Archivos de Bronconeumología 58 (2022) T345–T351

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

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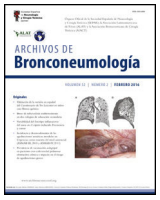

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[Translated article] Spanish COPD Guidelines (GesEPOC 2021): Non-pharmacological Treatment Update

Borja G. Cosío[a,b,*], Carme Hernández[b,c], Eusebi Chiner[d], Elena Gimeno-Santos[e,f], Eulogio Pleguezuelos[g], Nuria Seijas[c], David Rigau[h], José Luis López-Campos[b,i], Juan José Soler-Cataluña[b,j], Myriam Calle[k], Marc Miravitlles[b,l], Ciro Casanova[m], on behalf of the GesEPOC 2021 task force[◊]

[a] Servicio de Neumología, Hospital Universitario Son Espases-IdISBa, Palma de Mallorca, Spain
[b] Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain
[c] Dispositivo Transversal de Hospitalización a Domicilio, Hospital Clínic de Barcelona, Barcelona, Spain
[d] Servicio de Neumología, Hospital Universitario San Juan de Alicante, Alicante, Spain
[e] Servicio de Neumología, Hospital Clínico de Barcelona, Spain
[f] Programa de enfermedades no transmisibles y medio ambiente, Instituto de Salud Global (ISGlobal) de Barcelona, Barcelona, Spain
[g] Servicio de Medicina Física y Rehabilitación, Hospital de Mataró, Mataró (Barcelona), Spain
[h] Centro Cochrane Iberoamericano, Barcelona, Spain
[i] Unidad Médico-Quirúrgica de Enfermedades Respiratorias, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío, Universidad de Sevilla, Spain
[j] Servicio de Neumología, Hospital Arnau de Vilanova, Valencia, Spain
[k] Servicio de Neumología, Hospital Clínico San Carlos, Departamento de Medicina, Facultad de Medicina, Universidad Complutense de Madrid; Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain
[l] Servicio de Neumología, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain
[m] Servicio de Neumología-Unidad de Investigación, Hospital Universitario de La Candelaria, Universidad de La Laguna, Tenerife, Spain

ARTICLE INFO

Article history:
Received 18 August 2021
Accepted 19 August 2021
Available online 26 February 2022

Keywords:
Nutrition
Lung volume reduction
Lung rehabilitation
Physical activity
Oxygen therapy
Lung transplantation

ABSTRACT

In addition to recommendations for pharmacological treatment stratified for risk and phenotype, the new 2021 edition of the Spanish COPD Guidelines (GesEPOC 2021) proposes a personalized approach to treatable traits, defined as a characteristic (clinical, physiological, or biological) that can be identified by diagnostic tests or biomarkers, for which a specific treatment is available. Some treatable traits, such as malnutrition, sedentarism, emphysema or respiratory failure, can be treated with non-pharmacological therapies, and this was not covered in detail in the guidelines. This section of GesEPOC 2021 includes a narrative update with recommendations on dietary treatment, physical activity, respiratory rehabilitation, oxygen therapy, non-invasive ventilation, lung volume reduction, and lung transplantation. A PICO question with recommendations on the use of supplemental oxygen during exercise in COPD patients without severe hypoxemia is also included.

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Actualización 2021 de la Guía Española de la EPOC (GesEPOC). Tratamiento no farmacológico

Palabras clave:
Nutrición
Reducción de volumen pulmonar
Rehabilitación pulmonar
Actividad física
Oxigenoterapia
Trasplante pulmonar

RESUMEN

La nueva edición de 2021 de la Guía Española de la EPOC (GesEPOC 2021) propone, junto al tratamiento farmacológico ajustado por estratificación de riesgo y fenotipo, el abordaje personalizado de los rasgos tratables, definidos como una característica (clínica, fisiológica o biológica) que se puede identificar mediante pruebas diagnósticas o biomarcadores y que tiene un tratamiento específico. Existen algunos rasgos tratables que tienen un tratamiento no farmacológico y que no fueron contemplados en detalle en la guía, como puede ser la desnutrición, el sedentarismo, el enfisema o la insuficiencia respiratoria. En este

DOI of original article: https://doi.org/10.1016/j.arbres.2021.08.010
* Corresponding author.
E-mail address: borja.cosio@ssib.es (B.G. Cosío).
◊ Appendix A lists the members of the GesEPOC 2021 task force.

https://doi.org/10.1016/j.arbres.2021.08.024
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capítulo de GesEPOC 2021 se presenta una actualización narrativa con recomendaciones sobre tratamiento dietético, actividad física, rehabilitación respiratoria, oxigenoterapia, ventilación no invasiva, reducción de volumen y trasplante pulmonar. Además, se incluye una pregunta PICO con recomendación sobre el uso de oxígeno suplementario durante el ejercicio en pacientes con EPOC sin hipoxemia grave.
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Introduction

Although the treatment of chronic obstructive pulmonary disease (COPD) relies mainly on medications, mostly inhaled, some other equally important aspects of disease management need to be fully explored in each patient. One of the recommendations of the recently updated GesEPOC pharmacological treatment guidelines[1] is to evaluate a series of general measures in all patients diagnosed with COPD that include, along with other interventions, adequate nutrition and regular physical activity adapted to age and physical conditions. An innovative therapeutic approach described in the new guidelines is that of treatable traits, defined as characteristics (clinical, physiological, or biological) that can be identified by diagnostic tests or biomarkers for which a specific treatment is available. Some general characteristics, such as malnutrition or a sedentary lifestyle, can also be considered treatable traits, and these will be addressed as such in this article. Of particular interest in GesEPOC 2021 is the review of the guidelines on the specific approach to some treatable traits. Accordingly, the scientific evidence will be reviewed to develop dietary guidelines for patients with malnutrition, physical activity for sedentary patients, respiratory rehabilitation for the management of dyspnea, lung volume reduction for emphysema patients, lung transplantation for patients with advanced disease, and oxygen therapy and non-invasive mechanical ventilation for patients with respiratory failure.

This article also includes a PICO question and a clinical recommendation on the use of supplemental oxygen during exercise in COPD patients without severe hypoxemia. The main recommendations are listed in Table 1.

The methodology used to develop the recommendations included in this article is described in the latest update of GesEPOC 2021.[1]

Table 1
Guidelines and general observations on the medical approach to treatable traits in COPD.

Approach to treatable trait	Guidelines
Malnutrition	Assessment of the nutritional status is critical in COPD patients. Avoiding low weight and malnutrition improves exercise capacity and survival.
Sedentary lifestyle	Avoiding a sedentary lifestyle and encouraging daily physical exercise is beneficial for the COPD patient and should be widely recommended.
Rehabilitation for the management of dyspnea	Pulmonary rehabilitation improves dyspnea, exercise capacity, and quality of life and should be recommended in all COPD patients. Early initiation of pulmonary rehabilitation (<4 weeks) after hospitalization reduces the risk of hospital readmission and mortality.
Respiratory failure	Chronic home oxygen therapy for at least 16 h a day in patients with COPD and respiratory failure improves survival. In patients with hypoxemia and desaturation on exertion, there is no evidence that home oxygen therapy improves survival and exercise capacity, so an individualized approach should be taken in symptomatic patients, based on its effect on dyspnea.
Chronic hypercapnia	Long-term home mechanical ventilation in patients with stable hypercapnic COPD with a history of previous acidotic exacerbations should be recommended, given its benefit in patient prognosis.

Non-pharmacological treatment of treatable traits

Nutrition

Low weight and malnutrition constitute a common treatable trait in COPD patients (25%–35% of cases) and have a negative impact on the respiratory system, peripheral muscle function, and immune system.[2] This leads to a greater loss of lung function expressed by forced expiratory volume in 1 s (FEV_1), greater deterioration of lung tissue with a higher rate of emphysema, decreased exercise capacity, and increased mortality.[3,4]

The GesEPOC task force believes that nutritional status should be assessed in all COPD patients. The patient's nutritional status will initially be assessed using the body mass index (BMI).[5] Patients with malnutrition (defined by the World Health Organization as BMI < 18.5 kg/m^2) and obese patients (BMI > 30 kg/m^2) may require a more comprehensive assessment of their nutritional status with electrical bioimpedance for the estimation of their fat-free mass index and referral to nutrition units to optimize nutritional support.

The GesEPOC task force believes that malnourished patients should be offered nutritional support, although the intensity and duration of such treatments are not well established, reflecting the lack of knowledge about the etiopathogenic mechanisms that lead to this situation in COPD. Despite these limitations, dietary nutritional supplementation with high polyunsaturated fatty acid and antioxidant (vitamins C and E and selenium) content will improve weight and muscle strength, physical activity, exercise capacity, and quality of life in malnourished patients with COPD.[6–8]

The future challenge for clinical nutritionists involved in the management of malnutrition associated with COPD will be to identify and characterize the specific areas of nutritional deficit (energy imbalance, sarcopenia, cachexia, and frailty) that will respond best to targeted interventions.

Obesity is another possible detrimental factor in COPD patients, as it may limit exercise capacity, cause respiratory restriction, and aggravate dyspnea.[9] However, it has less impact on disease prognosis than malnutrition. The objective of obesity management is to reduce the fat mass, so it is essential to offer dietary advice and promote physical activity.[10]

Finally, special consideration should be given to dietary supplementation with vitamin D. A recent meta-analysis of 4 controlled trials showed that oral administration of vitamin D reduces moderate-to-severe exacerbations in COPD patients, but only in cases with vitamin D levels <25 nmol/L.[11] On this basis, we propose the routine assessment of vitamin D levels in exacerbating phenotype COPD patients and the administration of replacement therapy to maintain levels >25 nmol/L.[11]

Physical activity

Scientific evidence on the effects of physical activity on COPD consistently shows that reduced physical activity is associated with an increased risk of mortality, hospitalization, and readmission for disease exacerbation the following year.[12] It is important to identify sedentary behavior in patients with COPD, since the evidence, while still limited, indicates that an extremely sedentary lifestyle is associated with an increased risk of mortality and cardiometabolic disease in people with COPD.[13,14]

It is well established that pulmonary rehabilitation (PR) improves exercise tolerance in patients with COPD.[15,16] However, this improvement does not necessarily change or increase daily physical activity in these patients in the long term.[17] Physical activity does not show a linear relationship with exercise capacity, and should therefore be considered independently when planning a PR program.[16] We will, therefore, encounter patients who only need to increase their exercise capacity (e.g., with physical training within PR programs), patients who only need to increase their physical activity (e.g., with programs fostering physical activity), and patients who may need a more comprehensive intervention that includes both approaches.

According to current strategies, a combination of physical training and behavioral interventions can be considered at different time points during PR programs.[18] Ideally, behavioral strategies should be implemented in the final phase of PR, when patients have greater exercise capacity and fewer symptoms because they have already undergone the physical training adaptation phase.

New PROactive Physical Activity Instruments in COPD have been published that combine questionnaires with accelerometer data to measure physical activity in terms of amount, difficulty, and patient experience.[19] These instruments have been shown to be sensitive to change following pharmacological and non-pharmacological interventions. The feedback that the patient receives from their pedometer or activity monitor (including the latest mobile technology) is effective in encouraging them to increase their physical activity and optimizes physical activity counseling programs in patients with COPD.[20]

To address physical inactivity, long-term outcomes from studies that combine behavioral interventions (such as motivational interviews) with unsupervised walking and collection of pedometer data are effective in increasing physical activity (mean increase of 957 steps a day) after 12 months of follow-up.[21] Nevertheless, most long-term studies (12 months) remain ineffective in maintaining physical activity behavior changes in patients with COPD.[22–24]

The GesEPOC task force believes that patients should perform moderate physical activity for a minimum of 30 min a day, 5 days a week. However, strategies adapted to each patient's activities of daily living, backed up with specific quantifiable, feasible objectives set down in writing, must be designed and agreed on with the patient.

Pulmonary rehabilitation

The GesEPOC Pulmonary Rehabilitation (PR) guidelines are in line with the consensus reached between the American Thoracic Society (ATS) and the European Respiratory Society (ERS), which designated PR as a central part of comprehensive chronic patient care.[15,25] The ATS and ERS have also developed guidelines to improve the implementation of PR, since access to programs and referral by professionals are still limited, despite current evidence supporting the inclusion of PR in the comprehensive treatment of COPD patients.[26] In line with the definition of PR agreed by ERS and ATS,[15] the latest evidence and recommendations also adopted in the GesEPOC guidelines are summarized below:

Table 2
Indications for long-term home oxygen therapy.

Patient with stable COPD at rest and at sea level, breathing room air with PaO_2 < 55 mmHg
PaO_2 between 55 and 60 mmHg resulting in hypoxemia
Pulmonary arterial hypertension/*Cor pulmonale*
Congestive heart failure/arrhythmias
Hematocrit > 55%

- All COPD patients should be included in a PR program as part of their treatment.[27] However, the scientific evidence is more robust in patients with moderate-to-severe COPD,[28] who are now considered by GesEPOC to be high-risk.
- Structured therapeutic education programs should be initiated at the time of diagnosis and maintained as an integral part of PR until the end of life. PR programs will be adapted to the needs of the patient and will take into account any comorbidities.[15]
- Behavioral change interventions can help improve participation in COPD self-management programs.[29,30]
- PR may be initiated during hospital admission or within 4 weeks after hospital discharge, since it has been shown to be a safe intervention that reduces the number of days in hospital, the number of readmissions, and mortality.[31,32] The risk of readmission is only significantly decreased when programs are initiated 4 weeks after hospital discharge.
- Home-based PR programs with minimal supervision have shown an effectiveness similar to that of conventional PR performed in the hospital.[33]
- Understanding of the use of technology in physical training, therapeutic education, disease management, and physical activity in PR is still limited.[17,34,35] However, telerehabilitation is potentially a useful treatment modality, as the results do not differ from conventional rehabilitation programs.[36,37]
- Psychosocial factors and patients' own perceptions may contribute to the long-term adherence and maintenance of the effects of PR.[31] It is, therefore, essential for PR to offer an integrated approach for personalized treatment of COPD patients based on a comprehensive assessment of treatable traits.[38]

Long-term home oxygen therapy

Long-term home oxygen therapy (LTOT) increases survival in patients with COPD and respiratory failure. Evidence of its effect on the reduction of exacerbations and hospitalizations and other relevant clinical outcomes, such as quality of life, appears to be inconsistent,[39] so no recommendations can be made in this regard. LTOT indications are shown in Table 2.

LTOT should be adjusted to maintain sea level $PaO_2 \geq 60$ mmHg or oxygen saturation ≥90% at rest. It should be indicated when patients are clinically stable on the basis of arterial blood gas determinations.[40] To improve survival, LTOT should be administered at least 16 h a day (Table 3).

The indication of LTOT in patients with mild–moderate hypoxemia at rest or during exercise has not been shown to affect survival, time to first hospital admission, or other clinical parameters, so its use is controversial.[41]

For this section of the guidelines, we developed a PICO question (Patient, Intervention, Comparison, and Outcomes) on oxygen therapy during exercise in COPD patients without severe hypoxemia (Appendix B).

PICO question: should supplemental oxygen be recommended during exercise in COPD patients without severe hypoxemia?

We identified a systematic review[42] of 44 randomized trials that evaluated the effects of oxygen supplementation in COPD patients

Table 3
Surgical approach to treatable traits in COPD.

Surgical approach to treatable trait	Main indications
Bullae	Bullectomy recommended in selected patients with dyspnea on exertion and bullae occupying more than 30% of the hemithorax, FEV_1 < 50%, and compression of the adjacent lung parenchyma. This technique has shown improvement in exercise tolerance, lung function, and decreased dyspnea[13]
Emphysema and pulmonary hyperinflation	Volume reduction. For patients with severe emphysema with large areas of pulmonary hyperinflation that remain symptomatic despite medical treatment, an initial evaluation of lung volume reduction with endobronchial valves is indicated, reserving surgery for patients who do not meet the criteria due to the presence of collateral ventilation or who do not improve after the placement of endobronchial valves.
Emphysema and pulmonary hyperinflation	Lung transplantation. Lung transplantation should be considered in case of BODE index > 7, FEV_1 < 20%, DLCO < 20%, pCO_2 > 50 mmHg, or the presence of *cor pulmonale* in patients who are receiving correct treatment and have a high risk of death (greater than 50% within 2 years), but who also have a greater than 80% probability of surviving the postoperative period and up to 5 years after the transplant.

without hypoxemia or with moderate hypoxemia who were not candidates for LTOT. The studies evaluated oxygen supplementation (FiO_2 > 21%) with nasal prongs during exercise performed in the context of activities of daily living over defined periods of time or for longer periods. Dyspnea during or after exercise and quality of life were assessed. Most studies were crossover with a very short follow-up of hours or a few days.

Subsequent to this review, 4 more recent randomized clinical trials were identified.[41,43–45] Due to the disparity of measurements and scales used, results have been expressed as effect size. Subgroup analyses have also been performed for studies with a parallel design or for those in which oxygen was administered not only during exercise but also during all activities of daily living.

A single study[41] evaluated patients after 1–6 years of follow-up and reported clinical outcomes such as mortality, exacerbations, or hospitalization. Patients received continuous oxygen therapy if they had COPD criteria with moderate hypoxemia and desaturation during exercise. The control group did not receive supplemental oxygen.

Analysis of the evidence shows that oxygen therapy during exercise or activities of daily living helps reduce dyspnea, although these conclusions are based on studies with low methodological quality and limited confidence levels. No significant effects were observed on mortality, reduction of hospitalizations or exacerbations, or quality of life.

Recommendation: oxygen therapy should be prescribed for walking activities in COPD patients who have moderate hypoxemia during exercise and dyspnea during or after exertion. Benefits should be evaluated individually with the patient and their caregiver (weak recommendation, low evidence).

Specifications: in patients with COPD and moderate hypoxemia with exercise desaturation, defined blood oxygen levels of less than 88% in the walking test, oxygen therapy while walking improves dyspnea after exercise and scores in the dyspnea and fatigue domains of quality of life assessments. However, there is no evidence that it improves mortality or exercise capacity.[46] Both patients and their caregivers should receive training on the use of oxygen equipment and safety.[39]

Regarding the efficacy of oxygen therapy for the treatment of isolated nocturnal hypoxemia, a recent randomized, double-blind, placebo-controlled trial failed to show any decrease in mortality, worsening of disease, or progression to LTOT,[47] so this intervention is not recommended.

Non-invasive ventilation

Patients with persistent hypercapnia after a COPD exacerbation requiring acute non-invasive ventilation have a greater likelihood of readmission or death than patients who achieve normal $PaCO_2$. Long-term home mechanical ventilation has shown survival benefits in hypercapnic patients with stable COPD who have a history of previous acidotic exacerbations. It is also indicated in individuals who remain hypercapnic 2–4 weeks after an episode of hypercapnic respiratory failure requiring hospital ventilatory support, given its benefits in extending time until hospital readmission or death.[48–50]

For more information on home mechanical ventilation, please consult the specific Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) guidelines.[51]

High-flow oxygen therapy in stable patients

High-flow nasal cannula therapy, capable of delivering oxygen-enriched humidified air through a nasal cannula at flow rates up to 60 L/min, has been recently introduced in COPD patients. In stable patients, high-flow nasal therapy improves mucociliary clearance, reduces nasopharyngeal dead space, and increases CO_2 washout. It also improves alveolar recruitment and gas exchange and reduces work of breathing.[52]

At present, evidence of its usefulness in stable-phase disease is limited, although it appears to reduce $PaCO_2$ in the short and long term, improve quality of life, and reduce the rate of acute exacerbation at 1 year. However, it does not improve exercise capacity, hospitalization rate, or mortality,[53] so its use cannot yet be recommended.

Surgical treatment

Bullectomy

Bullectomy is a surgical procedure for patients who have a giant bulla or complicated bullas associated with pneumothorax or infections. A giant bulla is defined as an air space that occupies more than 30% of the lung, and is typically associated with smoking, but also with marijuana use, intravenous drug abuse, and HIV infection.[54] Bullectomy is indicated in selected patients with dyspnea on exertion and bullae occupying more than 30% of the hemithorax, FEV_1 < 50%, and compression of the adjacent lung parenchyma. This technique has shown improvement in exercise tolerance, lung function, and decreased dyspnea.[55]

Lung transplantation

According to the International Society for Heart and Lung Transplantation (ISHLT), lung transplantation should be considered in patients who are receiving correct treatment and have a high risk of death (greater than 50% within 2 years), but who also have a greater than 80% probability of surviving the postoperative period and up to 5 years after the transplant.[56]

Specific indications for lung transplantation in COPD are a BODE index (BMI, obstruction, dyspnea, and exercise) >7, FEV_1 < 20%, CO transfer capacity (DLCO) < 20%, pCO_2 > 50 mmHg, or the presence of *cor pulmonale*.[56] Absolute contraindications include malignant disease in the previous 5 years (or 2 years in the case of melanoma), smoking cessation less than 6 months previously, BMI > 35, irreversible organ dysfunction, and functional limitation that prevents

rehabilitation after transplantation.[55] Age is a relative contraindication, ranging between 65 years maximum for single-lung and 60 years maximum for double-lung transplantation.[57] However, transplantation beyond those ages is feasible, but an individualized assessment must be made.

Data on the effect of transplantation on the survival of COPD patients are still conflicting, but the recognized effects on lung function, quality of life, and exercise tolerance justify this procedure.[58] Double-lung transplantation offers a median survival of 7.7 years, which is longer than the 5 years reported for single-lung interventions,[59] especially in patients younger than 60 years.[60]

GesEPOC recommends following current SEPAR lung transplantation guidelines[57]:

1. Refer patient lung transplant assessment if BODE > 5.
2. Indicate lung transplantation if BODE = 7–10 and any of the following criteria are present:
- Hospitalization with documented hypercapnia (pCO_2 > 50 mmHg)
- Cor pulmonale
- FEV_1 < 20% and DLCO < 20% or diffuse homogeneous emphysema

Lung volume reduction techniques

Surgical lung volume reduction techniques

Lung volume reduction surgery consists of eliminating emphysematous lung areas that do not contribute to gas exchange in order to improve ventilatory mechanics in the remaining lung parenchyma. The most extensive study to date (NETT) has shown that patients who benefit most from this reduction have emphysema in the upper lobes and low exercise capacity,[61] defined as <40 W in men and <25 watts in women on a cardiopulmonary exercise test. This reduction surgery improves symptoms, lung function, exercise tolerance and increases survival in a defined group of emphysematous patients. It should be carried out exclusively in centers with experience.[55] Patients with FEV_1 < 20% and homogeneous emphysema on computed tomography or DLCO < 20% have higher mortality than patients treated medically.[62]

Endoscopic lung volume reduction techniques

Although lung volume reduction surgery may be beneficial in carefully selected patients in whom medical treatment fails, the morbidity and mortality associated with surgery have led us to consider the role of endoscopic techniques in the non-surgical reduction of lung volumes.[63] Randomized clinical trials have shown that unidirectional endobronchial valves significantly improve FEV_1 and the 6-minute walk test 6 and 12 months after the endoscopic procedure compared with a control group.[64] A randomized controlled trial has shown clinically relevant improvements in dyspnea, lung function, exercise capacity, and quality of life 12 months after valve placement, particularly in patients with heterogeneous emphysema and those with no evidence of collateral ventilation.[65] The most common side effects of this procedure are pneumothorax and valve repositioning. Another clinical trial, which used a different type of valves in patients with interlobar fissure integrity evaluated by high-resolution CT, has shown improvement in FEV_1 and quality of life with reduction of hyperinflation and dyspnea.[66,67] The benefits of endobronchial valves are comparable to volume reduction surgery, but with fewer complications.[63]

Other endoscopic techniques in which the benefit does not seem to depend on fissure integrity or the absence of collateral ventilation include wire coils or water vapor ablation. Two multicenter studies have shown improvement in the 6-minute walk test, lung function, and health status 6 months after coil placement in patients with homogeneous and heterogeneous emphysema.[64,68] Thermal vapor ablation has also shown clinically significant improvements in lung function and health status in randomized, controlled clinical trials persisting 12 months after surgery.[69,70] These techniques are not available at most centers and experience is limited.

For patients with severe emphysema with large areas of pulmonary hyperinflation that remain symptomatic despite medical treatment, lung reduction volume using endoscopic techniques should first be evaluated, while surgery should be reserved for patients who are not candidates for this approach or who do not improve after endoscopic procedures.[54]

Funding

These guidelines were developed and prepared without any external funding.

Conflict of interests

Borja G. Cosio has received honoraria for speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, AstraZeneca, Menarini, and Novartis; consulting fees from AstraZeneca, Chiesi, GlaxoSmithKline, Novartis, and Sanofi; and research grants from GlaxoSmithKline, Menarini, Chiesi, and AstraZeneca.

Jose Luis López-Campos has received honoraria in the past 3 years for lectures, scientific consultancy, clinical trial participation, and preparation of publications from (in alphabetical order): AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, Esteve, Ferrer, Gebro, GlaxoSmithKline, Grifols, Menarini, Novartis, Rovi, and Teva.

Marc Miravitlles has received honoraria for speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, AstraZeneca, GlaxoSmithKline, Menarini, Rovi, Bial, Sandoz, Zambon, CSL Behring, Grifols and Novartis; consultancy fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Ferrer, GlaxoSmithKline, Bial, Gebro Pharma, Palobiofarma SL, CSL Behring, Laboratorios Esteve, Ferrer, Mereo Biopharma, Verona Pharma, Spin Therapeutics, pH Pharma, Palobiofarma SL, Novartis, Sanofi, and Grifols; and research grants from Grifols.

Myriam Calle has received honoraria for speaking engagements from Novartis, Chiesi, AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline.

Juan José Soler-Cataluña has received honoraria for scientific consultancy and for speaking at conferences organized by AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, Grupo Ferrer, GlaxoSmithKline, Laboratorios Esteve, Teva, Menarini, Mundipharma, Novartis, Rovi, and Zambon.

Ciro Casanova has received honoraria for speaking engagements and consultancy and has received research grants from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, and Novartis.

Eusebi Chiner has received fees honoraria for speaking engagements and consultancy or research grants from AstraZeneca, Boehringer Ingelheim, Chiesi, FAES Pharma, GlaxoSmithKline, AstraZeneca, Menarini, Novartis, and Sanofi.

Carme Hernandez has received honoraria for speaking engagements and for scientific consultancy from AstraZeneca, GSK, and Sanofi.

Elena Gimeno-Santos has received honoraria for speaking engagements and for scientific consultancy from Chiesi and Boehringer Ingelheim.

The other authors state that they have no conflict of interests.

Appendix A. GesEPOC Task Force 2021

Coordinator: Marc Miravitlles, Sociedad Española de Neumología y Cirugía Torácica (SEPAR).

Steering committee: Pere Almagro, *Sociedad Española de Medicina Interna (SEMI)*; Julio Ancochea, Myriam Calle, Ciro Casanova, Eusebi Chiner, Borja G. Cosío, Elena Gimeno-Santos, Carme Hernández, José Luis López-Campos, Juan Antonio Riesco, Nuria Seijas, Joan B. Soriano, Juan José Soler-Cataluña *(SEPAR)*; Jesús Molina, *Sociedad Española de Medicina Familiar y Comunitaria (semFYC)*; Dolors Navarro; *Asociación de Pacientes y Familiares de EPOC y Apneas del Sueño (APEAS), Federación Nacional de Asociaciones de Pacientes Respiratorios (FENAER), Foro Español de Pacientes (FEP)*; Leopoldo Palacios Gómez; *Federación de Asociaciones de Enfermería Comunitaria y Atención Primaria (FAECAP)*; Pascual Piñera Salmerón *Sociedad Española de Medicina de Urgencias y Emergencias (SEMES)*; Eulogio Pleguezuelos, *Sociedad Española de Rehabilitación y Medicina* Física (SERMEF), *Sociedad de Rehabilitación Cardiorrespiratoria (SORECAR)*; Sebastià Santaeugenia, *Sociedad Española de Geriatría y Gerontología (SEGG)*; Pere Simonet, *Grupo de Respiratorio en Atención Primaria (GRAP);)* José Tomás Gómez, *Sociedad Española de Médicos de Atención Primaria (SEMERGEN)*; Juan Antonio Trigueros, *Sociedad Española de Médicos Generales y de Familia (SEMG).*

Methodology: David Rigau; Centro Cochrane Iberoamericano, Barcelona, España.

Eusebi Chiner and Carme Hernández represent SEPAR patients.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2021.08.010.

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