

## Spanish Guideline for COPD (GesEPOC). Update 2014

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### Introduction

The publication of the Spanish guideline for chronic obstructive pulmonary disease –COPD– (GesEPOC) has brought about a change in the approach to the treatment of this disease. The recognition of clinical phenotypes and severity rating scales based on the multidimensional BODE/BODEx requires greater involvement of clinicians in the daily care of patients with COPD, but in exchange, they help in customizing the treatment according to the characteristics of each particular patient<sup>1,2</sup>. In the time since its publication, new studies have been published that reinforce or challenge the statements made in the guideline. The professionals involved in the guidelines should provide a regular update on the published advances and place them within the context of the guideline principles. For this purpose, we have prepared this update, which is a prelude to a major revision that shall be carried out 4 or 5 years after the initial publication.

The most innovative aspects in this update are:

1. In order to avoid confusion with the terms used in other guidelines<sup>3</sup>, GesEPOC decided to remove the letter accompanying

clinical phenotypes. Likewise, the non-exacerbator phenotype with emphysema and/or chronic bronchitis, is now termed non-exacerbator phenotype. Therefore, the four GesEPOC clinical phenotypes proposed are the following: *a*) non-exacerbator phenotype; *b*) mixed COPD-asthma phenotype; *c*) exacerbator phenotype with emphysema; and *d*) exacerbator phenotype with chronic bronchitis (Fig. 1).

2. Its contribution to the dissemination of SEPAR guidelines for tobacco dependence treatment in EPOC<sup>4</sup>.

3. The inclusion of two new drugs for the treatment of stable COPD: acilidium and glycopyrronium.

4. The combination of LAMA + inhaled corticosteroids (ICS) has been removed from the list of suggested treatments due to lack of evidence, as suggested in the update of the GOLD document<sup>3</sup>.

### Epidemiology

New issues appearing since the publication of GesEPOC and those released during the past year on the epidemiology of COPD and, in particular, on its screening, can be summarized as:

1. The recently published study by the World Health Organization (WHO) on the Global Burden of Disease (Global Burden of Disease Study –GBD–) 2010<sup>5</sup> updates the previous global estimates of COPD and other respiratory diseases and also provides some new estimates for asthma, sleep related disorders, lower respiratory tract infections,

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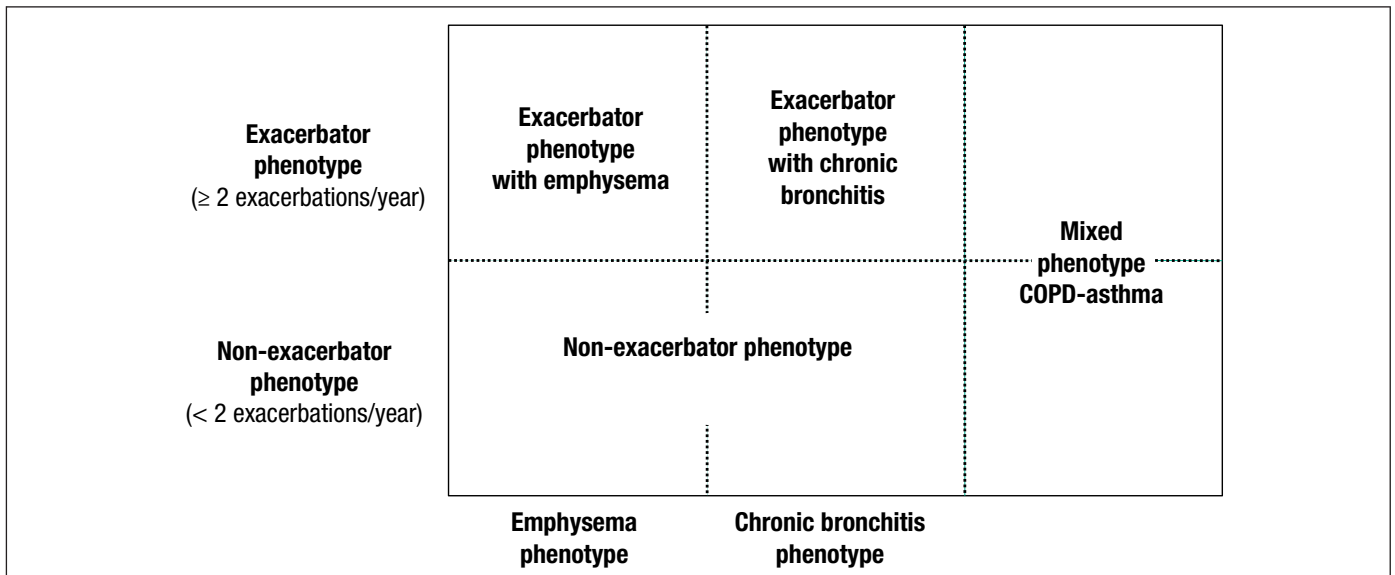


Figure 1. Clinical phenotypes proposed by GesEPOC.

lung cancer and tuberculosis. In general, chronic respiratory diseases accounted for 6.3% of global years lived with disease (YLD), and COPD is the largest contributor (29.4 million YLD), followed by asthma with 13.8 million YLD. In addition, chronic respiratory diseases, as a group, accounted for 4.7% of global disability-adjusted lost years (DALYs)<sup>6</sup>. Regarding COPD, the new information on worldwide mortality and prevalence is as follows: in the global ranking of causes of death, respiratory diseases account for 4 (or 5) positions within the top 10. COPD rose from fourth in 1990 to third in 2010, just below ischemic heart disease and stroke, while tracheobronchitis is now the fourth leading cause of death, lung cancer the fifth, and tuberculosis the tenth. We could also include a significant proportion (up to 1 in 3) of deaths in road accidents (eighth leading cause in this category) associated with sleep apnea<sup>7</sup>.

The 2010 GBD update indicates an increase in the number of people with COPD. The earlier figure in 1990 was 210 million people with COPD worldwide, and the current figure is 328,615,000 (168 million males and 160 million females)<sup>5</sup>.

2. A recent publication of the EPI-SCAN study estimated that, currently, of 21.4 million Spaniards aged between 40 and 80 years, 2,185,764 have COPD. By gender, the figures are 1,571,868 males and 628,102 females. Since 73% is not diagnosed, it can be said that more than 1,595,000 Spaniards do not know they suffer from COPD and, therefore, do not receive any treatment for their COPD<sup>8</sup>. The same study identified a significant geographical variability in the underdiagnosis of COPD, but with a marked predominance in women.

3. Following the proposal of an earlier study of the PLATINO initiative<sup>9</sup>, BOLD expands the option to use the peak expiratory flow (PEF) for the screening of COPD. Thus, in a sophisticated analysis conducted in BOLD participants from 14 countries, the study proposes 2.2 l/m<sup>2</sup>/s as the threshold pre-BD peak flow, expressed in liters per second by height in square meters, to identify moderate to severe COPD<sup>10</sup>. This threshold of 2.2 l/m<sup>2</sup>/s has been proposed because it has the best sensitivity to the positive predictive value and the best cost-benefit ratio in five different scenarios combining PEF, questionnaires and spirometry. Ultimately, BOLD concludes that the measurement of PEF worldwide, without bronchodilation and within the context of any health system, is a fast, cheap and convenient step forward in the improvement of COPD detection, and its authors recommend the measurement and recording of PEF as a standard vital sign, like blood pressure and weight, although its actual effectiveness, particularly in the field of primary care without quality control, needs to be

demonstrated<sup>11</sup>. Until more evidence is available, GesEPOC still recommends the use of the screening questionnaire COPD-PS and spirometry in adults aged over 35, smokers or former smokers with respiratory symptoms (case detection).

#### Comorbidities in COPD

Comorbidities are common in COPD and may complicate diagnosis and treatment. It is also possible that some comorbidity treatments may have a beneficial effect on the course of COPD. This past year has seen the publication of more studies on the potential utility of statins or angiotensin converting enzyme inhibitors in COPD, but these are still retrospective observational studies that reinforce the idea of their utility, but do not confirm it. Several studies with randomized clinical trial design are currently ongoing to prove this hypothesis, but they have not been completed yet.

In a preclinical study in mice<sup>12</sup>, simvastatin pretreatment of mice that were subsequently exposed intensively to tobacco smoke decreased the presence of leukocytes, neutrophils and macrophages in the lung parenchyma, and in the sub-epithelial and interstitial spaces of the airway. This finding may guide further work in humans, designed to explore the mechanism by which simvastatin is involved in inflammation caused by tobacco.

In this line, a case-control study within a broader study with a population-based cohort (Rotterdam study in the elderly –ERGO–)<sup>13</sup> with a follow-up of 17 years analyzed the results of 363 patients with COPD who died during follow-up. These were matched with 2,345 COPD cases, depending on age and gender. The use of statins for over two years reduced mortality by 78% in patients with high sensitivity CRP levels greater than 3 mg/l. These results support the hypothesis of the inflammatory pathway in explaining the effect of statins, further suggesting the existence of a group of patients in whom they would be most useful.

One area of considerable study is the analysis of COPD comorbidities in different scenarios. In this respect, two studies carried out in Spain have studied comorbidities in two different care settings. One study conducted in an area of Madrid<sup>14</sup> with a population of almost 200,000 people attended by 129 general practitioners found a COPD prevalence of 3.2% among the population over 40 years, with 90% of these patients presenting with comorbidities associated with their COPD, and an average of four chronic diseases per patient. After adjustment for age and gender, the prevalence of ten chronic

diseases was higher than expected: heart failure, chronic liver disease, asthma, arteriosclerosis, osteoporosis, ischemic heart disease, anxiety/depression, arrhythmias and obesity.

The Charlson index was used to quantify comorbidities in a study in patients hospitalized for worsening of their EPOC<sup>15</sup>. This index was found to be an independent predictor of mortality, even after adjusting for age, lung function and overall functional status according to the Katz index. An association of comorbidity with the need for admission, duration of hospital stay and readmissions was also observed. This same research group recently published two other studies on the same topic<sup>16,17</sup>.

In the study we describe, the Charlson index was used to quantify the relevance of comorbidities in patients with COPD, but this index does not consider some common comorbidities in these patients. In order to overcome this problem, the authors used a questionnaire and made some corrections. However, another study undertaken by the "BODE collaborative group", a new index was proposed: COTE<sup>18</sup>. With a methodology similar to that used for the calculation of the BODE index, the authors established the risk of death or survival in a given time interval. The diseases scoring in this index, in order of relevance in relation to the worsening prognosis, are certain cancers (lung, esophagus, pancreas or breast), anxiety, any other cancer, liver cirrhosis, atrial fibrillation or flutter, diabetes mellitus with neuropathy, pulmonary fibrosis, congestive heart failure, ischemic heart disease and peptic ulcer.

Finally, notwithstanding the fact that it is not an original study, a recent review should be noted, in which knowledge of the most important comorbidities is updated<sup>19</sup>. An outline of the most common comorbidities of COPD, with its diagnosis and treatment, is presented in Table 1. Pending more evidence allowing the inclusion of new comorbidity indices, assessment of comorbidity in COPD should be carried out individually.

### COPD phenotypes

Following the publication of GesEPOC, new studies provide useful information on the importance of the characterization of clinical phenotypes in COPD, as suggested in the guidelines. Identifying clinical phenotypes may help in determining differential treatment, and to identify groups of patients with different medium and long-term mortality<sup>20,21</sup>. Several recent studies support the identification of the four phenotypes proposed in the GesEPOC guidelines:

- Non-exacerbator phenotype.
- Mixed COPD-asthma phenotype.
- Exacerbator with emphysema phenotype.
- Phenotype exacerbator with chronic bronchitis.

The mixed phenotype is revealed as a clinical reality in a study in primary care setting, where the difficulty for making a differential diagnosis between asthma and COPD was analyzed<sup>22</sup>. In this study, 11% of patients could not be classified by their physicians, as they presented characteristics of both diseases.

Another study supporting the characterization of this phenotype is that of Jamieson et al.<sup>23</sup>, which identifies a group of patients with COPD, defined as allergic phenotype. These were characterized by having a positive sensitization to airborne allergens, and allergic symptoms of upper airway, showing that they are more symptomatic and have a higher risk of exacerbations.

This clinical reality is also endorsed in the EPI-SCAN study, conducted at the population level, in which 17% of subjects were classified as mixed COPD-asthma phenotype, characterized by more dyspnea, wheezing, poorer quality life, less physical activity, and frequent exacerbations<sup>24</sup>. Importantly, in these three studies, the criterion used to identify the mixed COPD-asthma phenotype was only having a previous diagnosis of asthma. GesEPOC proposes

additional criteria that may affect the actual prevalence figures of this clinical phenotype, although validation is needed.

The importance of identifying the chronic bronchitis phenotype lies in the fact that bronchial hypersecretion in COPD is associated with increased airway inflammation and increased risk of respiratory infection. Recent studies show that the presence of microorganisms in the lower respiratory tract induces low-grade inflammation, thus favoring exacerbations and further deterioration of lung function. Therefore, this should be considered as chronic infection and not as mere colonization<sup>25</sup>. Furthermore, the presence of bacterial load in the airways during the stable phase is associated with a greater severity of obstruction<sup>26</sup>, and isolation of *Pseudomonas aeruginosa* in sputum after hospitalization for an exacerbation of COPD is associated with increased long-term mortality, regardless of the severity of COPD as measured by BODE, and comorbidities<sup>27</sup>. In patients with chronic bronchitis and recurrent exacerbations, the presence of bronchiectasis should be assessed, as this will have a negative impact on survival<sup>28</sup>. Some authors have suggested the existence of a specific COPD-bronchiectasis clinical phenotype<sup>29</sup>, while others<sup>25</sup> suggest the possibility of an infectious clinical phenotype. Possibly, both features of the disease are associated; GesEPOC recognizes the need to identify bronchiectasis and chronic bronchial infection in patients of exacerbator phenotype with chronic bronchitis. Maybe in the future they can be considered as clinical phenotypes with their own clinical relevance. However, we believe that the guideline, in its original version, already includes both aspects.

From the analysis of the COPD-Gene study cohort, we know that the emphysema phenotype is associated with increased mortality, although this phenotype will be characterized by a lower association with exacerbations than the chronic bronchitis phenotype, except in the most severe forms, with an involvement of more than 30%<sup>30</sup>. Therefore, this clinical form will identify patients with a worse prognosis, increased mortality and greater annual decline in forced expiratory volume in one second (FEV<sub>1</sub>)<sup>31</sup>. A recent study<sup>32</sup> has also found an association between emphysema and increased mortality, both overall and due to lung cancer.

Identifying patients with the exacerbator phenotype is based on prior history of exacerbations reported by the patient, and defines patients with a poorer prognosis, both in terms of mortality and greater annual decline in FEV<sub>1</sub>, as evidenced by the ECLIPSE<sup>33</sup> cohort study.

On the other hand, recent data from the analysis of COPD-Gene and ECLIPSE cohorts, performed by Wells et al.<sup>34</sup> have identified another risk factor associated with severe exacerbations, related to the enlargement of the pulmonary artery. This study establishes as cutoff a pulmonary artery/aorta ratio (PA/A) > 1, measured by computed tomography (HRCT). Systemic inflammation, as assessed through a combination of several inflammatory mediators, has also been associated with the presence of future exacerbations, although it is still unknown whether this systemic inflammation is the cause or the consequence of exacerbations<sup>35</sup>.

### Severity rating. Multicomponent indices

In recent decades, the classification of COPD severity has been based almost exclusively on determining the degree of airflow limitation, assessed by FEV<sub>1</sub> expressed as percent of predicted value after bronchodilator test (FEV<sub>1</sub> [%]). However, COPD is a heterogeneous disease and the data obtained from a single parameter such as FEV<sub>1</sub> do not allow for stratification of patients with sufficient reliability.

In order to assess the severity of the disease, GesEPOC guidelines recommend the use of the BODE index, which is considered the best validated and of wider use. Alternatively, if the walking test is not available, and also in the initial stages of the disease, the BODEx index can be used (replacing the walking test for a record of severe exacerbations in the previous year). In patients with more severe

**Table 1**  
Highlights of major comorbidities in COPD patients

Comorbidity	Epidemiological features	Diagnostic features	Therapeutic features
Heart failure	<p>P: 9% in GP/25% in COPD patients aged over 65 years</p> <p>Mortality: 31% in GP/71% in COPD during 5-year evolution</p> <p>Mortality: 12.1% in GP/25.6% in elderly patients with COPD during 5 years of evolution</p>	<p>Difficult diagnosis: presents symptoms in common with COPD</p> <p>80% of HF is not diagnosed in COPD</p> <p>Echocardiography is useful for diagnosis Cardiovascular MRI if images obtained by echocardiography are not good</p> <p>HF predictors: previous history of HF, obesity, HR &gt; 90 ppm, NT-proBNP &gt; 125 GP/ml, ECG changes</p>	<p>The treatment in COPD can be the same as used in GP</p> <p>Cardioselective beta-blockers are useful in HF. They decrease overall mortality and exacerbations in COPD</p> <p>Ivabradine and digoxin may also be used</p> <p>Diuretics are useful if there is fluid retention. Avoid high doses. Aldosterone system inhibitors are also useful</p> <p>The use of inhaled long-acting beta-2-agonists is safe in patients with COPD and HF</p> <p>Inhaled long-acting anticholinergic agents are also safe</p> <p>Inhaled corticosteroids do not cause problems in patients with HF. Oral corticosteroids administered in one-week cycles in case of exacerbations are also well tolerated in patients with HF. Systemic corticosteroids for long-term treatment may be harmful, as they produce sodium and water retention</p>
Ischemic heart disease	<p>P: 3% in GP/9% in COPD</p> <p>Mortality of acute coronary syndrome: 9% in GP/21% in COPD</p> <p>8.3% incidence of AMI in the 30-day period after COPD exacerbation</p>	<p>Some common symptoms with COPD: chest pain in exacerbations, dyspnea as anginal equivalent</p>	<p>Beta-blockers may reduce exacerbations and improve survival in patients with COPD</p> <p>Statins may reduce overall mortality, exacerbations, admissions, intubations and deterioration of FEV<sub>1</sub></p> <p>ACE inhibitors + statins reduce hospitalizations and mortality due to AMI</p> <p>COPD worsens the outcomes of coronary reperfusion techniques Oxygen therapy and pulmonary rehabilitation have not shown benefit in IHD</p>
CVA	<p>P: 3.2% in GP/9.9% in COPD</p>		
Lung cancer	<p>Incidence 2-5 times higher in COPD than in GP</p> <p>Incidence is increased: obstruction severity and the presence of signs of emphysema</p> <p>Mortality: 40 in 100 patient-years in GP/75 in 100 patient-years in COPD</p> <p>Survival: 26% in GP/15% in COPD in the first 3 years</p>	<p>Development of techniques for early diagnosis of lung cancer in patients with COPD is needed (low-dose CT for screening)</p>	
Anxiety	<p>P: 5.1% in GP/16% in COPD</p> <p>Dyspnea-related panic attacks in advanced stages</p>		<p>Start with cognitive therapy</p> <p>Use selective serotonin reuptake inhibitors, venlafaxine or imipramine, as drug therapy</p> <p>Avoid long-term benzodiazepines</p> <p>Pulmonary rehabilitation is helpful in reducing the incidence of anxiety in patients with COPD</p>
Depression	<p>P: 12% in GP/25% in COPD</p> <p>Factors that increase the risk of depression: dyspnea, severity of obstruction, ambulatory oxygen therapy, recent exacerbation, low scores in HRQOL questionnaires or lack of family support</p> <p>Increases mortality in patients with COPD</p>	<p>Depression should be actively screened in patients with COPD</p> <p>Various scores may be used, especially the HADS (Hospital Anxiety and Depression Scale), Hamilton scale for anxiety and the Geriatric Depression Scale</p>	<p>Selective serotonin reuptake inhibitors are recommended</p> <p>Alternatives: venlafaxine and mirtazapine</p> <p>Pulmonary rehabilitation is helpful in reducing the incidence of depression in patients with COPD</p>
Diabetes mellitus	<p>Metabolic syndrome and type II DM are 1.5 to 3 times more common in patients with COPD</p>		<p>Useful measures for COPD and metabolic syndrome: control of risk factors (smoking, obesity, sedentary lifestyle, dyslipidemia, hypertension)</p>

Continued on next page

**Table 1**  
Highlights of major comorbidities in COPD patients (continuation)

Comorbidity	Epidemiological features	Diagnostic features	Therapeutic features
Osteoporosis	P: 5% in GP/24% in COPD  Factors that increase the risk of osteoporosis: obesity, smoking, use of oral corticosteroids, age, severity of obstruction, emphysema		Calcium plus vitamin D supplements can prevent osteoporosis  Bisphosphonates are useful for preventing fractures in patients with osteoporosis and in patients on long-term treatment with oral corticosteroids
Hypertension	P: 34% in GP/40-60% in COPD		Same treatment as used for GP
OSAS	P: 5% in GP/5% in COPD  OSAS increases the mortality and hospitalization risks		Better prognosis with CPAP
Pneumonia	Factors that increase the risk of CAP: age, severity of obstruction, worsening in the last year, worse results in the dyspnea score, low BMI or use of inhaled corticosteroids (alone or in combination)  Pneumonia causes < 1% of mortality in COPD		
Chronic kidney disease	P: 10% in GP/21% in COPD		

CVA: cerebrovascular accident; IHD: ischemic heart disease; CPAP: continuous positive airway pressure; HRQOL: health-related quality of life; DM: diabetes mellitus; ECG: electrocardiogram; HR: heart rate; HAD: hospital anxiety and depression; AMI: acute myocardial infarction; HF: heart failure; ACE: angiotensin-converting enzyme; CAP: community-acquired pneumonia; NT-proBNP: amino-terminal pro-brain natriuretic peptide; P: prevalence, GP: general population; OSAS: obstructive sleep apnea syndrome; CT: computerized tomography.

disease, BODE should always be used, provided that patient characteristics allow for it. Additionally, an alternative assessment of severity is provided, based on FEV<sub>1</sub> (%), dyspnea level, physical activity level, and severe exacerbations.

The most significant developments since the publication of the GesEPOC guidelines have been based on validation and comparison of previous indices in different populations, as well as the reevaluation of some of them in larger cohorts, and the development of new indices for patient subpopulations.

The COCOMICS study (COllaborative COhorts to assess Multicomponent Indices of COPD in Spain) pools individual data from 11 Spanish cohorts with a longitudinal follow-up for mortality. Overall, 3,633 patients were included in the study, with a total follow-up of 15,878 person-years. Thanks to the large number of patients and the long follow-up, COCOMICS was able to compare the prognostic reliability of existing indices (BODE, BODEx, ADO and DOSE, among others) for mortality, both short- (6 months), medium- and long-term (10 years). The main conclusion was that none of the indices was able to reliably assess short-term mortality, while the medium- and long-term predictive reliability of ADO was superior to other indexes. However, after adjusting for age, those that kept better prognostic reliability were BODE and BODEx, which are recommended by GesEPOC<sup>36</sup>.

Two other studies have shown the usefulness of DOSE index—initially developed to predict the risk of exacerbations—in assessing the risk of mortality and impaired quality of life<sup>37,38</sup>. In another study conducted in 183 outpatients, BODE, ADO and DOSE were all three good predictors of exacerbation risk in the year after study enrollment, although the predictive ability of DOSE was superior<sup>39</sup>. Meanwhile, Puhan et al.<sup>40</sup> published an adaptation of the ADO applied to 10 cohorts with 13,914 patients. The new classification of 15 points improved the original, although the weight given to age still seems excessive (being between 60 and 69 years of age rates the same as presenting FEV<sub>1</sub> ≤ 35% or a dyspnea grade 4 in mMRC).

Other studies have attempted to validate the prognostic ability of the multidimensional assessment proposed by the GOLD guidelines with similar results. Overall, the GOLD proposal does

not improve the predictive ability of previous proposals (GOLD 2007), although it identifies the increased risk of exacerbation/hospitalization. The COCOMICS initiative showed that the new GOLD classification resulted in an uneven distribution of patients, with an accumulation of two-thirds in groups A (low risk, few symptoms) and D (high risk, more symptoms), and only 16% and 17% in groups B (low risk, more symptoms) and C (high risk, fewer symptoms). In addition, the new classification was not better than the prior system based solely on FEV<sub>1</sub> (%), and produced an inversion of the mortality risk in the early years between the B and C groups, with a greater burden of mortality in group B, supposedly a low risk group<sup>41</sup>. These findings have been endorsed in other publications<sup>42-44</sup>. More recently, in a new analysis of the ECLIPSE study data, Agustí et al.<sup>45</sup> also found an increased risk of mortality and hospitalization in group B than in C, probably due to a higher burden of comorbidity in these patients.

Possibly, given the complexity of COPD, new multicomponent scales will appear in future that better fit the prognostic prediction in different subpopulations and clinical phenotypes<sup>46</sup>. In the meantime, the GesEPOC guidelines continue to recommend the use of the BODE/BODEx severity scales.

### Treatment of tobacco dependence in smokers with COPD

The SEPAR recommendations for the treatment of tobacco dependence in smokers with EPOC have been recently published<sup>4</sup>. These constitute the most important development in this section.

This new guideline provides a novel diagnostic and therapeutic approach, depending on whether patients with newly diagnosed COPD or patients with previous diagnosis are treated.

#### Diagnostic intervention for tobacco dependence in smokers with COPD

##### Diagnosis in smokers with newly diagnosed COPD

The following protocol should be used to carry out the correct diagnosis of the smoking habit: ascertain the number of packages/



year (NPY); identify the level of motivation to quit smoking; study the degree of physical dependence on nicotine using the Fagerström test; reward test; analyze the previous attempts to quit smoking, and determine the CO levels in the subject's exhaled breath. On occasion, and if available, the determination of cotinine in body fluids, especially in serum, would be appropriate.

The diagnosis of tobacco dependence can be made considering all the data obtained when analyzing the different variables, according to four aspects: *a)* smoking degree; *b)* motivation to quit; *c)* degree of physical dependence on nicotine; and *d)* type of reward.

#### Diagnosis in smokers with previously diagnosed COPD

Up to 30–70% of patients with COPD continue smoking, despite being diagnosed with this process, and having been advised by their doctor several times on the advisability of quitting smoking. Among these patients, the smoker should be approached in a specific manner and should be engaged by the doctor with empathy, respect and understanding of the patient.

The most important aspects to be addressed in this group of subjects are the identification of tobacco consumption, oximetry, cotinine determination in body fluids (especially in serum), analysis of the degree of physical dependence on nicotine, analysis of the degree of motivation to quit, self-efficacy analysis, mood assessment, and assessment of previous attempts to quit smoking.

#### Therapeutic intervention for tobacco dependence in smokers with COPD

The therapeutic intervention for the smoking habit of these patients combines cognitive-behavioral therapy (CBT) with pharmacological treatment (Fig. 2):

#### Cognitive behavioral therapy for smokers with newly diagnosed COPD

This type of intervention in this subgroup of patients should include the following aspects:

– Explanation of the intimate relationship between smoking and COPD. Subjects should be informed that tobacco consumption is the

direct cause of their illness. They should also be alerted to the following points: *a)* Smoking cessation is the only therapeutic measure that has been shown effective in improving their condition; *b)* the efficacy of pharmacological treatments for their disease is very low if they continue to smoke; and *c)* on the contrary, a marked improvement in the course of their disease and the response to COPD treatment will follow smoke cessation.

– In those smokers who feel ready to make a serious attempt at quitting smoking, the intervention shall be devoted to the choice of the day of quitting (D-day), the identification of high-risk situations, the development of alternative behaviors, and the explanation of the symptoms of withdrawal syndrome and its evolution, combined with the dispensation of health information brochures on smoking and COPD, with self-help brochures for quitting smoking.

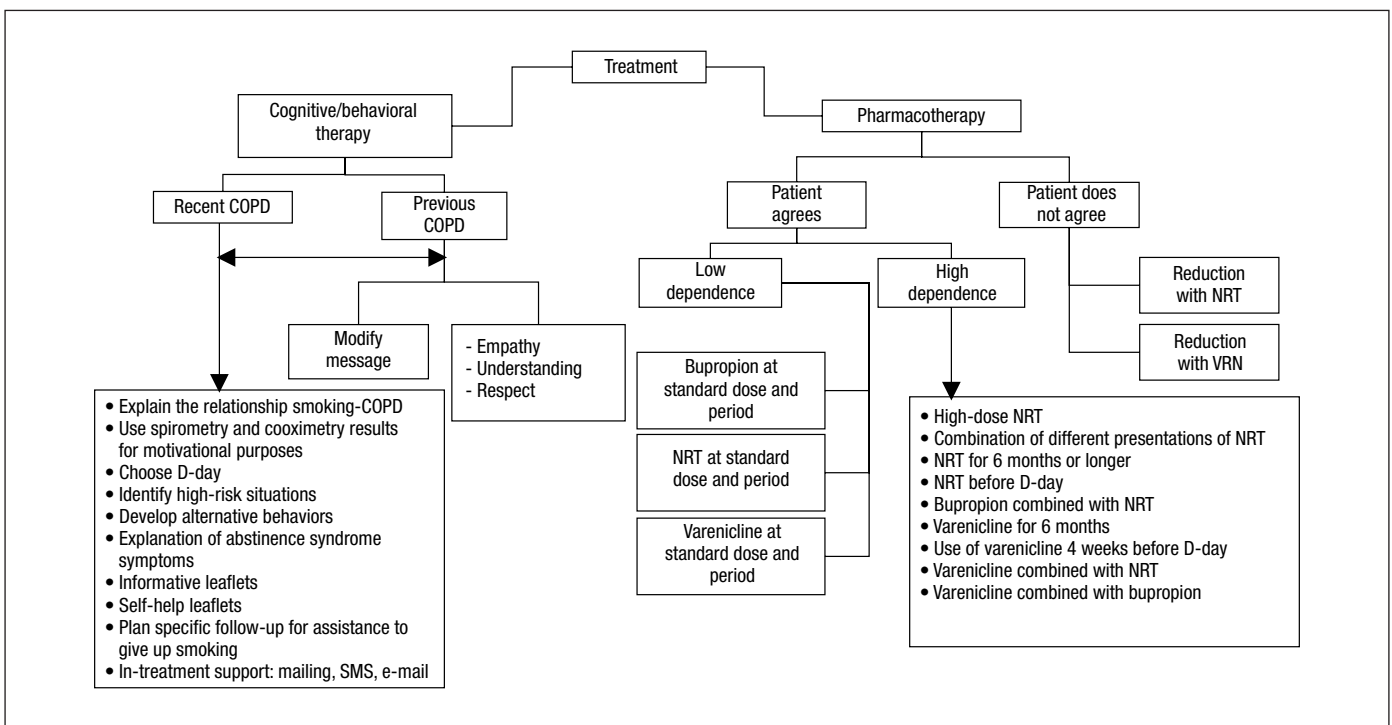
– In the case of smokers who are unwilling to make a serious attempt at the time, the need to stop smoking will be emphasized in each of the visits to their doctor or nurse. The emphasis will be made with empathy, warmth, and understanding, but firmly while offering all kinds of help.

#### Cognitive behavioral therapy for smokers with previously diagnosed COPD

The components of cognitive behavioral therapy (CBT) for these patients should be the same as those described in the previous section. However, an appropriate health intervention in these patients, who have previously been in contact with health professionals, requires us not only to change our message, but also how it is offered. Therefore, the intervention in these subjects should be carried out with empathy, respect, and understanding with the aim of increasing the patients' motivation, self-efficacy and self-esteem.

#### Pharmacological treatment of smoking in smokers with COPD who want to make a serious attempt to quit smoking

Pharmacological treatment of tobacco dependence in smokers with COPD is mandatory. The characteristics of this type of



**Figure 2.** Therapeutic intervention in smokers with COPD. NRT: nicotine replacement therapy; VRN: varenicline.

smokers and the urgent need for them to quit the habit always requires the use of drug treatment, and sometimes intensively. In patients who want to attempt to quit, the recommended treatments include nicotine replacement therapy (NRT), bupropion and varenicline.

*Pharmacological treatment of tobacco dependence in smokers with COPD who do not want to make a serious attempt to quit smoking at present*

In this group, the need to make a serious attempt to quit smoking should be stressed in all follow-up visits. The use of drugs such as NRT and varenicline has been shown in some studies to effectively and safely help patients quit smoking who, while not wanting to quit at the time, were willing to reduce their consumption.

### Treatment of COPD in stable phase

The basis of the pharmacological treatment of COPD are long-acting bronchodilators. During the first half of 2013 two new long-acting antimuscarinic agents (LAMAs) have been marketed in Spain.

Aclidinium bromide is a new inhaled LAMA with little systemic activity, developed for the maintenance treatment of COPD. It hydrolyzes rapidly to inactive metabolites, resulting in very low circulating concentrations after inhalation, which suggests a low potential for systemic adverse effects<sup>47</sup>.

The recommended dose is 322 µg twice a day, which has shown improvements of 124 ml mean in trough FEV<sub>1</sub> at 12 weeks compared placebo (95% confidence interval [95% CI], 83-164 ml) and of 192 ml in peak FEV<sub>1</sub> (95% CI, 148-236 ml). In secondary variables, aclidinium also showed a statistically significant improvement over placebo in quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ), although without reaching the average improvement of 4 units, and a significant improvement in the transition dyspnea index<sup>48</sup>.

Maltais et al.<sup>49</sup> conducted a study in 181 patients, who were treated with 200 µg aclidinium or placebo once a day for 6 weeks in order to see the effect of the drug on exercise tolerance. Patients treated with aclidinium significantly increased their exercise tolerance time above the threshold considered clinically significant. This result was similar to the magnitude observed in studies with tiotropium<sup>50</sup>.

In a double-blind, crossover study comparing aclidinium 400 µg/12 h versus tiotropium 18 µg/24 h and placebo in three treatment periods of 15 days, both bronchodilators showed significant improvement in lung function over placebo. Interestingly, the area under the curve in lung function as measured by serial FEV<sub>1</sub> in the second 12-hour interval of the day (night time) was significantly higher for aclidinium versus tiotropium ( $p < 0.05$ )<sup>51</sup>. This improvement in spirometric values resulted in an improvement in nocturnal symptoms (secondary endpoint of the study), although it should be noted that a duly validated questionnaire was not used for the assessment of nocturnal symptoms<sup>51</sup>. In a more recent phase IIIb study, aclidinium 400 µg/12 h was compared with placebo and tiotropium 18 µg/24 h for 6 weeks. Pulmonary function expressed as area under the curve of FEV<sub>1</sub> between 0 and 24 h and between 12 and 24 h was higher with aclidinium and tiotropium than with placebo, with no significant differences between them. However, only aclidinium significantly reduced the severity of respiratory symptoms in the morning and the nocturnal symptoms versus placebo<sup>52</sup>. The importance of dosing every 12 h on the improvement of nocturnal symptoms in COPD is a new aspect that requires further research.

Glycopyrronium bromide is a LAMA developed to be inhaled. It displays a quaternary ammonium structure that minimizes its oral bioavailability, which should reduce potential systemic effects of possible ingestion of the inhaled dose<sup>53</sup>. The recommended dose of 50 µg every 24 h has been shown to produce significant bronchodilation

throughout the day. In a double-blind study versus placebo for 26 weeks, glycopyrronium demonstrated an improvement in trough FEV<sub>1</sub> of 108 ml (standard deviation 14.8 ml;  $p < 0.001$ ). Additionally, it improved FEV<sub>1</sub> over time, compared to placebo, in the measurements obtained for 24 h throughout the study. The transition dyspnea index improved 1.04 units on average ( $p < 0.001$ ) and SGRQ score improved 2.81 units versus placebo ( $p < 0.004$ )<sup>54</sup>.

In a placebo-controlled, double-blind study of 1-year duration with an open-label tiotropium arm, glycopyrronium demonstrated a 97 ml improvement in trough FEV<sub>1</sub> versus placebo, and 83 ml of tiotropium versus placebo (both significant with  $p < 0.001$ ). Glycopyrronium also reduced the risk of moderate or severe exacerbations by 34% compared to placebo ( $p = 0.001$ ). Differences between glycopyrronium and placebo and between tiotropium and placebo were comparable for all evaluation parameters<sup>55</sup>.

In a more recent study, Beeh et al.<sup>56</sup> showed that treatment with glycopyrronium was superior to placebo in exercise tolerance, measured in a submaximal exercise test with a cycle ergometer, and produced statistically significant changes in inspiratory capacity at rest and during exercise.

Another feature of glycopyrronium is its rapid onset of action compared to the rest of LAMAs. It has been suggested that this faster action would allow the improvement of morning symptoms and activity of patients during the morning. The clinical significance of these differences should be demonstrated in studies specifically designed for this purpose.

In summary, aclidinium and glycopyrronium are two valid alternatives for first-line bronchodilator therapy in COPD. They have some minor differences among themselves and in relation to tiotropium, but none of these differences supports a recommendation for a particular LAMA. The new list of COPD drugs is presented in Table 2.

Regarding long-acting beta-adrenoceptor agonists (LABAs), a combined analysis of multiple clinical trials showed that indacaterol at a dose of 150 µg was more effective in improving lung function, dyspnea and quality of life in patients with FEV<sub>1</sub> > 50% not taking inhaled corticosteroids (ICS), whereas doses > 300 µg were more effective than the 150 mg dose in more severely ill patients (FEV<sub>1</sub> < 50%) and/or patients with concomitant medication with ICS<sup>57</sup>.

In the area of prevention, the new 13-valent pneumococcal conjugate vaccine confers greater immune response, even in patients over 70 who have previously been immunized with pneumococcal polysaccharide vaccine<sup>58</sup>. This is especially relevant for COPD, because it confers a high risk of invasive pneumococcal disease<sup>59</sup> and most patients are elderly, so vaccination should be recommended. Consequently, the SEPAR tobacco dependence workgroup also recommends pneumococcal vaccination with a single dose of 13-valent pneumococcal conjugate vaccine (PCV13) in all smokers, regardless of age and consumption intensity and/or load who suffer respiratory diseases such as COPD<sup>60</sup>.

### Treatment by phenotypes

#### Non-exacerbator phenotype

The mainstay of treatment for the non-exacerbator phenotype are long-acting bronchodilators, initially as monotherapy and in combination in severe cases.

In this regard, the publication of the studies INTRUST 1 and 2 is to be noted. These investigated the efficacy and safety of the combination of indacaterol and tiotropium compared to tiotropium monotherapy in double-blind treatment for 12 weeks. The results showed that the administration of both drugs improved pulmonary function, measured by the area under the curve of FEV<sub>1</sub> (130 and 120 ml for each study,  $p < 0.001$ ) and trough FEV<sub>1</sub> (80 and 70 ml,  $p < 0.001$ ). A significant improvement of the inspiratory capacity with the administration of both bronchodilators ( $p < 0.001$  for 130 and 100

**Table 2**  
Features of bronchodilators for COPD treatment

	Active ingredient	Presentation	Recommended dose	Maximum dose	Action initiation	Maximum effect	Action duration
Beta-2 adrenergic	Salbutamol	PICS: 100 µg/inh	200 µg/4-6 h	1.600 µg/day	40-50 s	15-20 min	3-6 h
	Terbutaline	TH: 500 µg/inh	500 µg/6 h	6 mg/day	40-50 s	15-30 min	4-6 h
	Salmeterol	PICS: 25 µg /inh	50 µg/12 h	200 µg/day	20 min	3-4 h	12 h
		AH: 50 µg/inh					
	Formoterol	PICS: 12 µg inh	12 µg/12 h	48 µg/day	1-3 min	2 h	12 h
TH: 9 µg/inh							
AL: 12 µg/inh							
Indacaterol	BH: 150 µg/inh	150 µg/24 h	300 µg/day	1-3 min	2 h	24 h	
	BH: 300 µg/inh						
Antimuscarinics	Ipratropium bromide	PICS: 20 µg inh	20-40 µg/6-8 h	320 µg/day	15 min	30-60 min	4-8 h
	Tiotropium bromide	HA: 18 µg/inh	18 µg/24 h	18 µg/day	30 min	3 h	24 h
		RM: 5 µg /inh	5 µg/24 h	5 µg/day			
	Aclidinium	GE: 322 µg/inh	322 µg/12 h	644 µg/day	15-30 min	2 h	12 h
Glycopyrronium	BH: 44 µg/inh	44 µg/24 h	44 µg/day	5 min	2 h	24 h	
Methylxanthines	Theophylline	Orally: 100-600 mg	5-6 mg/kg (loading)	2-7 mg/kg/12 h	3 h	6 h	12 h
			2-7 mg/kg/12 h (maintenance dose)				

AH: Accuhaler®; AL: Aerolizer®; BH: Breezhaler®; ICS: inhaled corticosteroids; HA: Handihaler®; PICS: pressurized inhalation cartridge; GE: Genuair®; inh: inhalation; TH: Turbuhaler®; RM: Respimat®.

ml over tiotropium) was also observed. There was no difference in the incidence of adverse effects. These results support the recommendation to combine various long-acting bronchodilators of different mechanism of action in symptomatic patients despite monotherapy<sup>61</sup>.

GesEPOC recommended as second-line treatment in non-exacerbator patients two long-acting bronchodilators with different mechanisms (LABA + LAMA). This treatment choice is supported by the results of the ILLUMINATE study, which compared treatment with indacaterol/glycopyrronium administered in one single device (Breezhaler®) once a day versus salmeterol/fluticasone (50/500) administered twice a day via Accuhaler® in patients with moderate to severe COPD who had not experienced any exacerbation during the year preceding their inclusion in the trial<sup>62</sup>. The indacaterol/glycopyrronium combination was superior to salmeterol/fluticasone in the principal study parameter, area under the FEV<sub>1</sub> curve from 0 to 12 h at week 26 (difference 138 ml, 95% CI, 100-176 ml; p < 0.0001). But the most interesting finding was that there was no increase in the frequency of adverse effects, including worsening of COPD, among patients treated with bronchodilators without ICS. Among the patients randomized to indacaterol/glycopyrronium group, 32.9% were taking ICS chronically before randomization. Nevertheless, there was no increase in the worsening of COPD in this group after discontinuation of ICS<sup>62</sup>. These results support the recommendation of bronchodilator therapy without antiinflammatories in patients of non-exacerbator phenotype, and suggest no significant effect on increased risk of exacerbation due to the withdrawal of ICS in this selected population.

#### Mixed asthma-COPD phenotype

A double-blind, placebo-controlled study investigated tiotropium in adult patients with severe asthma with or without emphysema. All patients were receiving ICS and LABA. Improvement of FEV<sub>1</sub> was observed in both groups: 12.6% in FEV<sub>1</sub> (%) in patients with asthma

and emphysema and 5.4% in those without emphysema. This study supports the use of tiotropium as part of triple therapy in patients with mixed COPD-asthma phenotype<sup>63</sup>.

#### Exacerbator phenotype with chronic bronchitis

An example of treatment according to phenotype can be found in clinical trials with roflumilast. A recent study in patients with frequent exacerbator phenotype (defined as a history of at least two exacerbations in the previous year) and chronic bronchitis has shown that treatment with roflumilast was effective in converting the frequent exacerbators in infrequent exacerbators, and in preventing more often exacerbations among infrequent exacerbators. This effect was independent of concomitant LABA or ICS<sup>64</sup>. This study supports the recommendation of treatment with roflumilast from the second stage of severity in patients with chronic bronchitis and exacerbator phenotype.

A recent Cochrane review on the efficacy of treatment with mucolytics in the prevention of COPD exacerbations has provided more evidence for the use of these compounds in patients of exacerbator phenotype with chronic bronchitis. Thirty studies involving 7,430 patients were reviewed, and the main conclusion was that treatment with mucolytics was associated with a discrete but significant reduction in the frequency of exacerbations, with no changes in quality of life or lung function. Mucolytics were not associated with increased adverse effects or mortality. In general, exacerbation was prevented in one of seven patients, if treated for at least 10 months. The authors concluded that mucolytics should be considered especially for patients who are not candidates for other therapies, such as ICS<sup>65</sup>.

A randomized, double-blind clinical trial conducted in China compared the treatment with N-acetylcysteine (NAC) at doses of 600 mg twice a day with placebo for one year in 120 patients. Patients had COPD with mean postbronchodilator FEV<sub>1</sub> (%) between 58.6 and 60.6%, and all had had at least one exacerbation in the previous year.



Patients on high-dose NAC significantly improved the function of the small airways and showed a significant reduction in the frequency of exacerbations from 1.71 exacerbations/year in the placebo group to 0.96 in the NAC group ( $p = 0.019$ ). There were no differences between groups in dyspnea, quality of life and the distance walked in the 6-minute walking test. It is worth remarking that between 74 and 84% of patients, depending on the group, were receiving concomitant ICS<sup>66</sup>. This study supports the recommendation to consider treatment with mucolytics in exacerbator patients, especially if they have chronic bronchitis.

In exacerbator patients, the LAMA + ICS treatment option has been removed due to lack of evidence (Table 3).

#### Exacerbator phenotype with emphysema

In patients with exacerbator phenotype, emphysema and severity levels III or IV, GesEPOC recommends triple therapy LAMA + LABA + ICS. Wedzicha et al.<sup>67</sup> published a study that supports this recommendation. This is a double-blind clinical trial comparing the combination of indacaterol/glycopyrronium once a day administered in a single device (Breezhaler<sup>®</sup>) versus glycopyrronium with an open-label tiotropium arm, for 1 year. The study population consisted of patients with  $FEV_1 < 50\%$  of the theoretical value who had had at least one exacerbation in the previous year. It is noteworthy that 75% of patients were receiving ICS before and during the study, so, in these cases, the patients in the indacaterol/glycopyrronium group were receiving triple therapy. The main study parameter was the incidence of exacerbations, and the results showed a significant 12% reduction in the rate of moderate or severe exacerbations versus glycopyrronium ( $p = 0.038$ ), and a 15% reduction in the total number of exacerbations ( $p = 0.0012$ ). The results with glycopyrronium and tiotropium were superimposable. This study demonstrates for the first time that dual bronchodilation is superior to treatment with a LAMA in preventing exacerbations in COPD. An interesting observation in this study is that, despite the severity of the obstruction in these patients, the mean age was only 63, and reversibility of obstruction between 17.2% and 18.9% was observed, depending on the treatment arm. This, together with the high prevalence of ICS therapy, suggests that a significant part of the recruited population could have presented features compatible with the mixed phenotype asthma-COPD.

GesEPOC also recommends triple therapy for these cases from severity level III. The combination of indacaterol/glycopyrronium in a single inhaler (Breezhaler<sup>®</sup>) is not approved for use in Spain at the time of writing this update.

Two replicated clinical trials with a total population of 1,622 patients explored the efficacy of a new combination of ICS with LABA in preventing COPD exacerbations. Administration of fluticasone furoate/vilanterol (FF/V) was investigated in a single daily dose using a single inhaler, compared to vilanterol monotherapy in patients who had had at least one exacerbation in the previous year. In this study, three different doses of FF were tested (50, 100 and 200  $\mu\text{g}$ ) and the population had a mean age between 63 and 64 years, mean  $FEV_1$  (%) between 44.3 and 46.4% and reversibility between 13.8 and 15.2%. In this sample, 65.4 and 75.6% were receiving ICS before inclusion<sup>68</sup>. In one study there was no significant difference in reducing exacerbations with the combination compared to LABA alone, while the second study found significant differences with the combination compared to LABA. The combined analysis of both studies also revealed significant differences. It is remarkable that there was not a dose response to FF, and the authors recommend in their conclusions that investigation of the dose of 100  $\mu\text{g}$  should be continued. There was no difference in the rate of severe exacerbations requiring hospitalization, but there was a higher frequency of pneumonia and fractures in the FF treatment groups. Eight deaths from pneumonia were reported in the FF group, while none occurred with V. Prevention of exacerbations was higher in patients with two or more exacerbations in the previous year (between 33 and 44% of the participants in the various treatment groups). A dose-response relationship of FF in improving trough  $FEV_1$  was not observed during the study. These results indicate that the benefits of adding an ICS to LABA in preventing exacerbations are small, but greater in patients with more frequent exacerbations, and nonexistent in preventing hospitalizations. These benefits should be assessed in the light of the increased side effects seen with FF. With regard to GesEPOC, these results reinforce the recommendation of initiating ICS in exacerbator patients only after optimizing bronchodilator therapy, which is the first choice. At the time of writing this update, the combination of FF/V is not approved for use in Spain.

**Table 3**

Pharmacological treatment of COPD phenotypes according to severity levels (for severity stages I to IV)

Phenotype	Severity level			
	I	II	III	IV
Non-exacerbator	LAMA or LABA SABA or SAMA*	LAMA or LABA LAMA + LABA	LAMA + LABA	LAMA + LABA + theophylline
Mixed COPD-asthma	LABA + ICS	LABA + ICS	LAMA + LABA + ICS	LAMA + LABA + ICS (consider addition of theophylline or PDI4 if there are exacerbations and sputum)
Exacerbator with emphysema	LAMA or LABA	LABA + ICS LAMA + LABA LAMA or LABA	LAMA + LABA + ICS	LAMA + LABA + ICS (consider addition of theophylline)
Exacerbator with CB	LAMA or LABA	LABA + ICS LAMA + LABA LAMA or LABA (LAMA or LABA) + PDI4	LAMA + LABA + (ICS or PDI4) (LAMA or LABA) + ICS + PDI4 (consider addition of carbocysteine)	LAMA + LABA + (ICS or PDI4) LAMA + LABA + ICS + PDI4 (consider addition of carbocysteine) Consider addition of theophylline Consider addition of antibiotic

CB: chronic bronchitis; ICS: inhaled corticosteroids; PDI-4: phosphodiesterase 4 inhibitor; LABA: long-acting beta-2-adrenoceptor agonist; LAMA: long-acting antimuscarinic agent; SABA: short-acting beta-2 adrenergic agonist; SAMA: short-acting antimuscarinic antagonist. \*In case of intermittent symptoms.

### Safety of inhalation devices

In registrational clinical trials, some imbalance was observed in the number of deaths among patients receiving tiotropium in HandiHaler® or Respimat®. The relative increase in deaths in patients treated with Respimat® led to surmise that the reason could be cardiovascular side effects. In order to know exactly whether this effect existed and assess its possible magnitude, Tiospir study was designed, including 17,135 COPD patients randomized into three groups to receive 18 µg tiotropium with HandiHaler® or 2.5 µg or 5 µg with Respimat®. Mortality with these three treatments was compared<sup>69</sup>. During a mean follow-up of 2.3 years, the results showed that both doses of tiotropium in Respimat® were not different from HandiHaler® in relation to mortality risk or exacerbations. These results have ensured the adequate safety profile of tiotropium administered by Respimat®.

### Treatment of COPD exacerbations

Since the publication of GesEPOC in July 2012, new evidence has accumulated regarding the importance, diagnosis, classification and treatment of COPD exacerbations. The main information in this field can be grouped into the following sections:

- Impact of exacerbations and variability in healthcare.
- Criteria for exacerbation severity.
- Pharmacological treatment: antibiotics and systemic corticosteroids.

#### Impact of exacerbations and variability in healthcare

Various studies have shown that exacerbations deteriorate health-related quality of life, result in high costs, affect disease progression, and increase the risk of death. In this latter area, some recent data reinforce the role of hospitalizations as the episodes producing increased mortality, regardless of baseline disease severity. According to Suissa et al.<sup>70</sup>, severe exacerbations are associated with a mortality peak during the first three months after the episode, and the risk reduces from that date. In addition, the authors also observed that mortality dramatically increases if the episode is repeated, especially after a few weeks, shortening the interval between hospitalizations as frequency increases. Although the precise reasons for this increased risk of death is unknown, it is certain that the mortality figures vary widely from one center to another. This variability is related not only with the organization of the centers and the patients' characteristics, but also with healthcare practice, which results in large differences in health outcomes. According to the AUDIPOC study<sup>71</sup>, a clinical audit of 129 hospitals, overall mortality at 90 days from hospitalization for exacerbation of COPD was 11.6%, with variations ranging between 0 and 50%. The readmission rate was 37%, also with wide variations between 0 and 62%.

#### Criteria for exacerbation severity

Predictive risk scores can be of great interest for stratifying patients and designing healthcare performances of different intensity and/or complexity. CURB-65 (confusion, urea, respiratory rate, blood pressure, age > 65) has been used to assess the risk and decide the antibiotic regimen in patients hospitalized with an exacerbation of COPD complicated with alveolar consolidation. However, in patients with COPD, this index may be suboptimal<sup>72</sup>. Recently, Steer et al.<sup>73</sup> developed the DECAF index from five mortality predictors with more specific weight (baseline dyspnea, eosinopenia, consolidation, acidemia and atrial fibrillation) (Table 4). Baseline dyspnea during the stable phase of the disease was assessed by the extended Medical Research Council Dyspnea index<sup>72</sup> (eMRCD). On this score, grade 5 dyspnea, equivalent to level 4 in the mMRC scale recommended by

**Table 4**

DECAF index for patients hospitalized for COPD exacerbation

Variable	Score
Dyspnea	
eMRCD 5a	1
eMRCD 5b	2
Eosinopenia (< 0,05 × 10 <sup>9</sup> /l)	1
Consolidation	1
Acidemia (pH < 7.3)	1
Atrial fibrillation	1
Total DECAF index	6

DECAF: dyspnea, eosinopenia, consolidation, acidemia and atrial fibrillation; eMRCD: extended version of the Medical Research Council Dyspnea Scale. From Steer et al.<sup>72</sup>

GesEPOC, was subdivided into 5a, for patients who are able to wash or dress independently, and 5b, for those who require assistance to both tasks. This index showed excellent discrimination for mortality with a C statistic of 0.86 (95% CI, from 0.82 to 0.89) and was more accurate than other clinical mortality predictors.

In the subgroup of patients with coexisting pneumonia, DECAF was also superior to CURB-65. Table 5 shows the hospital mortality and 30 days after hospitalization applying DECAF. Although this new index requires external validation, GesEPOC considers it a useful tool for stratifying the risk of death in patients hospitalized for COPD exacerbation.

#### Pharmacological treatment of exacerbation

There has always been some controversy on the effectiveness of antibiotics. A recent systematic review<sup>74</sup> indicates that antibiotic use has significant and consistent benefits in patients admitted to intensive care. However, in patients hospitalized in departments other than intensive inpatient and in outpatients, the results are inconsistent and statistically significant effects on mortality or hospital length of stay have not been found. The results are probably not consistent because the patients included were highly diverse, to such an extent that the authors recommend investigating some clinical signs or specific biomarkers to identify cases that will benefit from antibiotics.

GesEPOC does not recommend the indiscriminate use of antibiotics. Instead they should be used only in outpatients when a change in sputum color appears as an indirect expression of possible bacterial infection. In this last year, and in line with this recommendation, Soler et al.<sup>75</sup> have also shown how antibiotic therapy guided by sputum purulence may be a good strategy in hospitalized patients with exacerbation of COPD, finding no short-term difference in therapeutic failure between the group that received antibiotics because of purulent sputum and the group that received no antibiotic because their sputum was mucoid (9% in the non-purulent group without antibiotics, compared to 10% in the purulent group with antibiotics, p = 0.51).

Similarly, in exacerbated patients with mild to moderate COPD [FEV<sub>1</sub> (% > 50%)] in which the level of evidence was lower, Llor et al.<sup>76</sup> have confirmed, in a randomized multicenter clinical trial, that administration of amoxicillin/clavulanate (500/125 mg/3 times a day) produced a higher cure rate and reduced recurrences, compared with placebo. In addition, sputum purulence is the best sign to guide the need for antibiotics, since patients with non-purulent sputum in the placebo group showed a failure rate similar to the antibiotic group<sup>77</sup>.

Systemic corticosteroids have been shown to speed up recovery from symptoms, to improve lung function and to decrease treatment

**Table 5**  
DECAF index and hospital mortality

DECAF index	n	Hospital mortality (%)	Sensitivity	Specificity	30-day mortality (%)
0	201	0.5	1	0	1.5
1	291	2.1	0.99	0.24	3.8
2	226	8.4	0.93	0.59	11.9
3	125	24	0.73	0.84	27.2
4	57	45.6	0.42	0.96	45.6
5	20	70	0.15	0.99	70
6	0	NA	NA	NA	NA

DECAF: dyspnea, eosinopenia, consolidation, acidemia and atrial fibrillation. Low risk was defined as DECAF score 0-1; moderate risk: DECAF score 2; high risk: DECAF score  $\geq$  3 points. From Steer et al.<sup>2</sup>

failures. For this reason, GesEPOC recommended their use in all exacerbations of at least moderate severity. Treatment duration greatly varies between studies and, for this reason, GesEPOC recommended in the initial version a short course of 7 to 10 days duration. However, new data suggest that the course could be even shorter. According to the REDUCE study<sup>78</sup>, a non-inferiority trial of patients attending the emergency department with exacerbations of COPD, treatment with systemic corticosteroids for 5 days was non-inferior to a regimen of 14 days. Similar results in the emergence of new exacerbations at 6 months (37.2 versus 38.4%,  $p =$  not significant), in death rates and a lower rate of exposure to glucocorticoids were observed. This supports the use of short 5-day courses for these exacerbations that do not require hospitalization.

### Non-pharmacological therapy. Respiratory rehabilitation

Since the publication of GesEPOC in 2012, the accumulated evidence regarding respiratory rehabilitation is grouped in three main sections:

- Composition of pulmonary rehabilitation programs.
- Importance of rehabilitation in exacerbated COPD.
- Adjuvant therapies in rehabilitation programs.

#### Components of pulmonary rehabilitation programs

Although training peripheral muscle remains the main component of rehabilitation<sup>79</sup>, specific respiratory muscle training and nutritional intervention are incorporated systematically in pulmonary rehabilitation programs (Table 6 and Figure 3)<sup>80-82</sup>.

A meta-analysis of 32 randomized controlled trials concluded that inspiratory muscle training improves muscle strength and endurance, exercise capacity, dyspnea and quality of life, and that it should be applied in patients with COPD and inspiratory muscle weakness<sup>83</sup>. Therefore, we may conclude that there is proven evidence on the effectiveness of inspiratory muscle training in patients with COPD, although more studies are needed to determine the clinical impact of expiratory training in these patients.

Protein-energy malnutrition is associated with loss of muscle mass and, consequently, to the perception of dyspnea, exercise intolerance and impaired quality of life. A recent clinical trial has shown that dietary supplementation with creatine and coenzyme Q10 not only improves dyspnea, exercise capacity and quality of life, but also the performance of basic activities, reducing the number of exacerbations<sup>84</sup>. Adherence to rehabilitation programs remains a topic that requires further investigation. A recent study indicates that smoking, family support and severity markers are predictors of attendance and adherence to rehabilitation programs<sup>85</sup>.

**Table 6**

Main components of pulmonary rehabilitation programs

1. Physical training
Lower and upper extremities
Respiratory muscles
2. Education and behavioral/psychosocial interventions
Self-care education
Psychotherapy
3. Chest physiotherapy
Techniques for airway permeabilization (in hypersecretory patients)
Breathing exercises
4. Occupational therapy
5. Dietary intervention
6. Adjuvant therapies

#### Importance of rehabilitation in COPD exacerbations

GesEPOC, in its 2012 publication, recommended that respiratory rehabilitation should be initiated immediately after the end of the exacerbation treatment or within 3 weeks. A systematic review on exercise prescription in patients with disease exacerbation demonstrates the safety and feasibility of exercise during hospitalization<sup>86,87</sup>. Although more research is needed regarding the characteristics of optimal training, current evidence recommends low-intensity muscular training (40% of maximum intensity), as well as measures to prevent physical deconditioning, especially in long hospital admissions<sup>87</sup>. An operational outline in COPD exacerbations is presented in Figure 4.

#### Adjuvant therapies in COPD rehabilitation

In patients with advanced COPD and/or intolerance to conventional training, other therapeutic strategies in rehabilitation programs can be considered. Neuromuscular electrical stimulation improves muscle weakness in patients with chronic progressive diseases such as EPOC<sup>88</sup>. Another promising training mode for this group of patients is mechanical vibration. The publication of two randomized clinical trials stands out for demonstrating a greater increase in 6-minute walk test and the sit-to-stand test in the group of patients who performed exercise on a vibrating platform<sup>89,90</sup>.

Research in pharmacological interventions to improve muscle function in patients with COPD is expected to acquire a greater role in the coming years, but there is still not enough evidence to recommend their use<sup>91,92</sup>.

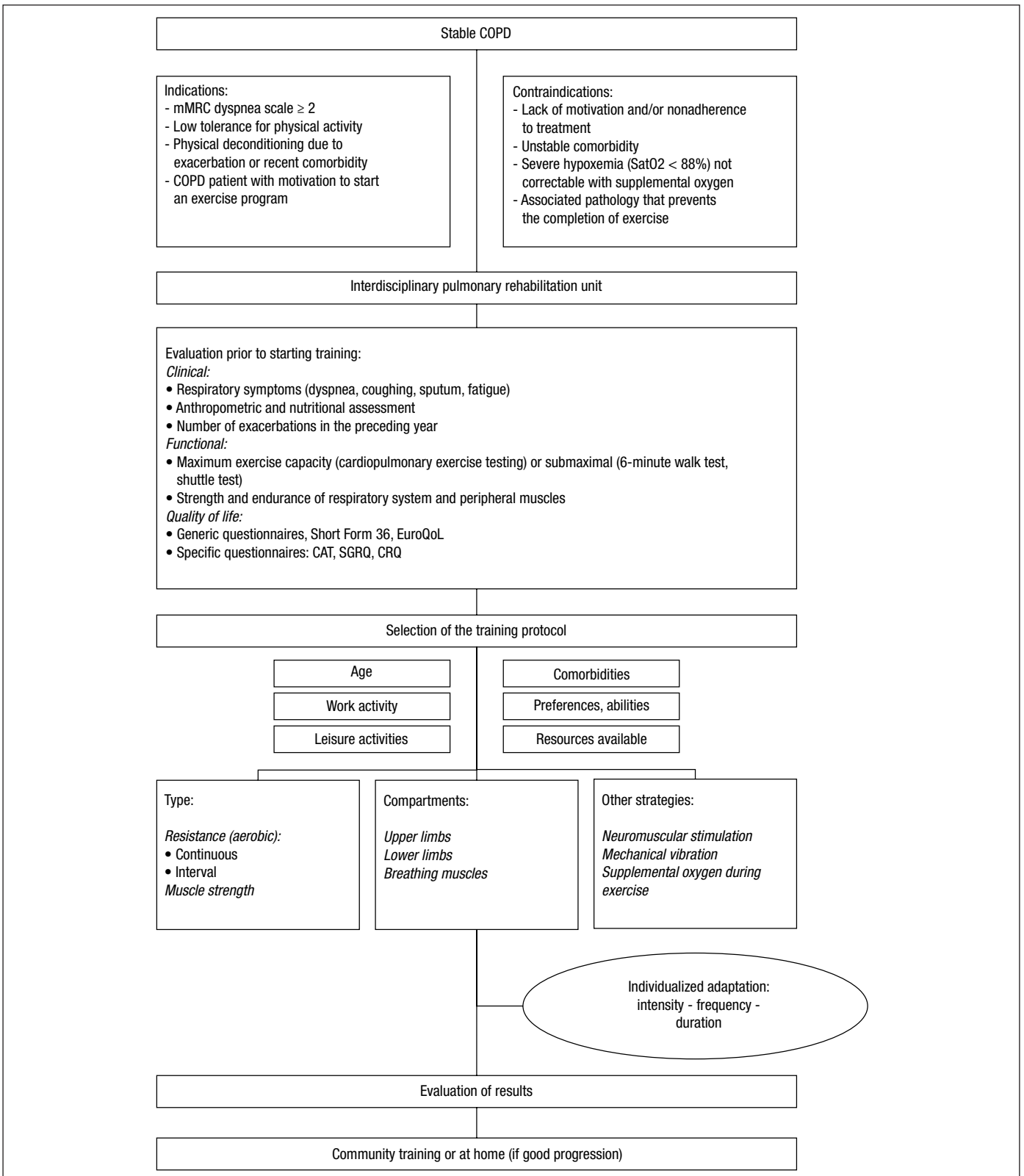


Figure 3. Physical training algorithm in stable COPD.

**Physical activity**

One of the most important studies is a systematic review of the scientific literature on the relationship between physical activity and the risk of hospitalization for EPOC<sup>93</sup>. The results indicate that

COPD patients who are less physically active are at increased risk of hospitalization<sup>93</sup>. It is difficult to establish causality because hospitalizations are also associated with a longer period of physical inactivity and deconditioning but, in any case, this study highlights the importance of physical activity level, as GesEPOC

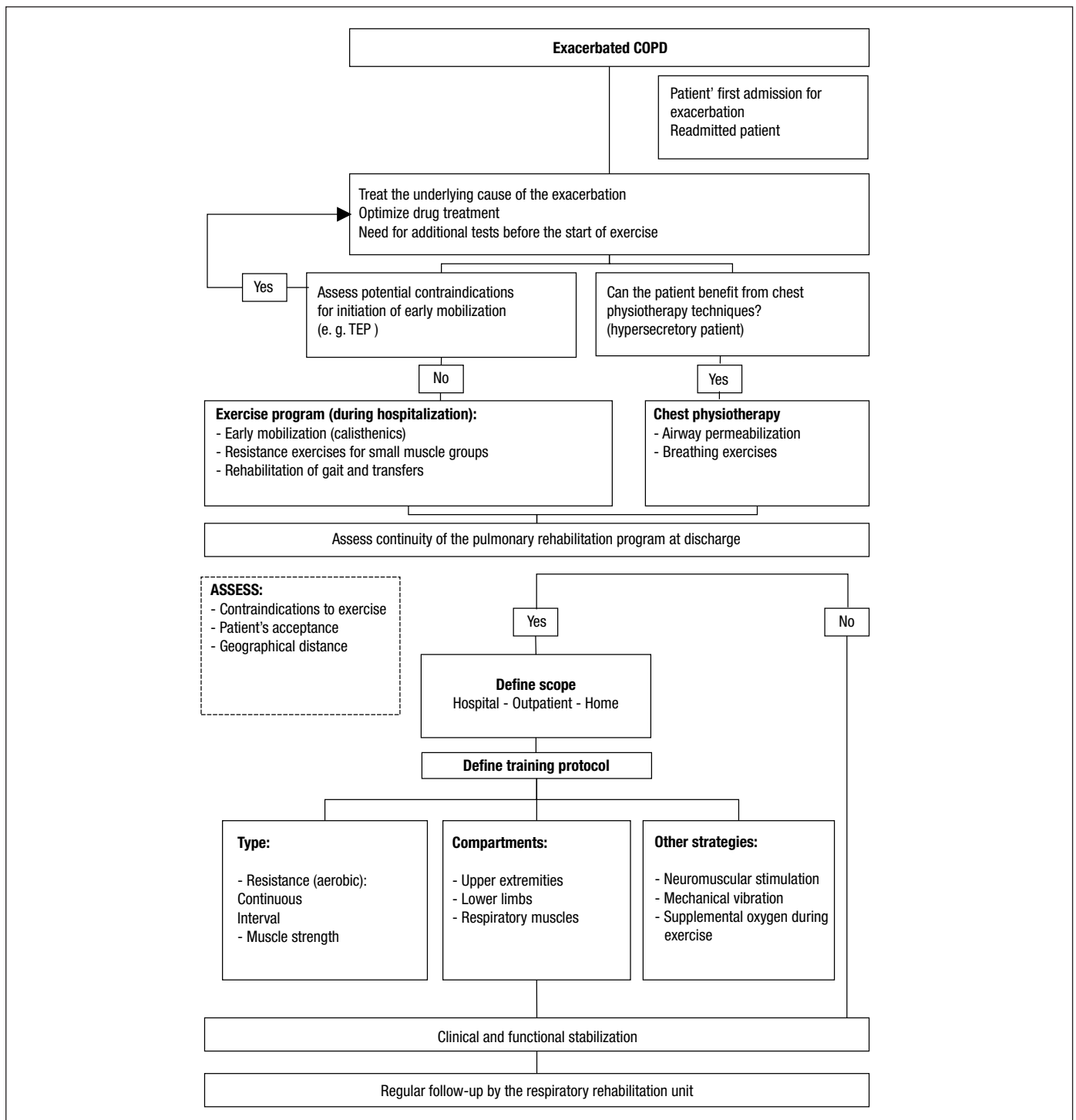


Figure 4. Algorithm for respiratory rehabilitation in exacerbated COPD.

reflected by including it in the group's alternative severity classification.

Reduced physical activity begins early in the natural history of the disease, even before subjects are diagnosed with COPD. Inactivity is more pronounced in subjects with mild symptoms of dyspnea, lower levels of CO diffusing capacity and less exercise capacity<sup>94</sup>. In particular, it seems that even in mild COPD, daily physical activity is reduced, indicating the need for early intervention and the inclusion of early-phase patients in rehabilitation programs<sup>95</sup>. Consistent with their lower level of physical activity, patients tend to have a shorter

walking time and spend less time outdoors. In multivariate regression analysis, self-reported physical activity was used to predict hospitalization in patients with COPD in the general population and readmission in patients hospitalized for exacerbation<sup>94</sup>. Available data in favor of an association between physical activity and the risk of hospitalization for this disease are limited to a few prospective cohort studies. New studies are required to quantify the level of physical activity associated with decreased risk of hospitalization.

Current studies show that the effect of exercise in people with COPD on their exercise capacity and quality of life is significant<sup>96</sup>.



These studies also suggest that there is an association between exercise and reduced exacerbations, so an extension of the period of intervention for patients experiencing an exacerbation of their disease is recommended.

The prescription of physical activity for patients hospitalized for exacerbation may be complicated by the presence of various comorbidities. However, a recent systematic review showed strong evidence of the benefits of physical activity during the EPOC exacerbation<sup>97</sup>.

In addition, it should be noted that in a sample of 177 Spanish patients with COPD from the PAC-COPD cohort, the measurement of physical activity using an accelerometer for 8 consecutive days revealed that patients with severe and very severe COPD performed their daily activities in fewer and shorter periods than patients in mild and moderate stages<sup>98</sup>. This pattern should be taken into account when recommending physical activity to the most severe patients, which should be aimed at achieving several short intervals throughout the day instead of continuous intervals of 20-30 minutes.

## Conclusions

This publication summarizes some of the major advances published in the past year on various aspects of COPD collected in the GesEPOC guidelines. Reassessment of the evidence or modifications in the guideline recommendations have not been made.

In general, the new studies reviewed support the diagnostic and therapeutic approach of GesEPOC, which has already been imitated in other national and international recommendations<sup>99,100</sup>. One of the aims of guidelines is to keep the information updated; in this respect, GesEPOC intends to provide clinicians with assistance in their daily practice.

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## Conflicts of interest

Marc Miravittles has received fees for lecturing, and/or giving scientific advice from Boehringer Ingelheim, Pfizer, AstraZeneca, Bayer Schering, Novartis, Grifols, Mediimmune, Takeda-Nycomed, Merck Sharp & Dohme, Grupo Ferrer, Gebro, GlaxoSmithKline, and Menarini Almirall. Pere Almagro has received honoraria for lecturing at educational events, and/or giving scientific advice, and/or investigation from Boehringer Ingelheim, Pfizer, Takeda-Nycomed, Merck Sharp & Dohme, Almirall, GlaxoSmithKline, Chiesi, and Esteve. Julio Ancochea has received honoraria for lecturing at educational events, and/or giving scientific advice, and/or investigation from Boehringer Ingelheim, Novartis, Takeda-Nycomed, Almirall, GlaxoSmithKline, Intermonne, Faes Farma, Chiesi, and Actelion. Myriam Calle has received honoraria for lecturing at educational events, and/or giving scientific advice, and/or investigation of Carbueros Médica, AstraZeneca, Merck Sharp & Dohme, and Almirall. Daniel Lopez has received honoraria for lecturing at educational events, and/or giving scientific advice, and/or research from Esteve Teijin, Lilly, and Pfizer. José Antonio Quintano has received honoraria for lecturing at educational events, and/or giving scientific advice, and/or investigation from Almirall, Bayer, Faes Farma, Grupo Ferrer, Menarini, and Novartis. Juan José

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