Medicina de Familia. SEMERGEN 50 (2024) 102192

Medicina de Familia
SEMERGEN

www.elsevier.es/semergen

REVISION

COPD patient profiles in primary care. Referral criteria

E. Trillo-Calvo[a], J. de Miguel Díez[b,*], C. González Villaescusa[c,d], P. Panero Hidalgo[e], J.E. Cimas Hernando[f], M. Villanueva Pérez[g], F.J. Plaza Zamora[h], M. Sanz Almazán[i], J.M. Figueira-Gonçalves[j,k]

[a] *Institute for Health Research, Aragón, Centro de Salud Campo de Belchite, Zaragoza, Spain*
[b] *Servicio de Neumología, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Universidad Complutense de Madrid, Madrid, Spain*
[c] *Servicio de Neumología, Hospital Clínico Universitario de Valencia, Spain*
[d] *Instituto de Investigación Sanitaria INCLIVA, Spain*
[e] *UGC Valle de Lecrín, Granada, Spain*
[f] *Departamento de Medicina de la Universidad de Oviedo, Centro de Salud de Contrueces-Vega, Gijón, Spain*
[g] *EAP Ribes-Olivella (SAP Alt Penedés Garraf), Institut Català de la Salut, Barcelona, Spain*
[h] *Farmacéutico Comunitario, Mazarrón, Murcia, Spain*
[i] *Centro de Salud de Riaza, Segovia, Spain*
[j] *Servicio de Respiratorio, Unidad de Investigación, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain*
[k] *Instituto Canario de Enfermedades Tropicales y Salud Pública, Universidad de La Laguna, Santa Cruz de Tenerife, Spain*

Received 24 November 2023; accepted 6 January 2024
Available online 1 February 2024

KEYWORDS
Chronic obstructive pulmonary disease;
Continuity of patient care;
Referral and consultation

Abstract COPD is a disease with a high prevalence that diminishes the quality of life of many patients. Despite this, there are still high rates of under-diagnosis in Spain, partly due to a lack of recognition of the pathology by patients. In this context, the role played by primary care teams becomes fundamental, as they are one of the first lines of entry into the health system. In this paper we explain the different COPD profiles that may be present, and update the tools for diagnosis and treatment, which, together with an attitude of active suspicion of the disease, can help in the correct management of patients, whether they are undiagnosed or have subsequent complications.

Abbreviations: COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council scale; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FVC, forced vital capacity; FEV1, forced expiratory volume in the first second; LABD, long-acting bronchodilators; SABD, short-acting bronchodilators; SAMA, short-acting muscarinic-antagonist; LAMA, long-acting muscarinic-antagonist; ICs, inhaled corticosteroids; CES, COPD exacerbation syndrome.

* Corresponding author.
E-mail address: jdemigueldiez@telefonica.net (J. de Miguel Díez).

https://doi.org/10.1016/j.semerg.2024.102192

PALABRAS CLAVE
Enfermedad pulmonar obstructiva crónica;
Continuidad de la atención al paciente;
Derivación y consulta

Perfiles de pacientes con EPOC en Atención Primaria. Criterios de derivación

Resumen La EPOC es una enfermedad con una elevada prevalencia que disminuye la calidad de vida de muchos pacientes. A pesar de esto, en España siguen existiendo altas tasas de infradiagnóstico, en parte, debido a la falta de reconocimiento de la patología por parte de los pacientes. En este contexto, el papel que desempeñan los equipos de atención primaria es fundamental, ya que son una de las primeras líneas de entrada al sistema sanitario. En este trabajo se revisan los diferentes perfiles de EPOC que pueden presentarse, y se actualizan las herramientas de diagnóstico y tratamiento, las cuales, unidas a una actitud de sospecha activa de la enfermedad, pueden ayudar en el correcto manejo de los pacientes, tanto si no cuentan con un diagnóstico como si se presentan complicaciones posteriores.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable condition characterised by persistent respiratory symptoms and chronic airflow limitation. The disease remains a growing cause of morbidity, mortality and disability, affecting 392 million people worldwide.[1] COPD is the third leading cause of mortality globally and the fourth in Spain.[2] According to data from the EPISCAN II study, the prevalence of COPD in the Spanish population, aged 40 years and older, in 2021 was 11.8%, with a high variability between the different communities.[3] In the octogenarian population this prevalence can be as high as 30%.

Despite these data, COPD remains as an underdiagnosed disease in Spain. Indeed, the IBERPOC and EPISCAN studies estimated that the rates were 78% in 1997 and 73% in 2007.[4] Nowadays, this figure remains high, as reported by EPISCAN II results (74.7%).[3]

Lack of public awareness of the disease may be another factor delaying diagnosis. For example, chronic cough, which is usually the first symptom to manifest itself, may be the first symptom to be recognised, is frequently discounted by the patient as an expected consequence of smoking and/or environmental exposures.[5]

The primary care physician is usually the first contact for patients who consult for chronic respiratory symptoms such as cough, dyspnoea or expectoration. If the patient is also a smoker, the possibility of COPD should be assessed. The anamnesis, the physical examination and the exposure to tobacco smoke should lead to suspicion of COPD diagnosis, which will be confirmed by chronic airflow obstruction on forced spirometry.[6] This situation of the primary care physician, at the gateway to the health system, gives him/her an important responsibility to reduce the high under-diagnosis of COPD and to improve the quality of life of these patients.[7] However, this role requires the physician to be aware of the particularities of the different types of COPD patients. This document will review the diagnostic tests and possible treatments required for different COPD patient profiles, as well as the reasons why they may be referred to higher levels of care.

Profiles of COPD patients in primary care

There are several classes of patients in the primary care setting, and they may be classified according to whether or not they have a diagnosis of COPD, disease control or exacerbations.

Undiagnosed patient with an exacerbation of the disease

Suspicion of undiagnosed COPD should be triggered in an adult smoker or ex-smoker of more than 10 pack-years, or chronic exposure to inhaled toxicants, who presents with respiratory symptoms (dyspnoea or chronic cough with or without associated expectoration). Another important factor is age, as symptoms in patients who are smokers or ex-smokers usually appear after the age of 35 years.[8,9]

The clinical manifestations of COPD are non-specific and often remain asymptomatic until late in the disease.[10]

Dyspnoea is the main symptom; it particularly occurs during exertion or physical activity. Moderate-to-severe dyspnoea has been reported by>40% of patients diagnosed with COPD in primary care.[11] This clinical manifestation is measured by the 5-level modified Medical Research Council scale (mMRC), which is integrated in the GOLD clinical classification scheme. It consists of five statements about perceived breathlessness: grade 0: ''I only get breathless with strenuous exercise''; grade 1: ''I get short of breath when hurrying on the level or up a slight hill''; grade 2: ''I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level''; grade 3: ''I stop for breath after walking 100 metres or after a few minutes on the level''; grade 4: ''I am too breathless to leave the house''.[12]

Chronic cough is often the first symptom of COPD. Initially, the cough may be intermittent, but subsequently it may be present every day, often throughout the day, and may be unproductive or productive,[5] with a sputum production which is usually mucoid. Inspiratory and/or expiratory wheezes and chest tightness are symptoms that may vary between days, and over the course of a single day.

Chest tightness often follows exertion, is poorly localised, is muscular in character, and may arise from isometric contraction of the intercostal muscles. An absence of wheezing or chest tightness does not exclude a diagnosis of COPD, nor does the presence of these symptoms confirm a diagnosis of asthma.[11] Additionally, fatigue is one of the most common and distressing symptoms experienced by people with COPD.[13] Finally, other symptomatology in advanced stages can include weight loss, anorexia, muscle dysfunction, depressive symptoms or anxiety are common.[6]

Tests to be performed for diagnosis

Forced spirometry is a noninvasive, reproducible, cheap, and essential test for confirming the diagnosis and assessing the severity of obstruction in COPD. It is a test that measures the volume of air moved by the lungs as a function of time and determines airflow obstruction.[8] Good quality spirometric measurement is possible in any healthcare setting and all healthcare workers who care for people with COPD should have access to it.[11] To achieve quality spirometry, it is important that the patient comes correctly prepared for the test. To this end, written instructions should be given in advance, explaining exactly what the manoeuvre consists of and the importance of their cooperation.[14] In Spain, the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and other primary care societies have published guidelines with recommendations for the correct execution of a spirometry test.[14,15]

Once the correct performance of manoeuvres has been confirmed, their interpretation will be done through three parameters such as FEV_1, FVC and FEV_1/FVC, and their results are evaluated in relation to the value that a healthy individual of the same sex, height, age and weight should have.[16] Forced vital capacity (FVC), which is the largest volume of air expelled in a forced expiratory manoeuvre from a maximal inspiration (considering normal more than 80% of its reference value). Another relevant parameter is the forced expiratory volume in the first second (FEV_1), which represents the volume of mobilised air in the first second of forced expiration (being normal more than 80% of its theoretical value). Finally, FEV_1/FVC ratio is the percentage of FVC exhaled in the first second (higher than 70% is the normal reference).

A minimum of three acceptable manoeuvres to a maximum of eight shall be performed, allowing sufficient time in between for the patient to recover from the effort.[14]

Then, the bronchodilator test should be performed, which consists of a repeat spirometry test after administration of a short-acting bronchodilator (salbutamol or terbutaline) in a chamber. In patients with heart rhythm disturbances or intolerance to beta-2 agonists, the use of ipratropium bromide is an alternative, although the waiting time will increase. The test is positive (i.e. the obstruction is reversible) when the post-bronchodilation FEV_1 improves at least 12% and more than 200 ml regarding the pre-bronchodilation value. The diagnosis of COPD will be confirmed if after bronchodilator testing the FEV_1/FVC is less than 70%. It is recommended to perform a forced spirometry after 3 months of treatment to confirm the existence of a chronic airflow obstruction.

Other diagnostic tests are available to help clarify the diagnosis, such as plain chest radiography, useful to rule out other respiratory, cardiac and musculoskeletal pathologies,[8,10] pulse oximetry, where a COPD patient may present with a value below 92%,[17] and physical activity assessment, as sedentary lifestyles in some patients cause dyspnoea to be unclear.[11]

Once the diagnosis is stablished, the level of risk must be assessed. This classification relies on the likelihood to experience exacerbations, disease progression, future complications, increased consumption of healthcare resources or increased mortality. Spanish COPD Guidelines (GesEPOC) proposes a classification into low and high risk,[9] considering the degree of obstruction (measured by post-bronchodilator FEV_1(%)), the level of dyspnoea (regarding the modified Medical Research Council (mMRC) scale) and the history of exacerbations during the previous year.

Patients with post-bronchodilation FEV_1 equal to or greater than 50%, a mMRC 0–1 and, maximum, one exacerbation without hospitalisation in the last year, will be categorised as low risk. All of the above criteria must be met. Therefore, patients who do not meet at least one of the above-mentioned conditions will be considered high-risk patients. That is, post-bronchodilation FEV_1 less than 50%, mMRC between 2 and 4 or who have had more than one exacerbation that resolved with outpatient treatment and/or an exacerbation that required hospital admission.[9]

Phenotype characterisation

In high-risk patients, GesEPOC 2021 recognises three phenotypes in the pharmacological treatment scheme: non-exacerbator, eosinophilic exacerbator and non-eosinophilic exacerbator. This represents an update to the GesEPOC 2017 guideline, based on the new evidence available.[9]

The non-exacerbator is characterised by a maximum of one exacerbation in the previous year without requiring hospital care.[9] Exacerbator phenotype is defined as any patient with COPD who has two or more moderate outpatient exacerbations in the previous year, or at least one severe exacerbation, requiring hospital care.[18] Due to the different response to drug treatments, it is important to differentiate those with an eosinophilic or non-eosinophilic phenotype. Patients with >300 eosinophils/mm^3 in stable phase will be classified as eosinophilic exacerbator.[9] Non-eosinophilic exacerbator phenotype are those who meets the criteria for the exacerbating phenotype, but at the same time has <300 eosinophils/mm^3 in peripheral blood.[9]

Treatment

The general objectives of COPD treatment are summarised as: reducing the symptoms of the disease, reducing the frequency and severity of exacerbations, improving quality of life and survival. With regard to the initial pharmacological treatment of a newly diagnosed patient, the GesEPOC guidelines propose a treatment based on risk and phenotype.[9]

Inhaled treatment of the low-risk patient

In the low-risk patient, no oral or anti-inflammatory treatment is indicated, and pharmacological treatment will consist of prescription of long-acting bronchodilators

(LABD). Short-acting bronchodilators (SABD) can be of two types: anticholinergics (SAMAs) such as ipratropium bromide and short-acting beta-2 agonists (SABAs) such as salbutamol or terbutaline. Due to their rapid mechanism of action, these drugs, added to regular treatment, are the drugs of choice for on-demand treatment of symptoms at any level of disease severity.[9]

LABD can be beta-2 adrenergic (LABA) or anticholinergic (LAMA). The LABAs available in Spain are salmeterol, formoterol, indacaterol, olodaterol and vilanterol and the LAMAs are tiotropium, aclidinium, glycopyrronium and umeclidinium. LABD should be used as the first step in the treatment of all patients with persistent symptoms who require regular treatment, because they provide better symptom control than SABD and improve lung function, exercise capacity and quality of life.[19]

Inhaled treatment of the high-risk patient

It shall be chosen according to the phenotype of the patient. The initial treatment in a patient with non-exacerbator high-risk COPD is dual bronchodilation. This recommendation is based on the demonstration of greater bronchodilator efficacy compared to monotherapy, accompanied by a significant improvement in dyspnoea, quality of life and a reduction in the use of rescue medication.[20]

Frequent exacerbator patients with a high concentration of eosinophils (>300 cells/mm^3) in the blood experience a greater clinical response to inhaled corticosteroids (ICs) and justify the use of ICs associated with a LABA as a first option to reduce the risk of exacerbations.[21]

In non-eosinophilic exacerbator phenotype: LABA/LAMA treatment is recommended as first choice in most non-eosinophilic exacerbating patients. Although GesEPOC 2021 recommends initial therapy with LABA/ICS for eosinophilic exacerbator patients,[9] the GOLD document, in its 2023 version, advocates the use of triple therapy,[22] discarding LABA/ICS as initial treatment. In non-eosinophilic exacerbator patients who continue to present exacerbations despite double bronchodilation, triple therapy could be considered in the case of exacerbations with a good response to systemic corticosteroids and if its eosinophil count is close to 300 eosinophils/mm^3. IC in the form of triple therapy may be useful if they have eosinophil counts between 100 and 300 cells/mm^3. The efficacy of ICs in patients with eosinophil counts <100 cells/mm^3 is very limited and their use is discouraged to avoid adverse effects.[2] In this case, or if exacerbations are observed in spite of triple therapy, initiation of roflumilast or prolonged use of azithromycin should be considered, as well as to check the inhalation technique, assess comorbidity and test the possibility of chronic bronchial infection through sputum culture.

The ''Criteria for referral in COPD. Continuity of care'' document supports the use of initial treatment with triple therapy (LAMA–LABA–ICS) in COPD patients with an eosinophils count >100 cells/mm^3 who develop an exacerbation requiring hospital admission.[23]

Derivation criteria

As described in the document ''Criteria for referral in COPD. Continuity of care'',[23] they should be referred to pneumology those patients who arrive at the primary care clinic without a diagnosis of COPD is related to the impossibility of performing spirometry, either because of a lack of a spirometer or because unavailable qualified personnel. Patients whose diagnosis is in doubt after a valid spirometry test will also be referred.[23]

Uncontrolled diagnosed patient

The patient classified as uncontrolled has an increased risk of both short-term exacerbation in the next six months and long-term exacerbation and increased risk of deterioration in their health-related quality of life,[24] so a detailed analysis of the possible causes of this lack of control is required and an increase in treatment intensity may be necessary.[9]

Tests to be performed for diagnosis.

The objective will be to classify the degree to which COPD patients are controlled and to reassess their risk group, in order to consider whether they need a readjustment of medication or a referral to the next level of care. According to GOLD, to determine the risk group, lung function is not assessed, only the clinical condition is taken into account by means of the degree of dyspnoea mMRC or the COPD Assessment Test (CAT) and the number and type of exacerbations in the previous year.[6]

CAT consists of eight simple questions that measure aspects of cough, expectoration, chest tightness, dyspnoea, household activities, self-confidence, sleep and energy. Each of these questions can be weighted by a score ranging from 0 (best) to 5 (worst).[25] It is very useful in aiding doctor–patient communication, as it helps to identify aspects of the impact of the disease that may go unnoticed in routine questioning. It is important in follow-up to detect clinically important changes.[8] CAT scores greater than or equal to 10 indicate a significant impact on disease-related health status, suggesting that a personalised assessment should be performed. An increase in this score of more than two points should alert that there is a decompensation of the process which should be evaluated.

Another prognostic tool, supported by the mMRC, are BODE and BODEx indexes. BODE index is a multicomponent index of prognostic severity of COPD that integrates information from BMI (body mass index), FEV_1, mMRC and six-minute walk test.[8] Although the determination of the four components of BODE is relatively simple, the generalisation of the index has been slower than expected, especially in primary care, probably due to the need to perform the six-minute walk test ≤which, although of low complexity and cost, requires time and adequate space for its performance. For this reason, some authors have proposed replacing this exercise test (E of the BODE index) with the recording of severe exacerbations (Ex of severe exacerbations), in what is called BODEx index, whose score ranges from 0 to 9 and is grouped into four risk groups, expressed in quartiles. Result between 0–2 points would correspond to the first quartile, 3–4 to the second, 5–6 to the third and 7–9 to the fourth one.[26] Body mass index is scored as 0 (>21 kg/m^2) or 1 (21 kg/m^2); FEV_1 (%) as 0 (>65), 1 (50–64), 2 (36–49) or 3 (<35); mMRC as 0 (0–1), 1 (2), 2 (3) or 3 (4); finally, exacerbations (those

involving emergency room visits or hospital admissions) as 0 (0), 1 (1–2) or 2 (>2).

Treatment

Once the patient's degree of control has been assessed, treatment can be adjusted. GesEPOC 2021 proposes a treatment guided by the patient's risk level and phenotype.

In low-risk patients not controlled with monotherapy, the first step is to check for proper device technique. If this is correct, a change of monotherapy (LABA instead of LAMA, or vice versa) or the introduction of dual bronchodilator therapy (LABA and LAMA) can be considered.[9]

In non-exacerbator high-risk patients an evaluation of the treatable traits will be required and if the uncontrolled symptom is dyspnoea, theophylline will be added to the double bronchodilator therapy.[9] In high-risk exacerbator patients, who continue to have frequent exacerbations despite treatment with LAMA–LABA, escalation to triple therapy will be indicated if they present an eosinophil count above 100 cells/mm^3.

Recent studies of fixed triple therapy have shown greater efficacy in improving lung function, respiratory symptoms and a greater reduction in the risk of exacerbations than the LABA/IC combination.[21] Triple therapy has also shown a greater reduction in the risk of exacerbations than the LABA/LAMA combination, especially in patients who had a higher blood eosinophil concentration.[8] In patients in whom triple therapy does not work, parallel assessment or treatment of treatable traits such as dyspnoea, chronic bronchial infection, sleep apnea or cardiac disease should be considered.

For both types of exacerbator profiles (eosinophilic and non-eosinophilic), it is indicated the use of roflumilast as a second-line therapy or, in case of patients with at least three exacerbations in the previous year, long-term treatment with macrolides.[9]

Although there is no clear time period to assess the effects of a change in medication, six to twelve weeks may be a reasonable time to estimate changes in the degree of dyspnoea. For the effect on quality of life and exacerbations, longer time periods are required.[27]

Derivation criteria

In general, a patient diagnosed with COPD should be referred to Pneumology when, despite appropriate treatment, there is no improvement, worsening, frequent exacerbations or a disproportion between lung function and symptoms, as well as in high-risk patients for complex tests only available at hospital level, when it is considered necessary to indicate continuous home oxygen therapy or to indicate surgical techniques.[8,26]

Other reasons for referral are related to the occurrence of symptoms or unexpected clinical manifestations such as haemoptysis, appearance of peripheral oedema or persistent infections, as well as patients in need of non-pharmacological treatment such as non-invasive ventilation or home oxygen therapy (these have oxygen saturations that are consistently below 90%). Finally, a BODEx score above 5 should also be a reason for patient escalation.[6,28]

Diagnosed patient presenting with an exacerbation.

COPD exacerbation syndrome (CES) is defined as an episode of clinical instability that occurs as a consequence of worsening expiratory airflow limitation or the underlying inflammatory process compared to the individual's baseline condition. From a pathophysiological point of view, CES is a complex and heterogeneous event comprising a set of diverse alterations, which either in isolation or more frequently in combination are expressed clinically in a similar manner in the COPD patient.[29]

Many CES are observed in clusters, which raises the question of whether they are actually new events or incomplete resolutions of previous episodes. To distinguish these situations, the following definitions are established.[8] First, therapeutic failure is defined as a worsening of symptoms that occurs during the CES and requires additional treatment.[30] A relapse, it is when a new worsening of symptoms occurs between the end of CES treatment and four weeks thereafter.[8] Finally, recurrence, which occurs when symptoms recur less than one year after the previous CES, after a period of relative good health. This is defined as at least four weeks after completion of treatment for the previous CES or six weeks after the onset of symptoms. Recurrences are considered as new episodes of CES.[30]

The cause of exacerbation of COPD in 50–70% of cases is infectious, of which 30% are viral infections, and in 5–10% the cause is environmental pollution. However, the aetiology is unknown in one third of cases.[8]

Tests to be performed for diagnosis

In order to establish the diagnosis of COPD exacerbation in primary care, it is very important to carry out a detailed anamnesis and physical examination.

Step 1: Diagnosis of exacerbation syndrome of COPD

Clinical suspicion is established by an acute, sustained and significant worsening of respiratory symptoms (dyspnoea, cough, changes in sputum colour or volume) compared to baseline in a patient with a previous diagnosis of COPD. The cardinal symptom of CES is a significant increase in dyspnoea. GesEPOC recommends the use of the modified Medical Research Council (mMRC) scale to assess this clinical manifestation.[31]

Increased cough or changes in colour and/or increased volume of sputum are also considered symptoms.

Sometimes it is difficult to discriminate whether the origin of the condition is COPD-specific or related to comorbidity. In these cases, it is recommended to diagnose and treat both conditions. However, there is a fine line between COPD exacerbation and pneumonia. The symptomatology is virtually identical and the underlying mechanisms are similar. The pulmonary microbiome between COPD patients with and without pulmonary infiltrate does not differ, the triggering factors are similar and so is the treatment.[32] The main difference is that in the presence of pneumonia, inflammation is higher and the prognosis worse, suggesting that we may be dealing with different expressions of the same pathological process. For this reason, pneumonia, classified

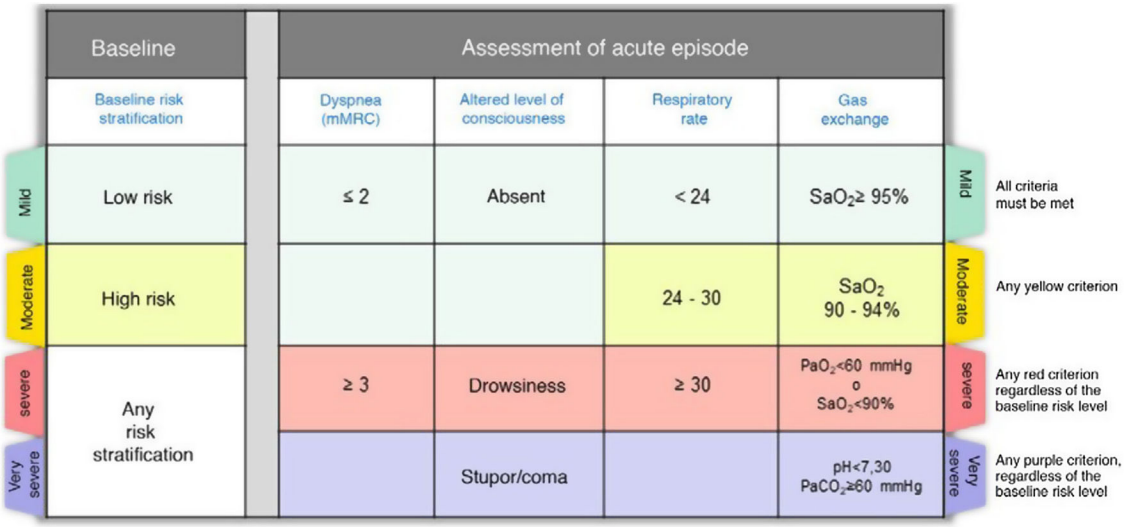

Figure 1 COPD exacerbation syndrome (CES) severity criteria. Mild: all green-coloured criteria must be met; moderate: in the presence of any yellow criteria; severe: any red criteria, regardless of baseline risk stratification; very severe: any purple criteria, regardless of baseline risk stratification.[29]

in previous editions of GesEPOC as a comorbidity, is now considered a type of CES.[28]

Step 2: Assess the severity of the episode
This should be done after diagnosis and is important for deciding on appropriate treatment. The classification of severity according to GesEPOC is shown in Fig. 1.[29]

Treatment

Outpatient treatment will be initiated in cases of mild or moderate severity, or referral to the hospital emergency department if the exacerbation is severe or very severe.[10] More than 80% of exacerbations are managed in primary care and the objective here is to resolve the current process by minimising its negative effects and preventing new exacerbations.[10]

Pharmacological treatment
The first action is to optimise bronchodilation by increasing the dose and/or frequency of short-acting bronchodilators. These are the drugs of choice due to their rapid onset of action and efficacy in bronchodilation. SABAs (salbutamol or terbutaline) should be used first and if necessary, a SAMA (ipratropium)[8] could be added. If the patient was using a long-acting bronchodilator, it should not be discontinued during exacerbation.[8,33]

Systemic glucocorticoids
They can improve lung function, oxygenation and decrease recovery time.[8,10] Currently, short courses of 5–7 days of 0.5 mg/kg/day of prednisone (or equivalent) up to a maximum of 40 mg/day are recommended.[6]

Antibiotics
Its use reduces the risk of treatment failure and increases the time to the next exacerbation, without affecting health-related quality of life (HRQoL), recurrences or mortality.[34] Antibiotic administration is especially indicated when there is a change in sputum colour (from mucous to dark)[34]; when the patient requires both invasive and non-invasive ventilatory support[34,35] and in cases with elevated C-reactive protein (≥20 mg/dL), even if the sputum appearance is inconclusive.[36] Antibiotics are also recommended in all patients with CES presenting with pneumonia, in accordance with the recommendations of the clinical practice guidelines on pneumonia.[37]

The recommended antibiotics are prescribed according to the severity of the exacerbation. In case of mild exacerbation, amoxicillin–clavulanic acid 875/125 mg/8 h for 7 days. Moderate to very severe exacerbation without risk of *Pseudomonas* infection, amoxicillin–clavulanic acid, ceftriaxone or cefotaxime would be the antibiotics of choice. The alternative, moxifloxacin 400 mg/24 h for 5 days or levofloxacin 500 mg/24 h for 7 days. When severe to very severe exacerbation with risk of *Pseudomonas* infection is handled the treatment will be a β-lactam with anti-pseudomonal activity, such as ceftazidime or piperacillin–tazobactam. As second line, ciprofloxacin 500–750 mg/12 h for 10 days or levofloxacin 500 mg/12 h for 7 days would be considered.[8,38]

Venous thromboembolic disease prophylaxis
The use of low-molecular-weight heparins is recommended in severe/very severe or moderate exacerbations where the patient is to remain in bed or inactive.[29]

Non-pharmacological treatment
Oxygen therapy is considered one of the key elements in the management of severe CES with respiratory failure. Its goal is to achieve a SaO_2 between 88 and 92%. However, oxygen administration must be controlled, as in some patients the main stimulus to the respiratory centre depends on the degree of hypoxaemia rather than the usual hypercapnic stimulus.[29] Moreover, pulmonary rehabilitation after hospi-

tal discharge has been shown to improve patients' quality of life and reduce readmissions.[6]

Derivation criteria

The reasons for referral from primary care are diverse. All cases of CES classified as severe or very severe, patients who cannot comply with treatment at home or those who cannot be properly diagnosed due to the impossibility of performing the relevant tests should be referred to a specialist. Likewise, patients with severe comorbidities or unexpected complications, such as heart disease, arrhythmias, or renal or hepatic failure, should also be referred.[6]

After diagnosis, and once treatment has been prescribed, the correct follow-up of the patient who has presented a CES is a key point that can be carried out in primary care, with the aim of preventing new exacerbations. Whenever possible, after the diagnosis of CES or hospital discharge, the patient should be evaluated by the primary care physician within the following 3–5 days. Those who required hospital admission should also be referred to the specialist within a maximum of 2–4 weeks.[39]

Conclusions

COPD is a disease with a high under-diagnosis rate. The role of primary care, as one of the entry points for COPD patients into the healthcare system, is essential to prevent this. The active suspicion of the disease in patients with risk factors, the correct management of those already diagnosed or those suffering exacerbations, as well as the provision of diagnostic equipment such as spirometers, will be key to providing the primary care physician with the necessary tools to improve the quality of life of the COPD patient. In carrying out these tasks, the necessary tests should be in place to assess the patient's profile and, based on this, to prescribe appropriate treatment. When the diagnosis is not clear, when the necessary means for such diagnosis are not available, or when the treatment does not achieve an adequate level of control over the symptoms, coordination with higher levels of care should be established to refer patients who cannot be managed by primary care.

Authors' contributions

All authors have contributed in the conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing – original draft preparation, writing – review and editing, visualisation, supervision and project administration. All authors have read and agreed to the published version of the manuscript.

Funding

This research has not received specific support from public sector agencies, the commercial sector or non-profit organisations.

Conflicts of interest

Eva Trillo-Calvo has received honoraria for speaking engagements and funding for conference attendance from Laboratories Menarini, GlaxoSmithKline, AstraZeneca, Lundbeck, Esteve, FAES, Boehringer Ingelheim, and Servier.

Javier de Miguel Díez has received honoraria and funding from Laboratories AstraZeneca, Bial, Boehringer, Chiesi, Esteve, FAES, Ferrer, Gebro Pharma, GlaxoSmithKline, Janssen, Menarini, MundiPharma, Novartis, Roche, Rovi, Teva y Pfizer.

Cruz González Villaescusa has received honoraria and funding from Laboratories AstraZeneca, Bial, Boehringer, Chiesi, FAES, Ferrer, Gebro Pharma, GlaxoSmithKline, Menarini y Teva.

Pablo Panero Hidalgo has received honoraria for speaking engagements and funding for conference attendance from Laboratories GSK, Menarini, Lilly, AstraZeneca, Lundbeck, Esteve, FAES, Boehringer Ingelheim, Almirall, Chiesi and Novartis.

Juan Enrique Cimas has received honoraria in the last three years for spirometry and COPD courses from semfyc and SESPA.

Marta Villanueva Pérez has received honoraria for speaking engagements and funding from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Teva.

Francisco Javier Plaza Zamora has received honoraria for speaking engagements and funding from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, and Teva.

María Sanz Almazán has received honoraria for speaking engagements and funding for conference attendance from Laboratories Menarini, GlaxoSmithKline, Vifor Pharma, AstraZeneca, Novo Nordisk, and Bial.

Juan Marco Figueira-Gonçalves has received honoraria for speaking engagements and funding for conference attendance from Laboratories Esteve, MundiPharma, AstraZeneca, Boehringer Ingelheim, Ferrer, Menarini, Rovi, GlaxoSmithKline, Chiesi, Novartis, and Gebro Pharma.

Acknowledgments

The authors want to thank the rest of people implicated in the project: Alberto Fernández Villar, Esperanza Doña Díaz, Marta Padilla Bernáldez, Jesús Molina Paris, Miriam Barrecheguren Fernández, José Miguel Valero Pérez and María Teresa Ramírez Prieto.

References

1. Global Initiative for Chronic Obstructive Lung Disease. GOLD REPORT 2022 V1.1 22NOV2021_WMV; 2022. Available from: https://goldcopd.org/archived-reports/gold-report-2022-v1-1-22nov2021_wmv/ [accessed September 2023].
2. Calderón Montero A. Cardiopulmonary axis and cardiovascular mortality in patients with COPD. Semergen. 2023;49:101928.
3. Soriano JB, Alfageme I, Miravitlles M, de Lucas P, Soler-Cataluña JJ, García-Río F, et al. Prevalence and determinants of COPD in Spain: EPISCAN II. Arch Bronconeumol (Engl Ed). 2021;57:61–9.
4. Soriano JB, Miravitlles M. Datos epidemiológicos de EPOC en España. Arch Bronconeumol. 2007;43:2–9.

5. Cho SH, Lin HC, Ghoshal AG, Bin Abdul Muttalif AR, Thanaviratananich S, Bagga S, et al. Respiratory disease in the Asia-Pacific region: cough as a key symptom. Allergy Asthma Proc. 2016;37:131-40.
6. Romero Sanz VF, Sanz Almazán M, Bárcena Camaño M. Documento SEMG. Manejo y derivación: Enfermedad Pulmonar Obstructiva Crónica (EPOC) en AP. Madrid; 2018. Available from: https://www.semg.es/images/documentos/2018/manejo_derivacion_EPOC_AP.pdf [accessed September 2023].
7. Llauger MA, Pou MA, Domínguez L, Freixas M, Valverde P, Valero C. Atención a la EPOC en el abordaje al paciente crónico en Atención Primaria. Arch Bronconeumol. 2011;47:561–70.
8. Guía Española de la EPOC (GesEPOC). Versión 2017. Arch Bronconeumol. 2017;53 Suppl. 1:2–64.
9. Miratvilles M, Calle M, Molina J, Almagro P, Gómez JT, Trigueros A, et al. Actualización 2021 de la Guía Española de la EPOC (GesEPOC). Tratamiento farmacológico de la EPOC estable. Arch Bronconeumol. 2022;58:69–81.
10. Vogelmeier CF, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Criner G, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Report; 2018. Available from: https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf [accessed September 2023].
11. Global Initiative for Chronic Obstructive Lung Disease. GOLD REPORT 2023; 2023. Available from: https://goldcopd.org/2023-gold-report-2/ [accessed September 2023].
12. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54:581–6.
13. Goërtz YMJ, Looijmans M, Prins JB, Janssen DJA, Thong MSY, Peters JB, et al. Fatigue in patients with chronic obstructive pulmonary disease: protocol of the Dutch multicentre, longitudinal, observational FAntasTIGUE study. BMJ Open. 2018;8:e021745.
14. García Río F, Calle M, Burgos F, Casan P, Del Campo F, Galdiz JB, et al. Normativa SEPAR: espirometría. Arch Bronconeumol. 2013;49:388–401.
15. semFYC. Guía de procedimiento para la ESPIROMETRÍA en Atención Primaria; 2021. Available from: https://www.semfyc.es/wp-content/uploads/2016/11/Gu%C3%ADa-Espirometria_2021.pdf [accessed October 2023].
16. Viejo Bañuelos JL, Hernánez Hernández J, Herrero Roa J, Jorge Bravo MT, Moche Loeri JA, Simón Rodríguez A. Guía de práctica clínica para el diagnóstico y tratamiento de la enfermedad pulmonar obstructiva crónica (EPOC) en pacientes ambulatorios en Castilla y León. Documento de Consenso 2014; 2014. Available from: https://www.socalemfyc.org/wp-content/uploads/2016/06/guia-epoc.pdf [accessed September 2023].
17. Lacasse Y, Thériault S, St-Pierre B, Bernard S, Sériès F, Bernatchez HJ, et al. Oximetry neither to prescribe long-term oxygen therapy nor to screen for severe hypoxaemia. ERJ Open Res. 2021;7:00272–2021.
18. Soler Cataluña JJ, Martínez García MA, Catalán Serra P. The frequent exacerbator. A new phenotype in COPD? Hot Topics Respir Med. 2011;6:7–12.
19. Sestini P, Renzoni E, Robinson S, Poole P, Ram FS. Short-acting beta 2 agonists for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2002;4:CD001495.
20. Anzueto A, Miravitlles M. The role of fixed-dose dual bronchodilator therapy in treating COPD. Am J Med. 2018;131:608–22.
21. Calzetta L, Rogliani P, Matera MG, Cazzola M. A systematic review with meta-analysis of dual bronchodilation with LAMA/LABA for the treatment of stable COPD. Chest. 2016;149:1181–96.
22. Global Strategy for Prevention, Diagnosis and Management of COPD: 2024 Report; 2023. Available from: https://goldcopd.org/2024-gold-report/ [accessed November 2023].
23. SEMERGEN, SEPAR, semFYC, SEMG, SEFAC, GRAP. Criterios de derivación en EPOC. Continuidad asistencial. IMC 2023, Madrid. ISBN: 978-84-19457-41-7. Depósito legal: M-18163-2023.
24. Miravitlles M, Sliwinski P, Rhee CK, Costello RW, Carter V, Tan JHY, et al. Predictive value of control of COPD for risk of exacerbations: an international, prospective study. Respirology. 2020;25:1136–43.
25. Jones P, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34:648–54. Available from: https://erj.ersjournals.com/content/34/3/648
26. Soler-Cataluña JJ, Martínez-García MA, Sánchez L, Perpiña M, Román P. Severe exacerbations and BODE index: two independent risk factors for death in male COPD patients. Respir Med. 2009;103:692–9.
27. Yang IA, Dabscheck EJ, George J, Jenkins SC, McDonald CF, McDonald VM, et al. COPD-X concise guide for primary care. Brisbane: Lung Foundation Australia; 2017.
28. Andrés JM, Anoro L, Aguilar C, Buestué M, Cabestre R, Cilleruelo S, et al. Plan de atención integral a personas con EPOC en Aragón. Actualización 2023; 2023. Available from: https://www.aragon.es/documents/20127/47412580/Plan+de+Atenci%C3%B3n+Integral+a+personas+con+EPOC+en+Arag%C3%B3n.pdf/e557816a-2078-95d8-03ac-087c565c90cf?t=1680677102304
29. Soler-Cataluña JJ, Piñera P, Trigueros JA, Calle M, Casanova C, Cosío BG, et al. Actualización 2021 de la guía española de la EPOC (GesEPOC). Diagnóstico y tratamiento del síndrome de agudización de la EPOC. Arch Bronconeumol. 2022;58:159–70.
30. Soler-Cataluña JJ, Rodriguez-Roisin R. Frequent chronic obstructive pulmonary disease exacerbators: how much real, how much fictitious? COPD. 2010;7:276–84.
31. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha J. Usufulness of the Medical Research Council (MRC) dyspnea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54:581–6.
32. Williams NP, Ostridge K, Devaster JM, Kim V, Coombs N, Bourne S, et al. Impact of radiologically stratified exacerbations: insights into pneumonia aetiology in COPD. Respir Res. 2018;19:143.
33. Turner MO, Patel A, Ginsburg S, FitzGerald JM. Bronchodilator delivery in acute air flow obstruction. A meta-analysis. Arch Intern Med. 1997;157:1736–44.
34. Wedzicha JA, Miravitlles M, Hurst JR, Calverley PMA, Albert RK, Anzueto A, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society (ERS/ATS) guideline. Eur Respir J. 2017;49:1600791.
35. Nouira S, Marghli S, Belghith M, Besbes L, Elatrous S, Abroug F. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial. Lancet. 2001;358:2020–5.
36. Francis NA, Gillespie D, White P, Bates J, Lowe R, Sewell B, et al. C-reactive protein point-of-care testing for safely reducing antibiotics for acute exacerbations of chronic obstructive pulmonary disease: the PACE RCT. Health Technol Assess. 2020;24:1–108.
37. Metlay JP, Waterer G, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia: an official clinical practice guideline of

the American Thoracic Society and Infectious Disease Society of America. Am J Respir Crit Care Med. 2019;200:e45–67.
38. Rodríguez JM, Izquierdo JL. Tratamiento antibiótico oral de la exacerbación de la EPOC. Más allá de la COVID-19. Rev Esp Quimioter. 2021;34:429–40.
39. Ginel Mendoza L, Gonzálvez Rey J, Trigueros Carrero JA, Piñera Salmerón P. Protocolo de manejo de pacientes con enfermedad pulmonar obstructiva crónica tras agudización en urgencias. Med Fam SEMERGEN. 2023;49:101998.