



NCT

Neumología y Cirugía de Tórax

Fundada en 1939

GMEP^{OC} 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



www.revistanct.org.mx

REVISTA OFICIAL DE:

SOCIEDAD MEXICANA DE NEUMOLOGÍA Y CIRUGÍA DE TÓRAX,
INSTITUTO NACIONAL DE ENFERMEDADES RESPIRATORIAS ISMAEL COSÍO VILLEGAS

Neumología y Cirugía de Tórax

www.revistanct.org.mx

Founded in 1939 as Revista Mexicana de Tuberculosis y Enfermedades del Aparato Respiratorio (Mexican Journal of Tuberculosis and Respiratory Diseases).

Official journal:

Mexican Society of Pulmonology and Thoracic Surgery
National Institute of Respiratory Diseases Ismael Cosío Villegas

Editor-in-chief

Juan Carlos Vázquez García
Directorate of Education, National Institute of Respiratory Diseases Ismael Cosío Villegas/Mexican Society of Pulmonology and Thoracic Surgery

Associated publishers

Pulmonary Medicine:

Renata Báez Saldaña
Directorate of Education, National Institute of Respiratory Diseases Ismael Cosío Villegas

Pediatric Pulmonary Medicine:

María del Carmen Cano Salas
Asthma Clinic, National Institute of Respiratory Diseases Ismael Cosío Villegas

Thoracic Surgery:

Francina Valezka Bolaños Morales
Subdirector of Surgery, National Institute of Respiratory Diseases Ismael Cosío Villegas

Critical Care Medicine:

Carmen Margarita Hernández Cárdenas
General Directorate, National Institute of Respiratory Diseases Ismael Cosío Villegas

Editorial Board

José Rogelio Pérez Padilla
Research in Smoking and COPD, National Institute of Respiratory Diseases Ismael Cosío Villegas

Patricio Santillán Doherty
National Bioethics Commission, Ministry of Health, Mexico

Andrés Palomar Lever
ABC Medical Center, Mexico City

Mayra Edith Mejía Ávila
Clinic of Interstitial Lung Diseases, Ismael Cosío Villegas National Institute of Respiratory Diseases, Mexico

Mario Vargas Becerra
Research in Bronchial Hyperreactivity, National Institute of Respiratory Diseases Ismael Cosío Villegas

Assistant editors

Irene Sánchez Cuahutitla
V. Beatriz Ayala Robles
Library and Publishing Office, National Institute of Respiratory Diseases Ismael Cosío Villegas

Cover art and design

Diana Beatriz Campos Puebla
Department of Technical Support in Teaching National Institute of Respiratory Diseases Ismael Cosío Villegas

Emma Samantha González Benítez
Audiovisual Office, National Institute of Respiratory Diseases Ismael Cosío Villegas

Editorial Board

Luis Felipe Alva López
Radiology and Molecular Imaging, Hospital Médica Sur, Mexico City, Mexico

Luis M. Argote Greene
Regional Director Thoracic and Esophageal Surgery Cleveland Clinic Florida Cleveland, USA

Ivette Buendía Roldán
Research Laboratory on Aging and Fibrous Diseases, National Institute of Respiratory Diseases Ismael Cosío Villegas, Mexico City

Guillermo Careaga Reyna
High Specialty Medical Unit, General Hospital "Dr. Gaudencio Garza" CMN La Raza, IMSS. Mexico City

José Luis Carrillo Alduenda
Sleep Clinic, National Institute of Respiratory Diseases Ismael Cosío Villegas, Mexico City

Armando Castorena Maldonado
Medical Subdirector, National Institute of Respiratory Diseases Ismael Cosío Villegas, Mexico City

Miguel Gaxiola Gaxiola
Morphology Laboratory, National Institute of Respiratory Diseases Ismael Cosío Villegas, Mexico City

Laura Graciela Gochicoa Rangel
Department of Physiology, National Institute of Respiratory Diseases Ismael Cosío Villegas, Mexico City

Alejandro Gómez y Gómez
Autonomous University of San Luis Potosí, Center for Respiratory Diseases (CERSLP), San Luis Potosí, Mexico

Julio Edgardo González Aguirre
University Hospital, Autonomous University of Nuevo León, Nuevo León, Mexico

Rogelio Jasso Victoria
Department of Research in Experimental Surgery, National Institute of Respiratory Diseases Ismael Cosío Villegas, Mexico City

Rafael Laniado-Laborín
Tuberculosis Clinic and Laboratory Tijuana General Hospital, Tijuana, Mexico

José Antonio Loaiza Martínez
Fundación de los Niños de las Californias, Children's Hospital of Las Californias, Tijuana, Mexico

Fernando Alfredo Mata Ávalos
José E. González University Hospital, Autonomous University of Nuevo León, Nuevo León, Mexico

Raúl Olmos Zúñiga
Experimental Lung Transplant Unit, National Institute of Respiratory Diseases Ismael Cosío Villegas, Mexico City

Luis Adrián Rendón Pérez
Pneumology Service, CIPTIR. Autonomous University of Nuevo León, Nuevo León, Mexico

Mauricio Salcedo Vargas
Research Unit in Biomedicine and Genomic Oncology, Hospital de Gineco-Pediatría 3-A, OOAD Norte, Mexican Institute of Social Security, Mexico City

Christian Sánchez Castrillo
Vivian Pellas Hospital, Managua, Nicaragua

Julio Sandoval Zárate
ABC Medical Center, Mexico City

Sara del Carmen Toral Freyre
Technical Training School, National Institute of Respiratory Diseases Ismael Cosío Villegas, Mexico City

Claudia Vargas Domínguez
PPD- Thermo Fisher, Medical Associate Director, Madrid, Spain

Joaquín A. Zúñiga Ramos
Directorate of Research, National Institute of Respiratory Diseases Ismael Cosío Villegas, Mexico City



**Sociedad Mexicana de Neumología
y Cirugía de Tórax, A.C.**

José Luis Sandoval Gutiérrez
President

Catalina Casillas Suárez
Vice-President

Jesús Javier Vázquez Cortés
Past President

Uriel Rumbo Nava
Secretary

Luis Albrecht Septién Stute
Treasurer



**Instituto Nacional de Enfermedades
Respiratorias Ismael Cosío Villegas**

Carmen Margarita Hernández Cárdenas
General Directorate Head

Renata Báez Saldaña
Head of the Education Directorate

Joaquín A. Zúñiga Ramos
Head of the Research Directorate

Armando Roberto Castorena Maldonado
Head of the Medical Directorate

Pulmonology and Thoracic Surgery

Address correspondence to: Dr. Juan Carlos Vázquez García, Editor-in-Chief, Revista Neumología y Cirugía de Tórax, Oficina de Biblioteca y Editorial, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas; Calzada de Tlalpan 4502, colonia Sección XVI, Mexico City, 14080. Telephone 55-5487-1700, ext., 5145. E-mail: neumolcirtorax@gmail.com

On the internet indexed and compiled in:

www.revistanct.org.mx,
www.medigraphic.com/neumologia,
www.smnyct.org.mx,
www.iner.salud.gob.mx,

www.socune.sld.cu
www.neumoparaguay.org,
www.soboneumo.com,
www.neumofedeca.org

Cover image: GMEPOC 2025. Mexican Guideline for Chronic Obstructive Pulmonary Disease.

NCT Pneumology and Thoracic Surgery, is the Official Organ of the Mexican Society of Pneumology and Thoracic Surgery, the National Institute of Respiratory Diseases Ismael Cosío Villegas, Cuban Society of Pneumology, Paraguayan Society of Pneumology, Bolivian Society of Pneumology, South American Association of Respiratory Endoscopy, International Association of Non Invasive Mechanical Ventilation and the Central American and Caribbean Federation of Pneumology and Thoracic Surgery. The rights of reproduction of the content and graphic characteristics of the present edition (including by electronic means) are reserved in accordance with the Law in the signatory countries of the Pan-American and International Copyright Conventions. The intellectual responsibility of the signed articles and photographs reverts to their authors.

NCT Pneumology and Thoracic Surgery, Vol. 84, Suppl. 1, January-March - 2025. It is published quarterly by the Sociedad Mexicana de Neumología y Cirugía de Tórax, A.C., calle Montecito No. 38 - interior: 32nd floor, office 26, colonia Nápoles, alcaldía Benito Juárez, C.P. 03810, Mexico City, Mexico. Tel. 55-8589-8532. <http://www.medigraphic.com/neumologia>, martin@medigraphic.com Editor in charge: Dr. Juan Carlos Vázquez García. Reservation of Exclusive Use Rights: species diffusion via computer network No. 04-2022-111709231200-203, e-ISSN 2594-1526, granted by the Instituto Nacional del Derecho de Autor. Art, design and formation by Graphimedic, S.A. de C.V., emyc@medigraphic.com calle Coquimbo 936, colonia Lindavista Norte, alcaldía Gustavo A. Madero, C.P. 07300, Mexico City, Mexico, phones: 55-8589-8527 to 31. Responsible for the last update of this number for its electronic format, Internet Department, Graphimedic, S.A. de C.V., Ing. Luis Rosales Jiménez, date of last modification, abril 21, 2025.

Electronic libraries and indexes in which the journal of Neumología y Cirugía de Tórax has been registered

Medigraphic, literatura biomédica
<http://www.medigraphic.org.mx>

Free Medical Journals
<http://www.freemedicaljournals.com/f.php?f=es>

Biblioteca de la Universidad de Regensburg,
Alemania
<https://ezb.uni-regensburg.de/>

Biblioteca del Instituto de Investigaciones
Biomédicas, UNAM
<http://www.revbiomedicas.unam.mx/>

LATINDEX. Sistema Regional de Información
en Línea para Revistas Científicas de América Latina,
el Caribe, España y Portugal
<https://www.latindex.org/>

Biblioteca Virtual en Salud (BVS, Brasil)
<http://portal.revistas.bvs.br>

Biblioteca del Instituto de Biotecnología UNAM
<http://www.biblioteca.ibt.unam.mx/revistas.php>

Fundación Ginebrina para la Formación
y la Investigación Médica, Suiza
https://www.gfmer.ch/Medical_journals/Revistas_medicas_acceso_libre.htm

PERIODICA
(Índice de Revistas Latinoamericanas en Ciencias)
UNAM
<https://periodica.dgb.unam.mx>

Google Académico
<https://scholar.google.es>

Wissenschaftszentrum Berlin für Sozialforschung,
Berlin WZB
<https://www.wzb.eu/de/literatur-daten/bereiche/bibliothek>

Virtuelle Bibliothek Universität des Saarlandes,
German
<https://ezb.ur.de/ezeit/search.phtml?bibid=SULB&colors=7&lang=de>

Biblioteca electrónica de la Universidad de
Heidelberg, Alemania
<https://ezb.uni-heidelberg.de/ezeit/search.phtml?bibid=UBHE&colors=3&lang=de>

Biblioteca de la Universidad de Bielefeld, Alemania
<https://ub-bielefeld.digibib.net/eres>

University of Washington Libraries
<http://guides.lib.washington.edu/ejournals>

Journals for free
<http://www.journals4free.com/>

Research Institute of Molecular Pathology (IMP)/
Institute of Molecular Biotechnology (IMBA)
Electronic Journals Library, Viena, Austria
<https://ezb.uni-regensburg.de/ezeit/index.phtml?bibid=IMP&colors=7&lang=en>

Scielo México
http://www.scielo.org.mx/scielo.php?script=sci_serial&pid=0028-3746&lng=es&nrm=iso

Biblioteca de la Universidad de Ciencias
Aplicadas y Artes, Hochschule Hannover (HSH),
Alemania

<https://www.hs-hannover.de/ueber-uns/organisation/bibliothek/literatursuche/elektronische-zeitschriften/?libconnect%5Bsubject%5D=23>

Max Planck Institute for
Comparative Public Law and International Law
<https://ezb.uni-regensburg.de/ezeit/index.phtml?bibid=MPIV&colors=7&lang=en>

Library of the Carinthia University
of Applied Sciences (Austria)
<https://ezb.ur.de/ezeit/fl.phtml?bibid=FHTK&colors=7&lang=en>

Biblat (Bibliografía Latinoamericana en revistas
de investigación científica y social) UNAM
<https://biblat.unam.mx>

Universitat de Barcelona. MIAR (Matriz de
Información para el Análisis de Revistas)
<https://miar.ub.edu/issn/0028-3746>

Scilit (scientific literature)
base de datos de trabajos académicos
https://www.scilit.net/wcg/container_group/48539

CROSSREF
https://search.crossref.org/?q=0028-3746&from_ui=yes

CONTENTS

Vol. 84 - Suppl. 1 / January-March 2025

MESSAGES

GMEPOC 2025.

Message from the Mexican Society of Pulmonology and Thoracic Surgery..... s6
José Luis Sandoval-Gutiérrez, Catalina Casillas-Suárez, Jesús Javier Vázquez-Cortés

Message from the National Institute of Respiratory Diseases Ismael Cosío Villegas.....s7
Carmen Margarita Hernández-Cárdenas

GMEPOC 2025

Mexican Clinical Practice Guideline for COPD 2025.....s8

Abbreviations s11

Introduction s13

The burden of COPD in Mexico.....s14

Methodology s17

Material and methods s17

CPG Development Group s17

Scope definition s18

Structured clinical questions s18

Exhaustive search for scientific evidence s18

Quality assessment and evidence hierarchy s20

Evidence extraction and analysis s20

Formal expert consensus..... s21

Drafting of recommendations..... s21

Evaluation and diagnosis of copd..... s23

The definition of COPD and its clinical utility s25
Clinical Question 1: *What is the current definition of COPD?*

Risk factors..... s25
Clinical Question 2: *What are the risk factors associated with the development of COPD?*

Case finding and diagnosis s28
Clinical Question 3: *What are the indicated studies for case-finding and diagnosis of COPD?*

Spirometric diagnostic criteria s30
Clinical Question 4: *What are the spirometric diagnostic criteria for COPD?*

Other diagnostic tests s31
Clinical Question 5: *What is the diagnostic utility of additional pulmonary function testing in patients with COPD?*

Imaging studies	s33
Clinical Question 6: <i>What is the diagnostic accuracy of the imaging studies in patients with COPD?</i>	
Laboratory studies and biomarkers	s34
Clinical Question 7: <i>What is the usefulness of laboratory studies and biomarkers during the approach and follow up of COPD?</i>	
Clinimetric scales	s35
Clinical Question 8: <i>What is the utility of clinimetric scales in the initial assessment of COPD patients?</i>	
Impact of comorbidities.....	s39
Question 9: <i>What is the impact of comorbidities on the prognosis of COPD?</i>	
Comprehensive treatment of stable COPD.....	s42
Treatment goals and strategies	s42
Smoking cessation	s44
Clinical Question 10: <i>What is the efficacy of the different strategies for smoking cessation in patients with chronic obstructive pulmonary disease?</i>	
Exposure control.....	s45
Clinical Question 11: <i>What is the benefit of different strategies for controlling other COPD-associated exposures?</i>	
Lifestyles	s48
Clinical Question 12: <i>What is the efficacy and safety of lifestyle, diet and exercise changes in COPD patients?</i>	
Inhaled pharmacological treatment for stable COPD	s50
Clinical Question 13: <i>What is the efficacy and safety of inhaled drug therapy for the treatment of stable COPD?</i>	
Other pharmacological treatment to prevent exacerbations.....	s57
Clinical Question 14: <i>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)?</i>	
Not recommended therapies for stable COPD	s60
Clinical Question 15: <i>What is the efficacy and safety of various therapies (bacterial lysates, immunoglobulins, antileukotrienes and transfer factor) in patients with COPD?</i>	
Long-term oxygen therapy (LTOT).....	s60
Clinical Question 16: <i>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?</i>	

Pulmonary rehabilitation.....	s64
Clinical Question 17: <i>What is the efficacy and safety of pulmonary rehabilitation in patients with COPD?</i>	
Vaccination.....	s65
Clinical Question 18: <i>What is the efficacy and safety of different vaccines in reducing exacerbations in patients with COPD?</i>	
Interventionism and surgery.....	s69
Clinical Question 19: <i>What is the efficacy and safety of different treatment alternatives with bronchoscopic intervention and surgery in patients with COPD?</i>	
COPD exacerbation.....	s72
Diagnosis of COPD exacerbation	s72
Clinical Question 20: <i>What are the diagnostic criteria for defining COPD exacerbation?</i>	
Outpatient management and hospitalization for exacerbations	s73
Clinical Question 21: <i>What are the criteria for outpatient and hospital management of patients with COPD exacerbation?</i>	
Pharmacological treatment of exacerbation of COPD.....	s74
Question 22: <i>What is the efficacy and safety of pharmacological treatment for COPD exacerbation?</i>	
Oxygen therapy and ventilatory support in exacerbations.....	s78
Clinical Question 23: <i>What is the efficacy and safety of oxygen therapy and ventilatory support in the management of patients with COPD exacerbation?</i>	
Discharge criteria.....	s81
Clinical Question 24: <i>What are the criteria for hospital discharge of patients with severe COPD exacerbation?</i>	
Palliative care	s82
Question 25: <i>What are effective measures for palliative care and end-of-life support for COPD patients?</i>	



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!



How to cite: Sandoval-Gutiérrez JL, Casillas-Suárez C, Vázquez-Cortés JJ. GMEPOC 2025. Message from the Mexican Society of Pulmonology and Thoracic Surgery. *Neumol Cir Torax*. 2025; 84 (Suppl. 1):s6. <https://dx.doi.org/10.35366/119440>

Open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



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.



How to cite: Hernández-Cárdenas CM. Message from the National Institute of Respiratory Diseases Ismael Cosío Villegas. *Neumol Cir Torax*. 2025; 84 (Suppl. 1):s7. <https://dx.doi.org/10.35366/119441>

Open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Mexican Clinical Practice Guideline for COPD 2025

Guía de Práctica Clínica Mexicana de EPOC 2025

Mexican COPD Group Executive Committee and Nuclear Group

Juan Carlos Vázquez-García,¹ Rafael de Jesús Hernández-Zenteno,¹ Marisol Arroyo-Hernández,² Abelardo Elizondo-Ríos,³ Catalina Casillas-Suárez,⁴ Arturo Cortés-Telles,⁵ José Rogelio Pérez-Padilla,¹ José Luis Sandoval-Gutiérrez,^{1,5} Jesús Javier Vázquez-Cortés,⁶ Ileri Isadora Thiriión-Romero,¹ Sergio Monraz-Pérez,¹ Robinson Emmanuel Robles-Hernández,¹ Mario Rodríguez-Vega,⁷ José Luis Mayorga-Butrón⁸

Co-authors

Luis Adrián Rendón-Pérez,⁸ Sebastián Rodríguez-Llamazares,¹ Andrés Palomar Lever,⁹ Saraí del Carmen Toral-Freyre,^{1,10} Alejandra Ramírez-Venegas,¹ Janet Real-Ramírez,¹¹ Dulce González-Islas,¹ Aloisia Paloma Hernández-Morales,¹ Eusebio Pérez-Flores,¹ Teresa Aguirre-Pérez,¹ Olivia Sánchez-Cabral,¹ Francina Valezka Bolaños-Morales,¹ Moisés Acuña-Kaldman,¹² Jonathan Álvarez-Pinto,¹³ José Omar Barreto-Rodríguez,¹ Rosaura Esperanza Benítez-Pérez,¹ Josué Daniel Cadeza-Aguilar,¹ Robert Camargo-Ángeles,¹⁴ Rafael Patricio Castañón-Rodríguez,¹ Andrea Alicia Colli-Domínguez,¹⁵ María Guadalupe Espitia-Hernández,¹⁶ Rogelio Alejandro García-Torrentera,¹ Julio Edgardo González-Aguirre,³ Fernando Carlos Guillén-Ortega,¹⁷ Simón Hernández-Campos,¹⁸ José Carlos Herrera-García,¹⁹ Ricardo Lemus-Rangel,²⁰ Marco Antonio Loustaunau-Andrade,²¹ Gerardo Ezequiel Magdaleno-Maldonado,²² Fernando Morett-Vera,²³ Enrique Eduardo Olaya-López,²⁴ Rafael Francisco Páramo-Arroyo,²⁵ Ana Sofía Ramírez-García-Luna,²⁶ Luis Albrecht Septién-Estute,²⁷ Juan Silva-Gallardo,²⁸ Héctor Gleen Valdéz-López,²⁹ Alejandra Velázquez-Montero,¹ José Felipe Villegas-Elizondo,³ Edgar Gerardo Zozoaga-Velázquez³⁰

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.

¹Instituto Nacional de Enfermedades Respiratorias. Tlalpan, Ciudad de México.

²Instituto Nacional de Cancerología. Ciudad de México.

³Hospital Universitario "Dr. José Eleuterio González". Monterrey, Nuevo León.

⁴Hospital General de México "Dr. Eduardo Liceaga". Ciudad de México.

⁵Hospital Regional de Alta Especialidad de la Península de Yucatán-IMSS Bienestar. Yucatán.

⁶Hospital Ángeles Lomas. Ciudad de México.

⁷A2DAHT, Agencia Ibero Americana para el Desarrollo y Evaluación de Tecnologías de la Salud.

⁸Universidad Autónoma de Nuevo León. Monterrey, Nuevo León.

⁹Centro Médico ABC. Ciudad de México.

¹⁰Asociación Mexicana de Terapia Respiratoria, AC. Ciudad de México.

¹¹Instituto Nacional de Salud Pública. Ciudad de México.

¹²Facultad de Medicina de la Universidad de Sonora. Hermosillo, Sonora.

¹³Hospital Valentín Gómez Farías-ISSSTE. Zapopan, Jalisco.

- ¹⁴Centro Nacional de Programas Preventivos y Control de Enfermedades, CENAPRECE, Secretaría de Salud. Ciudad de México.
¹⁵NeumoLab, Oaxaca.
- ¹⁶Hospital Regional 1º de Octubre, ISSSTE. Ciudad de México.
- ¹⁷Hospital General Belisario Domínguez, ISSSTE. Tuxtla Gutiérrez, Chiapas.
- ¹⁸Hospital General 450, Secretaría de Salud. Durango, México.
- ¹⁹Universidad Popular del Estado de Puebla. Puebla, México.
- ²⁰Centro Médico Nacional La Raza, IMSS. Ciudad de México.
²¹ISSSTECALI UABC. Mexicali, Baja California.
- ²²Hospital Central Militar. Ciudad de México.
- ²³Hospital San Javier, Instituto de Pensiones del Estado de Jalisco. Guadalajara, Jalisco.
²⁴Hospital Español de México. Ciudad de México.
- ²⁵Hospital TEC 100, Universidad Anáhuac Querétaro. Querétaro, México.
- ²⁶Hospital Universitario de Puebla. Benemérita Universidad Autónoma de Puebla. Puebla, México.
- ²⁷Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Ciudad de México.
²⁸Instituto Mexicano del Seguro Social. México.
- ²⁹Hospital de Cardiología No. 34 del IMSS, Centro Médico Nacional del Noreste. Monterrey, Nuevo León.
³⁰UMAE Hospital de Especialidades Número 1 Bajío, IMSS. León, Guanajuato.

Correspondence:

Dr. Juan Carlos Vázquez García

CIEMBE, Coordinación de Investigación Educativa y Medicina Basada en Evidencia,
Dirección de Enseñanza, Instituto Nacional de Enfermedades Respiratorias.

E-mail: drjcvazquez@gmail.com

How to cite: Vázquez-García JC, Hernández-Zenteno RJ, Arroyo-Hernández M, Elizondo-Ríos A, Casillas-Suárez C, Cortés-Telles A, et al. Mexican Clinical Practice Guideline for COPD 2025. *Neumol Cir Torax*. 2025; 84 (Suppl. 1):s8-s104. <https://dx.doi.org/10.35366/119442>

Open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



ABSTRACT. Introducción: 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 consensaron 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	DWAE = difference of the weighted averages of the effects
95%CI = 95% confidence interval	EBV = endobronchial valves
AATD = Z-Alpha-1 antitrypsin deficiency	ENDS = electronic nicotine delivery systems
ACIP = Advisory Committee on Immunization Practices	FDA = Food and Drug Administration
ACS = Acute COPD Syndrome	FeNO = fractional exhaled nitric oxide
ADO = age, dyspnea and airflow obstruction	FEV ₁ = forced expiratory volume in 1 second
AF = atrial fibrillation	FEV ₁ /FVC = ratio of forced expiratory volume in 1 second to forced vital capacity
ALAT = Latin American Thoracic Association (for its Spanish meaning <i>Asociación Latinoamericana de Tórax</i>)	FiO ₂ = fraction of inspired oxygen
AMBMT = active mind-body movement therapies	FVC = forced vital capacity
ATS/ERS = American Thoracic Society/European Respiratory Society	GBD = global burden of disease
AUC = area under the curve	GDG = guideline development group
BCSS = breathlessness, cough, and sputum scale	GesEPOC = Spanish COPD guidelines (for its Spanish meaning <i>Guía Española de la EPOC</i>)
BDI = baseline dyspnea index	GMEPOC = Mexican clinical practice guideline on COPD (for its Spanish meaning <i>Guía de Práctica Clínica Mexicana de EPOC</i>)
BMI = body mass index	GOLD = Global Initiative for Chronic Obstructive Lung Disease
BODE = body mass index, obstruction, dyspnea, and exercise capacity	GRADE = Grading of Recommendations Assessment, Development and Evaluation
BODEx = body mass index, obstruction, dyspnea, and exacerbations	HEPA = high efficiency particle arrester
BODEx-S90 = body mass index, obstruction, dyspnea, exacerbations and oxygen saturation less than 90%	HFNC = high flow nasal cannula
BOSA-90 = body mass index, obstruction, smoke, age, SpO ₂ < 90	HIV = human immunodeficiency virus
BOSEA-90 = body mass index, obstruction, smoke, exercise, age, SpO ₂ < 90	HR = hazard ratio
BTVA = bronchoscopic thermal vapor ablation	HZ = herpes zoster
CAPTURE = COPD assessment in primary care to identify undiagnosed respiratory disease and exacerbation risk	ICS = inhaled corticosteroids
CAT = COPD assessment test	ICSI = Institute for Clinical System Improvement
CC16 = club cell secretory protein-16	IgG = immunoglobulin G
CCQ = clinical COPD questionnaire	IMT = inspiratory muscle training
CCT = controlled clinical trials	IMV = invasive mechanical ventilation
CDC = Centers for Disease Control and Prevention	INEGI = National Institute of Statistics and Geography (for its Spanish meaning <i>Instituto Nacional de Estadística y Geografía</i>)
CDQ = COPD diagnostic questionnaire	INER = National Institute of Respiratory Diseases Ismael Cosío Villegas (for its Spanish meaning <i>Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas</i>)
CERT = COPD exacerbation recognition tool	IPAG = International Primary Care Airway Group questionnaire
CG = core group	LABA = long-acting beta-agonist
CO = carbon monoxide	LAMA = long-acting muscarinic antagonist
COPD = chronic obstructive pulmonary disease	LFQ = lung function questionnaire
COPD-PS = COPD population screener	LLN = lower limit of normal
COTE = COPD-specific comorbidity test	LTOT = long-term oxygen therapy
COVID-19 = infectious disease caused by Coronavirus	MCID = minimal clinically important difference
CPG = clinical practice guidelines	MD = mean difference
CRP = C-reactive protein	MDI = metered-dose inhaler
CRQ = chronic respiratory questionnaire	MLD = mean lung density
CT = computed tomography	mMRC = modified medical research council
CTGS = comprehensive treatment goals and strategies	NAC = N-acetyl cysteine
DLCO = diffusing capacity of the lungs for carbon monoxide	NHANES III = national health and nutrition examination survey
DOSE = dyspnea, obstruction, smoking and exacerbations	NICE = National Institute for Clinical Excellence

NIV = non-invasive ventilation	RV = residual volume
NNT = number needed to be treated	SABA = short-acting beta-agonists
NO ₂ = nitrogen dioxide	SAMA = short-acting muscarinic antagonists
NST or NRT = nicotine substitution or replacement therapy	SaO ₂ = arterial oxygen saturation
NZGG = New Zealand Guidelines Group	SGRQ = Saint George's respiratory questionnaire
OR = odds ratio	SIGN = Scottish Intercollegiate Guidelines Network
PaCO ₂ = partial pressure of carbon dioxide	SLR = systematic literature reviews
PaO ₂ = partial pressure of oxygen in arterial blood	SMD = standardized mean difference
PCV = pneumococcal conjugate vaccine	SMNyCT = Mexican Society of Pneumology and Thoracic Surgery (for its Spanish meaning <i>Sociedad Mexicana de Neumología y Cirugía de Tórax, A.C.</i>)
PDE ₄ = phosphodiesterase-4	SO ₂ = sulfur dioxide
PEF = peak expiratory flow	SP-D = surfactant protein D
PICO = population, intervention, comparison and outcome	SpO ₂ = partial oxygen saturation
Pimax = maximum inspiratory mouth pressure	sRAGE = soluble receptor for advanced glycation end products
PLATINO = Latin American Research Project on Pulmonary Obstruction (for its Spanish meaning <i>Proyecto LATinoamericano de Investigación en Obstrucción pulmonar</i>)	Tdap = tetanus, diphtheria and pertussis
PLATINOq = PLATINO questionnaire	TDI = transition dyspnea index
PM ₁₀ = particulate matter less than 10 microns	TIO/OLO = tiotropium and olodaterol
PM _{2.5} = particulate matter less than 2.5 microns	TLC = total lung capacity
PPSV23 = polysaccharide vaccines	TS90 = total sleep time with SaO ₂ < 90%.
PR = pulmonary rehabilitation	UMEC/VI = umeclidinium and vilanterol
PRISm = preserved ratio impaired spirometry	USPSTF = United States Preventive Services Task Force
PTS = pneumology and thoracic surgery	V/Q = ventilation/perfusion
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 <i>Prevalencia y práctica habitual (diagnóstico y tratamiento) en población de riesgo de EPOC en Médicos generales de cuatro países de América Latina</i>)	VA = ventricular arrhythmias
RR = relative risk	VAFOSQ = Veterans' Airflow Screening Questionnaire
Rrs = resistance	VF = ventricular fibrillation
RSV = respiratory syncytial virus	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

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

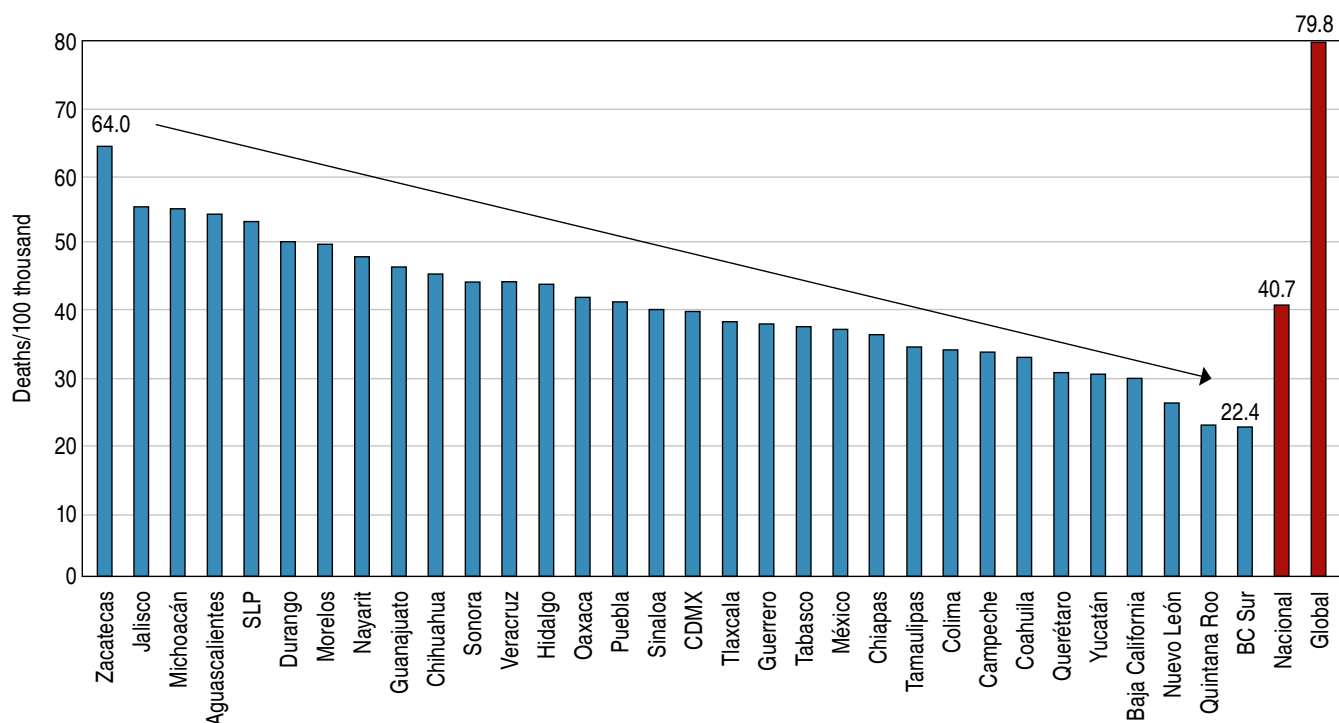


Figure 1: COPD mortality rate in Mexico, 2021.

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

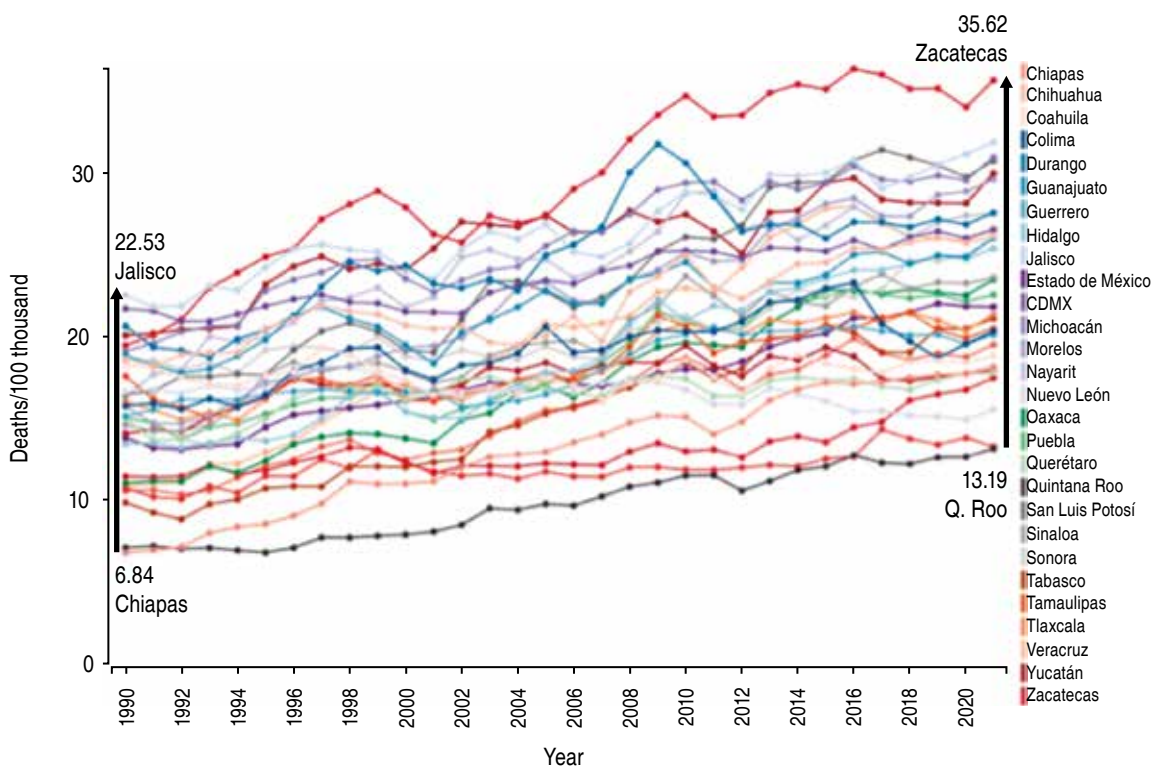


Figure 2: COPD mortality rate in Mexico from 1990 to 2021.

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

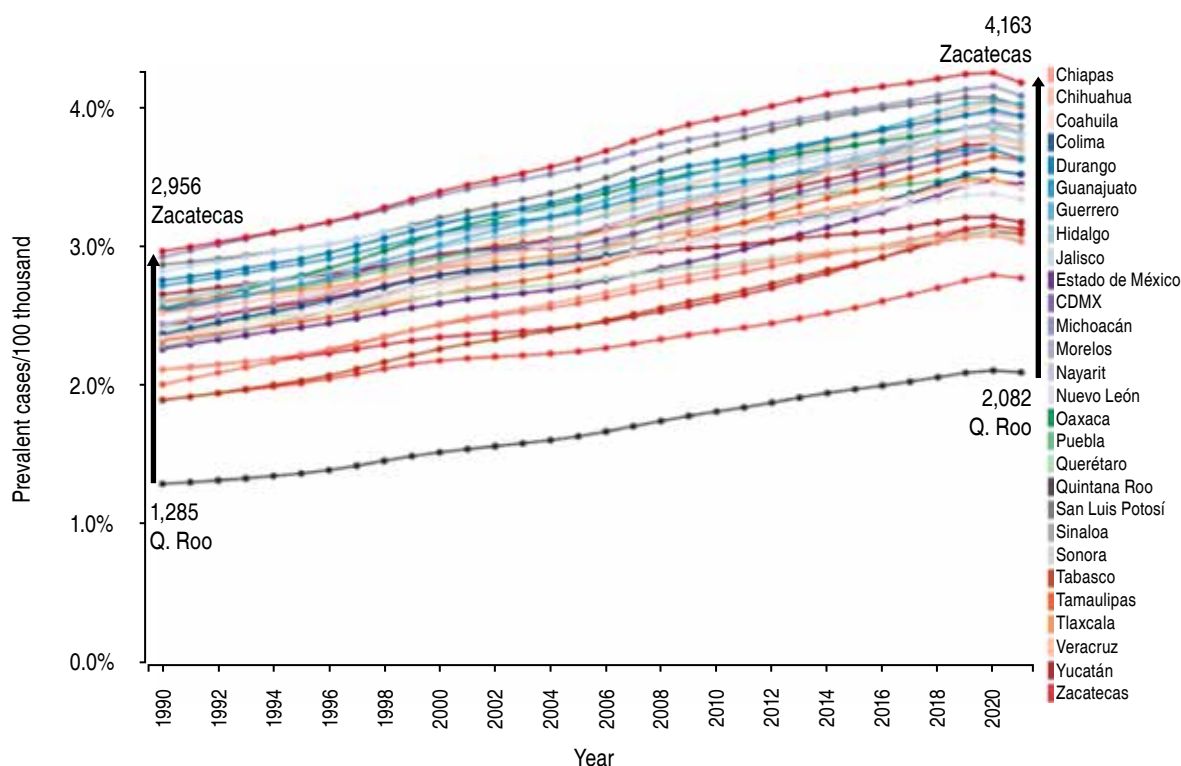


Figure 3: Prevalent cases of COPD in Mexico from 1990 to 2021.

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

\$1,255

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

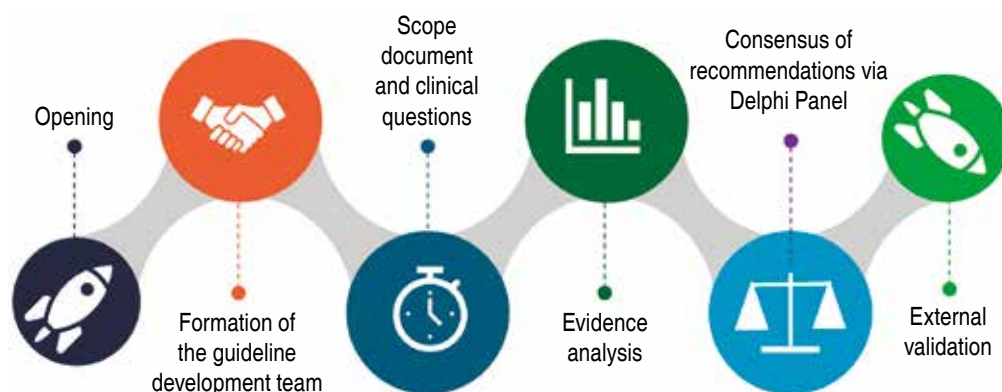


Figure 4:

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?

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 SLR¹⁸ (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.

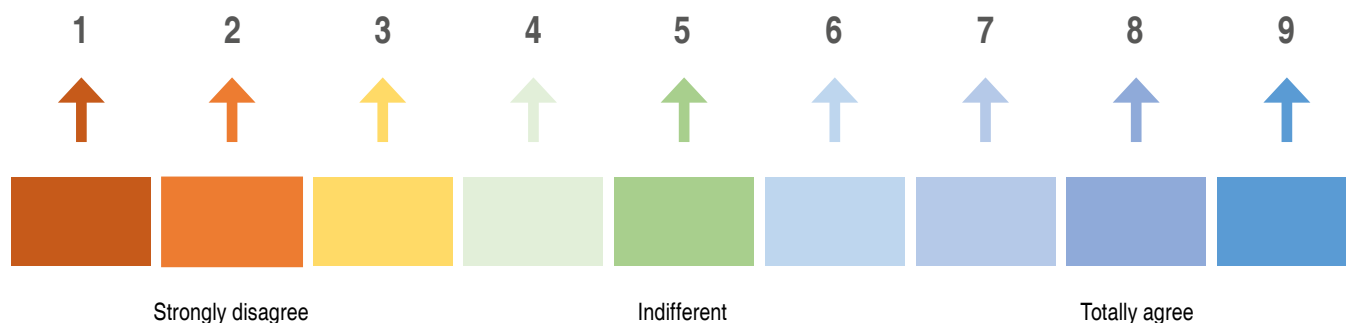


Figure 5: Likert scale used in the modified Delphi Panel.

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.

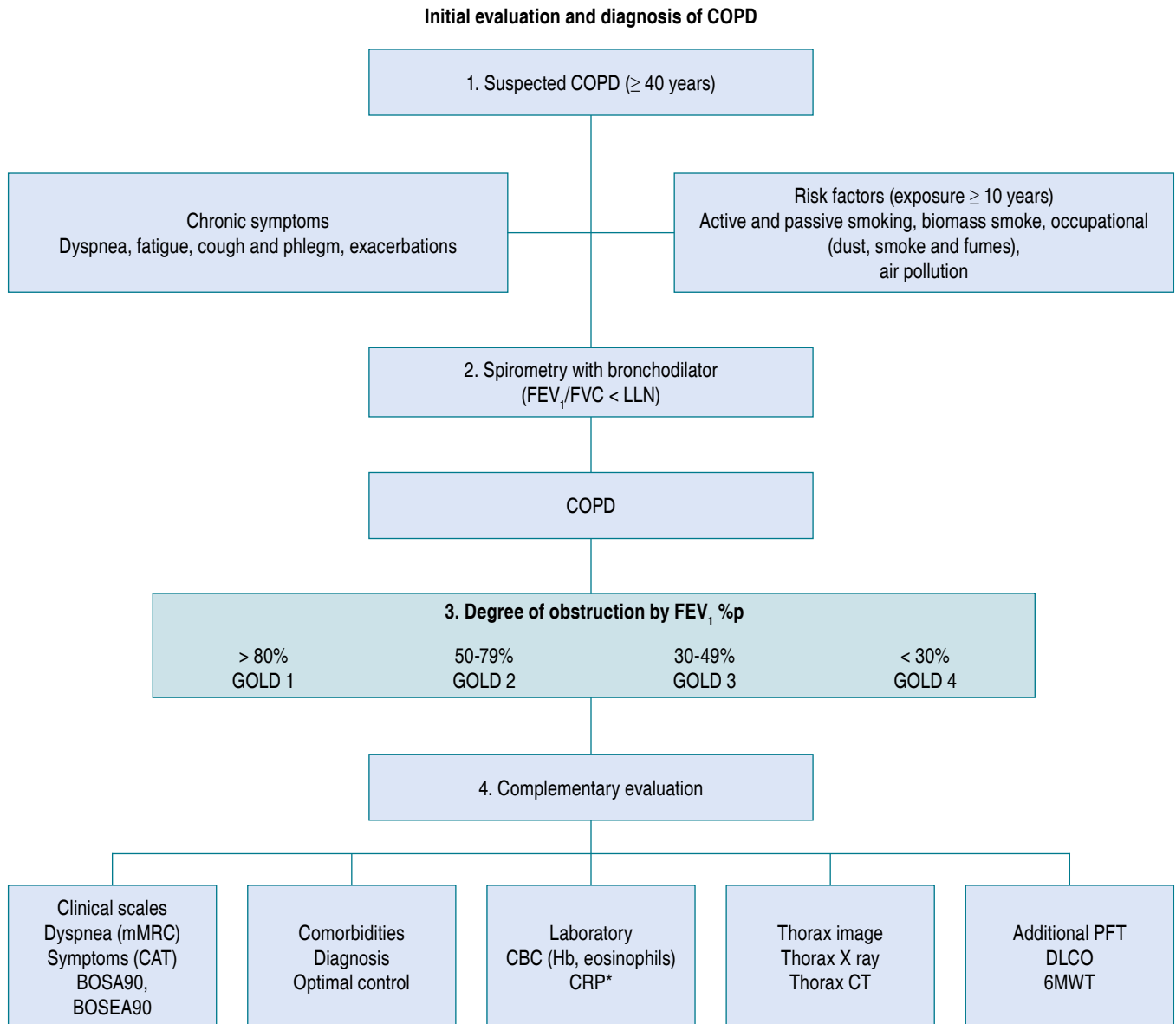
EVALUATION AND DIAGNOSIS OF COPD

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/ μ L) 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 weight²¹ (Body mass index), degree of airflow Obstruction, active Smoking, low Exercise 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.

FEV₁ = 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

COPD²³ 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 FEV₁/FVC ratio > 0.70 after bronchodilator, but with an FEV₁ 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 (PM₁₀ and PM_{2.5}).**⁵² Contributes up to 35% to the increased prevalence of COPD⁵³ (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 <i>et al.</i> , 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. The time it takes for a smoker to develop COPD is approximately 30 years
Forey <i>et al.</i> , 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) 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) 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 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 <i>et al.</i> , 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 <i>et al.</i> , 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. 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 <i>et al.</i> , 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 PM₁₀), sulfur dioxide (SO₂) and nitrogen dioxide (NO₂), and COPD morbidity and mortality. Exposure to SO₂ (RR 1.012, 95%CI 1.001-1.023) and NO₂ (RR 1.019, 95%CI 1.014-1.024). An increase of 10 µg/m³ in NO₂ showed an HR of 1.07 (95%CI 1.00-1.16),^{41,57} while an increase of 10 µg/m³ 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

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.

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}

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 areas⁸⁶ (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 studies⁷³					
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 PLATINO: 66.7	Montevideo: 62.1 PLATINO: 66.5	–	70.9 89.9
Colombia, Venezuela, Uruguay, 2016. ⁸⁹	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 CAPTURE + peak flow meter	95.7 89.7	44.4 78.1	–	–
Mexico, 2013. ⁸⁵	PLATINOq + pocket spirometer (cut-off point ≥ 10)	PLATINOq 82-92 PLATINOq + Spirometer 64-70	PLATINOq 47 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.

VAFOSQ = 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++ 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 FEV₁/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 ≥ 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++ 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 FEV₁/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 FEV₁/FVC value of 0.7.^{25,28,89} However, the FEV₁/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 FEV₁/FVC ratio accompanied by a FEV₁ 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 FEV₁/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 FEV₁ 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 FEV₁/FVC ratio, the severity of the airflow obstruction must be graduated. GOLD 2025 continues to recommend using the percentage of the predicted post-bronchodilator FEV₁ for definition purposes and with the following stages of severity: mild FEV₁ ≥ 80% (GOLD 1); moderate, FEV₁ from 50 to 79% (GOLD 2); severe, FEV₁ from 30 to 49% (GOLD 3); and very severe, FEV₁ < 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 FEV₁ 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+ Recommendation C

2	Pulse Oximetry (SpO₂): 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++ 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+ 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++ 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+ 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 (SpO₂) at rest. The oxygen saturation measure by oximetry can identify candidates for oxygen therapy. In patients with COPD and hypoxemia (PaO₂ < 55 mmHg and/or arterial oxygen saturation (SaO₂) < 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 PCO₂ and acid base status, which is essential to identify patients with hypercapnic respiratory failure (PaCO₂ 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 (SpO₂) < 92% at sea level²⁸ or SpO₂ < 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 (R²: 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 established.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. 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– 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). 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. Its quantitative analysis requires iterative reconstructions of the volumetric analysis in inspiration and expiration, so it can define early disease.	Evidence 1+ 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 FEV₁ 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 FEV₁/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 collapse of the airways on exhalation.¹⁰¹

Quantitative analysis of CT gives information about the severity and prognosis. Emphysema is associated with accelerated loss of FEV₁, 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 (FEV₁% pred and FEV₁/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+ 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++ 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+ 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 $\times 10^6/\text{mL}$ [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 $1 \times 10^3/\text{mm}^3$ 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/ μ L, 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 $\geq 2\%$ of eosinophils (RR 0.80, 95%CI 0.74-0.85), 35% with ≥ 150 cells/ μ L (RR 0.65, 95%CI 0.52-0.79) and 39% with ≥ 300 cells/ μ L (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/ μ L.²⁸ Suggested indicate triple therapy (LABA + LAMA + ICS) to exacerbator patients, with greater benefit in those with eosinophil levels ≥ 100 cells/ μ L.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: FEV₁ with a standardized mean difference (SMD)¹⁶⁶ of 1.21 (95%CI 0.76-1.66, $p < 0.01$), FEV₁/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 FEV₁ (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+ Recommendation B

2	<p>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 obstruction, active 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.</p>	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 reevaluation

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



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).

COPD Assessment Test and the CAT logo are trademarks of the GSK group of companies. ©2009-2022 GSK group of companies or its licensor. All rights reserved www.CATestonline.org (<https://www.catestonline.org/patient-site-test-page-english.html>).¹⁷⁸

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: OR 3.2 (95%CI 2.0-5.0, p < 0.0001) 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: OR 5.6 (95%CI 3.2-9.7, p < 0.001) OR 2.57 (95%CI 1.90-3.47, p < 0.0001) Main cause of hospitalization and death in COPD patients younger than 65 years of age
	Angina pectoris ²⁰¹	15.8%	Greater probability in COPD: 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: OR 1.33 (95%CI 1.13-1.56, p = 0.0007) OR 1.45 (95%CI 1.31-1.61, p < 0.00001) 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: OR 9 (95%CI 0.06-0.12) OR 12 (95%CI 9-16) OR 17.2 (95%CI 13.4-21.3) 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 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). More risk of ventricular arrhythmias (VA): RR 2.01 (95%CI 1.42-2.85). VF + sudden death 21.4% VT + asystole 5.7%	Meta-OR 1.94 (95%CI 1.55-2.43, p < 0.0001) AF is associated with reduction in FEV ₁ 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) 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) 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%. Inpatient 10-55%	Patients with anxiety and/or depression have a first hospitalization for COPD earlier The effect of anxiety on treatment adherence is not clear due to the heterogeneity of the data
	Depression ²²⁶⁻²²⁸	Stable COPD 10-42% Acute exacerbation 10-86%	Three times more likely to fail prescribed medication, exercise, diet, and health-related behaviors 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%CI 11.8-33.3)	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. FEV₁ = 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 Respirat. VT = ventricular tachycardia. UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium.

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 (FEV₁), 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 proposes¹⁰ 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 (FEV₁), 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 PaO₂ ≤ 55 mmHg or SpO₂ ≤ 88% or with a PaO₂ between 56-59 mmHg or SpO₂ de 89-90%, with evidence of pulmonary hypertension, right heart failure or polycythemia (hematocrit ≥ 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.

Goals and strategies of comprehensive treatment in stable COPD with focus on prognostic variables

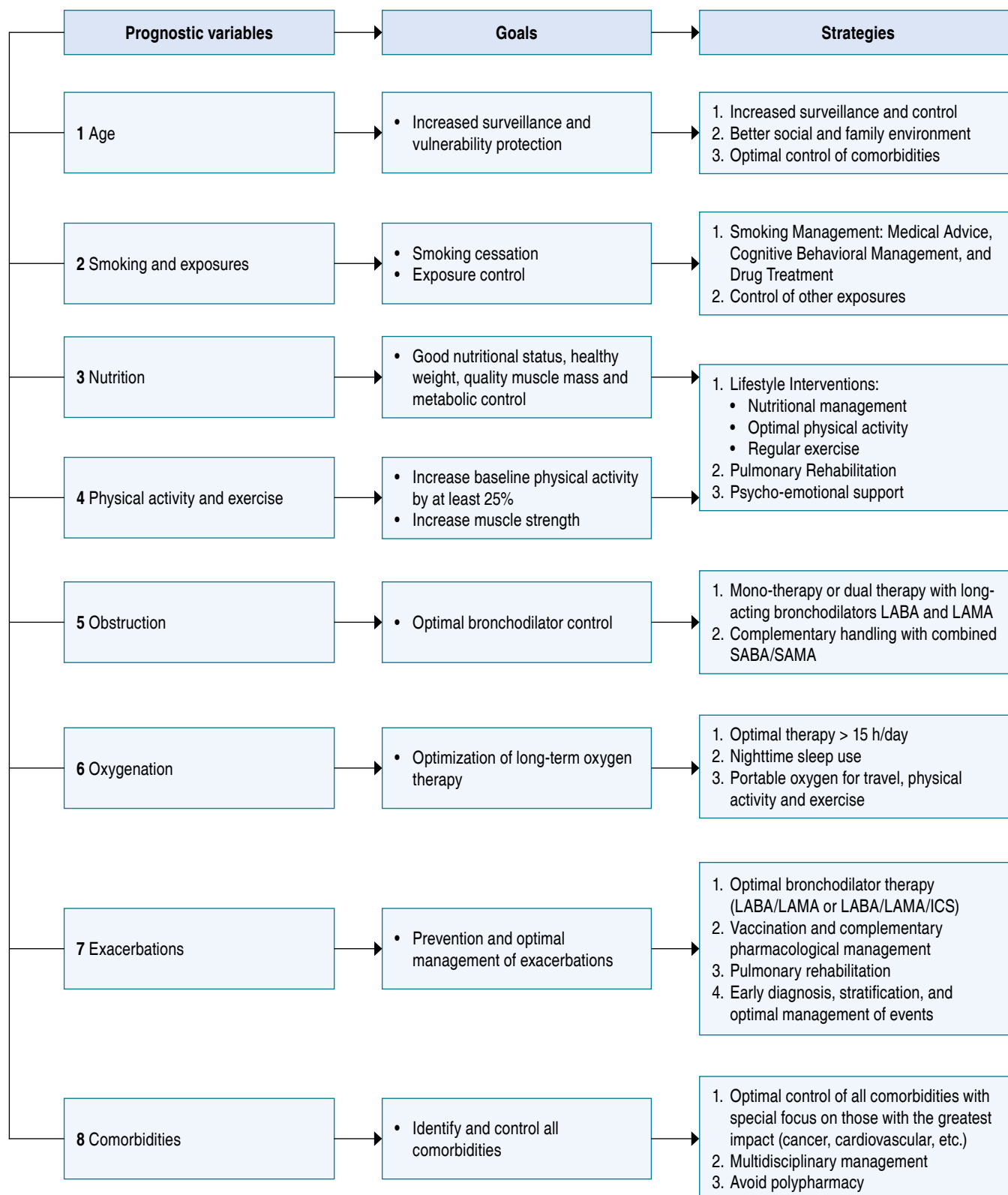


Figure 8.

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+ 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+ 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+ 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 success 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 success 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 \leq 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 intradomestic 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 $\mu\text{g}/\text{m}^3$. 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 FEV₁ (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 NO₂. 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 FEV₁ 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 FEV₁/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+ 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 FEV₁ 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 FEV₁) 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 FEV₁ values. A controlled clinical trial reported that changing diet to a diet rich in fruits and vegetables was associated with increased FEV₁ 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 FEV₁ 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++ Recommendation A
2	The use of oral bronchodilators is not recommended.	Evidence 3 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++ 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++ 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– Recommendation C
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+ Recommendation B	Recommendations for monotherapy, dual therapy and inhaled triple therapy		
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+ Recommendation B	1	Inhaled monotherapy (LABA or LABA): at all levels of care, initial and maintenance inhaled therapy with a single long-acting bronchodilator (LABA 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+ Recommendation A
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+ Recommendation B	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++ Recommendation A
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+ 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 ($CAT \geq 10$) 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/ μ L. 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/ μ L). Patients under this treatment condition should preferably be treated or supervised at the second or third level of care. | Evidence 1+
Recommendation A |
|---|--|---------------------------------|

- | | | |
|---|--|---------------------------------|
| 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/ μ L) 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 β_2 -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

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/ μ L. 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 |
|---|---|---------------------------------|

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 FEV₁ at 12 and 24 weeks compared with placebo. At 12 weeks, umeclidinium showed the greatest increase in FEV₁ (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 FEV₁, 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 FEV₁ 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 FEV₁ (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 FEV₁ (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 FEV₁ 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/ μ L; and 2) those with exacerbations despite dual therapy (LABA/LAMA) and who have an eosinophil count ≥ 100 cells/ μ L. 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 FEV₁ (+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 FEV₁ (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 FEV₁ (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/ μ L–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, FEV₁ 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 FEV₁, although an increase in exacerbations was observed in patients with eosinophils ≥ 300 cells/ μ L (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	<p>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.</p>	Evidence 1+ Recommendation B
2	<p>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.</p> <p>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.</p>	Evidence 1- Recommendation B Evidence 1+ Recommendation A

3	<p>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.</p>	Evidence 1+ Recommendation B
4	<p>Mucolytics: in selected patients, mucolytics may improve respiratory symptoms (chronic bronchitis). However, they do not impact clinical outcomes such as exacerbation reduction and survival.</p>	Evidence 1+ 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

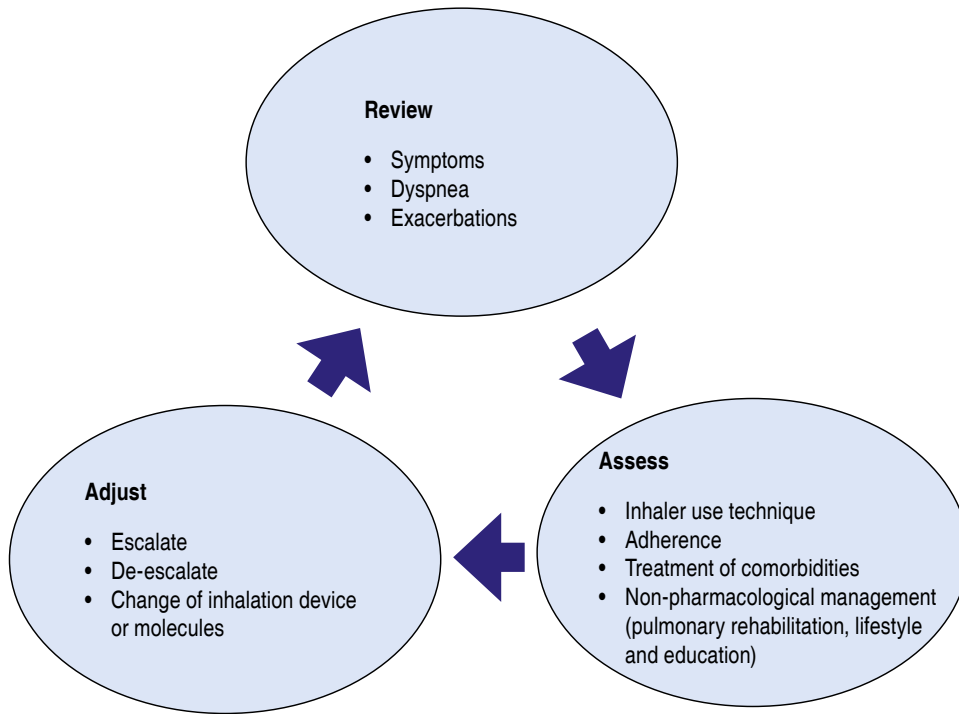


Figure 9:

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 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 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 Patients on triple therapy who persist with exacerbations should receive additional medication**

CAT = COPD Assessment Test. FEV₁, %p = percentage of predicted forced expiratory volume in one second. mMRC = modified Medical Research Council scale.

* The FEV₁ 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 (PDE₄) isoenzyme; they inhibit inflammation by preventing the degradation of cAMP (intracellular cyclic adenosine monophosphate). The PDE₄ 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 FEV₁ 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/ μ L) 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%CI 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 carbocysteine, 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 needed 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, FEV₁, 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++ 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++ Recommendation A

exercise or rehabilitation periods) under one of the following internationally standardized criteria and regardless of the altitude of the location:

1. PaO₂ with levels ≤ 55 mmHg or SpO₂ ≤ 88% with or without hypercapnia and confirmed on two occasions within a three-week period
2. PaO₂ between 56-59 mmHg or SpO₂ of 89-90%, but with evidence of pulmonary hypertension, right heart failure or polycythemia (hematocrit ≥ 55%).

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 | <p>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.</p> | Evidence 1+ Recommendation B |
| 3 | <p>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.</p> | Evidence 1++ Recommendation A |
| 4 | <p>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.</p> | Evidence 1+ Recommendation B |
| 5 | <p>Oxygen use during travel: At all levels of care, patients with COPD planning air or ground travel</p> | Evidence 3 Recommendation C |

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 PaO₂ > 50 mmHg, which can be achieved with a flow rate of three liters per minute with nasal prongs or FiO₂ 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}

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.

- | | | |
|---|---|-----------------------------|
| 6 | <p>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 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. 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</p> | Evidence 3 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 | <p>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.</p> | <p>Evidence 4
Recommendation
D</p> |
|---|--|--|

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. PaO₂ levels ≤ 55 mmHg or SpO₂ ≤ 88% with or without hypercapnia; confirmed twice within a three-week period.
2. PaO₂ between 56-59 mmHg or SpO₂ 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 (PaO₂ ≤ 55 mmHg), but not when hypoxemia is moderate (PaO₂ 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 (PaO₂ 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) PaO₂ ≤ 55 mmHg or SpO₂ ≤ 88% with or without hypercapnia, confirmed twice within a three-week period; and 2) PaO₂ between 56-59 mmHg or SpO₂ 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 PaO₂ > 50 mmHg or SpO₂ > 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 ($\text{PaO}_2 \leq 55$ 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 $\text{PaO}_2 \leq 55$ 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 ($\text{PaO}_2 > 55$ 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 ($\text{PaO}_2 > 55$ mmHg) but who had nocturnal oxygen desaturation, defined as an $\text{SpO}_2 < 90\%$ 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 ($\text{PaO}_2 < 55$ mmHg or $\text{SpO}_2 < 88\%$). Patients already using oxygen therapy should continue using it during the flight to maintain a $\text{PaO}_2 > 50$ 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 across 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 PaCO₂ (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 PaO₂ (MD -0.36, 95%CI -2.23-1.54). In chronic hypercapnia, HFNC did not significantly reduce PaCO₂ (MD -1.21, 95%CI -3.81-1.39) or PaO₂ (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		
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+ 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- 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

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.

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+ 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
- Evidence 1+ Recommendation B

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.

- 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+ 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. 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+ 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 2. Weights with machines 3. Elastic bands 4. Electrical stimulation 5. Tubes 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 2. Walking on a treadmill 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 2. 0-80% of 1 OR	1. Walk once a day 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 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

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+ 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 FEV₁ 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 FEV₁ of 0.09 L (95%CI 0.06-0.12) at three months and an improvement in FEV₁ 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 FEV₁ (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 FEV₁, 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 FEV₁ 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 FEV₁, 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 FEV₁; however, post-lung transplant FEV₁ was significantly higher than post-volume reduction FEV₁ 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 ($> 3\%$ SpO₂) 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 SpO₂, 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, PaO₂ < 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 SpO₂ 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 2025³ 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 ($\text{PaO}_2 < 40$ mmHg and/or $\text{pH} < 7.25$) or indication for invasive mechanical ventilation, should be considered for admission and management in the intensive care unit (ICU). | Evidence 2++
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 criteria³ 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 ($\text{PaO}_2 < 60$ or $\text{SpO}_2 < 90\%$; $\text{PaCO}_2 > 60$ mmHg and $\text{pH} < 7.30$).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+ Recommendation A
2	<p>Bronchodilators:</p> <ul style="list-style-type: none"> • 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++ 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.

- 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.
- Routine use of bronchodilators such as methylxanthines (theophylline or aminophylline) is not recommended due to reduced therapeutic effectiveness and significant side effects.

3 Corticosteroids:

- 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.
- 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++
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+ 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+ 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 (FEV₁) 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

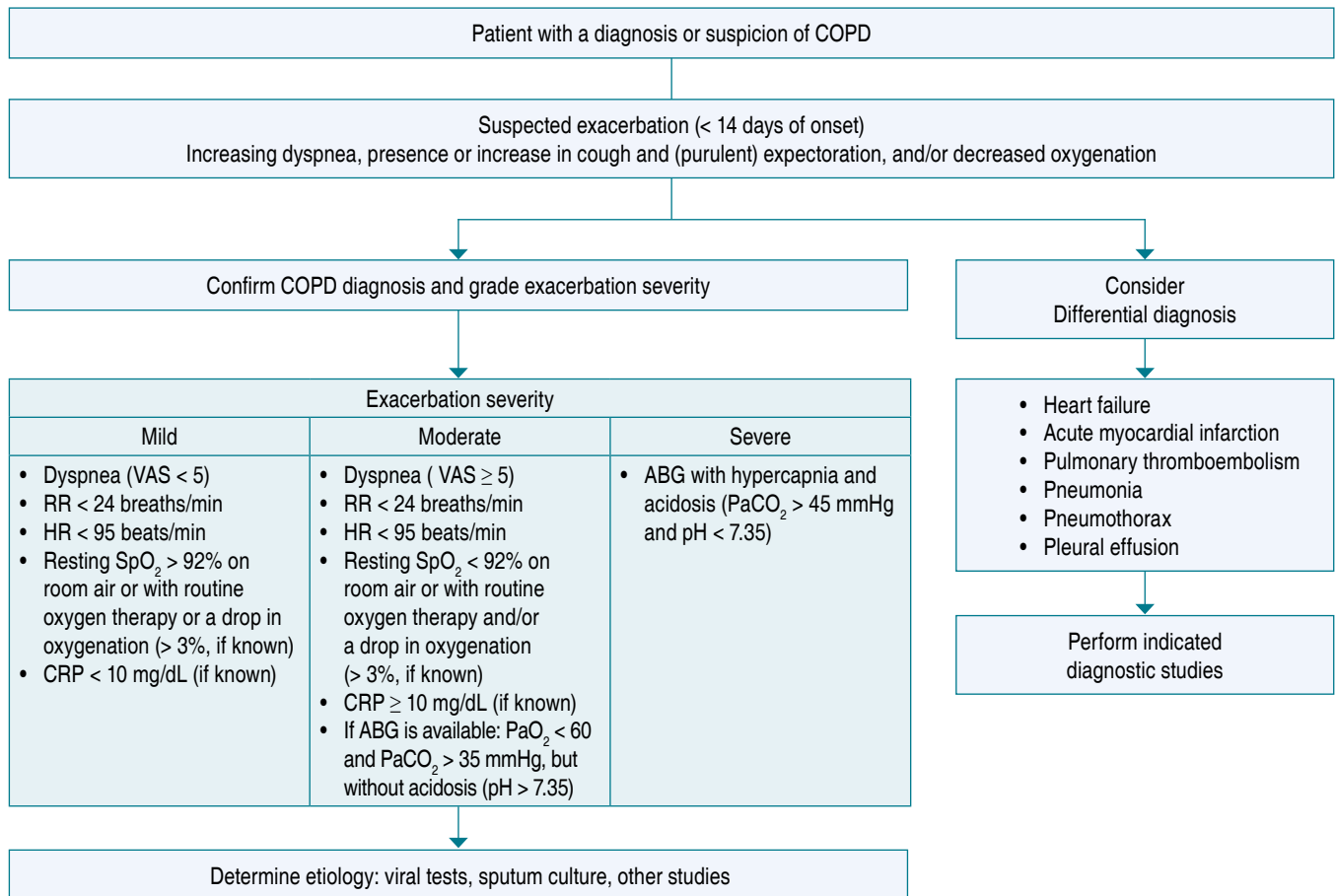


Figure 10: Rome proposal for classifying the severity of COPD exacerbations. In Mexico, it is recommended that SpO₂ and PaCO₂ values be adjusted according to altitude. For example, in Mexico City, at 2,240 m above sea level, an SpO₂ value of 88% is recommended as the lower limit of normal¹⁰⁷ and a PaCO₂ 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

PaCO₂ associated with simultaneous administration of bronchodilators and oxygen.³

Corticosteroids. GOLD 2025 states that systemic corticosteroids shorten recovery time, improve lung function (FEV₁), 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/ERS⁴⁴⁷ 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 FEV₁ 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 daily⁴⁵⁷⁻⁴⁵⁹ 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.

<ul style="list-style-type: none"> • 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 (SpO₂ > 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
<ul style="list-style-type: none"> • Severe symptoms such as dyspnea at rest, significant tachypnea, decreased oxygenation, and altered alertness • Acute respiratory failure (PaO₂ < 50 mmHg and/or pH < 7.35) • New-onset signs such as cyanosis and peripheral edema • Lack of improvement with initial outpatient management (< 24 hours) • Need for respiratory support: high-flow nasal prongs or noninvasive ventilation • Severe comorbidity (differential diagnoses): heart failure, acute myocardial infarction, pulmonary thromboembolism, pneumonia, pneumothorax, pleural effusion, others) • Inadequate home care 	<ul style="list-style-type: none"> • Severe dyspnea unresponsive to initial management • Changes in mental status and alertness (confusion, lethargy, or coma) • Severe worsening of hypoxemia (PaO₂ < 40 mmHg) or severe respiratory acidosis (pH < 7.25) • Indication for invasive mechanical ventilation • Hemodynamic instability and/or vasopressor requirement

Modified admission criteria from the recommendations of the GesEPOC 2021³⁵⁷ and GOLD 2025³ 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: <ul style="list-style-type: none"> • Every patient with suspected moderate or severe COPD exacerbation (Rome Proposal) in second or third level of care, 	Evidence 4 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^-).

- 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.

- 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++
Recommendation
C

Evidence 4
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–
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++
Recommendation
B

5 Invasive mechanical ventilation (IMV):

- 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 ($\text{FEV}_1 < 30\%$) and association with comorbidities.
- 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+
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 ($\text{PaO}_2 < 60$ mmHg and/or $\text{SpO}_2 < 88\%$). 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 ($\text{FiO}_2 > 28\%$) 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 PaCO₂ 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 PaO₂ (MD -0.36, 95%CI -2.23-1.54). In chronic hypercapnia, HFNC did not significantly reduce PaCO₂ (MD -1.21, 95%CI -3.81-1.39) or PaO₂ (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 (PaO₂) was reported 1 hour after treatment, but no improvement in PaCO₂. 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 × 10⁹/L or reduction of leukocytes by 2 × 10⁹/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 (FEV₁ < 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	<p>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 tapering 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</p>

Evidence 1+
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 ($\text{PaO}_2 \geq 55$ mmHg or $\text{SpO}_2 \geq 88\%$ 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 maintenance, 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 PaCO₂ 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 assistance, 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.

Acknowledgments

The authors would like to thank Vanessa Escárcega, logistics coordinator of SMNyCT, Leonor Mota Morales, administrative assistant at CIEMBE, INER, and Gustavo Giraldo Buitrago (INER and SMNyCT) for their logistical and administrative assistance in the development of GMEPOC 2025.

Funding: this Guide was sponsored with unrestricted financial support for education and/or research for the Mexican Society of Pulmonology and Thoracic Surgery by: Boehringer Ingelheim, GSK, AstraZeneca and Chiesi.

Conflict of interest declaration: JL Mayorga Buitrón, M Arroyo Hernández, and M Rodríguez Vega declare having received honoraria as part of the independent methodological group (A2DAHT). The other authors declare no conflict of interest.

REFERENCES

1. IHME. Institute for health metrics and evaluation. Global burden of disease 2021: findings from the GBD 2021 study. Seattle, WA2021. Available in: <https://www.healthdata.org/research-analysis/library/global-burden-disease-2021-findings-gbd-2021-study>
2. Perez-Padilla JR, Thirion-Romero I, Robles-Hernández R, Cagney J, Razo C, Ríos-Blancas MJ. Respiratory diseases in Mexico: analysis from the Global Burden of Disease study 2021. *Gac Med Mex.* 2023;159(6):582-595. Available in: <http://doi.org/10.24875/GMM.M24000840>
3. 2025 Gold Report. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. 2025. Available in: www.goldcopd.org
4. Vázquez-García JC, Hernández-Zenteno RJ, Pérez-Padilla JR, Cano-Salas MC, Fernández-Vega M, Salas-Hernández J, et al. Guía de Práctica Clínica Mexicana para el diagnóstico y tratamiento de la Enfermedad Pulmonar Obstructiva Crónica. Guía mexicana de EPOC, 2020. *Neumol Cir Tórax.* 2019;78(Supl. 1):4-76. Available in: <http://doi.org/doi:10.35366/NTS191A>
5. INEGI. Estadísticas de defunciones registradas (EDR). Comunicado de prensa número 661/24 8 de noviembre de 2024.; 2024. Available in: https://www.inegi.org.mx/contenidos/saladeprensa/boletines/2024/EDR/EDR2023_Dtivas.pdf
6. Menezes AM, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, Valdivia G, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet.* 2005;366(9500):1875-1881. Available in: [http://doi.org/10.1016/S0140-6736\(05\)67632-5](http://doi.org/10.1016/S0140-6736(05)67632-5)
7. Perez-Padilla R, Menezes AMB. Chronic obstructive pulmonary disease in Latin America. *Ann Glob Health.* 2019;85(1):7. Available in: <http://doi.org/10.5334/aogh.2418>
8. Franco-Marina F, Fernandez-Plata R, Torre-Bouscoulet L, Garcia-Sancho C, Sanchez-Gallen E, Martinez D, et al. Efficient screening for COPD using three steps: a cross-sectional study in Mexico City. *NPJ Prim Care Respir Med.* 2014;24:14002. Available in: <http://doi.org/10.1038/npjpcrm.2014.2>
9. Ramirez-Venegas A, Velazquez-Uncal M, Perez-Hernandez R, Guzman-Bouilloud NE, Falfan-Valencia R, Mayar-Maya ME, et al. Prevalence of COPD and respiratory symptoms associated with biomass smoke exposure in a suburban area. *Int J Chron Obstruct Pulmon Dis.* 2018;13:1727-1734. Available in: <http://doi.org/10.2147/COPD.S156409>
10. Regalado J, Perez-Padilla R, Sansores R, Paramo Ramirez JI, Brauer M, Pare P, et al. The effect of biomass burning on respiratory symptoms and lung function in rural Mexican women. *Am J Respir Crit Care Med.* 2006;174(8):901-905. Available in: <http://doi.org/10.1164/rccm.200503-479OC>
11. Talamo C, De Oca MM, Halbert R, Perez-Padilla R, Jardim JR, Muino A, et al. Diagnostic labeling of COPD in five Latin American cities. *Chest.* 2007;131(1):60-67. Available in: <http://doi.org/10.1378/chest.06-1149>
12. Lamprecht B, Soriano JB, Studnicka M, Kaiser B, Vanfleteren LE, Gnatiuc L, et al. Determinants of underdiagnosis of COPD in national and international surveys. *Chest.* 2015;148(4):971-985. Available in: <http://doi.org/10.1378/chest.14-2535>
13. Reynales-Shigematsu LM. Costos de atención médica de las enfermedades atribuibles al consumo de tabaco en América: revisión de la literatura. *Salud pública Méx [Revista en la Internet].* 2006;48:S190-S200. Available in: http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S0036-36342006000700023&lng=es
14. Fernández-Plata R, Martínez-Briseño D, García-Sancho F, Cano-Jimenez D, Ramírez-Venegas A, Sansores-Martínez R, et al. Métodos para la estimación de costos en salud de la EPOC: resultados basales. *Neumol Cir Tórax.* 2016;75(1):4-11.
15. Zenteno R, Lemus-Rangel R, Martínez-Pacheco V, Guzmán-Vázquez S, Soto-Molina H, Juárez K, et al. Evaluation of the cost in patients with chronic obstructive pulmonary disease (COPD) within the public health perspective in Mexico. *Value in Health.* 2022;25(7):S340.
16. Mannino DM. Counting costs in COPD: what do the numbers mean? *Chest.* 2015;147(1):3-5. Available in: <http://doi.org/10.1378/chest.14-1976>
17. Carrera-Rivera A, Ochoa W, Larrinaga F, Lasa G. How-to conduct a systematic literature review: a quick guide for computer science research. *MethodsX.* 2022;9:101895. Available in: <http://doi.org/10.1016/j.mex.2022.101895>
18. SIGN. Scottish Intercollegiate Guidelines Network SIGN 50. A guideline developer's handbook. Edinburgh2019. Available in: <http://www.sign.ac.uk>
19. Mayorga Butrón J, Velasco Hidalgo L, Ochoa-Carrillo F. Guías de Práctica Clínica Basadas en Evidencia, cerrando la brecha entre el conocimiento científico y la toma de decisiones clínicas. Documento de la serie MBE, 3 de 3. *Gaceta Mexicana de Oncología.* 2015;14(6):329-334. Available in: <http://doi.org/10.1016/j.gamo.2015.12.005>
20. Duda C, Mahon I, Chen MH, Snyder B, Barr R, Chiles C, et al. Impact and costs of targeted recruitment of minorities to the National Lung Screening Trial. *Clin Trials.* 2011;8(2):214-223. Available in: <http://doi.org/10.1177/1740774510396742>
21. Zhang T, Joubert P, Ansari-Pour N, Zhao W, Hoang PH, Lokanga R, et al. Genomic and evolutionary classification of lung cancer in never smokers. *Nat Genet.* 2021;53(9):1348-1359. Available in: <http://doi.org/10.1038/s41588-021-00920-0>
22. Robles-Hernandez R, Centeno-Saenz GI, Ramirez-Venegas A, Thirion-Romero I, Hernandez-Zenteno R, Guinto-Ramirez SP, et al. Validation of new predictors of mortality and BODE index variants in patients with COPD at moderate altitude. *ERJ Open Res.* 2025;11(1):00333-2024. Available in: <http://doi.org/10.1183/23120541.00333-2024>
23. Soler-Cataluna JJ, Pinera P, Trigueros JA, Calle M, Casanova C, Cosio BG, et al. Spanish COPD Guidelines (GesEPOC) 2021 Update Diagnosis and Treatment of COPD Exacerbation Syndrome. *Arch Bronconeumol.* 2022;58(2):159-170. Available in: <http://doi.org/10.1016/j.arbres.2021.05.011>
24. About Gold. "Global initiative for chronic obstructive lung disease" global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2023 Report. 2023. Available in: https://goldcopd.org/wp-content/uploads/2023/03/GOLD-2023-ver-1.3-17Feb2023_WMV.pdf
25. De Oca MM, López Varela MV, Acuña A, Schiavi E, Casas A, Tokumoto A, et al. Guía de Práctica Clínica Latinoamericana de EPOC-2019 (LatinEPOC-2019). *Respirar.* 2019;1:70. Available in: https://alatorax.org/es/publicaciones/respirar/numero/28/download/28_file_es_WmojWI_epoc2019-27jun2020-spain-print.pdf

26. US Preventive Services Task Force (USPSTF); Siu AL, Bibbins-Domingo K, Grossman DC, Davidson KW, Epling JW Jr, et al. Screening for chronic obstructive pulmonary disease: US preventive services task force recommendation statement. *JAMA*. 2016;315(13):1372-1377. Available in: <http://doi.org/10.1001/jama.2016.2638>
27. Celli B, Fabbri L, Criner G, Martinez FJ, Mannino D, Vogelmeier C, et al. Definition and nomenclature of chronic obstructive pulmonary disease: time for its revision. *Am J Respir Crit Care Med*. 2022;206(11):1317-1325. Available in: <http://doi.org/10.1164/rccm.202204-0671PP>
28. Gold. "Global Initiative for Chronic Obstructive Lung Disease" Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2024 Report. 2024. Available in: https://goldcopd.org/wp-content/uploads/2023/11/GOLD-2024_v1.0-30Oct23_WMv.pdf
29. Alfageme I, De Lucas P, Ancochea J, Miravittles M, Soler-Cataluna JJ, Garcia-Rio F, et al. 10 years after EPISCAN: a new study on the prevalence of COPD in Spain - a summary of the EPISCAN II protocol. *Arch Bronconeumol (Engl Ed)*. 2019;55(1):38-47. Available in: <http://doi.org/10.1016/j.arbres.2018.05.011>
30. Stanley SE, Merck SJ, Armanios M. Telomerase and the genetics of emphysema susceptibility. implications for pathogenesis paradigms and patient care. *Ann Am Thorac Soc*. 2016;13 Suppl 5(Suppl 5):S447-S51. Available in: <http://doi.org/10.1513/AnnalsATS.201609-718AW>
31. Wang T, Jia Z, Li S, Li Y, Yu T, Lu T, et al. The association between leukocyte telomere length and chronic obstructive pulmonary disease is partially mediated by inflammation: a meta-analysis and population-based mediation study. *BMC Pulm Med*. 2022;22(1):320. Available in: <http://doi.org/10.1186/s12890-022-02114-8>
32. Fonseca Wald ELA, Van Den Borst B, Gosker HR, Schols A. Dietary fibre and fatty acids in chronic obstructive pulmonary disease risk and progression: a systematic review. *Respirology*. 2014;19(2):176-184. Available in: <http://doi.org/10.1111/resp.12229>
33. Valisoltani N, Ghoreishy SM, Imani H, Rajabi Harsini A, Jowshan M, Travica N, et al. Fiber intake and risk of chronic obstructive pulmonary disease: A systematic review and dose response meta-analysis. *Food Sci Nutr*. 2023;11(11):6775-6788. Available in: <http://doi.org/10.1002/fsn3.3640>
34. Zhu M, Wang T, Wang C, Ji Y. The association between vitamin D and COPD risk, severity, and exacerbation: an updated systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2597-2607. Available in: <http://doi.org/10.2147/COPD.S101382>
35. Mornex JF, Traclet J, Guillaud O, Dechomet M, Lombard C, Ruiz M, et al. Alpha1-antitrypsin deficiency: an updated review. *Presse Med*. 2023;52(3):104170. Available in: <http://doi.org/10.1016/j.lpm.2023.104170>
36. Duan P, Wang Y, Lin R, Zeng Y, Chen C, Yang L, et al. Impact of early life exposures on COPD in adulthood: a systematic review and meta-analysis. *Respirology*. 2021;26(12):1131-1151. Available in: <http://doi.org/10.1111/resp.14144>
37. Fan H, Wu F, Liu J, Zeng W, Zheng S, Tian H, et al. Pulmonary tuberculosis as a risk factor for chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Ann Transl Med*. 2021;9(5):390. Available in: <https://atm.amegroups.org/article/view/63278>
38. Menezes AM, Hallal PC, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, et al. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. *Eur Respir J*. 2007;30(6):1180-1185. Available in: <http://doi.org/10.1183/09031936.00083507>
39. Bigna JJ, Kenne AM, Asangbeh SL, Sibetcheu AT. Prevalence of chronic obstructive pulmonary disease in the global population with HIV: a systematic review and meta-analysis. *Lancet Glob Health*. 2018;6(2):e193-e202. Available in: [http://doi.org/10.1016/S2214-109X\(17\)30451-5](http://doi.org/10.1016/S2214-109X(17)30451-5)
40. Mucha L, Stephenson J, Morandi N, Dirani R. Meta-analysis of disease risk associated with smoking, by gender and intensity of smoking. *Gen Med*. 2006;3(4):279-291. Available in: [http://doi.org/10.1016/s1550-8579\(06\)80216-0](http://doi.org/10.1016/s1550-8579(06)80216-0)
41. Holtjer JCS, Bloemsma LD, Beijers RJHCG, Cornelissen MEB, Hilvering B, Houweling L, et al. Identifying risk factors for COPD and adult-onset asthma: an umbrella review. *Eur Respir Rev*. 2023;32(168). Available in: <http://doi.org/10.1183/16000617.0009-2023>
42. World Health Organization. Chronic obstructive pulmonary disease (COPD) 2023 [Available in: [https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease\(copd\)#:~:text=Tobacco%20smoking%20accounts%20for%20over,is%20a%20major%20risk%20factor](https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease(copd)#:~:text=Tobacco%20smoking%20accounts%20for%20over,is%20a%20major%20risk%20factor)
43. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. *BMC Pulm Med*. 2011;11:36. Available in: <http://doi.org/10.1186/1471-2466-11-36>
44. Rennard SI, Vestbo J. COPD: the dangerous underestimate of 15%. *Lancet*. 2006;367(9518):1216-1219. Available in: [http://doi.org/10.1016/S0140-6736\(06\)68516-4](http://doi.org/10.1016/S0140-6736(06)68516-4)
45. Jayes L, Haslam PL, Gratziou CG, Powell P, Britton J, Vardavas C, et al. SmokeHaz: systematic reviews and meta-analyses of the effects of smoking on respiratory health. *Chest*. 2016;150(1):164-179. Available in: <http://doi.org/10.1016/j.chest.2016.03.060>
46. Fischer F, Kraemer A. Meta-analysis of the association between second-hand smoke exposure and ischaemic heart diseases, COPD and stroke. *BMC Public Health*. 2015;15:1202. Available in: <http://doi.org/10.1186/s12889-015-2489-4>
47. Chen P, Li Y, Wu D, Liu F, Cao C. Secondhand smoke exposure and the risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2023;18:1067-76. Available in: <http://doi.org/10.2147/COPD.S403158>
48. Cunalata-Paredes AV, Gea-Izquierdo E. COPD in the major nonsmoking adult: A systematic review and meta-analysis. *Arch Environ Occup Health*. 2021;76(6):319-329. Available in: <http://doi.org/10.1080/19338244.2020.1828243>
49. Waziry R, Jawad M, Ballout RA, Al Akel M, Akl EA. The effects of waterpipe tobacco smoking on health outcomes: an updated systematic review and meta-analysis. *Int J Epidemiol*. 2017;46(1):32-43. Available in: <http://doi.org/10.1093/ije/dyw021>
50. Tan WC, Lo C, Jong A, Xing L, Fitzgerald MJ, Vollmer WM, et al. Marijuana and chronic obstructive lung disease: a population-based study. *CMAJ*. 2009;180(8):814-820. Available in: <http://doi.org/10.1503/cmaj.081040>
51. Vasconez-Gonzalez J, Delgado-Moreira K, Lopez-Molina B, Izquierdo-Condoy JS, Gamez-Rivera E, Ortiz-Prado E. Effects of smoking marijuana on the respiratory system: a systematic review. *Subst Abus*. 2023;44(3):249-260. Available in: <http://doi.org/10.1177/08897077231186228>
52. Po JY, Fitzgerald JM, Carlsten C. Respiratory disease associated with solid biomass fuel exposure in rural women and children: systematic

- review and meta-analysis. *Thorax*. 2011;66(3):232-239. Available in: <http://doi.org/10.1136/thx.2010.147884>
53. Shetty BSP, D'Souza G, Padukudru Anand M. Effect of indoor air pollution on chronic obstructive pulmonary disease (COPD) deaths in Southern Asia-A systematic review and meta-analysis. *Toxics*. 2021;9(4). Available in: <http://doi.org/10.3390/toxics9040085>
 54. Hu G, Zhou Y, Tian J, Yao W, Li J, Li B, et al. Risk of COPD from exposure to biomass smoke: a metaanalysis. *Chest*. 2010;138(1):20-31. Available in: <http://doi.org/10.1378/chest.08-2114>
 55. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, et al. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med*. 2003;167(5):787-797. Available in: <http://doi.org/10.1164/rccm.167.5.787>
 56. Ryu JY, Sunwoo YE, Lee SY, Lee CK, Kim JH, Lee JT, et al. Chronic obstructive pulmonary disease (COPD) and vapors, gases, dusts, or fumes (VGDF): a meta-analysis. *COPD*. 2015;12(4):374-380. Available in: <http://doi.org/10.3109/15412555.2014.949000>
 57. Park J, Kim HJ, Lee CH, Lee CH, Lee HW. Impact of long-term exposure to ambient air pollution on the incidence of chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Environ Res*. 2021;194:110703. Available in: <http://doi.org/10.1016/j.envres.2020.110703>
 58. Bloemsma LD, Hoek G, Smit LAM. Panel studies of air pollution in patients with COPD: Systematic review and meta-analysis. *Environ Res*. 2016;151:458-468. Available in: <http://doi.org/10.1016/j.envres.2016.08.018>
 59. Pando-Sandoval A, Ruano-Ravina A, Candal-Pedreira C, Rodriguez-Garcia C, Represas-Represas C, Golpe R, et al. Risk factors for chronic obstructive pulmonary disease in never-smokers: a systematic review. *Clin Respir J*. 2022;16(4):261-275. Available in: <http://doi.org/10.1111/crj.13479>
 60. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. *Lancet Respir Med*. 2022;10(5):447-458. Available in: [http://doi.org/10.1016/s2213-2600\(21\)00511-7](http://doi.org/10.1016/s2213-2600(21)00511-7)
 61. Rey-Brandariz J, Perez-Rios M, Ahluwalia JS, Beheshtian K, Fernandez-Villar A, Represas-Represas C, et al. Tobacco patterns and risk of chronic obstructive pulmonary disease: results from a cross-sectional study. *Arch Bronconeumol*. 2023;59(11):717-724. Available in: <http://doi.org/10.1016/j.arbres.2023.07.009>
 62. Torres-Duque CA, Jaramillo C, Caballero A, Proanos-Jurado NJ, Pareja-Zabala MJ, Soriano JB, et al. Chronic obstructive pulmonary disease related to wood smoke and impact of the combined exposure to tobacco. *IJTL Open*. 2024;1(3):130-135. Available in: <http://doi.org/10.5588/ijtdopen.24.0004>
 63. Caballero A, Torres-Duque CA, Jaramillo C, Bolivar F, Sanabria F, Osorio P, et al. Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude (PREPOCOL study). *Chest*. 2008;133(2):343-349. Available in: <http://doi.org/10.1378/chest.07-1361>
 64. NICE. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. National Institute for Health and Care Excellence: Guidelines. London, 2019.
 65. Sethi DK, Rhodes J, Ferris R, Banka R, Clarke A, Mishra EK. Breathlessness predicts mortality in adults: a systematic review and meta-analysis. *Cureus*. 2023;15(5):e39192. Available in: <http://doi.org/10.7759/cureus.39192>
 66. Lin K, Watkins B, Johnson T, Rodriguez JA, Barton MB, Force USPST. Screening for chronic obstructive pulmonary disease using spirometry: summary of the evidence for the U.S. preventive services task force. *Ann Intern Med*. 2008;148(7):535-543. Available in: <http://doi.org/10.7326/0003-4819-148-7-200804010-00213>
 67. US Preventive Services Task Force; Mangione CM, Barry MJ, Nicholson WK, Cabana M, Caughey AB, et al. Screening for chronic obstructive pulmonary disease: US preventive services task force reaffirmation recommendation statement. *JAMA*. 2022;327(18):1806-1811. Available in: <http://doi.org/10.1001/jama.2022.5692>
 68. Schiavi E, Stirbulov R, Hernandez Vecino R, Mercurio S, Di Boscio V, Puma T. COPD screening in primary care in four Latin American countries: methodology of the PUMA study. *Arch Bronconeumol*. 2014;50(11):469-474. Available in: <http://doi.org/10.1016/j.arbres.2014.03.006>
 69. Lopez Varela MV, De Oca MM, Rey A, Casas A, Stirbulov R, Di Boscio V, et al. Development of a simple screening tool for opportunistic COPD case finding in primary care in Latin America: The PUMA study. *Respirology*. 2016;21(7):1227-34. Available in: <http://doi.org/10.1111/resp.12834>
 70. Gu Y, Zhang Y, Wen Q, Ouyang Y, Shen Y, Yu H, et al. Performance of COPD population screener questionnaire in COPD screening: a validation study and meta-analysis. *Ann Med*. 2021;53(1):1198-1206. Available in: <http://doi.org/10.1080/07853890.2021.1949486>
 71. Haroon S, Jordan R, Takwoingi Y, Adab P. Diagnostic accuracy of screening tests for COPD: a systematic review and meta-analysis. *BMJ Open*. 2015;5(10):e008133. Available in: <http://doi.org/10.1136/bmjopen-2015-008133>
 72. Rosero Arenas MDLÁ, García García MÁ, Briones Urtiaga MDM, Martínez Cornejo A. Utilidad del miniespirómetro COPD-6 en el diagnóstico precoz de EPOC. *Open Respiratory Archives*. 2020;2(3):132-140. Available in: <http://doi.org/10.1016/j.opresp.2020.05.011>
 73. Schnieders E, Unal E, Winkler V, Dambach P, Louis VR, Horstick O, et al. Performance of alternative COPD case-finding tools: a systematic review and meta-analysis. *Eur Respir Rev*. 2021;30(160): 200350. Available in: <http://doi.org/10.1183/16000617.0350-2020>
 74. Pagano L, Mckeough Z, Wootton S, Zwar N, Dennis S. Accuracy of the COPD diagnostic questionnaire as a screening tool in primary care. *BMC Prim Care*. 2022;23(1):78. Available in: <http://doi.org/10.1186/s12875-022-01685-z>
 75. Hanania NA, Mannino DM, Yawn BP, Mapel DW, Martinez FJ, Donohue JF, et al. Predicting risk of airflow obstruction in primary care: Validation of the lung function questionnaire (LFQ). *Respir Med*. 2010;104(8):1160-1170. Available in: <http://doi.org/10.1016/j.rmed.2010.02.009>
 76. Sichletidis L, Spyrtatos D, Papaioannou M, Chloros D, Tsiotsios A, Tsagaraki V, et al. A combination of the IPAG questionnaire and PiKo-6(R) flow meter is a valuable screening tool for COPD in the primary care setting. *Prim Care Respir J*. 2011;20(2):184-189, 1 p following 9. Available in: <http://doi.org/10.4104/pcrj.2011.00038>
 77. Weiss G, Steinacher I, Lamprecht B, Kaiser B, Mikes R, Sator L, et al. Development and validation of the Salzburg COPD-screening questionnaire (SCSQ): a questionnaire development and validation study. *NPJ Prim Care Respir Med*. 2017;27(1):4. Available in: <http://doi.org/10.1038/s41533-016-0005-7>
 78. Fujita M, Nagashima K, Takahashi S, Suzuki K, Fujisawa T, Hata A. Handheld flow meter improves COPD detectability regardless of using a conventional questionnaire: a split-sample validation study.

- Respirology. 2020;25(2):191-197. Available in: <http://doi.org/10.1111/resp.13602>
79. Sogbetun F, Eschenbacher WL, Welge JA, Panos RJ. Veterans airflow obstruction screening questionnaire: a survey to identify veterans with airflow obstruction. *Chronic Obstr Pulm Dis.* 2016;3(4):705-15. Available in: <http://doi.org/10.15326/jcopdf.3.4.2016.0128>
 80. Miravittles M, Llor C, Calvo E, Diaz S, Diaz-Cuervo H, Gonzalez-Rojas N. [Validation of the Spanish version of the Chronic Obstructive Pulmonary Disease-Population Screener (COPD-PS). Its usefulness and that of FEV(1)/FEV(6) for the diagnosis of COPD]. *Med Clin (Barc).* 2012;139(12):522-530. Available in: <http://doi.org/10.1016/j.medcli.2011.06.022>
 81. Bastidas G. AR, Estupiñán B. MF, Arias B. JS, Estrada H. M, López O. J, Mateus M. SL, et al. Validación externa y reproducibilidad del cuestionario PUMA para el diagnóstico de EPOC en una población latinoamericana: Validación externa del cuestionario PUMA. *Rev Chil Enferm Respir.* 2022;38:11-19. Available in: http://www.scielo.cl/scielo.php?script=sci_arttext&pid=S0717-73482022000100011&nrm=iso
 82. Lopez Varela MV, Montes De Oca M, Wehrmeister FC, Rodriguez C, Ramirez L, Menezes A. External validation of the PUMA COPD diagnostic questionnaire in a general practice sample and the PLATINO study population. *Int J Chron Obstruct Pulmon Dis.* 2019;14:1901-1911. Available in: <http://doi.org/10.2147/COPD.S206250>
 83. Demirci H, Eniste K, Basaran EO, Ocakoglu G, Yilmaz Z, Tuna S. A multicenter family practitioners' research on chronic obstructive pulmonary disease screening using the COPD assessment test. *Prim Health Care Res Dev.* 2017;18(6):603-607. Available in: <http://doi.org/10.1017/S1463423617000408>
 84. Martinez FJ, Mannino D, Leidy NK, Malley KG, Bacci ED, Barr RG, et al. A new approach for identifying patients with undiagnosed chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2017;195(6):748-756. Available in: <http://doi.org/10.1164/rccm.201603-0622OC>
 85. Fernández-Plata R, Thirión-Romero I, Martínez-Briseño D, Franco-Marina F, Pérez-Padilla R. Screening tool for restrictive and obstructive ventilatory abnormalities in a population-based survey. *Rev Invest Clin.* 2021;72(6):386-393. Available in: <http://doi.org/10.24875/RIC.20000235>
 86. Siddharthan T, Pollard SL, Quaderi SA, Rykiel NA, Wosu AC, Alupo P, et al. Discriminative accuracy of chronic obstructive pulmonary disease screening instruments in 3 low- and middle-income country settings. *JAMA.* 2022;327(2):151-160. Available in: <http://doi.org/10.1001/jama.2021.23065>
 87. Quezada WA, Whippo BA, Jellen PA, Leidy NK, Mannino DM, Kim KJ, et al. How Well Does CAPTURE Translate?: an exploratory analysis of a COPD case-finding method for spanish-speaking patients. *Chest.* 2017;152(4):761-770. Available in: <http://doi.org/10.1016/j.chest.2017.03.047>
 88. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med.* 2019;200(8):e70-e88. Available in: <http://doi.org/10.1164/rccm.201908-1590ST>
 89. Stanojevic S, Kaminsky DA, Miller MR, Thompson B, Aliverti A, Barjaktarevic I, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J.* 2022;60(1):2101499. Available in: <http://doi.org/10.1183/13993003.01499-2021>
 90. Van Dijk WD, Gupta N, Tan WC, Bourbeau J. Clinical relevance of diagnosing COPD by fixed ratio or lower limit of normal: a systematic review. *COPD.* 2014;11(1):113-120. Available in: <http://doi.org/10.3109/15412555.2013.781996>
 91. Quanjer PH, Enright PL, Miller MR, Stocks J, Ruppel G, Swanney MP, et al. The need to change the method for defining mild airway obstruction. *Eur Respir J.* 2011;37(3):720-722. Available in: <http://doi.org/10.1183/09031936.00135110>
 92. Enright PL, Kaminsky DA. Strategies for screening for chronic obstructive pulmonary disease. *Respir Care.* 2003;48(12):1194-1201; discussion 201-3. Available in: <https://www.ncbi.nlm.nih.gov/pubmed/14651760>
 93. Vázquez GJC, Pérez PR. Manual de espirometría. Graphimedica: Instituto Nacional de Enfermedades Respiratorias; 2018.
 94. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med.* 1999;159(1):179-187. Available in: <http://doi.org/10.1164/ajrccm.159.1.9712108>
 95. Koblicek V, Novotna B, Zbozinkova Z, Hejduk K. Diagnosing COPD: advances in training and practice - a systematic review. *Adv Med Educ Pract.* 2016;7:219-231. Available in: <http://doi.org/10.2147/AMEP.S76976>
 96. Bourbeau J, Bhutani M, Hernandez P, Aaron SD, Balter M, Beauchesne M-F, et al. Canadian Thoracic Society Clinical Practice Guideline on pharmacotherapy in patients with COPD—2019 update of evidence. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine.* 2019;3(4):210-232. Available in: <http://doi.org/10.1080/24745332.2019.1668652>
 97. Brusasco V, Pellegrino R. Pulmonary function interpretative strategies: from statistics to clinical practice. *Eur Respir J.* 2022;60(1):2200317. Available in: <http://doi.org/10.1183/13993003.00317-2022>
 98. Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, et al. Executive Summary: 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J.* 2017;49(1):1600016. Available in: <http://doi.org/10.1183/13993003.E0016-2016>
 99. Balasubramanian A, Macintyre NR, Henderson RJ, Jensen RL, Kinney G, Stringer WW, et al. Diffusing Capacity of Carbon Monoxide in Assessment of COPD. *Chest.* 2019;156(6):1111-1119. Available in: <http://doi.org/10.1016/j.chest.2019.06.035>
 100. Ni Y, Yu Y, Dai R, Shi G. Diffusing capacity in chronic obstructive pulmonary disease assessment: a meta-analysis. *Chron Respir Dis.* 2021;18:14799731211056340. Available in: <http://doi.org/10.1177/14799731211056340>
 101. Hernández-Morales AP, Robles-Hernández RE, Vázquez-García JC. Estereología pulmonar en enfermedad pulmonar obstructiva crónica: exploración funcional pulmonar por imagen. *Neumol Cir Tórax.* 2023;82(1):21-28. Available in: <http://doi.org/10.35366/114225>
 102. Gould GA, Redpath AT, Ryan M, Warren PM, Best JJ, Flenley DC, et al. Lung CT density correlates with measurements of airflow limitation and the diffusing capacity. *Eur Respir J.* 1991;4(2):141-146. Available in: <https://www.ncbi.nlm.nih.gov/pubmed/2044729>
 103. Nambu A, Zach J, Schroeder J, Jin GY, Kim SS, Kim YI, et al. Relationships between diffusing capacity for carbon monoxide (DLCO), and quantitative computed tomography measurements and visual assessment for chronic obstructive pulmonary disease. *Eur J Radiol.* 2015;84(5):980-985. Available in: <http://doi.org/10.1016/j.ejrad.2015.01.010>
 104. Harvey BG, Strulovici-Barel Y, Kaner RJ, Sanders A, Vincent TL, Mezey JG, et al. Risk of COPD with obstruction in active smokers with normal spirometry and reduced diffusion capacity. *Eur Respir J.* 2015;46(6):1589-1597. Available in: <http://doi.org/10.1183/13993003.02377-2014>

105. Anthonisen NR. Long-term oxygen therapy. *Ann Intern Med.* 1983;99(4):519-527. Available in: <http://doi.org/10.7326/0003-4819-99-4-519>
106. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet.* 1981;1(8222):681-686. Available in: <https://www.ncbi.nlm.nih.gov/pubmed/6110912>
107. Perez-Padilla R, Torre-Bouscoulet L, Muino A, Marquez MN, Lopez MV, De Oca MM, et al. Prevalence of oxygen desaturation and use of oxygen at home in adults at sea level and at moderate altitude. *Eur Respir J.* 2006;27(3):594-599. Available in: <http://doi.org/10.1183/09031936.06.00075005>
108. Pérez-Padilla J, Vázquez-García J. [Estimation of gasometric values at different altitudes above sea level in Mexico]. *Rev Invest Clin.* 2000;52(2):148-155. Available in: <https://www.ncbi.nlm.nih.gov/pubmed/10846438>
109. Oostveen E, Macleod D, Lorino H, Farre R, Hantos Z, Desager K, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J.* 2003;22(6):1026-1041. Available in: <http://doi.org/10.1183/09031936.03.00089403>
110. Gochicoa-Rangel L, Cantú-González G, Miguel-Reyes JL, Rodríguez-Moreno L, Torre-Bouscoulet L. Oscilometría de impulso. Recomendaciones y procedimiento. *Neumol Cir Tórax.* 2019;78:124-134. Available in: <http://doi.org/10.35366/NTS192E>
111. Vázquez-García JC, Pérez-Padilla JR. Valores gasométricos estimados para las principales poblaciones y sitios a mayor altitud en México. *Rev Inst Nal Enf Resp Mex.* 2000;13:06-13.
112. Su ZQ, Guan WJ, Li SY, Ding M, Chen Y, Jiang M, et al. Significances of spirometry and impulse oscillometry for detecting small airway disorders assessed with endobronchial optical coherence tomography in COPD. *Int J Chron Obstruct Pulmon Dis.* 2018;13:3031-3044. Available in: <http://doi.org/10.2147/COPD.S172639>
113. Wei X, Shi Z, Cui Y, Mi J, Ma Z, Ren J, et al. Impulse oscillometry system as an alternative diagnostic method for chronic obstructive pulmonary disease. *Medicine (Baltimore).* 2017;96(46):e8543. Available in: <http://doi.org/10.1097/MD.00000000000008543>
114. Vargas-Domínguez C, Gochicoa-Rangel L, Velázquez-Uncal M, Mejía-Alfaro R, Vázquez-García J, Pérez-Padilla J, et al. Pruebas de función respiratoria, ¿cuál y a quién? *Neumol Cir Tórax.* 2011;70(2):101-117.
115. Guerrero-Zúñiga S, Vázquez-García JC, Gochicoa-Rangel L, Cid-Juárez S, Benítez-Pérez R, Del-Río-Hidalgo R. Pletismografía corporal: recomendaciones y procedimiento. *Neumol Cir Tórax.* 2016;75(4):296-307.
116. Fermont JM, Masconi KL, Jensen MT, Ferrari R, Di Lorenzo VaP, Marott JM, et al. Biomarkers and clinical outcomes in COPD: a systematic review and meta-analysis. *Thorax.* 2019;74(5):439-446. Available in: <http://doi.org/10.1136/thoraxjnl-2018-211855>
117. Enright PL. The six-minute walk test. *Respir Care.* 2003;48(8):783-5. Available in: <https://www.ncbi.nlm.nih.gov/pubmed/12890299>.
118. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J.* 2004;23(1):28-33. Available in: <http://doi.org/10.1183/09031936.03.00034603>
119. Celli B, Tetzlaff K, Criner G, Polkey MI, Sciruba F, Casaburi R, et al. The 6-minute-walk distance test as a chronic obstructive pulmonary disease stratification tool. Insights from the COPD biomarker qualification consortium. *Am J Respir Crit Care Med.* 2016;194(12):1483-1493. Available in: <http://doi.org/10.1164/rccm.201508-1653OC>
120. Cote CG, Pinto-Plata V, Kasprzyk K, Dordelly LJ, Celli BR. The 6-min walk distance, peak oxygen uptake, and mortality in COPD. *Chest.* 2007;132(6):1778-1785. Available in: <http://doi.org/10.1378/chest.07-2050>
121. Casanova C, Cote C, Marin JM, Pinto-Plata V, De Torres JP, Aguirre-Jaime A, et al. Distance and oxygen desaturation during the 6-min walk test as predictors of long-term mortality in patients with COPD. *Chest.* 2008;134(4):746-752. Available in: <http://doi.org/10.1378/chest.08-0520>
122. Celli BR, Cote CG, Marin JM, Casanova C, De Oca MM, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350(10):1005-1012. Available in: <http://doi.org/10.1056/NEJMoa021322>
123. Gochicoa-Rangel L, Mora-Romero U, Guerrero-Zúñiga S, Silva-Cerón M, Cid-Juárez S, Velázquez-Uncal M, et al. Prueba de caminata de 6 minutos: recomendaciones y procedimientos. *Neumol Cir Tórax.* 2015;74(2):127-136.
124. Zhang C, Zhang M, Wang Y, Su X, Lei T, Yu H, et al. Diagnostic value of fractional exhaled nitric oxide in differentiating the asthma-COPD overlap from COPD: a systematic review and meta-analysis. *Expert Rev Respir Med.* 2022;16(6):679-687. Available in: <http://doi.org/10.1080/17476348.2022.2011221>
125. Gong S, Pu Y, Xie L, Yang X, Mao H. Fraction of exhaled nitric oxide is elevated in patients with stable chronic obstructive pulmonary disease: a meta-analysis. *Am J Med Sci.* 2020;360(2):166-175. Available in: <http://doi.org/10.1016/j.amjms.2020.04.038>
126. Lu Z, Huang W, Wang L, Xu N, Ding Q, Cao C. Exhaled nitric oxide in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2018;13:2695-2705. Available in: <http://doi.org/10.2147/COPD.S165780>
127. Wei XM, Kim HS, Kumar RK, Heywood GJ, Hunt JE, Mcneil HP, et al. Effects of cigarette smoke on degranulation and NO production by mast cells and epithelial cells. *Respir Res.* 2005;6(1):108. Available in: <http://doi.org/10.1186/1465-9921-6-108>
128. Bergeron C, Boulet LP, Page N, Laviolette M, Zimmermann N, Rothenberg ME, et al. Influence of cigarette smoke on the arginine pathway in asthmatic airways: increased expression of arginase I. *J Allergy Clin Immunol.* 2007;119(2):391-397. Available in: <http://doi.org/10.1016/j.jaci.2006.10.030>
129. Hogman M, Thornadtsson A, Broms K, Janson C, Lisspers K, Stallberg B, et al. Different relationships between F(E)NO and COPD characteristics in smokers and ex-smokers. *COPD.* 2019;16(3-4):227-233. Available in: <http://doi.org/10.1080/15412555.2019.1638355>
130. Higham A, Beech A, Singh D. Exhaled nitric oxide levels in COPD patients who use electronic cigarettes. *Nitric Oxide.* 2024;145:57-59. Available in: <http://doi.org/10.1016/j.niox.2024.02.006>
131. Lim CS, Rani FA, Tan LE. Response of exhaled nitric oxide to inhaled corticosteroids in patients with stable COPD: a systematic review and meta-analysis. *Clin Respir J.* 2018;12(1):218-226. Available in: <http://doi.org/10.1111/crj.12518>
132. Raof S, Shah M, Make B, Allaqaband H, Bowler R, Fernando S, et al. Lung imaging in COPD part 1: clinical usefulness. *Chest.* 2023;164(1):69-84. Available in: <http://doi.org/10.1016/j.chest.2023.03.007>

133. Wallace GM, Winter JH, Winter JE, Taylor A, Taylor TW, Cameron RC. Chest X-rays in COPD screening: are they worthwhile? *Respir Med.* 2009;103(12):1862-1865. Available in: <http://doi.org/10.1016/j.rmed.2009.07.001>
134. Li JS, Zhang HL, Bai YP, Wang YF, Wang HF, Wang MH, et al. Diagnostic value of computed tomography in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *COPD.* 2012;9(5):563-570. Available in: <http://doi.org/10.3109/15412555.2012.692000>
135. Li T, Zhou HP, Zhou ZJ, Guo LQ, Zhou L. Computed tomography-identified phenotypes of small airway obstructions in chronic obstructive pulmonary disease. *Chin Med J (Engl).* 2021;134(17):2025-2036. Available in: <http://doi.org/10.1097/CM9.0000000000001724>
136. Wang Y, Chai L, Chen Y, Liu J, Wang Q, Zhang Q, et al. Quantitative CT parameters correlate with lung function in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Front Surg.* 2022;9:1066031. Available in: <http://doi.org/10.3389/fsurg.2022.1066031>
137. Xie X, De Jong PA, Oudkerk M, Wang Y, Ten Hacken NH, Miao J, et al. Morphological measurements in computed tomography correlate with airflow obstruction in chronic obstructive pulmonary disease: systematic review and meta-analysis. *Eur Radiol.* 2012;22(10):2085-2093. Available in: <http://doi.org/10.1007/s00330-012-2480-8>
138. Williams MC, Murchison JT, Edwards LD, Agusti A, Bakke P, Calverley PM, et al. Coronary artery calcification is increased in patients with COPD and associated with increased morbidity and mortality. *Thorax.* 2014;69(8):718-723. Available in: <http://doi.org/10.1136/thoraxjnl-2012-203151>
139. Wells JM, Washko GR, Han MK, Abbas N, Nath H, Mamary AJ, et al. Pulmonary arterial enlargement and acute exacerbations of COPD. *N Engl J Med.* 2012;367(10):913-921. Available in: <http://doi.org/10.1056/NEJMoa1203830>
140. Shi L, Wei F, Ma T, Zhou W, Li M, Wan Y. Impact of Radiographic Bronchiectasis in COPD. *Respir Care.* 2020;65(10):1561-1573. Available in: <http://doi.org/10.4187/respcare.07390>
141. Du Q, Jin J, Liu X, Sun Y. Bronchiectasis as a comorbidity of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *PLoS One.* 2016;11(3):e0150532. Available in: <http://doi.org/10.1371/journal.pone.0150532>
142. Nicholson JM, Orsso CE, Nourouzpour S, Elangeswaran B, Chohan K, Orchanian-Cheff A, et al. Computed tomography-based body composition measures in COPD and their association with clinical outcomes: a systematic review. *Chron Respir Dis.* 2022;19:14799731221133387. Available in: <http://doi.org/10.1177/14799731221133387>
143. Siouta N, Van Beek K, Preston N, Hasselaar J, Hughes S, Payne S, et al. Towards integration of palliative care in patients with chronic heart failure and chronic obstructive pulmonary disease: a systematic literature review of European guidelines and pathways. *BMC Palliat Care.* 2016;15:18. Available in: <http://doi.org/10.1186/s12904-016-0089-4>
144. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax.* 2004;59(7):574-580. Available in: <http://doi.org/10.1136/thx.2003.019588>
145. Vestbo J, Agusti A, Wouters EF, Bakke P, Calverley PM, Celli B, et al. Should we view chronic obstructive pulmonary disease differently after ECLIPSE? A clinical perspective from the study team. *Am J Respir Crit Care Med.* 2014;189(9):1022-1030. Available in: <http://doi.org/10.1164/rccm.201311-2006PP>
146. Zhou B, Liu S, He D, Wang K, Wang Y, Yang T, et al. Fibrinogen is a promising biomarker for chronic obstructive pulmonary disease: evidence from a meta-analysis. *Biosci Rep.* 2020;40(7):BSR20193542. Available in: <http://doi.org/10.1042/BSR20193542>
147. Mohan M, Parthasarathi A, S KC, Biligere Siddaiah J, Mahesh PA. Fibrinogen: a feasible biomarker in identifying the severity and acute exacerbation of chronic obstructive pulmonary disease. *Cureus.* 2021;13(8):e16864. Available in: <http://doi.org/10.7759/cureus.16864>
148. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med.* 2010;363(12):1128-1138. Available in: <http://doi.org/10.1056/NEJMoa0909883>
149. Kunter E, Ilvan A, Ozmen N, Demirer E, Ozturk A, Avsar K, et al. Effect of corticosteroids on hemostasis and pulmonary arterial pressure during chronic obstructive pulmonary disease exacerbation. *Respiration.* 2008;75(2):145-154. Available in: <http://doi.org/10.1159/000097748>
150. Mannino DM, Valvi D, Mullerova H, Tal-Singer R. Fibrinogen, COPD and mortality in a nationally representative U.S. cohort. *COPD.* 2012;9(4):359-366. Available in: <http://doi.org/10.3109/15412555.2012.668249>
151. Celli BR, Locantore N, Yates J, Tal-Singer R, Miller BE, Bakke P, et al. Inflammatory biomarkers improve clinical prediction of mortality in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2012;185(10):1065-1072. Available in: <http://doi.org/10.1164/rccm.201110-1792OC>
152. Leuzzi G, Galeone C, Taverna F, Suatoni P, Morelli D, Pastorino U. C-reactive protein level predicts mortality in COPD: a systematic review and meta-analysis. *Eur Respir Rev.* 2017 Jan 31;26(143):160070. Available in: <http://doi.org/10.1183/16000617.0070-2016>
153. Davis BB, Shen YH, Tancredi DJ, Flores V, Davis RP, Pinkerton KE. Leukocytes are recruited through the bronchial circulation to the lung in a spontaneously hypertensive rat model of COPD. *PLoS One.* 2012;7(3):e33304. Available in: <http://doi.org/10.1371/journal.pone.0033304>
154. Agusti A, Edwards LD, Rennard SI, Macnee W, Tal-Singer R, Miller BE, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One.* 2012;7(5):e37483. Available in: <http://doi.org/10.1371/journal.pone.0037483>
155. Singh D, Edwards L, Tal-Singer R, Rennard S. Sputum neutrophils as a biomarker in COPD: findings from the ECLIPSE study. *Respir Res.* 2010;11(1):77. Available in: <http://doi.org/10.1186/1465-9921-11-77>
156. George L, Taylor AR, Esteve-Codina A, Soler Artigas M, Thun GA, Bates S, et al. Blood eosinophil count and airway epithelial transcriptome relationships in COPD versus asthma. *Allergy.* 2020;75(2):370-80. Available in: <http://doi.org/10.1111/all.14016>
157. Higham A, Beech A, Wolosianka S, Jackson N, Long G, Kolsum U, et al. Type 2 inflammation in eosinophilic chronic obstructive pulmonary disease. *Allergy.* 2021;76(6):1861-1864. Available in: <http://doi.org/10.1111/all.14661>
158. Dalin DA, Lokke A, Kristiansen P, Jensen C, Birkefoss K, Christensen HR, et al. A systematic review of blood eosinophils and continued treatment with inhaled corticosteroids in patients with COPD. *Respir Med.* 2022;198:106880. Available in: <http://doi.org/10.1016/j.rmed.2022.106880>
159. Stockley RA, Halpin DMG, Celli BR, Singh D. Chronic obstructive pulmonary disease biomarkers and their interpretation. *Am J Respir Crit Care Med.* 2019;199(10):1195-1204. Available in: <http://doi.org/10.1164/rccm.201810-1860SO>

160. Harries TH, Rowland V, Corrigan CJ, Marshall IJ, McDonnell L, Prasad V, et al. Blood eosinophil count, a marker of inhaled corticosteroid effectiveness in preventing COPD exacerbations in post-hoc RCT and observational studies: systematic review and meta-analysis. *Respir Res.* 2020;21(1):3. Available in: <http://doi.org/10.1186/s12931-019-1268-7>
161. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med.* 2015;3(6):435-442. Available in: [http://doi.org/10.1016/S2213-2600\(15\)00106-X](http://doi.org/10.1016/S2213-2600(15)00106-X)
162. Cheng SL. Blood eosinophils and inhaled corticosteroids in patients with COPD: systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2018;13:2775-2784. Available in: <http://doi.org/10.2147/COPD.S175017>
163. Horita N, Miyazawa N, Tomaru K, Inoue M, Ishigatsubo Y, Kaneko T. Vitamin D binding protein genotype variants and risk of chronic obstructive pulmonary disease: a meta-analysis. *Respirology.* 2015;20(2):219-225. Available in: <http://doi.org/10.1111/resp.12448>
164. Wang YL, Kong H, Xie WP, Wang H. Association of vitamin D-binding protein variants with chronic obstructive pulmonary disease: a meta-analysis. *Genet Mol Res.* 2015;14(3):10774-10785. Available in: <http://doi.org/10.4238/2015.September.9.16>
165. Xiao M, Wang T, Zhu T, Wen F. Dual role of vitamin D-binding protein 1F allele in chronic obstructive pulmonary disease susceptibility: a meta-analysis. *Genet Mol Res.* 2015;14(2):3534-3540. Available in: <http://doi.org/10.4238/2015.April.17.1>
166. Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA.* 2013;309(21):2223-2231. Available in: <http://doi.org/10.1001/jama.2013.5023>
167. Li X, He J, Yu M, Sun J. The efficacy of vitamin D therapy for patients with COPD: a meta-analysis of randomized controlled trials. *Ann Palliat Med.* 2020;9(2):286-297. Available in: <http://doi.org/10.21037/apm.2020.02.26>
168. Zhu B, Zhu B, Xiao C, Zheng Z. Vitamin D deficiency is associated with the severity of COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2015;10:1907-1916. Available in: <http://doi.org/10.2147/COPD.S89763>
169. Hua Y, Jiang T, Feng J, Zou M. Negligible effect of vitamin D supplementation on exacerbation in patients with chronic obstructive pulmonary disease: meta-analysis. *Biochem Med (Zagreb).* 2023;33(3):030703. Available in: <http://doi.org/10.11613/BM.2023.030703>
170. Keene JD, Jacobson S, Kechris K, Kinney GL, Foreman MG, Doerschuk CM, et al. Biomarkers predictive of exacerbations in the SPIROMICS and COPD Gene cohorts. *Am J Respir Crit Care Med.* 2017;195(4):473-481. Available in: <http://doi.org/10.1164/rccm.201607-1330OC>
171. Zemans RL, Jacobson S, Keene J, Kechris K, Miller BE, Tal-Singer R, et al. Multiple biomarkers predict disease severity, progression and mortality in COPD. *Respir Res.* 2017;18(1):117. Available in: <http://doi.org/10.1186/s12931-017-0597-7>
172. Perez-Rubio G, Jimenez-Valverde LO, Ramirez-Venegas A, Camarena A, Sansores RH, Flores-Trujillo F, et al. Prevalence of alpha-1 antitrypsin high-risk variants in Mexican mestizo population and their association with lung function values. *Arch Bronconeumol.* 2015;51(2):80-85. Available in: <http://doi.org/10.1016/j.arbres.2014.09.010>
173. Kon SS, Canavan JL, Jones SE, Nolan CM, Clark AL, Dickson MJ, et al. Minimum clinically important difference for the COPD assessment test: a prospective analysis. *Lancet Respir Med.* 2014;2(3):195-203. Available in: [http://doi.org/10.1016/S2213-2600\(14\)70001-3](http://doi.org/10.1016/S2213-2600(14)70001-3)
174. Karloh M, Fleig Mayer A, Maurici R, Pizzichini MMM, Jones PW, Pizzichini E. The COPD assessment test: what do we know so far?: a systematic review and meta-analysis about clinical outcomes prediction and classification of patients into GOLD Stages. *Chest.* 2016;149(2):413-425. Available in: <http://doi.org/10.1378/chest.15-1752>
175. Gupta N, Pinto LM, Morogan A, Bourbeau J. The COPD assessment test: a systematic review. *Eur Respir J.* 2014;44(4):873-884. Available in: <http://doi.org/10.1183/09031936.00025214>
176. Jones PW, Tabberer M, Chen WH. Creating scenarios of the impact of COPD and their relationship to COPD Assessment Test (CAT) scores. *BMC Pulm Med.* 2011;11:42. Available in: <http://doi.org/10.1186/1471-2466-11-42>
177. Morishita-Katsu M, Nishimura K, Taniguchi H, Kimura T, Kondoh Y, Kataoka K, et al. The COPD assessment test and St George's Respiratory Questionnaire: are they equivalent in subjects with COPD? *Int J Chron Obstruct Pulmon Dis.* 2016;11:1543-1551. Available in: <http://doi.org/10.2147/COPD.S104947>
178. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. *Eur Respir J.* 2009;34(3):648-654. Available in: <http://doi.org/10.1183/09031936.00102509>
179. Gustafsson D, Elmberg V, Schioler L, Jensen D, Ekstrom M. The modified Medical Research Council scale misclassifies exertional breathlessness among people referred for exercise testing. *ERJ Open Res.* 2023;9(6):00592-2023. Available in: <http://doi.org/10.1183/23120541.00592-2023>
180. Corlateanu A, Plahotniuc A, Corlateanu O, Botnaru V, Bikov A, Mathioudakis AG, et al. Multidimensional indices in the assessment of chronic obstructive pulmonary disease. *Respir Med.* 2021;185:106519. Available in: <http://doi.org/10.1016/j.rmed.2021.106519>
181. Soler-Cataluna JJ, Martinez-Garcia MA, Sanchez LS, Tordera MP, Sanchez PR. Severe exacerbations and BODE index: two independent risk factors for death in male COPD patients. *Respir Med.* 2009;103(5):692-699. Available in: <http://doi.org/10.1016/j.rmed.2008.12.005>
182. Golpe R, Esteban C, Figueira-Gon Alves JM, Amado-Diago CA, Blanco-Cid N, Aramburu A, et al. Development and validation of a prognostic index (BODEXS90) for mortality in stable chronic obstructive pulmonary disease. *Pulmonology.* 2023;29(4):276-283. Available in: <http://doi.org/10.1016/j.pulmoe.2020.10.008>
183. Jones RC, Donaldson GC, Chavannes NH, Kida K, Dickson-Spillmann M, Harding S, et al. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE Index. *Am J Respir Crit Care Med.* 2009;180(12):1189-1195. Available in: <http://doi.org/10.1164/rccm.200902-0271OC>
184. Puhan MA, Garcia-Aymerich J, Frey M, Ter Riet G, Anto JM, Agusti AG, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet.* 2009;374(9691):704-711. Available in: [http://doi.org/10.1016/S0140-6736\(09\)61301-5](http://doi.org/10.1016/S0140-6736(09)61301-5)
185. Tsiiligianni IG, Alma HJ, De Jong C, Jelusic D, Wittmann M, Schuler M, et al. Investigating sensitivity, specificity, and area under the curve

- of the Clinical COPD Questionnaire, COPD Assessment Test, and Modified Medical Research Council scale according to GOLD using St George's Respiratory Questionnaire cutoff 25 (and 20) as reference. *Int J Chron Obstruct Pulmon Dis.* 2016;11:1045-1052. Available in: <http://doi.org/10.2147/COPD.S99793>
186. Zhou J, Yu N, Li X, Wang W. Accuracy of six chronic obstructive pulmonary disease screening questionnaires in the chinese population. *Int J Chron Obstruct Pulmon Dis.* 2022;17:317-327. Available in: <http://doi.org/10.2147/COPD.S341648>
 187. Schunemann HJ, Puhan M, Goldstein R, Jaeschke R, Guyatt GH. Measurement properties and interpretability of the Chronic respiratory disease questionnaire (CRQ). *COPD.* 2005;2(1):81-89. Available in: <http://doi.org/10.1081/copd-200050651>
 188. Zhou Z, Zhou A, Zhao Y, Chen P. Evaluating the clinical COPD questionnaire: a systematic review. *Respirology.* 2017;22(2):251-262. Available in: <http://doi.org/10.1111/resp.12970>
 189. Zhang J, Chen F, Wang Y, Chen Y. Early detection and prediction of acute exacerbation of chronic obstructive pulmonary disease. *Chinese Medical Journal Pulmonary and Critical Care Medicine.* 2023;1(2):102-107. Available in: <http://doi.org/10.1016/j.pccm.2023.04.004>
 190. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest.* 1984;85(6):751-758. Available in: <http://doi.org/10.1378/chest.85.6.751>
 191. Mahler DA, Waterman LA, Ward J, Mccusker C, Zuwallack R, Baird JC. Validity and responsiveness of the self-administered computerized versions of the baseline and transition dyspnea indexes. *Chest.* 2007;132(4):1283-1290. Available in: <http://doi.org/10.1378/chest.07-0703>
 192. Mahler DA, Ward J, Waterman LA, Mccusker C, Zuwallack R, Baird JC. Patient-reported dyspnea in COPD reliability and association with stage of disease. *Chest.* 2009;136(6):1473-1479. Available in: <http://doi.org/10.1378/chest.09-0934>
 193. Chhabra SK, Gupta AK, Khuma MZ. Evaluation of three scales of dyspnea in chronic obstructive pulmonary disease. *Ann Thorac Med.* 2009;4(3):128-132. Available in: <http://doi.org/10.4103/1817-1737.53351>
 194. Kim Y, Kim Y-J, Cho W-K. Effect of multiple comorbidities on mortality in chronic obstructive pulmonary disease among Korean population: a nationwide cohort study. *BMC Pulm Med.* 2021;21(1):56. Available in: <http://doi.org/10.1186/s12890-021-01424-7>
 195. Eroglu SA, Gunen H, Yakar HI, Yildiz E, Kavas M, Duman D. Influence of comorbidities in long-term survival of chronic obstructive pulmonary disease patients. *J Thorac Dis.* 2019;11(4):1379-1386. Available in: <https://jtd.amegroups.org/article/view/28054>
 196. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol.* 1994;47(11):1245-1251. Available in: [http://doi.org/10.1016/0895-4356\(94\)90129-5](http://doi.org/10.1016/0895-4356(94)90129-5)
 197. De Torres JP, Casanova C, Marin JM, Pinto-Plata V, Divo M, Zulueta JJ, et al. Prognostic evaluation of COPD patients: GOLD 2011 versus BODE and the COPD comorbidity index COTE. *Thorax.* 2014;69(9):799-804. Available in: <http://doi.org/10.1136/thoraxjnl-2014-205770>
 198. Owusuaa C, Dijkland SA, Nieboer D, Van Der Rijt CCD, Van Der Heide A. Predictors of mortality in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *BMC Pulmonary Medicine.* 2022;22(1):125. Available in: <http://doi.org/10.1186/s12890-022-01911-5>
 199. Divo M, Cote C, De Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2012;186(2):155-161. Available in: <http://doi.org/10.1164/rccm.201201-0034OC>
 200. Chen H, Luo X, Du Y, He C, Lu Y, Shi Z, et al. Association between chronic obstructive pulmonary disease and cardiovascular disease in adults aged 40 years and above: data from NHANES 2013-2018. *BMC Pulmonary Medicine.* 2023;23(1):318. Available in: <http://doi.org/10.1186/s12890-023-02606-1>
 201. Chen W, Thomas J, Sadatsafavi M, Fitzgerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med.* 2015;3(8):631-639. Available in: [http://doi.org/10.1016/s2213-2600\(15\)00241-6](http://doi.org/10.1016/s2213-2600(15)00241-6)
 202. Corlateanu A, Covantev S, Mathioudakis AG, Botnaru V, Cazzola M, Siafakas N. Chronic obstructive pulmonary disease and stroke. *COPD.* 2018;15(4):405-413. Available in: <http://doi.org/10.1080/15412555.2018.1464551>
 203. Kim YR, Hwang IC, Lee YJ, Ham EB, Park DK, Kim S. Stroke risk among patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Clinics (Sao Paulo).* 2018;73:e177. Available in: <http://doi.org/10.6061/clinics/2018/e177>
 204. Freixa X, Portillo K, Paré C, Garcia-Aymerich J, Gomez FP, Benet M, et al. Echocardiographic abnormalities in patients with COPD at their first hospital admission. *Eur Respir J.* 2013;41(4):784-791. Available in: <http://doi.org/10.1183/09031936.00222511>
 205. Rodriguez LA, Wallander MA, Martin-Merino E, Johansson S. Heart failure, myocardial infarction, lung cancer and death in COPD patients: a UK primary care study. *Respir Med.* 2010;104(11):1691-1699. Available in: <http://doi.org/10.1016/j.rmed.2010.04.018>
 206. Fabbri LM, Luppi F, Beghe B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J.* 2008;31(1):204-212. Available in: <http://doi.org/10.1183/09031936.00114307>
 207. Santos NCD, Miravittles M, Camelier AA, Almeida VDC, Maciel R, Camelier FWR. Prevalence and impact of comorbidities in individuals with chronic obstructive pulmonary disease: a systematic review. *Tuberc Respir Dis (Seoul).* 2022;85(3):205-220. Available in: <http://doi.org/10.4046/trd.2021.0179>
 208. Yin HL, Yin SQ, Lin QY, Xu Y, Xu HW, Liu T. Prevalence of comorbidities in chronic obstructive pulmonary disease patients: a meta-analysis. *Medicine (Baltimore).* 2017;96(19):e6836. Available in: <http://doi.org/10.1097/md.0000000000006836>
 209. Tillie-Leblond I, Marquette CH, Perez T, Scherpereel A, Zanetti C, Tonnel AB, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med.* 2006;144(6):390-396. Available in: <http://doi.org/10.7326/0003-4819-144-6-200603210-00005>
 210. Gunen H, Gulbas G, In E, Yetkin O, Hacievliyagil SS. Venous thromboemboli and exacerbations of COPD. *Eur Respir J.* 2010;35(6):1243-1248. Available in: <http://doi.org/10.1183/09031936.00120909>
 211. Han W, Wang M, Xie Y, Ruan H, Zhao H, Li J. Prevalence of pulmonary embolism and deep venous thromboembolism in patients with acute exacerbation of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Front Cardiovasc Med.* 2022;9:732855. Available in: <http://doi.org/10.3389/fcvm.2022.732855>
 212. Sato R, Hasegawa D, Nishida K, Takahashi K, Schleicher M, Chaisson N. Prevalence of pulmonary embolism in patients with acute

- exacerbations of COPD: A systematic review and meta-analysis. *Am J Emerg Med.* 2021;50:606-617. Available in: <http://doi.org/10.1016/j.ajem.2021.09.041>
213. Fu X, Zhong Y, Xu W, Ju J, Yu M, Ge M, et al. The prevalence and clinical features of pulmonary embolism in patients with AE-COPD: A meta-analysis and systematic review. *PLoS One.* 2021;16(9):e0256480. Available in: <http://doi.org/10.1371/journal.pone.0256480>
 214. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J.* 2008;32(5):1371-1385. Available in: <http://doi.org/10.1183/09031936.00015608>
 215. Chaouat A, Bugnet AS, Kadaoui N, Schott R, Enache I, Ducolone A, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2005;172(2):189-194. Available in: <http://doi.org/10.1164/rccm.200401-006OC>
 216. Arif R, Pandey A, Zhao Y, Arsenault-Mehta K, Khoujah D, Mehta S. Treatment of pulmonary hypertension associated with COPD: a systematic review. *ERJ Open Res.* 2022;8(1):00348-2021. Available in: <http://doi.org/10.1183/23120541.00348-2021>
 217. Schuster M, Müller J, Schwarz EI, Saxer S, Schneider SR, Ulrich S, et al. Oxygen therapy in pulmonary vascular disease: a systematic review, meta-analysis, and comment. *Heart Fail Clin.* 2023;19(1s):e1-e11. Available in: <http://doi.org/10.1016/j.hfc.2022.11.001>
 218. Rizkallah J, Man SFP, Sin DD. Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis. *Chest.* 2009;135(3):786-793. Available in: <http://doi.org/10.1378/chest.08-1516>
 219. Zhang L, Liu Y, Zhao S, Wang Z, Zhang M, Zhang S, et al. The incidence and prevalence of pulmonary hypertension in the COPD population: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2022;17:1365-1379. Available in: <http://doi.org/10.2147/copd.S359873>
 220. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc.* 2005;2(1):8-11. Available in: <http://doi.org/10.1513/pats.200404-032MS>
 221. Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen city heart study. *Eur Respir J.* 2003;21(6):1012-1016. Available in: <http://doi.org/10.1183/09031936.03.00051502>
 222. Al-Khatib SM, Granger CB, Huang Y, Lee KL, Califf RM, Simoons ML, et al. Sustained ventricular arrhythmias among patients with acute coronary syndromes with no ST-segment elevation: incidence, predictors, and outcomes. *Circulation.* 2002;106(3):309-312. Available in: <http://doi.org/10.1161/01.cir.0000022692.49934.e3>
 223. Romiti GF, Corica B, Pipitone E, Vitolo M, Raparelli V, Basili S, et al. Prevalence, management and impact of chronic obstructive pulmonary disease in atrial fibrillation: a systematic review and meta-analysis of 4,200,000 patients. *European Heart Journal.* 2021;42(35):3541-3554. Available in: <http://doi.org/10.1093/eurheartj/ehab453>
 224. Ye J, Yao P, Shi X, Yu X. A systematic literature review and meta-analysis on the impact of COPD on atrial fibrillation patient outcome. *Heart Lung.* 2022;51:67-74. Available in: <http://doi.org/10.1016/j.hrtlng.2021.09.001>
 225. Regvat J, Zmitek A, Vegnuti M, Kosnik M, Suskovic S. Anxiety and depression during hospital treatment of exacerbation of chronic obstructive pulmonary disease. *J Int Med Res.* 2011;39(3):1028-1038. Available in: <http://doi.org/10.1177/147323001103900338>
 226. Volpato E, Toniolo S, Pagnini F, Banfi P. The relationship between anxiety, depression and treatment adherence in chronic obstructive pulmonary disease: a systematic review. *Int J Chron Obstruct Pulmon Dis.* 2021;16:2001-2021. Available in: <http://doi.org/10.2147/copd.S313841>
 227. Schneider C, Jick SS, Bothner U, Meier CR. COPD and the risk of depression. *Chest.* 2010;137(2):341-347. Available in: <http://doi.org/10.1378/chest.09-0614>
 228. Koenig HG, Cohen HJ, Blazer DG, Krishnan KR, Sibert TE. Profile of depressive symptoms in younger and older medical inpatients with major depression. *J Am Geriatr Soc.* 1993;41(11):1169-1176. Available in: <http://doi.org/10.1111/j.1532-5415.1993.tb07298.x>
 229. Leone N, Courbon D, Thomas F, Bean K, Jegou B, Leynaert B, et al. Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *Am J Respir Crit Care Med.* 2009;179(6):509-516. Available in: <http://doi.org/10.1164/rccm.200807-1195OC>
 230. Funakoshi Y, Omori H, Mihara S, Marubayashi T, Katoh T. Association between airflow obstruction and the metabolic syndrome or its components in Japanese men. *Intern Med.* 2010;49(19):2093-2099. Available in: <http://doi.org/10.2169/internalmedicine.49.3882>
 231. Cebron Lipovec N, Beijers RJ, Van Den Borst B, Doehner W, Lainscak M, Schols AM. The prevalence of metabolic syndrome in chronic obstructive pulmonary disease: a systematic review. *COPD.* 2016;13(3):399-406. Available in: <http://doi.org/10.3109/15412555.2016.1140732>
 232. Wagner PD. Possible mechanisms underlying the development of cachexia in COPD. *Eur Respir J.* 2008;31(3):492-501. Available in: <http://doi.org/10.1183/09031936.00074807>
 233. Vestbo J, Prescott E, Almdal T, Dahl M, Nordestgaard BG, Andersen T, et al. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *Am J Respir Crit Care Med.* 2006;173(1):79-83. Available in: <http://doi.org/10.1164/rccm.200506-969OC>
 234. Deng M, Lu Y, Zhang Q, Bian Y, Zhou X, Hou G. Global prevalence of malnutrition in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis. *Clin Nutr.* 2023;42(6):848-858. Available in: <http://doi.org/10.1016/j.clnu.2023.04.005>
 235. Gattermann Pereira T, Lima J, Silva FM. Undernutrition is associated with mortality, exacerbation, and poorer quality of life in patients with chronic obstructive pulmonary disease: a systematic review with meta-analysis of observational studies. *JPEN J Parenter Enteral Nutr.* 2022;46(5):977-996. Available in: <http://doi.org/10.1002/jpen.2350>
 236. Sepúlveda-Loyola W, Osadnik C, Phu S, Morita AA, Duque G, Probst VS. Diagnosis, prevalence, and clinical impact of sarcopenia in COPD: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle.* 2020;11(5):1164-1176. Available in: <http://doi.org/10.1002/jcsm.12600>
 237. Benz E, Trajanoska K, Lahousse L, Schoufour JD, Terzikhan N, De Roos E, et al. Sarcopenia in COPD: a systematic review and meta-analysis. *Eur Respir Rev.* 2019;28(154):190049. Available in: <http://doi.org/10.1183/16000617.0049-2019>
 238. De Blasio F, Di Gregorio A, De Blasio F, Bianco A, Bellofiore B, Scalfi L. Malnutrition and sarcopenia assessment in patients with chronic obstructive pulmonary disease according to international diagnostic criteria, and evaluation of raw BIA variables. *Respir Med.* 2018;134:1-5. Available in: <http://doi.org/10.1016/j.rmed.2017.11.006>
 239. Brigham EP, Anderson JA, Brook RD, Calverley PMA, Celli BR, Cowans NJ, et al. Challenging the obesity paradox: extreme obesity and COPD mortality in the SUMMIT trial. *ERJ Open Res.* 2021;7(3):00902-2020. Available in: <http://doi.org/10.1183/23120541.00902-2020>

240. Putcha N, Anzueto AR, Calverley PMA, Celli BR, Tashkin DP, Metzdorf N, et al. Mortality and exacerbation risk by body mass index in patients with COPD in TIOSPIR and UPLIFT. *Ann Am Thorac Soc.* 2022;19(2):204-213. Available in: <http://doi.org/10.1513/AnnalsATS.202006-722OC>
241. Maggi S, Siviero P, Gonnelli S, Schiraldi C, Malavolta N, Nuti R, et al. Osteoporosis risk in patients with chronic obstructive pulmonary disease: the EOLO study. *J Clin Densitom.* 2009;12(3):345-352. Available in: <http://doi.org/10.1016/j.jocd.2009.05.003>
242. Graat-Verboom L, Wouters EF, Smeenk FW, Van Den Borne BE, Lunde R, Spruit MA. Current status of research on osteoporosis in COPD: a systematic review. *Eur Respir J.* 2009;34(1):209-218. Available in: <http://doi.org/10.1183/09031936.50130408>
243. Bitar AN, Syed Sulaiman SA, Ali laH, Khan I, Khan AH. Osteoporosis among patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of prevalence, severity, and therapeutic outcomes. *J Pharm Bioallied Sci.* 2019;11(4):310-320. Available in: http://doi.org/10.4103/jpbs.JPBS_126_19
244. Cote C, Zilberberg MD, Mody SH, Dordelly LJ, Celli B. Haemoglobin level and its clinical impact in a cohort of patients with COPD. *Eur Respir J.* 2007;29(5):923-9. Available in: <http://doi.org/10.1183/09031936.00137106>
245. Yohannes AM, Ershler WB. Anemia in COPD: a systematic review of the prevalence, quality of life, and mortality. *Respir Care.* 2011;56(5):644-652. Available in: <http://doi.org/10.4187/respcare.01002>
246. Alisamir M, Ebrahimi M, Rahim F. Anemia in chronic obstructive pulmonary disease: a systematic review. *Respir Investig.* 2022;60(4):510-521. Available in: <http://doi.org/10.1016/j.resinv.2022.03.006>
247. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med.* 2005;352(10):1011-1023. Available in: <http://doi.org/10.1056/NEJMr041809>
248. Zeng Z, Song Y, He X, Yang H, Yue F, Xiong M, et al. Obstructive sleep apnea is associated with an increased prevalence of polycythemia in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2022;17:195-204. Available in: <http://doi.org/10.2147/copd.S338824>
249. Zhang J, Demeo DL, Silverman EK, Make BJ, Wade RC, Wells JM, et al. Secondary polycythemia in chronic obstructive pulmonary disease: prevalence and risk factors. *BMC Pulm Med.* 2021;21(1):235. Available in: <http://doi.org/10.1186/s12890-021-01585-5>
250. Du D, Zhang G, Xu D, Liu L, Hu X, Chen L, et al. Prevalence and clinical characteristics of sleep disorders in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Sleep Med.* 2023;112:282-290. Available in: <http://doi.org/10.1016/j.sleep.2023.10.034>
251. Olaithe M, Bucks RS, Hillman DR, Eastwood PR. Cognitive deficits in obstructive sleep apnea: insights from a meta-review and comparison with deficits observed in COPD, insomnia, and sleep deprivation. *Sleep Med Rev.* 2018;38:39-49. Available in: <http://doi.org/10.1016/j.smrv.2017.03.005>
252. Loganathan RS, Stover DE, Shi W, Venkatraman E. Prevalence of COPD in women compared to men around the time of diagnosis of primary lung cancer. *Chest.* 2006;129(5):1305-1312. Available in: <http://doi.org/10.1378/chest.129.5.1305>
253. Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. *Eur Respir J.* 2009;34(2):380-386. Available in: <http://doi.org/10.1183/09031936.00144208>
254. Sekine Y, Katsura H, Koh E, Hiroshima K, Fujisawa T. Early detection of COPD is important for lung cancer surveillance. *Eur Respir J.* 2012;39(5):1230-1240. Available in: <http://doi.org/10.1183/09031936.00126011>
255. Takiguchi Y, Sekine I, Iwasawa S, Kurimoto R, Tatsumi K. Chronic obstructive pulmonary disease as a risk factor for lung cancer. *World J Clin Oncol.* 2014;5(4):660-666. Available in: <http://doi.org/10.5306/wjco.v5.i4.660>
256. Wang W, Dou S, Dong W, Xie M, Cui L, Zheng C, et al. Impact of COPD on prognosis of lung cancer: from a perspective on disease heterogeneity. *Int J Chron Obstruct Pulmon Dis.* 2018;13:3767-3776. Available in: <http://doi.org/10.2147/COPD.S168048>
257. Wu K, Wang J, Zhao L, Wang P, Duan Q. The prognosis of non-small cell lung cancer combined with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Clin Respir J.* 2020;14(4):389-396. Available in: <http://doi.org/10.1111/crj.13144>
258. Lin H, Lu Y, Lin L, Meng K, Fan J. Does chronic obstructive pulmonary disease relate to poor prognosis in patients with lung cancer?: a meta-analysis. *Medicine (Baltimore).* 2019;98(11):e14837. Available in: <http://doi.org/10.1097/md.00000000000014837>
259. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med.* 2005;142(4):233-239. Available in: <http://doi.org/10.7326/0003-4819-142-4-200502150-00005>
260. Shahab L, Jarvis MJ, Britton J, West R. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. *Thorax.* 2006;61(12):1043-1047. Available in: <http://doi.org/10.1136/thx.2006.064410>
261. Willemse BW, Postma DS, Timens W, Ten Hacken NH. The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. *Eur Respir J.* 2004;23(3):464-476. Available in: <http://doi.org/10.1183/09031936.04.00012704>
262. Warnier MJ, Van Riet EE, Rutten FH, De Bruin ML, Sachs AP. Smoking cessation strategies in patients with COPD. *Eur Respir J.* 2013;41(3):727-734. Available in: <http://doi.org/10.1183/09031936.00014012>
263. Kirsch F. A systematic review of quality and cost-effectiveness derived from Markov models evaluating smoking cessation interventions in patients with chronic obstructive pulmonary disease. *Expert Rev Pharmacoecon Outcomes Res.* 2015;15(2):301-316. Available in: <http://doi.org/10.1586/14737167.2015.1001976>
264. Jiménez-Ruiz CA, Masa F, Miravittles M, Gabriel R, Viejo JL, Villasante C, et al. Smoking characteristics: differences in attitudes and dependence between healthy smokers and smokers with COPD. *Chest.* 2001;119(5):1365-1370. Available in: <http://doi.org/10.1378/chest.119.5.1365>
265. Van Eerd EA, Van Der Meer RM, Van Schayck OC, Kotz D. Smoking cessation for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2016;2016(8):CD010744. Available in: <http://doi.org/10.1002/14651858.CD010744.pub2>
266. Zabert GE. Una oportunidad que no debe ser desaprovechada. *Neumol Cir Tórax.* 2024;83(2):121-122. Available in: <http://doi.org/10.35366/119280>
267. García-Gómez L, Hernández-Pérez A, Noé-Díaz V, Riesco-Miranda JA, Jiménez-Ruiz C. Smoking cessation treatments: current psychological and pharmacological options. *Rev Invest Clin.* 2019;71(1):7-16. Available in: <http://doi.org/10.24875/ric.18002629>
268. Cheng CCW, He WJA, Gouda H, Zhang MJ, Luk TT, Wang MP, et al. Effectiveness of very brief advice on tobacco cessation: a systematic

- review and meta-analysis. *J Gen Intern Med.* 2024;39(9):1721-1734. Available in: <http://doi.org/10.1007/s11606-024-08786-8>
269. Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev.* 2018;5(5):CD000146. Available in: <http://doi.org/10.1002/14651858.CD000146.pub5>
270. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA.* 1994;272(19):1497-1505. Available in: <https://www.ncbi.nlm.nih.gov/pubmed/7966841>
271. Tonnesen P, Mikkelsen K, Bremann L. Nurse-conducted smoking cessation in patients with COPD using nicotine sublingual tablets and behavioral support. *Chest.* 2006;130(2):334-342. Available in: <http://doi.org/10.1378/chest.130.2.334>
272. Theodoulou A, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J, et al. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2023;6(6):CD013308. Available in: <http://doi.org/10.1002/14651858.CD013308.pub2>
273. Bedolla-Tinoco A, Ortiz-González YG, García-Peña L, Thirión-Romero I, Robles-Hernández R, Hernández-Pérez A, et al. Propuesta de abordaje terapéutico para el abandono del tabaco en pacientes hospitalizados. *Neumol Cir Tórax.* 2024;83(2):134-142. Available in: <http://doi.org/10.35366/119283>
274. Tashkin D, Kanner R, Bailey W, Buist S, Anderson P, Nides M, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet.* 2001;357(9268):1571-1575. Available in: [http://doi.org/10.1016/s0140-6736\(00\)04724-3](http://doi.org/10.1016/s0140-6736(00)04724-3)
275. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev.* 2013;2013(5):CD009329. Available in: <http://doi.org/10.1002/14651858.CD009329.pub2>
276. Hernandez Zenteno RJ, Lara DF, Venegas AR, Sansores RH, Pineda JR, Trujillo FF, et al. Varenicline for long term smoking cessation in patients with COPD. *Pulm Pharmacol Ther.* 2018;53:116-120. Available in: <http://doi.org/10.1016/j.pupt.2018.11.001>
277. Hajek P, McRobbie H, Myers K. Efficacy of cytisine in helping smokers quit: systematic review and meta-analysis. *Thorax.* 2013;68(11):1037-1042. Available in: <http://doi.org/10.1136/thoraxjnl-2012-203035>
278. Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev.* 2016;3(3):CD008286. Available in: <http://doi.org/10.1002/14651858.CD008286.pub3>
279. Rasmussen M, Lauridsen SV, Pedersen B, Backer V, Tonnesen H. Intensive versus short face-to-face smoking cessation interventions: a meta-analysis. *Eur Respir Rev.* 2022;31(165):220063. Available in: <http://doi.org/10.1183/16000617.0063-2022>
280. Hanewinkel R, Niederberger K, Pedersen A, Unger JB, Galimov A. E-cigarettes and nicotine abstinence: a meta-analysis of randomised controlled trials. *Eur Respir Rev.* 2022;31(163):210215. Available in: <http://doi.org/10.1183/16000617.0215-2021>
281. Lindson N, Butler AR, McRobbie H, Bullen C, Hajek P, Begh R, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev.* 2024;1(1):CD010216. Available in: <http://doi.org/10.1002/14651858.CD010216.pub8>
282. Foulds J, Burke M, Steinberg M, Williams JM, Ziedonis DM. Advances in pharmacotherapy for tobacco dependence. *Expert Opin Emerg Drugs.* 2004;9(1):39-53. Available in: <http://doi.org/10.1517/eoed.9.1.39.32951>
283. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. *Am J Prev Med.* 2008;35(2):158-176. Available in: <http://doi.org/10.1016/j.amepre.2008.04.009>
284. Giulietti F, Filippini A, Rosettani G, Giordano P, Iacoacci C, Spannella F, et al. Pharmacological approach to smoking cessation: an updated review for daily clinical practice. *High Blood Press Cardiovasc Prev.* 2020;27(5):349-362. Available in: <http://doi.org/10.1007/s40292-020-00396-9>
285. Organización Mundial de la Salud. MPOWER: un plan de medidas para hacer retroceder la epidemia de tabaquismo. 2008. Available in: <https://iris.who.int/handle/10665/43891>
286. Skogstad M, Kjaerheim K, Fladseth G, Gjolstad M, Daae HL, Olsen R, et al. Cross shift changes in lung function among bar and restaurant workers before and after implementation of a smoking ban. *Occup Environ Med.* 2006;63(7):482-487. Available in: <http://doi.org/10.1136/oem.2005.024638>
287. Eisner MD, Smith AK, Blanc PD. Bartenders' respiratory health after establishment of smoke-free bars and taverns. *JAMA.* 1998;280(22):1909-1914. Available in: <http://doi.org/10.1001/jama.280.22.1909>
288. Allwright S, Paul G, Greiner B, Mullally BJ, Pursell L, Kelly A, et al. Legislation for smoke-free workplaces and health of bar workers in Ireland: before and after study. *BMJ.* 2005;331(7525):1117. Available in: <http://doi.org/10.1136/bmj.38636.499225.55>
289. Eagan TM, Hetland J, Aaro LE. Decline in respiratory symptoms in service workers five months after a public smoking ban. *Tob Control.* 2006;15(3):242-246. Available in: <http://doi.org/10.1136/tc.2005.015479>
290. Menzies D, Nair A, Williamson PA, Schembri S, Al-Khairalla MZ, Barnes M, et al. Respiratory symptoms, pulmonary function, and markers of inflammation among bar workers before and after a legislative ban on smoking in public places. *JAMA.* 2006;296(14):1742-1748. Available in: <http://doi.org/10.1001/jama.296.14.1742>
291. Frazer K, Callinan JE, Mchugh J, Van Baarsel S, Clarke A, Doherty K, et al. Legislative smoking bans for reducing harms from secondhand smoke exposure, smoking prevalence and tobacco consumption. *Cochrane Database Syst Rev.* 2016;2(2):CD005992. Available in: <http://doi.org/10.1002/14651858.CD005992.pub3>
292. Lim CCW, Rutherford B, Gartner C, McClure-Thomas C, Foo S, Su FY, et al. A systematic review of second-hand smoking mass media campaigns (2002-2022). *BMC Public Health.* 2024;24(1):693. Available in: <http://doi.org/10.1186/s12889-024-18222-5>
293. Dherani M, Zehra SN, Jackson C, Satyanaryana V, Huque R, Chandra P, et al. Behaviour change interventions to reduce second-hand smoke exposure at home in pregnant women - a systematic review and intervention appraisal. *BMC Pregnancy Childbirth.* 2017;17(1):378. Available in: <http://doi.org/10.1186/s12884-017-1562-7>
294. Pope D, Johnson M, Fleeman N, Jagoe K, Duarte R, Maden M, et al. Are cleaner cooking solutions clean enough? A systematic review and meta-analysis of particulate and carbon monoxide concentrations and exposures. *Environ Res Lett.* 2021;16(8):083002. Available in: <http://doi.org/10.1088/1748-9326/ac13ec>
295. Thomas E, Wickramasinghe K, Mendis S, Roberts N, Foster C. Improved stove interventions to reduce household air pollution in low and middle income countries: a descriptive systematic review. *BMC Public Health.* 2015;15:650. Available in: <http://doi.org/10.1186/s12889-015-2024-7>

296. Thakur M, Nuyts PaW, Boudewijns EA, Flores Kim J, Faber T, Babu GR, et al. Impact of improved cookstoves on women's and child health in low and middle income countries: a systematic review and meta-analysis. *Thorax*. 2018;73(11):1026-1040. Available in: <http://doi.org/10.1136/thoraxjnl-2017-210952>
297. Chapman RS, He X, Blair AE, Lan Q. Improvement in household stoves and risk of chronic obstructive pulmonary disease in Xuanwei, China: retrospective cohort study. *BMJ*. 2005;331(7524):1050. Available in: <http://doi.org/10.1136/bmj.38628.676088.55>
298. Schilman A, Riojas-Rodriguez H, Catalan-Vazquez M, Estevez-Garcia JA, Maserá O, Berrueta-Soriano V, et al. A follow-up study after an improved cookstove intervention in rural Mexico: Estimation of household energy use and chronic PM(2.5) exposure. *Environ Int*. 2019;131:105013. Available in: <http://doi.org/10.1016/j.envint.2019.105013>
299. Cynthia AA, Edwards RD, Johnson M, Zuk M, Rojas L, Jimenez RD, et al. Reduction in personal exposures to particulate matter and carbon monoxide as a result of the installation of a Patsari improved cook stove in Michoacan Mexico. *Indoor Air*. 2008;18(2):93-105. Available in: <http://doi.org/10.1111/j.1600-0668.2007.00509.x>
300. Omar R, Maserá RD, Víctor Berrueta. From cookstoves to cooking systems: the integrated program on sustainable household energy use in Mexico. *Energy for Sustainable Development*. 2005;9(1):25-36. Available in: [http://doi.org/10.1016/S0973-0826\(08\)60480-9](http://doi.org/10.1016/S0973-0826(08)60480-9)
301. De Matteis S, Jarvis D, Darnton A, Hutchings S, Sadhra S, Fishwick D, et al. The occupations at increased risk of COPD: analysis of lifetime job-histories in the population-based UK Biobank Cohort. *Eur Respir J*. 2019;54(1):1900186. Available in: <http://doi.org/10.1183/13993003.00186-2019>
302. Ryu MH, Murphy S, Hinkley M, Carlsten C. COPD exposed to air pollution: a path to understand and protect a susceptible population. *Chest*. 2024;165(4):836-846. Available in: <http://doi.org/10.1016/j.chest.2023.11.012>
303. Hansel NN, Putcha N, Woo H, Peng R, Diette GB, Fawzy A, et al. Randomized clinical trial of air cleaners to improve indoor air quality and chronic obstructive pulmonary disease health: results of the CLEAN AIR study. *Am J Respir Crit Care Med*. 2022;205(4):421-430. Available in: <http://doi.org/10.1164/rccm.202103-0604OC>
304. Lorizio W, Woo H, McCormack MC, Liu C, Putcha N, Wood M, et al. Patterns and predictors of air cleaner adherence among adults with COPD. *Chronic Obstr Pulm Dis*. 2022;9(3):366-376. Available in: <http://doi.org/10.15326/jcopdf.2022.0309>
305. Woo H, Koehler K, Putcha N, Lorizio W, McCormack M, Peng R, et al. Principal stratification analysis to determine health benefit of indoor air pollution reduction in a randomized environmental intervention in COPD: Results from the CLEAN AIR study. *Sci Total Environ*. 2023;868:161573. Available in: <http://doi.org/10.1016/j.scitotenv.2023.161573>
306. Kang J, Jung JY, Huh JY, Ji HW, Kim HC, Lee SW. Behavioral interventions to reduce particulate matter exposure in patients with COPD. *Medicine (Baltimore)*. 2021;100(49):e28119. Available in: <http://doi.org/10.1097/MD.00000000000028119>
307. Zhou Y, Hu G, Wang D, Wang S, Wang Y, Liu Z, et al. Community based integrated intervention for prevention and management of chronic obstructive pulmonary disease (COPD) in Guangdong, China: cluster randomised controlled trial. *BMJ*. 2010;341:c6387. Available in: <http://doi.org/10.1136/bmj.c6387>
308. Ambrosino N, Bertella E. Lifestyle interventions in prevention and comprehensive management of COPD. *Breathe (Sheff)*. 2018;14(3):186-194. Available in: <http://doi.org/10.1183/20734735.018618>
309. Beijers R, Steiner MC, Schols A. The role of diet and nutrition in the management of COPD. *Eur Respir Rev*. 2023;32(168):230003. Available in: <http://doi.org/10.1183/16000617.0003-2023>
310. Van Iersel LEJ, Beijers R, Gosker HR, Schols A. Nutrition as a modifiable factor in the onset and progression of pulmonary function impairment in COPD: a systematic review. *Nutr Rev*. 2022;80(6):1434-1444. Available in: <http://doi.org/10.1093/nutrit/nuab077>
311. Zheng PF, Shu L, Si CJ, Zhang XY, Yu XL, Gao W. Dietary patterns and chronic obstructive pulmonary disease: a meta-analysis. *COPD*. 2016;13(4):515-522. Available in: <http://doi.org/10.3109/15412555.2015.1098606>
312. Hanson C, Sayles H, Rutten E, Wouters EFM, Macnee W, Calverley P, et al. The association between dietary intake and phenotypical characteristics of COPD in the ECLIPSE cohort. *Chronic Obstr Pulm Dis*. 2014;1(1):115-124. Available in: <http://doi.org/10.15326/jcopdf.1.1.2014.0113>
313. Salari-Moghaddam A, Milajerdi A, Larijani B, Esmailzadeh A. Processed red meat intake and risk of COPD: A systematic review and dose-response meta-analysis of prospective cohort studies. *Clin Nutr*. 2019;38(3):1109-1116. Available in: <http://doi.org/10.1016/j.clnu.2018.05.020>
314. Okubo H, Shaheen SO, Ntani G, Jameson KA, Syddall HE, Sayer AA, et al. Processed meat consumption and lung function: modification by antioxidants and smoking. *Eur Respir J*. 2014;43(4):972-982.
315. Zhai H, Wang Y, Jiang W. Fruit and vegetable intake and the risk of chronic obstructive pulmonary disease: a dose-response meta-analysis of observational studies. *Biomed Res Int*. 2020;2020:3783481. Available in: <http://doi.org/10.1155/2020/3783481>
316. Keranis E, Makris D, Rodopoulou P, Martinou H, Papamakarios G, Daniil Z, et al. Impact of dietary shift to higher-antioxidant foods in COPD: a randomised trial. *Eur Respir J*. 2010;36(4):774-780.
317. Piao Z, Chai B, Wu Y, Diao H, He Q, Zheng Q, et al. The association between polyunsaturated fatty acids and chronic obstructive pulmonary disease: a meta-analysis. *Food Funct*. 2024;15(11):5929-5941. Available in: <http://doi.org/10.1039/d3fo04675c>
318. Engelen MP, Jonker R, Sulaiman H, Fisk HL, Calder PC, Deutz NE. ω -3 polyunsaturated fatty acid supplementation improves postabsorptive and prandial protein metabolism in patients with chronic obstructive pulmonary disease: a randomized clinical trial. *Am J Clin Nutr*. 2022;116(3):686-698.
319. Engelen M, Simbo SY, Ruebush LE, Thaden JJ, Ten Have GaM, Harrykissoon RI, et al. Functional and metabolic effects of omega-3 polyunsaturated fatty acid supplementation and the role of β -hydroxy- β -methylbutyrate addition in chronic obstructive pulmonary disease: a randomized clinical trial. *Clin Nutr*. 2024;43(9):2263-2278. Available in: <http://doi.org/10.1016/j.clnu.2024.08.004>
320. Szmídt MK, Kaluza J, Harris HR, Linden A, Wolk A. Long-term dietary fiber intake and risk of chronic obstructive pulmonary disease: a prospective cohort study of women. *Eur J Nutr*. 2020;59(5):1869-1879. Available in: <http://doi.org/10.1007/s00394-019-02038-w>
321. Bernardes S, Eckert IDC, Búrgel CF, Teixeira PJZ, Silva FM. Increased energy and/or protein intake improves anthropometry and muscle strength in chronic obstructive pulmonary disease patients: a systematic review with meta-analysis on randomised controlled clinical trials. *Br J Nutr*. 2022;1-18. Available in: <http://doi.org/10.1017/S000714522000976>
322. Furulund E, Bemanian M, Berggren N, Madebo T, Rivedal SH, Lid TG, et al. Effects of nutritional interventions in individuals with chronic obstructive lung disease: a systematic review of randomized controlled

- trials. *Int J Chron Obstruct Pulmon Dis.* 2021;16:3145-1456. Available in: <http://doi.org/10.2147/COPD.S323736>
323. Parvizian MK, Dhaliwal M, Li J, Satia I, Kurmi OP. Relationship between dietary patterns and COPD: a systematic review and meta-analysis. *ERJ Open Res.* 2020;6(2):00168-2019. Available in: <http://doi.org/10.1183/23120541.00168-2019>
 324. Rausch-Osthoff AK, Kohler M, Sievi NA, Clarenbach CF, Van Gestel AJ. Association between peripheral muscle strength, exercise performance, and physical activity in daily life in patients with chronic obstructive pulmonary disease. *Multidiscip Respir Med.* 2014;9(1):37. Available in: <http://doi.org/10.1186/2049-6958-9-37>
 325. Priego-Jimenez S, Torres-Costosó A, Guzman-Pavon MJ, Lorenzo-García P, Luceron-Lucas-Torres MI, Alvarez-Bueno C. Efficacy of different types of physical activity interventions on exercise capacity in patients with chronic obstructive pulmonary disease (COPD): a network meta-analysis. *Int J Environ Res Public Health.* 2022;19(21):14539. Available in: <http://doi.org/10.3390/ijerph192114539>
 326. Zangger G, Bricca A, Liaghat B, Juhl CB, Mortensen SR, Andersen RM, et al. Benefits and harms of digital health interventions promoting physical activity in people with chronic conditions: systematic review and meta-analysis. *J Med Internet Res.* 2023;25:e46439. Available in: <http://doi.org/10.2196/46439>
 327. Reilly C, Sails J, Stavropoulos-Kalinoglou A, Birch RJ, McKenna J, Clifton IJ, et al. Physical activity promotion interventions in chronic airways disease: a systematic review and meta-analysis. *Eur Respir Rev.* 2023;32(167):220109. Available in: <http://doi.org/10.1183/16000617.0109-2022>
 328. Tanimura K, Sato S, Fujita Y, Yamamoto Y, Hajiro T, Horita N, et al. The efficacy and safety of additional treatment with short-acting muscarinic antagonist combined with long-acting beta-2 agonist in stable patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Chron Respir Dis.* 2023;20:14799731231166008. Available in: <http://doi.org/10.1177/14799731231166008>
 329. Kitaguchi Y, Fujimoto K, Komatsu Y, Hanaoka M, Honda T, Kubo K. Additive efficacy of short-acting bronchodilators on dynamic hyperinflation and exercise tolerance in stable COPD patients treated with long-acting bronchodilators. *Respir Med.* 2013;107(3):394-400. Available in: <http://doi.org/10.1016/j.rmed.2012.11.013>
 330. Bourbeau J, Bhutani M, Hernandez P, Aaron SD, Beaulieu MF, Kermelley SB, et al. 2023 Canadian Thoracic Society Guideline on Pharmacotherapy in Patients With Stable COPD. *Chest.* 2023;164(5):1159-1183. Available in: <http://doi.org/10.1016/j.chest.2023.08.014>
 331. Álvarez FV, Trueba IM, Sanchis JB, López-Rodó LM, Rodríguez Suárez PM, De Cos Escuin JS, et al. Recommendations of the Spanish Society of Pneumology and Thoracic Surgery on the diagnosis and treatment of non-small-cell lung cancer. *Arch Bronconeumol.* 2016;52 Suppl 1:2-62. Available in: [http://doi.org/10.1016/s0300-2896\(16\)30198-3](http://doi.org/10.1016/s0300-2896(16)30198-3)
 332. Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. *Cochrane Database Syst Rev.* 2014;2014(3):CD010844. Available in: <http://doi.org/10.1002/14651858.CD010844.pub2>
 333. Ismaila AS, Huisman EL, Punekar YS, Karabis A. Comparative efficacy of long-acting muscarinic antagonist monotherapies in COPD: a systematic review and network meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2015;10:2495-2517. Available in: <http://doi.org/10.2147/COPD.S92412>
 334. Zhang C, Zhang M, Wang Y, Xiong H, Huang Q, Shuai T, et al. Efficacy and cardiovascular safety of LAMA in patients with COPD: a systematic review and meta-analysis. *J Investig Med.* 2021;69(8):1391-1398. Available in: <http://doi.org/10.1136/jim-2021-001931>
 335. Di Marco F, Sotgiu G, Santus P, O'Donnell DE, Beeh KM, Dore S, et al. Long-acting bronchodilators improve exercise capacity in COPD patients: a systematic review and meta-analysis. *Respir Res.* 2018;19(1):18. Available in: <http://doi.org/10.1186/s12931-018-0721-3>
 336. Calzetta L, Ora J, Cavalli F, Rogliani P, O'Donnell DE, Cazzola M. Impact of LABA/LAMA combination on exercise endurance and lung hyperinflation in COPD: A pair-wise and network meta-analysis. *Respir Med.* 2017;129:189-198. Available in: <http://doi.org/10.1016/j.rmed.2017.06.020>
 337. Miravittles M, Urrutia G, Mathioudakis AG, Ancochea J. Efficacy and safety of tiotropium and olodaterol in COPD: a systematic review and meta-analysis. *Respir Res.* 2017;18(1):196. Available in: <http://doi.org/10.1186/s12931-017-0683-x>
 338. Huisman EL, Cockle SM, Ismaila AS, Karabis A, Punekar YS. Comparative efficacy of combination bronchodilator therapies in COPD: a network meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2015;10:1863-1881. Available in: <http://doi.org/10.2147/COPD.S87082>
 339. Hurst JR, Gruffydd-Jones K, Biswas M, Guranlioglu D, Jenkins M, Stjepanovic N, et al. Efficacy and safety of LAMA/LABA fixed-dose combination therapies in chronic obstructive pulmonary disease: a systematic review of direct and indirect treatment comparisons. *Int J Chron Obstruct Pulmon Dis.* 2020;15:1529-1543. Available in: <http://doi.org/10.2147/COPD.S230955>
 340. Miravittles M, Garcia-Rivero JL, Ribera X, Galera J, Garcia A, Palomino R, et al. Exercise capacity and physical activity in COPD patients treated with a LAMA/LABA combination: a systematic review and meta-analysis. *Respir Res.* 2022;23(1):347. Available in: <http://doi.org/10.1186/s12931-022-02268-3>
 341. Lopez-Campos JL, Calero-Acuna C, Marquez-Martin E, Quintana Gallego E, Carrasco-Hernandez L, Abad Arranz M, et al. Double bronchodilation in chronic obstructive pulmonary disease: a crude analysis from a systematic review. *Int J Chron Obstruct Pulmon Dis.* 2017;12:1867-1876. Available in: <http://doi.org/10.2147/COPD.S132962>
 342. Mammen MJ, Pai V, Aaron SD, Nici L, Alhazzani W, Alexander PE. Dual LABA/LAMA Therapy versus LABA or LAMA monotherapy for chronic obstructive pulmonary disease: a systematic review and meta-analysis in support of the American Thoracic Society clinical practice guideline. *Ann Am Thorac Soc.* 2020;17(9):1133-1143. Available in: <http://doi.org/10.1513/AnnalsATS.201912-915OC>
 343. Rodrigo GJ, Price D, Anzueto A, Singh D, Altman P, Bader G, et al. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2017;12:907-922. Available in: <http://doi.org/10.2147/COPD.S130482>
 344. Langham S, Lewis J, Pooley N, Embleton N, Langham J, Han MK, et al. Single-inhaler triple therapy in patients with chronic obstructive pulmonary disease: a systematic review. *Respir Res.* 2019;20(1):242. Available in: <http://doi.org/10.1186/s12931-019-1213-9>
 345. Long H, Xu H, Janssens JP, Guo Y. Single-inhaler triple vs single-inhaler dual therapy in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized control trials. *Respir Res.* 2021;22(1):209. Available in: <http://doi.org/10.1186/s12931-021-01794-w>
 346. Mammen MJ, Lloyd DR, Kumar S, Ahmed AS, Pai V, Kunadharaju R, et al. Triple therapy versus dual or monotherapy with long-

- acting bronchodilators for chronic obstructive pulmonary disease. a systematic review and meta-analysis. *Ann Am Thorac Soc.* 2020;17(10):1308-1318. Available in: <http://doi.org/10.1513/AnnalsATS.202001-023OC>
347. Erratum: triple therapy versus dual or monotherapy with long-acting bronchodilators for chronic obstructive pulmonary disease. a systematic review and meta-analysis. *Ann Am Thorac Soc.* 2021;18(2):377. Available in: <http://doi.org/10.1513/AnnalsATS.v18erratum3>
348. Cazzola M, Rogliani P, Calzetta L, Matera MG. Triple therapy versus single and dual long-acting bronchodilator therapy in COPD: a systematic review and meta-analysis. *Eur Respir J.* 2018;52(6):1801586. Available in: <http://doi.org/10.1183/13993003.01586-2018>
349. Kwak MS, Kim E, Jang EJ, Kim HJ, Lee CH. The efficacy and safety of triple inhaled treatment in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis using Bayesian methods. *Int J Chron Obstruct Pulmon Dis.* 2015;10:2365-2376. Available in: <http://doi.org/10.2147/COPD.S93191>
350. Van Geffen WH, Tan DJ, Walters JA, Walters EH. Inhaled corticosteroids with combination inhaled long-acting beta2-agonists and long-acting muscarinic antagonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2023;12(12):CD011600. Available in: <http://doi.org/10.1002/14651858.CD011600.pub3>
351. Regard L, Burgel PR, Roche N. Inhaled therapy, cardiovascular risk and benefit-risk considerations in COPD: innocent until proven guilty, or vice versa? *Eur Respir J.* 2023;61(2):2202135. Available in: <http://doi.org/10.1183/13993003.02135-2022>
352. Yang IA, Ferry OR, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids versus placebo for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2023;3(3):CD002991. Available in: <http://doi.org/10.1002/14651858.CD002991.pub4>
353. Ding Y, Sun L, Wang Y, Zhang J, Chen Y. Efficacy of ICS versus Non-ICS combination therapy in COPD: a meta-analysis of randomised controlled trials. *Int J Chron Obstruct Pulmon Dis.* 2022;17:1051-1067. Available in: <http://doi.org/10.2147/COPD.S347588>
354. Pirera E, Di Raimondo D, Tuttolomondo A. Triple therapy de-escalation and withdrawal of inhaled corticosteroids to dual bronchodilator therapy in patients with chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *J Clin Med.* 2024;13(20):6199. Available in: <http://doi.org/10.3390/jcm13206199>
355. Rogliani P, Ritondo BL, Gabriele M, Cazzola M, Calzetta L. Optimizing de-escalation of inhaled corticosteroids in COPD: a systematic review of real-world findings. *Expert Rev Clin Pharmacol.* 2020;13(9):977-990. Available in: <http://doi.org/10.1080/17512433.2020.1817739>
356. Chrystyn H, Van Der Palen J, Sharma R, Barnes N, Delafont B, Mahajan A, et al. Device errors in asthma and COPD: systematic literature review and meta-analysis. *NPJ Prim Care Respir Med.* 2017;27(1):22. Available in: <http://doi.org/10.1038/s41533-017-0016-z>
357. Cosio BG, Hernandez C, Chiner E, Gimeno-Santos E, Pleguezuelos E, Seijas N, et al. Spanish COPD Guidelines (GesEPOC 2021): Non-pharmacological Treatment Update. *Arch Bronconeumol.* 2022;58(4):345-351. Available in: <http://doi.org/10.1016/j.arbres.2021.08.010>
358. Donath E, Chaudhry A, Hernandez-Aya LF, Lit L. A meta-analysis on the prophylactic use of macrolide antibiotics for the prevention of disease exacerbations in patients with chronic obstructive pulmonary disease. *Respir Med.* 2013;107(9):1385-1392. Available in: <http://doi.org/10.1016/j.rmed.2013.05.004>
359. Lee JS, Park DA, Hong Y, Jo KW, Lee SW, Huh JW, et al. Systematic review and meta-analysis of prophylactic antibiotics in COPD and/or chronic bronchitis. *Int J Tuberc Lung Dis.* 2013;17(2):153-162. Available in: <http://doi.org/10.5588/ijtld.12.0401>
360. Cui Y, Luo L, Li C, Chen P, Chen Y. Long-term macrolide treatment for the prevention of acute exacerbations in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2018;13:3813-3829. Available in: <http://doi.org/10.2147/COPD.S181246>
361. Wang Y, Zipp TR, Bahar MA, Kocks JWH, Wilffert B, Hak E. Effects of prophylactic antibiotics on patients with stable COPD: a systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother.* 2018;73(12):3231-3243. Available in: <http://doi.org/10.1093/jac/dky326>
362. Li H, Liu DH, Chen LL, Zhao Q, Yu YZ, Ding JJ, et al. Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. *Antimicrob Agents Chemother.* 2014;58(1):511-517. Available in: <http://doi.org/10.1128/aac.02067-13>
363. Phillips JE. Inhaled phosphodiesterase 4 (PDE4) inhibitors for inflammatory respiratory diseases. *Front Pharmacol.* 2020;11:259. Available in: <http://doi.org/10.3389/fphar.2020.00259>
364. Chong J, Leung B, Poole P. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2017;9(9):Cd002309. Available in: <http://doi.org/10.1002/14651858.CD002309.pub5>
365. Janjua S, Fortescue R, Poole P. Phosphodiesterase-4 inhibitors for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2020;5(5):Cd002309. Available in: <http://doi.org/10.1002/14651858.CD002309.pub6>
366. Oba Y, Lone NA. Efficacy and safety of roflumilast in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Ther Adv Respir Dis.* 2013;7(1):13-24. Available in: <http://doi.org/10.1177/1753465812466167>
367. Luo J, Wang K, Liu D, Liang BM, Liu CT. Can roflumilast, a phosphodiesterase-4 inhibitor, improve clinical outcomes in patients with moderate-to-severe chronic obstructive pulmonary disease? A meta-analysis. *Respir Res.* 2016;17:18. doi: 10.1186/s12931-016-0330-y.
368. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M, et al. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. *N Engl J Med.* 2023;389(3):205-214. Available in: <http://doi.org/10.1056/NEJMoa2303951>
369. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Bafadhel M, Christenson SA, et al. Dupilumab for COPD with blood eosinophil evidence of type 2 inflammation. *N Engl J Med.* 2024;390(24):2274-2283. Available in: <http://doi.org/10.1056/NEJMoa2401304>
370. Papi A, Avdeev S, Calverley PMA, Cordeiro CR, Jesenak M, Koblizek V, et al. Use of mucolytics in COPD: A Delphi consensus study. *Respir Med.* 2020;175:106190. Available in: <http://doi.org/10.1016/j.rmed.2020.106190>
371. Cazzola M, Rogliani P, Calzetta L, Hanania NA, Matera MG. Impact of mucolytic agents on COPD exacerbations: a pair-wise and network meta-analysis. *COPD.* 2017;14(5):552-563. Available in: <http://doi.org/10.1080/15412555.2017.1347918>
372. Poole P, Sathananthan K, Fortescue R. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2019;5(5):Cd001287. Available in: <http://doi.org/10.1002/14651858.CD001287.pub6>
373. Janjua S, Mathioudakis AG, Fortescue R, Walker RA, Sharif S, Threapleton CJ, et al. Prophylactic antibiotics for adults with chronic

- obstructive pulmonary disease: a network meta-analysis. *Cochrane Database Syst Rev.* 2021;1(1):CD013198. Available in: <http://doi.org/10.1002/14651858.CD013198.pub2>
374. Huang C, Kuo S, Lin L, Yang Y. The efficacy of N-acetylcysteine in chronic obstructive pulmonary disease patients: a meta-analysis. *Ther Adv Respir Dis.* 2023;17:17534666231158563. Available in: <http://doi.org/10.1177/17534666231158563>
375. Cazzola M, Anapurapu S, Page CP. Polyvalent mechanical bacterial lysate for the prevention of recurrent respiratory infections: a meta-analysis. *Pulm Pharmacol Ther.* 2012;25(1):62-68. Available in: <http://doi.org/10.1016/j.pupt.2011.11.002>
376. Huang Y, Pei Y, Qian Y, Yao Z, Chen C, Du J, et al. A meta-analysis on the efficacy and safety of bacterial lysates in chronic obstructive pulmonary disease. *Front Med (Lausanne).* 2022;9:877124. Available in: <http://doi.org/10.3389/fmed.2022.877124>
377. Lee JH, Kim HJ, Kim YH. The effectiveness of anti-leukotriene agents in patients with COPD: a systemic review and meta-analysis. *Lung.* 2015;193(4):477-486. Available in: <http://doi.org/10.1007/s00408-015-9743-5>
378. Liu L, Wang JL, Xu XY, Feng M, Hou Y, Chen L. Leukotriene receptor antagonists do not improve lung function decline in COPD: a meta-analysis. *Eur Rev Med Pharmacol Sci.* 2018;22(3):829-834. Available in: http://doi.org/10.26355/eurrev_201802_14319
379. Kim JJY, Dennett L, Ospina MB, Hicks A, Vliagoftis H, Adatia A. Effectiveness of immunoglobulin replacement therapy in preventing infections in patients with chronic obstructive pulmonary disease: a systematic review. *Allergy Asthma Clin Immunol.* 2024;20(1):30. Available in: <http://doi.org/10.1186/s13223-024-00886-8>
380. Noguera OMJ, Pérez TB, Barrientos CV, Robles GR, Sierra MJG. Escala de ansiedad y depresión hospitalaria (HADS): validación en pacientes mexicanos con infección por VIH. *Psicología Iberoamericana.* 2013;21(2):12-31.
381. Jacobs SS, Krishnan JA, Lederer DJ, Ghazipura M, Hossain T, Tan AM, et al. Home oxygen therapy for adults with chronic lung disease. an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med.* 2020;202(10):e121-e41. Available in: <http://doi.org/10.1164/rccm.202009-3608ST>
382. Perez-Padilla R. Impact of moderate altitude on lung diseases and risk of high altitude illnesses. *Rev Invest Clin.* 2022;74(5):232-243. Available in: <http://doi.org/10.24875/RIC.22000088>
383. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. nocturnal oxygen therapy trial group. *Ann Intern Med.* 1980;93(3):391-398. Available in: <http://doi.org/10.7326/0003-4819-93-3-391>
384. Long term domiciliary oxygen therapy in chronic hypoxic *cor pulmonale* complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet.* 1981;1(8222):681-6. Available in: <https://www.ncbi.nlm.nih.gov/pubmed/6110912>
385. Doherty DE, Petty TL, Bailey W, Carlin B, Cassaburi R, Christopher K, et al. Recommendations of the 6th long-term oxygen therapy consensus conference. *Respir Care.* 2006;51(5):519-525. Available in: <https://www.ncbi.nlm.nih.gov/pubmed/16710952>.
386. Croxton TL, Bailey WC. Long-term oxygen treatment in chronic obstructive pulmonary disease: recommendations for future research: an NHLBI workshop report. *Am J Respir Crit Care Med.* 2006;174(4):373-378. Available in: <http://doi.org/10.1164/rccm.200507-1161WS>
387. Lacasse Y, Casaburi R, Sliwinski P, Chaouat A, Fletcher E, Haidl P, et al. Home oxygen for moderate hypoxaemia in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med.* 2022;10(11):1029-1037. Available in: [http://doi.org/10.1016/S2213-2600\(22\)00179-5](http://doi.org/10.1016/S2213-2600(22)00179-5)
388. Sami R, Savari MA, Mansourian M, Ghazavi R, Meamar R. Effect of long-term oxygen therapy on reducing rehospitalization of patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Pulm Ther.* 2023;9(2):255-270. Available in: <http://doi.org/10.1007/s41030-023-00221-3>
389. Jacobs SS, Krishnan JA, Lederer DJ, Ghazipura M, Hossain T, Tan AM, et al. Home oxygen therapy for adults with chronic lung disease. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med.* 2021;203(8):1045-1046. Available in: <http://doi.org/10.1164/rccm.v203erratum7>
390. Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2005;2005(4):CD001744. Available in: <http://doi.org/10.1002/14651858.CD001744.pub2>
391. Ekstrom M, Andersson A, Papadopoulos S, Kipper T, Pedersen B, Kricka O, et al. Long-term oxygen therapy for 24 or 15 hours per day in severe hypoxemia. *N Engl J Med.* 2024;391(11):977-988. Available in: <http://doi.org/10.1056/NEJMoa2402638>
392. Long-Term Oxygen Treatment Trial Research G, Albert RK, Au DH, Blackford AL, Casaburi R, Cooper JA, Jr., et al. A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med.* 2016;375(17):1617-1627. Available in: <http://doi.org/10.1056/NEJMoa1604344>
393. Céspedes GJ, Arancibia HF. Oxígeno terapia y rehabilitación respiratoria en el paciente con enfermedad pulmonar obstructiva crónica. *Rev Chil Enferm Respir.* 2011;27:124-127. Available in: <http://doi.org/10.4067/S0717-73482011000200007>
394. Daher A, Dreher M. Supplemental oxygen therapy in chronic obstructive pulmonary disease: is less is more? How much is too much? *Curr Opin Pulm Med.* 2024;30(2):179-184. Available in: <http://doi.org/10.1097/MCP.0000000000001025>
395. Nonoyama ML, Brooks D, Lacasse Y, Guyatt GH, Goldstein RS. Oxygen therapy during exercise training in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2007;2007(2):CD005372. Available in: <http://doi.org/10.1002/14651858.CD005372.pub2>
396. Alison JA, Mckeough ZJ, Leung RWM, Holland AE, Hill K, Morris NR, et al. Oxygen compared to air during exercise training in COPD with exercise-induced desaturation. *Eur Respir J.* 2019;53(5): 1802429. Available in: <http://doi.org/10.1183/13993003.02429-2018>
397. Lacasse Y, Series F, Corbeil F, Baltzan M, Paradis B, Simao P, et al. Randomized trial of nocturnal oxygen in chronic obstructive pulmonary disease. *N Engl J Med.* 2020;383(12):1129-1138. Available in: <http://doi.org/10.1056/NEJMoa2013219>
398. Berg BW, Dillard TA, Rajagopal KR, Mehm WJ. Oxygen supplementation during air travel in patients with chronic obstructive lung disease. *Chest.* 1992;101(3):638-641. Available in: <http://doi.org/10.1378/chest.101.3.638>
399. Edvardsen A, Akerø A, Christensen CC, Ryg M, Skjonsberg OH. Air travel and chronic obstructive pulmonary disease: a new algorithm for pre-flight evaluation. *Thorax.* 2012;67(11):964-969. Available in: <http://doi.org/10.1136/thoraxjnl-2012-201855>
400. Christensen CC, Ryg M, Refvem OK, Skjonsberg OH. Development of severe hypoxaemia in chronic obstructive pulmonary disease patients at 2,438 m (8,000 ft) altitude. *Eur Respir J.* 2000;15(4):635-9. Available in: <http://doi.org/10.1183/09031936.00.15463500>.

401. Zhang L, Wang Y, Ye Y, Gao J, Zhu F, Min L. Comparison of high-flow nasal cannula with conventional oxygen therapy in patients with hypercapnic chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2023;18:895-906. Available in: <http://doi.org/10.2147/COPD.S402506>
402. Xu C, Yang F, Wang Q, Gao W. Comparison of high flow nasal therapy with non-invasive ventilation and conventional oxygen therapy for acute hypercapnic respiratory failure: a meta-analysis of randomized controlled trials. *Int J Chron Obstruct Pulmon Dis.* 2023;18:955-973. Available in: <http://doi.org/10.2147/COPD.S410958>
403. Duan L, Xie C, Zhao N. Effect of high-flow nasal cannula oxygen therapy in patients with chronic obstructive pulmonary disease: a meta-analysis. *J Clin Nurs.* 2022;31(1-2):87-98. Available in: <http://doi.org/10.1111/jocn.15957>
404. Chen X, Xu L, Li S, Yang C, Wu X, Feng M, et al. Efficacy of respiratory support therapies during pulmonary rehabilitation exercise training in chronic obstructive pulmonary disease patients: a systematic review and network meta-analysis. *BMC Med.* 2024;22(1):389. Available in: <http://doi.org/10.1186/s12916-024-03605-7>
405. Andrews L, Barlow R, Easton I. Differences in patient outcomes between a 6, 7 and 8 week pulmonary rehabilitation programme: a service evaluation. *Physiotherapy.* 2015;101(1):62-68. Available in: <http://doi.org/10.1016/j.physio.2014.04.002>
406. Solanes I, Guell R, Casan P, Sotomayor C, Gonzalez A, Feixas T, et al. Duration of pulmonary rehabilitation to achieve a plateau in quality of life and walk test in COPD. *Respir Med.* 2009;103(5):722-728. Available in: <http://doi.org/10.1016/j.rmed.2008.11.013>
407. Chuatrakoon B, Uthaiakhp S, Ngai SP, Liwsrisakun C, Pothirat C, Sungkarat S. The effectiveness of home-based balance and pulmonary rehabilitation program in individuals with chronic obstructive pulmonary disease: a randomized controlled trial. *Eur J Phys Rehabil Med.* 2022;58(3):478-486. Available in: <http://doi.org/10.23736/S1973-9087.22.07383-X>
408. Zhu Z, Muhamad AS, Omar N, Ooi FK, Pan X, Ong MLY. Efficacy of exercise treatments for chronic obstructive pulmonary disease: a systematic review. *J Bodyw Mov Ther.* 2024;38:106-127. Available in: <http://doi.org/10.1016/j.jbmt.2024.01.019>
409. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2015;2015(2):CD003793. Available in: <http://doi.org/10.1002/14651858.CD003793.pub3>
410. Jenkins AR, Burtin C, Camp PG, Lindenauer P, Carlin B, Alison JA, et al. Do pulmonary rehabilitation programmes improve outcomes in patients with COPD posthospital discharge for exacerbation: a systematic review and meta-analysis. *Thorax.* 2024;79(5):438-447. Available in: <http://doi.org/10.1136/thorax-2023-220333>
411. Meneses-Echavez JF, Chavez Guapo N, Loaiza-Betancur AF, Machado A, Bidonde J. Pulmonary rehabilitation for acute exacerbations of COPD: a systematic review. *Respir Med.* 2023;219:107425. Available in: <http://doi.org/10.1016/j.rmed.2023.107425>
412. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The Physical Activity Guidelines for Americans. *JAMA.* 2018;320(19):2020-2028. Available in: <http://doi.org/10.1001/jama.2018.14854>
413. Tin Tin Htar M, Stuurman AL, Ferreira G, Alicino C, Bollaerts K, Paganino C, et al. Effectiveness of pneumococcal vaccines in preventing pneumonia in adults, a systematic review and meta-analyses of observational studies. *PLoS One.* 2017;12(5):e0177985. Available in: <http://doi.org/10.1371/journal.pone.0177985>
414. Walters JA, Tang JN, Poole P, Wood-Baker R. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2017;1(1):CD001390. Available in: <http://doi.org/10.1002/14651858.CD001390.pub4>
415. Furumoto A, Ohkusa Y, Chen M, Kawakami K, Masaki H, Sueyasu Y, et al. Additive effect of pneumococcal vaccine and influenza vaccine on acute exacerbation in patients with chronic lung disease. *Vaccine.* 2008;26(33):4284-4289. Available in: <http://doi.org/10.1016/j.vaccine.2008.05.037>
416. Chen H, Huang Z, Chang S, Hu M, Lu Q, Zhang Y, et al. Immunogenicity and safety of an inactivated SARS-CoV-2 vaccine (Sinopharm BBIBP-CorV) coadministered with quadrivalent split-virion inactivated influenza vaccine and 23-valent pneumococcal polysaccharide vaccine in China: a multicentre, non-inferiority, open-label, randomised, controlled, phase 4 trial. *Vaccine.* 2022;40(36):5322-5332. Available in: <http://doi.org/10.1016/j.vaccine.2022.07.033>
417. Secretaría de Salud. Lineamientos de vacunación para la temporada invernal 2024-2025. Mexico; 2024. Available in: https://www.gob.mx/cms/uploads/attachment/file/945894/LINEAMIENTOS_CAMP_VAC_INVERNAL_24-25_pdf
418. Jang JG, Ahn JH, Jin HJ. Incidence and prognostic factors of respiratory viral infections in severe acute exacerbation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2021;16:1265-1273. Available in: <http://doi.org/10.2147/COPD.S306916>
419. Bekkat-Berkani R, Wilkinson T, Buchy P, Dos Santos G, Stefanidis D, Devaster JM, et al. Seasonal influenza vaccination in patients with COPD: a systematic literature review. *BMC Pulm Med.* 2017;17(1):79. Available in: <http://doi.org/10.1186/s12890-017-0420-8>
420. Bao W, Li Y, Wang T, Li X, He J, Wang Y, et al. Effects of influenza vaccination on clinical outcomes of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Ageing Res Rev.* 2021;68:101337. Available in: <http://doi.org/10.1016/j.arr.2021.101337>
421. Kopsaftis Z, Wood-Baker R, Poole P. Influenza vaccine for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev.* 2018;6(6):CD002733. Available in: <http://doi.org/10.1002/14651858.CD002733.pub3>
422. Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2006(1):CD002733. Available in: <http://doi.org/10.1002/14651858.CD002733.pub2>
423. Kefala AM, Fortescue R, Alimani GS, Kanavidis P, McDonnell MJ, Magiorkinis E, et al. Prevalence and clinical implications of respiratory viruses in stable chronic obstructive pulmonary disease (COPD) and exacerbations: a systematic review and meta-analysis protocol. *BMJ Open.* 2020;10(4):e035640. Available in: <http://doi.org/10.1136/bmjopen-2019-035640>
424. Walsh EE, Perez Marc G, Zareba AM, Falsey AR, Jiang Q, Patton M, et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. *N Engl J Med.* 2023;388(16):1465-1477. Available in: <http://doi.org/10.1056/NEJMoa2213836>
425. Melgar M, Britton A, Roper LE, Talbot HK, Long SS, Kotton CN, et al. Use of respiratory syncytial virus vaccines in older adults: recommendations of the advisory committee on immunization Practices - United States, 2023. *Weekly.* 2023;72(29):793-801. Available in: <http://doi.org/10.15585/mmwr.mm7229a4>
426. Naeger S, Pool V, Macina D. Increased burden of pertussis among adolescents and adults with asthma or COPD in the United States, 2007 to 2019. *Chest.* 2024;165(6):1352-1361. Available in: <http://doi.org/10.1016/j.chest.2023.12.020>

427. Van Den Steen P, Cheuvart B, Deraedt Q, Valdes Verelst L, Shamarina D. Immunogenicity and safety of reduced-antigen tetanus, diphtheria and acellular pertussis vaccination in adults treated for obstructive airway diseases. *Hum Vaccin Immunother.* 2023;19(1):2159731. Available in: <http://doi.org/10.1080/21645515.2022.2159731>
428. Anderson TC, Masters NB, Guo A, Shepersky L, Leidner AJ, Lee GM, et al. Use of recombinant zoster vaccine in immunocompromised adults aged ≥ 19 years: recommendations of the advisory committee on immunization practices - United States, 2022. *MMWR Morb Mortal Wkly Rep.* 2022;71(3):80-84. Available in: <http://doi.org/10.15585/mmwr.mm7103a2>
429. Marra F, Parhar K, Huang B, Vadlamudi N. Risk factors for herpes zoster infection: a meta-analysis. *Open Forum Infect Dis.* 2020;7(1):ofaa005. Available in: <http://doi.org/10.1093/ofid/ofaa005>
430. Kawai K, Yawn BP. Risk Factors for Herpes Zoster: a systematic review and meta-analysis. *Mayo Clin Proc.* 2017;92(12):1806-1821. Available in: <http://doi.org/10.1016/j.mayocp.2017.10.009>
431. Marijam A, Vroom N, Bhavsar A, Posiuniene I, Lecrenier N, Vroling H. Systematic literature review on the incidence of herpes zoster in populations at increased risk of disease in the EU/EEA, Switzerland, and the UK. *Infect Dis Ther.* 2024;13(5):1083-1104. Available in: <http://doi.org/10.1007/s40121-024-00963-w>
432. Iftikhar IH, Schimmel M, Sardi A, Mehta I, Gonzalez E, Musani AI. Bronchoscopic lung volume reduction with valves and coils. A network meta-analysis. *Ann Am Thorac Soc.* 2020;17(11):1468-1475. Available in: <http://doi.org/10.1513/AnnalsATS.202002-151OC>
433. Patel M, Chowdhury J, Zhao H, Lu X, Roth S, Giovacchini CX, et al. Meta-analysis and systematic review of bronchoscopic lung volume reduction through endobronchial valves in severe emphysema. *J Bronchology Interv Pulmonol.* 2022;29(3):224-237. Available in: <http://doi.org/10.1097/LBR.0000000000000872>
434. Roodenburg SA, Hartman JE, Deslee G, Herth FJF, Klooster K, Sciruba FC, et al. Bronchoscopic lung volume reduction coil treatment for severe emphysema: a systematic review and meta-analysis of individual participant data. *Respiration.* 2022;101(7):697-705. Available in: <http://doi.org/10.1159/000524148>
435. Zhang R, Zheng Z, Bian Y, Deng M, Herth FFJ, Hou G. Efficacy and safety of bronchoscopic lung volume reduction for chronic obstructive pulmonary disease: a systematic review and network meta-analysis. *Expert Rev Respir Med.* 2024;18(8):631-644. Available in: <http://doi.org/10.1080/17476348.2024.2388293>
436. Yamamoto S, Horita N, Imai R, Niitsu T. Surgical and bronchoscopic lung volume reduction for severe emphysema: a systematic review and network meta-analysis. *Lung.* 2025;203(1):22. Available in: <http://doi.org/10.1007/s00408-024-00777-0>
437. Van Geffen WH, Slebos DJ, Herth FJ, Kemp SV, Weder W, Shah PL. Surgical and endoscopic interventions that reduce lung volume for emphysema: a systemic review and meta-analysis. *Lancet Respir Med.* 2019;7(4):313-324. Available in: [http://doi.org/10.1016/S2213-2600\(18\)30431-4](http://doi.org/10.1016/S2213-2600(18)30431-4)
438. Slebos DJ, Hartman JE, Klooster K, Blaas S, Deslee G, Gesierich W, et al. Bronchoscopic coil treatment for patients with severe emphysema: a meta-analysis. *Respiration.* 2015;90(2):136-145. Available in: <http://doi.org/10.1159/000431384>
439. Zhi L, Liao L, Wu Z, Wang T, Ye Y, Li H, et al. Impact of bronchoscopic thermal vapor ablation on lung volume reduction in patients with emphysema: a meta-analysis. *BMC Pulm Med.* 2023;23(1):405. Available in: <http://doi.org/10.1186/s12890-023-02689-w>
440. Van Dijk M, Klooster K, Ten Hacken NHT, Sciruba F, Kerstjens HaM, Slebos DJ. The effects of lung volume reduction treatment on diffusing capacity and gas exchange. *Eur Respir Rev.* 2020;29(158):190171. Available in: <http://doi.org/10.1183/16000617.0171-2019>
441. Marchetti N, Criner GJ. Surgical approaches to treating emphysema: lung volume reduction surgery, bullectomy, and lung transplantation. *Semin Respir Crit Care Med.* 2015;36(4):592-608. Available in: <http://doi.org/10.1055/s-0035-1556064>
442. Yusen RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, et al. The registry of the international society for heart and lung transplantation: thirty-third adult lung and heart-lung transplant report-2016; focus theme: primary diagnostic indications for transplant. *J Heart Lung Transplant.* 2016;35(10):1170-1184. Available in: <http://doi.org/10.1016/j.healun.2016.09.001>
443. Ahmad D, Ferrell BE, Saxena A, Jimenez DC, O'Malley TJ, Dispagna MA, et al. Comparative outcomes of lung volume reduction surgery and lung transplantation: a systematic review and meta-analysis. *J Thorac Dis.* 2023;15(7):3627-3635. Available in: <http://doi.org/10.21037/jtd-23-63>
444. Mansour R, Nakanishi H, Al Sabbakh N, El Ghazal N, Haddad J, Adra M, et al. Single vs bilateral lung transplant in the management of patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Transplant Proc.* 2023;55(9):2203-2211. Available in: <http://doi.org/10.1016/j.transproceed.2023.08.013>
445. Fang YC, Cheng WH, Lu HI, Wang YS, Chuang KH, Lai HH, et al. Double lung transplantation is better than single lung transplantation for end-stage chronic obstructive pulmonary disease: a meta-analysis. *J Cardiothorac Surg.* 2024;19(1):162. Available in: <http://doi.org/10.1186/s13019-024-02654-6>
446. Chambers DC, Perch M, Zuckermann A, Cherikh WS, Harhay MO, Hayes D, Jr., et al. The international thoracic organ transplant registry of the international society for heart and lung transplantation: thirty-eighth adult lung transplantation report - 2021; focus on recipient characteristics. *J Heart Lung Transplant.* 2021;40(10):1060-1072. Available in: <http://doi.org/10.1016/j.healun.2021.07.021>
447. Wedzicha JaEC-C, Miravittles M, Hurst JR, Calverley PM, Albert RK, Anzueto A, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J.* 2017;49(3): 1600791. Available in: <http://doi.org/10.1183/13993003.00791-2016>
448. Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook R, Criner GJ, et al. An Updated definition and severity classification of chronic obstructive pulmonary disease exacerbations: the rome proposal. *Am J Respir Crit Care Med.* 2021;204(11):1251-1258. Available in: <http://doi.org/10.1164/rccm.202108-1819PP>
449. Althobiani MA, Shah AJ, Khan B, Hurst JR. Clinicians' and researchers' perspectives on a new chronic obstructive pulmonary disease exacerbation definition: rome wasn't built in a day. *Am J Respir Crit Care Med.* 2023;207(8):1095-1097. Available in: <http://doi.org/10.1164/rccm.202210-1949LE>
450. Reumkens C, Endres A, Simons SO, Savelkoul PHM, Sprooten RTM, Franssen FME. Application of the Rome severity classification of COPD exacerbations in a real-world cohort of hospitalised patients. *ERJ Open Res.* 2023;9(3):00569-2022. Available in: <http://doi.org/10.1183/23120541.00569-2022>
451. Jacobson PK, Lind L, Persson HL. Applying the rome proposal on exacerbations of chronic obstructive pulmonary disease: does comorbid chronic heart failure matter? *Int J Chron Obstruct Pulmon Dis.* 2023;18:2055-2064. Available in: <http://doi.org/10.2147/COPD.S425592>

452. Cid-Juarez S, Tellez-Navarrete NA, Bautista-Bernal A, Leon-Gomez P, Salas-Escamilla I, Gochicoa-Rangel L, et al. Arterial blood gases in normal subjects at 2240 meters above sea level: impact of age, gender, and body mass index. *Rev Invest Clin.* 2023;75(1):29-36. Available in: <http://doi.org/10.24875/RIC.22000281>
453. Kopsaftis ZA, Sulaiman NS, Mountain OD, Carson-Chahhoud KV, Phillips PA, Smith BJ. Short-acting bronchodilators for the management of acute exacerbations of chronic obstructive pulmonary disease in the hospital setting: systematic review. *Syst Rev.* 2018;7(1):213. Available in: <http://doi.org/10.1186/s13643-018-0860-0>
454. Van Geffen WH, Douma WR, Slebos DJ, Kerstjens HA. Bronchodilators delivered by nebuliser versus pMDI with spacer or DPI for exacerbations of COPD. *Cochrane Database Syst Rev.* 2016;2016(8):CD011826. Available in: <http://doi.org/10.1002/14651858.CD011826.pub2>
455. Woods JA, Wheeler JS, Finch CK, Pinner NA. Corticosteroids in the treatment of acute exacerbations of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2014;9:421-430. Available in: <http://doi.org/10.2147/COPD.S51012>
456. Walters JA, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2014;2014(9):CD001288. Available in: <http://doi.org/10.1002/14651858.CD001288.pub4>
457. Maltais F, Ostinelli J, Bourbeau J, Tonnel AB, Jacquemet N, Haddon J, et al. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Am J Respir Crit Care Med.* 2002;165(5):698-703. Available in: <http://doi.org/10.1164/ajrccm.165.5.2109093>
458. Gunen H, Hacievliyagil SS, Kosar F, Mutlu LC, Gulbas G, Pehlivan E, et al. Factors affecting survival of hospitalised patients with COPD. *Eur Respir J.* 2005;26(2):234-241. Available in: <http://doi.org/10.1183/09031936.05.00024804>
459. Ding Z, Li X, Lu Y, Rong G, Yang R, Zhang R, et al. A randomized, controlled multicentric study of inhaled budesonide and intravenous methylprednisolone in the treatment on acute exacerbation of chronic obstructive pulmonary disease. *Respir Med.* 2016;121:39-47. Available in: <http://doi.org/10.1016/j.rmed.2016.10.013>
460. Vollenweider DJ, Frei A, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2018;10(10):CD010257. Available in: <http://doi.org/10.1002/14651858.CD010257.pub2>
461. Hout G, Gillespie D, Wilkinson TMA, Thomas M, Francis NA. Biomarkers to guide the use of antibiotics for acute exacerbations of COPD (AECOPD): a systematic review and meta-analysis. *BMC Pulm Med.* 2022;22(1):194. Available in: <http://doi.org/10.1186/s12890-022-01958-4>
462. McKeever TM, Hearson G, Housley G, Reynolds C, Kinnear W, Harrison TW, et al. Using venous blood gas analysis in the assessment of COPD exacerbations: a prospective cohort study. *Thorax.* 2016;71(3):210-215. Available in: <http://doi.org/10.1136/thoraxjnl-2015-207573>
463. Cabrini L, Landoni G, Oriani A, Plumari VP, Nobile L, Greco M, et al. Noninvasive ventilation and survival in acute care settings: a comprehensive systematic review and metaanalysis of randomized controlled trials. *Crit Care Med.* 2015;43(4):880-888. Available in: <http://doi.org/10.1097/CCM.0000000000000819>
464. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2017;7(7):CD004104. Available in: <http://doi.org/10.1002/14651858.CD004104.pub4>
465. Peng L, Ren PW, Liu XT, Zhang C, Zuo HX, Kang DY, et al. Use of noninvasive ventilation at the pulmonary infection control window for acute respiratory failure in AECOPD patients: a systematic review and meta-analysis based on GRADE approach. *Medicine (Baltimore).* 2016;95(24):e3880. Available in: <http://doi.org/10.1097/MD.0000000000003880>
466. Abualhamel SA, Alasmi AT, Alqurayqiri AF, Alzahrani AA, Alsehli AD, Althikra AH, et al. Role of non-invasive ventilation (NIV) in managing acute exacerbations of chronic obstructive pulmonary disease (COPD): a systematic review. *Cureus.* 2024;16(8):e67418. Available in: <http://doi.org/10.7759/cureus.67418>
467. Dabscheck E, George J, Hermann K, Mcdonald CF, Mcdonald VM, Mcnamara R, et al. COPD-X Australian guidelines for the diagnosis and management of chronic obstructive pulmonary disease: 2022 update. *Med J Aust.* 2022;217(8):415-423. Available in: <http://doi.org/10.5694/mja2.51708>
468. Ospina MB, Mrklas K, Deuchar L, Rowe BH, Leigh R, Bhutani M, et al. A systematic review of the effectiveness of discharge care bundles for patients with COPD. *Thorax.* 2017;72(1):31-39. Available in: <http://doi.org/10.1136/thoraxjnl-2016-208820>
469. Gomez-Angelats E, Sanchez C. Care Bundles after Discharging Patients with Chronic Obstructive Pulmonary Disease Exacerbation from the Emergency Department. *Med Sci (Basel).* 2018;6(3):63. Available in: <http://doi.org/10.3390/medsci6030063>
470. Miravittles M, Bhutani M, Hurst JR, Franssen FME, Van Boven JFM, Khoo EM, et al. Implementing an evidence-based COPD hospital discharge protocol: a narrative review and expert recommendations. *Adv Ther.* 2023;40(10):4236-4263. Available in: <http://doi.org/10.1007/s12325-023-02609-8>
471. Hernández-Zenteno RJ, Elizondo-Ríos A, Robles-Hernández RE, Thiri6n-Romero II, P6r6mo-Arroyo RF, Septien-Stute LA, et al. Consenso formal de expertos sobre el protocolo de manejo y cuidados post hospitalarios de la exacerbaci6n grave y muy grave de la EPOC. *Neumol Cir Torax (pr6xima publicaci6n).* 2025.
472. Tavares N, Jarrett N, Hunt K, Wilkinson T. Palliative and end-of-life care conversations in COPD: a systematic literature review. *ERJ Open Res.* 2017;3(2):00068-02016. Available in: <http://doi.org/10.1183/23120541.00068-2016>
473. Broese JM, De Heij AH, Janssen DJ, Skora JA, Kerstjens HA, Chavannes NH, et al. Effectiveness and implementation of palliative care interventions for patients with chronic obstructive pulmonary disease: a systematic review. *Palliat Med.* 2021;35(3):486-502. Available in: <http://doi.org/10.1177/0269216320981294>
474. Philip J, Collins A, Smallwood N, Chang YK, Mo L, Yang IA, et al. Referral criteria to palliative care for patients with respiratory disease: a systematic review. *Eur Respir J.* 2021;58(4):2004307. Available in: <http://doi.org/10.1183/13993003.04307-2020>
475. Almagro P, Yun S, Sangil A, Rodriguez-Carballeira M, Marine M, Landete P, et al. Palliative care and prognosis in COPD: a systematic review with a validation cohort. *Int J Chron Obstruct Pulmon Dis.* 2017;12:1721-1729. Available in: <http://doi.org/10.2147/COPD.S135657>
476. Smith LE, Moore E, Ali I, Smeeth L, Stone P, Quint JK. Prognostic variables and scores identifying the end of life in COPD: a systematic review. *Int J Chron Obstruct Pulmon Dis.* 2017;12:2239-2256. Available in: <http://doi.org/10.2147/COPD.S137868>

477. Janssen DJA, Bajwah S, Boon MH, Coleman C, Currow DC, Devillers A, *et al.* European Respiratory Society clinical practice guideline: palliative care for people with COPD or interstitial lung disease. *Eur Respir J.* 2023;62(2):2202014. Available in: <http://doi.org/10.1183/13993003.02014-2022>
478. Quinn KL, Shurrab M, Gitau K, Kavalieratos D, Isenberg SR, Stall NM, *et al.* Association of receipt of palliative care interventions with health care use, quality of life, and symptom burden among adults with chronic noncancer illness: a systematic review and meta-analysis. *JAMA.* 2020;324(14):1439-1450. Available in: <http://doi.org/10.1001/jama.2020.14205>
479. Singer AE, Goebel JR, Kim YS, Dy SM, Ahluwalia SC, Clifford M, *et al.* Populations and interventions for palliative and end-of-life care: a systematic review. *J Palliat Med.* 2016;19(9):995-1008. Available in: <http://doi.org/10.1089/jpm.2015.0367>
480. Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database Syst Rev.* 2016;3(3):CD011008. Available in: <http://doi.org/10.1002/14651858.CD011008.pub2>
481. Smallwood NE, Pascoe A, Wijsenbeek M, Russell AM, Holland AE, Romero L, *et al.* Opioids for the palliation of symptoms in people with serious respiratory illness: a systematic review and meta-analysis. *Eur Respir Rev.* 2024;33(174):230265. Available in: <http://doi.org/10.1183/16000617.0265-2023>
482. Ekstrom M, Nilsson F, Abernethy AA, Currow DC. Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review. *Ann Am Thorac Soc.* 2015;12(7):1079-1092. Available in: <http://doi.org/10.1513/AnnalsATS.201501-034OC>
483. Ekstrom M, Ferreira D, Chang S, Louw S, Johnson MJ, Eckert DJ, *et al.* Effect of regular, low-dose, extended-release morphine on chronic breathlessness in chronic obstructive pulmonary disease: the BEAMS randomized clinical trial. *JAMA.* 2022;328(20):2022-2032. Available in: <http://doi.org/10.1001/jama.2022.20206>
484. Currow D, Louw S, Mccloud P, Fazekas B, Plummer J, McDonald CF, *et al.* Regular, sustained-release morphine for chronic breathlessness: a multicentre, double-blind, randomised, placebo-controlled trial. *Thorax.* 2020;75(1):50-56. Available in: <http://doi.org/10.1136/thoraxjnl-2019-213681>
485. Verberkt CA, Van Den Beuken-Van Everdingen MHJ, Schols J, Hameleers N, Wouters EFM, Janssen DJA. Effect of sustained-release morphine for refractory breathlessness in chronic obstructive pulmonary disease on health status: a randomized clinical trial. *JAMA Intern Med.* 2020;180(10):1306-1314. Available in: <http://doi.org/10.1001/jamainternmed.2020.3134>
486. Simon ST, Higginson IJ, Booth S, Harding R, Weingartner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev.* 2016;10(10):CD007354. Available in: <http://doi.org/10.1002/14651858.CD007354.pub3>
487. Kochovska S, Ferreira DH, Garcia MV, Phillips JL, Currow DC. Perspectives on palliative oxygen for breathlessness: systematic review and meta-synthesis. *Eur Respir J.* 2021;58(4):2004613. Available in: <http://doi.org/10.1183/13993003.04613-2020>
488. Uronis HE, Ekstrom MP, Currow DC, Mccrory DC, Samsa GP, Abernethy AP. Oxygen for relief of dyspnoea in people with chronic obstructive pulmonary disease who would not qualify for home oxygen: a systematic review and meta-analysis. *Thorax.* 2015;70(5):492-494. Available in: <http://doi.org/10.1136/thoraxjnl-2014-205720>
489. Iyer AS, Sullivan DR, Lindell KO, Reinke LF. The role of palliative care in COPD. *Chest.* 2022;161(5):1250-1262. Available in: <http://doi.org/10.1016/j.chest.2021.10.032>
490. Farver-Vestergaard I, Jacobsen D, Zachariae R. Efficacy of psychosocial interventions on psychological and physical health outcomes in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Psychother Psychosom.* 2015;84(1):37-50. Available in: <http://doi.org/10.1159/000367635>
491. Farver-Vestergaard I, Danielsen JTT, Lokke A, Zachariae R. Psychosocial intervention in chronic obstructive pulmonary disease: meta-analysis of randomized controlled trials. *Psychosom Med.* 2022;84(3):347-358. Available in: <http://doi.org/10.1097/PSY.0000000000001043>
492. Jabbarian LJ, Zwakman M, Van Der Heide A, Kars MC, Janssen DJA, Van Delden JJ, *et al.* Advance care planning for patients with chronic respiratory diseases: a systematic review of preferences and practices. *Thorax.* 2018;73(3):222-230. Available in: <http://doi.org/10.1136/thoraxjnl-2016-209806>
493. Rajnoveanu RM, Rajnoveanu AG, Fildan AP, Todea DA, Man MA, Motoc NS, *et al.* Palliative care initiation in chronic obstructive pulmonary disease: prognosis-based, symptoms-based or needs-based? *Int J Chron Obstruct Pulmon Dis.* 2020;15:1591-1600. Available in: <http://doi.org/10.2147/COPD.S254104>

