RECOMMENDATIONS OF THE SPANISH SOCIETY OF PULMONOLOGY AND THORACIC SURGERY (SEPAR)

Joint Guidelines of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) and the Latin American Thoracic Society (ALAT) on the Diagnosis and Management of Chronic Obstructive Pulmonary Disease

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Introduction

Key Points

– Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation that is not fully reversible, associated with an abnormal inflammatory response, principally to tobacco smoke.

– Airflow limitation, measured by spirometry after bronchodilation, is defined as a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) of less than 0.7 (or below the lower limit of normal in persons over 60 years of age) .

– COPD is characterized by chronic inflammation associated with remodeling of the airway, lung parenchyma, and pulmonary arteries.

– The severity of COPD is classified on the basis of the postbronchodilator FEV_1 value taking into account symptoms, such as air trapping, respiratory insufficiency, systemic involvement, and associated comorbidity.

– The estimated prevalence of COPD in the adult Spanish population is 9%, while in Latin America this figure ranges from 8% to 20%. COPD is the fourth leading cause of death in Spain and the world.

COPD is characterized by chronic airflow limitation that is not fully reversible, associated with an abnormal inflammatory response, principally to tobacco smoke, although only 1 smoker out of 4 develops the disease.[1] Long-term exposure to biomass smoke in enclosed spaces has also been associated with COPD,[2] and early-onset emphysema among smokers is associated with a homozygous α_1-antitrypsin deficiency.[3] Airflow limitation is defined as a postbronchodilator FEV_1/FVC of less than 0.7. FEV_1 is the best indicator of the severity of airflow limitation and the main parameter used to classify disease severity (Table 1). However, because of the heterogeneous and systemic nature of COPD, other variables besides FEV_1 should also be taken into account in the assessment of these patients. These include gas exchange, lung volumes, patients' perception of symptoms, exercise capacity, exacerbation frequency, nutritional alterations (unintentional weight loss), and multidimensional scales, such as the BODE index (based on body mass index, airflow obstruction as measured by FEV_1, dyspnea, and exercise capacity measured by

TABLE 1
Classification of Chronic Obstructive Pulmonary Disease (Ratio of Forced Expiratory Volume in the First Second [FEV_1] to Forced Vital Capacity <0.7[a])

Degree of Severity	Postbronchodilator FEV_1 % Predicted
Mild	≥80
Moderate	≥50 and <80
Severe	≥30 and <50
Very severe	<30 or <50 with chronic respiratory insufficiency[b]

[a]Or below the lower limit of normal in patients over 60 years of age.[6]
[b]PaO_2 <60 mm Hg with or without hypercapnia ($PaCO_2$ ≥50 mmHg) breathing ambient air at sea level.

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the 6-minute walk test). In Spain, the estimated prevalence of COPD is 9.1% in the population aged between 40 and 70 years.[4] In Latin America, the estimated prevalence of COPD ranges from 7.8% in Mexico City to 19.7% in Montevideo, Uruguay.[5]

Clinical Evaluation of COPD

Key Points

– The patient with COPD is a current smoker or someone with a long-term history of smoking who presents with the following symptoms: cough, sputum, and/or dyspnea.

– Dyspnea appears in the advanced stages of the disease and develops progressively until it restricts the normal activities of daily living.

– In patients with COPD, lung function tests are used to establish a diagnosis, assess disease severity, evaluate prognosis, monitor the course of the disease, and assess the severity of exacerbations.

– A chest radiograph should be obtained for the initial assessment and at any time during follow-up when new symptoms appear. The use of high-resolution chest computed tomography is recommended when assessing candidates for surgery and for the diagnosis of concurrent disease.

– While the assessment of the patient's health-related quality of life is of interest for research purposes, the information obtained is of only limited use in clinical practice.

– A complete blood count and an electrocardiogram should be performed as part of the initial assessment. Other diagnostic tests are only required in selected cases.

– Both the initial assessment and subsequent care of these patients should be coordinated between primary care clinicians and respiratory specialists.

– Any person over 40 years of age with a history of exposure to tobacco or biomass smoke may have COPD and should undergo spirometry.

Patients with COPD usually have been or are long-term smokers and report onset of symptoms after the age of 40 years. The intensity of exposure to tobacco smoke should be quantified by calculating pack-years (1 pack-year is the equivalent of having smoked 1 pack per day for 1 year). In the case of COPD caused by inhalation of smoke from biomass fuel combustion in enclosed spaces, the period during which the patient was exposed for a least 10 hours a day should be recorded. The chief symptoms of COPD are dyspnea, cough, and sputum. Dyspnea is the principal symptom, but it may be perceived to varying degrees, especially among older patients, as individuals often adapt their level of physical activity in order to reduce symptoms. Dyspnea appears in the most advanced stages of the disease and develops gradually until it restricts the normal activities of daily living. While various instruments for measuring dyspnea are available, the Medical Research Council scale is recommended because of its ease of use.[7] Chronic cough—often productive and occurring mainly in the morning—is sometimes the most obvious sign of disease, although the severity of this symptom does not correlate with the degree of airflow limitation. The characteristics of sputum can be of clinical use. Purulence or an increase in sputum production may indicate an exacerbation, and excessive sputum production is an indication of bronchiectasis. When sputum is blood-stained, other possible diagnoses, in particular lung cancer, must be ruled out. Patients with mild COPD may report few symptoms or even be asymptomatic.

The presence or absence of symptoms related to associated complications should also be recorded together with the history of exacerbations. The presence of comorbidities, such as cardiovascular disease, diabetes mellitus, anxiety or depression, and osteoporosis should be noted because of their impact on the natural history of COPD.

Physical examination provides very little information in patients with mild-to-moderate disease. In patients with severe COPD, exercise capacity and nutritional state (body mass index) should be assessed regularly. A body mass index of less than 21 kg/m^2 is associated with a poor prognosis (level B evidence).[8]

Functional Evaluation of COPD

Key Points

– Spirometry is essential in the diagnosis, initial assessment, and subsequent management of these patients.

– Static lung volumes are useful in diagnosis and in the assessment of response to treatment.

– Bronchodilator reversibility testing is useful in the initial assessment and to rule out asthma.

– Analysis of arterial blood gas composition is indicated if the patient's FEV_1 is less than 50% of the predicted value and when prescribing home oxygen therapy.

– Carbon monoxide diffusing capacity (DLCO) should be measured if FEV_1 is below 50% of the reference value, when emphysema is suspected, and in the preoperative assessment of candidates for lung resection surgery.

– Exercise tests provide overall information about the impact of the disease on lung function. Exercise testing is of use in assessing the risk of lung surgery, monitoring treatment response, and evaluating occupational disability.

– Sleep studies are indicated when concomitant sleep apnea syndrome is suspected.

– Respiratory muscle function should only be tested when respiratory muscle dysfunction or diaphragm paralysis is suspected, and when the degree of dyspnea is disproportionately high with respect to FEV_1.

– Lung compliance testing is not routinely indicated.

– Multidimensional tools, such as the BODE index, are better predictors of the risk of death due to COPD than is FEV_1 alone.

In patients with COPD, lung function testing is used to *a)* establish a diagnosis, *b)* quantify disease severity, *c)* assess prognosis, *d)* monitor lung function and response to treatment, and *e)* assess the severity of exacerbations and their response to treatment.

Spirometry is essential for establishing a diagnosis of COPD and assessing the severity of airflow limitation.

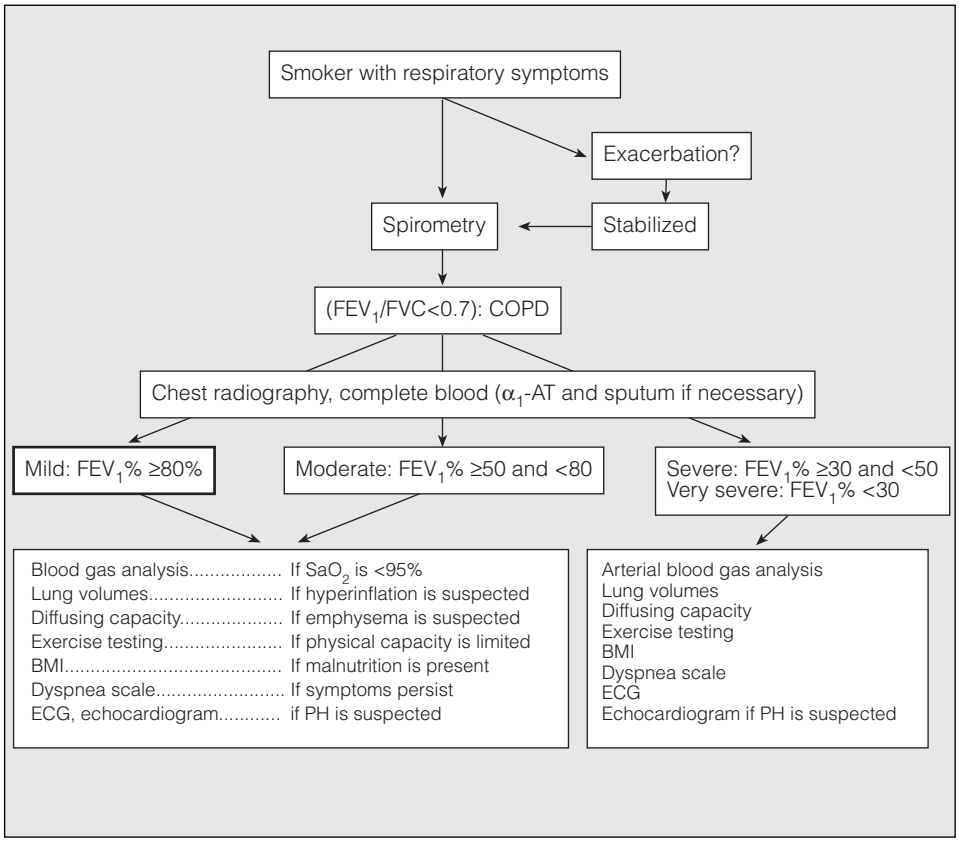

Figure 1. Assessment of chronic obstructive pulmonary disease (COPD). FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; α_1-AT, α_1-antitrypsin; SaO_2, arterial oxygen saturation, BMI, body mass index; ECG, electrocardiogram; PH, pulmonary hypertension.

It is indicated in any smoker over 40 years of age whether or not respiratory symptoms are present. Airflow limitation is defined as a postbronchodilator FEV_1/FVC of less than 0.7. In patients over 60 years of age, the lower limit of normality may be used as the threshold in order to avoid overdiagnosis,[6] although, in any case, the interpretation of spirometry results should always take the clinical situation into account. Disease severity is classified on the basis of FEV_1 expressed as a percentage of the predicted value (Table 1). Spirometry should be repeated annually in all patients diagnosed with COPD (level D evidence).

Bronchodilator reversibility testing is essential in the initial assessment to rule out bronchial asthma. Static lung volumes are used as an index of pulmonary hyperinflation and air trapping. They should be measured in all patients with severe or very severe COPD, in the selection of candidates for lung surgery, and in patients with mild-to-moderate COPD when air trapping is suspected. The measurement of inspiratory capacity is a useful index in the assessment of both air trapping and response to treatment. The ratio of inspiratory capacity to total lung capacity has prognostic value. DLCO decreases in patients with primarily emphysematous COPD and can be useful in ruling out the presence of asthma (level D evidence). DLCO should therefore be measured in the following cases: when the patient has severe or very severe COPD, when selecting candidates for lung surgery, and whenever emphysema is suspected. Analysis of arterial blood gas composition is indicated in patients with severe or very severe COPD to diagnose respiratory insufficiency and when prescribing and monitoring home oxygen therapy. Blood gases should also be analyzed in patients with moderate COPD whose arterial oxygen saturation (SaO_2) is less than 95% at sea level. The presence of respiratory insufficiency increases the severity of COPD and has prognostic value (Table 1). Exercise testing can be performed on a cycle or treadmill ergometer or using simple walking tests (the 6-minute walk test or shuttle walk test). These tests provide overall information about the functional impact of the disease, have prognostic value, and reflect the patients' physical capacity. The 6-minute walk is a simple test that correlates with objective measurements of the routine physical activities of daily living.[9] Exercise testing is indicated in cases of severe COPD, in monitoring the response to different types of treatment (pharmacotherapy, surgery, and rehabilitation), in the assessment of the risk of lung surgery or work capacity (occupational disability), and in all optimally treated patients who have highly symptomatic disease or reduced physical activity.

Sleep studies (nocturnal pulse oximetry or polysomography) are only indicated if there is a high erythrocyte count, a suspicion of concurrent sleep apnea, or signs of right heart failure. Respiratory and peripheral muscle function should be assessed if respiratory muscle

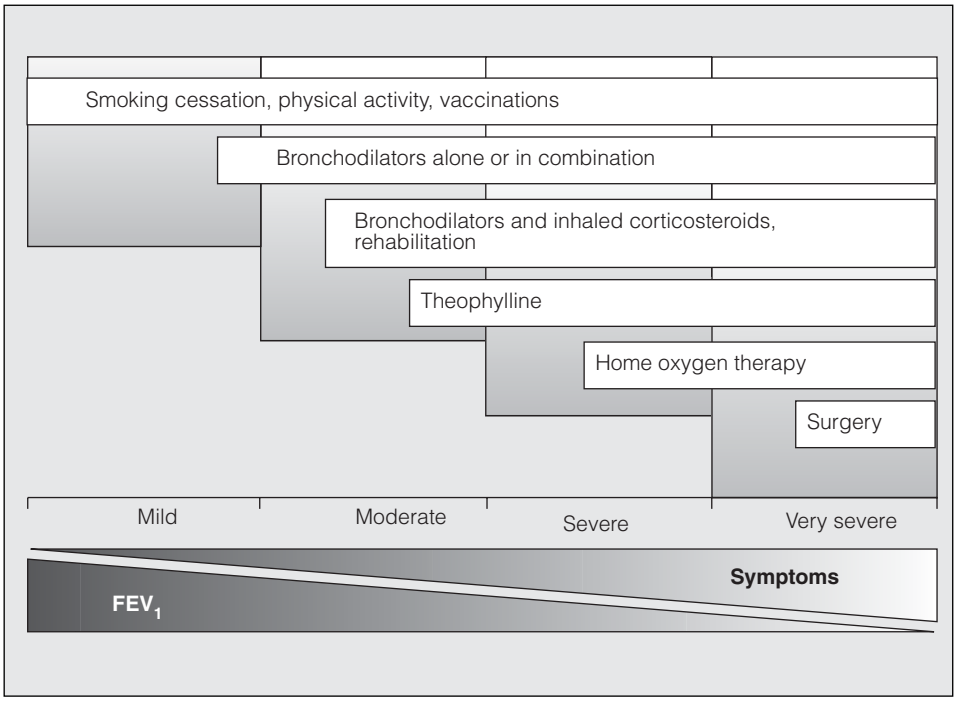

Figure 2. Management of stable chronic obstructive pulmonary disease. FEV_1 indicates forced expiratory volume in 1 second.

dysfunction or paralysis of the diaphragm is suspected, and when the degree of dyspnea is disproportionately high with respect to FEV_1. Analysis of lung compliance is not recommended as part of the routine assessment of patients with COPD. Other measurements, such as midexpiratory flow or peak flow are not relevant in the functional assessment of patients with COPD. The BODE index is a multidimensional grading system that predicts risk of death in patients with advanced COPD better than FEV_1.[10] This index is based on 4 factors: body mass index (B), the degree of airflow obstruction (O) as measured by FEV_1 expressed as a percentage of the predicted value, dyspnea (D) measured using the Medical Research Council scale, and exercise capacity (E) as assessed by the 6-minute walk test. The results give a score on a 10-point scale that is useful in predicting the likelihood of survival. Figure 1 summarizes the protocol for the initial assessment of COPD.

Management of Patients With Stable COPD (Figure 2)

General Measures

Smoking cessation is a cost-effective intervention and the most important measure that should be implemented to avoid further development and progression of COPD (level A evidence). Tobacco addiction is a chronic and recurring disease with far reaching biological repercussions. In patients who are conscious of the dangers of smoking and motivated to quit but who are moderately or highly nicotine-dependent, smoking addiction must be treated as a chronic disease. In such cases, it is advisable to prescribe nicotine replacement therapy, bupropion, or varenicline (level A evidence).[11-13] There is no scientific evidence to support the use of other measures, such as acupuncture or hypnosis. SEPAR has published specific guidelines on the treatment of tobacco dependence.[14] All patients with COPD should be advised to undergo annual influenza vaccination because this measure has been shown to reduce mortality and the number of hospitalizations during periods of epidemic (level B evidence).[15] Pneumococcal vaccination should be offered to patients with COPD aged 65 years or older because it reduces the risk of bacteremia (level B evidence) and prevents the onset of pneumonia, especially in patients under 65 years of age and those with severe airflow limitation (level B evidence).[16] There is insufficient evidence to support the use of vaccines against *Haemophilus influenzae* or polyvalent bacterial vaccines.

Pharmacotherapy

Key Points

– In patients with occasional symptoms, treatment with short-acting bronchodilators reduces symptoms and improves exercise tolerance (level B evidence).

– In patients with continuous symptoms, long-acting bronchodilators afford greater control of symptoms and improve the patient's lung function and quality of life (level A evidence). They may also reduce the frequency of exacerbations (level A evidence).

– In patients with moderate-to-severe COPD, the use of inhaled corticosteroids reduces the frequency of exacerbations and improves the patient's quality of life (level A evidence).

– Inhaled corticosteroids, used in conjunction with long-acting β_2-agonists, have an even greater clinical effect on lung function, symptoms, and frequency of exacerbations (level A evidence), in addition to a positive effect on survival (level C evidence).

– Theophylline can be added to the treatment regimen of patients who remain symptomatic despite optimal treatment or of individuals who require oral administration (level D evidence).

– The use of mucolytics and/or antioxidants can be considered in patients with chronic sputum production and/or frequent exacerbations (level B evidence).

– α_1-antitrypsin deficiency augmentation therapy is indicated in selected patients who have a deficiency (level B evidence).

– There is currently no evidence to support the use of antitussive drugs, antileukotrienes, prophylactic antibiotics, or respiratory stimulants.

Bronchodilators. In most COPD patients, symptoms respond favorably to treatment with bronchodilators. Improvements in dyspnea and exercise tolerance do not always correlate with spirometric changes (level A evidence), but they do seem to be more closely associated with reductions in air trapping and lung hyperinflation.[17]

Short-acting bronchodilators (ipratropium bromide and short-acting β_2-agonists) have been shown to afford effective and rapid control of symptoms. Patients should use these agents when required to alleviate symptoms (level B evidence). The use of preparations containing a combination of ipratropium bromide and short-acting β_2-agonists has been shown to produce greater bronchodilation than either of these agents alone.[18]

Long-acting bronchodilators (salmeterol, formoterol, and tiotropium bromide) should be used in all patients who require regular treatment because these agents improve quality of life by alleviating symptoms and reducing the frequency of exacerbations (level A evidence).[19-21] Tiotropium has been shown to achieve a greater increase in exercise tolerance than placebo and to improve the results of rehabilitation (level A evidence).[21] There is insufficient data available to support the recommendation of any particular bronchodilator at the start of treatment. A combination of long-acting β_2-agonists with tiotropium achieved greater bronchodilator effect than the administration of either agent alone.[22]

The methylxanthines have been shown to produce slight improvement in clinical and spirometric parameters[23] (level D evidence) and should be regarded as second-line drugs for use in the treatment of patients with symptomatic COPD. However, treatment should only be continued when it is associated with significant clinical improvement and there are no notable adverse effects. The dose should be adjusted according to response with a view to achieving peak drug concentrations in blood of between 5 µg/mL and 15 µg/mL (level D evidence).

Corticosteroids. Treatment with inhaled corticosteroids in moderate-to-severe COPD reduces the number of exacerbations, produces a slight increase in FEV_1, and improves quality of life (level A evidence).[24,25] Although earlier studies indicated that inhaled corticosteroids had a positive effect on survival (level C evidence),[26] a recent multicenter controlled trial failed to demonstrate this effect.[27] The response to inhaled corticosteroids is not uniform and cannot be predicted by response to either systemic corticosteroids or inhaled bronchodilators.[28] Long-term use of systemic corticosteroids is not indicated.

Combination therapy with corticosteroids and long-acting β_2-agonists is indicated in patients with moderate-to-severe COPD in whom it has been shown to produce additional improvement in lung function and symptoms and a greater reduction in frequency of exacerbations (level A evidence).[29-31] A recent 3-year study enrolling patients with an FEV_1 of less than 60% of the predicted value confirmed the positive impact of combination therapy with salmeterol and fluticasone on quality of life and frequency of exacerbations (level A evidence).[27] Those authors also observed a positive effect on lung function evidenced by a smaller decline in FEV_1 (level A evidence), although the improvement in survival did not reach statistical significance. A combination regimen of corticosteroids and long-acting β_2-agonists is indicated in patients who have severe COPD or who report more than 1 exacerbation a year and when withdrawal of such therapy gives rise to clinical deterioration (level A evidence).[32]

Other pharmacological therapies. There is no evidence to support the use of respiratory stimulants, prophylactic antibiotics, antileukotrienes, or nedocromil sodium. The use of purified α_1-antitrypsin is indicated in patients with emphysema who have a homozygous PiZZ phenotype and low serum levels of this enzyme (level C evidence).[3] Treatment with mucolytic-antioxidants has been shown to reduce the frequency of exacerbations (level B evidence).[33] The administration of N-acetylcysteine can reduce exacerbation frequency in patients not being treated with inhaled corticosteroids (level D evidence).[34] There is currently insufficient evidence to support the use of phosphodiesterase-4 inhibitors in these patients.[35]

Oxygen Therapy

Key Points

– Continuous home oxygen therapy increases survival in patients with severe COPD and respiratory insufficiency (level A evidence).

– Home oxygen therapy is indicated when a patient has a PaO_2 (measured when breathing ambient air at sea level) of less than 55 mm Hg, or between 55 mm Hg and 60 mm Hg if accompanied by erythrocytosis or signs of right heart failure (level A evidence). The therapeutic goal is to maintain a PaO_2 of more than 60 mm Hg or a SaO_2 of more than 90% (level D evidence).

– Arterial blood gas analysis is required to establish the indication and provide information on the acid-base balance.

– The effect of oxygen therapy depends on the number of hours a day it is used. The results obtained when oxygen is administered for 18 hours a day are better than those obtained with 12 or 15 hours a day (level A evidence).

Administration of supplemental oxygen for less than 12 hours a day is not recommended.

– When a patient with limited exercise tolerance due to dyspnea does not meet the criteria for continuous oxygen therapy, supplemental oxygen during exercise is indicated if it produces clinical improvement.

– Nocturnal oxygen therapy is indicated in patients who do not meet the criteria for continuous therapy but have prolonged desaturations and either erythrocytosis or signs of right heart failure.

The administration of supplemental oxygen for more than 15 hours a day improves prognosis in patients with COPD and respiratory failure (level A evidence).[36,37] Long-term oxygen therapy does not reduce mortality in patients with moderate hypoxemia (PaO_2 >60 mm Hg).[38] Patient education about the benefits of using supplemental oxygen improves compliance (level D evidence). There is insufficient data available to define criteria for the prescription of home oxygen therapy to patients living at high altitudes or to predict the effects of supplemental oxygen under such conditions. In patients with exercise limitation due to dyspnea who fulfill the criteria for long-term oxygen therapy, supplemental oxygen can be delivered by way of portable systems that facilitate mobility (level C evidence). Supplemental oxygen during exercise can be considered for patients who do not meet the criteria for continuous therapy when there is objective evidence of improvement in symptoms and exercise tolerance (level D evidence). In patients with a daytime PaO_2 of more than 60 mm Hg, nocturnal oxygen therapy can only be considered if the SaO_2 falls below 90% for over 30% of the night, or pulmonary hypertension, right heart failure, or erythrocytosis are present (level D evidence).

Pulmonary Rehabilitation

Key Points

– Pulmonary rehabilitation improves dyspnea, exercise capacity, and health-related quality of life (level A evidence).

– Pulmonary rehabilitation reduces patient use of health care resources and hospital admissions (level B evidence), is cost effective (level B evidence), and improves BODE index scores.

– Rehabilitation programs including extremity exercise and training are the most effective (level A evidence).

– Home-based maintenance programs are a valid alternative to rehabilitation undertaken in the hospital setting from the early stages of the disease (level B evidence).

– Daily activity and physical exercise are beneficial for COPD patients (level B evidence).

– Rehabilitation should be recommended to all patients with COPD who continue to be restricted in their daily activities by dyspnea despite optimal treatment (level A evidence).

Avoiding a sedentary lifestyle, and increasing daily activity and physical exercise are all beneficial strategies for patients with COPD that should be generally recommended (level B evidence).[39] Pulmonary rehabilitation improves symptoms, quality of life, and exercise capacity (level A evidence).[40] Rehabilitation is therefore recommended in patients whose activity is restricted by symptoms despite optimal pharmacotherapy. Home-based maintenance programs are a valid alternative to rehabilitation undertaken in the hospital setting from the early stages of the disease (level B evidence).[41,42] SEPAR and the European Respiratory Society/American Thoracic Society have published specific recommendations on pulmonary rehabilitation.[43,44]

Rehabilitation programs should include lower (level A evidence) and upper (level B evidence) limb training and should incorporate educational components.[43,44] Respiratory muscle training should not be recommended routinely, but can be considered in patients who present with respiratory muscle weakness. To facilitate subsequent evaluation of the results of rehabilitation, the intensity of dyspnea, exercise capacity, and quality of life should be assessed before the patient starts the program. The use of supplemental oxygen during rehabilitation activities has not been shown to improve results among hypoxemic patients.

Home Ventilatory Assistance

Home ventilatory support in stable COPD can be either noninvasive or invasive (via a tracheostomy). Because noninvasive positive pressure ventilation is more comfortable and associated with fewer adverse effects, it is currently the first-line option. This intervention has been associated with only slight benefit in a few controlled studies, and the evidence is still insufficient to support a generalized recommendation in favor of this type of treatment in the routine clinical management of patients with stable COPD.[45,46]

Final Stages of the Disease

The care of patients with very advanced COPD tends to be characterized by shortcomings that stem from the lack of an appropriate definition of the patient's situation.[47] However, recent studies based on a more integrated view of these patients have started to define a prognostic picture of the advanced stages of COPD.[10] It is essential to discuss the relevant issues and plan future care together with the patient and his or her close family and/or friends well in advance. To make advance-care planning decisions, the patient must be in a stable clinical situation, have good cognitive capacity, and be adequately informed about the problems that may arise and the different treatment options available. Decisions about treatment should take into account all the dimensions of the illness (respiratory, emotional, and systemic) and the social repercussions, with the objective of improving the patient's autonomy and quality of life. The plan may vary depending on the course the disease takes.

Exacerbations

Key Points

– A COPD exacerbation is an acute change in the patient's baseline clinical situation (beyond normal day-

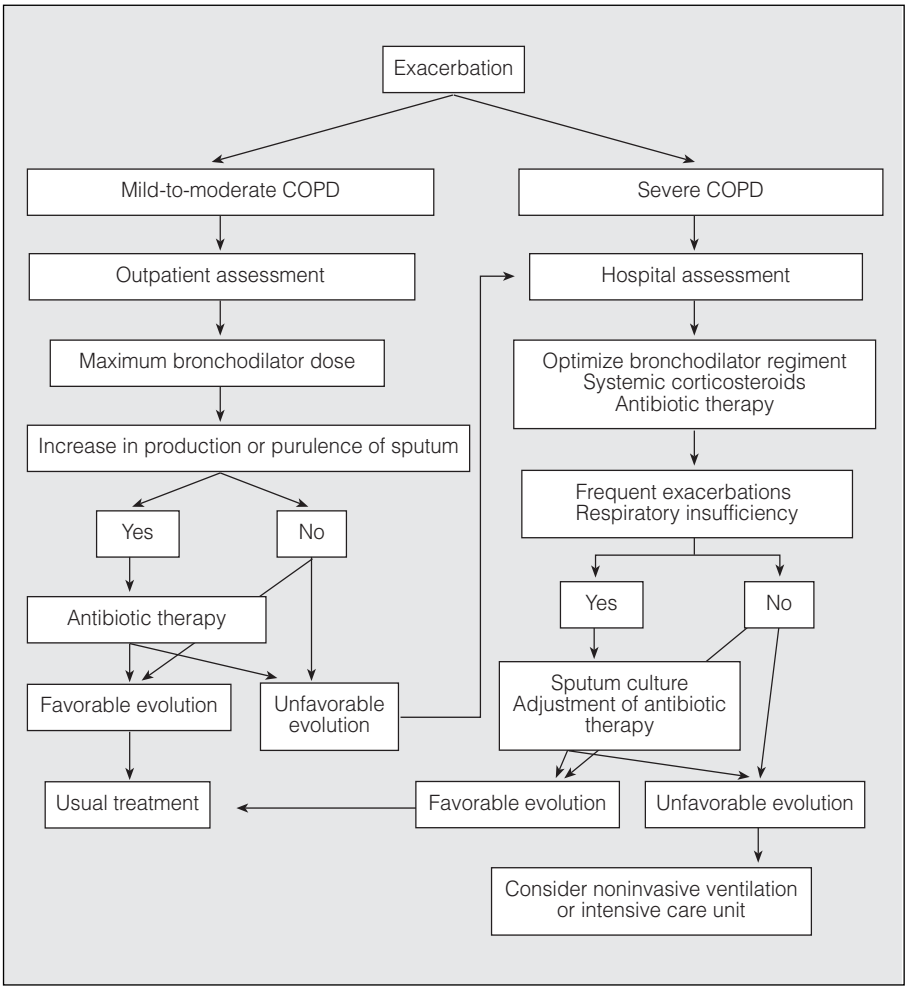

Figure 3. In-hospital and outpatient management of exacerbations of chronic obstructive pulmonary disease (COPD).

to-day variability) characterized by an increase in dyspnea, sputum production, purulent sputum, or any combination of these 3 symptoms, and sufficient to warrant a change in treatment.

– A mild-to-moderate COPD exacerbation can, at least initially, be treated in an outpatient setting.

– During an exacerbation, bronchodilator treatment should be reinforced through the addition of ipratropium bromide and/or a short-acting β_2-agonist, and physicians should aim to reach the maximum optimal dose.

– Systemic corticosteroid therapy is the first-line treatment in exacerbations of severe COPD. In exacerbations of mild-to-moderate COPD, systemic corticosteroid therapy is recommended when the patient has bronchial hyperactivity or when the initial course is unfavorable.

– In 50% to 75% of COPD exacerbations, an infectious agent is isolated in sputum (bacterial in half of the cases and viral in one third).

– In patients with frequent exacerbations or an exacerbation requiring ventilatory support, the infection may be caused by *Pseudomonas aeruginosa.*

– Antibiotic therapy is recommended in exacerbations that present, in addition to dyspnea, with an increase in sputum volume or purulence with respect to the patient's usual baseline.

– The criteria for hospital discharge are based on clinical findings, arterial blood gas parameters and the patient's ability to manage the disease at home.

– Home hospitalization can be as effective as conventional inpatient care in COPD exacerbations.

An exacerbation is defined as an acute change in the patient's baseline clinical situation (beyond normal day-to-day variability) characterized by an increase in dyspnea, sputum production, purulent sputum, or any combination of these 3 symptoms,[48] and sufficient to warrant a change in therapy.

In 50% to 75% of COPD exacerbations, an infectious agent is isolated in sputum (either a virus and/or a potentially pathogenic microorganism). In the remaining cases, the causal agent is not clear, but these exacerbations are very probably related to exposure to air pollution, dust, vapors, or smoke. Exacerbation of COPD must be distinguished from other conditions that may give rise to similar symptoms, such as pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism, and arrhythmia.

The first-line option for patients with mild-to-moderate COPD is outpatient treatment (level D evidence),[49] although all patients with exacerbation of COPD should be re-evaluated within the first 72 hours.

Outpatient Treatment (Figure 3)

During an exacerbation, usual treatment is not suspended but inhalation therapy must be optimized to achieve the maximum bronchodilatory effect. Antibiotics are only used in exacerbations that present, in addition to dyspnea, an increase with respect to the patient's usual baseline in the volume and/or purulence of sputum, and the relevant patterns of bacterial resistance should always be taken into account (Table 2).[50] Oral corticosteroid therapy is recommended (an initial dose of no more than 40 mg/d of prednisone for a maximum of 10 days) in exacerbations of severe COPD and in cases of mild-to-moderate COPD when the initial course is unfavorable (level D evidence).[51]

Hospitalization (Figure 3)

The following tests should be performed in the emergency department: complete blood count, electrocardiogram, chest radiograph, arterial blood gas analysis, in addition to the measurement of creatinine, ions and blood sugar in plasma. When infection with *P aeruginosa* is suspected (because of frequent exacerbations or respiratory insufficiency), a sputum sample should be obtained before antibiotic therapy is initiated.

Home hospitalization has been shown to be as effective as conventional inpatient management in the treatment of COPD exacerbations and is the option preferred by patients,[52] but it can only be used in about one quarter of cases because home treatment is not advised and hospitalization is considered essential when the exacerbation is characterized by signs of severity, such as confusion or a diminished level of consciousness, abnormal chest radiograph, hypercapnia with acidosis, or when the patient has severe comorbidities or insufficient home support. Discharge from hospital should be considered when clinical improvement returns the patient to a situation close to baseline, the patient's clinical condition and arterial blood parameters are stable, and he or she is in a position to manage the disease at home even though hypoxemia or hypercapnia may persist. Early discharge supported by a home-care program is another option that has yielded satisfactory results.[53] Systemic corticosteroid therapy should be tapered gradually and discontinued after discharge. A follow-up visit 2 weeks after discharge is always recommendable since relapse occurs during this period in 25% of patients, usually in cases where there is hypercapnia, a condition associated with a high risk of death during the months immediately following discharge.[54] When patients require supplemental oxygen after discharge, arterial blood gas composition should be analyzed once their condition has stabilized (no earlier than 2 months following discharge) to determine whether they are candidates for long-term oxygen therapy.

TABLE 2
Antibiotic Therapy in Exacerbations of Chronic Obstructive Pulmonary Disease

Circumstances	Drug (Alphabetical Order)	Route of Administration
General	Amoxicillin + clavulanic acid	Oral/parenteral
	Azithromycin	Oral
	Cefditoren	Oral
	Levofloxacin	Oral
	Moxifloxacin	Oral
	Telithromycin	Oral
Suspected infection with *Pseudomonas aeruginosa*[a]	Cefepime	Parenteral
	Ciprofloxacin	Oral/parenteral
	Imipenem	Parenteral
	Levofloxacin	Oral/parenteral
	Meropenem	Parenteral
	Piperacillin-tazobactam	Parenteral

[a]Frequent exacerbations during the preceding year and/or respiratory insufficiency, and only after obtaining a culture specimen of respiratory secretions.

Oxygen Therapy in Exacerbations of COPD

Key Points

– The goal is to achieve a PaO_2 of at least 60 mm Hg without provoking respiratory acidosis.

– A fraction of inspired oxygen (FiO_2) of between 24% and 35% is generally sufficient.

– Initially, the oxygen should be administered using a Venturi type mask; subsequently nasal cannula can be used.

– Response to treatment should be monitored by arterial blood gas analysis. The patient should be monitored 30 minutes after start of treatment and whenever there is a change in FiO_2 or signs of deterioration.

– Pulse oximetry is useful in the monitoring and subsequent adjustment of FiO_2.

The correction of hypoxemia through the administration of supplemental oxygen is one of the most important goals in the treatment of COPD exacerbations. The delivery of oxygen at low concentrations—between 24% and 28%—is usually sufficient to achieve the threshold of clinical safety (PaO_2 >60 mm Hg or SaO_2 >90%).[55] Attention should also be paid to other factors involved in oxygen transport (hemoglobin levels and cardiac output). High concentration oxygen therapy (FiO_2>40%) may give rise to carbon dioxide retention and respiratory acidosis caused by central hypoventilation and deterioration of the ventilation-perfusion ratio. Since patient response varies, an initial arterial blood gas analysis should be performed 20 to 30 minutes after therapy is started.[56] High-flow systems, such as the Venturi mask, are recommended to achieve better control of the oxygen concentration administered. Once the patient improves and the pH value returns to normal, pulse oximetry can be used to reduce the frequency of arterial blood gas analysis. At this stage, oxygen can be delivered by way of nasal cannula, a more comfortable system for the patient.

Mechanical Ventilation in Exacerbations of COPD

Key Points

– Mechanical ventilation is indicated when, despite pharmacotherapy and supplemental oxygen, the patient's pH value remains below 7.35 (level A evidence).

– Mechanical ventilation can be invasive (via an endotracheal tube) or noninvasive.

– Survival among patients with COPD exacerbations who require invasive ventilation is no lower than the rate observed among patients receiving invasive ventilation for other reasons.

Patients with COPD and acute respiratory insufficiency who fail to improve with medical treatment and oxygen therapy may require ventilatory assistance. Since noninvasive ventilatory support significantly reduces mortality, obviates the need for endotracheal intubation, and shortens the length of stay in hospital,[57,58] it should be available 24 hours a day in hospitals that provide care for these patients. It should be implemented by well trained health care personnel, and proper monitoring is essential. Noninvasive ventilatory support should be delivered preferably in an intermediate or intensive care unit, but in selected cases of mild-to-moderate respiratory acidosis (pH, 7.30-7.35) treatment can be administered in a normal hospital ward.[58] A combination of pressure support ventilation (10-15 cm H_2O) and positive end-expiratory pressure (4-6 cm H_2O) has been found to be the most effective form of ventilation. Although most cases can be managed with noninvasive ventilation (preferably using a face mask), in certain circumstances invasive ventilatory support should be used.

Surgical Treatment of COPD

Key Points

– There are a number of surgical interventions that may result in clinical improvement in highly selected patients with very severe COPD.

– Lung transplantation results in improvements in symptoms and lung function (level C evidence). Surgery can be considered in patients under 65 years of age with very advanced disease who meet the general criteria for transplantation.

– Lung volume reduction surgery may result in improved lung function and symptoms in patients with heterogeneous predominantly upper-lobe emphysema and low exercise tolerance (level A evidence).

– In such patients, volume reduction surgery has a positive effect on survival (level B evidence).

– Lung volume reduction surgery is contraindicated in patients with homogeneous emphysema, or an FEV_1 or DLCO under 20% (level A evidence).

– Bullectomy can improve lung function and dyspnea in highly selected patients (level C evidence).

Certain highly selected patients may benefit from surgery (lung transplantation, lung volume reduction surgery, or bullectomy) undertaken to improve pulmonary function, exercise tolerance, symptoms, and quality of life. Lung transplantation, especially when bilateral, results in significant improvement in pulmonary function, gas exchange, exercise tolerance, and quality of life (level C evidence).[59] The question of whether lung transplantation results in significantly improved survival among patients with COPD is still subject to debate. When considering a candidate for transplantation, national and international guidelines specifying the general indications and contraindications for this procedure must be taken into account.[60,61]

Lung volume reduction surgery is a procedure involving resection of the most damaged areas of the parenchyma in patients with severe heterogeneous emphysema. In selected patients (those with heterogeneous predominantly upper-lobe emphysema, low exercise tolerance, and FEV_1 and DLCO >20%), this procedure results in improvements in airflow, exercise tolerance, and quality of life (level A evidence). In a subgroup of patients with heterogenous predominantly upper-lobe emphysema and low baseline exercise capacity, lung volume reduction surgery also had a positive effect on survival in addition to the benefits mentioned above (level B evidence).[62] Since postoperative mortality is higher and the clinical benefits of this surgery are slight in patients with very severe airflow limitation (FEV_1<20% of the predicted value) who have homogeneous emphysema or a DLCO value under 20% of the predicted value, lung volume reduction surgery is not indicated in this subgroup (level A evidence).[63] Two recent articles describe endoscopic lung volume reduction procedures involving the installation of endobronchial valves[64] and the instillation of fibrosing agents,[65] but these procedures must at present be considered experimental.

Some uncontrolled studies have indicated that selected patients with large bullae can benefit from bullectomy (level C evidence).[66] Although no verified selection procedures have yet been defined, the following criteria have been suggested: bullae larger than one third of a hemithorax, radiographic evidence of parenchymal compression, and relatively well preserved lung function.[66] When large bullae are associated with generalized emphysema, bullectomy can give rise to serious complications, making it advisable to consider lung transplantation (level D evidence).

COPD is a known risk factor for postoperative morbidity. The probability of complications increases with the severity of disease and is related to the location of the intervention: thoracic surgery and surgery affecting the upper abdomen are associated with higher risk. SEPAR has recently published guidelines on the preoperative assessment of patients who are candidates for lung resection.[67]

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