily medication and slight improvements in FEV_1 are seen when it is added to long-acting bronchodilators. There are no comparison or add-on studies of roflumilast and inhaled corticosteroids (ICS). Patients have to be informed about the potential side effects i.e. diarrhea and weight loss.

Glucocorticosteroids

When considering the position of glucocorticosteroids in the management of COPD, their role during exacerbations and during stable phases (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 any 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, chronic treatment with oral glucocorticosteroids should be avoided in COPD (Evidence A) [62–66]. A short course of oral corticosteroids is not a reliable predictor of the long-term response to inhaled glucocorticosteroids in COPD, but can be helpful to differentiate COPD from bronchial asthma. The effect of a steroid trial should be objectively assessed based on FEV_1 measurements during a stable phase of the disease (at least 6 weeks after an exacerbation) [67]. However, a short course of oral corticosteroids is indicated in COPD exacerbations.

Inhaled Glucocorticosteroids

The dose-response relationships and long-term safety of ICS in COPD are not known. Only moderate to high doses have been used in long-term clinical trials. The effects of ICS on pulmonary and systemic inflammation in patients with COPD are controversial. ICS, particularly in fixed combinations with LABA, are overused and their role should be limited to specific indications. Regular treatment with ICS does not modify the long-term decline of FEV_1 or mortality in patients with COPD (Evidence A). ICS improve symptoms, lung function and quality of life, and reduce the frequency of exacerbations in COPD patients with an FEV_1 <60% pred. (Evidence A). ICS in combination with a LABA are more effective than the individual components in improving lung function, health status and reducing exacerbations when the COPD is moderate (Evidence B) to very severe (Evidence A). In summary, the use of ICS is recommended in severe and very severe COPD and in GOLD stage II COPD with an FEV_1 <60% pred. and frequent exacerbations. In the TORCH trial, combination therapy was associated with an increased risk of pneumonia, but not with overall mortality (Evidence A) [58, 68–74].

The addition of a LABA/ICS combination to tiotropium is frequently used in severe to very severe COPD. This triple combination improves lung function and quality of life and may further reduce exacerbations compared to tiotropium monotherapy or LABA/ICS dual therapy [75, 76].

Antibiotics

The use of antibiotics in stable disease (i.e. outside of exacerbations) is not recommended. A recent trial of daily azithromycin, a macrolide antibiotic, showed efficacy on exacerbation end points [77]. However, general use is not recommended until further studies confirm effectiveness and exclude relevant long-term side effects.

Mucolytics

A review article has recently been published about the effects of mucoactive therapy in COPD [78]. Most trials have been performed with N-acetylcysteine or carbocysteine. Overall, the authors found a significant reduction in exacerbations and in the number of days with disability. Mucolytics were well tolerated and the number of adverse events was lower than with placebo. However, in the largest and best-designed study with N-acetylcysteine in 523 patients with COPD, the reduction in exacerbations was only observed in patients not taking ICS [79]. The use of mucolytics is not generally recommended, but may be an option in COPD patients with frequent exacerbations.

Immunostimulating Agents

Immunostimulating agents made from bacterial extracts represent a class of medications whose potential benefit results from a nonspecific stimulation of the immune system.

A systematic review of the studies on the use of bacterial extracts in COPD patients has shown a reduction in the symptoms of COPD exacerbations but no reduction of the rate of the exacerbations [80].

Vaccination

Influenza Vaccination

Influenza vaccination can reduce lower-tract respiratory infections that require hospitalization or cause death (Evidence A) [81]. Vaccination does not increase consultations, corticosteroid prescriptions or exacerbations in subjects with asthma or COPD [82, 83]. The strains are adjusted annually for appropriate effectiveness and should be given each year in autumn (or possibly twice, in autumn and winter).

Pneumococcal Vaccine

The 23-valent pneumococcal polysaccharide vaccine protects against invasive pneumococcal disease, such as bacteremia and meningitis, but does not reduce all-cause pneumonia. In a small study, a decreased rate of pneumonia was found only in younger people (<65 years) and in those with severe airflow obstruction (FEV_1 <40%) [84]. In spite of this weak evidence, the 23-valent pneumococcal polysaccharide vaccine is recommended for all sufferers of chronic lung disease (Evidence B). Results on the effect of a conjugated 13-valent pneumococcal vaccine in adults are not available for the time being.

Oxygen Therapy

It has been shown that the survival of patients with chronic respiratory failure due to COPD is improved by long-term oxygen administration (>15 h per day) (Evidence B) [85–87].

Long-term oxygen therapy [88] is indicated if the PaO_2 is:

- at or below 7.3 kPa (55 mm Hg) with or without hypercapnia confirmed twice over a 3-week period (Evidence B)
- between 7.3 kPa (55 mm Hg) and 8.0 kPa (59 mm Hg), if there is evidence of pulmonary hypertension or polycythemia (hematocrit > 55%) (Evidence D).

Long-term oxygen therapy may be considered in:

- situative hypoxemia, i.e. hypoxemia (<90% saturation) during sleep or during exercise.

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%. Smoking cessation is a requirement for long-term oxygen therapy. The prescription of oxygen should always include the source of supplemental oxygen (gas or liquid), the method of delivery (via nasal cannula or transtracheal), the duration of use (>15 h or, if possible, 24 h per day) and the flow rate at rest, during exercise and sleep. Oxygen given during exercise may increase walking distance and endurance most likely by optimizing oxygen delivery to the tissues and its utilization by muscles. However, there are no data to suggest that long-term oxygen therapy changes exercise capacity per se.

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

Alpha-1-Antitrypsin Replacement

Intravenous replacement with α_1-antitrypsin (AAT) increases AAT levels and antielastase activity in serum and in bronchoalveolar lavage fluid [15]. Uncontrolled trials have shown positive effects with augmentation therapy in COPD patients with AAT deficiency. Two small, randomized, double-blind, placebo-controlled tri-

als have investigated the efficacy of intravenous AAT augmentation therapy on emphysema progression using CT densitometry [89, 90]. Data from these similar trials, the 2-center Danish-Dutch study (n = 54) and the 3-center EXACTLE study (n = 65), have been pooled to increase the statistical power [91]. All subjects, i.e. 60 under replacement and 59 in the placebo group, were assessed by a CT scan at baseline and after treatment, with a mean follow-up of approximately 2.5 years. The combined data, as analyzed by one of four analytical methods, showed a significantly reduced decline in lung density. However, clinical end points (decline of FEV_1, exacerbation rate and quality of life) did not demonstrate statistical differences. Due to this and to a lack of accepted criteria to assess the efficiency of this costly treatment, a recommendation for AAT replacement cannot be given.

Ventilatory Support

Noninvasive ventilation in combination with long-term oxygen therapy may be used in a selected subset of patients, particularly in those with pronounced daytime hypercapnia. In patients with both COPD and obstructive sleep apnea, there are clear benefits from continuous positive airway pressure (CPAP) in relation to both survival and the risk of hospital admission [92, 93].

Pulmonary Rehabilitation, Psychological Support and Nutrition

Rehabilitation

Exercise capacity and the level of physical activity are strong prognostic factors in COPD. Pulmonary rehabilitation and maintenance of physical activity have the potential to improve exercise tolerance, to decrease dyspnea and anxiety and to reduce the number of hospitalizations (Evidence A) [94, 95]. Comprehensive pulmonary rehabilitation includes patient education, instruction for self-management (action plans), nutritional counseling and exercise training. The type of exercise (stair climbing, walking, treadmill and bicycle ergometer) may vary and is best determined by patient preference. Interval exercise training is usually better tolerated by patients. Whether pulmonary rehabilitation is conducted in an inpatient or outpatient setting depends on local availability and a patient's preference and comorbidity. Pulmonary rehabilitation is also effective soon after exacerbations [96]. Comorbidities are not a contraindication for pulmonary rehabilitation [97]. The benefit in exercise performance and quality of life is maintained if patients follow a regular exercise program at home [98]. The routine use of respiratory muscle training cannot be recommended, but individual patients may benefit from this.

Psychological Support

COPD is a progressive disease that will eventually severely impair the patient's quality of life. Even with the best care, shortness of breath, once it starts occurring during daily activities, profoundly modifies family life, sexuality and social interaction. The patient becomes more isolated, dependent and depressed. This complex burden of suffering can be overwhelming, and a patient's coping mechanisms may be insufficient. The prevalence of anxiety and depression is higher in certain COPD patients and is associated with dyspnea and a reduced quality of life [99–101]. Exercise training and antidepressant drugs are often effective in ameliorating dyspnea and anxiety [102]. Pulmonary rehabilitation may decrease psychosocial morbidity even without specific psychological interventions [103].

Nutrition

Weight loss is a common feature in patients with advanced COPD. The clinical importance of weight loss, particularly of fat-free mass, and its adverse effects on physical performance and quality of life have been demonstrated [104]. Moreover, a low BMI is an independent predictor for increased mortality [105]. 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 [106]. Supplementation may, however, improve the outcome of training in some patients [107].

Invasive Interventions

Lung Volume Reduction Surgery

Bullectomy, i.e. the removal of large bulla that compress the adjacent lung structures, is a well-established surgical procedure and can be performed thoracoscopically. It is effective in reducing dyspnea and improving lung function [108, 109]. Lung volume reduction surgery (LVRS) reduces emphysematous parts of the lung to reduce hyperinflation. It 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 [110,

111]. Patients with heterogeneous types of emphysema and low exercise capacity have the greatest improvement in pulmonary function after LVRS [112], but patients with homogeneous emphysema may also experience significantly better health status and lung function compared to with usual medical care – when high-risk candidates with an extremely low FEV_1 and a homogeneous emphysema or a diffusing capacity of <20% pred. were excluded.

Bronchoscopic Lung Volume Reduction

A range of different techniques such as endobronchial valves, coils, airway bypass, thermal vapor ablation and biological sealants have been employed in both homogeneous as well as heterogeneous types of emphysema. Carefully selected patients with very severe COPD may benefit from bronchoscopic lung volume reduction [113]. However, the currently available data on the efficacy and safety of different types of bronchoscopic lung volume reduction procedures are not conclusive and further data is therefore needed.

Lung Transplantation

The decision to proceed with lung transplantation for severe COPD is complex. There is plenty of evidence suggesting that functional capacity is improved following the procedure, but the presence of a survival benefit is less clear. It is important to define disease severity as precisely as possible in order to determine which patients have the most urgent need for lung transplantation and are likely to have the longest survival afterwards. Transplantation is usually deferred until the BODE index is 7 or higher, the FEV_1 is <20% pred., the diffusing capacity for carbon monoxide is <20% pred. or the clinical course becomes more aggressive with life-threatening exacerbations. Since many patients with advanced COPD are older and affected by comorbidities, the selection of suitable transplant candidates is a particular challenge. Contraindications for lung transplantation are malignancies, renal or liver failure, drug abuse and emotional instability. It is essential to refer possible lung transplantation candidates for evaluation to a lung transplant center early enough [114–116].

Exacerbation of COPD

Definition, Impact, Severity and Etiology

An exacerbation, as defined by the GOLD, is 'an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough and/or sputum that is beyond normal day to day variation, is acute in onset and may warrant a change in regular medication in a patient with underlying COPD' [117]. Exacerbations in COPD are characterized by a broad variation in clinical presentation and are triggered by several factors.

It has been recognized that there is a subgroup of COPD patients who experience frequent exacerbations (≥2 per year). Recurrent exacerbations have a strong negative impact on quality of life, often lead to hospitalization and are associated with higher rates of morbidity and mortality in COPD. The association of several clinical features with frequent exacerbations has been demonstrated, including a higher degree of airway obstruction, an advanced GOLD stage or BODE category, the presence of chronic cough and sputum production, advanced age and clinical depression.

The current American Thoracic Society and European Respiratory Society guidelines provide a descriptive means of defining the severity of exacerbations [23]. The classification of exacerbation severity is thereby defined by the necessary extent of the acute medical intervention. Exacerbations are divided into 3 categories, level I with treatment at home, level II requiring hospitalization and level III requiring ICU admission for respiratory failure, respectively. The classification of exacerbations into types I–III according to the criteria by Anthonisen et al. [118] does not reflect disease severity but is often used to estimate the likelihood of a of COPD exacerbation having a bacterial cause.

Although less than 50% of exacerbations have a bacterial cause, the presence of bacteria detected by sputum examination varied between 17 and 87% in certain investigations. In recognition of these diagnostic limitations, sputum cultures should not be performed during most exacerbations. Only selected cases, e.g. patients with FEV_1 <30% pred., extensive bronchiectasis, prior evidence of Gram-negative rods or contemporary or previous antibiotic therapy warrant sputum cultures at exacerbation (Evidence C).

Therapy

Pharmacological Therapy

Bronchodilators, systemic corticosteroids, antibiotic agents, oxygen and noninvasive positive-pressure ventilation are the most common therapeutic measures in exacerbations of COPD.

Bronchodilators

Short-acting β_2 agonists are the cornerstone of the treatment of exacerbations of COPD (Evidence D). The addition of an anticholinergic is generally recommended (Evidence D).

Glucocorticoids

Several randomized, controlled trials suggest that systemic glucocorticoids in COPD exacerbations accelerate the recovery of FEV_1, decrease the length of hospital stay and improve clinical outcome (Evidence A) [119]. The strongest treatment effect of steroids occurs probably within the first 72 h and it levels off thereafter, suggesting a lack of benefit beyond 5 days of treatment. Despite a lack of well-designed randomized trials evaluating the most effective steroid dose, we recommend oral steroids be administered once daily in doses of 20 to 60 mg of prednisone [120] for 5–15 days (Evidence C).

Antibiotics

The role of antibiotics in the treatment of COPD exacerbations is much less prominent than the role of steroids [121, 122]. Viral infections are known to be the most common cause of acute exacerbations in COPD. Paradoxically, viral exacerbations were associated with more severe exacerbations and more prolonged symptom recovery than nonviral exacerbations. However, there is currently no reliable method to clearly distinguish bacterial exacerbations from those due to other etiologies. General recommendations for antibiotic use are not uniform and are often based on less-evaluated clinical parameters. Taking the risk of antibiotic overuse into account, routine antibiotic use has to be examined critically in outpatient exacerbations which often occur with a high spontaneous recovery rate (Evidence C). Antibiotics may be prescribed to patients who have 3 cardinal symptoms: an increase in dyspnea, sputum volume and sputum purulence (Evidence B), and also to patients with severe exacerbation who are admitted to an ICU (Evidence A) [123]. The determination of serum procalcitonin was shown to reduce the use of antibiotics in COPD exacerbations and may be of value in the decision to use antibiotics (Evidence A) [124]. If antibiotics are deemed needed, a short treatment course of $\leq$5 days is preferred, as these have an outcome equal to a conventional treatment with antibiotics of 7–10 days (Evidence C) [125]. Longer courses of antibiotics should be considered for patients with more severe exacerbations requiring a hospital admission or ICU stay and those with proven colonization or infection with Gram-negative rods.

The effectiveness of older first-line antibiotics (amoxicillin, ampicillin and doxycyclin) and the newer broad-spectrum second-line antibiotics (amoxicillin/clavulanic acid, 2nd and 3rd generation cephalosporins and quinolones) is comparable with regard to mortality, microbial outcome and the rate of adverse events (Evidence C). Second-line agents might present a small benefit in patients with more severe disease or more common exacerbations (Evidence C). Currently, the choice of antibiotic agent should therefore be guided by a recent history of antibiotic use and local microbial resistance patterns.

Oxygen

Oxygen therapy should be considered in the treatment of severe COPD exacerbations (Evidence D). Oxygen should be titrated to provide adequate levels of oxygenation (PaO_2 >8.0 kPa or SaO_2 >90%). It is reasonable to assess arterial blood gases within 30–60 min after the institution of oxygen therapy to exclude significant CO_2 retention.

Nonpharmacological Therapy

Several randomized trials and meta-analyses indicated that noninvasive positive pressure ventilation improves important clinical outcomes, such as intubation rate, treatment failure and inhospital mortality in patients with an acute exacerbation complicated by hypercapnic acidosis (Evidence A) [126].

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