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NCT
Neumología y Cirugía de Tórax
Fundada en 1939

# GMEPOC 2025

## Mexican Guideline for Chronic Obstructive Pulmonary Disease

## SPECIAL ISSUE

MEXICAN CLINICAL PRACTICE GUIDELINE FOR COPD 2025

An Official SMNyCT and INER Clinical Practice Guideline

**REVISTA OFICIAL DE:**
SOCIEDAD MEXICANA DE NEUMOLOGÍA Y CIRUGÍA DE TÓRAX,
INSTITUTO NACIONAL DE ENFERMEDADES RESPIRATORIAS ISMAEL COSÍO VILLEGAS

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*Message*

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# GMEPOC 2025. Message from the Mexican Society of Pulmonology and Thoracic Surgery

## GMEPOC 2025. Mensaje de la Sociedad Mexicana de Neumología y Cirugía de Tórax

José Luis Sandoval-Gutiérrez,*,‡ Catalina Casillas-Suárez,*,§ Jesús Javier Vázquez-Cortés*,¶

* Sociedad Mexicana de Neumología y Cirugía de Tórax. Mexico.
‡ Presidente.
§ Vicepresidenta.
¶ Presidente pasado.

Chronic obstructive pulmonary disease is currently the third leading cause of death in the world; if this trend continues, it could become the second leading cause of death in the future. Continuous education of health personnel in our country on this respiratory problem is an obligation of health institutions and medical professional associations. The Sociedad Mexicana de Neumología y Cirugía de Tórax has given, for several years, face-to-face and virtual courses through online seminars during the National COPD Week. Undoubtedly, the publication of GMEPOC 2025 will be a great tool to achieve this goal.

We congratulate all the authors who contributed their time and knowledge to have this educational element available, which results in better learning and benefits the health of our patients.

A special mention to Dr. Juan Carlos Vázquez for leading this project.

Congratulations!

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# Message from the National Institute of Respiratory Diseases Ismael Cosío Villegas

## Mensaje del Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas

Carmen Margarita Hernández-Cárdenas*

*Titular de la Dirección General, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico.

Among the chronic respiratory diseases, chronic obstructive pulmonary disease (COPD) has the greatest impact in terms of mortality, morbidity, work incapacity and social structure in the world. Latin America is immersed in this problem due to tobacco consumption, but also to the region's own habits that make it vulnerable due to the number of patients who present with symptoms secondary to exposure to fossil fuels.

Although there are various guidelines worldwide, the particularities of our populations, territory and the availability of drugs require a reference document written by experts who directly include our characteristics and preferences, in order to make the principles expressed as recommendations more applicable.

A document like this, renewed, updated and verified with the correct methodology, is of great value for the standardization of our practice as a country, for the consideration of correct public sector purchases and for the dissemination of a correct practice in physicians with availability in the most remote regions of Mexico.

Even more meritorious is the achievement of these guidelines that emerge from an international reference in the treatment of respiratory and associated diseases, such as the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, joining forces with the Sociedad Mexicana de Neumología y Cirugía de Tórax, institutions that, although independent, have traveled the academic world joining efforts to have greater achievements together.

One of these successes is the delivery of these superb joint clinical practice guidelines, GMEPOC 2025, the result of an exhaustive search and analysis to review an extraordinary amount of literature.

These guidelines, in a scientific world that is achieving more and more and better evidence, propose specific recommendations for the three levels of care, taking into account their characteristics and favoring the necessary knowledge to propose referrals when the situations of feasibility of care and treatment require it.

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# Mexican Clinical Practice Guideline for COPD 2025

## Guía de Práctica Clínica Mexicana de EPOC 2025

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**Official Clinical Practice Guidelines of the Sociedad Mexicana de Neumología y Cirugía de Tórax and the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (INER), Mexico.**

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**ABSTRACT. Introduction:** in 2020, the first edition of the Mexican Clinical Practice Guideline (CPG) for COPD (GMEPOC) was published. Given the progress of evidence in the diagnosis and treatment of the disease, it is essential to have an updated CPG. **Objective:** to develop an original CPG for the diagnosis and treatment of COPD aimed at the three levels of care in Mexico and for health professionals, as well as for patients and their caregivers, health institutions and stakeholders. **Methods:** GMEPOC 2025 was developed in compliance with international standards. An interdisciplinary Development Group was integrated, mainly expert on pulmonary medicine and methodologists. The scope and clinical questions were defined by consensus, international guidelines were evaluated, an exhaustive search for evidence was carried out followed by its evaluation and grading; finally, recommendations were formulated for each question by, which were agreed upon through a formal panel of experts. **Results:** a total of 25 structured and clinically relevant questions were defined, grouped into three categories: initial evaluation and diagnosis, comprehensive treatment of stable COPD, and treatment of COPD exacerbation. The formulated recommendations reached an average consensus value of 98.5% (91-100%) in a single round of a Delphi Panel. **Conclusions:** GMEPOC 2025 provides clinical recommendations based on scientific evidence, which were formulated by consensus of experts. These recommendations are objective, applicable, comprehensive and suitable for the Mexican health system and are expected to contribute to improving the quality of care.

**Keywords:** Clinical Practice Guidelines, Evidence-Based Medicine, Chronic Obstructive Pulmonary Disease, Mexico.

**RESUMEN. Introducción:** en 2020, fue publicada la primera edición de la Guía de Práctica Clínica (GPC) Mexicana de EPOC (GMEPOC). Debido al progreso de la evidencia en el diagnóstico y tratamiento de la enfermedad es fundamental contar con una GPC actualizada. **Objetivo:** desarrollar una GPC original para el diagnóstico y tratamiento de la EPOC dirigida a los tres niveles de atención en México y para profesionales de la salud, así como para los pacientes y sus cuidadores, las instituciones de salud y los tomadores de decisiones. **Métodos:** GMEPOC 2025 se desarrolló en cumplimiento con estándares internacionales. Se integró un Grupo de Desarrollo interdisciplinario, principalmente neumólogos y metodólogos expertos. Se consensuaron los alcances y las preguntas clínicas, se evaluaron las guías internacionales, se realizó una búsqueda exhaustiva de la evidencia seguida de su evaluación y jerarquización; finalmente, se formularon y graduaron recomendaciones para cada pregunta, las cuales fueron consensuadas a través de un panel formal de expertos. **Resultados:** se definieron un total de 25 preguntas estructuradas y clínicamente relevantes, agrupadas en tres categorías: evaluación inicial y diagnóstico, tratamiento integral de EPOC estable y tratamiento de la exacerbación de EPOC. Las recomendaciones formuladas alcanzaron un valor promedio de consenso de 98.5% (91-100%) en una sola ronda de Panel Delphi. **Conclusiones:** GMEPOC 2025 proporciona recomendaciones clínicas basadas en evidencia científica, las cuales fueron formuladas por consenso de expertos. Estas recomendaciones son objetivas, aplicables, integrales y adecuadas para el sistema de salud mexicano y se espera que contribuyan a mejorar la calidad de la atención.

**Palabras clave:** Guías de Práctica Clínica, Medicina Basada en Evidencia, Enfermedad Pulmonar Obstructiva Crónica, México.

## ABBREVIATIONS

6MWT = six-minute walk test
95%CI = 95% confidence interval
AATD = Z-Alpha-1 antitrypsin deficiency
ACIP = Advisory Committee on Immunization Practices
ACS = Acute COPD Syndrome
ADO = age, dyspnea and airflow obstruction
AF = atrial fibrillation
ALAT = Latin American Thoracic Association (for its Spanish meaning *Asociación LatinoAmericana de Tórax)*
AMBMT = active mind-body movement therapies
ATS/ERS = American Thoracic Society/European Respiratory Society
AUC = area under the curve
BCSS = breathlessness, cough, and sputum scale
BDI = baseline dyspnea index
BMI = body mass index
BODE = body mass index, obstruction, dyspnea, and exercise capacity
BODEx = body mass index, obstruction, dyspnea, and exacerbations
BODEx-S90 = body mass index, obstruction, dyspnea, exacerbations and oxygen saturation less than 90%
BOSA-90 = body mass index, obstruction, smoke, age, SpO2 < 90
BOSEA-90 = body mass index, obstruction, smoke, exercise, age, $SpO_2$ < 90
BTVA = bronchoscopic thermal vapor ablation
CAPTURE = COPD assessment in primary care to identify undiagnosed respiratory disease and exacerbation risk
CAT = COPD assessment test
CC16 = club cell secretory protein-16
CCQ = clinical COPD questionnaire
CCT = controlled clinical trials
CDC = Centers for Disease Control and Prevention
CDQ = COPD diagnostic questionnaire
CERT = COPD exacerbation recognition tool
CG = core group
CO = carbon monoxide
COPD = chronic obstructive pulmonary disease
COPD-PS = COPD population screener
COTE = COPD-specific comorbidity test
COVID-19 = infectious disease caused by Coronavirus
CPG = clinical practice guidelines
CRP = C-reactive protein
CRQ = chronic respiratory questionnaire
CT = computed tomography
CTGS = comprehensive treatment goals and strategies
DLCO = diffusing capacity of the lungs for carbon monoxide
DOSE = dyspnea, obstruction, smoking and exacerbations
DWAE = difference of the weighted averages of the effects
EBV = endobronchial valves
ENDS = electronic nicotine delivery systems
FDA = Food and Drug Administration
FeNO = fractional exhaled nitric oxide
$FEV_1$ = forced expiratory volume in 1 second
$FEV_1/FVC$ = ratio of forced expiratory volume in 1 second to forced vital capacity
$FiO_2$ = fraction of inspired oxygen
FVC = forced vital capacity
GBD = global burden of disease
GDG = guideline development group
GesEPOC = Spanish COPD guidelines (for its Spanish meaning *Guía Española de la EPOC)*
GMEPOC = Mexican clinical practice guideline on COPD (for its Spanish meaning *Guía de Práctica Clínica Mexicana de EPOC)*
GOLD = Global Initiative for Chronic Obstructive Lung Disease
GRADE = Grading of Recommendations Assessment, Development and Evaluation
HEPA = high efficiency particle arrester
HFNC = high flow nasal cannula
HIV = human immunodeficiency virus
HR = hazard ratio
HZ = herpes zoster
ICS = inhaled corticosteroids
ICSI = Institute for Clinical System Improvement
IgG = immunoglobulin G
IMT = inspiratory muscle training
IMV = invasive mechanical ventilation
INEGI = National Institute of Statistics and Geography (for its Spanish meaning *Instituto Nacional de Estadística y Geografía)*
INER = National Institute of Respiratory Diseases Ismael Cosío Villegas (for its Spanish meaning *Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas)*
IPAG = International Primary Care Airway Group questionnaire
LABA = long-acting beta-agonist
LAMA = long-acting muscarinic antagonist
LFQ = lung function questionnaire
LLN = lower limit of normal
LTOT = long-term oxygen therapy
MCID = minimal clinically important difference
MD = mean difference
MDI = metered-dose inhaler
MLD = mean lung density
mMRC = modified medical research council
NAC = N-acetyl cysteine
NHANES III = national health and nutrition examination survey
NICE = National Institute for Clinical Excellence

Contents

NIV = non-invasive ventilation
NNT = number needed to be treated
$NO_2$ = nitrogen dioxide
NST or NRT = nicotine substitution or replacement therapy
NZGG = New Zealand Guidelines Group
OR = odds ratio
$PaCO_2$ = partial pressure of carbon dioxide
$PaO_2$ = partial pressure of oxygen in arterial blood
PCV = pneumococcal conjugate vaccine
$PDE_4$ = phosphodiesterase-4
PEF = peak expiratory flow
PICO = population, intervention, comparison and outcome
Pimax = maximum inspiratory mouth pressure
PLATINO = Latin American Research Project on Pulmonary Obstruction (for its Spanish meaning *Proyecto LATinoamericano de INvestigación en Obstrucción pulmonar)*
PLATINOq = PLATINO questionnaire
$PM_{10}$ = particulate matter less than 10 microns
$PM_{2.5}$ = particulate matter less than 2.5 microns
PPSV23 = polysaccharide vaccines
PR = pulmonary rehabilitation
PRISm = preserved ratio impaired spirometry
PTS = pneumology and thoracic surgery
PUMA = Prevalence and routine practice (diagnosis and treatment) in the population at risk of COPD in general physicians in four Latin American countries (for its Spanish meaning ***P****revalencia y práctica habit****U****al (diagnóstico y tratamiento) en población de riesgo de EPOC en ****M****édicos generales de cuatro países de ****A****mérica Latina)*
RR = relative risk
Rrs = resistance
RSV = respiratory syncytial virus
RV = residual volume
SABA = short-acting beta-agonists
SAMA = short-acting muscarinic antagonists
$SaO_2$ = arterial oxygen saturation
SGRQ = Saint George's respiratory questionnaire
SIGN = Scottish Intercollegiate Guidelines Network
SLR = systematic literature reviews
SMD = standardized mean difference
SMNyCT = Mexican Society of Pneumology and Thoracic Surgery (for its Spanish meaning *Sociedad Mexicana de Neumología y Cirugía de Tórax, A.C.)*
$SO_2$ = sulfur dioxide
SP-D = surfactant protein D
$SpO_2$ = partial oxygen saturation
sRAGE = soluble receptor for advanced glycation end products
Tdap = tetanus, diphteria and pertussis
TDI = transition dyspnea index
TIO/OLO = tiotropium and olodaterol
TLC = total lung capacity
TS90 = total sleep time with $SaO_2$ < 90%.
UMEC/VI = umeclidinium and vilanterol
USPSTF = United States Preventive Services Task Force
V/Q = ventilation/perfusion
VA = ventricular arrhythmias
VAFOSQ = Veterans' Airflow Screening Questionnaire
VF = ventricular fibrillation
VT = ventricular tachycardia
WA% = wall area percentage
WHO = World Health Organization
WMD = weighted mean difference
WT = wall thickness
Xrs = reactances
R-CDQ = revised COPD diagnostic questionnaire
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death in Mexico and the world. The burden of this disease on the health of Mexicans is greater, not only in terms of fatalities, but also in terms of the disability it causes, the impact on the quality of life of patients and their families, and the personal and health system costs. However, in recent decades, great progress has been made in the incorporation of new treatments and in the comprehensive management of patients, which also means a major challenge for the continuing education and training of medical professionals, as well as for the care and education of people suffering from the disease.

Decision-making, both by medical professionals and by healthcare institutions and/or stakeholders, should be based on the best analysis of scientific evidence, as well as on expert recommendations made by consensus and with the greatest transparency. Worldwide, more and more efforts are being made to generate these recommendations, generally for both the diagnosis and treatment of major communicable and non-communicable diseases, including COPD. These recommendations are grouped in official documents called Clinical Practice Guidelines (CPG), which are usually managed and developed by governmental or non-governmental organizations, such as professional medical associations. CPG should be developed under standardized and validated procedures and methodology, as well as strict quality criteria.

The inequity of health systems in Mexico is an unavoidable reality; clearly, there is a lower availability of resources and specialists, particularly in respiratory medicine, as well as outside large cities and hospital centers. This contrasts with an increasing mortality and prevalence of COPD, as well as the other respiratory diseases that are a public health problem. Therefore, CPG recommendations should take into account the current state and organization of health systems, the availability of resources, cultural differences and patient preference, considering and respecting their values and beliefs.

The Mexican CPG on COPD (GMEPOC 2020) was born as an effort of the authors and their institutions, under the management of the Sociedad Mexicana de Neumología y Cirugía de Tórax, A.C. (SMNyCT). In this new version of the Mexican CPG on COPD (GMEPOC 2025), the development group decided to produce an original CPG, under the highest methodological and quality standards. For the first time in Mexico, a CPG, GMEPOC 2025, is presented as an official document of the major institutions of respiratory medicine, the SMNyCT and the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (INER). Its development, but most of all its implementation, seeks mainly to contribute to reduce the gap in the diagnosis and treatment of people with COPD, among the different institutions and at all levels of care of our health system.

## THE BURDEN OF COPD IN MEXICO

The Global Burden of Disease 2021 (GBD) study contains information on diseases and risk factors covering nearly 330,000 data from different sources and from 204 countries and territories globally, including Mexico.[1,2] In 2017, this study placed COPD as the third leading cause of death overall with 46.1 deaths/100 thousand; displaced to fourth place in mortality in 2021 (45.2 deaths/100 thousand) only by the advent of the COVID-19 pandemic, which ranked third during that year. COPD mortality corresponds to 5.48% of all fatalities, more than 3 million deaths annually worldwide.[1,3]

In 2017, in Mexico it was estimated that 4.07% of all deaths were due to COPD, almost 29 thousand fatalities; while, in 2021, during the COVID-19 pandemic, it accounted for 2.75% of deaths (23.75 deaths/100 thousand) with increasing mortality since 1990.[4] In the last two decades, this disease has fluctuated between the fourth and ninth cause of death according to official statistics in our country. In 2022, according to the National Institute of Statistics and Geography (INEGI for its Spanish meaning Instituto Nacional de Estadística y Geografía), COPD ranked as the ninth leading cause of death with a total of 18,605 deaths, 39% in women and 61% in men.[5] Mortality data in Mexico should be interpreted with caution since the disease designations are still very varied within the International Classification of Diseases (ICD J40-J44); these include COPD, emphysema, chronic bronchitis, although there are separate groups for asthma (J45-J46) and bronchiectasis (J47), they are grouped together with COPD, emphysema and chronic bronchitis, as obstructive diseases. The accuracy of records can also be affected by underdiagnosis and misdiagnosis of the disease since obstructive diseases are easily confused or overlap with each other.

In general, the COPD mortality rate in Mexico is lower than the world average (40.7 versus 79.8 deaths/100 thousand) for men and women aged 25 years and older. However, if mortality is reviewed in detail for each state of the republic, it fluctuates from 22.4 to 64.0/100 thousand, for Baja California Sur and Zacatecas, respectively, a difference of 2.85 times within the national territory *(Figure 1)*. Geographical differences in mortality could be influenced by risk factors, such as exposures, population factors and the quality of local registries. What is clear is that mortality has been rising throughout the territory and has nearly doubled

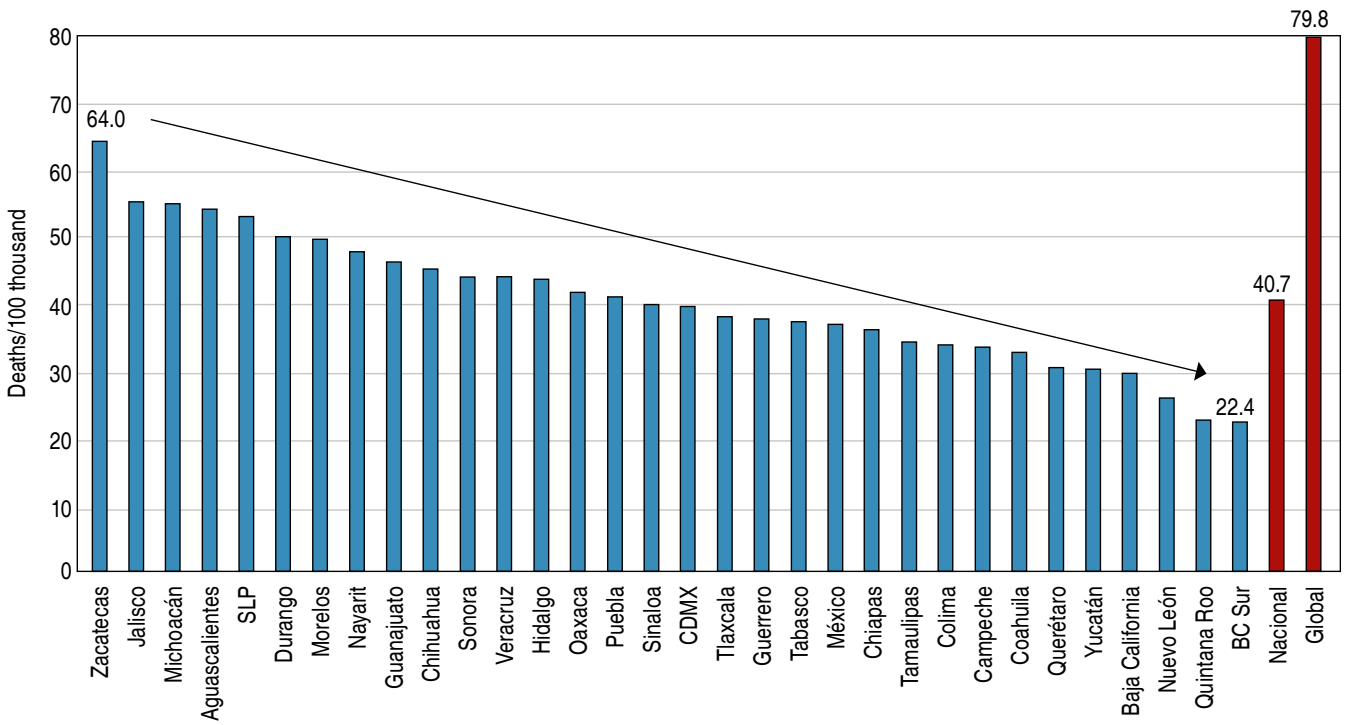


**Figure 1:** COPD mortality rate in Mexico, 2021.
COPD mortality rate by Mexican states in 2021, deaths/100 thousand aged 25 years or older and both sexes, according to the Global Burden of Disease study.[1]

since 1990; *Figure 2* illustrates the trend for the overall mortality rate by state from 1990 to 2021.

Data on COPD prevalence are still limited for the dimensions of the disease in our country, since they do not represent the entire national territory. The PLATINO study, a population-based study conducted in the metropolitan area of Mexico City in subjects aged 40 years or older, showed a prevalence of COPD of 7.8%, a diagnosis made with the gold standard, spirometry and its criterion of $FEV_1$/FVC < 0.70 post-bronchodilator.[6] This survey is more than 20 years old (2002) and the definition may include a significant proportion of false positives, particularly in persons older than 60 years. More recent analyses of this same data estimate that the actual prevalence in Mexico is close to 4%, one of the lowest globally.[7] Similarly, another study with the same PLATINO population base conducted in 2010 found a COPD prevalence of only 2.5%.[8] COPD associated with biomass smoke is also an important condition in Mexico. A study of a suburban population in Mexico City described a prevalence of exposure to biomass smoke of 47%, with a COPD prevalence of 2.5% of the entire population studied and 3.1% for women exposed to biomass smoke.[9] Similarly, in women in a rural area of the Estado de México, an overall prevalence of COPD of 13.1% (GOLD 1-4) and 2.5% of COPD GOLD 2-4 was described.[10] Like mortality, prevalence could suffer the same significant territorial differences, as can be seen in the GBD 2021 study.[1] *Figure 3* plots the prevalences estimated by the GBD study for each state from 1990 to 2021. Although these are estimates based on mortality, the prevalence is clearly rising in a linear fashion.

Underdiagnosis and misdiagnosis are two of the most challenging aspects of COPD in Mexico and worldwide. The PLATINO study described that 86% of people with COPD had not been previously diagnosed (underdiagnosis); in addition, it was found that approximately half of the individuals with a previous medical diagnosis of COPD, chronic bronchitis or emphysema never had a spirometry test (diagnostic error).[11] Underdiagnosis was > 85% in cases with mild-moderate airflow obstruction (GOLD 1 and 2), 60% in severe cases (GOLD 3) and 25% in very severe cases (GOLD 4). The diagnosis of COPD requires confirmation by spirometry with bronchodilator, a method that demonstrates airflow obstruction and is still insufficiently available in our country. In 2015, a study of 44 cities in 27 countries found a population-level underdiagnosed COPD frequency of 81.4% on average (50-98%) and included Mexico City with 81.6%.[12]

Causal risk factors may explain the behavior and burden of COPD, and predict an increase in the burden of the disease in the coming decades; explained by the persistence

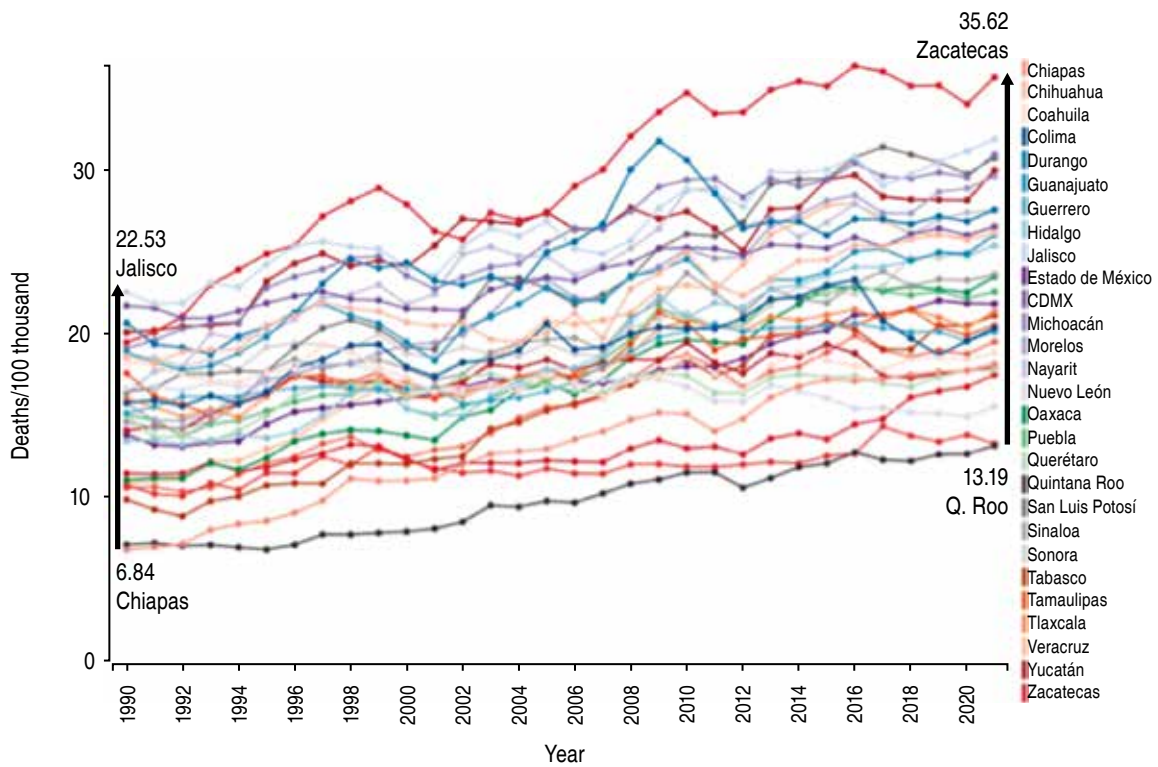


**Figure 2:** COPD mortality rate in Mexico from 1990 to 2021.
COPD mortality rate and by state from 1990 to 2021, for both sexes and all ages, according to the Global Burden of Disease study.[1]

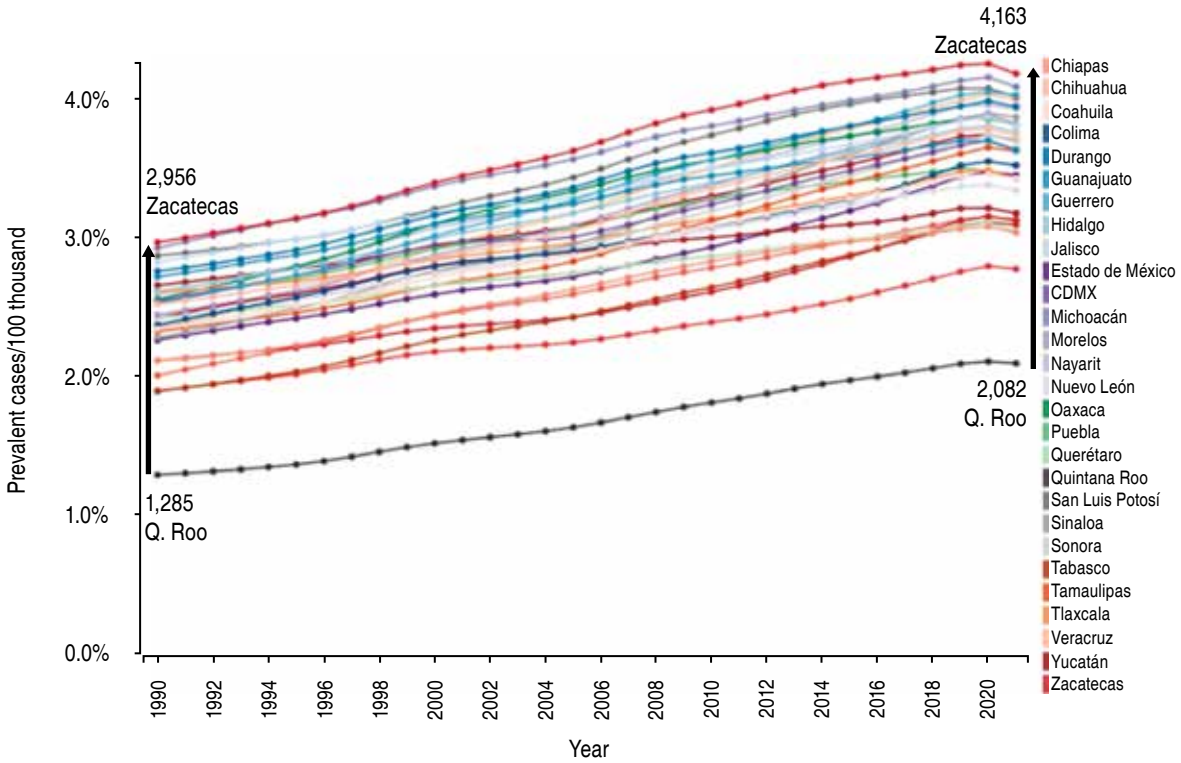


**Figure 3:** Prevalent cases of COPD in Mexico from 1990 to 2021.
Prevalent cases per 100 thousand and by state during 1990 to 2021, for men and women aged 25 years and older, according to the Global Burden of Disease study.[1]

of causal exposures, population aging and related lifestyles. The GBD 2017 study, estimated that COPD mortality was 67% attributable to harmful air exposures: 37% to smoking, 14% to biomass smoke exposure, and 16% to air pollution (particulate matter 6%, ozone 5%, and occupational ambient pollutants 5%).[4]

The expenses derived from respiratory diseases are enormous. In 2006, the National Institute of Public Health estimated that the annual cost of smoking-related diseases was 45 billion pesos; it corresponded to 8-15% of health spending for four conditions alone: COPD, lung cancer, myocardial ischemic disease and cerebrovascular disease.[13] In 2016, at the INER, COPD spending was 52 million pesos for 508 patients, an average of 102,362 pesos per patient.[14] In 2022, a study in Mexico using the microcosts technique and with a time horizon of one year, estimated the average cost for COPD diagnosis at $1,255 USD while for disease control it was $1,500 to $5,110 for GOLD stages 1 to 4; the average cost for patients with exacerbation was $1,164 to $23,718 for the same stages; a clear increase in costs related to severity and exacerbations.[15] In addition, patients' out-of-pocket expenses are also proportional to the severity of the disease; in 2014, in the United States they were estimated at $1,116 to $2,240 USD per year, with a total annual national cost of 36 billion USD for 13.7 million people with COPD.[16]

# METHODOLOGY

## Material and methods

The continuous and progressive learning process, which requires time and is gradually refined, aims to develop the diagnostic and therapeutic skills necessary to provide better patient care. This process leads to clinical experience, which also requires tools that facilitate the incorporation of emerging scientific knowledge to support clinical decision making. Systematic literature reviews (SLR) are fundamental, as they present explicit, rigorous and exhaustive research protocols that allow the identification, critical evaluation and synthesis of relevant studies, thus becoming the basis of evidence-based medicine.[17] In this context, our document has been prepared in accordance with the highest international quality standards.

CPG require a well-defined protocol for their development, integrating the best available evidence together with the clinical experience of multidisciplinary expert groups. The classification of the scientific evidence was performed following the system instituted by the Scottish Intercollegiate Guidelines Network (SIGN) *(Table 1)*. In this system, the highest level of evidence is given to systematic reviews of controlled clinical trials (CCT) with very low risk of bias, and the quality of evidence progressively decreases through CCT with high risk of bias, cohort studies, case-control studies, and non-analytical studies, such as case series and case reports. At the lowest level of evidence is the experts' opinion.[18]

## CPG Development Group

The Mexican Society of Pulmonology and Thoracic Surgery formed a multi-collaborative and interdisciplinary working group composed of clinical experts from various therapeutic areas, such as pulmonary and cardiopulmonary medicine, respiratory physiology, geriatrics, palliative care, rehabilitation, critical medicine, public health, epidemiology, internal medicine and emergency medicine. Methodological experts with experience in the development

**Table 1:** Quality assessment of evidence, SIGN 50.

| | |
|---|---|
| **Level of evidence** | |
| **1++** | Systematic reviews with or without meta-analysis of CCT, or CCT with very low risk of bias |
| **1+** | Systematic reviews with or without well-developed meta-analysis or CCT with low risk of bias |
| **1−** | Systematic reviews with or without meta-analysis of CCT with high risk of bias |
| **2++** | High-quality systematic reviews of cohort or case-control studies. High-quality cohort or case-control studies with a very low risk of bias and a high probability that the association is causal |
| **2+** | Well-developed cohort and case-control studies with a low risk of bias and a high probability that the association is causal |
| **3** | Non-analytical observational studies, such as case series and case reports |
| **4** | Experts' opinion |
| **Levels of recommendation** | |
| **A** | At least one systematic review with or without meta-analysis or CCT rated 1++, and directly applicable to the population under study, or a body of evidence consisting mainly of studies rated 1+, directly applicable to the population under study and demonstrating consistent results |
| **B** | A body of evidence that includes studies classified as 2++, directly applicable to the population under study and that has demonstrated consistent results, or evidence extrapolated from studies classified as 1++ or 1+ |
| **C** | A body of evidence that includes studies classified as 2+, directly applicable to the population under study and that has demonstrated consistent results, or evidence extrapolated from studies classified as 1++ |
| **D** | A body of evidence classified as 3 or 4, or evidence extrapolated from studies classified as 2+ |

CCT = controlled clinical trials.
It is important to note that the degree of recommendation relates to the strength of the evidence on which the clinical recommendation is based. It does not reflect the clinical importance of the recommendation.
Modified from *Scottish Intercollegiate Guidelines Network* (SIGN).[18]

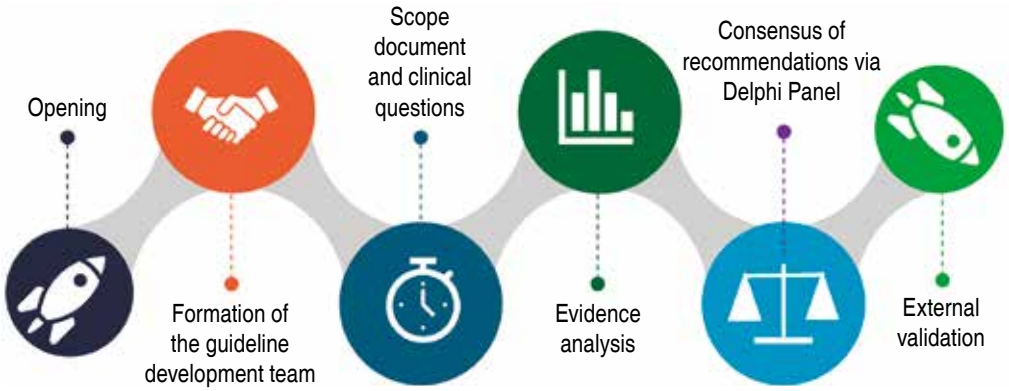


**Figure 4:**

Global development of the Clinical Practice Guideline. Modified from Mayorga J, et al.[19]

of SLR and CPG were also included. The working group was composed of a Core Group (CG) headed by two coordinators. This group met on multiple occasions remotely, through online platforms, to define the work method, deadlines and distribution of responsibilities, as well as key aspects in the definition of the general scope of the CPG and the structured clinical questions. On July 17, 2023, the methodology and members of the CPG Development Group were presented. On July 24 of the same year, the scope document and the list of clinical questions were agreed upon. Subsequently, biweekly remote meetings were held via electronic platforms to discuss the results of the systematized searches and the drafting of the initial recommendations *(Figure 4)*.

## Scope definition

The CPG Development Group elaborated by consensus the document that defined the general scope of the guideline, in which the characteristics of the population to be treated were established, as well as those of the population excluded from the scope of the document. This section defined the general framework for the development of the CPG. The general aspects of the disease and the clinical aspects addressed were detailed, in addition to specifying the target audience of the CPG, to which the clinical recommendations are addressed.

## Structured clinical questions

The CPG Development Group jointly prepared the complete list of clinical questions that address the core topics of the guideline. The clinical questions address gaps in knowledge and the most relevant clinical issues, as assessed by the members of the Development Group. In addition, new therapies and diagnostic methods that are changing the way COPD patients are treated today were included. The questions were intended to be clear, precise and specific, in order to facilitate the search for and identification of the scientific evidence, avoiding recommendations that were not adequately aligned with the clinical problems posed by the CPG. For its formulation, the PICO scheme was applied, which considers the "population", the "intervention", the "comparator" and the "clinical outcome", thus facilitating the identification and collection of the relevant scientific evidence *(Table 2)*.

## Exhaustive search for scientific evidence

The evidence was identified following internationally validated algorithms and strategies. Medical Subject Headings (MeSH) terms were identified and used to assemble a sensitive, specific, and explicit search strategy for future reproducibility. According to the nature of the clinical question to be answered, we established the type of study that was most reliable for answering it and, from there, other types of studies that help to provide an answer, although with less confidence, in the results following the evidence classification models.

The preliminary literature review included locating relevant existing CPG on the same topic. This facilitated the assembly of the scope document and the identification of relevant clinical questions on the topic. Based on this, the identification, evaluation and synthesis of the scientific evidence was carried out. The CPG identified were evaluated with the AGREE II (Appraisal of Guidelines for Research & Evaluation) tool, which was designed to assess the methodological quality and variability of the CPG.

The databases that compile CPG were consulted using the MeSH terms if they existed or, failing that, medical terms endorsed in published SLR. In the United Kingdom, the Guidelines Finder National Electronic Library for Health and the Trip Database were consulted for the identification of CPG, and in Spain, Guiasalud. The databases of the main international societies and academies in the area of specialty were also consulted in search of published CPG. NICE (National Institute for Clinical Excellence in the

United Kingdom), SIGN (Scottish Intercollegiate Guidelines Network), ICSI (Institute for Clinical System Improvement) in the USA, the Australian National Health and Medical Research Council (Australia), NZGG (New Zealand Guidelines Group) were consulted. Finally, databases of medical societies recognized for their work in research and development of evidence-based documents on COPD were consulted.

The comprehensive search for SLR assembled different search strategies and used various general and specialized

**Table 2:** Clinical questions from the Mexican Clinical Practice Guideline for COPD (GMEPOC) 2025.

| | |
|---|---|
| | **Evaluation and diagnosis** |
| 1 | What is the current definition of COPD? |
| 2 | What are the risk factors associated with developing COPD? |
| 3 | What tests are recommended for screening and diagnosis of COPD? |
| 4 | What are the spirometric diagnostic criteria for COPD? |
| 5 | What is the diagnostic utility of additional pulmonary function testing in patients with COPD? |
| 6 | What is the diagnostic accuracy of imaging studies in patients with COPD? |
| 7 | What is the usefulness of laboratory tests and biomarkers during the approach and follow-up of COPD? |
| 8 | What is the usefulness of clinimetric scales in the initial assessment of patients with COPD? |
| 9 | What is the impact of comorbidities on the diagnosis of COPD? |
| | **Treatment of stable COPD** |
| 10 | How effective are different smoking cessation strategies in patients with COPD? |
| 11 | What is the benefit of different strategies for controlling other exposures associated with COPD? |
| 12 | What is the efficacy and safety of lifestyle changes, diet, and exercise in patients with COPD? |
| 13 | What is the efficacy and safety of inhaled pharmacological therapy for the treatment of stable COPD? |
| 14 | What is the efficacy and safety of other non-inhaled medications (macrolides, phosphodiesterase 4 inhibitors, dupilumab, and mucolytics) for preventing COPD exacerbations despite optimal inhaled treatment (triple therapy LABA-LAMA-ICS)? |
| 15 | What is the efficacy and safety of various therapies (bacterial lysates, immunoglobulins, antileukotrienes, transfer factor, and immunotherapy) in patients with COPD? |
| 16 | In patients with stable COPD, what is the efficacy and safety of long-term oxygen therapy according to its indications, use in different conditions and activities, as well as the different devices available? |
| 17 | What is the efficacy and safety of pulmonary rehabilitation in patients with COPD? |
| 18 | What is the efficacy and safety of different vaccines in reducing exacerbations in patients with COPD? |
| 19 | What is the efficacy and safety of different treatment options involving bronchoscopic intervention and surgery in patients with COPD? |
| | **COPD exacerbation** |
| 20 | What are the diagnostic criteria for defining COPD exacerbation? |
| 21 | What are the criteria for outpatient and hospital management of patients with COPD exacerbation? |
| 22 | What is the efficacy and safety of pharmacological treatment for COPD exacerbation? |
| 23 | What is the efficacy and safety of oxygen therapy and ventilatory support in the management of patients with COPD exacerbation? |
| 24 | What are the criteria for hospital discharge for patients with severe exacerbation of COPD? |
| 25 | What are the effective measures for palliative care and end-of-life support for patients with COPD? |

ICS = inhaled corticosteroids. LABA = long-acting beta-agonist. LAMA = long-acting muscarinic antagonist.

**Table 3:** Types of recommendations.

| Evidence and clinical consensus | Recommendation |
|---|---|
| Undesirable consequences clearly outweigh the benefits | Strong recommendation against |
| Undesirable consequences probably outweigh the benefits | Conditioned recommendation against |
| The balance between undesirable consequences and clinical benefits is equilibrated or uncertain | Recommendation for research and possibly conditional recommendation for use in clinical trials |
| Clinical benefits probably outweigh undesirable consequences | Conditioned recommendation |
| Clinical benefits clearly outweigh undesirable consequences | Strong recommendation |
| **Drafting of recommendations** | |
| A "***strong recommendation***" can be made when there is confidence that, for the majority of our patients, the intervention or action offers more benefit than risk (or more risk than benefit). The recommendation should clearly direct and contain "should/should not" in its wording | |
| "***Conditional recommendations***" may be made when the intervention or action will provide more benefit than risk in most patients. Conditional recommendations may include "may be considered" in the wording of the recommendations | |

Modified from Scottish Intercollegiate Guidelines Network (SIGN).[18]

SLR databases. We used published and validated search strategies that have proven to be sensitive and specific, as well as MeSH terms.

The comprehensive search strategy included the following terms for PubMed: (((((((chronic obstructive airway disease[MeSH Terms]) OR (chronic obstructive lung disease[MeSH Terms])) OR (chronic obstructive pulmonary disease[MeSH Terms])) OR (pulmonary disease, chronic obstructive[MeSH Terms])) OR (chronic obstructive airway disease[Text Word])) OR (chronic obstructive lung disease[Text Word])) OR (chronic obstructive pulmonary disease[Text Word])) OR (COPD[Text Word])) OR (pulmonary emphysema[Text Word]) and the following terms for Embase: chronic obstructive lung disease'/exp.

Cochrane Library, The Campbell Collaboration Library of Systematic Reviews, Centre for Reviews and Dissemination databases (includes DARE) Centre for Reviews and Dissemination, MEDLINE, PubMed (National Library of Medicine in the United States) and EMBASE were consulted through Elsevier. Only in cases where clinical questions did not find an SLR to be answered or CPG had not identified high quality scientific evidence, extensive literature searches were conducted to identify clinical studies that answered that question.

The databases consulted to identify published clinical studies were: The Cochrane Library, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects20 (Issue 1 2023), Medline 1950-2023 (OVID), Embase 1980-2023 (OVID), Cinahl 1982-2023 (NLH Search 2.0), LILACS (1998 to 2023), ARTEMISA (1999 - 2023) and SCIELO (1999-2023).

## Quality assessment and evidence hierarchy

The evidence classification proposed by SIGN 2019 was employed, which uses two attributes to assess the quality of scientific evidence (level of evidence), which are study design and risk of bias. Numbers 1 to 4 are used to classify the study design. The number 1 corresponds to clinical trials or SLR, and 4 to expert opinion. To assess the risk of bias, signs are used that report the degree of compliance with the key criteria related to this potential risk (++, + and -). Thus, with the help of the critical reading template, each study is evaluated, whether they are individual studies (CCT, cohorts, etc.) or SLR[18] *(Table 3)*.

## Evidence extraction and analysis

Once the SLR were evaluated for quality and incorporated into the body of scientific evidence, meetings were held with the Guideline Development Group (GDG) to review the full text of each SLR in order to extract the results. The measures of association resulting from the meta-analyses reported in the CPG were considered to determine the overall effect size, either odds ratio (OR), relative risk (RR), difference of the weighted averages of the effects (DWAE) or mean difference (MD), according to the different outcomes defined by the GDG. For diagnostic test studies, other measures of association were considered, such as sensitivity, specificity, and positive and negative predictive values. In the cases of clinical questions, where no good quality published SLR were found, SLR was carried out to identify relevant clinical studies.

## Formal expert consensus

A modified Delphi Panel was conducted as a process to gather the experts' opinion. GDG members received an invitation via e-mail to review each of the clinical recommendations suggested by the GDG, which were posted on a digital platform designed for this purpose (Survey Monkey - https://es.surveymonkey.com). Each of the clinical experts assigned a rating using a "Likert scale" based on the degree of agreement they had with the content, applicability, wording and timeliness of each of the clinical recommendations. The Likert scale used has a lower limit of 1 and an upper limit of 9; the number 1 determines that the expert "strongly disagrees" with the approach of the recommendation and the number 9 determines that the expert "strongly agrees" with the recommendation. The intermediate numbers indicate that the expert does not have a well-defined position regarding the approach or wording of the recommendation. In addition, they were asked to include a clinical argument associated with their quantitative response in order to be able to make adjustments to the recommendation in the event that a satisfactory level of agreement among the experts was not achieved. The mean, standard deviation, median, interval and percentage of consensus were calculated for each of the recommendations. The minimum level of consensus was established as a mean of 7.0 and a percentage of at least 75% of responses in the range of 7-9 on the Likert scale. The GDG members kept control of the interaction between the participants, processing the information and filtering the relevant content, as well as modifying the recommendations according to the clinical arguments of all the panelists in order to send the new text to the next round of the Delphi Panel, to be re-evaluated by the same participants of the previous round *(Figure 5)*.

## Drafting of recommendations

The GDG members met on several occasions to review the body of evidence that would answer the structured clinical questions and to determine the level of recommendation. Both the scientific evidence analyzed and the clinical experience of the GDG and the risk/benefit ratio were considered in the drafting of the recommendations, in which we were especially careful to avoid ambiguities. The results of the Delphi Panel are presented in *Table 4* for the 25 clinical questions. The recommendations formulated reached an average consensus value of 98.5% (91-100%) in a single round.

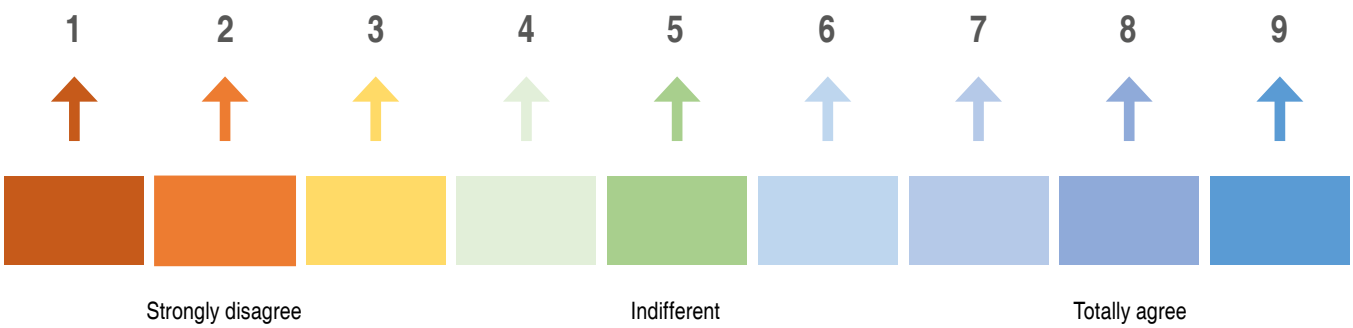


**Figure 5:** Likert scale used in the modified Delphi Panel.
The Likert scale evaluates the degree of consensus among experts regarding the content and wording of each of the clinical recommendations.
Modified from Mayorga J, et al.[19]

**Table 4:** Results of modified Delphi panel.

| | Clinical question | Mean ± SD | Median [range] | Consensus (%) |
|---|---|---|---|---|
| 1 | What is the current definition of COPD? | 7.9 ± 1.61 | 9 [2-9] | **91** |
| 2 | What are the risk factors associated with developing COPD? | 8.6 ± 0.67 | 9 [7-9] | **100** |
| 3 | What tests are recommended for screening and diagnosis of COPD? | 8.4 ± 0.83 | 9 [6-9] | **98** |
| 4 | What are the spirometric diagnostic criteria for COPD? | 8.3 ± 1.04 | 9 [5-9] | **95** |
| 5 | What is the diagnostic utility of additional pulmonary function testing in patients with COPD? | 8.4 ± 0.98 | 9 [4-9] | **98** |
| 6 | What is the diagnostic accuracy of imaging studies in patients with COPD? | 8.3 ± 1.00 | 9 [5-9] | **93** |
| 7 | What is the usefulness of laboratory tests and biomarkers during the approach and follow-up of COPD? | 8.3 ± 1.00 | 9 [5-9] | **95** |
| 8 | What is the usefulness of clinimetric scales in the initial assessment of patients with COPD? | 8.3 ± 0.81 | 9 [7-9] | **100** |
| 9 | What is the impact of comorbidities on the diagnosis of COPD? | 8.6 ± 0.66 | 9 [7-9] | **100** |
| 10 | How effective are different smoking cessation strategies in patients with COPD? | 8.5 ± 0.63 | 9 [7-9] | **100** |
| 11 | What is the benefit of different strategies for controlling other exposures associated with COPD? | 8.6 ± 0.73 | 9 [7-9] | **100** |
| 12 | What is the efficacy and safety of lifestyle changes, diet, and exercise in patients with COPD? | 8.5 ± 0.83 | 9 [6-9] | **98** |
| 13 | What is the efficacy and safety of inhaled pharmacological therapy for the treatment of stable COPD? | 8.7 ± 0.60 | 9 [7-9] | **100** |
| 14 | What is the efficacy and safety of other non-inhaled medicaments (macrolides, phosphodiesterase 4 inhibitors, dupilumab, and mucolytics) for preventing COPD exacerbations despite optimal inhaled treatment (triple therapy LABA-LAMA-ICS)? | 8.5 ± 0.70 | 9 [7-9] | **100** |
| 15 | What is the efficacy and safety of various therapies (bacterial lysates, immunoglobulins, antileukotrienes, transfer factor, and immunotherapy) in patients with COPD? | 8.6 ± 0.70 | 9 [7-9] | **100** |
| 16 | In patients with stable COPD, what is the efficacy and safety of long-term oxygen therapy (LTOT) according to its indications, use in different conditions and activities, as well as the different devices available? | 8.6 ± 0.54 | 9 [7-9] | **100** |
| 17 | What is the efficacy and safety of pulmonary rehabilitation in patients with COPD? | 8.6 ± 0.74 | 9 [7-9] | **100** |
| 18 | What is the efficacy and safety of different vaccines in reducing exacerbations in patients with COPD? | 8.7 ± 0.60 | 9 [7-9] | **98** |
| 19 | What is the efficacy and safety of different treatment options involving bronchoscopic intervention and surgery in patients with COPD? | 8.5 ± 0.77 | 9 [6-9] | **98** |
| 20 | What are the diagnostic criteria for defining COPD exacerbation? | 8.6 ± 0.66 | 9 [7-9] | **100** |
| 21 | What are the criteria for outpatient and hospital management of patients with COPD exacerbation? | 8.7 ± 0.6 | 9 [7-9] | **100** |
| 22 | What is the efficacy and safety of pharmacological treatment for COPD exacerbation? | 8.5 ± 0.74 | 9 [7-9] | **100** |
| 23 | What is the efficacy and safety of oxygen therapy and ventilatory support in the management of patients with COPD exacerbation? | 8.5 ± 0.89 | 9 [5-9] | **98** |
| 24 | What are the criteria for hospital discharge for patients with severe exacerbation of COPD? | 8.6 ± 0.62 | 9 [7-9] | **100** |
| 25 | What are the effective measures for palliative care and end-of-life support for patients with COPD? | 8.6 ± 0.66 | 9 [7-9] | **100** |

The mean, standard deviation, median, and range were calculated, as well as the percentage of agreement among the members of the Guide Development Group. A 75% consensus was established as an adequate percentage, and only one round was required to reach the level of agreement among participants.
ICS = inhaled corticosteroids. COPD = chronic obstructive pulmonary disease.
LABA = long-acting beta-agonist. LAMA = long-acting muscarinic antagonist.

## EVALUATION AND DIAGNOSIS OF COPD

Key points on COPD assessment and diagnosis are presented in *Table 5 and Figure 6*.

**Table 5: Key points:** clinical evaluation and diagnosis of COPD.

- The definition of COPD characterizes it as a public health problem with major challenges; it integrates its chronic symptoms (dyspnea, cough, phlegm, and exacerbations) with its pathophysiology, chronic, progressive, and not completely reversible airflow obstruction, only demonstrable by spirometry and secondary to chronic exposure to harmful respiratory agents.
- The main causal risk factors for COPD are chronic exposures (greater than 10 years), such as active smoking (≥ 10 pack-years) and passive smoking, biomass smoke, occupational exposures (dust, vapors, gases, and fumes), and direct exposure to air pollution.
- At all levels of care, individuals aged 40 years and older with chronic respiratory symptoms and/or causal risk factors for COPD should be referred for spirometry with bronchodilator, the gold standard for COPD diagnosis.
- In secondary and tertiary care, additional lung function tests are recommended, such as the DLCO test, which measures lung oxygenation capacity (correlated with emphysema, symptoms, and prognostic variables), and the six-minute walk test, which objectively measures individuals' functional capacity.
- All patients with suspected or diagnosed COPD should undergo imaging tests, including at least a plain chest X-ray, which can reveal hyperinflation (not diagnostic of COPD) and confirm comorbidities such as pneumonia, pleural disease, pulmonary nodules or masses, and others.
- Laboratory tests useful in evaluating people with COPD include: hemoglobin and hematocrit values to investigate anemia or polycythemia; blood eosinophil count (≥ 300 cells/µL) predicts risk of exacerbations and response to inhaled corticosteroids; and C-reactive protein (CRP), which helps classify exacerbations as moderate (≥ 10 mg/dL).
- Dyspnea and symptom scales (mMRC and CAT) help measure symptoms more accurately, which is a useful strategy for evaluating, monitoring, and adjusting patient treatment.
- Survival prediction scales (BODE variants) validated in the Mexican population (BOSA90 and BOSEA90) can be used to define strategic treatment objectives and goals, according to their prognostic variables: low weight[21] (Body mass index), degree of airflow Obstruction, active Smoking, low Excercise capacity, advanced Age, and low Oxigenation.
- In all patients with COPD, comorbidities must be identified and controlled. For prognostic purposes, those with cardiovascular risk and others should be highlighted: cancer, atrial fibrillation, heart failure, coronary heart disease, diabetes with neuropathy, gastric or duodenal ulcer, and pulmonary fibrosis.

BODE = body mass index, obstruction, dyspnea, and exercise capacity. CAT = COPD assessment test. DLCO = diffusing capacity of the lungs for carbon monoxide. mMRC = modified Medical Research Council.

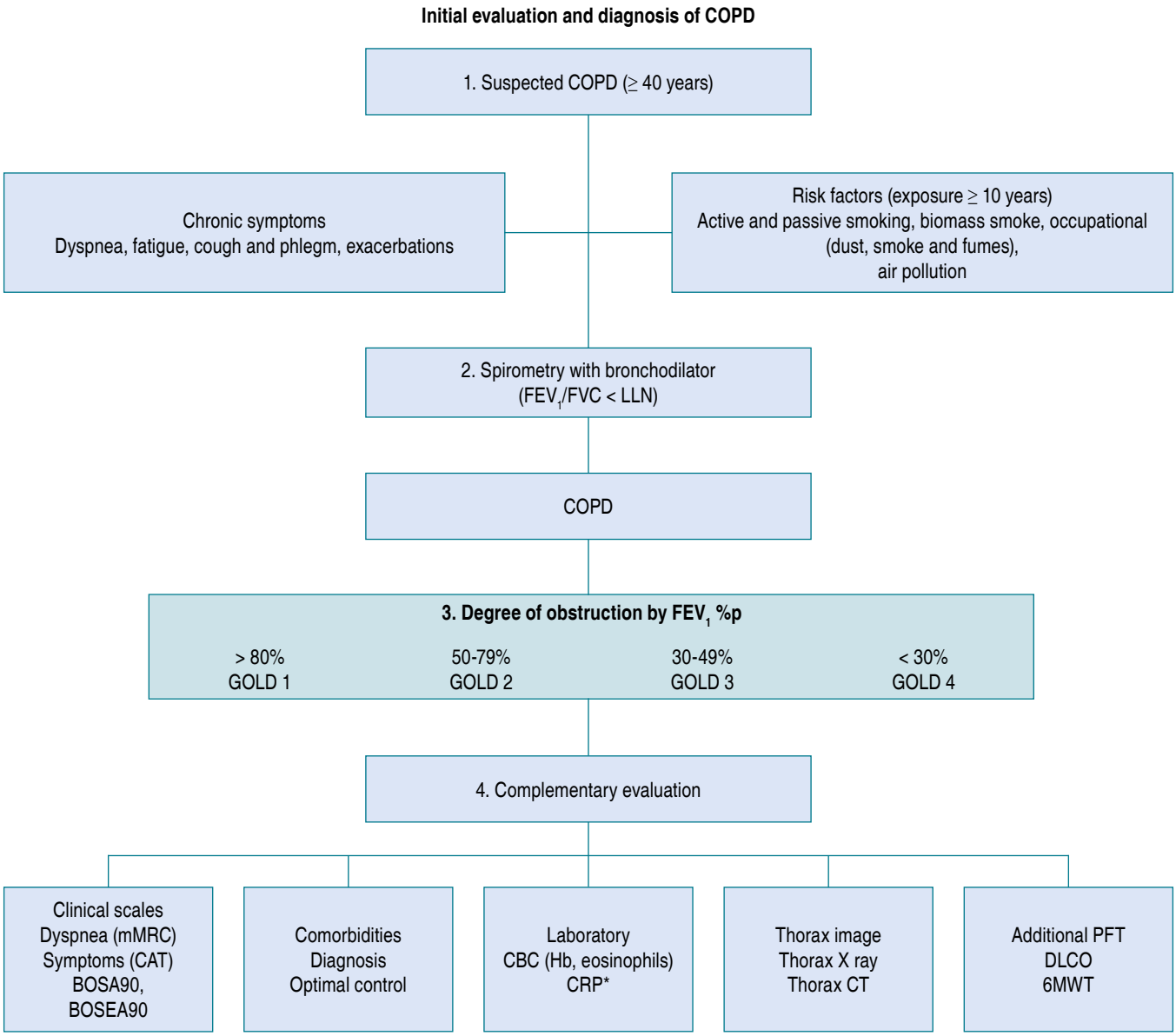


**Figure 6:**
The BOSA90 and BOSEA90 clinical scales are variants of the BODE prognostic scale validated in Mexico.[22]
* CRP is indicated in suspected exacerbation; a value of ≥ 10 mg/dL is compatible with moderate or severe exacerbation.
CBC = complete blood count. 6MWT = six-minute walk test. CAT = COPD assessment test. DLCO = diffusing capacity of the lungs for carbon monoxide. $FEV_1$ = forced expiratory volume in 1 second. FVC = forced vital capacity. Hb = hemoglobin. LLN = lower limit of normal. mMRC = medical research council dyspnea scale. CRP = C-reactive protein. PFT = pulmonary function testing. CT = computed tomography.

## The definition of COPD and its clinical utility

### Clinical Question 1: *What is the current definition of COPD?*

| Recommendations | | |
|---|---|---|
| 1 | The definition of COPD should be considered for the purpose of detection, diagnosis and treatment of patients; it is a comprehensive concept that can have an impact on the first level of care as it is a public health problem; it characterizes the disease by its chronic symptoms (dyspnea, fatigue, cough, expectoration and exacerbations), frequently underdiagnosed and with high morbidity and mortality. In addition, it deals with its pathophysiology as progressive and not completely reversible airflow obstruction, which establishes its main diagnostic criteria based on spirometry with bronchodilator and can be complemented with other physiological or structural tests | Evidence 1+ Recommendation A |
| 2 | New nosological terms such as early COPD, mild COPD, young COPD, Pre-COPD and PRISm have been recently proposed (GOLD 2023) to facilitate their future research as new opportunities for early diagnosis and prevention. These new definitions are still under investigation and it is not recommended that they be widely incorporated into clinical practice at the primary care level | Evidence 4 Recommendation D |

*Supporting text and analysis*

#### COPD definition

COPD[23] is a bronchopulmonary affection, condition or syndrome, heterogeneous in its presentation and evolution. It presents with chronic respiratory symptoms such as dyspnea, fatigue, cough, expectoration and/or exacerbations. This disease results from airway (bronchitis, bronchiolitis) and/or alveolar (emphysema) dysfunction that is linked to an abnormal pulmonary inflammatory response to chronic exposure to noxious particles or gases.[24-26] It represents a significant public health challenge because it is highly prevalent, frequently underdiagnosed, and has high morbidity and mortality rates.[25] In addition, it is characterized by persistent and commonly progressive airflow obstruction, which is primarily assessed by spirometry and other functional or imaging tests.[27,28] COPD may or may not be accompanied by extrapulmonary manifestations or coexist with other chronic diseases.[25]

Recently, the GOLD guideline has incorporated new nosological terms to facilitate future research as new opportunities for early diagnosis and prevention. The role of these conditions is yet to be defined for incorporation into widespread clinical practice; they include:

**Early COPD:** proposed only to analyze the first biological steps of the disease within an experimental model.

**Mild COPD:** this term is recommended only to describe mild disease related to airflow obstruction measured by spirometry (mild obstruction). In addition, this definition should exclude early COPD.

**Young COPD:** COPD seen in patients aged 20 to 50 years. It may be associated with structural and functional abnormalities and is not necessarily synonymous with mild COPD.

**Pre-COPD:** term proposed to classify individuals without airflow obstruction measured by spirometry, but with symptoms or other structural or functional abnormalities. These individuals may or may not develop airflow obstruction over time.

**PRISm:** acronym defined as Preserved Ratio Impaired Spirometry, refers to individuals with an $FEV_1/FVC$ ratio > 0.70 after bronchodilator, but with an $FEV_1$ value < 80% of predicted. This term was coined because its prevalence is high in the general population (7.1 to 11%) and in smokers (10.4-11.3%) and may be associated with respiratory symptoms, cardiopulmonary disease, cardiovascular mortality, hospitalizations and increased risk of developing airflow obstruction.[23]

## Risk factors

### Clinical Question 2: *What are the risk factors associated with the development of COPD?*

| Recommendation | | |
|---|---|---|
| 1 | In the evaluation of people with suspected COPD, risk factors for developing the disease (smoking and other causal factors) should always be questioned, for the purpose of early detection, diagnosis and comprehensive evaluation of patients. | Evidence 1++ Recommendation A |

Risk factors can be intrinsic and extrinsic. Intrinsic risk factors include: genetic factors (alpha1-antitrypsin deficiency), age older than 40 years, sex (women exhibit a higher risk of developing the disease at the same degree of exposure) and history of severe respiratory infections in childhood. Extrinsic factors include: active (smoking index ≥ 10 pack-years) and passive smoking, other forms of tobacco use, exposure to smoke from solid fuels, occupational factors (exposure to dusts, vapors, gases and fumes) and direct exposure to air pollution. Chronicity of exposure is an important component of the risk of developing disease, so COPD should be investigated in people with long-term risk exposures (≥ 10 years)

### *Supporting text and analysis*

The pathogenesis of COPD involves a complex interaction between intrinsic risk factors such as ethnicity, race, sex, age and genes, and environmental exposure to factors such as smoking, biomass, gases and dusts *(Table 6)*. In addition, inflammatory diseases, such as asthma and bronchial hyperreactivity, and respiratory infections (Mycobacterium tuberculosis, among others) affect normal developmental or aging processes.[29]

### *Intrinsic factors*

1. **Genetic factors:** alpha1-antitrypsin deficiency (SERPINA1 gene) affects approximately 1% of COPD patients and up to 2% of emphysema cases.[30]
2. **Pulmonary aging:** due to excessive telomere shortening.[31]
3. **Nutrition and patient weight:** some studies have reported contradictory results regarding the nutritional status of individuals and the risk of developing COPD. Deficiency in antioxidant (vitamin) intake and low fiber intake increase the risk of COPD.[32-35]
4. **Infections:** a history of severe respiratory infections during childhood has been associated with reduced lung function and risk of developing COPD in adulthood (OR: 2.23, 95%CI: 1.63-3.07).[36] The prevalence of COPD in people with a history of pulmonary tuberculosis (PTB) is 21%.[37] The risk of obstruction is 2.33 times higher compared to those without a history of TB.[25,38] It is estimated that in up to 69% of these cases, the only predisposing factor is tuberculosis disease.[25] On the other hand, patients with human immunodeficiency virus (HIV) infection are at increased risk of COPD, probably due to alterations in airway epithelial methylation.[39]
5. **Age and sex:** an increased prevalence of COPD in women has been described. Some studies suggest that women may be more vulnerable to the harmful effects of smoking, resulting in a more severe disease with a similar number of cigarettes consumed. For women who smoke at high levels (> 20 cigarettes per day), the risk of developing COPD is 2.75 times (95%CI 2.14-3.52), exceeding the estimate of 1.95 (95%CI 1.70-2.24) in men.[40] Likewise, biomass smoke constitutes a significant risk for both men (OR 4.30, 95%CI 1.85-10.01) and women (OR 2.73, 95%CI 2.28-3.28). Patients aged 50-69 years have a higher risk of developing the disease than those aged 40-49 years (OR 2.20, 95%CI 1.60-3.00 versus OR 4.70, 95%CI 3.50-6.40).[41]

### *Extrinsic factors*

1. **Smoking:** in developed countries, smoking accounts for 70% of COPD cases, while in lower-middle income countries it is responsible for 30-40%.[42] Smoking, with up to three times the risk (RR 2.89, 95%CI 2.63-3.17; active smoking RR 3.51, 95%CI 3.08-3.99)[41] contributes significantly to 54% of COPD-related mortality in men aged 30-69 years.[28,43,44] Likewise, passive exposure to cigarette smoke increases the risk (RR 1.72, 95%CI 1.31-2.23),[45] contributing up to 46% to its occurrence (OR 2.25, 95%CI 1.40-3.62) *(Table 7)*.[41,46-48]

   1.1 Risk associated with other forms of tobacco use: waterpipe use: OR 3.18, 95%CI 1.25-8.08.[49] Marijuana use: OR 2.45, 95%CI 1.55-3.88, when combined with tobacco: OR 2.90, 95%CI 1.53-5.51.[50,51]

2. **Exposure to solid fuels ($PM_{10}$ and $PM_{2.5}$).**[52] Contributes up to 35% to the increased prevalence of COPD[53] (OR 2.40, 95%CI 1.47-3.93).[54] Exposure to smoke from solid fuels is associated with the development of COPD (OR 2.80, 95%CI 1.85-4.0). This risk doubles when combined with smoking (OR 4.39, 95%CI 3.38-5.70) *(Table 7)*.[54]
3. **Occupational exposures:** constitute 10-20% of cases.[28,55] There is an association between exposure to vapors, gases, dusts and fumes with an increased risk of COPD (OR 1.43, 95%CI 1.19-1.73).[56]

**Table 6:** Risk factors for COPD.[59,60]

| Intrinsic | Extrinsic |
|---|---|
| Genetic factors | Smoking |
| Pulmonary aging | Solid fuels |
| Age | Occupational exposures |
| Gender | Environmental pollution |
| Ethnicity and race | Infections |
| Inflammatory lung disease | Lower-middle socioeconomic status |

COPD = chronic obstructive pulmonary disease.

**Table 7:** Main evidence of smoking and exposure to biomass smoke as risk factors for COPD.

| Authors and year | Study | Outcome | Conclusion |
|---|---|---|---|
| Rey-Brandariz *et al.,* 2023.[61] | Cross-sectional analysis | The risk of COPD increased with the duration of smoking up to ≥ 50 years OR 3.5 (95%CI 2.3-5.4), ≥ 39 cigarettes/day OR 10.1 (95%CI 5.3-18.4), lifetime smoking up to > 29 pack-years OR 3.8 (95%CI 3.1-4.8) | After 15-25 years of quitting, the risk of COPD could be the same as that of a person who has never smoked.<br>The time it takes for a smoker to develop COPD is approximately 30 years |
| Forey *et al.,* 2011.[43] | Systematic review | **Ever smoked** (COPD: RR 2.89, 95%CI 2.63-3.17; CB: RR 2.69, 95%CI 2.50-2.90; emphysema: RR 4.51, 95%CI 3.38-6.02)<br>**Current smoking** (COPD: RR 3.51, 95%CI 3.08-3.99; CB: RR 3.41, 95%CI 3.13-3.72; emphysema: RR 4.87, 95%CI 2.83-8.41)<br>**Former smokers** (COPD: RR 2.35, 95%CI 2.11-2.63; CB: RR 1.63, 95%CI 1.50-1.78; emphysema: RR 3.52, 95%CI 2.51-4.94) | Limited evidence available on age of initiation<br><br>RR for a given smoking index were markedly heterogeneous |
| PLATINO, 2005.[6] | Cohort | The average number of cigarettes smoked also varied considerably, from six cigarettes/day in Mexico City to 15 cigarettes/day in São Paulo; cumulative smoking history ranged from 10 pack-years in Mexico to 24 pack-years in São Paulo. 2008 | |
| Hu G *et al.,* 2010.[54] | Meta-analysis | Exposure-Response Relationships Between Biomass Smoke and COPD | Several metrics of smoke exposure were used, making it impractical to combine the results of the studies. All seven exposure response analyses found a positive trend, with a correlation between the development of COPD and increased level or duration of exposure to biomass smoke |
| Torres-Duque *et al.,* 2024.[62] | Population study | Exposure to wood smoke for ≥ 10 years was associated with an increased risk in both genders (women: OR 1.84, 95%CI 1.31-2.60; men: OR 1.53, 95%CI 1.08-2.18), and the prevalence of COPD reached 23.2% in those exposed for ≥ 30 years.<br>The prevalence of COPD was higher in those exposed to both wood smoke and tobacco smoke (16.0%) compared to those exposed only to wood smoke (6.7%) or only to tobacco smoke (7.8%) p < 0.001 | |
| Caballero A *et al.,* 2007.[63] | Population study | A large proportion of the subjects (60.7%) had used firewood for cooking at some point, and 39.3% had done so for more than 10 years | The prevalence of COPD, according to any definition, was significantly higher in people exposed to wood smoke, particularly in those exposed for more than 10 years (p < 0.001) |

CB = chronic bronchitis. COPD = chronic obstructive pulmonary disease. 95%CI = 95% confidence interval OR = odds ratio. RR = relative risk.

4. **Environmental pollution:** a negative association has been observed between short-term exposure to particulate matter ($PM_{2.5}$ and $PM_{10}$), sulfur dioxide ($SO_2$) and nitrogen dioxide ($NO_2$), and COPD morbidity and mortality. Exposure to $SO_2$ (RR 1.012, 95%CI 1.001-1.023) and $NO_2$ (RR 1.019, 95%CI 1.014-1.024). An increase of 10 $\mu g/m^3$ in $NO_2$ showed an HR of 1.07 (95%CI 1.00-1.16),[41,57] while an increase of 10 $\mu g/m^3$ in $PM_{2.5}$ showed an HR of 1.18 (95%CI 1.13-1.23).[58] In addition, unfavorable socioeconomic factors, such as poverty, are linked to increased exposure to various risk elements.[28,41]

## Case finding and diagnosis

### Clinical Question 3: *What are the indicated studies for case-finding and diagnosis of COPD?*

| Recommendations | | |
|---|---|---|
| 1 | It is recommended to search for cases of the disease at all levels of care, mainly at the first and second level. It should be investigated in people aged 40 years or older, with risk factors (see risk factors recommendation) and/or chronic respiratory symptoms (dyspnea and chronic bronchitis). These individuals must complete a clinical prediction scale and spirometry with bronchodilator. Clinical prediction scales generally show low sensitivity, but good specificity | Evidence 1+ Recommendation B |
| 2 | Use of the PUMA scale is recommended; individuals with a score ≥ 5 should be referred for bronchodilator spirometry, the primary diagnostic test. The sequential use of this clinical scale and spirometry increases diagnostic sensitivity and facilitates case finding | Evidence 2- Recommendation C |
| 3 | Screening or case-finding with spirometry or other diagnostic tests in asymptomatic adults without risk factors is not recommended | Evidence 2+ Recommendation B |

There is a population underdiagnosis of COPD estimated at 50-90%. About 30% of cases with risk factors are asymptomatic, and considerable time may elapse between the onset of symptoms and the identification of airflow limitation. Early detection is relevant to intervene (tobacco cessation and pulmonary rehabilitation), improving quality of life.[28]

It is recommended to search for cases from the age of 40 years in subjects with significant risk factors with or without symptoms, applying questionnaires and using spirometry with bronchodilator.[25,64] Dyspnea is the leading cause of medical attention and is associated with clinical outcomes. The mMRC (Modified Medical Research Council) dyspnea scale is used to categorize the degree of dyspnea in relation to exercise capacity *(Table 8)*.[28,64,65]

**Table 8:** Modified MRC dyspnea assessment scale.

| Grade | Description |
|---|---|
| mMRC 0 | Dyspnea with strenuous exercise |
| mMRC 1 | Dyspnea when hurrying on level or walking up on a slight hill |
| mMRC 2 | I walk slower than people of the same age for breathlessness on level, or I have to stop to breath when walking at my own pace on level |
| mMRC 3 | I stop for breath after walking about 100 meters or after walking for a few minutes on level |
| mMRC 4 | I am breathless to leave the house, or I am breathless when dressing, and undressing |

mMRC = modified Medical Research Council.

Previously, GMEPOC proposed simplifying the degrees of dyspnea into: no dyspnea or mild (mMRC 0 and 1), moderate (mMRC 2), and severe dyspnea (mMRC 4).[4]

*Table 9* summarizes the main evidence on COPD screening or case-finding strategies. Although the use of clinical prediction scales can improve early detection of COPD, the USPSTF (United States Preventive Services Task Force) advises against screening asymptomatic adults because of the good sensitivity, but modest specificity of screening questionnaires.[66,67] In our setting, we consider that the PUMA questionnaire should accompany spirometry as an early detection strategy[68,69] *(Table 10)*.

CAPTURE is a Spanish-validated questionnaire, which was developed to identify people at high risk or COPD exacerbation (area under the curve [AUC] 0.7954), and uses a set of items that can be easily applied in primary care.[84] This questionnaire has demonstrated its feasibility for application in low- and middle-income areas[86] *(Table 11)*.

**Table 9:** Diagnostic performance of different case-finding tools.

| Location, year | Study tool | Sensitivity % (95%CI) | Specificity % (95%CI) | PPV | NPV |
|---|---|---|---|---|---|
| **Meta-analysis** | | | | | |
| China, 2021.[70] | COPD-PS | 66 (47-63) | 86 | | |
| International, 2015.[71] | CDQ (cut-off point ≥ 19.5) | 64.5 (59.9-68.8) | 65.2 (52.9- 75.8) | 9.7 (6.9- 14.2) | 96.9 (95.8-97.7) |
| International, 2015.[71] | Peak flow meter/mini spirometer (Piko-6 or COPD-6) | 79.9 (74.2-84.7) | 84.4 (68.9- 93.0) | 23.0 (12.2-41.3) | 98.6 (97.9-99.1) |
| Spain, 2020.[72] | Mini spirometer (COPD-6) | 65 (63-68) | 80 (78-81) | – | – |
| **Observational studies**[73] | | | | | |
| Netherlands, 2022.[74] | CDQ (cut-off point ≥ 16.5 o > 17) | 87.5 (83.1-90.9) | 38.8 (27.7-51.3) | 7.7 (6.3-9.8) | 98.2 (96.6- 99.0) |
| USA, 2010.[75] | LFQ (cut-off point ≤ 18) | 79-93 (75-106) | 25-71 (21-77) | – | – |
| Greece, 2011.[76] | COPD-PS + peak flow meter | 20 | 92.9 | 14.3 | 95.1 |
| Greece, 2011.[71] | CDQ + peak flow meter | 74.4 (64.2-83.1) | 97 (95.2-98.3) | 59.1 (43.8-74.0) | 98.5 (97.9-99.0) |
| Austria, 2017.[77] | SCSQ (cut-off point ≥ 2) | 69.1 (56.6-79.5) | 60 (54.9-64.9) | 23.2 (17.7-29.7) | 91.8 (87.5-95.7) |
| Japan, 2020.[78] | IPAG + peak flow meter (cut-off point ≥ 18) | 81.6 | 59.7 | – | – |
| USA, 2016.[79] | VAFOSQ (cut-off point ≥ 25) | 59.9 | 69.8 | 37.7 | 85.1 |
| Spain, 2012.[80] | COPD-PS (Spanish version) (cut-off point ≥ 4) | 93.6 | 64.8 | – | – |
| Colombia, 2022.[81] | PUMA (cut-off point ≥ 5) | 60 | 66 | 29 | 88 |
| Uruguay.[82] | PUMA (Uruguay and PLATINO) | Montevideo: 69.9<br>PLATINO: 66.7 | Montevideo: 62.1<br>PLATINO: 66.5 | – | 70.9<br>89.9 |
| Colombia, Venezuela, Uruguay, 2016.[69] | PUMA (cut-off point ≥ 5) | 74.2 (68.6-79.2) | 64.8 (61.9-67.6) | 34.7 (30.9-38.6) | 90.9 (88.7-92.8) |
| Turkey, 2017.[83] | CAT | 66.67 | 75.15 | 10.53 | 98.09 |
| USA, 2017.[84] | CAPTURE<br>CAPTURE + peak flow meter | 95.7<br>89.7 | 44.4<br>78.1 | – | – |
| Mexico, 2013.[85] | PLATINOq + pocket spirometer (cut-off point ≥ 10) | PLATINOq 82-92<br>PLATINOq + Spirometer 64-70 | PLATINOq 47<br>PLATINOq + Spirometer 89 | – | – |
| Mexico, 2020.[8] | COPD-6 | 81 | 88 | 21 | 97-99 |

CAPTURE = COPD assessment in primary care to identify undiagnosed respiratory disease and exacerbation risk. CAT = COPD assessment test.
CDQ = COPD diagnostic questionnaire. COPD-PS = COPD population screener. IPAG = International Primary Care Airway Group questionnaire.
LFQ = lung function questionnaire. PLATINOq = platino questionnaire. PUMA = Prevalence and routine practice (diagnosis and treatment) in the population at risk of COPD in general physicians in four Latin American countries. SCSQ = Salzburg COPD-screening questionnaire.
VASFOSQ = Veterans Airflow Screening Questionnaire. NPV = negative predictive value. PPV = positive predictive value.

**Table 10:** PUMA questionnaire.[68,69]

| | Assigned score |
|---|---|
| What is your patient's gender? | Male (1), female (0) |
| How old (in years) is your patient?* | 40-49 (0), 50-59 (1), ≥ 60 (2) |
| Does your patient smoke or used to smoke? | No (0), yes (1) |
| **If the answer is yes:** | **Yes, package/years** |
| Average number of cigarettes per day × number of years smoking/20 = total | < 20 (0), 20-30 (1), ≥ 31 (2) |
| Does the patient have dyspnea? | No (0), yes (1) |
| Does the patient have chronic phlegm production or expectoration? | No (0), yes (1) |
| Does the patient have a chronic cough? | No (0), yes (1) |
| Has the patient ever had a spirometry test during their lifetime? | No (0), yes (1) |

Interpretation: result ≥ 5 points, spirometry is recommended to confirm the diagnosis of COPD.
PUMA = Prevalence and routine practice (diagnosis and treatment) in the population at risk of COPD in general physicians in four Latin American countries.

**Table 11:** CAPTURE-S questionnaire.[87]

| | No | Yes | |
|---|---|---|---|
| 1. Have you ever lived or worked in a place with dirty or polluted air, smoke, second hand smoke, or dust? | | | |
| 2. Does your breathing change with the seasons, the weather, or the air quality? | | | |
| 3. Does your breathing make it difficult to do things like carry heavy loads, remove dirt or snow with a shovel, jog, play tennis, or swim? | | | |
| 4. Compared to other people of your age, do you get tired easily? | | | |
| | 0 | 1 | 2 or more |
| 5. In the last 12 months, how many times have you missed school, work, or other activities due to a cold, bronchitis, or pneumonia? | | | |

CAPTURE scores 0-1: low risk for exacerbation or COPD. Score 5-6: high risk for COPD or exacerbation. Score 2-4: undergo peak expiratory flow (PEF) measurement.[84]
CAPTURE-S: COPD assessment in primary care to identify undiagnosed respiratory disease and exacerbation risk.

## Spirometric diagnostic criteria

### Clinical Question 4: *What are the spirometric diagnostic criteria for COPD?*

| Recommendations | | |
|---|---|---|
| 1 | At all levels of care, it is recommended that persons ≥ 40 years and scoring ≥ 5 on the PUMA scale (see case-finding and diagnostic recommendations) complete spirometry with bronchodilator testing. | Evidence 2++<br>Recommendation B |

Spirometry must be of good technical quality and for this it must be performed under own specifications and international quality standards (ATS/ERS, 2019); for the purpose of defining airflow obstruction confirming COPD, it is recommended to use the lower limit of normal (LLN) of the $FEV_1$/FVC ratio of the post-bronchodilator test and the reference values based on the algorithms of Martínez Briseño, Pérez Padilla, PLATINO or, in their absence, NHANES III of Mexican Americans

| | | |
|---|---|---|
| 2 | For grading the severity of obstruction it is recommended to use the GOLD stages based on the percentage of predicted $FEV_1$: mild obstruction $FEV_1 \geq 80\%$ (GOLD 1); moderate $FEV_1$ 50 to 79% (GOLD 2); severe $FEV_1$ 30-49% (GOLD 3); and very severe $FEV_1 < 30\%$ (GOLD 4) | Evidence 2++<br>Recommendation B |

It is recommended that in those individuals with age ≥ 40 years, with a score ≥ 5 on the PUMA questionnaire or exposure to other risk factors (see case-finding and diagnostic recommendations), spirometry with bronchodilator testing should be performed to confirm the diagnosis.[4] Spirometry is a physiological test that measures the maximum volume of air exhaled from a point of maximum inspiration in a forced maneuver.[88] The term "airflow obstruction" is used to describe the pathological reduction of airflow as evidenced by an $FEV_1$/FVC ratio below the lower limit of normal (LLN).[89] Spirometric definitions of airflow obstruction differ between the GMEPOC 2020 and ATS/ERS 2021 recommendations and those proposed by GOLD 2024 and ALAT 2019, which use a fixed $FEV_1$/FVC value of 0.7.[25,28,89] However, the $FEV_1$/FVC < 0.70 criterion may not detect obstruction in young people with risk factors and has a higher risk of false positives in people > 60 years of age without risk factors, being preferable the use of LLN.[90-92] The referred LLN values are based on the normal distribution and classify the lower 5% of the healthy population as abnormal (below the LLN). Spirometric variables should be compared with population reference values, calculated according to height, sex, age and racial population. For Mexico, the reference algorithms of Martínez Briseño, Pérez Padilla, PLATINO or, in their absence, NHANES III of Mexican Americans are recommended because they are adjusted to the Mexican population.[93-95] According to the ATS/ERS 2019 recommendations, proper interpretation of pulmonary function tests requires measurements that meet appropriate technical specifications and quality levels.[88]

In healthy individuals, a low $FEV_1$/FVC ratio accompanied by a $FEV_1$ within the normal range may be attributed to uneven growth of the airways and lung parenchyma, termed "pulmonary dysanaptic". Although it has been considered a normal physiological variant, it may be associated with propensity to COPD.[89] Some guidelines recommend repeat spirometry when borderline $FEV_1$/FVC values (between 0.6 and 0.8) are obtained, as this ratio may be affected by biological variations.[96] GOLD recommends not to perform spirometry with bronchodilator when COPD is suspected, if pre-bronchodilator spirometry does not show obstruction.[28] The bronchodilator test evaluates the degree of airflow improvement in response to bronchodilator administration, as measured by changes in $FEV_1$ and FVC. However, in recent years, it has become increasingly clear that the bronchodilator response has a poor value in differentiating between asthma and COPD.[88,97]

### *Graduation airflow obstruction*

Once the presence of the airflow obstruction is confirmed based on the $FEV_1$/FVC ratio, the severity of the airflow obstruction must be graduated. GOLD 2025 continues to recommend using the percentage of the predicted post-bronchodilator $FEV_1$ for definition purposes and with the following stages of severity: mild $FEV_1 \geq 80\%$ (GOLD 1); moderated, $FEV_1$ from 50 to 79% (GOLD 2); severe, $FEV_1$ from 30 to 49% (GOLD 3); and very severe, $FEV_1 < 30\%$ (GOLD 4). In contrast the ERS/ATS recommendations for the interpretation of the respiratory function tests (2022) recommend three stages of severity based on the $FEV_1$ z-score: normal > −1.65; mild obstruction between −1.65 and −2.5; moderate between −2.51 and −4; and severe < −4.1. Because these standards are recently incorporated, they are not available in all centers and/or in current spirometers. In addition, they require continuing education strategies to update them. The differences between these definitions generate different classifications of patients without having evidence on the management and prognosis impact. Also, GOLD 2025 argues that most of the studies that support the evidence of effective treatment are based on GOLD stages, so it recommends maintaining their use.

Spirometry limitations to identify the lung damage in absence of obstruction are recognized. The use of other tests allows to identify dyspnea during exercise, alterations in gas exchange (DLCO test), respiratory symptoms and structural alterations by image such as emphysema, air entrapment or thickening of airways.[28] These complementary tools are useful for specialists, mainly in patients with bordering blockage, allowing to assess lung damage before the obstruction appears. Even though they used to be available at many referral centers, in situations in where the diagnosis of obstruction is unclear, it is recommended to refer the patient to a specialist.

## Other diagnostic tests

### Clinical Question 5: *What is the diagnostic utility of additional pulmonary function testing in patients with COPD?*

| Recommendation | | |
|---|---|---|
| 1 | The use of additional pulmonary function testing is recommended for diagnostic assessment and to complement the functional assessment of those people suspected or diagnosed with COPD. | Evidence 2+<br>Recommendation C |

| | | |
|---|---|---|
| 2 | **Pulse Oximetry ($SpO_2$):** should be used at all levels of care to identify possible candidates for oxygen therapy; generally and regardless of altitude, a $SpO_2$ value < 88% is considered for the prescription of supplemental oxygen. | Evidence 2++<br>Recommendation B |
| 3 | **Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO):** it is recommended in the second and third level of care as a complementary test; it is associated with the severity of obstruction and the proportion of emphysema on tomography, it also predicts quality of life, morbidity, respiratory symptoms, exercise tolerance, pulmonary hypertension, exacerbations, hospitalizations and mortality | Evidence 1+<br>Recommendation B |
| 4 | **Six-minute walk test:** it is recommended in the second and third level of care; it measures the distance covered in meters during a six-minute walk, reflects functional capacity and predicts quality of life and mortality. It is particularly useful in patients with low perception of dyspnea and sedentary lifestyle; it is also used to measure effects of treatments and rehabilitation. | Evidence 2++<br>Recommendation B |
| 5 | It is suggested not to routinely perform other tests during the patients' assessment, such as lung volume measurement, oscillometry and FeNO measurement. | Evidence 2+<br>Recommendation C |

Patients exposed to risk factors for COPD can experience functional abnormalities in gas exchange, lung capacity and exercise tolerance even before the diagnosis is made by spirometry. So, the assessment of the lung function provides complementary information to spirometry.

**Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO).** Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO) measure in a single breath assesses the of gas exchange properties at alveolar level, including the ventilation (V), perfusion (Q) and V/Q distribution components, also it quantifies lung volumes.[28,98-100] The reduction of DLCO in COPD is associated with greater airflow obstruction and severity of emphysema measured by CT.[101-103] It also predicts, morbidity (quality of life, exercise tolerance and exacerbations), symptomatology. Pulmonary hypertension, frequent hospitalizations and higher mortality. It also predicts the development of obstruction in smokers with normal spirometry.[29,98,99,104]

**Pulse Oximetry ($SpO_2$) at rest.** The oxygen saturation measure by oximetry can identify candidates for oxygen therapy. In patients with COPD and hypoxemia ($PaO_2$ < 55 mmHg and/or arterial oxygen saturation ($SaO_2$) < 88%), *cor pulmonale* or polycythemia data, the survival rate is reduced and it can be improved with oxygen therapy.[105-108] Pulse Oximetry doesn't assess $PCO_2$ and acid base status, which is essential to identify patients with hypercapnic respiratory failure ($PaCO_2$ adjusted by altitude) and who can be candidates to non-invasive mechanical ventilation. GOLD 2024 recommends performing an arterial blood gas in those subjects with partial oxygen saturation ($SpO_2$) < 92% at sea level[28] or $SpO_2$ < 88% at moderate altitudes such as Mexico City (2,240 m).[109,110]

**Impulse Oscillometry (IOS).** IOS assesses the impedance of the respiratory system to the movement of air and tissues. In COPD an increase in resistances (Rrs) and a reduction in reactances (Xrs) are observed; indicative of obstruction in small airways, correlating with the severity of the obstruction.[108-111] IOS is more sensitive than spirometry and can identify abnormalities in smokers or exposed to other risk factors before spirometry obstruction,[110,111-113] but with less repeatability and reproducibility.

**Lung Volumes.** The measure of lung volumes identifies air entrapment (increase of residual volume [RV]), as well as lung hyperinflation (increase of the total lung capacity [TLC]). The most recommended tests to obtain these measures are body plethysmography and dilution technique of inert gases, such as helium.[28,114,115] The values of the TLC by plethysmography correlate weakly, but positively with the emphysema percentage ($R^2$: 0.33).[101] Even when these test are useful for assessing severity and detecting functional alterations in people exposed without obstruction, they are not essential for patient management.[28]

**Exercise test.** The six-minute walk test (6MWT) is a sub maximum exercise test that assesses the functional capacity by measuring the distanced covered in six minutes, reflecting the quality of life and mortality. It is useful for adjusting treatment in patients with low dyspnea perception or sedentary lifestyle.[116-121] It is also used to assess the exercise tolerance, calculate the BODE index and assess the training effect in lung rehabilitation programs and other therapeutic interventions.[122,123]

**FeNO.** Fractional exhaled nitric oxide (FeNO) reflects eosinophilic-type TH2 inflammation of the airway and

is useful in differentiating between COPD-asthma and COPD (AUC 0.76, sensitivity and specificity of 0.71).[124] The state of smoking influences FeNO levels in patients with COPD, showing in stable COPD higher FeNO levels than in healthy subjects.[125] A clear association between FeNO levels and exacerbations of COPD has not been stablished.[126] Smoking can reduce FeNO levels, possibly by interfering with nitric oxide- synthases and increasing arginase 1 expression.[125,127-129] On the other hand, the effect of chronic use of electronic nicotine delivery systems (ENDS) on FeNO is unclear, according to short term exposure studies.[130] In addition, inhale corticosteroids significantly reduce levels in ex-smokers with COPD.[131]

## Imaging studies

### Clinical Question 6: *What is the diagnostic accuracy of the imaging studies in patients with COPD?*

| Recommendations | | |
|---|---|---|
| 1 | It is recommendable that people with suspected or diagnosed COPD have, at all levels of care, at least a plain chest x-ray as an imaging study. It should not be used to confirm diagnosis; the most characteristic finding is the lung hyperinflation.<br>In addition, it can confirm comorbidities such as pneumonia, pleural pathology, fibrosis, lung nodules or masses, cardiomegaly and bone alterations such as kyphoscoliosis. | Evidence 2–<br>Recommendation C |
| 2 | It is recommended that when available, people with suspected or diagnosed COPD have a simple chest CT-scan with the objective of assessing the morphological phenotype (phenotypes of: airway, emphysema or combined).<br>It also allows a better structural assessment of associated comorbidities and other alterations such as nodules or masses, bronchiectasis, pulmonary artery dilation (suggestive of pulmonary hypertension) and the presence of aortic and coronary calcifications.<br>Its quantitative analysis requires iterative reconstructions of the volumetric analysis in inspiration and expiration, so it can define early disease. | Evidence 1+<br>Recommendation B |

Chest radiography provides useful information on COPD phenotypes and concomitant diseases and allows to follow the natural course of the disease.[132] This study, because it is easily accessible and inexpensive, is frequently used in the initial evaluation to rule out cardiovascular pathologies, oncology, interstitial diseases, infectious diseases and structural alteration.[28,133] Hyperinflation can be observed as the main finding per image; however, it is not specific to COPD.[4]

Despite not being routinely recommended for the diagnosis of COPD, the chest computerized tomography (CT) shows a sensitivity of 0.83 (95%CI 0.73-0.89) and a specificity of 0.87 (95%CI 0.70-0.95) as detection tools.[4,134] Its usefulness has increased in situations of persistent exacerbations, disproportionate symptoms, risk factors for lung cancer or a $FEV_1$ of 15 to 45% with marked hyperinflation.[25] NICE Guides recommend a clinical respiratory assessment and a spirometry in individuals with emphysema or with signs of chronic lung disease in imaging studies.[64]

Decreased in lung attenuation in the expiratory phase of CT can be used as an indirect sign of small airways dysfunction.[135] The areas of low attenuations in CT are associated with $FEV_1$/FVC, indicating that smokers with normal spirometry but abnormal findings in CT, such as emphysema, can develop obstruction in the airways in the future; this concept is considered defining of the term *pre-COPD* by GOLD 2024 document.[28] The air entrapment, seen as a decrease in lung attenuation in the expiratory phase of CT, indirectly indicates, dysfunction in small airways in COPD and can be quantified volumetrically, associated with early colapse of the airways on exhalation.[101]

Quantitative analysis of CT gives information about the severity and prognosis. Emphysema is associated with accelerated loss of $FEV_1$, increased risk of lung cancer, and increased mortality.[28]

Systematic and meta-analysis revisions have proven a correlation of 0.26 (95%CI 0.18-0.33) to 0.70 (95%CI 0.65-0.75) on inspiratory CT and 0.56 (95%CI 0.51-0.60) to 0.74 (95%CI, 0.68-0.80) on expiratory CT, between the tomography of quantitative parameters measure (mean lung density [MLD], the percentage area of attenuation less than −950 Hounsfield units [%LAA−950HU], the percentage of the area of walls of the airways [WA%], air entrapment rate [AER] and walls thickness of airways [WT]) and obstruction of the airways in patients with COPD ($FEV_1$% pred and $FEV_1$/FVC).[136,137]

The presence of the coronary arteries calcifications is associated with an increased dyspnea, a reduced exercise capacity and increased mortality.[138] The dilation of the lung artery (a ratio of lung artery diameter to aortic diameter > 1) by CT scan was associated with an increase in severe exacerbations of COPD.[139]

The tomographic analysis supports therapeutic decisions such as the surgery of lung volume reduction and the placement of endobronchial valves. CT also provides detailed information on comorbidities. It is estimated that 30-50% of patients present bronchiectasis linked to exacerbations and mortality, although the influence of the treatment is not clear.[28,140,141] On the other hand, the relationship between low muscular mass and the adiposity, measured by CT, are associated with lower exercise capacity and survival in COPD.[142]

## Laboratory studies and biomarkers

### Clinical Question 7: *What is the usefulness of laboratory studies and biomarkers during the approach and follow up of COPD?*

| Recommendations | | |
|---|---|---|
| 1 | During the initial assessment of people with COPD, blood biometry is recommended to investigate polycythemia or anemia and the number of eosinophils in peripheral blood; a figure of ≥ 300 cells/µL is associated with high risk of exacerbations and predicts response to inhaled corticosteroids[143] and monoclonal antibodies (Dupilumab) in selected cases. | Evidence 1+<br>Recommendation B |
| 2 | Elevated levels of circulating molecules such as C-reactive protein (CRP), fibrinogen, and leukocytes are significantly associated with exacerbations, hospitalizations, and mortality. In the case of exacerbation, CRP measurement is recommended to classify severity; a value ≥ 10 mg/dL defines an at least moderate exacerbation. Otherwise, the routine use of these biomarkers is not recommended due to their variability and difficulty in interpretation. | Evidence 2++<br>Recommendation B |
| 3 | In Mexico, the routine determination of alpha-1 antitrypsin deficiency is not recommended, because it is of very low prevalence in the population. However, it is recommended to investigate in patients younger than 45 years who show panlobular basal emphysema. | Evidence 2+<br>Recommendation C |

Patients with stable COPD present with persistent low-grade systemic inflammation, with elevated levels of circulating molecules such as C-reactive protein (CRP), fibrinogen, and leukocytes.[144,145] These are associated with exacerbations, hospitalizations, and mortality, and with less consistent results are interleukins (IL)-6 and IL-8. The routine use of biomarkers is controversial due to the lack of clear and robust evidence.25 Some of the biomarkers that have been studied in COPD are described below:

**Fibrinogen.** It is a useful biomarker for assessing the risk of future exacerbations and mortality in COPD patients. During exacerbations, up to a three-fold increase in plasma levels has been reported compared to stable patients, and these levels gradually increase as the disease progresses.[146,147] In the ECLIPSE cohort, GOLD 2 patients were at increased risk of exacerbations if their plasma fibrinogen levels exceeded one standard deviation (SD) above the mean.[148] It needs to be considered that the use of systemic corticosteroids can modify fibrinogen levels during exacerbations, as part of the inflammatory response.[149] A meta-analysis that included more than 154,000 individuals showed an association between elevated fibrinogen and COPD mortality (HR 3.7, 95%CI 2.75-4.97) for every 100 mg/dL increase in fibrinogen.[150] In addition, decreased lung function ($FEV_1$) and increased fibrinogen levels are related, which could have important implications for the treatment of stable COPD, regardless of smoking status.[144]

**CRP.** It is a useful biomarker in the management of COPD, both in hospital and outpatient settings. Elevated baseline CRP levels are associated with higher mortality in these patients (HR 1.53, 95%CI 1.32-1.77, $I^2 = 68.7\%$, $p < 0.001$). This association increases with a cut-off value of 3 mg/L (HR 1.61, 95%CI 1.12-2.30).[151,152]

**Leukocytes.** Leukocytes recruited into the lung in response to smoking contribute to the development of COPD by releasing in a positive feedback process, reactive oxygen metabolites and proteolytic enzymes, resulting in damage to the airway and alveoli.[153] In the ECLIPSE cohort, elevated circulating leukocyte counts were associated with persistent systemic inflammation (median $\times 10^6$/mL [interquartile range]), COPD: 7.6 [6.3-9.0], smokers 7.1 [6.1-8.6], nonsmokers 5.8 [5.0-7.0], $p < 0.001$,[154] frequent exacerbations (for every $1 \times 10^3/mm^3$ increase in leukocytes OR 1.08 (95%CI 1.03-1.14)[148] and increase in three-year mortality HR 1.26 (95%CI 1.13-1.42).[151]

**Neutrophils.** The ECLIPSE study observed no association between the number of neutrophils in sputum/mL and the predicted % $FEV_1$ at baseline and at one year ($p = 0.64$ and $p = 0.19$) in patients with COPD. Likewise, there was

no association between neutrophils and exacerbation or emphysema rates.[155]

**Eosinophils.** Elevated eosinophil count in COPD patients is associated with increased markers of type 2 airway inflammation.[156,157] Blood eosinophil count is proposed as a predictor of response to inhaled corticosteroids (ICS)[143] in the prevention of exacerbations. It is recommended to identify patients with eosinophils ≥ 300 cells/μL, as they indicate a high risk of exacerbations and a possible benefit of ICS.[158,159] ICS reduce the risk of exacerbation by 20% with a count ≥ 2% of eosinophils (RR 0.80, 95%CI 0.74-0.85), 35% with ≥ 150 cells/μL (RR 0.65, 95%CI 0.52-0.79) and 39% with ≥ 300 cells/μL (RR 0.61, 95%CI 0.44-0.78).[160,161] In exacerbations, the individualized use of antibiotics is recommended according to severity and biomarkers, especially with purulent expectoration and elevated CRP.[25] A systematic review of 12,496 patients reported that a blood eosinophil count of 2% can predict response to ICS treatment in patients with COPD and the risk of pneumonia in patients with ICS-based treatment (RR 1,969, 95%CI 1,369-2,833, $p < 0.001$).[162] The GOLD 2024 guideline recommends measuring eosinophils at baseline and adding the use of ICS to pharmacological management in patients with phenotype E or with ≥ 300 cells/μL.[28] Suggested indicate triple therapy (LABA + LAMA + ICS) to exacerbator patients, with greater benefit in those with eosinophil levels ≥ 100 cells/μL.[28] Additionally, a high eosinophil count in mild and moderate COPD predicts greater loss of lung function.[28] The eosinophil count in sputum is promising for predicting outcomes and response to ICS.

**Vitamin D.** The published information on the usefulness of measuring vitamin D levels as a risk factor for COPD or exacerbations of this disease is heterogeneous, which requires caution in its interpretation. Vitamin D binding protein polymorphism GC-1F-1F is associated with increased risk of COPD (OR 1.44, 95%CI 1.14-1.83, $p = 0.002$).[163] In Asian populations, both the GC-1F-1F genotype and the GC-1F allele are associated with increased susceptibility to COPD (OR 1.73, 95%CI 1.07-2.81, $p = 0.03$).[164,165] A meta-analysis of 25 studies evaluated the effects of vitamin D therapy in patients with COPD. A benefit was reported on: $FEV_1$ with a standardized mean difference (SMD)[166] of 1.21 (95%CI 0.76-1.66, $p < 0.01$), $FEV_1$/FVC ratio (SMD 1.07, 95%CI 0.56-1.58, $p < 0.01$), exacerbation reduction (SMD 0.39, 95%CI 0.23-0.64, $p < 0.01$), sputum volume (SMD −6.02, 95%CI −8.25-3.79, $p < 0.01$), 6-minute walking distance (SMD: 8.82, 95%CI 1.67-15.98, $p = 0.02$) and COPD assessment test score (SMD: −1.19, 95%CI −1.74 to 0.63, $p < 0.01$). Importantly, the dose of vitamin D used and the characteristics of the sample were different between the included studies.[167] In contrast, Zhu *et al.*, observed that low serum levels of 25(OH)D (< 20 mg/mL) did not increase the risk of COPD. In addition, the rate of 25(OH)D deficiency in patients with severe COPD was lower than that in patients with moderate COPD, with a pooled RR of 0.743 (95%CI 0.561-0.984, $p = 0.038$). Additionally, vitamin D used as a supplement to prevent exacerbations in COPD also shows discordant results.[168,169]

**Alpha-1-antitrypsin.** For the detection of patients with alpha-1 antitrypsin deficiency, WHO suggests performing an enzyme determination at least once in the follow-up of the COPD patient, especially in areas of high prevalence. A low concentration (< 20% of the normal value) suggests homozygous deficiency, and it is recommended to screen family members and refer them to specialized centers for their management.[4,28] Other biomarkers such as oxidative stress, extracellular vesicles and different genetic factors, proteins among others, are in the study protocol for use. The COPDgene study identified genetic and environmental factors that contribute to the development, progression, and variability of COPD symptoms.[170] In this cohort, biomarker combinations improve performance to predict airflow limitation and mortality (CC16, sRAGE, fibrinogen, CRP and SP-D, $p < 10^{-4}$ and $p < 0.05$), presence and progression of emphysema (SP-D, CRP, sRAGE and fibrinogen, $p < 10^{-3}$), and decrease in $FEV_1$ (CC16, fibrinogen and sRAGE, $p < 0.05$).[171] In the Mexican mestizo population, the prevalence of alpha-1 antitrypsin deficiency is very low, so its investigation on a routine basis would not be justifiable. Deficient patients are typically younger than 45 and exhibit baseline panlobular emphysema, which may be an indicator for their study.[172]

## Clinimetric scales

### Clinical Question 8: *What is the utility of clinimetric scales in the initial assessment of COPD patients?*

| Recommendations | | |
|---|---|---|
| 1 | At all levels of care, during the evaluation of people with COPD, the routine use of the modified Medical Research Council Scale (mMRC) of dyspnea or the COPD Assessment Test (CAT) for symptomatic definition purposes is recommended. A score ≥ 2 on the mMRC scale or a value ≥ 10 points on the CAT scale define symptomatic individuals eligible for dual therapy with inhaled bronchodilators. | Evidence 1+<br>Recommendation B |

| | | |
|---|---|---|
| 2 | Predictive survival scales, such as the BODE scale and its variants, are not recommended for routine use at the first level of care. However, the survival scales validated in the Mexican population that show better predictive performance, include: Body mass index, airflow Obtruction, acive Smoking, Age, and the variant that includes Exercise (BOSEA-90) can be used in the second and third levels of care for better clinical assessment and to establish strategic treatment goals that impact the prognosis of the disease. | Evidence 2– Recommendation C |

«Clinimetry» comprises multidimensional tools such as indices, rating scales, and other expressions that are used to describe or measure symptoms, physical signs, and other clinical phenomena. It is essential to complement its use with a comprehensive assessment of the patient, since the perception of symptoms and functional capacity can vary significantly between individuals and be influenced by external factors such as the patient's emotional state. In COPD, the most commonly used clinimetric scales are: mMRC scale (modified Medical Research Council scale) to assess dyspnea; Chronic Respiratory Questionnaire (CRQ); Saint George Respiratory Questionnaire (SGRQ); COPD Assessment Test (CAT); COPD Clinical Questionnaire (CCQ); BODE scale (BMI, obstruction, dyspnea and exercise).

**COPD Assessment Test (CAT).** It is a self-assessment questionnaire consisting of eight items *(Figure 7)*. It evaluates the patient's health status, level of symptoms and quality of life in COPD. A reduction in the CAT score indicates improvement in health status, while an increase suggests deterioration. This questionnaire has been incorporated into the combined assessment of COPD according to GOLD guidelines, as a symptomatic threshold to guide pharmacological treatment. The GOLD 2024 recommended cut-off for identifying a patient as symptomatic is ≥ 10.[28] The minimum clinically important difference (MCID), which represents the minimum change in score that patients perceive as favorable or detrimental, ranges from −1.2 to −2.8.[173] CAT scores have predictive capacity for exacerbations, depression, acute deterioration of health status, and mortality. However, the cut-off points differ from those recommended by GOLD 2024 (≥ 10 for the CAT and ≥ 2 for the mMRC) to predict these outcomes.[28,174] The CAT has an internal consistency (reliability) between 0.85 and 0.98, and a consistency between test and revaluation of 0.80 to 0.96.[175] In addition, the total scores of the CAT and SGRQ have been shown to have excellent internal consistencies (Cronbach alpha coefficients of 0.890 and 0.933, respectively) and a significant correlation between them ($R = 0.668$, $p < 0.001$).[176,177]

**mMRC scale.** The modified dyspnea rating scale (mMRC) is widely used to categorize the degree of dyspnea related to certain activities that a person presents. The range is from 0 to 4. The MCID is 1. The GOLD 2024 suggested cut-off for a symptomatic patient is ≥ 2. In addition, it is used to classify the symptomatic burden of the disease.[28] Although this scale reflects the level of effort (e.g. dyspnea when climbing a slight slope) at which the dyspnea presents, it does not show the intensity of the symptom itself, and may be influenced by other factors such as the level of physical condition of the person, particularly when evaluating dyspnea with great efforts. An observational study analyzed the ability of the mMRC scale to detect abnormal dyspnea with great efforts, and its link with low exercise capacity. A score on the mMRC ≥ 2 scale is more accurate (71%) in detecting abnormal dyspnea with great efforts, with a specificity of 93%, but a sensitivity of only 28%. However, to detect a low exercise capacity he had an accuracy of 64%, specificity of 88% and sensitivity of 19%. In sum, it was shown that the mMRC scale does not adequately predict dyspnea in intense exercise, nor is it useful in predicting people with low exercise capacity.[179]

**BODE scale (BMI, obstruction, dyspnea, exercise capacity).** It is a composite scale, made up of BMI, obstruction to airflow measured by $FEV_1$, dyspnea measured by mMRC, and exercise capacity measured with the 6-minute walk. Its range of values is from 0 to 10 points, where 10 indicates the highest risk of mortality. The one-point increase reflects a significant increase in mortality for all the causes. This scale is divided into the following quartiles to determine the probability of survival at 52 months: quartile 1 (0-2 points – 82%), quartile 2 (3-4 points – 69%), quartile 3 (5-6 points – 60%), quartile 4 (7-10 points – 25%). One observational study compared the efficacy of the BODE scale versus $FEV_1$ in classifying disease and predicting outcomes. The results showed more accurate behavior with the BODE scale (C statistic: 0.74), compared to $FEV_1$ (C statistic: 0.65).[122,180]

Other variants of the BODE scale that have been validated incorporate other survival predictors, such as the frequency of exacerbations (BODEx), oxygen saturation measured by pulse oximetry (BODEx-S90). Other reference scales are: Charlson index including comorbidities, DOSE index (dyspnoea, obstruction, smoking and exacerbations) and ADO index (age, dyspnoea and obstruction).[181-184]

A new BODE variant has recently been validated for the Mexican population that shows better predictive

CAT
COPD Assessment Test

## How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

If you wish to complete the questionnaire by hand on paper, **please click here** and then print the questionnaire.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

**Example:** I am very happy 0 X 2 3 4 5 I am very sad

| | | | SCORE |
|---|---|---|---|
| I never cough | 0 1 2 3 4 5 | I cough all the time | |
| I have no phlegm (mucus) in my chest at all | 0 1 2 3 4 5 | My chest is completely full of phlegm (mucus) | |
| My chest does not feel tight at all | 0 1 2 3 4 5 | My chest feels very tight | |
| When I walk up a hill or one flight of stairs I am not breathless | 0 1 2 3 4 5 | When I walk up a hill or one flight of stairs I am very breathless | |
| I am not limited doing any activities at home | 0 1 2 3 4 5 | I am very limited doing activities at home | |
| I am confident leaving my home despite my lung condition | 0 1 2 3 4 5 | I am not at all confident leaving my home because of my lung condition | |
| I sleep soundly | 0 1 2 3 4 5 | I don't sleep soundly because of my lung condition | |
| I have lots of energy | 0 1 2 3 4 5 | I have no energy at all | |
| | | TOTAL SCORE | |

**Figure 7:** COPD Assessment Test (CAT).
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performance; it includes Body mass index, airflow Obstruction, Smoking, Age and oxygen saturation less than 90% (BOSA-90) and the variant that includes Exercise (BOSEA-90).[22] The variables of these predictive scales can be used for treatment strategies with impact on prognostic factors *(Table 12)*.

**Other questionnaires.** The SGRQ, with 50 items, evaluates the patient's health status in three domains. It uses a score scale from 0 to 100. Although commonly employed in research, its use is limited due to its extent and complexity. GOLD 2024 recommends a score ≥ 25 for highly symptomatic patients, although studies suggest that ≥ 20 correlates better with other clinical scales, improving the sensitivity of CCQ, CAT, and mMRC.[185]

Two questionnaires have been developed for the diagnosis of COPD:[23] the COPD Diagnostic Questionnaire (CDQ) and the revised COPD Diagnostic Questionnaire (R-CDQ). The CDQ consists of eight items, including age, BMI, smoking, climate-related cough, sputum production, among others, with a total of 38 points and a cut-off of 17 for screening (AUC of 0.762). On the other hand, the R-CDQ, with 11 items, considers exposure to passive smoking, dyspnea, dust exposure, and childhood respiratory history, with a cut-off of 17 (AUC of 0.731).[186]

In addition, there is the Chronic Respiratory Disease Questionnaire (CRQ) to evaluate the quality of life associated with health. The questionnaire is available for interview or self-completion, comprises four domains with four to seven items, graduated on the seven-point Likert scale. It has high internal consistency and test reliability, as well as moderate to strong constructive and convergent validity.[187]

Finally, the 10-item Clinical COPD Questionnaire (CCQ) assesses symptoms, function, and mental status, with a reliability of 0.84-0.94 and a score ≥ 1 to categorize the patient as symptomatic. The latter questionnaire is considered fundamental for use in the first level of care and has a higher correlation with the SGRQ and CAT.[188]

**Table 12: A)** Prognostic risk grading in patients with COPD according to the BOSA90 and BOSEA90 scales validated in Mexico.

| Variable | BOSA-90 | BOSEA-90 | Comment |
|---|---|---|---|
| $SpO_2$ < 90% | 4 | 4 | Reflects hypoxemia and COPD progression. |
| Age < 60 years | 0 | 0 | Young patient: better prognosis. |
| Age 60-79 years | 2 | 2 | Older, more risk |
| Age > 70 years | 3 | 3 | Older, more risk |
| Active smoker | 5 | 4 | Higher mortality impact |
| $FEV_1$ < 35% of the predicted value | 2 | 2 | Severe pulmonar obstruction |
| BMI < 21 kg/m$^2$ | 2 | 2 | Low body weight, worse muscle reserve. |
| 6-minute walk < 200 meters | — | 3 | Applies only to BOSEA-90: if the patient does not run an adequate distance, it indicates functional limitation. |
| Maximum total score | 16 | 18 | The points of each variable are added |

**B)** Rapid clinical interpretation (BOSA-90 / BOSEA-90).

| Quartile | Mild (Q1) | Moderated (Q2) | Severe (Q3) | Very severe (Q4) |
|---|---|---|---|---|
| Punctuation | 0-3 | 4-7 | 8-11 | ≥ 12 |
| Color | Green | Yellow | Orange | Red |
| Comment | Low risk of death | Moderate risk of death; reinforce control and measures targeting modifiable risks (oxygen, smoking cessation, rehabilitation and nutrition) | High risk of death; specialized management. | Very high risk of mortality; requires intensive surveillance. |

Summary: Each patient gets points according to their risk factors or their clinical status (age, saturation, smoking, etc.). The points are then added to determine which quartile your patient falls into (Q1-Q4). Quartiles indicate severity and help predict the likelihood of complications. After adding the points, a quartile is assigned that indicates the level of severity.

The COPD Exacerbation Recognition Tool (CERT) developed in the Asian population provides patients with easy-to-follow guidance on when to seek medical care when they have a moderate or severe exacerbation.[189] Worsening of two or more symptoms has good sensitivity and specificity for the presence of an exacerbation.

The baseline dyspnea index (BDI) has been designed for a multidimensional assessment of dyspnea, and the transition dyspnea index (TDI) is more sensitive to change than the mMRC.[190] BDI/TDI has been widely validated in COPD and remains the most widely used questionnaire in clinical research, especially in therapeutic trials.[191] Correlations between mMRC and BDI scores for the assessment of dyspnea have been reported with correlation coefficients between 0.61 and 0.73.[192,193]

## Impact of comorbidities

### Question 9: *What is the impact of comorbidities on the prognosis of COPD?*

| Recommendations | | |
|---|---|---|
| 1 | It is recommended to identify other diseases or disorders (comorbidities) that coexist in people with COPD and that may impact their prognosis. Particular attention should be paid to the comorbidities with the greatest prognostic impact (COTE index) and which include in order of relevance: lung, esophageal, pancreatic and breast cancer; anxiety; other cancers; liver cirrhosis; atrial fibrillation; diabetes with neuropathy; pulmonary fibrosis; chronic heart failure; gastric or duodenal ulcer; and coronary heart disease. | Evidence 1– Recommendation C |
| 2 | The presence of comorbidities should not modify the approach and treatment of COPD or vice versa, the treatment of COPD should not modify that of comorbidities. However, management should be comprehensive and multidisciplinary, and polypharmacy should be avoided. | Evidence 3 Recommendation C |

COPD commonly coexists with other diseases (comorbidities) that can affect its course. GOLD 2025 emphasizes that the presence of these comorbidities should not modify the approach and treatment of COPD or vice versa, the treatment of COPD should not modify that of comorbidities. Some comorbidities are independent of COPD, while others share risk factors and inflammatory mechanisms.[194,195] Additionally, it is recommended to address these conditions according to established guidelines, regardless of the presence of COPD.[28] Comorbidities can be assessed by the Charlson index (19 comorbidities)[196] or the COTE index (12 comorbidities) *(Table 13)*.[197] While the Charlson index has shown no association with mortality,[198] a score ≥ 4 on the COTE index independently increases the risk of death by 2.2-fold (HR 2.26-2.68, $p < 0.001$), also relating to an increased risk of death from COPD (HR 1.13, 95%CI 1.08-1.18, $p < 0.001$) as from causes unrelated to this disease (HR 1.18. 95%CI 1.15-1.21, $p < 0.001$).[199]

### *Main comorbidities in COPD*

*Table 14* summarizes the main diseases that affect patients with stable and exacerbated COPD, highlighting their impact on prognosis and the need for clinical surveillance.

**Table 13:** Comorbidity Index in COPD (COTE).

| Comorbidity | Puntos |
|---|---|
| Lung, esophageal, pancreatic, breast* cancer | 6 |
| Anxiety* | 6 |
| All other types of cancer | 2 |
| Hepatic cirrhosis | 2 |
| Atrial fibrillation flutter | 2 |
| Diabetic neuropathy | 2 |
| Pulmonary fibrosis | 2 |
| Congestive heart failure | 1 |
| Gastric/ duodenal ulcer | 1 |
| Heart disease | 1 |

* Valid only in female population
COTE = COPD-specific Comorbidity Test.

**Table 14:** Comorbidities in COPD.

| Comorbidities | Disease | Prevalence | Prognosis or clinical impact |
|---|---|---|---|
| **Cardiovascular diseases** | Acute myocardial infarction/ischemic heart disease[200,201] | 21.9%/2.8 times more frequent | Greater probability in two series of patients with COPD:<br>OR 3.2 (95%CI 2.0-5.0, p < 0.0001)<br>OR 2.71 (95%CI 1.69-4.35, p < 0.0001) adjusted for smoking and other risk factors |
| | Stroke or ictus[200,202,203] | 14.1% | Greater probability in COPD: OR 1.2 (95%CI 0.6-2.1) |
| | Heart failure[200,201,204,205] | 18.9-70% | Greater probability in two series of patients with COPD:<br>OR 5.6 (95%CI 3.2-9.7, p < 0.001)<br>OR 2.57 (95%CI 1.90-3.47, p < 0.0001)<br>Main cause of hospitalization and death in COPD patients younger than 65 years of age |
| | Angina pectoris[201] | 15.8% | Greater probability in COPD:<br>OR 8.16 (95%CI 3.08-21.59, p < 0.0001) |
| | High blood pressure[199,201,206-208] | 17-64.7% | Greater probability in COPD:<br>OR 1.33 (95%CI 1.13-1.56, p = 0.0007)<br>OR 1.45 (95%CI 1.31-1.61, p < 0.00001)<br>Associated to exercise intolerance and can simulate exacerbations |
| | Systemic venous thromboembolism[209-211] | COPD exacerbations 3-29% | Increases hospital stay (4.4 days) and increases 30% mortality rate |
| | Pulmonary thromboembolism[212,213] | 16% exacerbations | Probabilistic association in exacerbations:<br>OR 9 (95%CI 0.06-0.12)<br>OR 12 (95%CI 9-16)<br>OR 17.2 (95%CI 13.4-21.3)<br>Increased mortality: OR 5.30 (95%CI 2.48-11.30, p < 0.001) |
| | Pulmonary hypertension[214-219] | ~20-91% | Deterioration in gas exchange, increase in dyspnea and mortality, and is directly proportional to the severity of COPD<br>Five-year survival (HP > 40 mmHg) 15% |
| | Coronary heart disease[21,220] | | For every 10% reduction in $FEV_1$, the frequency of non-fatal coronary events increases by 20% |
| | Arrhythmia[28,221-224] | More or Higher risk of AF: RR 1.99 (95%CI 1.46-2.70).<br>More risk of ventricular arrhythmias (VA): RR 2.01 (95%CI 1.42-2.85).<br>VF + sudden death 21.4%<br>VT + asystole 5.7% | Meta-OR 1.94 (95%CI 1.55-2.43, p < 0.0001)<br>AF is associated with reduction in $FEV_1$<br>COPD is a predictor of AF OR 2.5 (95%CI 1.6-4.1) and VT OR 1.9 (95%CI 1.1-3.1)<br>AF is associated with increased risk of mortality OR 2.22 (95%CI 1.93-2.55), cardiovascular death OR 1.84 (95%CI 1.39-2.43) and increased bleeding OR 1.45 (95%CI 1.17-1.80)<br>COPD has a deleterious impact on AF progression in terms of overall mortality OR 1.70 (95%CI 1.47-1.97, p < 0.0001), cardiovascular death OR 1.80 (95%CI 1.29-2.52, p = 0.0005), stroke, and bleeding complications OR 1.84 (95%CI 1.58-2.14, p < 0.00001) |
| **Psychiatric** | Anxiety[208,225,226] | Outpatient 13-46%.<br>Inpatient 10-55% | Patients with anxiety and/or depression have a first hospitalization for COPD earlier<br>The effect of anxiety on treatment adherence is not clear due to the heterogeneity of the data |
| | Depression[226-228] | Stable COPD 10-42% | Three times more likely to fail prescribed medication, exercise, diet, and health-related behaviors |
| | | Acute exacerbation 10-86% | Those on treatment are more likely to adhere to COPD treatment |
| **Metabolic** | Metabolic syndrome[229-231] | 32 versus 34%, p = 0.001 (versus controls) | Negatively affect lung function, showing a restrictive pattern with lower $FEV_1$ and FVC values |

**Table 14 continues:** Comorbidities in COPD.

| Comorbidities | Disease | Prevalence | Prognosis or clinical impact |
|---|---|---|---|
| | Malnutrition[232-235] | 30.0% (95%CI 20.3-40.6) | Risk of morbidity and mortality in COPD patients with $FEV_1$ < 50% HR 1.62 (95%CI 1.15-2.31) for a BMI < 20 kg/m$^2$ Associated with mortality RR 1.97 (95%CI 1.55-2.50, $I^2$ = 98%), exacerbation RR 1.73 (95%CI 1.03-2.91, $I^2$ = 96%) and a worse quality of life RR 8.25 (95%CI 5.40-11.10, $I^2$ = 79%) |
| | Sarcopenia[236-238] | 15.5% (95%CI 11.8-19.1) a 34% (95%CI 20.6-47.3) Higher in sever COPD patients 37.6% (95%CI 24.8-50.4) than mild 19.1% (95%CI 10.2-28.0), p = 0.020 | Lower $FEV_1$ mean difference (MD) −7.1% (95%CI −9.0 a −5.1%), worse exercise tolerance MD −0.8 (95%CI −1.4 a −0.2), worse quality of life MD 0.26 (95%CI 0.2-0.4) They have more severe airflow obstruction (lower $FEV_1$) and reduced physical activity, functional performance, and exercise capacity |
| | Overweight and underweight[239,240] | TIOSPIR/UPLIFT studies has prevalence of 22%, overweight 32% | Underweight increased risk of mortality HR 1.88 (95%CI 1.62-2.20, p < 0.0001) and severe exacerbations HR 1.31 (95%CI 1.16-1.47, p < 0.0001) SUMMIT study, underweight showed higher mortality HR 1.31 (95%CI 1.04-1.64), lower in overweight HR 0.62 (95%CI 0.52-0.73) and obese class I HR 0.75 (95%CI 0.62-0.90). Mortality increased in obese class III HR 1.36 (95%CI 1.00-1.86) |
| | Osteoporosis[241-243] | 37.62% | High prevalence with a negative association with lung function ($FEV_1$) |
| | Diabetes[200,201,208] | 10.3-29.6% | Greater probability in two series of patients with COPD: OR 1.36 (95%CI 1.21-1.53, p < 0.0001) OR 1.22 (95%CI 1.07-1.38, p = 0.003) |
| **Hematological** | Anemia[244-246] | 7.5-34% | Associated with reduced quality of life and exercise capacity and reduced survival |
| | Polycythemia[244,247-249] | 2.9% | The percentage of total sleep time with $SaO_2$ < 90% (TS90) is associated with polycythemia OR 1.030 (95%CI 1.015-1.046) COPDGene study severe hypoxemia at rest OR 3.50 (95%CI 1.41-8.66), deterioration of DLCO OR 1.28 (95%CI 1.09-1.49), male OR 3.60 (95%CI 2.20-5.90), non-Hispanic white race OR 3.33 (95%CI 1.71-6.50), current smoking OR 2.55 (95%CI 1.49-4.38) and hospital admission OR 4.42 (95%CI 2.38-8.21) were associated with increased risk of polycythemia |
| **Sleep disorder** | Obstructive sleep apnea[250,251] | 29.1% (95%CI 27.2-30.9) | It is associated with poor quality of life and chronic hypercapnia Increased risk of hypertension OR 1.68 (95%CI 1.21-2.35) Hypoxia/hypoxemia is associated with deficits in attention, memory, executive function, psychomotor function and language skills |
| | Restless legs syndrome[250] | 21.6% (95%CI11.8-33.3) | More frequent in females, young people, more limitation of airflow and increase of creatinine |
| | Insomnia[250] | 29.5% (95%CI 16.9-44.0) | It is associated with a higher score on the Epworth MD 3.444 scale (95%CI 1.880-5.008) and a longer duration (years) of COPD MD 3.656 (95%CI 2.209-5.103) |
| **Oncological** | Lung cancer[252-258] | OR 5.08 (95%CI 4.17-6.0). Adenocarcinoma OR 1.59 (95%CI 0.23-2.94). Epidermoid OR 1.35 (95%CI 0.57-3.23) | Worst overall survival HR 1.16 (95%CI 1.08-1.25) Worst five-year survival OR 1.18 (95%CI 1.11-1.25) Increases risk of bronchopleural fistula, pneumonia, prolonged air leakage and prolonged mechanical ventilation |

VA = ventricular arrhythmias. DLCO =pulmonary diffusion of carbon monoxide. MD = mean difference. COPD = chronic obstructive pulmonary disease. AF = atrial fibrillation. $FEV_1$ = forced expiratory volume in the first second. VF = ventricular fibrillation. PH = pulmonary hypertension. HR = hazard ratio. 95%CI = 95% confidence interval. BMI = body mass index. OR = odds ratio. RR = relative risk. SUMMIT = Study to Understand Mortality and MorbidITy. TIOSPIR = TIOtropium Safety and Performance In Respimat. VT = ventricular tachycardia. UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium.

Contents

# COMPREHENSIVE TREATMENT OF STABLE COPD

## Treatment goals and strategies

This section includes 10 clinical questions raised in relation to the comprehensive treatment of stable COPD. These questions and their recommendations address all therapeutic interventions that have been demonstrated with sufficient evidence to be incorporated into a comprehensive disease treatment plan. This plan includes: exposure control measures (smoking and other exposures), lifestyle interventions (nutrition, physical activity and exercise), inhaled pharmacological treatment, complementary pharmacological treatment (recommended and not recommended), as well as long-term oxygen therapy, lung rehabilitation, vaccination and treatment alternatives with bronchoscopic intervention and surgery. It is very important that all medical professionals responsible for the management of patients with COPD, once their initial and diagnostic evaluation is completed, establish a comprehensive and individualized treatment plan. The GMEPOC working group recommends that this plan establish specific comprehensive treatment goals and strategies (CTGS) in each patient, based on an approach that seeks to address the prognostic variables consistently demonstrated and recently validated in the Mexican population as a variant of the BODE prognostic scale. To the prognostic variables of these Mexican scales (BOSA-90 and BOSEA-90)[22] that include age, smoking, nutritional status, exercise, degree of obstruction to airflow ($FEV_1$), the prevention and care of exacerbations and comorbidities have been added, with a prognostic impact on the natural history of the disease; with this, this guideline proposes[10] goals and 21 strategies for comprehensive treatment of the disease that are summarized in *Table 15 and Figure 8*.

**Table 15: Key Points:** Comprehensive treatment of stable COPD.

- Smoking cessation is the only intervention that decreases the risk of developing the disease; in addition, its success has a prognostic impact on patients. Medical advice, cognitive behavioral management, and pharmacological treatment are the most effective medical strategies.
- Controlling other harmful respiratory exposures can also have an impact on disease prevention and prognosis. Avoiding exposure to second-hand smoking, biomass smoke, as well as occupational exposure and air pollution are of the utmost importance.
- Lifestyle has prognostic impact on people with COPD. Improving nutritional status, maintaining a healthy weight, as well as preserving the quality and quantity of muscle mass should be promoted. Physical activity and exercise should also be encouraged in all patients.
- Inhaled bronchodilator therapy is the base of pharmacological treatment of stable COPD, as it improves lung function ($FEV_1$), reduces symptoms, particularly dyspnea, and prevents exacerbations.
- Other pharmacological treatments may be effective in reducing exacerbations in patients who, despite optimal inhaled treatment (LABA-LAMA-ICS triple therapy), show persistence of moderate or severe exacerbations, including: macrolides, roflumilast, dupilumab, and mucolytics.
- The routine use of other drugs to prevent exacerbations, such as: bacterial lysates, leukotriene receptor antagonists, immunoglobulins, desensitization immunotherapy, or transfer factor (transferon), is not recommended.
- Long-term oxygen therapy (LTOT) should be indicated for at least 15 hours a day, in all patients with $PaO_2 \leq 55$ mmHg or $SpO_2 \leq 88\%$ or with a $PaO_2$ between 56-59 mmHg or $SpO_2$ de 89-90%, with evidence of pulmonary hypertension, right heart failure or polycythemia (hematocrit $\geq 55\%$).
- Pulmonary rehabilitation is an effective and safe intervention in all patients; it improves symptoms, quality of life, functional ability, emotional state, sense of control, and effort tolerance.
- Vaccination is crucial for the prevention of COPD exacerbations or complications, including: pneumococcus, influenza, COVID-19, respiratory syncytial virus, and other vaccines such as pertussis and herpes zoster.

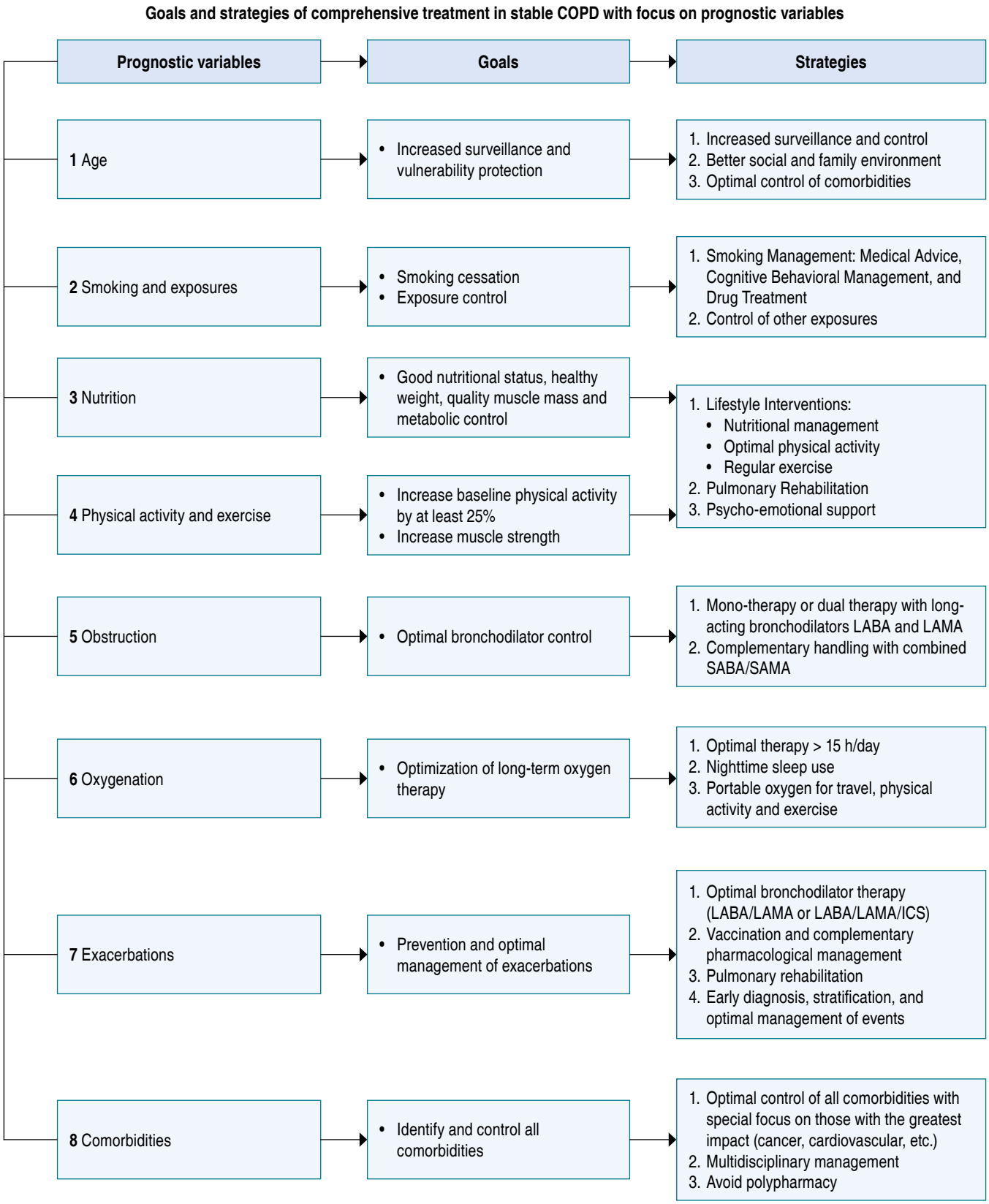


**Figure 8.**

Contents

## Smoking cessation

### Clinical Question 10: *What is the efficacy of the different strategies for smoking cessation in patients with chronic obstructive pulmonary disease?*

| Recommendations | | |
|---|---|---|
| 1 | Smoking cessation is the only intervention that decreases the risk of developing COPD; reduces symptoms; and improves lung function loss, exacerbations, and mortality, as well as being highly cost-effective. Healthcare professionals should always document smoking status in all patients and particularly in people with or at risk of COPD. Brief and timely advice aimed at smoking cessation should be offered at each medical visit; the intensity of the advice is associated with success in quitting, should last at least three to five minutes and should include «the five A's»: 1) Ask if the patient smokes; 2) Advise on the harms of tobacco to communicate why they should stop smoking; 3) Assess the degree of addiction and motivation to quit smoking; 4) Assist designing a plan to quit smoking; and 5) Arrange follow-up to reinforce and prevent relapses. | Evidence 1+<br>Recommendation A |
| 2 | The combination of pharmacological treatment and cognitive-behavioral management is the most effective intervention to quit smoking. In people with moderate to severe addiction, at least one of the most effective medications to quit smoking should always be prescribed, with an adequate safety profile: nicotine replacement therapy (NRT) mainly patches, bupropion and varenicline (first line) or when available in Mexico, cytisine should be considered. It is recommended to combine pharmacological treatment with cognitive-behavioral therapy with social support. In addition, in hospitalized patients, therapeutic intervention with nicotine patches alone or in combination with some other medication should always be initiated. | Evidence 1+<br>Recommendation A |
| 3 | The efficacy and safety of the electronic cigarette as a support in smoking cessation is uncertain, so its use is not recommended. | Evidence 1+<br>Recommendation A |

### *Evidence analysis*

Tobacco cessation is the only evidence-based intervention that reduces the risk of developing COPD.[28,259] Between 40-60% of COPD patients are active smokers. The cessation rate in COPD patients is 14-27%.[260] Tobacco cessation improves respiratory symptoms, reduces accelerated lung function decline by decreasing the frequency of exacerbations and mortality.[261,262] This impacts on the social and economic burden of the disease.[263]

Smoking cessation treatment poses a challenge in COPD patients due to high nicotine dependence and higher levels of depression leading to less success in smoking abstinence.[264,265] As in all patients, smoking cessation treatment must be individualized and the highest rate of effectiveness results from the combination of pharmacological treatment with cognitive-behavioral therapy.[28,262,266]

Counseling or «motivational interviewing» provided by physicians and other health professionals significantly increases cessation rates. There is an association between the intensity of medical advice and success in cessation.[267,268] Brief advice takes three to five minutes and consists of:[4]

1. **Ask**: identify if the patient smokes
2. **Advice**: rely on leaflets and information on the harms of tobacco to tell the patient why they should stop smoking
3. **Assess**: Consider the degree of addiction and motivation to quit
4. **Assist**: Design a plan to quit smoking
5. **Arrange**: follow-up to reinforce and prevent relapses.

Smoking cessation programs rely on behavioral treatment and pharmacological support to intervene effectively and achieve good quit rates. Nicotine replacement therapy (NRT) is aimed at suppressing the withdrawal syndrome in order to achieve cessation and avoid relapses. In patients with COPD, this therapy increases the rate of long-term abstinence and is significantly more effective than placebo.[269-271] The combined use of NRT increases the odds of success in smoking cessation by 17 to 37%. However, the time of use of treatment is variable and the therapy is personalized.[272,273] In Mexico, only nicotine patches and chewing gum are available for sale to the public *(Table 16)*.

NRT, bupropion, varenicline, nortriptyline, and cytisine have been shown to increase succes rates. The use of bupropion in combination with individual counseling achieved continuous abstinence at six months of 16%.[274] The combination of NRT and varenicline is equally effective as an aid to smoking cessation.[275] In Mexico, an observational study compared the one-year abstinence rate of COPD versus non-COPD patients with the use of varenicline; it found a similar response to the use of the drug, regardless of airflow obstruction and the degree of

nicotine addiction.[276] Cytisine has been used primarily in Eastern Europe and Canada, proving effective in smoking cessation rates.[277]

In patients with COPD, there is a greater benefit of combined pharmacotherapy and behavioral treatment compared to usual care, brief counseling, and less intensive behavioral support (RR 1.83, 95%CI 1.68-1.98).[265,278] Spirometry results regardless of their value should incentivize smoking cessation.[4] Different CPG recommend combining cognitive behavioral intervention with the use of first-line drugs such as NRT, bupropion, or varenicline. In addition, brief counseling is recommended in all health care settings to quit smoking.[4,25,28]

Counseling by physicians and other health professionals increases succes rates more than patient-initiated strategies. The likelihood of successfully maintaining smoking cessation is higher when receiving intensive behavioral interventions to quit smoking compared to shorter interventions.[279]

There is an increase in the use of e-cigarettes as a form of nicotine replacement therapy, favored by manufacturers' statements. The data on e-cigarettes as an effective and safe strategy to reduce the harms of traditional cigarette use are often contradictory and cannot be extrapolated to other brands of e-cigarettes or liquids used due to the heterogeneity of their quality and characteristics. Different meta-analyses have shown that the use of e-cigarettes as a therapeutic intervention to quit smoking can lead to permanent dependence on nicotine.[280] Evidence on the effectiveness and safety of e-cigarettes as a strategy to quit smoking is limited despite the fact that some meta-analyses have reported greater success for smoking cessation than the use of NRT.[281]

## Exposure control

### Clinical Question 11: *What is the benefit of different strategies for controlling other COPD-associated exposures?*

| Recommendations | | |
|---|---|---|
| 1 | The reduction of intra-domiciliary pollutants (second-hand smoking and biomass smoke), as well as air pollutants has a great impact on public health and could reduce the prevalence of COPD globally. However, it depends on public policies and legislation, as well as the availability of economic resources and cultural changes It is imperative to avoid secondhand smoking as a form of prevention of developing COPD and as part of its treatment; in addition, it has an impact on cardiovascular and perinatal health. | Evidence 2+ Recommendation C |
| 2 | The recommended effective measure to reduce exposure to biomass smoke pollutants in women is the use of cleaner fuels, such as ethanol, LP gas and electricity. Alternatively, the implementation of improved stoves with the installation of chimneys is recommended to decrease intra-domiciliary contamination, accompanied by adequate monitoring involving maintenance or replacement after its half-life time; however, the reduction in exposure is limited. | Evidence 2+ Recommendation C |

**Table 16:** Pharmacological treatment for smoking cessation.[282-284]

| Medicine | Dosage instructions | Administration | Common side effects | Advantages | Disadvantages |
|---|---|---|---|---|---|
| Nicotine patch (7 mg, 14 mg, 21 mg) | Start with dose adjusted to cigarettes smoked per day: Patch 21 mg/day> 10 cigarettes/day. After 6 weeks, decrease to 14 mg/day for two weeks, then to 7 mg/day for two weeks. | Apply to clean, dry, hairless skin on upper body or arm. Use in a different place each day. | Skin irritation, vivid dreams (insomnia). | Provides a consistent source of nicotine. Easy to use. | The user cannot adjust the dose if they have cravings during the day. |
| Nicotine lozenge (2 mg, 4 mg) | If the first cigarette is ≤ 30 minutes after waking, use 4 mg. If > 30 minutes, use 2 mg. Dissolve in mouth every 1-2 hours for 1 to 6 weeks; every 2-4 hours for 7 to 9 weeks; every 4-8 hours for 10 to 12 weeks. Up to 12 weeks | Place between cheek and gum until completely dissolved (~20-30 minutes). | Mouth irritation, hiccups, dyspepsia, nausea. | Controls nicotine cravings when used correctly. | Do not eat or drink 15 minutes before or during use. Cannot be used with dental prosthetics. |

**Table 16 continues:** Pharmacological treatment for smoking cessation.[282-284]

| Medicine | Dosage instructions | Administration | Common side effects | Advantages | Disadvantages |
|---|---|---|---|---|---|
| Nicotine gum (2 mg, 4 mg) | If the first cigarette is ≤ 30 minutes after waking, use 4 mg. If > 30 minutes, use 2 mg. Use one piece every 1-2 hours for 1-6 weeks; every 2-4 hours for 7-9 weeks; every 4-8 hours for 10-12 weeks. Up to 12 weeks | Chew slowly until you feel a tingling or taste, then «keep» between your cheek and gum. When the tingling disappears, repeat | Mouth irritation, hiccups, dyspepsia, nausea. | Controls nicotine cravings when used correctly | Do not eat or drink 15 minutes before or during use. Cannot be used with dental prosthetics |
| Nicotine inhaler (10 mg/cartridge) | 6-16 cartridges/day. Each cartridge has ~20 minutes of active use. Use up to six months | Inhale through the mouth piece at the back of the throat or inhale briefly | Mouth and throat irritation, cough, rhinitis | Controls nicotine cravings. The user can adjust the dose as needed | Some side effects can be unpleasant. |
| Nicotine nasal spray (0.5 mg nicotine/puff) | 1-2 applications in each nostril per hour, as needed to control withdrawal symptoms. Do not use more than five doses per hour or 40 doses per day. Use up to three months | Apply to each nostril | Nasal and throat irritation, runny nose, sneezing, cough | Control nicotine cravings. The dose can be adjusted as needed | Some side effects can be unpleasant |
| Varenicline (0.5 mg, 1 mg) | Days 1-3: 0.5 mg/day. Days 4-7: 0.5 mg twice a day. Days 8 to end of treatment: 1 mg twice a day. Start 1-2 weeks before the quit date. Use for 3-6 months | Drink with water after eating | Vivid dreams, insomnia, nausea, headache | Helps reduce withdrawal symptoms and cravings. It can be used with other nicotine replacement products | Due to FDA warnings, it is not recommended for use in people with a history of psychiatric or cardiovascular problems |
| Bupropion (150 mg) | 150 mg/day for three days, then 150 mg twice a day for 7-12 weeks. Start 1-2 weeks before the quit date. Use for 3-6 months | Drink with water after eating | Insomnia, agitation, dry mouth, headache | May decrease post-cessation weight gain | May increase the risk of seizures |
| Cytisine (1.5 mg tablet/ capsule) | One dose every two hours (Six doses per day) for days one to three, increasing the dosing interval to every 2.5 hours (five doses per day) on days four to 12, every four hours (four doses per day) on days 13 to 16, every five hours (three doses per day) on days 17 to 20, and every six hours (two doses per day) on days 21 to 25 | Take with water | Dyspepsia and nausea, headache, increased appetite, dry mouth, nightmares and irritability | High efficiency, safety and low cost | Contraindication: pregnancy and lactation, unstable angina, recent myocardial infarction, arrhythmias, history of stroke |

Smoking cessation treatment should be individualized in dose and duration. Not all nicotine presentations are available in Mexico. Varenicline was withdrawn from the market in Mexico, although it is likely to return and cytisine is not yet available in the Mexican market.
FDA = Food and Drug Administration.

| | | |
|---|---|---|
| 3 | The burden of COPD attributed to specific occupational exposures such as vapors, gases, dusts and fumes constitutes 10-15% of the total cases to be identified. The most effective strategy proposed to prevent occupational COPD includes reducing and preventing occupational exposures. Masks or devices that filter particles or fumes associated with occupational exposure should be used in addition to annual testing (post bronchodilator spirometry) to detect early exposed individuals with accelerated loss of lung function. | Evidence 2– Recommendation C |
| 4 | In people with COPD, interventions aimed at reducing exposure to particulate matter and other pollutants are recommended, as well as reducing exposure to extreme temperature changes, such as wearing masks, changing ventilation routines, and limiting outdoor activities on days of high pollution or extreme weather. However, so far, there is no strong evidence to support the effectiveness of these interventions. | Evidence 3 Recommendation C |

*Evidence analysis*

COPD develops as an inflammatory response to inhaled harmful substances, therefore it is essential to eliminate exposure to these substances to prevent it.

**Second-hand smoking**. Reducing exposure to tobacco smoke is important for both the prevention of COPD and the treatment of the disease. WHO promotes progress in this area through initiatives such as the Framework Convention on Tobacco Control.[285] In different countries, laws banning smoking in the workplace and public spaces have reduced exposure to secondhand smoke and rapidly improved workers' respiratory health. Both respiratory symptoms and lung function showed significant and sustained improvement up to six months after establishing smoke-free work environments.[286-290]

Legislative smoking bans have had a positive impact on public health, according to a systematic review of 77 studies. These laws have significantly reduced acute coronary syndrome admissions and mortality from smoking-related diseases, especially in cardiovascular health. However, its effect on respiratory and perinatal health and smoking prevalence is less consistent.[291,292] Additionally, a systematic review demonstrated the effectiveness of behavior change interventions in reducing secondhand smoking, especially in vulnerable groups such as pregnant women.[293]

**Domestic inhalation of biomass smoke.** The most effective measure to decrease exposure to biomass smoke, particularly suspended particulate matter ($PM_{2.5}$) and carbon monoxide (CO), is the use of cleaner fuels. Pope D *et al*., in an SLR and meta-analysis (2021) of 50 studies from Africa, Asia and Latin America, found that only the use of clean fuels, such as ethanol, liquefied petroleum gas (LPG) and electricity, are effectively consistent in decreasing $PM_{2.5}$ and CO exposure to levels recommended by WHO.[294]

Systematic reviews and meta-analyses indicate that interventions with improved stoves can reduce intradomiciliary pollution and its health effects.[295] When analyzing the health impact, a significant reduction in COPD development was observed in women RR = 0.74 (95%CI 0.61-0.90); however, no significant effect on children's health was found.[296] According to WHO, these interventions are unlikely to reduce pollutant levels to recommended levels. Therefore, it is crucial to properly implement and monitor these actions to achieve sustained benefits, given that many users continue to use traditional stoves.

A retrospective cohort study in Xuanwei, China, observed that the installation of chimneys in stoves was associated with a significant reduction in the incidence of COPD. Compared to households without a chimneys, the relative risk of COPD was 0.58 in men and 0.75 in women with improved stoves, with this reduction most evident after 10 years of follow-up.[297]

In Mexico, the average exposure to $PM_{2.5}$ in households with improved stoves varies between 51 and 319 $\mu g/m^3$. Improved stoves have an average lifespan of four years, after which many cease to be used, increasing the use of open fire, especially in indigenous communities.[298] In addition, improved stoves require maintenance or replacement over time, so programs should include monitoring and ensuring equitable access to clean energy options tailored to local needs.[299,300]

**Occupational exposure.** The burden of COPD attributed to occupational factors constitutes 10-15% of the total cases; it requires identifying specific exposures such as vapours, gases, dusts and fumes, known triggers of the disease.[23] Reducing these exposures at work, together with annual tests to rapidly detect the decline in lung function, is proposed as the most effective strategy to prevent occupational COPD.

According to UK Biobank data, occupations such as sculptors, gardeners and warehouse workers are associated with increased risk of COPD in individuals

without a history of smoking or asthma, which highlights the need to investigate work history to improve clinical management and develop specific preventive strategies for these high-risk jobs.[23,301]

To prevent work-related COPD, it is crucial to reduce the levels of risk factors and incentivize protective measures against organic dust and irritant chemicals, especially in agriculture, manufacturing, mining and construction. COPD, influenced by the interaction between genes and environment, is affected by occupational exposures. A retrospective study at five tertiary hospitals in China assessed the impact of occupational risk factors on the severity and progression of COPD. A total of 26% (n = 1,063) of patients had a history of occupational exposure, mainly in sectors such as agriculture, manufacturing and mining. Medium and high levels of occupational exposure were associated with increased COPD severity (OR 2.837 and 6,201, respectively, $p < 0.05$) and cumulative exposure is negatively related to $FEV_1$ (correlation coefficient of 0.68).

**Environmental pollution.** Environmental pollution in both open and closed spaces implies a greater threat to COPD patients.53 Among the environmental pollutants that contribute to COPD morbidity and mortality are those from occupational exposure, cooking with wood smoke, those from vehicular traffic, and forest fires.[302]

The CLEAN AIR controlled clinical trial evaluated the effect of high efficacy active portable air purifiers on the respiratory morbidity of ex-smokers with moderate to severe COPD. The group using active purifiers showed a significant reduction in the subscale of SGRQ symptoms and in respiratory symptoms such as dyspnea, cough, and expectoration. In addition, they experienced lower incidence of moderate exacerbations and reduced use of rescue medication compared to the control group. Adherence to purifier use was crucial for greater benefits, especially among those who spent more time indoors.[303]

In a six-month study with ex-smokers and COPD, 76.1% used air purifiers at least 80% of the time. Adherence was higher in households with income ≥ $35,000 (OR 4.4) and using electric heating (OR 6.1), but lower in those with poorer quality of life (OR 0.65) and more previous exacerbations (OR 0.26). Initial adhesion decreased in winter, evidencing the impact of climate and economic situation on the constant use of purifiers.[304]

One controlled clinical trial, which looked at ex-smokers with COPD, compared the usefulness of HEPA filters versus placebo for six months. Participants were assessed by the SGRQ questionnaire, CAT, mMRC, breathless, cough, sputum scale (BCSS), and measurement of $PM_{2.5}$ and $NO_2$. Those who achieved a 40% reduction in $PM_{2.5}$ with HEPA filters showed significant improvement in the SGRQ questionnaire (improvement of 7.7 points, 95%CI −14.3 to −1.1), as well as in CAT (β = −5.5, 95%CI −9.8 to −1.2), mMRC (β = −0.6, 95%CI −1.1 to −0.1), and BCSS (β = −1.8, 95%CI −3.0 to −0.5).[305]

Various interventions have been proposed in the behavior of people to reduce exposure to particulate matter, such as the use of masks, changes in ventilation routines and limitation of outdoor activities on days of high pollution. However, so far, there is no solid evidence to support the effectiveness of these interventions.[306]

In China, a comprehensive study on COPD combined health education, intensive interventions, treatment, and rehabilitation reducing the annual loss of $FEV_1$ by 19 mL/year and 0.9% of predicted values versus usual care ($p < 0.05$). In addition, there was a smaller reduction in the annual $FEV_1$/FVC ratio (0.6% less, $p = 0.029$), a notable increase in the smoking cessation rate (21 versus 8%, $p < 0.004$), and a significant reduction in cumulative all-cause mortality (1 versus 3%, $p < 0.009$). Although there were no significant differences in the cumulative incidence of COPD or COPD-specific mortality among the communities studied, the intervention demonstrated substantial improvements in respiratory health and symptom reduction.[307]

**Electronic cigarette.** Recommendations from various medical societies support the decision not to use ENDS, because the mechanism of associated harm is not yet fully understood.

## Lifestyles

### Clinical Question 12: *What is the efficacy and safety of lifestyle, diet and exercise changes in COPD patients?*

| Recomendaciones | | |
|---|---|---|
| 1 | All healthcare professionals and all levels of care must implement strategies to improve nutrition and increase physical activity for people with COPD, which can improve patients' survival and quality of life. When possible, nutritionally recommendation or intervention in a professional way must be done with the aim of improving nutritional status; focused on metabolic conditions, maintaining a healthy weight, as well as preserving quality and quantity of muscle mass. This is done through a normal calorie diet, high consumption of fruits, vegetables, grains and fish, in addition to a reduction in processed foods and avoiding excess of simple sugars and saturated and trans fats. | Evidence 1+ Recommendation A |

| | | |
|---|---|---|
| 2 | At all levels of care, and to the extent possible, the physical activity of people with COPD should be improved. Ideally and according to their availability, comprehensive rehabilitation programs should be recommended. It is advisable to implement promotion strategies for physical activity focused on increasing the number of steps (supported by the use of portable monitors such as watches or phones) or based on increasing the frequency and time of the routine dedicated to walking and physical activity. | Evidence 1+<br>Recommendation B |

### *Evidence analysis*

Lifestyle changes are possible and may be of benefit as additional strategies to the pharmacological management of COPD patients. There is evidence that systematically implementing strategies aimed at health promotion has beneficial effects. In addition, quitting tobacco use, immunizations, strategies such as increasing physical activity and improving nutrition, can increase life span with a good level of health.[308]

**Diet.** The European Respiratory Society published a position paper in 2014 recognizing that COPD patients have altered nutritional status that impacts disease burden, more symptoms, and worse prognosis. The prevalence of malnutrition in COPD is estimated to be 30%.[234] For a long time, the focus of research was on weight and muscle mass loss; however, obesity combined with sarcopenia has attracted interest in recent years and is today a challenge in the comprehensive management of COPD.[309]

Eating patterns have been shown to have an impact on both the development of COPD and its evolution. The Western diet -characterized by being hypercaloric, with high consumption of red and/or processed meats, refined flours, simple carbohydrates, saturated and trans fats, as well as ultra-processed foods - is considered an unhealthy diet. On the other hand, the Mediterranean diet includes a high content of polyunsaturated and monounsaturated fatty acids, is characterized by the intake of fruit, vegetables, fish, whole grains and oilseeds; it is considered by numerous international guidelines as healthy.[310] A meta-analysis showed that healthy eating patterns, such as the Mediterranean diet, reduce the risk of COPD; while less healthy eating patterns increase the risk.[311]

Two cross-sectional studies showed that the Western diet was associated with lower FVC and lower $FEV_1$ in COPD patients, in contrast to the Mediterranean diet. On the other hand, a longitudinal study showed that the intake of foods considered nutritious was associated with better lung function (FVC and $FEV_1$) over a three-year period.[312] Regarding processed foods, a meta-analysis that included five prospective cohort studies associated the consumption of processed meat with the development of COPD in the general population, showing that for every 50 grams of processed meat foods the risk of developing COPD increases by 8% (HR 1.08, 95%CI 1.03-1.13).[313] A cross-sectional study showed that a high consumption of processed meat was associated with lower values of lung function tests in the general population, especially in those with low consumption of fruits and vegetables.[314] However, there are no studies that have evaluated the association of processed meat consumption with disease progression with accelerated loss of lung function. A meta-analysis that included eight studies with 5,787 COPD patients and 244,154 people from the general population observed a 25% reduction in the lowest risk of developing COPD in people with high fruit and vegetable intake (RR 0.75, 95%CI 0.68-0.84).[315]

In patients with COPD, the change in diet with greater consumption of fruits and vegetables was associated with an increase in $FEV_1$ values. A controlled clinical trial reported that changing diet to a diet rich in fruits and vegetables was associated with increased $FEV_1$ values in COPD patients compared to a free diet. This suggests that a high intake of antioxidants may have positive effects on lung function.[316]

Regarding omega-3 polyunsaturated fatty acids, components of a Mediterranean diet, a lower risk of COPD has been observed.[317] On the other hand, there is insufficient evidence in the association of the intake of polyunsaturated fatty acids and the deterioration of pulmonary function tests in patients with COPD, where few studies have reported contradictory results. However, some clinical trials have reported that daily omega-3 supplementation promotes protein homeostasis and increased muscle mass.[318,319]

Regarding dietary fiber content, a prospective cohort study reported that fiber intake greater than 26.6 grams per day reduced the risk of developing COPD by 30% (HR 0.70, 95%CI 0.59-0.83) compared to less than 17.6 grams per day.[320] However, no clinical studies have evaluated the association of high fiber intake and clinical improvement in COPD patients.[310]

In 2022, Bernardes *et al.* published a meta-analysis where they analyze the benefit of a diet rich in protein and hypercaloric in patients with COPD. The authors included 31 controlled clinical studies with 1,414 participants. The results of the meta-analysis showed an increase in body weight (MD 1.44 kg, 95%CI 0.81-

2.08), increase in muscle mass (SMD 0.37, 95%CI 0.15-0.59), increase in muscle strength (SMD 0.39, 95%CI 0.07-0.71, as well as other secondary outcomes compared to controls. However, they did not assess the clinical benefit in COPD patients and the quality of the evidence was rated in a low or very low range, with a high risk of bias.[321]

Furulund *et al.*, in 2021, reported the effect of nutritional interventions in patients with COPD. The authors included 13 clinical studies with 916 participants; eight clinical studies evaluated the impact on pulmonary function tests. Only two studies found a positive association, one open-label study reported improvement in $FEV_1$ values compared to control (+8 versus −15%, p = 0.03) and the other showed similar results (+11 versus +5%, p = 0.001). However, six studies failed to find an improvement in lung parameters. It was not possible to perform meta-analyses due to the great heterogeneity of the interventions. In parallel, they analyzed information related to quality of life; however, the data are contrasting showing benefits and negative results without improvement in quality of life.[322] In sum, the evidence shows studies with a low, moderate and high risk of bias. Quality of life was assessed in seven studies, two of which reported improvement with the use of honey-rich preparation and the other with peptide-rich beverages. There was symptom improvement associated with improvement in quality of life; however, five studies failed to find differences.[322] Other published SLR were consistent with the findings.[32,323]

**Physical exercise.** There is clinical information demonstrating the association between decreased peripheral muscle strength and endurance, as well as a negative effect on physical activity performance and quality of life in people with COPD. Loss of muscle mass is also predictive of a worse prognosis for mortality, regardless of the degree of lung damage.[324]

Recently, exercise capacity has been studied more in people with COPD: the 6MW test, among others, has shown adequate precision in defining and planning programs that improve functional capacity in these patients.[325] Physical training is considered an essential part of pulmonary rehabilitation. Different types of training have been proposed, including resistance exercises, muscle growth, yoga, tai chi, among others.

In 2022, a network meta-analysis published by Priego *et al.*, analyzed the effects of different strategies to assess the effects on exercise capacity. The authors included 41 clinical studies and the results of the meta-analyses showed that the various strategies are beneficial. The different strategies were categorized into Active Mind-Body Movement Therapies (AMBMT), which includes yoga, tai chi and qi gong; combined training (COMB), which includes strength and endurance in a combined way; endurance treatment (endurance - END), which refers to aerobic training, such as walking or cycling; pilates, pulmonary rehabilitation and urban training, which includes physical activity in urban walking circuits. Thirteen studies were categorized as low risk of bias, two with some points of concern, and 26 with high risk of bias. The results of the «network meta-analysis» where physical capacity was measured with the 6MW showed a superiority of Pulmonary Rehabilitation + Urban Training (effect size (ES) 1.50, 95%CI: 0.52; 1.31), followed by Pilates (ES 1.32, 95%CI: 0.18; 2.45), and AMBMT (ES 0.96, 95%CI: 0.61; 1.31). The different physical activity strategies showed greater effectiveness when supervised.[325]

The impact of incorporating digital tools (including the use of portable monitors such as watches, phones, etc.) to improve the quality and frequency of physical activity in an objective way has even been reported. The use of these tools was associated with greater physical capacity, greater distance traveled in a day (based on the number of steps), longer exercise time and better quality of life.[326,327]

## Inhaled pharmacological treatment for stable COPD

### Clinical Question 13: *What is the efficacy and safety of inhaled pharmacological therapy for the treatment of stable COPD?*

| | Recommendations | |
|---|---|---|
| | **General recommendations for inhaled therapy** *(Table 17)* | |
| 1 | At all levels of care, inhaled bronchodilator therapy is the basis of pharmacological treatment of stable COPD, as they improve lung function ($FEV_1$) and reduce symptoms, particularly dyspnea. In addition, they show greater effectiveness when administered on a regular basis. | Evidence 1++<br>Recommendation A |
| 2 | The use of oral bronchodilators is not recommended. | Evidence 3<br>Recommendation C |
| 3 | Short-acting bronchodilators are indicated in combination (SABA/SAMA) as they are more effective compared to their separate use; they improve lung function ($FEV_1$) and symptoms. They should be administered, on a regular basis and/or as needed, as an adjunctive treatment to long-term bronchodilators (LABA and LAMA). | Evidence 1++<br>Recommendation A |

| | | |
|---|---|---|
| 4 | Long-acting inhaled bronchodilators (LABA and LAMA) are indicated as the first line in initial and maintenance therapy for their efficacy and safety in patients with stable COPD; they improve lung function and symptoms, decrease the rate of exacerbations and improve quality of life. It should be prescribed as LABA or LAMA mono therapy, combined (dual LABA/LAMA therapy) or combined with inhaled corticosteroids (triple LABA/LAMA/ICS therapy). The decision of your initial prescription and maintenance adjustment is primarily based on the severity of symptoms as well as the patient's history or risk of exacerbations. | Evidence 1++<br>Recommendation A |
| 5 | ICS should not be used as mono therapy; they are indicated only in combination with LABA and LAMA (triple LABA/LAMA/ICS therapy). Currently, the use of ICS combined only with LABA (LABA/ICS) is not recommended as it has lower efficacy compared to dual therapy and triple therapy. | Evidence 1+<br>Recommendation B |
| 6 | Oral corticosteroids are not indicated in stable COPD, since there is no evidence of the benefit and for its multiple side effects | Evidence 2+<br>Recommendation B |
| 7 | At all levels, the combination of two or three inhaled medications in a single inhalation device should be preferred since it facilitates its use, reduces application errors, improves adherence to treatment and is usually cheaper. | Evidence 2+<br>Recommendation B |
| 8 | The use of inhaled therapy requires the patient to demonstrate an appropriate technique of use. This can be achieved with education, training and retraining strategies. If necessary, family members and caregivers can be trained for its administration, which can be assisted with metered-dose inhalation devices (MDI or aerosols) and with the use of spacers. | Evidence 1+<br>Recommendation A |
| 9 | After establishing the initial inhaled therapy, the follow-up of patients can be up to every three months for surveillance, evaluating the response to pharmacological and non-pharmacological treatment; the adherence and proper use of inhalers must be evaluated, as well as making the necessary adjustments for maintenance therapy. | Evidence 2–<br>Recommendation C |

| Recommendations for monotherapy, dual therapy and inhaled triple therapy | | |
|---|---|---|
| 1 | Inhaled monotherapy (LAMA or LABA): at all levels of care, initial and maintenance inhaled therapy with a single long-acting bronchodilator (LAMA or LABA) is indicated in patients with stable COPD with mild or moderate obstruction ($FEV_1 \geq 60\%$), with mild dyspnea (mMRC 0-1) or few symptoms in general (CAT < 10), no history of exacerbation or only a mild or moderate exacerbation in the last year. LAMA bronchodilators are more effective compared to LABAs in reducing exacerbations and are usually the most widely available in Mexico. If the patient on monotherapy persists with dyspnea or has exacerbations, consideration should be given to escalating maintenance treatment with dual therapy. | Evidence 1+<br>Recommendation A |
| 2 | Dual therapy (LABA/LAMA): LABA/LAMA combination is more effective than monotherapy in improving lung function ($FEV_1$) and symptoms, quality of life and decreasing the rate of exacerbations. | Evidence 1++<br>Recommendation A |

**Table 17: Key points:** Inhaled pharmacological Therapy.

- Inhaled therapy is the mainstay of pharmacological treatment of stable COPD; it can improve lung function ($FEV_1$), reduce symptoms (dyspnea), decrease the rate of exacerbations and improve quality of life.
- Short-term bronchodilators should be used in combination (SABA/SAMA), on a regular and/or as needed basis, and as an adjunctive treatment to long-term bronchodilators (LABA and LAMA).
- LABA or LAMA monotherapy, LABA/LAMA dual therapy, and LABA/LAMA/ICS triple therapy are the indicated medications for initial and maintenance therapy.
- The use of oral bronchodilators is not recommended.
- ICS are indicated only in combination with LABA and LAMA (triple LABA/LAMA/ICS therapy).
- Oral corticosteroids are not indicated in stable COPD due to no evidence of benefit and multiple side effects.
- The combination of two or three medications in a single inhalation device is preferable.
- A technique of proper use of the inhalation device by the patient must always be confirmed.

| | | |
|---|---|---|
| | Inhaled therapy with two long-term bronchodilators (LABA/LAMA) is indicated as initial treatment in those patients with greater obstruction ($FEV_1$ < 60%), with moderate or severe dyspnea (mMRC 2-4) or greater symptoms in general (CAT ≥ 10) and with or without exacerbations in the last year. Dual therapy should be continued as maintenance therapy as long as the patient remains stable and adequate control of exacerbations is achieved. Patients under this treatment condition should preferably be treated or supervised at the second or third level of care. | |
| 3 | Triple therapy (LABA/LAMA/ICS): triple therapy is indicated as initial therapy in those patients with a history of frequent exacerbations (≥ 2 moderate exacerbations or ≥ 1 hospitalization in the previous 12 months) in any degree of dyspnea, symptoms or obstruction to airflow and who also show a number of blood eosinophils ≥ 300 cells/µL. Likewise, it is also recommended in those patients with asthma traits. As maintenance therapy it is indicated in those patients who persist with exacerbation despite previous treatment with dual therapy (LABA/LAMA) and show a blood eosinophil count ≥ 100 cells/µL). Patients under this treatment condition should preferably be treated or supervised at the second or third level of care. | Evidence 1+ Recommendation A |

| Special Inhaled Therapy Adjustments Recommendations | | |
|---|---|---|
| 1 | Withdrawal of inhaled corticosteroid: in the second and third levels of care, the withdrawal of ICS from inhaled maintenance therapy (change from triple LABA/LAMA/ICS therapy to dual LABA/LAMA therapy) can be assessed in those patients who do not have a clear indication, who do not show frequent exacerbations and the number of eosinophils in the blood is < 100 cells/µL. Caution should also be taken on account in patients with a history of mycobacterial infection, recent community-acquired pneumonia, or who do not have pneumococcal immunization (see vaccination recommendation). | Evidence 2– Recommendation C |
| 2 | Adjustment of patients with current LABA/ICS treatment: patients with stable COPD who are on combined treatment with LABA and ICS should be reviewed at the second and third levels of care for therapeutic adjustment. Those patients with indication of ICS (history of frequent exacerbations and eosinophils ≥ 100 cells/µL) should be adjusted to triple therapy (LABA/LAMA/ICS) for being more effective. If there is no relevant history of exacerbations and the number of eosinophils is less than 100, adjustment to dual therapy (LABA/LAMA) should be considered. | Evidence 2– Recommendation C |

### *Evidence analysis*

**Short-acting bronchodilators: SAMA and SABA.** Tanimura *et al.,* evaluated the efficacy and safety of a combination of a short-acting muscarinic antagonist (SAMA) and a long-acting β2-agonist (LABA) in patients with stable COPD. The results showed significant upgrades in $FEV_1$ (98.70 mL, $p < 0.00001$), the transient dyspnea index (TDI) (0.85, $p = 0.02$) and SGRQ (–2.00, $p = 0.008$) compared with the use of LABA alone. They found no differences in the risk of exacerbations ($p = 0.20$), but a trend towards a higher number of serious adverse events (OR 2.16, $p = 0.08$) and cardiovascular events (OR 2.38, $p = 0.06$) was observed.[328] Additionally, a controlled clinical trial reported that inhalation of SABA and SAMA improved airflow limitation and dynamic hyperinflation in patients with stable COPD treated with maintenance LAMA. However, SABA's efficacy was superior, as it also reduced respiratory resistance and improved dyspnea and exercise capacity. The use of SABA before exercise, in addition to treatment with LAMA, could be beneficial for these patients, improving their exercise tolerance.[329]

**Long-acting bronchodilators: LAMA and LABA.** Different CPG recommend, due to their efficacy and safety, starting long-acting bronchodilators alone or in combination *(Table 18)* in symptomatic patients with COPD confirmed by spirometry.[4,28,330] The inhaled treatment with this type of bronchodilator, and in indicated cases with inhaled corticosteroids,[331] offers significant benefits, including improvements in lung function and symptoms, resulting in improved quality of life and a reduction in the frequency of exacerbations.[332]

The GOLD 2025 guidelines recommend starting treatment based on the proposed classification according to the degree of obstruction by $FEV_1$, symptoms and exacerbations.[28]

**Monotherapy with long-acting bronchodilators: LAMA and LABA.**

Long-acting bronchodilators are preferred over short-acting bronchodilators in GOLD Group A (dyspnea or mild symptoms without frequent exacerbations) as they improve lung function, quality of life, and reduce exacerbations.[28] These bronchodilators are divided into two groups: long-acting antimuscarinic bronchodilators (LAMA), which block M3 receptors in bronchial smooth muscle, and LABA, which act on adrenergic receptors, increasing intracellular cyclic AMP.[4]

Evaluation of the efficacy of LAMA bronchodilators (tiotropium, aclidinium, glycopyrronium, and umeclidinium) in patients with stable COPD showed significant improvement in $FEV_1$ at 12 and 24 weeks compared with placebo. At 12 weeks, umeclidinium showed the greatest increase in $FEV_1$ (136.7 mL), followed by glycopyrronium (117.2 mL) and B. tiotropium (114.1 mL). At 24 weeks, glycopyrronium and aclidinium showed increases of 135.8 mL and 128.1 mL, respectively.[333] LAMAs also reduced the use of needed medication, with glycopyrronium and tiotropium being the most effective. Furthermore, these LAMA´s demonstrated significant improvements in $FEV_1$, dyspnea index and SGRQ, along with a reduction in the incidence of exacerbations (RR = 0.85, 95%CI 0.79-0.91).[334]

Additionally, long-acting bronchodilators (LAMA or LABA), either as monotherapy or dual therapy, improve exercise capacity in patients with COPD. Efficiency in terms of endurance time was greater in those with pulmonary hyperinflation, showing similar results in walking and bicycle ergometer.[335,336] Regarding safety, no significant differences were found in the incidence of adverse events (RR 1.01, 95%CI 1.00-1.02) or cardiovascular events (RR 0.98, 95%CI 0.88-1.09).[334]

**Dual therapy: LABA/LAMA.** Patients with moderate to severe dyspnea and/or poor health and a low risk of exacerbations should receive a LAMA/LABA combination.[330] When starting bronchodilator therapy, the combination of LABA and LAMA is preferred; however, most studies have been conducted in patients with a low exacerbation rate.[28]

**Pharmacological combinations.** Several studies have been conducted to compare the effectiveness of different bronchodilators; however, many of these studies have identified limitations that affect comparability and generalizability of the results.

The combination of tiotropium and olodaterol (TIO/OLO) has been shown to be effective as a first-line treatment for COPD. A meta-analysis of 10,918 patients revealed that TIO/OLO significantly improved $FEV_1$ compared with these components alone and with the LABA/ICS combination at 12 months. In addition, improvements were observed in the Transitional Dyspnea Index (TDI) and SGRQ, with a greater number of patients achieving clinically relevant improvements compared to monotherapy. A reduction in the use of rescue medications was also observed, with no differences in the frequency of serious adverse events compared to other active treatments.[337]

The combination of umeclidinium and vilanterol (UMEC/VI) has comparable efficacy to other dual bronchodilator combinations, with no significant differences. A meta-analysis compared UMEC/VI with indacaterol + glycopyrronium, formoterol + tiotropium, salmeterol + tiotropium, indacaterol + tiotropium, tiotropium monotherapy, and placebo as common comparators at 12 and 24 weeks. At 24 weeks, UMEC/VI demonstrated similar efficacy to indacaterol + glycopyrronium in terms of $FEV_1$ (14.1 mL, 95%CI −14.2-42.3), SGRQ (0.18, 95%CI −1.28-1.63), TDI (−0.30, 95%CI −0.73-0.13) and as needed medication use (0.02, 95%CI −0.27-0.32). It also showed comparable results to salmeterol + tiotropium B in $FEV_1$ (67.4 mL, 95%CI −25.3–159.4 mL), SGRQ (−0.11, 95%CI −1.84-1.61), and TDI (0.58, 95%CI −0.33-1.50), as well as to formoterol + tiotropium B in SGRQ (−0.68, 95%CI −1.77-0.39). The results obtained at 12 weeks were consistent with those at 24 weeks.[338]

In another meta-analysis comparing different LAMA/LABA combinations, although some inconsistencies were found between the outcomes for lung function, symptoms, exacerbations, and safety across the four CCT («head-to-head» direct comparisons) and six incorporated network meta-analyses (indirect comparisons) for lung function, symptoms, exacerbations, and safety, the data suggest that the currently available LAMA/LABA combinations have comparable efficacy and safety in COPD patients with severe to very severe airflow obstruction.[339]

**LABA/LAMA versus placebo and monotherapy.** LABA/LAMA combinations, such as indacaterol + glycopyrronium, umeclidinium + vilanterol, aclidinium + formoterol, tiotropium + olodaterol, in a single inhaler device improve lung function when compared with placebo and monotherapy (LAMA or LABA).[340] Furthermore, symptom improvement was observed compared to placebo, although variations depend on the specific pharmacological combination and the clinical endpoint evaluated. Regardless of the pharmacological combination, exacerbations were reduced compared to placebo, although data on the comparison with monotherapy are limited.[341]

Mammen MJ *et al.,* observed that, in patients with dyspnea and/or exercise intolerance, LABA/LAMA combination therapy significantly reduced the rate of hospitalizations (11% reduction, $p < 0.01$) and COPD exacerbations (20% reduction, $p < 0.002$) compared with monotherapy. Although a slight improvement in dyspnea and health-related

**Table 18:** Inhaled bronchodilators and corticosteroids alone or in combination available in a single device.

| Medication | Dose, µg | Posology (inhalations) | Presentation | Device |
|---|---|---|---|---|
| **SABA** | | | | |
| Salbutamol | 100 | 2-4 every 4-6 h | Solution | MDI |
| **SAMA** | | | | |
| Ipratropium bromide | 20 | 2-4 every 4-6 h | Solution | MDI |
| **SABA + SAMA** | | | | |
| Salbutamol + ipratropium bromide | 100/20 | 2-4 every 4-6 h | Solution | Respimat |
| Fenoterol + ipratropium bromide | 20/50 | 2-4 every 4-6 h | Solution | MDI |
| **LABA** | | | | |
| Formoterol | 12 | 1 every 12 hours | Dry powder | Aerolizer |
| Indacaterol | 150 | 1 every 24 hours | Dry powder | Breezhaler |
| Olodaterol | 5 | 2 every 24 hours | Solution | Respimat |
| Salmeterol | 25 | 2 every 12 hours | Solution | MDI |
| **LAMA** | | | | |
| Aclidinium | 322 | 1 every 12 hours | Dry powder | Genuair |
| Glycopyrronium | 50 | 1 every 24 hours | Dry powder | Breezhaler |
| Tiotropium | 5 | 2 every 24 hours | Solution | Respimat |
| Tiotropium | 18 | 1 every 24 hours | Dry powder | Handihaler |
| Umeclidinium | 62.5 | 1 every 24 hours | Dry powder | Ellipta |
| **LABA + LAMA** | | | | |
| Formoterol/aclidinium | 12/400 | 1 every 12 hours | Dry powder | Genuair |
| Indacaterol/glycopyrronium | 110/50 | 1 every 24 hours | Dry powder | Breezhaler |
| Olodaterol/tiotropium | 5/5 | 2 every 24 hours | Solution | Respimat |
| Vilanterol/umeclidinium | 25/62.5 | 1 every 24 hours | Dry powder | Ellipta |
| **ICS** | | | | |
| Beclomethasone | 100, 200, 250 | 1-4 every 8-12 h | Solution | MDI |
| Budesonide | 100 y 200 | 1-4 every 12 hours | Solution | MDI |
| Budesonide | 100 | 1-4 every 12 hours | Dry powder | Turbuhaler |
| Budesonide | 200, 400 | 1 every 12 hours | Dry powder | Breezhaler |
| Ciclesonide | 100, 200 | 1 every 24 hours | Solution | MDI |
| Fluticasone | 250 | 1-4 every 12 hours | Solution | MDI |
| **LABA + ICS** | | | | |
| Formoterol/beclomethasone | 6/100 | 2 every 12 hours | Dry powder | Nexthaler |
| Formoterol/beclomethasone | 6/100 | 2 every 12 hours | Solution | MDI |
| Formoterol/budesonide | 4.5/160, 9/320 | 1-2 every 12 hours | Dry powder | Turbuhaler |
| Formoterol/budesonide | 4.5/160 | 2 every 12 hours | Solution | MDI |
| Formoterol/mometasone | 5/100 | 2 every 12 hours | Solution | MDI |
| Salmeterol/fluticasone propionate | 50/250, 50/500 | 1 every 12 hours | Dry powder | Diskus |
| Salmeterol/fluticasone propionate | 25/250 | 2 every 12 hours | Solution | Evohaler |

**Table 18 continues:** Inhaled bronchodilators and corticosteroids alone or in combination available in a single device.

| Drug | Dose, µg | Posology (inhalations) | Presentation | Device |
|---|---|---|---|---|
| Vilanterol/fluticasone furoate | 25/100 | 1 every 24 hours | Dry powder | Ellipta |
| **LABA + LAMA + ICS** | | | | |
| Formoterol/glycopyrronium/beclomethasone | 6/12.5/100 | 2 every 12 hours | Solution | MDI |
| Formoterol/glycopyrronium/budesonide | 4.8/7.2/160 | 2 every 12 hours | Solution | MDI |
| Indacaterol/glycopyrronium/mometasone | 114/46/136 | 1 every 24 hours | Powder | Breezhaler |
| Vilanterol/umeclidinium/fluticasone furoate | 25/62.5/100 | 1 every 24 hours | Powder | Ellipta |

ICS = inhaled corticosteroids. LABA = long-acting beta-2 adrenergic bronchodilators. LAMA = long-acting muscarinic bronchodilators. MDI = metered-dose inhaler. SABA = short-acting beta-2 adrenergic bronchodilators. SAMA = short-acting muscarinic bronchodilators.

quality of life was observed, these changes were not clinically significant, and no differences in adverse effects were found between therapies (RR 0.99, p = 0.34).[342]

**LABA/LAMA versus LAMA versus LABA/ICS.** In moderate to severe COPD, LABA/LAMA combinations were shown to improve $FEV_1$ compared with LAMA (0.07 L) and LABA/inhaled corticosteroid (0.08 L) ($p < 0.0001$),[331] and increased the odds of achieving clinical improvement. The combination also improved dyspnea index and SGRQ scores ($p < 0.0001$), along with a reduction in as needed medication use. LABA/LAMA reduced moderate/severe exacerbations versus LABA/ICS (RR 0.82, 95%CI 0.75-0.91), had a lower incidence of adverse effects (RR 0.94, 95%CI 0.89-0.99) and a lower risk of pneumonia (RR 0.59, 95%CI 0.43-0.81). Furthermore, this combination showed a lower risk of discontinuation due to lack of efficacy compared to LAMA (RR 0.66, 95%CI 0.51-0.87) and due to adverse effects compared to LABA/ICS (RR 0.83, 95%CI 0.69-0.99). In a meta-analysis involving 17,734 COPD patients from 16 randomized controlled clinical trials (CCT) of LABA/LAMA treatment lasting from six to 52 weeks, they found that this combination was more effective than LABA/ICS for most of the outcomes evaluated. These results support its use as a first-line treatment in COPD.[343]

**Triple therapy: LABA/LAMA/ICS.** Switching to triple therapy (LABA/LAMA/ICS) can occur in several scenarios: 1) patients with frequent exacerbations (GOLD Group E) who have an eosinophil count ≥ 300 cells/µL; and 2) those with exacerbations despite dual therapy (LABA/LAMA) and who have an eosinophil count ≥ 100 cells/µL. Triple therapy has been shown to reduce annual moderate (treated with corticosteroids or antibiotics) and severe (hospitalization or death) exacerbations by 15-52% versus LAMA/LABA, 15-35% versus LABA/ICS, and 20% versus LAMA, with a number needed to treat (NNT) of 25-50 patients or 3-11 events.[344] It also prolonged the time to first exacerbation.[345] However, it did not show superiority over monotherapy (RR 0.75, 95%CI 0.68-0.82, $p < 0.001$), except in patients with a history of exacerbations.[346,347]

Cazzola M *et al.,* compared triple therapy with LABA/LAMA, LABA, or LAMA monotherapy, showing that the LABA/LAMA/ICS combination reduced the risk of exacerbations (RR 0.70, 95%CI 0.53-0.94) and improved $FEV_1$ (+37.94 mL, 95%CI 18.83-53.89) compared with LABA/LAMA. Approximately 38 patients required treatment with LABA/LAMA/ICS for one year to prevent one exacerbation versus LABA/LAMA, and 21 versus a single long-acting bronchodilator.[348] Results were similar to those reported by Long H *et al.,* where triple therapy improved prebronchodilator $FEV_1$ (MD 63.68 mL, CrI 45.29–82.73) and SGRQ scores (MD −3.11 points, CrI −6.00 to −0.80) more than tiotropium monotherapy and LABA/ICS combination therapy.[345,349]

A Cochrane systematic review evaluated the impact of triple therapy on exacerbations, quality of life, pneumonia, serious events, symptoms, lung function, physical capacity, and mortality. Triple therapy reduced moderate to severe exacerbations compared with LABA/LAMA (rate ratio 0.74, 95%CI 0.67-0.81, low certainty). It improved quality of life (OR 1.35, 95%CI 1.26-1.45, high certainty) and $FEV_1$ (38.68 mL, 95%CI 22.58-54.77, low certainty), although without clinically significant thresholds. However, it increased the risk of pneumonia (OR 1.74, 95%CI 1.39-2.18, moderate certainty), but showed no differences in serious adverse events (OR 0.95, 95%CI 0.87-1.03, low certainty). Additionally, all-cause mortality was lower with triple therapy (OR 0.70, 95%CI 0.54-0.90, low certainty).[345,350]

In patients with eosinophils ≥ 300 cells/µL−1, the reported number needed to treat (NNT) was 8.58, versus 46.28 in those with lower counts. The effect of triple therapy was more significant in these patients (RR 0.57, 95%CI 0.48-0.68).[348] The benefit is greater in patients with elevated

eosinophils, a higher frequency of previous exacerbations, and former smokers. Therefore, prescribing triple therapy based on patient phenotype, expected benefit, and risks is recommended, and further research is required to establish specific thresholds for treatment decision-making.[344,350]

**Adverse events.** An analysis of 51 clinical trials with 91,021 patients evaluated the impact of LAMA/LABA combinations and triple therapy on the risk of major cardiovascular events in patients with COPD. Results indicated that both LABA/LAMA (1.6 versus 1.3%; RR 1.42, 95%CI 1.11-1.81) and triple therapy (1.6 versus 1.4%; RR 1.29, 95%CI 1.03-1.61) increased the risk of major cardiovascular events compared with LABA/ICS, especially in studies with a baseline risk greater than 1% per year. Compared with LAMA, LABA, or placebo monotherapy, the LABA/LAMA combination did not show a significant increase in cardiovascular risk, although with low statistical power.[351]

Additionally, triple therapy has been shown in various systematic reviews and meta-analyses to increase the risk of pneumonia (RR 1.48, 95%CI 1.23-1.79, $p < 0.001$), 345 and the occurrence of up to 16 cases of pneumonia per 1,000 patients has been reported.[346,347]

**Inhaled corticosteroids.**[331] The role of ICS in COPD has been subject to uncertainty. Current clinical guidelines recommend its selective use, only in combination with long-acting bronchodilators, since combined therapy turns out to be more effective than ICS as monotherapy.[28]

Long-term use of ICS as monotherapy has been shown to reduce the rate of exacerbations (rate ratio 0.88, 95%CI 0.82-0.94, $I^2$ 48%) and delay the decline in quality of life (MD −1.22 units/year, 95%CI −1.83 to −0.60, $I^2$ 0%) compared with placebo. However, no significant difference was observed in all-cause mortality (OR 0.94, 95%CI 0.84-1.07). Furthermore, $FEV_1$ declined at a slower rate in ICS-treated patients (MD 6.31 mL/year, 95%CI 1.76-10.85). Despite these benefits, ICS use increased the risk of pneumonia (OR 1.38, 95%CI 1.02-1.88), oropharyngeal candidiasis (OR 2.66, 95%CI 1.91-3.68), and dysphonia (OR 1.98, 95%CI 1.44-2.74). No significant effects were observed on fractures or bone mineral density.[352]

On the other hand, combination therapies with ICS have been shown to significantly reduce moderate and severe exacerbations (RR 0.86, 95%CI 0.80-0.93), and the annual rate of exacerbations by 22% (RR 0.78, 95%CI 0.72-0.86) and those requiring hospitalization by 31% (RR 0.69, 95%CI 0.54-0.88). A reduction in exacerbations requiring oral steroids was also observed (RR 0.69, 95%CI 0.66-0.73). Furthermore, LABA/ICS and LABA/LAMA/ICS combinations improved lung function and quality of life compared with non-ICS treatments.[353] In the case of pneumonia, the ICS compared with placebo, the increase is minimal at 5% versus 3.5%.

**ICS Withdrawal.** Data on switching from triple to dual therapy (LAMA/LABA) in patients with COPD are limited. An analysis of three clinical trials and three observational studies showed that ICS withdrawal did not significantly affect moderate or severe exacerbations or $FEV_1$, although an increase in exacerbations was observed in patients with eosinophils ≥ 300 cells/µL (HR 1.35, 95%CI 1.00-1.82). No significant changes in mortality were found; therefore, patients with elevated eosinophils may benefit most from continuing triple therapy.[354] Real-life studies support that ICS withdrawal, with appropriate management, does not increase the risk of exacerbations, improves lung function and symptoms, and reduces the risk of pneumonia. This approach should be considered in patients without clear indications for ICS use, such as those without frequent exacerbations, according to the European Respiratory Society guidelines.[355]

**Inhalation therapy management.** Incorrect inhaler use is common and can compromise treatment effectiveness. Error rates vary considerably, ranging from 50% to 100% for general errors and from 14% to 92% for critical errors, with notable heterogeneity across studies (> 90%). Although a tendency toward more errors was observed with devices requiring more steps, no clear pattern was identified. Factors such as older age, female gender, and educational level influenced error frequency, with patients with a higher level of education reporting fewer errors. Furthermore, higher error rates were recorded in patients with COPD compared to those with asthma. Other factors, such as training received, duration of device use, and the use of multiple inhalers, contribute to increased confusion and error rates.[356]

NICE guidelines state that most patients with COPD can learn to use an inhaler correctly if they receive appropriate training *(Figure 9)*, although those with significant cognitive impairment may struggle to do so.[64]

1. For the administration of bronchodilators, the use of MDI is recommended, with spacers if necessary, and they should only be prescribed after patients demonstrate correct technique.
2. It is crucial to regularly assess patients' ability to use the inhaler and correct it if necessary.
3. As for spacers, they must be compatible with the patient's MDI inhaler, and appropriate instruction on their use and cleaning must be provided.
4. For those with severe COPD who experience breathing difficulties despite using inhalers, nebulizer therapy may be considered, always ensuring that the patient or caregiver can use them correctly.
5. Nebulizer therapy should be periodically re-evaluated to ensure its effectiveness, and the equipment should be offered along with ongoing support *(Table 19)*.

## Other pharmacological treatment to prevent exacerbations

### Clinical Question 14: *What is the efficacy and safety of other non-inhaled drugs (macrolides, phosphodiesterase 4 inhibitors, dupilumab, and mucolytics) in preventing COPD exacerbations despite optimal inhaled therapy (LABA/LAMA/ICS triple therapy)?*

| Recommendations | | |
|---|---|---|
| 1 | People with COPD who, despite optimal inhaled therapy (LABA/LAMA/ICS triple therapy), experience persistent moderate or severe exacerbations and/or chronic bronchitis should be managed by specialists in secondary or tertiary care settings and should be considered for other long-term non-inhaled pharmacological therapies, such as macrolides, roflumilast, dupilumab, and mucolytics. These treatments can reduce exacerbations and improve lung function and quality of life. | Evidence 1+<br>Recommendation B |
| 2 | **Macrolides:** long-term use of macrolides such as azithromycin (250 mg orally, three times a week) or erythromycin (250 mg orally, twice a day) for one year in nonsmoking patients may be effective in reducing exacerbations and improving patients' quality of life after one year of treatment. However, treatment with azithromycin is associated with a higher incidence of bacterial resistance and hearing damage. | Evidence 1−<br>Recommendation B |
| | **Roflumilast:** is a phosphodiesterase 4 inhibitor. People with COPD with severe obstructive pulmonary disease ($FEV_1 \leq 50\%$) and persistent exacerbations and/or chronic bronchitis may benefit from long-term treatment (roflumilast 500 μg orally every 24 h); it improves lung function and reduces moderate and severe exacerbations. However, its adverse effects, which include diarrhea, nausea, vomiting, weight loss, insomnia, and depression, should be considered. | Evidence 1+<br>Recommendation A |
| 3 | **Dupilumab:** people with COPD with persistent moderate or severe exacerbations, with peripheral eosinophilia (≥ 300 cells/mL) and a history of frequent exacerbations should be considered for treatment with dupilumab (300 mg subcutaneously twice monthly), which may improve exacerbations, lung function and quality of life at one year of treatment and without significant adverse effects. | Evidence 1+<br>Recommendation B |
| 4 | **Mucolytics:** in selected patients, mucolytics may improve respiratory symptoms (chronic bronchitis). However, they do not impact clinical outcomes such as exacerbation reduction and survival. | Evidence 1+<br>Recommendation B |

### *Evidence analysis*

People with COPD who, despite optimal management with inhaled drug therapy, persist with frequent exacerbations or chronic bronchitis, may benefit from other drug treatments.[3,357] These medications include long-term treatment with macrolides (azithromycin and erythromycin), phosphodiesterase 4 inhibitors (roflumilast), monoclonal antibodies in patients with eosinophilia (dupilumab), and mucolytics.

**Macrolides.** Macrolides are of interest in the prevention of exacerbations, since they have antibacterial, antiviral and anti-inflammatory properties. Azithromycin at doses of 250 to 500 mg three times a week or erythromycin 250 mg twice a day for one year has been shown to reduce the frequency of exacerbations with less benefit in active smokers and no demonstrated benefit for more than one year of treatment.[3] A Cochrane meta-analysis showed that the prophylactic use of different oral macrolides at different doses reduces exacerbations (HR 0.67, 95%CI 0.60-0.75) and improves quality of life (MD in the SGRQ: 2,298 points of improvement), in addition to reducing serious adverse events (RR 0.76, 95%CI 0.62-0.93). Likewise, other systematic reviews reported a reduction in the RR of exacerbations when compared with placebo.[358-360] Although erythromycin and azithromycin were the most effective macrolides, an increase in isolates resistant to these antibiotics was observed (OR 4.49, 95%CI 2.48-8.12).[361] The use of azithromycin was associated with an increased incidence of bacterial resistance (RR 2.69, 95%CI 1.25-5.21), QT interval prolongation, and hearing loss (RR 1.168, 95%CI 1.030-1.325).[362]

**Oral phosphodiesterase 4 inhibitors.** Phosphodiesterase 4 inhibitors are selective blockers of the phosphodiesterase

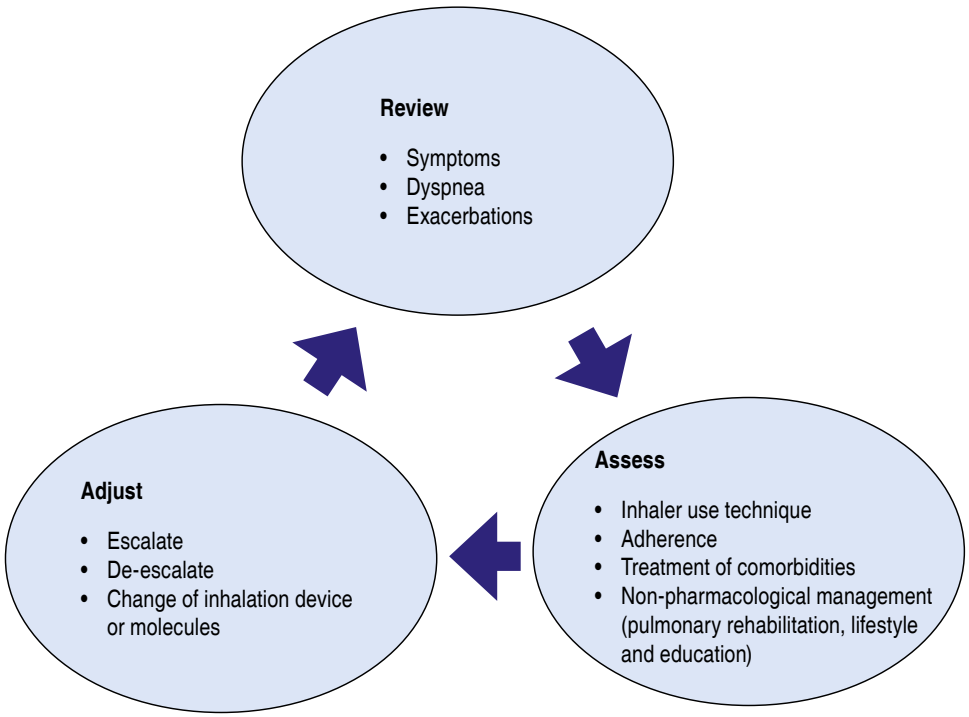


**Figure 9:**

Monitoring and treatment adjustment cycle of inhaled pharmacological therapy in stable COPD.
Modified from: GOLD 2025.[3]

**Table 19:** Criteria for adjusting inhaled pharmacological therapy in stable COPD.

| Initial setting | Monotherapy LABA/LAMA | Dual therapy LABA/LAMA | Triple therapy LABA/LAMA/ICS |
|---|---|---|---|
| Dyspnea (mMRC, score) | Mild (0-1) | Moderate to severe (2-4) | Any degree of dyspnea |
| Symptoms (CAT, score) | Mild (< 10) | Moderate to severe (≥ 10) | Any level of symptoms |
| Obstruction ($FEV_1$, %p)* | Mild to moderate obstruction (≥ 60%) | Moderate to severe obstruction (< 60%) | Any degree of obstruction |
| Exacerbations (number/year and severity) | 0-1 moderate | With or without frequent exacerbations | ≥ 2 moderate or one severe |
| Eosinophils (cells/µL) | < 300 | < 300 | ≥ 300 |
| Others | | | With asthma traits |
| **Maintenance adjustment** | It should be continued if dyspnea improves and the patient is stable<br><br>If dyspnea persists or worsens and/or frequent exacerbations occur, dual therapy should be escalated | It should be continued if the patient is stable and dyspnea and exacerbations have been reduced<br><br>If dyspnea or exacerbations persist and eosinophils ≥ 100 are present, triple therapy should be escalated | Patients on dual therapy who persist with dyspnea or frequent exacerbations and have eosinophils ≥ 100<br><br>Patients on triple therapy who persist with exacerbations should receive additional medication** |

CAT = COPD Assessment Test. $FEV_1$, %p = percentage of predicted forced expiratory volume in one second. mMRC = *modified* Medical *Research Council scale.*
* The $FEV_1$ cutoff point greater or less than 60% was determined by expert recommendations based on mortality prognostic values described in Mexico.[22] Frequent exacerbations are defined as two or more moderate exacerbations or one or more exacerbations requiring hospitalization in the past year.
** Patients with persistent exacerbations despite optimal treatment with triple therapy should be escalated to other medication for persistent exacerbations.

4 ($PDE_4$) isoenzyme; they inhibit inflammation by preventing the degradation of cAMP (intracellular cyclic adenosine monophosphate). The $PDE_4$ enzyme is expressed in a large number of cells that play a very important role in the pathophysiology of COPD, such as eosinophils, T lymphocytes, neutrophils, monocytes, among others.[363] Roflumilast at a daily oral dose of 500 µg has been shown to reduce moderate and severe exacerbations in patients with severe COPD. A 2020 SLR published by Janjua *et al.,* with the Cochrane Collaboration aimed to evaluate the efficacy and safety of oral phosphodiesterase 4 inhibitors for the management of stable COPD.[364]

The authors included 42 CCT that fulfilled their selection criteria, 28 studies for roflumilast (18,046 participants), 14 studies with cilomilast (6,457 participants), and one study with tetomilast (84 participants) with a duration of 6 weeks to 1 year of follow-up. The results of the meta-analyses showed that oral phosphodiesterase-4 inhibitors were associated with a modest but significant improvement in $FEV_1$ over an average of 40 weeks compared to placebo (MD 49.33 mL, 95%CI 44.17-54.49) with moderate quality of evidence. FVC also improved (MD 86.98 mL, 95%CI 74.65-99.31) with high quality of evidence and FEM (MD 6.54 L/min, 95%CI 3.95-9.13) with low quality of evidence.[365]

The incidence of exacerbations also showed a 22% decrease associated with the use of oral phosphodiesterase-4 inhibitors over an average of 40 weeks (RM 0.78, 95%CI 0.73-0.84) with high quality of evidence. This means that, for every 100 people treated, five more patients remained exacerbation-free during the study period compared to placebo. There was also an improvement in quality of life over a 33-week period on the SGRQ (MD-1.06 units, 95%CI -1.68 to 0.43) with moderate quality of evidence.

Regarding safety, there were more adverse events reported in the group treated with phosphodiesterase-4 inhibitors (RM 1.30, 95%CI 1.22; 1.38) with a low level of evidence. The most frequently reported adverse events were diarrhea, dyspepsia, vomiting and nausea. Diarrhea was the most frequently occurring adverse event (RM 3.20, 95%CI 2.74-3.50). There were reports of psychiatric events with roflumilast 500 µg compared to placebo (RM 2.13, 95%CI 1.79-2.54) and it was also associated with weight loss, insomnia and depression. The authors conclude that phosphodiesterase-4 inhibitors may have a place in therapeutics as additional treatment in patients who persist with symptoms or exacerbations even with optimal therapy according to international guidelines;[365] other published systematic reviews have also concluded the same.[366,367]

**Dupilumab**. Dupilumab is a human monoclonal antibody that blocks components of interleukin 4 and 13 receptors. Recently, two double-blind controlled clinical trials have been published with large samples of COPD patients (BOREAS and NOTUS studies), with peripheral eosinophilia (≥ 300 cells/µL) and history of frequent, moderate (≥ 2) or severe (≥ 1) exacerbations, despite optimal treatment with triple therapy (LABA/LAMA/ICS) during the previous year. Patients treated with dupilumab (300 mg subcutaneously twice a month for one year) showed significant improvement in exacerbations, lung function and quality of life over a 52-week period.[368,369] In addition, there was no difference in adverse effects compared to the placebo group.

**Mucolytics**. Mucolytic agents are medications that have been used extensively in the management of chronic lower airway conditions such as COPD; however, not all agents have sufficient evidence that demonstrates benefit in this disease. Hypersecretion of mucus into the airways and affected function of the mucociliary apparatus is part of the pathophysiology of COPD and is manifested by chronic cough and sputum production.[3,370] Some mucolytic agents accepted for use in COPD patients include carbocysteine, erdosteine and N-acetylcysteine. A consensus published by Papi et al. in 2020 on behalf of 53 European experts in COPD management concluded that regular use of mucolytic agents decreases the frequency of exacerbations, reduces the duration of mild to moderate exacerbations, and may increase the time to a new exacerbation.

The group consistently found erdosteine to be the most effective mucolytic. They also consider their antioxidant properties and that they all have an adequate safety profile.[3,370]

A SLR with «network meta-analysis» published by Cazzola *et al.,* in 2017 aimed to evaluate the efficacy and safety of mucolytic therapy for at least three months in patients with COPD. The authors included 11 controlled clinical trials, and the meta-analysis showed that mucolytic therapy significantly reduces the likelihood of exacerbations compared with placebo (OR 0.51, 95%CI 0.39-0.67). The mucolytic with the greatest efficacy was carbocysteine (SUCRA 79.0%), followed by erdosteine (SUCRA 70.4%), N-acetylcysteine (1,200 mg daily) (SUCRA 68.0%), and placebo (SUCRA 24.0%). There were no significant differences between ambroxol, N-acetylcysteine (600 mg daily), and placebo. Only N-acetylcysteine (1,200 mg daily) was shown to protect against exacerbations compared with placebo (OR 0.56, 95%IC 0.35-0.92). The evidence was graded as moderate according to the GRADE (Grade of Recommendations, Assessment, Development, and Evaluation) methodology.[371]

Another SLR published by Poole *et al.,* in 2019 with the Cochrane Collaboration aimed to evaluate the benefit of mucolytics in the management of patients with chronic lung disease (chronic bronchitis to COPD).[372] The authors included 38 controlled clinical trials (10,377 participants) in which carbocisteine, erdosteine, N-acetylcysteine, and

ambroxol were evaluated. The results of the meta-analyses with 28 studies showed that the use of mucolytics was associated with a longer exacerbation-free time compared to placebo (OR 1.73, 95%CI 1.56-1.91) with moderate quality of evidence. The number needded to treat (NNT) was 8, 95%CI 7-10). Mucolytic use was associated with a reduction of 0.43 disability days per participant per month compared with placebo (95%CI −0.56 to −0.30). The number of patients with one or more exacerbations was reduced with mucolytic use (OR 0.68, 95%CI 0.52-0.89). Quality of life was also improved with mucolytic use (MD −1.37, 95%CI −2.85 to 0.11). The safety profile also showed a reduction in adverse events (OR 0.84, 95%CI 0.74-0.94). The authors did not find sufficient evidence to demonstrate a reduction in mortality.[372,373]

N-acetylcysteine (NAC) may reduce acute exacerbations of COPD through its antioxidant effect, but available studies do not confirm its efficacy. A recent meta-analysis of randomized clinical trials conducted between 2000 and 2022 evaluated the efficacy of oral NAC in patients with COPD. Nine studies with a total of 2,137 patients were included. The results showed no significant differences between the NAC group and placebo in terms of acute exacerbations, $FEV_1$, FVC, quality of life, glutathione levels, or adverse events. Additionally, NAC did not reduce the risk of exacerbations or improve lung function in patients with COPD.[374]

## Not recommended therapies for stable COPD

### Clinical Question 15: *What is the efficacy and safety of various therapies (bacterial lysates, immunoglobulins, antileukotrienes and transfer factor) in patients with COPD?*

| Recommendation | | |
|---|---|---|
| 1 | At all three levels of care, routine use of bacterial lysates, leukotriene receptor antagonists, immunoglobulins, desensitization immunotherapy, or transfer factor (transferon) is not recommended for the prevention of infections or exacerbations in people with COPD. | Evidence 1++<br>Recommendation A |

*Evidence analysis*

**Bacterial lysates.** Multivalent mechanical bacterial lysosomes have been shown to reduce recurrent respiratory infections. A meta-analysis of 15 randomized controlled trials including COPD patients showed their efficacy in preventing infections, with a relative risk (RR) of 0.513 (95%CI −0.722 to −0.303, p = 0.00), implying that 1.15 patients need to be treated to benefit one. However, the effect on COPD exacerbations was not statistically significant, due to the limited number of studies with RR 0.404 (95%CI −0.864 to −0.057, p = 0.086).[375]

On the other hand, Huang *et al.,* in a meta-analysis including 12 studies, showed that bacterial lysates were effective in reducing the exacerbation rate (RR 0.83, 95%CI 0.72–0.96, p = 0.01) and the mean number of exacerbations (MD = −0.42, 95%CI −0.75 to −0.08, p = 0.01). However, bacterial lysates showed heterogeneous results in terms of symptom relief, side effects were mild and acceptable. Likewise, the authors consider several limitations in the included studies, such as methodological limitations, heterogeneity between studies, biases that limit the strength of the evidence.[376]

**Leukotriene receptor antagonists.** Several meta-analyses have not demonstrated improvements in lung function parameters or inflammatory biomarkers with treatment with leukotriene receptor antagonists, either short- or long-term. Some non-randomized clinical trials have reported a decrease in dyspnea and sputum production, suggesting symptom relief. However, the evidence regarding their therapeutic efficacy remains inconclusive.[377,378]

**Immunoglobulins.** A systematic review evaluated the impact of immunoglobulin G (IgG) replacement therapy on exacerbation frequency in patients with COPD and low IgG levels. The evidence showed no differences in exacerbation frequency compared with placebo or in lung function measured by spirometry. Furthermore, immunoglobulin therapy is expensive, and adverse reactions are common among those receiving intravenous immunoglobulin.[379]

**Other therapies (desensitization immunotherapy and transfer factor).** There is no evidence of the use of desensitization immunotherapy or transfer factor (transferon) for preventing infections or exacerbations in people with COPD.

## Long-term oxygen therapy (LTOT) *(Table 20)*

### Clinical Question 16: *In people with stable COPD, what is the efficacy and safety of long-term oxygen therapy (LTOT) according to its indications, use in different conditions and activities, as well as the different devices available?*

| Recommendations | | |
|---|---|---|
| 1 | **Absolute indications for LTOT:** In people with COPD and at all levels of care, it should be indicated for at least 15 h per day (including sleep and | Evidence 1++<br>Recommendation A |

| | | |
|---|---|---|
| | exercise or rehabilitation periods) under one of the following internationally standardized criteria and regardless of the altitude of the location:<br>1. $PaO_2$ with levels ≤ 55 mmHg or $SpO_2$ ≤ 88% with or without hypercapnia and confirmed on two occasions within a three-week period<br>2. $PaO_2$ between 56-59 mmHg or $SpO_2$ of 89-90%, but with evidence of pulmonary hypertension, right heart failure or polycythemia (hematocrit ≥ 55%).<br>Once LTOT is established, the patient should be re-evaluated after 60 to 90 days with arterial blood gas or pulse oximetry while breathing the same level of oxygen or room air to determine if oxygen is optimally therapeutic and if the indication should be continued. | |
| 2 | **Indication for portable oxygen:** Patients with indication for LTOT who leave their homes should be prescribed ambulatory devices (liquid oxygen, gaseous oxygen cylinders, or portable concentrators) in addition to the stationary oxygen device for home use. | Evidence 1+<br>Recommendation B |
| 3 | **Oxygen use only during exercise:** In people with stable COPD without an absolute indication for LTOT, but who present dyspnea or exercise-induced desaturation, evidence shows that this treatment does not prolong survival, nor increase the time to first hospitalization, nor improve the distance covered in the six-minute walk, nor provide a sustained benefit in lung function or quality of life, so its routine use is not recommended. | Evidence 1++<br>Recommendation A |
| 4 | **Use of oxygen only at night:** in people with stable COPD without an absolute indication for LTOT, but who have oxygen desaturation during sleep, in the absence of sleep apnea or alveolar hypoventilation syndrome, routine use of nocturnal oxygen therapy is not recommended, as it has no effect on long-term survival or disease progression. | Evidence 1+<br>Recommendation B |
| 5 | **Oxygen use during travel:** At all levels of care, patients with COPD planning air or ground travel to locations greater than 2,000 m above sea level should be evaluated by their physician. Patients indicated for LTOT should continue using it during the flight to maintain a $PaO_2$ > 50 mmHg, which can be achieved with a flow rate of three liters per minute with nasal prongs or $FiO_2$ at 31% with a Venturi face mask.[7,19] Only portable oxygen concentrators are internationally authorized devices for carry-on commercial flights, or alternatively, therapeutic oxygen can be supplied during the flight by the airline. Patients with resting oxygen saturation > 94% or > 84% on the six-minute walk may travel without further assessment, although it is important to emphasize that resting oxygenation at sea level does not exclude the development of hypoxemia during travel.[7,20]<br>Comorbidities (heart failure and anemia) that could impair tissue oxygen delivery should be considered. Walking during long journeys through airports can aggravate dyspnea and hypoxemia, so these individuals should be assisted with reduced mobility criteria. | Evidence 3<br>Recommendation C |
| 6 | **Recommended oxygen therapy devices:** LTOT should be administered for extended periods during the day and night, as well as on an outpatient basis to facilitate exercise and provide symptom relief, as achieved with rapid delivery devices.[380]<br>For this purpose, one or more devices that combine stationary or portable equipment may be used. These include: 1) stationary and portable oxygen concentrators; 2) compressed gaseous oxygen cylinders in the form of stationary (56 to 132 cm) and portable tanks (less than 26 inches or 66 cm); and 3) stationary liquid oxygen containers that include ambulatory oxygen equipment.<br>In secondary and tertiary care, specialist physicians may recommend high-flow nasal cannula (HFNC) devices designed for LTOT (flows between 30-60 L/min) to people with stable COPD and chronic hypercapnic respiratory failure. These devices can reduce inspiratory effort, increase lung | Evidence 3<br>Recommendation C |

| | | |
|---|---|---|
| | capacity, and reduce hypercapnia, as well as improve quality of life.[2] The selection of one or more devices depends on their commercial availability, cost, and coverage options for the healthcare system and/or patients. All delivery systems have advantages and disadvantages, so healthcare professionals should be thoroughly familiar with and trained in each to optimally prescribe LTOT. | |
| 7 | **Educational interventions:** At all levels of care, all people with COPD on LTOT and their families or caregivers should receive educational interventions from healthcare professionals and oxygen therapy providers. These interventions should be aimed at improving treatment adherence and the proper use of oxygen delivery equipment and systems, with a primary focus on safety and self-management for patients and families. | Evidence 4<br>Recommendation D |

*Evidence analysis*

**Indications and benefits of Long-Term Oxygen Therapy.** Hypoxemia in people with COPD is a common condition resulting from altered pulmonary ventilation/perfusion (V/Q) ratio and a reduction in oxygen diffusing capacity. When hypoxemia is significant and persistent at rest, it can be associated with dyspnea, neurocognitive disorders, pulmonary hypertension, and right heart failure, as well as an increased risk of mortality.[381] Furthermore, in Mexico, geographic conditions expose a large proportion of the population to high altitudes (greater than 2,000 m above sea level), which makes hypoxemia more frequent, more severe, and with greater prognostic consequences.[382] Since the publication of two longitudinal studies in the 1980s on the use of LTOT in patients with COPD, a 55% to 59% reduction in mortality at two and five years of treatment has been demonstrated, although the quality of evidence is moderate (3,4).[383,384] Currently, international recommendations for LTOT for patients with stable COPD have been standardized to at least 15 hours per day under the following conditions:[3,381,385,386]

1. $PaO_2$ levels ≤ 55 mmHg or $SpO_2$ ≤ 88% with or without hypercapnia; confirmed twice within a three-week period.
2. $PaO_2$ between 56-59 mmHg or $SpO_2$ of 89-90%, if there is evidence of pulmonary hypertension, right heart failure or polycythemia (hematocrit ≥ 55%).

Once long-term oxygen therapy is established, the patient should be re-evaluated after 60 to 90 days with arterial blood gas or pulse oximetry while breathing the same level of oxygen or room air to determine if oxygen is therapeutic and the indication should be continued, respectively.[3]

Overall, LTOT has been shown to improve mortality in patients with COPD and severe hypoxemia ($PaO_2$ ≤ 55 mmHg), but not when hypoxemia is moderate ($PaO_2$ 56-59 mmHg). A recent SLR published by Lacasse et al., in 2022 aimed to evaluate long-term oxygen therapy in patients with COPD and moderate hypoxemia ($PaO_2$ 56-59 mmHg) on overall survival. The authors included six clinical studies with high quality of evidence. The results of the meta-analysis showed that the use of LTOT for three years did not significantly decrease mortality (RR 0.91, 95%CI 0.72-1.16).[387] Another SLR published by Sami et al., in 2023 reported a decrease in readmission for exacerbations with conventional oxygen therapy in patients with COPD (RR 1.54, 95%CI 1.28-1.85) with an average treatment duration of eight months.[388] People currently receiving this treatment are often older and have more comorbidities than patients enrolled in the original long-term oxygen studies. Further studies and the development of national and possibly international

**Table 20: Key points:** long-term oxygen therapy (LTOT).

- The indications for LTOT are: 1) $PaO_2$ ≤ 55 mmHg or $SpO_2$ ≤ 88% with or without hypercapnia, confirmed twice within a three-week period; and 2) $PaO_2$ between 56-59 mmHg or $SpO_2$ of 89-90%, but with evidence of pulmonary hypertension, right heart failure, or polycythemia (hematocrit ≥ 55%).
- The LTOT prescription must include a home system and a portable system for travel, exercise, and physical activity.
- The prescription must be at least 15 hours per day, always covering sleep, travel, exercise, and pulmonary rehabilitation.
- Oxygen therapy should not be routinely prescribed for nocturnal or exercise desaturation alone in the absence of an absolute indication for LTOT.
- Patients with indication for LTOT should continue using oxygen for all air or ground transport at altitudes greater than 2,000 meters to maintain a $PaO_2$ > 50 mmHg or $SpO_2$ > 85%.
- Once indicated, it should be re-evaluated every 60 to 90 days with blood gas or oximetry for optimal adjustments or to determine whether the indication is maintained.
- All patients and their families or caregivers should receive educational interventions focused on safety and management aspects, aimed at improving adherence and proper use of oxygen equipment and systems.

registries should clarify the impact of oxygen therapy on COPD patients currently receiving oxygen therapy.

**Hours of daily oxygen therapy use.** LTOT for at least 15 h/day in people with stable COPD and severe hypoxemia at rest and breathing room air ($PaO_2 \leq 55$ mmHg) improves patient survival.[3,381,389-392] 24-h use compared with 15-h use does not appear to be superior in reducing mortality and the risk of hospitalization.[390,391] Likewise, LTOT does not appear to be beneficial in patients with moderate hypoxemia compared with no oxygen use. The main international guidelines consistently recommend strongly and absolutely generalized LTOT for at least 15 h/day in people with COPD with a $PaO_2 \leq 55$ mmHg at rest.[3,25,357,381,389]

**Specific conditions: dyspnea, physical activity, sleep, and air travel.** People with COPD and severe hypoxemia may experience worsening oxygen desaturation and dyspnea during physical activity, with significant limitations in performing certain activities of daily living, resulting in a significant impairment of their quality of life.[393] Evidence supports that these patients should be on LTOT and should also use oxygen during respiratory rehabilitation, as it significantly improves exercise tolerance and decreases dyspnea, although increased oxygen flow is often required during muscle training to avoid hypoxemia. Dreher *et al.,* showed that patients with severe COPD during physical exercise (walking) used the same oxygen flow as they used at home and found a drop in $PaO_2$ of an average of 10 mmHg, several of them with $PaO_2$ values less than 60 mmHg.[394] A SLR published by Nonoyama *et al.,* in 2007, with the Cochrane Collaboration, determined whether supplemental oxygen, compared with control (compressed air or room air) during muscle training in a pulmonary rehabilitation program, impacted exercise capacity, the magnitude of dyspnea, and quality of life in patients with COPD who did not qualify for home oxygen therapy. The authors included five clinical studies and reported significant improvement in patients who received supplemental oxygen compared with controls. Outcomes showed improvement in exercise time (weighted mean difference [WMD] 2.68 minutes, 95%CI 0.07-5.28 minutes), Borg score at end of exercise (WMD −1.22 units, 95%CI, −2.39 to −0.06), and change in Borg score after the progressive load walk test (WMD −1.46 units, 95%CI, −2.72 to −0.19). There were no significant differences in maximal exercise capacity, the six-minute walk test, or the progressive load walk test distance, nor in oxygenation or quality of life. However, most studies were rated as low quality.[395]

People with mild to moderate hypoxemia ($PaO_2$ 55-59 mmHg) or without hypoxemia but with oxygen desaturation and/or dyspnea during exercise or rehabilitation may report improvement of dyspnea with supplemental oxygen, but there is strong evidence that regular use of oxygen in these patients does not improve survival or time to first hospitalization, nor does it improve quality of life, lung function, or six-minute walk performance.[3,381,389,391,392,396]

Similarly, the use of supplemental oxygen in patients with mild-moderate or no hypoxemia at rest ($PaO_2 > 55$ mmHg), but who only desaturate during sleep, does not appear to benefit from oxygen prescription. Lacasse *et al.,* conducted a CCT in 28 hospitals; they included patients with stable COPD without criteria for LTOT ($PaO_2 > 55$ mmHg) but who had nocturnal oxygen desaturation, defined as an $SpO_2 < 90\%$ for at least 30% of the time recorded with continuous nocturnal oximetry. A total of 243 patients were proportionally randomized to nocturnal supplemental oxygen with an oxygen concentrator or placebo (compressed air from a sham concentrator). At three years of follow-up, 39% of patients on oxygen and 42% of those in the placebo group developed definitive criteria for LTOT or died. The authors concluded that oxygen use in these patients has no effect on long-term survival or disease progression.[397]

Patients with COPD planning air travel should be evaluated by their physician, particularly if they have severe hypoxemia ($PaO_2 < 55$ mmHg or $SpO_2 < 88\%$). Patients already using oxygen therapy should continue using it during the flight to maintain a $PaO_2 > 50$ mmHg throughout the flight, which can be achieved with a flow rate of three liters per minute with nasal prongs or 31% $FiO_2$ with a Venturi face mask.[3,398] Only portable oxygen concentrators are internationally authorized for commercial flights, and airlines usually require an updated prescription from a medical professional and may even request that patients and their physician complete a structured report in advance. Many airlines can also provide therapeutic oxygen during the flight upon request, scheduling, and at an additional cost. Patients with resting oxygen saturation > 94% or > 84% in the six-minute walk may travel without further assessment, although it is important to emphasize that resting oxygenation at sea level does not exclude the development of hypoxemia during the flight.[3,399] Comorbidities (heart failure and anemia) that could impair tissue oxygen delivery should be considered. Walking during prolonged travel in airports can aggravate dyspnea and hypoxemia, so these individuals should be treated as people with reduced mobility.[3,400] Although the referenced studies or international guidelines do not address or specify criteria for oxygen therapy during ground travel at high altitudes, for example, towns or highway points above 2,500 or 3,000 m above sea level, these are common in the central plateau of Mexico; the main land routes from Mexico

City accross towns and mountain ranges above 3,000 m. Under these circumstances, it makes sense to follow the same oxygen recommendations for flights.

**Oxygen delivery devices.** LTOT should be administered for extended periods during the day and night, as well as on an outpatient basis to facilitate exercise and provide symptom relief, as achieved with rapid delivery devices.[381] For this purpose, one or more devices that combine stationary or portable equipment can be used. These include: 1) stationary or portable oxygen concentrators; 2) compressed oxygen cylinders in the form of stationary (56 to 132 cm) or portable (less than 26 inches or 66 cm) tanks; and 3) stationary liquid oxygen containers that include ambulatory oxygen equipment. Whichever device is selected depends on commercial availability, cost, and coverage possibilities by the health system and/or patients. All delivery systems have advantages and disadvantages, so health professionals should be thoroughly familiar with them to optimally prescribe LTOT.

Conventional oxygen therapy remains the most commonly used method of support in patients with COPD; however, oxygen flow is limited, and some reports have associated it with an increased risk of requiring invasive ventilation and mechanical ventilatory support in cases of respiratory acidosis or in some patients receiving conventional oxygen therapy. High-flow nasal cannula (HFNC) is a non-invasive respiratory support device designed to deliver flows between 30 and 60 L/min. It provides oxygen with a thermal device that humidifies the air through a special nasal cannula. This device produces a modest positive end-expiratory pressure, which decreases inspiratory effort, increases lung capacity, and can reduce hypercapnia and improve quality of life in patients with stable hypercapnic COPD.[382] A SLR published by Zhang *et al.,* in 2023 aimed to evaluate the benefit of oxygen delivery through HFNC compared to conventional oxygen therapy in COPD patients with exacerbated hypercapnia. The authors included eight controlled clinical trials, five with acute hypercapnia and three with chronic hypercapnia. In patients with acute hypercapnia, short-term use of HFNC significantly reduced $PaCO_2$ (MD −1.55, 95%CI −2.85 to −0.25) and reduced treatment failure (OR 0.54, 95%CI 0.33-0.88), but there was no significant difference in $PaO_2$ (MD −0.36, 95%CI −2.23-1.54). In chronic hypercapnia, HFNC did not significantly reduce $PaCO_2$ (MD −1.21, 95%CI −3.81-1.39) or $PaO_2$ (MD 2.81, 95%CI −1.39-7.02). Exacerbations showed a reduction, although the authors were unable to perform a meta-analysis with the data due to high heterogeneity.[401] Another SLR published by Xu *et al.,* also compared the benefit of HFNC with conventional oxygen therapy and non-invasive ventilation (NIV) and reported, from a total of 10 clinical studies, comparable results between the three modalities with respect to intubation rate, mortality, and changes in blood gases. However, HFNC had fewer adverse events (OR 0.12, 95%CI 0.06-0.28) and significantly reduced the need for NIV (OR 0.57, 95%CI 0.35-0.91).[402] Another SLR published by Duan *et al.,* showed similar results.[403]

**Patient and family education interventions.** The CPGs for LTOT recommend, as good practice, educational interventions for patients and their families aimed at improving treatment adherence and the proper use of oxygen delivery equipment and systems, focusing primarily on safety and self-management by patients and families.[381] Safety measures include: reducing the risk of falls from the delivery systems; accidents due to falls from gas cylinders; reducing the risk of burns or fires from oxygen use, particularly in patients or family members who are active smokers; and dermal frostbite burns from liquid oxygen devices. All healthcare personnel responsible for caring for these patients should be adequately trained in this intervention. Although there is no consistent evidence on these interventions, they are considered a point of good medical practice.

## Pulmonary rehabilitation

### Clinical Question 17: *What is the efficacy and safety of pulmonary rehabilitation in patients with COPD?*

| Recommendations | | |
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| 1 | Pulmonary rehabilitation (PR) is an effective and safe intervention of great importance and should always accompany pharmacological interventions. It improves symptoms, quality of life, functional capacity, emotional state, sense of control, and exercise tolerance. At all levels of care, rehabilitation should be offered to all people with COPD, particularly those with symptoms and/or risk of exacerbation, and in accordance with the structure and capacity of health services. | Evidence 1+<br>Recommendation A |
| 2 | PR should be comprehensive and tailored to individual needs, abilities, requirements, and conditions. It should also be supervised, lasting at least eight weeks and performed at least twice a week. It should include trunk and limb strength and endurance exercises, flexibility, and walking. | Evidence 1–<br>Recommendation B |

| | | |
|---|---|---|
| 3 | Medical prescription of exercise and physical activity is an alternative to formal PR programs that should be implemented by all medical professionals responsible for the care of patients with COPD (see lifestyle recommendations). | Evidence 4 Recommendation D |
| 4 | During an exacerbation, it should be implemented as early as possible. In these patients, it reduces symptoms, complications, hospitalization, use of healthcare resources, and hospital readmissions. | Evidence 1– Recommendation B |

### *Evidence analysis*

Pulmonary rehabilitation (PR) consists of a structured program that includes multidisciplinary care, individualized plans, physical training, and lifestyle changes aimed at improving the physical and mental status of patients. PR should be considered a key component of comprehensive patient management.[404] The GOLD 2025 guidelines recommend establishing PR programs in all patients with symptoms and at increased risk of exacerbations, taking into account their individual characteristics and comorbidities, including their general physical condition and age.[3] PR programs lasting six to eight weeks have been shown to be the most effective; no benefit has been demonstrated in extending PR to 12 weeks.[405-408] Supervised exercise is recommended at least twice a week and may include resistance exercise, strength and endurance training, trunk, lower and upper extremity exercises, flexibility training, walking, inspiratory muscle strengthening, and electrical neuromuscular stimulation *(Table 21)*.

PR programs can also be incorporated without in-person supervision and with remote follow-up.[3] A complete assessment of the patient's physical condition is essential to structure the program according to their needs and capabilities.[3] The Canadian CPG also recommend incorporating a PR program in patients who remain symptomatic despite receiving adequate pharmacological management.[330] The 2019 NICE CPG also recommend considering PR in patients who have recently been hospitalized due to a disease exacerbation.[64]

A SLR published by McCarthy *et al.,* with the Cochrane Collaboration aimed to evaluate the impact of PR programs on quality of life and physical and functional capacity in patients with COPD.[409] The authors included a total of 65 CCT involving 3,822 participants. The results of the meta-analyses showed that PR programs were associated with improvements in all studied outcomes. There was a significant improvement in SGRQ scores (MD −6.89, 95%CI −9.26 to −4.52) with low quality of evidence. There was improvement in quality of life questionnaires, also considering improvement in individual domains such as dyspnea (MD 0.79, 95%CI 0.56-1.03), emotional function (MD 0.56, 95%CI 0.34-0.78), fatigue (MD 0.68, 95%CI 0.45-0.92). Functional exercise and maximal exercise also showed statistically significant improvement. Maximal capacity showed improvement (MD 6.77 Wmax, 95%CI 1.89-11.65), functional exercise capacity (6MW) improved significantly (MD 43.93, 95%CI 32.64; 55.21). The authors' conclusions are that PR programs improve dyspnea and fatigue, improve emotional function, and enhance individuals' sense of control over their disease, so PR functions as a component of COPD management and improves exercise capacity.[407]

PR has not only been shown to be beneficial in patients with stable COPD, but has also been shown to improve outcomes in patients who have recently experienced an exacerbation. Jenkins *et al.,* demonstrated that PR programs decreased the risk of hospital readmission (OR 0.48, 95%CI 0.30-0.77), improved exercise capacity (6MW) (MD 57 minutes, 95%CI 29-86), quality of life (SGRQ) (MD −8.7, 95%CI −12.5-4.9), and (CRQ) (MD 1, 95%CI 0.4-1.6).[410] These findings were confirmed by a systematic review published by Meneses *et al.,* in 2023.[411]

## Vaccination

### Clinical Question 18: *What is the efficacy and safety of different vaccines in reducing exacerbations in patients with COPD?*

| Recommendations | | |
|---|---|---|
| 1 | At least 70% of COPD exacerbations or complications are of infectious origin, and respiratory viruses are associated in approximately 30% of cases. Therefore, vaccines play a crucial role in medical management. At all three levels of care, every person with COPD should receive a complete vaccination schedule in accordance with local and international recommendations. | Evidence 1+ Recommendation A |
| 2 | **Pneumococcal vaccines:** These vaccines are made up of capsular polysaccharide antigens in both non-conjugated (PPSV23) and conjugated (PCV) forms. There are four conjugate vaccines of 13, 15, 20, and 21 serotypes (PCV13, PCV15, PCV20, and PCV21). In Mexico, only PCV13 is available. Recently, the US FDA approved the PCV21 vaccine, | Evidence 1+ Recommendation A |

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| | which offers greater polysaccharide coverage. Pneumococcal vaccination is recommended for all people aged 60 years and older, as well as for all people with COPD, regardless of age (those over 18 years of age); it has been shown to reduce the incidence of community-acquired pneumonia and exacerbations.<br>All patients with COPD should receive a 0.5 mL dose of pneumococcal conjugate vaccine (PCV13 or higher) intramuscularly in the deltoid region of the arm and do not require booster vaccination. They should also receive a single 0.5 mL dose of PPSV23, also intramuscularly in the deltoid region of the arm. The interval between vaccinations should be 12 months. | |
| 3 | **Influenza vaccine:** Internationally, influenza is the second viral cause of exacerbation and can cause severe illness and death in people with COPD. Influenza vaccination has demonstrated a significant reduction in exacerbations and, to a lesser extent, in hospitalizations in patients with severe obstruction ($FEV_1$ < 50%).Influenza vaccination can contain attenuated or killed viruses: two of type A (H1N1 and H3N2) and one or two B viruses (trivalent or tetravalent, respectively). Mexico's official vaccination schedule recommends an annual tetravalent dose, preferably at the beginning of the winter season, in all people 60 years of age or older and in adults with COPD, regardless of age or other comorbidities. The vaccine is administered intramuscularly in the deltoid region of the arm; it can be administered simultaneously with the pneumococcal vaccine in different arms or in the same arm, 2.5 to 5 cm apart. | Evidence 1+<br>Recommendation A |
| 4 | **SARS-CoV-2 (COVID-19) vaccines:** These vaccines have been shown to be highly effective against severe disease and death; although they are highly recommended as primary vaccination for people with COPD, there is insufficient data to consistently recommend periodic revaccination. Mexico's official vaccination schedule recommends any of the vaccines available in the country as primary vaccination starting at the age five, as well as a booster 12 months later for people 60 years of age or older, and for all people with COPD, among other comorbidities. This vaccine is available in the official 2024-2025 seasonal vaccination program. It is administered intramuscularly in the deltoid region of the arm and can be administered simultaneously with influenza and/or pneumococcal vaccines in the same or different arms. | Evidence 1+<br>Recommendation B |
| 5 | **Respiratory syncytial virus (RSV) vaccine:** RSV is a common cause of hospitalization and death in older adults and is estimated to be responsible for nearly 9% of exacerbations in people with COPD. The CDC (Centers for Disease Control and Prevention) the U.S. and the European Commission recommend the use of the new vaccines in people aged 60 or older, so their inclusion in the vaccination schedule for older adults and people with COPD should be recommended when available in Mexico. | Evidence 1+<br>Recommendation A |
| 6 | **Other vaccines (*pertussis* and herpes zoster):** According to international recommendations (GOLD 2025 and the CDC), people with COPD, vaccination for Tdap *pertussis* (tetanus, *Bordetella pertussis* and diphtheria) should be considered for those who were not vaccinated in adolescence.<br>In addition, two doses of the recombinant vaccine against herpes zoster (HZ) are recommended in adults ≥ 50 years of age; because both infections can cause COPD exacerbation. | Evidence 1+<br>Recommendation B |

### *Evidence analysis*

The prognosis of patients with COPD is linked to the frequency of exacerbations, and respiratory infections are one of the main causes. Vaccines play a crucial role in the management of people with COPD by significantly reducing the risk of serious complications and exacerbations caused by respiratory infections. At least 70% of exacerbations have an infectious origin, and respiratory viruses have been

**Table 21:** Types of physical conditioning for patients with stable COPD.

| Type of conditioning | What is it? | Objective | Equipment to perform it (examples) | Intensity | Number of repetitions | Number of series | Frequency | Duration |
|---|---|---|---|---|---|---|---|---|
| Strength exercise or Strengthening | This exercise requires the neuromuscular system to generate tension to overcome, maintain, or oppose external or intense resistance at a given speed. It generates a lower cardiorespiratory response, requires more oxygen consumption and minute ventilation, and causes less dyspnea | Increase maximum strength by muscle group, with increased intermuscular coordination at the beginning and after hypertrophy. Improve exercise capacity or tolerance | 1. Free weights<br>2. Weights with machines<br>3. Elastic bands<br>4. Electrical stimulation<br>5. Tubes<br>6. Steps | 60-70% of maximum workload, with dyspnea measured by Borg scale between 4-6 | Eight to 12 repetitions per muscle group | One to three sets per muscle group | Once a day, three to five times a week | Increase loads every six to eight weeks |
| Endurance or aerobic exercise | It is the exercise in which the neuromuscular system has the capacity to maintain a prolonged effort, it involves the efficient use of the cardiovascular, respiratory and muscular systems to sustain an activity for an extended period without excessive fatigue | Improve dyspnea and cardiovascular response. Improve exercise capacity or tolerance | 1. Walk outdoors<br>2. Walking on a treadmill<br>3. Stationary bike | 1. Speed of 75-80% of the initial 6MW test speed or incremental shuttle speed, or a modified Borg dyspnea scale of 3-4<br>2. 0-80% of 1 OR | 1. Walk once a day<br>2. Stationary bike 15-30 minutes | 3-5 times per week. Continuous or intervals | Once a day, three to five times a week | Per session 15-30 minutes, 6-8 weeks |
| Inspiratory Muscle Training | It is the exercise in which the neuromuscular system at the level of the diaphragmatic muscle has the ability to generate tension by opposing external resistance | Improve dyspnea by improving Pimax | 1. Threshold™ IMT<br>2. Powerbreath™ | 30-60% of Pimax | 10-20 times (20 minutes) | Two times a day | Three times a week | Until reaching its predicted |

6MW = Six-Minute Walk. IMT = Inspiratory Muscle Training. Pimax = maximum inspiratory mouth pressure.[412]

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identified in approximately 30% of cases. *Streptococcus pneumoniae* is one of the leading causes of morbidity and mortality in lower respiratory tract infections. Therefore, all patients with COPD should be vaccinated against influenza, pneumococcus, COVID-19, RSV, Tdap, and shingles, if they have not already received these vaccines.

**Pneumococcal vaccine.** Pneumococcal vaccines are primarily capsular polysaccharide antigens, available in both non-conjugated (PPSV23) and conjugated (PCV) forms. There are two types of pneumococcal vaccines: the 23-valent polysaccharide vaccine (PPSV23) and the 13-, 15-, and 20-valent conjugate vaccines (PCV13, PCV15, and PCV23, respectively). International guidelines recommend initial administration of PCV13 followed by PCV23 in patients with COPD aged ≥ 65 years.[4,25,28] Those who have only received PCV23 can receive PCV20 or PCV15 one year after their last dose.

The effectiveness of the PPV23 vaccine in preventing community-acquired pneumonia in immunocompromised patients or those with underlying risk factors such as COPD remains debated. According to Tin Tin Htar M *et al.*, in their systematic review and meta-analysis, found vaccine effectiveness ranged from −338% to 72% in patients with risk factors.[413] A systematic review determined the efficacy of pneumococcal vaccination in preventing pneumonia in patients with COPD. Polyvalent pneumococcal vaccination significantly protects against pneumonia (OR 0.62, 95%CI 0.43-0.89; grade: moderate). Although it does not decrease the risk of confirmed pneumococcal pneumonia, it does reduce COPD exacerbations. The evidence is moderate regarding the benefits of vaccination in people with COPD (OR 0.60, 95%CI 0.39-0.93; grade: moderate), but insufficient to compare different types of pneumococcal vaccines.[414]

A controlled clinical trial demonstrated that patients with COPD who received influenza and PCV23 vaccines experienced fewer exacerbations compared with those who received only one of the vaccines, although this effect lasted only the first year.[415] In another controlled clinical trial, 1,152 adults with no prior history of pneumococcal, influenza, or SARS-CoV-2 vaccination were evaluated for the safety and immunogenicity of coadministration of inactivated SARS-CoV-2 vaccine (Sinopharm BBIBP-CorV), quadrivalent inactivated influenza vaccine (IIV4), and PCV23 vaccine. In the group receiving SARS-CoV-2 + IIV4/PPSV23, the seroconversion rate of neutralizing antibodies against SARS-CoV-2 and influenza was comparable to that of the groups that did not receive this combination. Furthermore, the immunogenicity of the SARS-CoV-2 + IIV4/PPSV23 group, as measured by *S. pneumoniae* -specific IgG levels, was non-inferior to that of the IIV4/PPSV23 alone group, showing good tolerance and comparable immune responses.[416] PCV15, PCV20, or PPSV23 can be co-administered with influenza vaccine in adult patients, as concomitant administration (PCV15 or PPSV23 and QIV [Fluarix], PCV20 and QIV [Fluad]) with adjuvant has been shown to be immunogenic and safe, and to reduce the risk of acute exacerbation of COPD, pneumonia, and hospitalizations.[19,77]

The Mexican Ministry of Health's vaccination guidelines recommend pneumococcal vaccination for all individuals 60 years of age and older, as well as for all COPD patients regardless of age (those over 18 years of age). All individuals for whom vaccination is indicated should receive a 0.5 mL dose of pneumococcal conjugate vaccine (PCV13 or higher) intramuscularly in the deltoid region of the arm and do not require booster vaccination. In addition, they should receive a single 0.5 mL dose of PPSV23, also intramuscularly in the deltoid region of the arm. The interval between vaccinations should be 12 months.[417]

**Influenza vaccination.** Annual influenza vaccination is recommended internationally, as influenza is the second most common virus, after rhinovirus, associated with severe acute exacerbations of COPD.[418] Evidence supports a positive benefit-risk ratio for seasonal influenza vaccination in these patients, as more than 10% of influenza cases in patients with COPD could be prevented by expanding vaccination coverage.[4,25,419] According to the systematic review and meta-analysis by Wanying Beam *et al.*, influenza vaccination significantly reduces COPD exacerbations ($p = 0.0001$) and marginally reduces associated hospitalizations ($p = 0.09$). Furthermore, subgroup analysis found that the reduction in exacerbations and hospitalizations was significant in patients with an $FEV_1 < 50\%$ of predicted ($p = 0.01$ and $p < 0.0001$, respectively), but not in those with $FEV_1 \geq 50\%$ of predicted. However, no significant effect of influenza vaccination on all-cause mortality was observed.[420]

In a systematic review comparing live or inactivated virus vaccines with placebo, either alone or with another vaccine, in people with COPD, the inactivated virus vaccine reduced the total number of exacerbations compared with placebo (MD −0.37, 95%CI −0.64 to −0.11, $p = 0.006$; grade: low quality). This was due to a reduction in «late» exacerbations occurring after three to four weeks (MD −0.39, 95%CI −0.61 to −0.18, $p = 0.0004$; grade: low quality). In both people with COPD and older people (only a minority of whom had COPD), there were significantly more local adverse reactions in those who received the vaccine, but the effects were generally mild and transient.[421,422]

Mexico's official vaccination schedule recommends an annual quadrivalent dose, preferably at the beginning of the winter season, for all people 60 years of age and older and for adults with COPD, regardless of age, among other comorbidities. The vaccine is administered intramuscularly in the deltoid region of the arm; it can be administered

simultaneously with the pneumococcal vaccine in different arms or in the same arm, at a distance of 2.5 to 5 cm.[417]

**SARS-CoV-2 vaccine.** Although SARS-CoV-2 vaccines are highly recommended for patients with COPD, and the need to protect this vulnerable group is evident, more consistent data on vaccine effectiveness in COPD should be available in the future.[28] SARS-CoV-2 vaccines have been shown to be highly effective against infections requiring hospitalization, critical care, and death, so vaccination of the general population is recommended.

Mexico's official vaccination schedule recommends any of the vaccines available in the country as a primary vaccination starting at age five, and as a booster 12 months later for people 60 years of age or older, as well as for all people with COPD, among other comorbidities. It is administered intramuscularly in the deltoid region of the arm and can be administered simultaneously with influenza and/or pneumococcal vaccines in the same or different arms.

**Respiratory syncytial virus vaccine.** A meta-analysis of 31 studies found that the prevalence of respiratory syncytial virus (RSV) in patients with COPD was 3.7% (95%CI 1.3-7.3%).[423] Adults at increased risk for severe RSV disease include adults with chronic heart or lung disease, immunocompromised, and those living in nursing homes or long-term care facilities. The Advisory Committee on Immunization Practices (ACIP) Committee on Immunization The CDC and European Commission's Guidelines for the Prevention of Infections (Practice) recommend the use of the new vaccine for people 60 years of age and older. The current GOLD guidelines recommend its use in accordance with CDC guidelines.[28,424,425]

***Bordetella* vaccine *pertussis*.** The GOLD 2025 guidelines refer to CDC guidelines, which recommend Tdap vaccination (tetanus, *Bordetella pertussis* and diphtheria) for patients with COPD who were not vaccinated in adolescence (check timing of vaccination; children over 10 years of age require vaccination).[28] This recommendation is based on the high prevalence of pertussis in patients with COPD, which leads to exacerbations within 30 days of diagnosis.[426] A meta-analysis evaluated the immunogenicity of the Tdap vaccine in patients with COPD, observing that, one month after vaccination, 89.0% and 97.2% of patients achieved seroprotective concentrations of diphtheria and tetanus antibodies, respectively; 78.3%-96.1% showed booster responses across all three pertussis antigens. The vaccine was immunogenic and well tolerated, with a low incidence of mild adverse events.[427]

**Herpes zoster vaccine.** The CDC recommends two doses of the recombinant herpes zoster (HZ) vaccine for adults ≥ 50 years of age. It also recommends two doses of HZ for adults ≥ 19 years of age who are immunodeficient or immunosuppressed.[428] Two meta-analyses report an increased risk of developing HZ in patients with COPD (RR 1.4, 95%CI 1.28-1.55, p < 0.001) (RR 1.31, 95%CI 1.22-1.41).[429,430] The elevated risk of developing HZ is likely secondary to the immune dysregulation characteristic of this respiratory disease and the immunosuppressive effect of inhaled or systemic steroids. Although there are no specific data on the effectiveness of the vaccine in patients with COPD, vaccination is strongly recommended in this group due to their increased vulnerability to shingles, even in those under 50 years of age.[431]

## Interventionism and surgery

### Clinical Question 19: *What is the efficacy and safety of different treatment alternatives with bronchoscopic intervention and surgery in patients with COPD?*

| Recommendation | | |
|---|---|---|
| 1 | In tertiary care, provided that the necessary technological and physical resources and qualified professionals are available, bronchoscopic interventional procedures and surgery (volume reduction and lung transplantation) may be considered for carefully selected patients with COPD. Patients with severe disease should be considered if, despite exhausting medical treatment options, severe symptoms persist, and structural alterations susceptible to corrected (localized or heterogeneous emphysema), an adequate functional assessment (respiratory function tests and functional computed tomography) and surgical risk have been performed, comorbidities (respiratory and non-respiratory) are evaluated and optimally controlled, and patients complete a pulmonary rehabilitation program; in addition, the expected risks and benefits (medical team and patient) must be reviewed in detail. Patients with active malignancy should be excluded. | Evidence 1+<br>Recommendation B |

#### *Evidence analysis*

Pulmonary interventional and/or surgical options for people with COPD offer benefits in terms of quality of life,

symptoms, lung function, and survival; they are relatively safe if the candidate patient is appropriately selected. These treatment alternatives can be considered when conventional medical treatment for the disease has been exhausted. However, several conditions must be met for their implementation: patients persist with severe symptoms (dyspnea, cough, and expectoration) despite optimal medical treatment; there are specific structural abnormalities in imaging studies (computed tomography) that are amenable to intervention; there is an adequate assessment of respiratory function (through complete pulmonary function tests and also functional computed tomography) and surgical risk; respiratory and non-respiratory comorbidities are under optimal control; and an adequate risk- benefit analysis of the proposed procedure has been conducted between the medical team and the patient. Patients with active malignancy or those who do not complete a formal pulmonary rehabilitation program should be considered for exclusion. The main intervention options include lung volume reduction by bronchoscopic intervention, volume reduction surgery, and lung transplantation.[432]

**Bronchoscopic lung volume reduction.** Bronchoscopic lung volume reduction treatments include endobronchial valves (EBV), endobronchial coils, and bronchoscopic thermal vapor ablation (BTVA). Although these alternatives are technically significantly different, they offer less invasive volume reduction treatment options with a lower impact on morbidity and mortality compared to surgery in patients with advanced emphysema.

The results of a network meta-analysis showed similar efficacy between Zephyr and Spiration EBV in patients with heterogeneous emphysema without collateral ventilation, with significant improvements in $FEV_1$ of 0.11 L (95%CI 0.05-0.16) and 0.14 L (95%CI 0.08-0.19), as well as in SGRQ scores of 29.32 (95%CI 24.45-214.18) and 28.14 (95%CI 24.35-211.94), respectively. However, Zephyr valves demonstrated relative superiority in patients with mixed emphysema. The safety of these devices was not evaluated in this meta-analysis.[432]

Patel M *et al.*, in a SLR and meta-analysis on volume reduction by EBV, found that patients treated with this method, in terms of clinical effects, achieved a minimal clinically important difference (MCID) in 6MWT distance (WMD 57.05, 95%CI 12.08 to 102.01), dyspnea by mMRC (WMD −0.450, $p < 0.001$) and SGRQ score (WMD −7.101, $p = 0.003$) at six months. Patients treated with *coils* achieved a MCID in SGRQ at 12 months (WMD −9.228, 95%CI −10.692 to −7765).[433]

Roodenburg *et al.,* they observed an improvement in $FEV_1$ of 0.09 L (95%CI 0.06-0.12) at three months and an improvement in $FEV_1$ of 0.07 L (95%CI 0.03-0.10) at six months of follow-up, a significant reduction in residual volume at three months of −0.45 L (95%CI −0.62 to −0.28), six months of −0.33 L (95%CI −0.52 to −0.14), and 12 months of follow-up of −0.36 L (95%CI −0.64 to −0.08) and quality of life up to 12 months after treatment total SGRQ score at three months of −12.3 points (95%CI −15.8 to −8.8), six months of −10.1 points (95%CI −12.8 to −7.3) and 12 months of follow-up (−9.8 points [95%CI −15.0 to −4.7]), and a significant improvement in exercise capacity (six-minute walk) up to three months after treatment of 38 m (95%CI 18–58).[434]

Regarding safety, both hemoptysis and pneumothorax are the most common adverse events associated with EBV, although these events did not result in a significant increase in mortality.[433,435,436]

Regarding endobronchial coils, various systematic reviews and meta-analyses have shown that bronchoscopic treatment for lung volume reduction with *coil* placement in patients with advanced emphysema and evident hyperinflation significantly improves lung function and quality of life according to the SGRQ questionnaire.[437,438] Among bronchoscopic procedures, high efficacy was observed in the endobronchial valve and endobronchial coil (EBC) for changes in $FEV_1$ (EBV 111.8 mL, 95%CI 92.2-136.2; EBC 74.1 mL, 95%CI 47.6-101.7).[436]

BTVA consists of endobronchial ablation of the segments most affected by emphysema with the aim of producing fibrosis and atelectasis, which can improve lung function and the patient's health status. There are significant improvements in $FEV_1$, RV, TLC, 6MW and SGRQ at three months after treatment with BTVA. The most common adverse events are COPD exacerbations and BTVA-induced pneumonia. In this study, the most common complications at six months were COPD exacerbations (RR 12.49, 95%CI 3.06-50.99, $p < 0.001$) and pneumonia (RR 9.49, 95%CI 2.27-39.69, $p < 0.001$).[439]

**Surgery.** Surgery for COPD includes bullectomy, volume reduction surgery, and lung transplantation. Bullectomy is an effective procedure for resecting giant bullae that occupy more than one-third of the hemithorax and compress adjacent tissues. It improves symptoms, cardiopulmonary function, and exercise tolerance. Volume reduction surgery aims to resect the areas with the greatest pulmonary emphysema, impacting pulmonary hyperinflation and respiratory compliance. It improves symptoms, respiratory function, and muscular, thoracic, and cardiac mechanics. Finally, lung transplantation is indicated in patients with severe disease who have already received maximum medical treatment and are not candidates for volume reduction.[3]

Van Dijk M *et al.,* performed a comprehensive literature search on the impact of lung volume reduction surgery such as endoscopic EBV procedures and changes in DLCO. DLCO improved after these lung volume reduction surgery

treatments, with a mean absolute change from baseline in predicted DLCO of +5.7% (range −4.6% to +29%), while there were no significant changes in blood gas parameters.[440] However, other studies have reported increased medium-term mortality with lung volume reduction surgery (RR 3.26, 95%CI 1.98-6.21) and with EBV placement (RR 2.06, 95%CI 1.07-4.36). Lung volume reduction surgery improved $FEV_1$ by 187.2 mL (95%CI 166.4-209.6), 6MWT by 42.2 meters (95%CI 33.2-50.5 meters), and SGRQ by −13.29 points (95%CI −27.25-0.75 points).[440]

The NETT (National Emphysema Treatment Trial) compared volume reduction surgery versus standard medical therapy on exercise performance, quality of life, and lung function in patients with upper-lobe predominantly emphysema in the setting of advanced disease. Overall mortality (29.2 months) was not different between the two groups (RR 1.01, $p = 0.90$). Exercise capacity improved by more than 10 W in 28%, 22%, and 15% of patients undergoing volume reduction surgery at three, six, and 12 months, respectively, which was significantly greater than that in the medical group. Additionally, patients in the volume reduction surgery group increased 6MW distance, % predicted $FEV_1$, quality of life, and dyspnea.[441]

**Lung volume reduction versus lung transplantation.** Globally, the most common primary indication for lung transplantation is COPD.[441,442] Adhman *et al.,* compared lung volume reduction and lung transplantation in terms of survival and improvement in pulmonary physiological parameters. Following the interventions, both groups experienced an improvement in $FEV_1$; however, post-lung transplant $FEV_1$ was significantly higher than post-volume reduction $FEV_1$ at 54.9% (95%CI 41.4-68.4%) versus 32.5% (95%CI 30.1-34.8%), $p < 0.01$. 6MW also improved after both post-transplant procedures: 212.9 m (95%CI 119.0-306.9) to 454.4 m (95%CI 334.7-574.2), $p < 0.01$, and post-volume reduction: 286 m (95%CI 270.2-301.9) to 409.1 m (95%CI 392.1-426.0), $p < 0.01$, with no significant difference between groups.[443]

The safety and efficacy of unilateral lung transplantation compared with bilateral lung transplantation in end-stage COPD were evaluated. Overall survival rates were more favorable in the bilateral lung transplantation group in two meta-analyses.[444,445] Additionally, the survival rate in patients with alpha-1 antitrypsin deficiency showed a trend in favor of bilateral lung transplantation at one, five, and 10 years. The most frequently reported adverse event was postoperative infections, primarily in the unilateral lung transplantation group.[444] According to the International Society for Heart and Lung Transplantation (ISHLT), the survival rate after unilateral lung transplantation has improved in recent years.[446]

# COPD EXACERBATION *(Table 22)*

**Table 22: Key points:** COPD exacerbation management.

- COPD exacerbation is often referred to interchangeably as acute COPD syndrome or exacerbation
- It should be suspected when dyspnea and/or cough and/or sputum production (appearance or change to purulent characteristics) and/or a drop in oxygenation (> 3% $SpO_2$) are present or worsened in the last two weeks
- It is recommended to grade the severity of the exacerbation according to the Rome criteria (dyspnea, respiratory and heart rates, drop in $SpO_2$, and, when available, CRP level)
- Patients with mild exacerbation can receive outpatient management, provided there is no respiratory compromise, their general condition is good, their comorbidities are stable and controlled, and they have adequate family support
- The decision to hospitalize is based on criteria for respiratory failure, particularly ventilatory failure (dyspnea, tachypnea, $PaO_2$ < 50 mmHg and/or pH < 7.30), mental status and alertness (drowsiness, confusion, and lethargy), and concomitant conditions or uncontrolled comorbidities
- In moderate and severe exacerbations, respiratory and non-respiratory differential diagnoses should be considered, such as heart failure, acute myocardial infarction, pulmonary thromboembolism, pneumonia, pneumothorax, and pleural effusion
- Pharmacological interventions for COPD exacerbations are effective, safe, and crucial for control. They include the optimal use of short-acting bronchodilators, systemic corticosteroids, and antibiotics
- In moderate exacerbations, oxygen therapy should be managed to maintain $SpO_2$ between 88 and 92%
- In patients with acute hypercapnia and acidosis, direct or sequential management (depending on availability) should be considered, including high-flow oxygen therapy and NIV
- The current indication for IMV is NIV failure. The decision should be based on the reversibility of the precipitating event and the prognosis, the availability of resources and critical care, and the patient's wishes

IMV = invasive mechanical ventilation. NIV = non-invasive ventilation.

## Diagnosis of COPD exacerbation

### Clinical Question 20: *What are the diagnostic criteria that define COPD exacerbation?*

| Recommendations | | |
|---|---|---|
| 1 | Persons with COPD or high suspicion of COPD, at all levels of care, should be considered as having an exacerbation when they present or show worsening dyspnea and/or cough and/or expectoration (appearance or change to purulent features) and/or drop in oxygenation (> 3% $SpO_2$) in the last two weeks. | Evidence 1+ Recommendation A |
| 2 | At all levels of care, it is recommended to use the Rome Proposal criteria *(Figure 10)* to grade the severity of the exacerbation (mild, moderate or severe) based on the degree of dyspnea, respiratory rate, heart rate, change in oxygenation ($SpO_2$) and when available the values of C-reactive protein (CRP) and arterial blood gases in moderate and severe exacerbations (second and third levels of care). | Evidence 2- Recommendation B |
| 3 | In second and third level of care, in people with COPD or with probability of having the disease, whenever a moderate or severe exacerbation is suspected, differential diagnoses should be considered for proper evaluation; they include respiratory and non-respiratory conditions such as heart failure, acute myocardial infarction, pulmonary thromboembolism, pneumonia, pneumothorax and pleural effusion. | Evidence 3 Recommendation C |

### *Evidence analysis*

People with an established diagnosis of COPD or with a high probability of suffering from the disease, may frequently require outpatient or emergency room evaluation due to the appearance of respiratory symptoms or worsening of previous symptoms. This condition has been called acute syndrome, exacerbation or exacerbation of COPD. The GOLD guidelines refer to it as exacerbation and GMEPOC uses or worsening and exacerbation of COPD interchangeably; the term exacerbation is the most commonly used term in the medical vocabulary in our setting, while the term worsening is usually more easily understood by patients and their families.

The GOLD 2025[3] guideline defines COPD exacerbation as: «*An event characterized by an increase in dyspnea and/or cough and expectoration for a period of less than 14 days,*

*may be accompanied by tachypnea and/or tachycardia, and is often associated with local or systemic inflammation caused by infection, contamination or some factor harmful to the airways*». The ERS/ATS CPG define exacerbation as «*those episodes of increased respiratory symptoms, particularly dyspnea, cough and sputum production; in addition to a change in the characteristics of the expectoration (more purulent)*».[447]

The CPG GesEPOC 2021 propose a definition considering exacerbation as a Acute COPD Syndrome (ACS), as: *Episode of clinical instability in a patient with COPD translated into aggravation of the expiratory limitation to airflow or of the underlying inflammatory process and is characterized by an acute worsening of respiratory symptoms with respect to the individual's usual situation.* This ACS is a consequence of different pathophysiological mechanisms, with a similar clinical expression. GesEPOC classifies patients with ACS as: low risk, high risk and any risk stratification. These criteria are based on severity of dyspnea, level of consciousness, respiratory rate and gas exchange.[23]

Exacerbation of COPD is characterized by inflammation manifested by mucus production, as well as air trapping and dyspnea. Other symptoms may include purulent sputum, increased cough and wheezing. GOLD 2025 recommends comprehensive evaluation of the patient to rule out other respiratory and non-respiratory causes of dyspnea, such as pulmonary thromboembolism, acute myocardial infarction, heart failure, pleural effusion, pneumothorax and pneumonia. Assessment of the severity of the exacerbation can be done with the use of visual analog scales for dyspnea and cough assessment. The main signs are tachycardia and tachypnea, checking sputum and its purulent appearance. Also, alterations in some parameters can be documented to help classify the severity of the exacerbation; clinical laboratory findings (leukocytosis and increased CRP), decreased oxygenation (pulse oximetry) and/or alterations in arterial blood gases. Finally, it is important to look for the probable cause of the exacerbation based on viral tests, expectoration culture, among others.[3]

Since GOLD 2023, the «Rome Proposal» for classification of COPD exacerbation severity has been adopted.[24] In 2021, Celli et al., through a formal expert consensus process, established the criteria for this proposal with the aim of assisting in the clinical setting to establish the severity of COPD exacerbation. According to these criteria, exacerbation can be classified as mild, moderate or severe, each with prognostic values for mortality. The Rome criteria integrate six objectively measurable variables that serve as biomarkers of severity: degree of dyspnea, oxygen saturation, respiratory rate, heart rate, C-reactive protein (CRP) and, in some cases, arterial blood gases. It should be noted that spirometry should not be routinely performed in a patient with exacerbation, since their general condition does not allow them to generate the necessary and/or acceptable maneuvers. Total eosinophils may have some diagnostic value, especially for the decision to use systemic corticosteroids; however, they are not considered part of the diagnostic criteria.[448]

The Rome Proposal has been well received by clinical researchers, as evidenced by a study of 138 health professionals from 25 countries. Most participants agreed with the proposal, considered that it addresses shortcomings of previous definitions and showed interest in using it.[449] Reumkens et al., in a cohort study of 364 hospitalized patients, demonstrated the usefulness of the Rome classification in separating patients with mild (14%), moderate (56%) or severe (30%) exacerbation by reporting differences in mortality, 3.8, 6.9 and 13.9%, respectively.[450] Initially, it has been described that the Rome Proposal criteria are not affected for the purpose of classifying the severity of exacerbation in the presence of heart failure as a comorbidity.[451] The incorporation of the Rome Proposal will favor stratification that benefits optimal treatment.

## Outpatient management and hospitalization for exacerbations

### Clinical Question 21: *What are the criteria for outpatient and hospital management of patients with COPD exacerbation?*

| Recommendations | | |
|---|---|---|
| 1 | Patients with COPD exacerbation who can receive outpatient management at the first level of care will be those with a mild exacerbation, i.e., without respiratory compromise, in good general condition, with stable and controlled comorbidities, and with adequate family environment and support. | Evidence 2- Recommendation C |
| 2 | Any person with COPD with moderate or severe exacerbation criteria based on the Rome Proposal should be evaluated immediately at the second or third level of care to determine the need for hospitalization. | Evidence 2- Recommendation C |
| 3 | Medical professionals at the second and third level of care should establish the relevance of hospitalization based on clinical criteria of respiratory failure (dyspnea, cyanosis, peripheral edema) and mental status and alertness (drowsiness, confusion and lethargy), respiratory failure ($PaO_2$ < 50 mmHg and/or pH < 7. 30), | Evidence 1+ Recommendation B |

| | | |
|---|---|---|
| | as well as concomitant conditions or respiratory or non-respiratory comorbidities subject to evaluation, differential diagnosis and hospital management, such as: heart failure, acute myocardial infarction, pulmonary thromboembolism, pneumonia, pneumothorax, pleural effusion and others. | |
| 4 | Any patient with major compromise of mental status and consciousness (lethargy or coma), hemodynamic instability or requirement of vasopressors, severe respiratory failure ($PaO_2$ < 40 mmHg and/or pH < 7.25) or indication for invasive mechanical ventilation, should be considered for admission and management in the intensive care unit (ICU). | Evidence 2++<br>Recommendation B |

*Evidence analysis*

Individuals with COPD exacerbations should be properly evaluated and may often require admission and even, in severe conditions, when there is the possibility of treatment in intensive care units (ICU). The root causes may be exacerbation of COPD, which often has not been previously diagnosed, or other respiratory or non-respiratory causes that represent differential diagnoses (*Figure 10*, diagnosis of COPD exacerbation). International guidelines recommend establishing the severity of the condition, the factors that triggered it and the risk factors together with the concomitants with which the patient is presenting.[3,64,450] Within the clinical evaluation, it is essential to identify the level of respiratory failure, the patient's general condition, alertness and other clinical data that inform on the severity of the condition. The evaluation is complemented by chest imaging studies and general laboratory studies including inflammatory and sepsis markers, as well as other studies indicated in the differential diagnosis and concomitant conditions.

For outpatient management from the first level of care, patients with COPD exacerbation with mild exacerbation and some cases of moderate exacerbation can be considered according to the classification of the Rome criteria[3] and the NICE CPG 2019.[64] *Table 23* lists some considerations that should be taken into account for the management of these patients on an outpatient basis. In general, they summarize little change in symptoms, absence of respiratory and cardiovascular compromise, no respiratory failure or no significant change in supplemental oxygen requirement, adequate alertness and mobility; if studies are available, no new chest imaging findings and CRP < 10 m/dL. In addition, they must have a favorable family and social environment for care and support.

The GesEPOC 2021 CPG published before the Rome Proposal, considered a severe aggravation in those patients with change of dyspnea to a grade of 3 or 4 on the mMRC scale, presence of drowsiness, stupor or coma and alterations in gas exchange ($PaO_2$ < 60 or $SpO_2$ < 90%; $PaCO_2$ > 60 mmHg and pH < 7.30).[357] Likewise, the GOLD 2025 guideline proposes various criteria for considering admission, including critical care *(Table 24)*.[3] It is suggested to assess the severity of exacerbation based on the Rome Proposal, although they should not be considered as a general rule. Reumkens et al. found in a cohort of hospitalized patients that up to 14% had mild exacerbation based on these criteria.[450] It is reasonable to consider that some of the patients with moderate exacerbation and all of those with severe exacerbation should be considered for admission, particularly if the exacerbation is life-threatening. However, GOLD 2025 emphasizes the lack of global consensus on defining criteria for hospital admission beyond the severe setting. The patient should be managed in a setting that has the resources for adequate monitoring and care. Intensive care should be considered in patients with severe respiratory failure requiring invasive ventilatory and/or hemodynamic support.[3] It is possible that the incorporation of the Rome Proposal into the GOLD guidelines from 2023 will favor the generalization of the criteria and definitions of exacerbation, including the severity of exacerbation and indications for admission.[24]

## Pharmacological treatment of exacerbation of COPD

### Question 22: *What is the efficacy and safety of the medications used for COPD exacerbation?*

| Recommendations | | |
|---|---|---|
| 1 | All pharmacological interventions in the outpatient or inpatient management of COPD exacerbation are effective and safe, therefore, they should be initiated at all levels of care according to the severity of the exacerbation. | Evidence 1+<br>Recommendation A |
| 2 | **Bronchodilators:**<br>• Short-acting bronchodilators are a fundamental part of the management of COPD exacerbation at all levels of care, since they improve symptoms and pulmonary function. Inhaled administration (with or without spacer chamber) of salbutamol (400 to 600 µg every 4 to 6 h) and/or ipratropium bromide | Evidence 1++<br>Recommendation A |

| | | |
|---|---|---|
| | (80 to 120 μg every 4-6 h) is recommended preferably; the nebulized dose of salbutamol is 2.5 to 5 mg salbutamol and/or 0. 5 to 1 mg of ipratropium bromide every 4 to 6 h, with no significant difference between the routes of administration, inhaled (pressurized measured dose) versus nebulized, but whenever possible the inhaled route should be preferred.<br>• There are no clinical studies to recommend continuity or discontinuation of long-acting bronchodilators during exacerbation of COPD, so the decision should be individualized at the discretion of the medical professional. In case of suspension during aggravation in the second and third level of care, they should be restarted as soon as possible.<br>• Routine use of bronchodilators such as methylxanthines (theophylline or aminophylline) is not recommended due to reduced therapeutic effectiveness and significant side effects. | |
| 3 | Corticosteroids:<br>• In anyone with moderate or severe COPD exacerbation at all levels of care, oral systemic steroid such as oral prednisone 30 to 40 mg (preferred) or deflazacort (45 to 60 mg) or its intravenous equivalent (methylprednisolone 40 mg) is recommended usually for no more than five days (no tapering dose). Prolonged steroid use should be considered to increase the risk of pneumonia and mortality.<br>• An alternative in selected patients may be nebulized budesonide (1,500 to 2,000 μg every 6-8 h), although its use may be limited by a much higher cost compared to oral steroid. The use of intramuscular depot steroids (dexamethasone and betamethasone) is not recommended. | Evidence 1++<br>Recommendation A |
| 4 | **Antibiotics:** the use of antibiotics is recommended in people with COPD exacerbation who present increased sputum volume and/or purulence. It is suggested to consider as empirical choice amoxicillin with clavulanic acid, macrolides, cephalosporins (second and third generation) or fluoroquinolones in some selected patients. Whenever possible, expectoration cultures for isolation and specific treatment of the causal germs. | Evidence 1+<br>Recommendation A |
| 5 | Biomarkers for antibiotics: in patients with COPD exacerbation in second and third level of care, the use (when available) of CRP (> 15 mg/mL) and/or procalcitonin (> 0.76 ng/mL) is recommended as useful biomarkers for antibiotic indication. | Evidence 2+<br>Recommendation B |

## *Evidence analysis*

The majority (80%) of patients with COPD aggravation syndrome are successfully treated on an outpatient basis. When patients with exacerbation require admission, management with bronchodilators, corticosteroids and antibiotics is similar and fundamental as in outpatients, as well as the treatment and control of the different comorbidities, which should be considered according to the characteristics of each patient.[4,25]

**Bronchodilators.** The use of short-acting bronchodilators are cornerstones in the management of COPD exacerbation syndrome according to CPG.[3,4,23,25] Short-acting β2-agonists improve symptoms of exacerbation and improve lung function ($FEV_1$) by activating β2-adrenergic receptors, which relaxes airway smooth muscle, with increased cAMP and preventing bronchoconstriction. However, there is no rigorous evidence on the use of short-acting bronchodilators in patients hospitalized for acute exacerbation of COPD. After analyzing 10 clinical trials in a systematic review, no significant differences in outcomes, such as dose, method of administration, or type of short-acting β2-agonist used (SABA), were found. However, an increase in cardiac side effects was observed with higher doses of SABA.[453]

Alternatives for administration of SABA with or without antimuscarinics include pressurized metered-dose devices (with or without an inhalation chamber) or by nebulization devices; a Cochrane SLR in 2016 found no evidence of any difference between these methods of administration in COPD exacerbation.[454] According to GesEPOC 2021, the recommended doses are: salbutamol (400 to 600 μg/4 to 6 h and for ipratropium from 80 to 120 μg/4-6 h. The

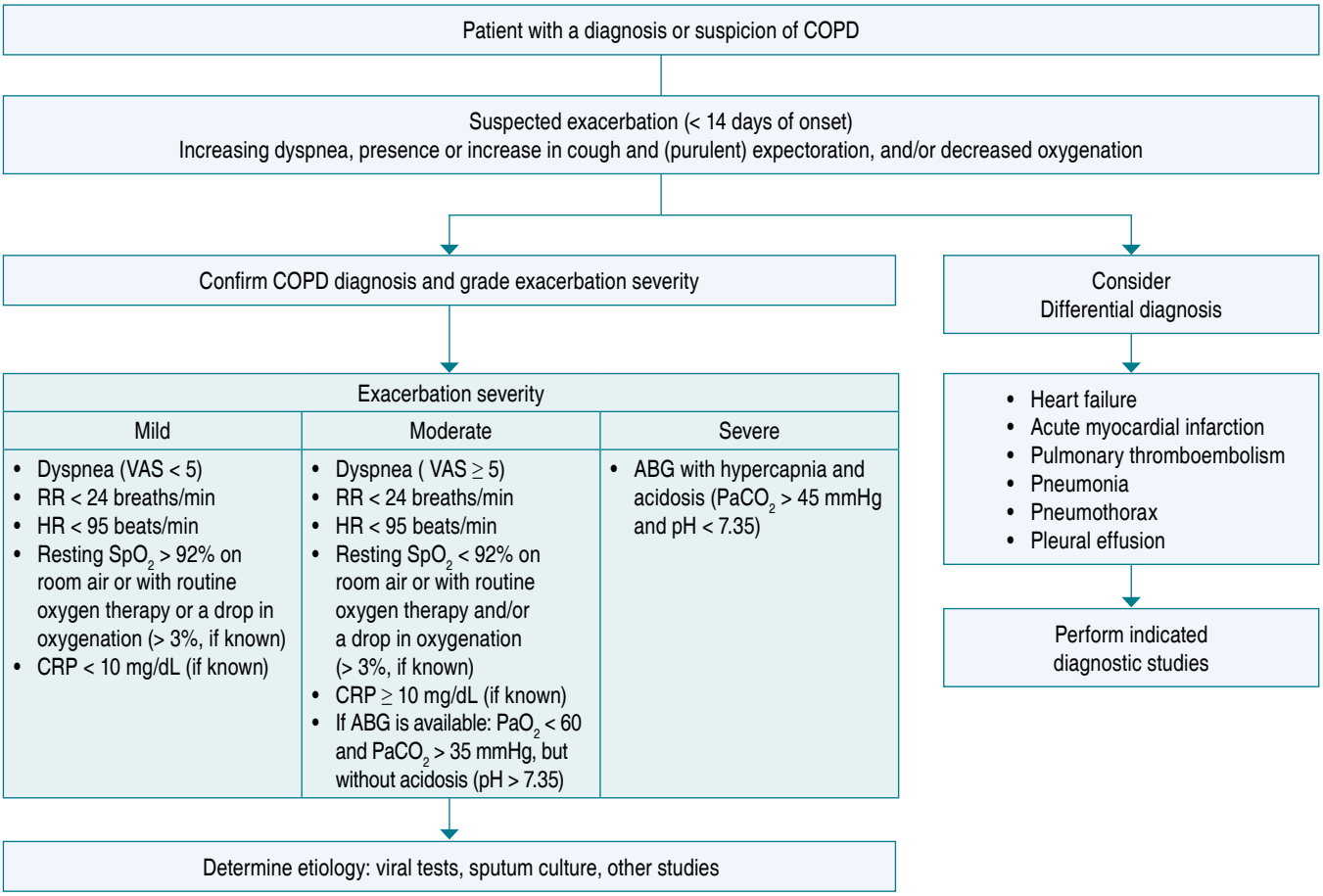


**Figure 10:** Rome proposal for classifying the severity of COPD exacerbations. In Mexico, it is recommended that $SpO_2$ and $PaCO_2$ values be adjusted according to altitude. For example, in Mexico City, at 2,240 m above sea level, an $SpO_2$ value of 88% is recommended as the lower limit of normal[107] and a $PaCO_2$ greater than 40 mmHg, above the upper limit of normal (37 mmHg).[452]
VAS = visual analog scale. HR = heart rate. RR = respiratory rate. ABG = arterial blood gases. CRP = C-reactive protein.
Modified from: Celli et al.[448]

nebulized dose is 2.5 to 5 mg of salbutamol and/or 0.5 to 1 mg of ipratropium every 4-6 h.[23] The GOLD 2025 guidelines state that, although there are no systematic reviews or CCT, the use of bronchodilators is still considered the initial treatment for the acute management of exacerbations.[3] There are no clinical studies that have evaluated the use of long-acting bronchodilators (β2 agonists or antimuscarinic agents) in patients with exacerbations; however, they suggest maintaining their use in outpatient management or resuming them as soon as the patient has been discharged from the hospital. The use of bronchodilators such as methylxanthines, theophylline or aminophylline are not recommended in these patients due to significant side effects and a reduced therapeutic window. The guidelines recommend that, if nebulized therapy has been chosen as the method of in-hospital administration, the use of compressed air-driven nebulized therapy is suggested instead of oxygen to avoid the risk of increased $PaCO_2$ associated with simultaneous administration of bronchodilators and oxygen.[3]

**Corticosteroids.** GOLD 2025 states that systemic corticosteroids shorten recovery time, improve lung function ($FEV_1$), improve oxygenation, decrease the risk of relapse and treatment failure, and reduce admission time. The recommended dose is 40 mg of prednisone or its bioequivalent per day for five days. The oral route of administration is similar to the parenteral route in terms of efficacy. Some studies suggest that longer use may increase the risk of pneumonia, sepsis and death, even when used in parenteral boluses, and that they are less effective in patients with lower blood eosinophil counts.[3]

International guidelines such as NICE 2019 CPG recommend the use of prednisone or its bioequivalence at doses of 30 mg daily for 7-14 days,[64] ATS/ERS[447] CPG recommend the use of prednisone or its bioequivalence at doses of 30-40 mg daily for 10-14 days, Canadian CPG

recommend the use of prednisone or its bioequivalence at doses of 25-50 mg daily for 10-14 days. The REDUCE study, a multicenter trial in five Swiss university hospitals, compared by intention-to-treat and per protocol, the non-inferiority of 40 mg prednisone daily for 5 versus 14 days. No difference in the relapse rate was observed in the medium and long term. The short five-day treatment results in non-inferior clinical performance, represents a lower cumulative prednisone dose, and reduces short-term adverse effects and admissions.[3,166]

Woods et al. published an SLR that evaluated the efficacy and safety of corticosteroids compared to placebo in patients with COPD exacerbation.[166,455] The authors conclude that the scientific evidence supports the fact that systemic corticosteroids are effective in the treatment of COPD exacerbations, improve symptoms and airflow, prevent treatment failure and relapses, and decrease hospital stay, therefore, they have positioned themselves as part of the standard of management in these patients. Also, the lowest effective dose and shortest duration of treatment should be considered.

An SLR published by Walters et al. in 2014 with the Cochrane Collaboration aimed to evaluate the impact of the use of systemic corticosteroids for the treatment of COPD exacerbations, in addition to comparing efficacy between different routes of systemic administration. The authors included 16 CCT (1,787 participants) whose mean age was 68 years and mean $FEV_1$ was 40% compared to predicted. The quality of the studies was generally rated as high, with a low or unknown risk of bias. The results of the meta-analysis showed that the use of corticosteroids decreases the risk of treatment failure by half with an average duration of 14 days (MR 0.48, 95%CI 0.35-0.67) with a high quality of evidence and a NNT of nine to avoid treatment failure. A decreased risk of relapse was also shown (hazard ratio [HR] 0.78, 95%CI 0.63-0.97). There was no difference in 30-day mortality (MR 1.00, 95%CI 0.60-1.66). Pulmonary function showed positive differences at 72 hours (MD 140 mL, 95%CI 90-200). Regarding treatment safety, an increase in the occurrence of adverse events (MR 2.33, 95%CI 1.59-3.43), hyperglycemia (MR 2.79, 95%CI 1.86-4.19) was observed. The mode of administration showed that there was no difference between patients receiving oral and parenteral corticosteroids with respect to most outcomes, although there were more side effects in parenteral administration (hyperglycemia: MR 4.89, 95%CI 1.20-19.94).[456]

The use of high doses of nebulized budesonide 1,500 to 2000 μg three to four times daily[457-459] and even inhaled also in high doses and combined with formoterol (320/9.0 μg every 6 h) (Stallberg, 2009 #2) has been shown to be as effective as systemic steroid in some CCT and in selected patients with COPD exacerbation. However, the high doses and frequency of administration may influence the choice of this treatment, due to a much higher cost compared to oral steroid.[3]

**Antibiotics.** The scientific evidence supporting the use of systemic antibiotics in patients with COPD exacerbation has been questioned because the studies have not had a controlled design, have lacked an adequate classification of patients and, on many occasions, have failed to differentiate between patients with COPD versus patients with chronic bronchitis. The GOLD 2025 guideline states that systemic antibiotics have demonstrated benefit in patients with clinical evidence of an underlying bacterial infection, increased purulent sputum; the secretion characteristic has been shown to have a sensitivity of 94.4% and a specificity of 52% for a significant bacterial load.[3,460] These guidelines, in addition to GMEPOC and ALAT 2019, recommend the use of antibiotics in patients with COPD exacerbation who present with these three clinical features: increased dyspnea, increased sputum volume and purulence, or if they present with two cardinal symptoms, while one of them is increased purulence; or who require mechanical ventilation (invasive or noninvasive). They recommend the use of 5-7 days of treatment, since the evidence for longer use (10-14 days) has not shown additional benefits and increases the risk of bacterial resistance and associated adverse events.[3,25] Antibiotic selection should be made considering local bacterial resistance patterns in an empirical manner. It is suggested to consider amoxicillin with clavulanic acid, macrolides (azithromycin), cephalosporins (second and third generation) or fluoroquinolones in selected patients. It is important to consider sputum or bronchial aspirate culture in patients with frequent exacerbations, severe obstruction or requiring mechanical ventilation.

An SLR published by Vollenweider et al. with the collaboration of Cochrane aimed to evaluate the benefit of antibiotics in the management of COPD exacerbations. The authors included 19 CCT with 2,663 participants (11 studies with ambulatory patients, seven with hospitalized patients and one with ICU patients). The results of the meta-analyses showed that, in ambulatory patients (mild to moderate exacerbations, low quality level of evidence), the use of antibiotics reduces the risk of treatment failure between seven days and one month after starting treatment (RR 0.72, 95%CI 0.56-0.94); few studies evaluated mortality and relapses. Regarding hospitalized patients (moderate quality level of evidence), it does not demonstrate a reduction in the risk of treatment failure (RR 0.65, 95%CI 0.38-1.12) or mortality (OR 2.48, 95%CI 0.94; 6.55). The analysis with ICU patients showed a significant effect in reducing the risk of treatment failure (RR 0.19, 95%CI 0.08-0.45) and mortality (OR 0.21, 95%CI 0.06-0.72). The authors' conclusion is that systemic antibiotics appear to have beneficial effects, although not very consistent, in both

**Table 23:** Considerations for outpatient management in COPD exacerbation.

- Patients gathering mild exacerbation criteria according to the Rome proposal (exacerbation severity).
- No confusion, mild dyspnea, and good general condition with a good activity level
- Normal level of consciousness, no tachypnea (RR < 24 bpm) or tachycardia (HR < 95 bpm), good color (no cyanosis), and no peripheral edema
- No comorbidities, or these are stable and well controlled
- No oxygen dependence, or require only a modest increase to maintain adequate oxygenation ($SpO_2$ > 88%)
- If chest imaging is available, no findings other than those consistent with COPD
- If CRP is available, it must be < 10 mg/dL
- Adequate social circumstances: family support, access to medications, and additional healthcare resources if necessary

HR = heart rate. RR = respiratory rate. bpm = beats per minute. CRP = C-reactive protein. bpm = breaths per minute.
Criteria modified according to the GOLD 2025 and NICE 2019 guidelines.[3,64]

**Table 24:** Hospital management criteria in people with COPD exacerbation.

| Criteria for considering admission | Criteria for critical care |
|---|---|
| • Severe symptoms such as dyspnea at rest, significant tachypnea, decreased oxygenation, and altered alertness<br>• Acute respiratory failure (PaO2 < 50 mmHg and/or pH < 7.35)<br>• New-onset signs such as cyanosis and peripheral edema<br>• Lack of improvement with initial outpatient management (< 24 hours)<br>• Need for respiratory support: high-flow nasal prongs or noninvasive ventilation<br>• Severe comorbidity (differential diagnoses): heart failure, acute myocardial infarction, pulmonary thromboembolism, pneumonia, pneumothorax, pleural effusion, others)<br>• Inadequate home care | • Severe dyspnea unresponsive to initial management<br>• Changes in mental status and alertness (confusion, lethargy, or coma)<br>• Severe worsening of hypoxemia (PaO2 < 40 mmHg) or severe respiratory acidosis (pH < 7.25)<br>• Indication for invasive mechanical ventilation<br>• Hemodynamic instability and/or vasopressor requirement |

Modified admission criteria from the recommendations of the GesEPOC 2021[357] and GOLD 2025[3] guidelines

outpatients and hospitalized patients, and particularly in patients treated in the ICU.[460]

**Antibiotic biomarkers.** Hoult et al.[461] published a SLR in 2022 that aimed to evaluate the diagnostic accuracy of different biomarkers in differentiating exacerbations associated with bacterial infection from those associated with viral infections. The results of the review showed the following:

*C-reactive protein:* there were 28 clinical studies; the results of the meta-analysis showed that exacerbations associated with bacterial infection had higher CRP values (MD 29.44, 95%CI 13.02–45.87). Several studies have attempted to find a cutoff point to aid decision-making, and only the one proposed by Hassan (15 mg/L) resulted in a sensitivity of 95.5% and a specificity of 100% in his clinical study with 30 patients.

*Serum procalcitonin:* the authors included 17 clinical studies, of which 15 presented numerical results and 11 found statistically significant differences regarding high serum procalcitonin concentrations in patients with exacerbation associated with bacterial infection. The results of the meta-analyses showed a significant difference in serum procalcitonin values in patients with exacerbation associated with bacterial infection (WMD 0.76 ng/mL, 95%CI 0.16–1.36 ng/mL). Some authors suggest a cutoff of 0.76 ng/mL, which results in a sensitivity of 78.95% and a specificity of 92.5%.

Other biomarkers evaluated in sputum were interleukin-8 (IL-8), tumor necrosis factor alpha (TNF-α), and IL-1B in sputum, as well as IL-6, myeloperoxidase, and neutrophil elastase. However, these are of very limited use in the general clinical setting, and the results were either nonsignificant or insufficient, so the evidence could not consistently demonstrate their diagnostic value.

## Oxygen therapy and ventilatory support in exacerbations

### Clinical Question 23: *What is the efficacy and safety of oxygen therapy and ventilatory support in the management of patients with COPD exacerbation?*

| Recommendations | | |
|---|---|---|
| 1 | Evaluation:<br>• Every patient with suspected moderate or severe COPD exacerbation (Rome Proposal) in second or third level of care, | Evidence 4<br>Recommendation D |

| | | |
|---|---|---|
| | should be optimally evaluated with arterial blood gases to determine their oxygenation status ($SaO_2$ and $PaO_2$) the level of hypercapnia ($PaCO_2$) and acid-base status (pH and $HCO_3$). Pulse oximetry ($SpO_2$) and venous blood gases are less difficult and painful alternatives to obtain; venous blood gases are reliable for assessing $CO_2$ retention and acid-base status ($PCO_2$, pH and $HCO_3$).<br>• Monitoring of patients without hypercapnia can be performed with pulse oximetry. In patients with respiratory failure, hypercapnia and acidosis, blood gases should be repeated on a regular basis, according to the response to treatment and until stability is achieved. | |
| 2 | **Oxygen therapy:** Oxygen therapy should be administered in a controlled manner to maintain an $SpO_2$ of 88 to 92%; this is usually achieved with flows of 1.0 to 3.0 L/min through nasal prongs or with oxygen concentrations of 24 to 28% with Venturi type oronasal masks.<br>• If the patient is hypercapnic, nebulizations should be administered with compressed air (without oxygen) to avoid worsening (further hypercapnia and narcosis); if required, additional oxygen therapy by nasal prongs can be administered. | Evidence 2++<br>Recommendation C<br><br>Evidence 4<br>Recommendation D |
| 3 | **High-flow nasal cannula (HFNC):** in patients with severe COPD worsening (Rome Proposal) with severe hypoxemia and acute hypercapnia and respiratory acidosis, oxygen therapy with high-flow nasal cannula (HFNC) of 30 to 60 L/min should be considered initially, according to their availability in health systems. Although its effectiveness is similar to conventional oxygen therapy and noninvasive ventilation in terms of the main outcomes (blood gas values, intubation rates, and mortality), it may decrease hypercapnia and has fewer adverse events. There is evidence that there is no significant difference between HFNC and noninvasive ventilation, but its use as a first option reduces the need for noninvasive ventilation. | Evidence 2–<br>Recommendation C |
| 4 | **Non-invasive ventilation (NIV):** is the ventilation of first choice in patients with COPD exacerbation who did not benefit or stabilize with HFNC. This treatment modality avoids or significantly reduces the risk of orotracheal intubation (80 to 85% success rate). NIV shortens hospital stay, reduces complications, mortality and lowers the cost of care, and is also useful in the process of withdrawal of invasive mechanical ventilation. | Evidence 2++<br>Recommendation B |
| 5 | **Invasive mechanical ventilation (IMV):**<br>• Its current indication in a generalized manner is NIV failure. It should be decided based on the reversibility of the precipitating event, the patient's wishes and the availability of resources and critical care. It is associated with greater morbidity and mortality, as well as longer hospital stay, particularly in patients with low respiratory reserve ($FEV_1$ < 30%) and association with comorbidities.<br>• Whenever possible, before the possible indication for IMV, it is essential to review the patient's wishes regarding palliative care and end-of-life support to avoid difficult decisions by the family and the medical team (see palliative care recommendations). | Evidence 1+<br>Recommendation B |

## *Evidence analysis*

**Oxygen therapy.** Oxygen administration is a fundamental component of the treatment of patients with moderate COPD exacerbation (Rome Proposal) who show significant hypoxemia ($PaO_2$ < 60 mmHg and/or $SpO_2$ < 88%). Optimally, arterial blood gases should be measured to assess $CO_2$ retention and acid-base status.[3,357] Venous blood gases may be a less difficult and painful alternative to obtain, as well as reliable for the measurement of $PCO_2$, pH and $HCO_3$.[3,462] Oxygen therapy is indicated to achieve a goal oxygen saturation between 88-92%.[3,357] Oxygen should be administered in a controlled manner and avoiding high concentrations ($FiO_2$ > 28%) as they may favor $CO_2$ retention and narcosis with progressive worsening. This is usually achieved with the use of nasal prongs at low oxygen flows (1.0 to 3.0 L/min) or with Venturi-type oronasal masks with oxygen concentrations ($FiO_2$) of 24 to 28%. If the patient is hypercapnic, nebulizations should

be administered with compressed air (without oxygen) and additional simultaneous oxygen therapy by nasal prongs can be administered.

**High-flow nasal cannula (HFNC).** While conventional oxygen therapy remains the most commonly employed method of support in COPD patients, oxygen flow is limited and some reports have associated it with an increased risk of requiring invasive ventilation and mechanical ventilatory support in respiratory acidosis. HFNC is a noninvasive respiratory support designed to deliver flows between 30-60 L/min that provides oxygen delivery with a heated, humidifying device through a special nasal cannula. This device produces a discrete positive end-expiratory pressure, which decreases inspiratory effort, increases lung capacity and can reduce hypercapnia and improve quality of life in subjects with stable hypercapnic COPD.[3,357]

An SLR published by Zhang et al. in 2023 aimed to evaluate the benefit of oxygen delivery by PNAF compared to conventional oxygen therapy in COPD patients with aggravated hypercapnia. The authors included eight controlled clinical studies, five of them with acute hypercapnia and the other three with chronic hypercapnia. In patients with acute hypercapnia, short-term use of HFNC reduced $PaCO_2$ significantly (MD -1.55, 95%CI -2.85 to -0.25) and a reduction in treatment failure (MR 0.54, 95%CI 0.33-0.88), but there was no significant difference in $PaO_2$ (MD -0.36, 95%CI -2.23-1.54). In chronic hypercapnia, HFNC did not significantly reduce $PaCO_2$ (MD -1.21, 95%CI -3.81-1.39) or $PaO_2$ (MD 2.81, 95%CI -1.39-7.02). Exacerbations showed reduction, although the authors were unable to meta-analyze the data due to high heterogeneity.[401]

Another SLR published by Xu et al. also compared the benefit of HFNC compared to conventional oxygen therapy and noninvasive ventilation (NIV) and reported, from a total of 10 clinical studies, comparable results between the three modalities regarding intubation rate, mortality and changes in blood gases.[402] However, HFNC had fewer adverse events (MR 0.12, 95%CI 0.06-0.28) and reduced the need for NIV significantly (MR 0.57, 95%CI 0.35-0.91). Another SLR published by Duan et al. showed similar results.[403]

**Non-invasive ventilation (NIV).** Gold 2025 states that NIV is the standard ventilatory treatment for patients hospitalized due to COPD exacerbation and acute respiratory failure, as it has success rates of 80-85% in different trials.[3] Previous reviews and meta-analyses have analyzed the impact of NIV on mortality in acute situations, as well as its effect on dyspnea during acute exacerbations and in the management of respiratory failure.[463]

A Cochrane review compared the efficacy of NIV and standard treatment in adults with acute respiratory failure due to COPD; it found that NIV reduces the risk of mortality by 46% (RR 0.54, 95%CI 0.38-0.76) and the risk of endotracheal intubation by 65% (RR 0.36, 95%CI 0.28-0.46), with moderate quality of evidence. In addition, a reduction in hospital stay (-3.39 days, 95%CI -5.93 to -0.85) and in the incidence of non-NIV complications (RR 0.26, 95%CI 0.13-0.53) was observed. Improvement in pH and partial pressure of oxygen ($PaO_2$) was reported 1 hour after treatment, but no improvement in $PaCO_2$. Although a trend towards improvement in dyspnea was observed, the difference was not statistically significant and treatment intolerance was greater with the use of NIV.[464]

Peng et al.[465] evaluated the efficacy and safety of switching from invasive mechanical ventilation (IMV) to NIV in patients ready for extubation, but not for complete withdrawal of mechanical ventilation known as the «pulmonary infection control window». This period covers six to seven days after invasive ventilation and antibiotic administration, when the pulmonary infection is controlled and a reduction in radiographic infiltrates, changes in expectoration (less quantity, less tenacity, lighter color) and at least one of the following signs are observed: temperature $< 37.5$ °C, leukocytes $< 10 \times 10^9$/L or reduction of leukocytes by $2 \times 10^9$/L. NIV significantly reduced mortality (RR 0.27, 95%CI 0.17-0.42, $p < 0.001$), ventilator-associated pneumonia, weaning failures, reintubations, duration of invasive and total ventilation, as well as ICU, hospital stay and costs, although the quality of evidence was moderate to low.

NIV demonstrated significant reductions in mortality rates, intubation, and length of hospital stay compared with IMV. Different modes of NIV showed comparable efficacy, and structured weaning protocols reduced relapse rates.[466]

**Invasive mechanical ventilation (IMV).** Because of the high success of NIV in patients with severe COPD exacerbation, the indication for IMV is precisely the failure of NIV.[3] However, IMV is associated with increased morbidity and mortality, as well as longer hospital stay and health-related costs. GOLD 2025 recommends deciding the decision for IMV based on the reversibility of the precipitating event, the patient's wishes and decisions, and the availability of resources and critical care. Not only is the severity of lung disease relevant, it is important to consider comorbidities, as mortality in COPD patients with respiratory failure is lower than mortality in patients ventilated for causes not associated with COPD. A study of patients with acute respiratory failure reported a mortality of 17-49%. Subsequently, deaths were documented in the following 12 months particularly in those with low pulmonary reserve from before ventilation ($FEV_1 < 30\%$ predicted), without respiratory comorbidities. Those without comorbidities had potentially reversible respiratory failure or were relatively mobile and did not use oxygen and had a good outcome. Also, whenever possible, it is essential to review the patient's wishes regarding palliative care and

end-of-life support to avoid difficult decisions by the family and medical team (see palliative care recommendations).[458]

## Discharge criteria

### Clinical Question 24: *What are the criteria for hospital discharge of patients with severe COPD exacerbation?*

| Recommendation | | |
|---|---|---|
| 1 | Hospital discharge of patients with COPD exacerbation (second and third level of care) should be considered when the patient has achieved clinical stability for a period of no less than 24 h and the following criteria have been documented: no parenteral medication support is required and bronchodilators have been tappering to an administration greater than every 4 h; the need for oxygen has ended or has returned to its previous requirement and can be implemented on an outpatient and home basis; the patient is now self-sufficient or has returned to previous status; symptoms, especially dyspnea, have been controlled; comorbidities should be controlled or susceptible to home management; all persons responsible for and involved in the management and care of the patient understand and implement the care and treatment plan in the hospital-home transition; and, sufficient out-of-hospital support and care is available | Evidence 1+<br>Recommendation A |

#### *Evidence analysis*

The criteria for hospital discharge of a patient with COPD exacerbation are not universally standardized, but include a number of parameters that define patient stability, management conditions that can already be implemented on an outpatient and home basis, and that reduce the risk of readmission. The Australian Thoracic Society's COPD-X Plan CPG details a number of key criteria which are listed in *Table 25*.[467]

An SLR published by Ospina et al. in 2017,[468] evaluated the efficacy of different post-hospitalization care strategies for COPD exacerbation. It identified that a significant proportion of patients do not receive information from well-established management programs, fail to receive adequate vaccinations, do not receive optimal therapeutic management, and do not establish formal smoking cessation treatments. The authors included 14 clinical studies, of which four were CCT. The elements that were included in the different programs were: ensuring correct inhalation technique (nine studies), individual pharmacological management strategies (eight studies), assessment and referral to rehabilitation therapy (eight studies), ensuring follow-up (eight studies) and referral to a smoking cessation program (seven studies). The results of the meta-analyses show that from the four CCT the hospital readmission rate was decreased by 20% with the discharge program strategies (RR 0.80, 95%CI 0.65-0.99). This percentage increases in the observational studies (range -6.111 to -48.5%). However, with respect to secondary outcomes, with the implementation of these programs, no decrease in long-term mortality could be demonstrated (RR 0.74, 95%CI 0.43-1.28), as well as in SGRQ values (MD 1.84, 95%CI -2.13-5.8).[468]

The GOLD 2025 guidelines point out that there are no universally accepted standards that consider the time and criteria for discharge of hospitalized patients. Mortality in patients with exacerbations is associated with increased age, the presence of respiratory acidosis, the need for ventilatory support, and comorbidities such as anxiety and depression. These guidelines also propose the incorporation of well-structured discharge care programs; however, they point out that the evidence is scarce and has not been shown to reduce the mortality of these patients.[3]

The benefit of early pulmonary rehabilitation is contradictory; some studies have associated it with increased mortality, while others with increased survival.[3] It is important to establish an early follow-up appointment (one month) after hospital discharge, as it has been associated with lower risk of readmission. Patients who miss that follow-up have an increased 90-day mortality. Another evaluation appointment at 90 days is also important to assess the patient's clinical condition, medication, perform pulmonary function testing and preferably arterial blood gases. Additional imaging studies may be performed especially in patients who are readmitted for COPD exacerbation.

**Additional considerations for the post-hospital management of patients with severe COPD exacerbation.** The different international guidelines briefly propose recommendations for the discharge and post-hospital management of patients with COPD exacerbation.[3] Different reviews on the subject, such as that of the European Respiratory Society,[469] propose a format for completing a list of discharge requirements,[470] and a systematic review of Care Bundles analyzes the effect of these strategies. Despite the heterogeneity of the studies, they have a beneficial effect in the short and medium term in terms of improvement of symptoms, quality of life and hospital readmissions, but with no impact on mortality.[468] These recommendations can help to define the aspects that require greater attention in the transition from

**Table 25: Key points:** for hospital discharge of patients with COPD exacerbation.[467]

- The patient must be in stable condition and have not required parenteral medications in the past 24 hours
- Inhaled bronchodilators must be required > every 4 hours
- Oxygen must have been discontinued for at least 24 hours or returned to its previous requirement and can be implemented on an outpatient and home basis
- The patient must be ambulatory independently and safely, if this was possible prior to the event
- The patient can eat and sleep without significant dyspnea
- Family members and/or caregivers must understand the patient's pharmacological management plan
- Arrangements and adjustments have been made for the patient's home or other place of residence

**Table 26: Key points:** post hospital management of severe COPD exacerbation.

- Hospital discharge after a COPD exacerbation involves gathering the patient's goals and requirements as safely as possible; greater compliance with these criteria leads to improved stability, facilitates follow-up, and reduces the likelihood of readmission
- Short-acting bronchodilators and nebulized steroids are safe and effective, especially in patients with cognitive or neuromuscular impairment or those who do not achieve optimal inspiratory flow. They reduce medical visits and hospital readmissions. However, they should be applied temporarily and then replaced with maintenance inhaled therapy
- Long-term continuation of systemic corticosteroids or restarting another course is not recommended unless the patient has not completed the in-hospital regimen
- A period of treatment with triple inhaled therapy (LABA/LAMA/ICS) is recommended for the first 30 days after discharge (which could extend up to three months) and regardless of the previous treatment regimen
- Oxygen therapy should be continued as long as the patient does not reach acceptable oxygenation levels ($PaO_2 \geq 55$ mmHg or $SpO_2 \geq 88\%$ at rest and in room air). All patients with a new prescription or previous therapy should have their oxygen requirements reassessed at one and three months
- Early, personalized, and supervised pulmonary rehabilitation is recommended and should include education and nutritional support until the patient achieves maximum benefit; it reduces the risk for manteinance, improves lung capacity, physical endurance, symptoms, and quality of life
- Adjusting inhaled therapy to dual or triple therapy is recommended, as this reduces the risk of exacerbations, resource use, and healthcare costs
- The patient's vaccination schedule should be reviewed and completed according to the recommendations (GMEPOC 2025), and if possible, should be administered prior to discharge

hospital to home care, a period in which most respiratory, cardiovascular and other eventualities occur.

Recently, a formal consensus of experts from Mexico has been published specifically for the post-hospital management of patients with severe exacerbation, a particularly high-risk period for morbidity and mortality in the natural history of COPD.[471] These recommendations are summarized in *Table 26* and are intended to reduce the risk of relapse, readmission and death in the short and long term, as well as to optimize related costs.

## Palliative care

### Question 25: *What are effective measures for palliative care and end-of-life support for COPD patients?*

| Recommendations | | |
|---|---|---|
| 1 | Palliative care and end-of-life support for people with COPD should be implemented by any health professional responsible for their care, as it decreases symptom burden and demand for emergency care. | Evidence 1+ Recommendation A |
| 2 | There are no prognostic variables or instruments to predict poor survival in patients with COPD; therefore, palliative care should be established as soon as possible in severe conditions, poor prognosis for life, presence of refractory symptoms and, above all, in the face of the patient's needs and decisions. | Evidence 2– Recommendation C |
| 3 | Palliative care and all end-of-life support measures should be discussed and decided with the patient and family members as clearly and in detail as possible, so effective and adequate communication is essential. The most important decisions should include the site of care and outcome (hospital or home), the decision on advance directives, the level of life support and advance life support code. | Evidence 2++ Recommendation B |
| 4 | The palliative care management plan in terms of pharmacological and non-pharmacological measures should be clear and documented. In addition, it should be reviewed with patients, | Evidence 2++ Recommendation B |

| | | |
|---|---|---|
| | family members and caregivers, as well as other healthcare professionals to ensure full respect for the patient's decisions. | |
| 5 | Palliative care measures and issues should encompass symptom management and control, mainly dyspnea, nutritional status, anxiety and depression, as well as pulmonary rehabilitation and education | Evidence 1++ Recommendation A |
| 6 | Pharmacologic interventions that should be considered for symptom management (dyspnea, anxiety, depression and fatigue) include bronchodilators, systemic corticosteroid anti-inflammatory medication, opioid medication (morphine) or benzodiazepines, oxygen therapy, nutritional support, high-flow nasal cannula, invasive or noninvasive ventilation. These measures are controversial, but help to improve symptoms | Evidence 1+ Recommendation A |
| 7 | Non-pharmacological interventions should be considered as part of palliative care, as they can improve psychological and physical outcomes. They include cognitive behavioral therapy, acupuncture, breathing strategies, music therapy and complete assistance. Although without sufficient evidence, they are considered safe and proactive and are part of a comprehensive, multidisciplinary model of care | Evidence 2++ Recommendation B |

## *Evidence analysis*

Palliative care in people with COPD should be recommended because it seeks to alleviate suffering by addressing physical, psychosocial, and spiritual problems.[472] However, its implementation is often difficult because of low evidence of its effectiveness.[472,473] CPG emphasize the priority of integrating palliative care for the reduction of suffering through effective symptom control.[143,474] Current recommendations for considering the initiation of palliative care in patients with COPD are often based on an expected poor prognosis; the decision of which COPD patients should start palliative care and at what time is controversial.[475,476] The European Respiratory Society (ERS) recommends considering palliative care when physical, psychological, social, or existential needs are identified through a comprehensive needs assessment of each subject.[477]

A systematic review and meta-analysis evaluated the association between palliative care, emergency care use, quality of life, and symptom burden in patients with non oncologic diseases, including COPD. It found that palliative care was significantly associated with lower emergency department use and lower symptom burden compared with conventional treatment, although there was no difference in quality of life.[478] High-quality research on intervention costs and economic outcomes in palliative care is limited.[479]

Within different care settings, both short-term palliative care assessments and longitudinal palliative care interventions with care coordination have been implemented. The most valued features of palliative care interventions for COPD patients include direct access to a professional for support, an ongoing relationship with the professional, and education about dyspnea. There are positive effects on aspects such as advance care planning and perceived symptom control and self-management.[473]

**Management of dyspnea.** Initial management of dyspnea in patients with advanced COPD consists of evaluating and addressing the underlying causes. Factors such as bronchospasm, pleural effusion, pulmonary edema, pulmonary embolism, hypoxemia, and infection may contribute to worsening dyspnea. Medications such as opioids, oxygen and/or benzodiazepines may be used to improve severe dyspnea.

**Opioids.** The use of opioids, such as morphine, has been recommended as a therapeutic option for chronic dyspnea when it persists despite optimization of disease management and implementation of nonpharmacological therapies. Different studies, including a Cochrane meta-analysis, have reported low quality level of evidence on the benefits of opioids in the treatment of refractory dyspnea and in improving quality of life in patients with advanced and terminal disease.[480] It is important to note that the mechanisms by which opioids reduce the sensation of dyspnea are not yet fully understood, and their use increases the frequency of side effects such as nausea, vomiting, constipation, and drowsiness.[481] Particularly in patients with COPD, opioid use improves dyspnea, but not exercise capacity.[482]

In patients with COPD and severe chronic dyspnea, a controlled clinical trial showed that extended-release morphine at different doses (e.g., 8 mg/day or 16 mg/day) did not significantly reduce the intensity of dyspnea after one week of treatment compared with placebo.[483,484] This contrasts with the results observed by Verberkt et al. who reported that oral extended-release morphine in low doses and administered regularly for four weeks improved dyspnea in COPD patients with grades 3-4 on the mMRC scale, as well as health status, without affecting $PaCO_2$ or causing serious adverse effects.[485]

**Benzodiazepines.** Benzodiazepines are widely used to relieve dyspnea in advanced disease and are

frequently recommended in the literature. However, a 2016 Cochrane analysis involving 214 participants with advanced cancer or COPD found no favorable effect of benzodiazepines in relieving dyspnea compared with placebo, midazolam, morphine, or promethazine (eight studies, 214 participants).[486]

**Oxygen.** There are different opinions about the benefits and burdens of palliative oxygen use. The use of oxygen may imply different therapeutic goals for both patients and caregivers. These perceptions must be considered when prescribing oxygen for the relief of chronic dyspnea in patients who do not qualify for long-term oxygen therapy.[487,488]

**Anxiety and depression.** Anxiety and depression are common in up to half of COPD patients, and often go untreated.[488] These disorders cause a significant impact on quality of life and are associated with an increased risk of exacerbations and mortality. They may be linked to refractory dyspnea and would benefit from a comprehensive therapeutic approach; however, factors such as previous hospitalizations and smoking also contribute to their development.[489] A multidisciplinary care approach, including palliative care clinicians and the primary care physician, could facilitate safe dosing and side effect monitoring of antidepressant or anxiolytic use.

It has been proposed that psychosocial interventions could be an effective complement to medical treatment in COPD. A SLR and meta-analysis indicated that, when analyzing different types of intervention, cognitive-behavioral therapy was found to be effective in improving psychological outcomes.[490] Other meta-analyses support psychosocial intervention as a valuable additional tool in the multidisciplinary approach to respiratory care, with the potential to improve both psychological and physical outcomes.[491] Although non-pharmacological interventions, such as cognitive-behavioral therapy, acupuncture, breathing strategies, music therapy, and complete assisstance, lack strong evidence in COPD, they are an integral part of the interdisciplinary model of palliative care and could be safely and proactively incorporated into the management of patients with COPD.

**Fatigue.** In patients with COPD, this can be improved through self-care, pulmonary rehabilitation, and nutritional support.

**Implementation of palliative care.** Various systematic reviews have established recommendations for addressing palliative care discussions in patients with COPD.[472,492] The main suggestions are:

1. Initiate discussions early, or when events arise such as the presence of *cor pulmonale*, the need for ventilation, severe lung impairment, or admissions, and involve family members if the patient allows it.
2. Share the clinician's treatment plan, taking the patient's wishes into account, offering emotional support, and resolving disagreements to reach a shared decision.
3. Set goals and plan for the future, especially if the patient requests heavy treatments, prioritizing harm reduction strategies when necessary.
4. Document discussions and collaborate with other professionals to ensure respect for the patient's decisions.

**Barriers.** A systematic review was conducted to help clinicians identify reliable tools for predicting survival in patients with COPD and the criteria for initiating palliative care early. Several complex barriers were identified, such as prognostic difficulties, unidimensional tools for assessing symptoms, and unmet needs. The review concluded that existing prognostic variables are not sufficiently reliable to predict poor survival, and that the decision to initiate palliative care should be based on refractory symptoms and patient needs.[493] Patients often focus on prolonging life without clarity about their preferences, while clinicians confront time and knowledge limitations. Uncertainty about prognosis and the perception of palliative care as exclusive for the end of life are also significant obstacles. Key challenges to implementation include appropriate referral timing, provider availability, and accessibility for patients.[473,474]

### Facilitators

1. Mutual trust between patient and physician, a strong physician-patient relationship, and the physician's expertise in lung diseases can facilitate these conversations.
2. Patients who have recently suffered the loss of a beloved may be more receptive to this type of dialogue.[472]

## ADDITIONAL CONSIDERATIONS

The Mexican Guideline for COPD 2025 provides evidence-based clinical recommendations formulated by expert consensus and classified into three categories: initial assessment and diagnosis of COPD; comprehensive treatment of stable COPD; and treatment of COPD exacerbations. These recommendations are objective, applicable, comprehensive, and appropriate for the Mexican healthcare system and are expected to contribute to improving the quality of care.

### Future research

There are topics within the guide that don't have answers or where the evidence hasn't reached adequate coverage to make certain recommendations, so there are working groups worldwide tasked with creating protocols aimed at addressing these issues.

### Update

A three- to four-year update period for the Clinical Practice Guideline is planned to incorporate new scientific evidence into the recommendations.

### Important information

This CPG and any documents published based on it represent tools developed by a consensus of clinical experts regarding current therapies and decision-making for the management of COPD. This document has been published so that medical professionals can consider the clinical recommendations and incorporate them into their daily clinical practice. However, these recommendations do not override the independent clinical judgment of each physician or the individual conditions of each patient.

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