Global Initiative for Chronic Obstructive Lung Disease

2027 REPORT



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

(2027 REPORT)

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

© 2026, 2027 Global Initiative for Chronic Obstructive Lung Disease, Inc.

Important Purpose & Liability Disclaimer

The information provided by Global Initiative for Chronic Obstructive Lung Disease ("GOLD") for inclusion in its materials, website, and applications (including but not limited to web based or digital applications) is provided for the convenience of users to help them understand the conclusions of GOLD as of the date of the specific information's approval by GOLD. That information's relevance to, and/or application to, a particular patient or case must be carefully assessed, evaluated, and determined by a qualified healthcare professional treating that patient or case. Users need to be aware of the fact that only the English language version of GOLD's information has been reviewed and approved by GOLD, and that users must ensure that they have the most current version of GOLD's information since GOLD's information may have been updated or changed after its original release. The information provided by GOLD is intended to support, not replace, independent clinical judgment. Especially in light of the above, GOLD expressly disclaims any liability arising out of any use or misuse of the information it provides.

GOLD BOARD OF DIRECTORS (2026)

Alvar Agusti, MD, *Chair*
Respiratory Institute
Hospital Clinic, IDIBAPS
Univ. Barcelona and Ciberes
Barcelona, Spain

Bartolome R. Celli, MD
Harvard Medical School
Boston, Massachusetts, USA

Gerard Criner, MD
Temple University School of Medicine
Philadelphia, Pennsylvania, USA

David Halpin, MD
University of Exeter Medical School
College of Medicine and Health
University of Exeter, Exeter
Devon, UK

Maria Montes de Oca, MD
Hospital Universitario de Caracas
Universidad Central de Venezuela
Centro Médico de Caracas
Caracas, Venezuela

Obianuju B. Ozoh, MD
University of Lagos
Lagos, Nigeria

Sundeep Salvi, MD
Pulmocare Research and Education (PURE) Foundation
Pune, India

Claus Vogelmeier, MD
University of Marburg
Marburg, Germany

Jinping Zheng, MD
Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University,
Guangzhou, China

GOLD SCIENCE COMMITTEE*
(2026)

Claus Vogelmeier, MD, *Chair*
University of Marburg
Marburg, Germany

Shawn Aaron, MD
University of Ottawa
Ottawa, Canada

Alvar Agusti, MD
Respiratory Institute
Hospital Clinic, IDIBAPS
Univ. Barcelona and Ciberes
Barcelona, Spain

Antonio Anzueto, MD
South Texas Veterans Health Care System,
University of Texas, Health
San Antonio, Texas, USA

Surya P. Bhatt, MD
University of Alabama at Birmingham
Birmingham, Alabama, USA

Jean Bourbeau, MD, MSPH
McGill University Health Centre
McGill University
Montreal, Canada

Gerard Criner, MD
Temple University School of Medicine
Philadelphia, Pennsylvania, USA

David Halpin, MD
University of Exeter Medical School
College of Medicine and Health
University of Exeter, Exeter
Devon, UK

MeiLan K. Han, MD MS
University of Michigan
Ann Arbor, MI, USA

Fernando J. Martinez, MD MS
University of Massachusetts Chan Medical School
Worcester, MA, USA

Maria Montes de Oca, MD
Hospital Universitario de Caracas
Universidad Central de Venezuela
Centro Médico de Caracas
Caracas, Venezuela

Obianuju B. Ozoh, MD
University of Lagos
Lagos, Nigeria

Alberto Papi, MD
University of Ferrara
Ferrara, Italy

Ian Pavord, DM FMedSci
Respiratory Medicine Unit and Oxford Respiratory NIHR Biomedical Research Centre, Nuffield Department of Medicine
University of Oxford
Oxford, UK

Nicolas Roche, MD
Pneumologie, Hôpital Cochin
AP-HP Centre – Université Paris Cité
UMR 1016
Institut Cochin
Paris, France

Don D. Sin, MD
St. Paul's Hospital
University of British Columbia
Vancouver, Canada

Dave Singh, MD
University of Manchester
Manchester, UK

Thierry Troosters
Research Group for Rehabilitation in Internal Disorders
Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE)
Leuven, Belgium

Jadwiga A. Wedzicha, MD
National Heart & Lung Institute
Imperial College London
London, UK

Jinping Zheng, MD
Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University
Guangzhou, China

GOLD EXECUTIVE DIRECTOR

Katie Langefeld, BS
Illinois, USA

LITERATURE RESEARCH & EDITORIAL COORDINATION

Ruth Hadfield, PhD
Macquarie University AIHI
Sydney, Australia

ADMINISTRATIVE ASSISTANCE

Ashley Dear

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

* Disclosure forms for GOLD Committees are posted on the GOLD Website, www.goldcopd.org

GOLD ASSEMBLY

The GOLD National Leaders are individuals from around the world with an interest in promoting the goals of GOLD within their home country. The group meets periodically to share information about programs of health education, COPD management, and prevention.

ARGENTINA
Andrés Echazarreta, MD PhD
Head of Pneumonology Service
San Juan de Dios de La Plata, Argentina

BANGLADESH
Dr Kazi S. Bennoor
Dhaka, Bangladesh
Prof Md Mostafizur Rahman
Dhaka, Bangladesh

BELGIUM
Prof Wim Janssens
Leuven, Belgium

BULGARIA
Dr Yavor Ivanov
Pleven, Bulgaria

CHINA
Fu-Qiang Wen, MD, PhD
Chengdu, China

COLOMBIA
Alejandro Casas, MD
General Director of the Fundación Neumológica Colombiana

CROATIA
Neven Miculinic, MD
Zagreb, Croatia

CZECH REPUBLIC
Norbert Pauk, PhD
Prague, Czech Republic

EGYPT
Hisham Tarraf, MD
Cairo, Egypt

FINLAND
Witold Mazur MD, PhD
Helsinki, Finland

FRANCE
Prof Gaetan Deslée
Reims, France

GEORGIA
Maia Gotua, MD, PhD
Tbilisi, Georgia

GERMANY
Daiana Stolz MD MPH
University Medical Center Freiburg
Freiburg, Germany

GREECE
Prof Konstantinos Kostikas
Ioannina, Greece

HONG KONG CHINA
David S.C. Hui, MD
Shatin, N.T. Hong Kong

ICELAND
Dr Gunnar Gudmundsson
Reykjavik, Iceland

INDIA
Dr R. Narasimhan, MD
Chennai, India
Dr Kshitij Agarwal, MD
New Delhi, India

INDONESIA
Prof Faisal Yunus
Jakarta, Indonesia

IRAN
Dr Masjedi Mohammad Reza
Tehran, Iran
Mohammad Ashkan Moslehi, MD
Shiraz, Iran

IRELAND
Sarah O'Beirne, MD PhD
Dublin, Ireland
Dr Breda Cushen, MD PhD
Beaumont Hospital
Dublin, Ireland

ISRAEL
Zvi G. Fridlender, MD, MSc
Jerusalem, Israel

ITALY
Prof. Antonio Spanevello, MD, FERS
Varese, Italy

JAPAN
Takahide Nagase, MD
Tokyo, Japan

KAZAKHSTAN
Tair Nurpeissov
Almaty, Kazakhstan

KOREA
Yeon-Mok Oh, MD
Seoul, South Korea

KUWAIT
Professor Mousa Khadadah
Kuwait University

KYRGYZSTAN
Talant Sooronbaev, MD
Bishkek, Kyrgyzstan

LEBANON
Mirna Waked, MD, FCCP
Balamand University, Lebanon

LITHUANIA
Prof Kestutis Malakauskas, MD, PhD
Kaunas, Lithuania

MALTA
Prof Joseph M Cacciotolo
Pieta, Malta

MALAYSIA
Mat Zuki Mat Jaeb, MD
Kelantan, Malaysia

MEXICO
Ana Sofía Ramírez-García Luna, MD
Mexico City, Mexico
Adrián Rendón, ATSF, FERS, FCCP, FALT
Monterrey, México

MOLDOVA
Alexandru Corlateanu, MD, PhD
ERS National Delegate
Republic of Moldova

NEPAL
Navin Kumar Mishra MD
Kathmandu Medical College
Nepal, Asia

PAKISTAN
Prof Javaid Khan
Karachi, Pakistan
Dr Jamil Ur Rehman Tahir
Kammanwala, Sialkot Cantt, Pakistan
Dr Mohammad Osman Yusuf
Islamabad, Pakistan

POLAND
Pawel Sliwinski, MD, PhD
Warsaw, Poland

ROMANIA
Florin Mihaltan, MD
Ruxandra Ulmeanu, MD
Bucharest, Romania

RUSSIA
Prof Zaurbek Aisanov, MD
Moscow, Russia
Prof Alexandre Vizel, MD
Kazan, Tatarstan Republic, Russian Federation
Sergey Fedosenko, MD, PhD
Siberian State Medical University, Tomsk, Russia

SAUDI ARABIA
Mohammed Al Ghobain, MD
Riyadh, Saudi Arabia

SINGAPORE
Kian-Chung Ong, MD
Wan-Cheng Tan, MD,
Chair, Asian Pacific COPD Roundtable

SLOVAK REPUBLIC
Ivan Solovič
Propad, Slovakia

SOUTH AFRICA
Prof Richard van Zyl-Smit

SPAIN
Marta Marín-Oto, MD, PhD
Associate professor of Medicine
Respiratory Division, Miguel Servet University Hospital
University of Zaragoza
Zaragoza, Spain

SYRIA
Yousser Mohammad, MD
Lattakia, Syria

TRINIDAD & TOBAGO
Dr. Sateesh Madhava Sakhamuri
The University of the West Indies,
Trinidad and Tobago

TURKEY
Prof Dr. Hakan Gunen
Malatya, Turkey
Prof Nurdan Kokturk, MD
Ankara, Turkey

UGANDA
Patricia Alupo, MBChB., MMED
Makerere University Lung Institute in Uganda, Africa

UKRAINE
Vitalii Poberezhets, MD
National Pirogov Memorial Medical University
Department of Propedeutics of Internal Medicine
Vinnytsia, Ukraine

UNITED STATES OF AMERICA
Ed Portilllo, PharmD
University of Wisconsin-Madison School of Pharmacy
Madison, Wisconsin

VIETNAM
Le Thi Tuyet Lan, MD, PhD
Ho Chi Minh City, Vietnam
Sy Duong-Quy, MD, PhD, FCCP
Lam Dong Medical College, Vietnam
Prof Chau Ngo Quy
Tam Anh General Hospital, Ha Noi

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

GOLD 2027 REPORT HIGHLIGHTS

The GOLD report is revised annually and has been used worldwide by healthcare professionals as a tool to implement effective management programs based on local healthcare systems. In the 2027 revision of the GOLD report changes have been made as follows:

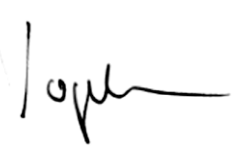
i. A new section on **'Addressing the Global Challenges of COPD and Asthma: a shared vision from GOLD & GINA'** and a new figure have been added (**Figure A**; Page 2).
ii. In Chapter 1 the definitions for 'Early COPD,' 'Mild COPD,' 'COPD in young people' and 'Pre-COPD' have been updated and refined (Page 13).
iii. A new figure (**Figure 1.3**) on the topic of pre-COPD has been added (Page 14).
iv. The section on **'Spirometric Criteria to Define Airflow Obstruction'** has been expanded and a new figure has been added (**Figure 2.8**; Page 32).
v. The **'Case for Universal Spirometry'** has been revised and new references included (Page 40).
vi. The **'Computed Tomography'** section has been updated (Page 51).
vii. **'Use of CT in COPD'** has been expanded (**Figure 2.16**; Page 53).
viii. In Chapter 2 and Chapter 3 the sections on '**Non-Pharmacological Treatment of COPD'** including **Rehabilitation, Physical Activity, Self-management and Integrated Care** have been updated (Page 77).
ix. Five new figures (**Figure 2.14**, **Figure 3.17**, **Figure 3.18**, **Figure 3.19**, **Figure 3.20**) have been added to expand the sections on Rehabilitation, Physical Activity, Self-management and Integrated Care; **Figure 3.15** has been revised (Page 77).
x. Information on **new inhaler propellants** has been added (Pages 62 & 170).
xi. **Vaccination** information has been updated (Page 62).
xii. The initial treatment recommendation for GOLD group A has been changed in the text and in **Figure 3.8** (Page 66).
xiii. In Chapter 2, Chapter 4 and Chapter 5, the sections on '**Cardiovascular Diseases'** have been revised and expanded (Page 126).
xiv. Two new figures (**Figure 4.5** and **Figure 5.3**) have been added to the cardiovascular disease information (Pages 112 & 128).
xv. Information on **new biologic treatments** has been included (Page 172).
xvi. A new figure (**Figure 6.1**) has been added to the **'AI in COPD'** chapter (Page 147).
xvii. New checklists for pharmacological and non-pharmacological treatment have been added (Appendix 2 & Appendix 3).
xviii. The evidence for non-pharmacological therapy (Appendix 6) has been updated with new text and references.
xix. **References** have been checked and updated throughout the document.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

GOLD has been fortunate to have a network of internationally distinguished health professionals from multiple disciplines. Many of these experts have initiated investigations into the causes and prevalence of COPD in their countries and have developed innovative approaches for the dissemination and implementation of the GOLD management strategy. The GOLD initiative will continue to work with National Leaders and other interested healthcare professionals to bring COPD to the attention of governments, public health officials, healthcare workers, and the public, to raise awareness of the burden of COPD and to develop programs for early detection, prevention and approaches to management.



Alvar G. Agusti, MD
Chair, GOLD Board of Directors



Claus Vogelmeier, MD
Chair, GOLD Science Committee

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT AND PREVENTION OF COPD 2027 UPDATE[a]

METHODOLOGY

When the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program was initiated in 1998, a goal was to produce recommendations for management of COPD based on the best scientific information available. The first report, *Global Strategy for the Diagnosis, Management and Prevention of COPD* was issued in 2001. In 2006 and again in 2011 a complete revision was prepared based on published research. These reports, and their companion documents, have been widely distributed and translated into many languages and can be found on the GOLD website (www.goldcopd.org).

The GOLD Science Committee[b] was established in 2002 to review published research on COPD management and prevention, to evaluate the impact of this research on recommendations in the GOLD documents related to management and prevention, and to post yearly updates on the GOLD website. Its members are recognized leaders in COPD research and clinical practice with the scientific credentials to contribute to the task of the Committee and are invited to serve in a voluntary capacity.

This 2027 report is an update of the 2026 GOLD Report. The 2026 GOLD Report was the 6th major revision of GOLD and incorporated a number of changes. Updates of the 2023-revised report were made in 2024 and 2025. Updates of the 2017-revised report were made in 2018, 2019, 2020, 2021 and 2022. Updates of the 2011-revised report were released in January 2013, 2014, 2015, and 2016.

***Process*:** To produce the GOLD report, a PubMed search (National Center for Biotechnology Information, US National Library of Medicine, Bethesda MD, USA) was completed using search fields established by the Committee: 1) *COPD or Chronic Obstructive Pulmonary Disease (All Fields)* AND 2) *Clinical Trials or Meta-analysis (All Fields)* OR 3) *articles in the top 20 medical or respiratory journals (available on request) or The Cochrane Database of Systematic Reviews*.

Publications in peer reviewed journals not captured by the PubMed searches may be submitted to the Chair, GOLD Science Committee, providing the full paper, including abstract, is submitted in (or translated into) English.

Members of the Committee receive a summary of citations and all abstracts. Each abstract is assigned to two unbiased Committee members, although all members are offered the opportunity to provide input on any abstract. Members evaluate the abstract or, subject to her/his judgment, the full publication, by answering four specific written questions from a short questionnaire, to indicate if the scientific data presented impacts on recommendations in the GOLD report. If so, the member is asked to specifically identify modifications that should be made.

The GOLD Science Committee meets twice yearly to discuss each publication that was considered by at least one member of the Committee to potentially have an impact on the management of COPD. The full Committee then reaches a consensus on whether to include it in the report, either as a reference supporting current recommendations, or to change the report. In the absence of consensus, disagreements are decided by an open vote of the full Committee. Only high-quality systematic reviews and meta-analyses that provide strong evidence for changing clinical

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

[a] The Global Strategy for Diagnosis, Management and Prevention of COPD (updated 2027), the Pocket Guide (updated 2027) and the complete list of references examined by the Committee is available on the GOLD website: www.goldcopd.org.

[b] GOLD Science Committee Members (2026-2027): C. Vogelmeier, Chair, S. Aaron, A. Agusti, A. Anzueto, S.Bhatt, J. Bourbeau, G. Criner, D. Halpin, M. Han, F. Martinez, M. Montes de Oca, O. Ozoh, A. Papi, I. Pavord, N. Roche, D. Sin, D. Singh, T. Troosters, J. Wedzicha, J. Zheng.

practice are cited in the GOLD report with preference given to citing the original randomized controlled trial(s).

Recommendations by the GOLD Committee for use of any medication are based on the best evidence available from the published literature and not on labeling directives from government regulators. The Committee does not make recommendations for therapies that have not been approved by at least one major regulatory agency.

NEW REFERENCES

Following systematic literature searches and double-blind review by the GOLD Science Committee, the GOLD report has been updated to include key peer-reviewed research publications from January 2025 to July 2026. In total, 150 new references have been added to the GOLD 2027 report.

ABBREVIATIONS

The abbreviations are expanded in **Appendix 1**.

ACKNOWLEDGEMENTS

The GOLD Board of Directors and the GOLD Science Committee acknowledge the following contributors:

Chris P. Gale	Contribution to the cardiovascular disease sections
Gabor Kovacs **Steven Nathan** **Oksana Shlobin** **Marc Humbert**	Pulmonary hypertension text
Leonardo Fabbri	Contribution to Chapter 5
Ed Portillo	Assistance with Figure A5.1

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

GLOBAL ALLIANCE AGAINST CHRONIC RESPIRATORY DISEASES

GOLD is a member of the Global Alliance against Chronic Respiratory Diseases (GARD)

TABLE OF CONTENTS

GOLD 2027 REPORT HIGHLIGHTS IV
METHODOLOGY V
NEW REFERENCES VI
ABBREVIATIONS VI
ACKNOWLEDGEMENTS VI
TABLE OF CONTENTS VII

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF COPD 1

INTRODUCTION 1
BACKGROUND 1
ADDRESSING THE GLOBAL CHALLENGES OF COPD AND ASTHMA: A SHARED VISION FROM GOLD & GINA 2
LEVELS OF EVIDENCE 3

CHAPTER 1: DEFINITION AND OVERVIEW 4

WHAT IS COPD? 4
Definition 4
Causes and risk factors 4
Diagnostic criteria 7
Clinical presentation 7
New opportunities 7
BURDEN OF COPD 7
Prevalence 8
Morbidity 9
Mortality 9
Economic burden 10
Social burden 11
PATHOGENESIS 11
Trajectories of lung function: development and aging 11
Asthma and airway hyper-reactivity 16
Chronic bronchitis 16
Infections 17
Sex 17
Race and ethnicity 17
Socioeconomic status 18
PATHOBIOLOGY 18
Inflammatory changes 18
Structural changes 18
Dysbiosis 19
PATHOPHYSIOLOGY 19
Airflow obstruction and gas trapping 19
Hyperinflation 20
Pulmonary gas exchange abnormalities 20
Pulmonary hypertension 20
Exacerbations 20
Multimorbidity 21
TAXONOMY 22

CHAPTER 2: DIAGNOSIS, ASSESSMENT AND MONITORING 23

DIAGNOSIS 23
CLINICAL PRESENTATION 24
Symptoms 24
Dyspnea 24
Chronic cough 25
Sputum production 25
Wheezing and chest tightness 25
Fatigue 25

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Additional clinical features in severe disease ... *25*
DIFFERENTIAL DIAGNOSIS OF COPD ... 26
MEDICAL HISTORY ... 27
PHYSICAL EXAMINATION ... 28
SPIROMETRY ... 28
Pre- or post-bronchodilator spirometry to confirm the diagnosis of COPD ... *30*
Spirometric criteria to define airflow obstruction ... *32*
Assessing the severity of airflow obstruction ... *34*
Assessing pulmonary function during airborne viral epidemics ... *35*
SCREENING AND CASE-FINDING ... 35
The impact of undiagnosed COPD ... *35*
Finding undiagnosed COPD: screening vs case-finding ... *36*
Active case-finding in the population ... *37*
Opportunistic case-finding in primary care ... *38*
Opportunistic case-finding for COPD in targeted populations ... *39*
The case for universal spirometry ... *40*
INITIAL ASSESSMENT ... 41
Severity of airflow obstruction ... *41*
Symptoms ... *41*
Exacerbation risk ... *43*
Blood eosinophil count ... *44*
Imaging ... *44*
Multimorbidity ... *44*
Combined initial COPD assessment ... *45*
MONITORING AND FOLLOW-UP ... 46
ADDITIONAL INVESTIGATIONS ... 48
Physiological tests ... *48*
Imaging ... *51*
Alpha-1 antitrypsin deficiency ... *54*
Composite scores ... *54*
Biomarkers ... *54*
Treatable traits ... *54*

CHAPTER 3: PREVENTION & MANAGEMENT OF COPD ... 55

INTRODUCTION ... 56
Disease activity ... *56*
RISK REDUCTION, LIFESTYLE, AND PATIENT EDUCATION ... 58
Risk reduction ... *58*
PHARMACOLOGICAL MAINTENANCE TREATMENT OF COPD ... 64
Algorithms for initial and follow-up pharmacological treatment ... *68*
Managing inhaled therapy ... *73*
NON-PHARMACOLOGICAL TREATMENT OF COPD ... 77
Algorithms for the initiation and follow-up of non-pharmacological treatment ... *77*
Education, self-management and integrative care ... *78*
Pulmonary Rehabilitation ... *80*
Oxygen therapy and ventilatory support ... *87*
THERAPEUTIC INTERVENTIONS THAT REDUCE COPD MORTALITY ... 89
Non-pharmacological therapy ... *89*
Pharmacological therapy ... *91*
SUPPORTIVE, PALLIATIVE, END-OF-LIFE & HOSPICE CARE ... 91
Symptom control and palliative care ... *91*
Therapy relevant to all people with COPD ... *92*
End-of-life and hospice care ... *93*
INTERVENTIONAL & SURGICAL TREATMENTS FOR COPD ... 95
Lung surgical treatments for patients with emphysema ... *96*
Lung volume reduction surgery ... *97*

CHAPTER 4: MANAGEMENT OF EXACERBATIONS ... 102

DEFINITION ... 103
Impact ... *103*

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Assessing the patient and confirming the diagnosis *103*
COPD exacerbation severity classification *104*
Conditions to be considered *107*
Decision-making about the management setting *108*
RISK FACTORS AND SYMPTOMS 109
Triggers *109*
Symptoms *109*
Risk factors and scores for future events *110*
TREATMENT OPTIONS 112
Treatment setting *112*
PHARMACOLOGICAL TREATMENT 114
Bronchodilators *114*
Glucocorticoids *114*
Antibiotics *115*
Other pharmacotherapy *116*
MANAGEMENT OF RESPIRATORY FAILURE 116
Oxygen therapy *116*
HOSPITAL DISCHARGE AND FOLLOW-UP 119
PREVENTION OF FURTHER EXACERBATIONS 121

CHAPTER 5: COPD AND MULTIMORBIDITY 123

INTRODUCTION 123
COPD, FRAILTY AND MULTIMORBIDITY 125
CARDIOVASCULAR DISEASES 126
Systemic hypertension *129*
Heart failure *129*
Coronary artery disease *130*
Arrhythmias *130*
Valvular heart disease *131*
Pulmonary hypertension *131*
Peripheral artery disease *133*
Stroke *133*
RESPIRATORY DISEASES 134
Lung cancer *134*
Asthma *135*
Pulmonary tuberculosis *136*
Bronchiectasis *136*
Interstitial lung disease / interstitial lung abnormalities *136*
Obstructive sleep apnea *137*
MENTAL CONDITIONS 137
Anxiety, depression and psychosis *137*
Cognitive impairment and dementia *138*
METABOLIC DISEASE 139
Diabetes mellitus *139*
Obesity *139*
Gastroesophageal reflux *139*
Liver steatosis *140*
DISEASES WITH MULTIPLE ORGANS LOSS OF TISSUE 140
Osteoporosis *140*
Renal failure *140*
Anemia *141*
Polycythemia *141*
POSTOPERATIVE RISK OF COPD ON GENERAL AND THORACIC SURGERY OUTCOMES 142
General surgery *142*
OTHER CONSIDERATIONS 142
Periodontitis and dental hygiene *142*
Vitamin D deficiency *143*
Guide to the practical tools available to evaluate and monitor multimorbid patients with COPD *143*
COPD as part of multimorbidity *143*

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

CHAPTER 6: ARTIFICIAL INTELLIGENCE AND EMERGING TECHNOLOGIES IN COPD 146

ARTIFICAL INTELLIGENCE IN COPD 146
Diagnosis 146
Underdiagnosis 146
Misdiagnosis 146
Late diagnosis 147
AI-assisted diagnostic alternatives to spirometry 147
Heterogeneity of COPD 148
Imaging biomarkers 148
Biologic biomarkers 148
Multimodal models 148
Management guidelines, multimorbidity and AI 149
Remote patient monitoring 149
Prognosis 149
TELEHEALTH, REMOTE MONITORING AND FOLLOW-UP 150
Triage and prioritizing process 150
Consideration and instruction for remote COPD follow-up 151
DELIVERY OF PULMONARY REHABILITATION: IN-PERSON VERSUS VIRTUAL 152
DELIVERY OF SELF-MANAGEMENT: IN-PERSON VERSUS VIRTUAL 152

APPENDICES 153

APPENDIX 1: ABBREVIATIONS 153
APPENDIX 2: PHARMACOLOGICAL THERAPY CHECKLIST 155
APPENDIX 3: NON-PHARMACOLOGICAL THERAPY CHECKLIST 156
APPENDIX 4: COPD FOLLOW-UP CHECKLIST 159
APPENDIX 5: OVERVIEW OF THE EVIDENCE: PHARMACOTHERAPY 161
Pharmacotherapies for smoking cessation 161
Maintenance therapy for stable COPD 162
Bronchodilators 164
Methylxanthines 166
Combination bronchodilator therapy 166
Anti-inflammatory agents 167
Inhaled corticosteroids 167
Triple therapy (LABA+LAMA+ICS) 170
New propellants for pMDI with lower global warming potential 170
Oral glucocorticoids 170
Phosphodiesterase-4 inhibitors 171
Antibiotics 171
Mucolytic (mucokinetics, mucoregulators) and antioxidant agents (N-acetylcysteine, carbocysteine, erdosteine) 171
Phosphodiesterase-3 and -4 inhibitors 171
Biologic therapy 172
Other drugs with potential to reduce exacerbations 172
Adherence to inhaled COPD medications 173
Other pharmacological treatments 174
Management of mucus hypersecretion 175
APPENDIX 6: OVERVIEW OF THE EVIDENCE: NON-PHARMACOLOGICAL THERAPY 177
Self-management 177
Physical activity 178
Exercise training 178
Pulmonary rehabilitation 179
Tele-rehabilitation 181
Nutritional support 182
Integrated care programs 183
TABLE OF FIGURES 184
REFERENCES 186

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF COPD

INTRODUCTION

The aim of the GOLD Report is to provide a non-biased review of the current evidence for the assessment, diagnosis and treatment of people with COPD. One of the strengths of GOLD reports is the treatment objectives. Treatment objectives are organized into two groups: objectives that are directed towards relieving and reducing the impact of symptoms, and objectives that reduce the risk of adverse health events that may affect the patient at some point in the future (exacerbations are an example of such events). This emphasizes the need for clinicians to focus on both the short-term and long-term impact of COPD on their patients.

Simple and reliable questionnaires designed for use in routine daily clinical practice are available in many languages. This has enabled an assessment system to be developed that draws together a measure of the impact of the patient's symptoms and an assessment of the patient's risk of having a serious adverse health event. This management approach can be used in any clinical setting anywhere in the world and moves COPD treatment towards individualized medicine – matching the patient's therapy more closely to his or her needs.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

BACKGROUND

COPD is now one of the top three causes of death worldwide and nearly 90% of these deaths occur in LMICs.[1,2] More than 3 million people died of COPD in 2021 accounting for 5% of all deaths globally.[3] COPD represents an important public health challenge that is both preventable and treatable. COPD is a major cause of chronic morbidity and mortality throughout the world; many people suffer from this disease for years and die prematurely from it or its complications. Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population.[4]

In 1998, with the cooperation of the NHLBI, NIH and the WHO, GOLD was implemented. Its goals were to increase awareness of the burden of COPD and to improve prevention and management of COPD through a concerted worldwide effort of people involved in all facets of healthcare and healthcare policy. An important and related goal was to encourage greater research interest in this highly prevalent disease.

In 2001, GOLD released its first report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*. This report was not intended to be a comprehensive textbook on COPD, but rather to summarize the current state of the field. It was developed by individuals with expertise in COPD research and patient care and was based on the best-validated concepts of COPD pathogenesis at that time, along with available evidence on the most appropriate management and prevention strategies. It provided state-of-the-art information about COPD for pulmonary specialists and other interested physicians and served as a source document for the production of various communications for other audiences, including an Executive Summary, a Pocket Guide for Healthcare Professionals, and a Patient Guide.

Immediately following the release of the first GOLD report in 2001, the GOLD Board of Directors appointed a Science Committee, charged with keeping the GOLD documents up to date by reviewing published research, evaluating the impact of this research on the management recommendations in the GOLD documents, and posting yearly updates of these documents on the GOLD website.

In 2018 GOLD held a one-day summit to consider information about the epidemiology, clinical features, approaches to prevention and control, and the availability of resources for COPD in LMICs.[1] Major conclusions of the summit included that: there are limited data about the epidemiological and clinical features of COPD in LMICs but the data available indicate there are important differences in these features around the world; there is widespread availability of affordable tobacco products as well as other exposures (e.g., household air pollution) thought to increase the risk of developing COPD; diagnostic spirometry services are not widely available and there are major problems with access to affordable quality-assured pharmacological and non-pharmacological therapies. GOLD is therefore concerned that COPD is not being taken seriously enough at any level, from individuals and communities, to national governments and international agencies.[5] It is time for this to change and the GOLD Board of Directors challenge all relevant stakeholders to work together in coalition with GOLD to address the avoidable burden of COPD worldwide. GOLD is committed to improving the health of people at risk of and with COPD, wherever they happen to have been born, and wishes to do its bit to help achieve the *United Nations Sustainable Development Goal 3.4* to reduce premature mortality from non-communicable diseases - including COPD - by one third by 2030.[6]

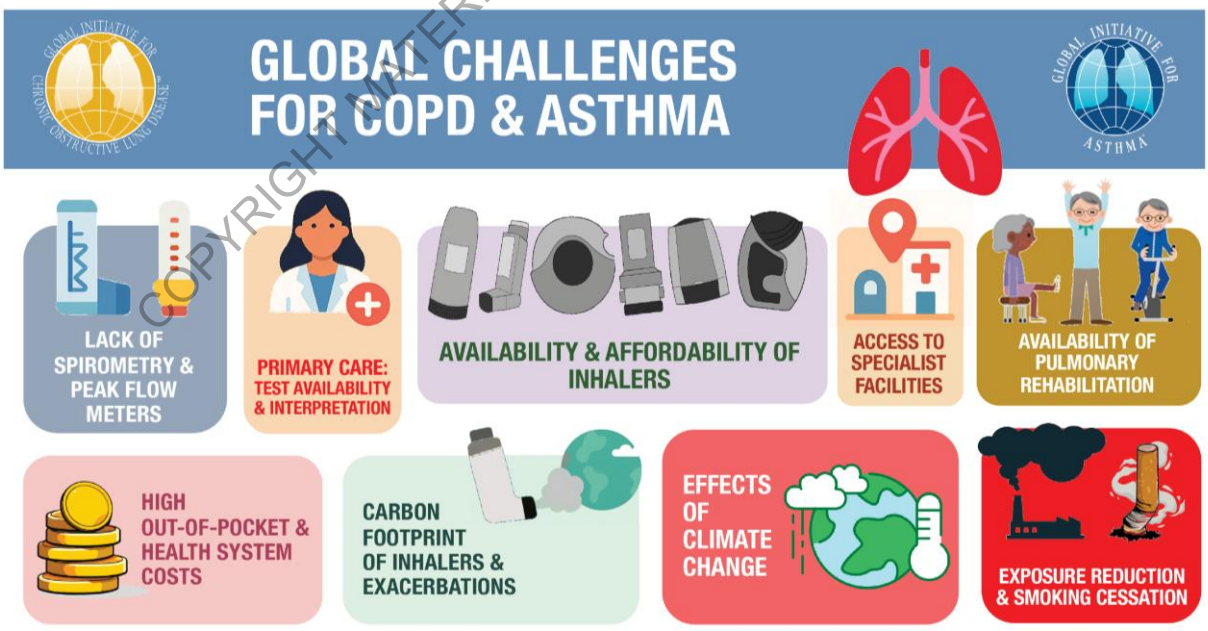
ADDRESSING THE GLOBAL CHALLENGES OF COPD AND ASTHMA: A SHARED VISION FROM GOLD & GINA

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Unlike other non-communicable diseases such as ischemic heart disease and diabetes, COPD has not been prioritized by policy makers, resulting in inadequate access to diagnostic tools and treatments. The same is true for asthma and in 2026 GOLD and the Global Initiative for Asthma (GINA) published a joint statement on the global diagnostic and management challenges facing COPD and asthma (**Figure A**).[7-11] GOLD is committed to addressing these challenges.

Global Challenges for COPD & Asthma

Figure A



Reproduced with permission of the American Thoracic Society (ATS).

Reference: Halpin et al. American Journal of Respiratory and Critical Care Medicine, February 2026, 212, 2, 97–302, https://doi.org/10.1164/rccm.202508-1894PP.

LEVELS OF EVIDENCE

Levels of evidence have been assigned to evidence-based recommendations where appropriate (**Figure B**). Evidence levels are indicated in boldface type enclosed in parentheses after the relevant statement e.g., (**Evidence A**). The methodological issues concerning the use of evidence from meta-analyses were carefully considered when i) treatment effect (or effect size) was consistent from one study to the next, and we needed to identify the common effect; ii) the effect varied from one study to the next, and there was a need to identify the reason for the variation.

Description of Levels of Evidence

Figure B

Evidence Category	Sources of Evidence	Definition
A	Randomized controlled trials (RCTs)	Evidence is from endpoints of well-designed RCTs that provide consistent findings in the population for which the recommendation is made without any important limitations.
	Rich body of high quality evidence without any significant limitation or bias	Requires high quality evidence from ≥ 2 clinical trials involving a substantial number of subjects, or a single high quality RCT involving substantial numbers of patient without any bias.
B	Randomized controlled trials (RCTs) with important limitations	Evidence is from RCTs that include only a limited number of patients, *post hoc* or subgroup analyses of RCTs or meta-analyses of RCTs.
	Limited body of evidence	Also pertains when few RCTs exist, or important limitations are evident (methodological flaws, small numbers, short duration, undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent).
C	Non-randomized trials Observational studies	Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies.
D	Panel consensus judgment	Provision of guidance is deemed valuable but clinical literature addressing the subject is insufficient. Panel consensus is based on clinical experience or knowledge that does not meet the above stated criteria.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

CHAPTER 1: DEFINITION AND OVERVIEW

KEY POINTS:

Definition

- COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.

Causes and risk factors

- COPD results from gene(G)-environment(E) interactions occurring over the lifetime(T) of the individual (GETomics) that can damage the lungs and/or alter their normal development/aging processes.
- The main environmental exposures leading to COPD are tobacco smoking and the inhalation of toxic particles and gases from household and outdoor air pollution, but other environmental and host factors (including abnormal lung development and accelerated lung aging) can also contribute.

Diagnostic criteria

- In the appropriate clinical context (see 'Definition' & 'Causes and Risk Factors' above), the presence of non-fully reversible airflow obstruction (i.e., FEV1/FVC < 0.7 post-bronchodilation) measured by spirometry confirms the diagnosis of COPD.

Clinical presentation

- Patients with COPD typically complain of dyspnea, activity limitation and/or cough with or without sputum production, and may experience acute respiratory events characterized by increased respiratory symptoms called exacerbations that require specific preventive and therapeutic measures.
- Patients with COPD frequently harbor other comorbid diseases that influence their clinical condition and prognosis and require specific treatment. These comorbid conditions can mimic and/or aggravate an acute exacerbation.

New opportunities

- COPD is a common, preventable, and treatable disease, but extensive under-diagnosis and misdiagnosis leads to patients receiving no treatment or incorrect treatment. Appropriate and earlier diagnosis of COPD can have a very significant public-health impact.
- The realization that environmental factors other than tobacco smoking can contribute to COPD, that it can start early in life and affect young individuals, and that there are precursor conditions (pre-COPD, PRISm), opens new windows of opportunity for its prevention, early diagnosis, and prompt and appropriate therapeutic intervention.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

WHAT IS COPD?

Definition

COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.[12]

Causes and risk factors

COPD results from gene(G)-environment(E) interactions occurring over the lifetime(T) of the individual (GETomics)

that can damage the lungs and/or alter their normal development/aging processes.[13]

The main environmental exposures leading to COPD are tobacco smoking and the inhalation of toxic particles and gases from household and outdoor air pollution, but other environmental[14,15] and host factors (including abnormal lung development and accelerated lung aging) can also contribute.[13]

Cigarette smoking

Cigarette smoking is a key environmental risk factor for COPD. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV1, and a greater COPD mortality rate than non-smokers.[16] Onset of smoking in childhood, prior to age 15, has been found to increase the relative risk of developing COPD, independent of cigarette pack-years and smoking duration.[17] Most COPD studies have included patients with a minimum cigarette exposure of 10 pack-years. However, one study has suggested that even at a reduced smoking exposure (< 10 pack-years) the 5-year risk of developing COPD is increased in middle-aged adults, and these individuals have an increased risk of severe exacerbation and early death.[18] Yet fewer than 50% of heavy smokers develop COPD[19] and it is estimated that half of all COPD cases worldwide are due to risk factors other than tobacco so other pathogenic factors beyond smoking need to be considered.[15]

Genetics modify the risk of COPD in smokers, but there may also be other risk factors involved. For example, gender and social pressure may influence whether a person takes up smoking or experiences certain occupational or environmental exposures; socioeconomic status may be linked to birthweight (which may impact lung growth and development, and in turn susceptibility to developing COPD);[20] and longer life expectancy will allow greater lifetime exposure to risk factors.

Other types of tobacco (e.g., pipe, cigar, water pipe)[21-23] are also risk factors for COPD. Passive exposure to cigarette smoke, also known as environmental tobacco smoke and second-hand smoking, may also contribute to respiratory symptoms and COPD,[24] especially after long-term exposure.[25] Data derived from the GBD 2021, showed that globally, ischemic heart disease, COPD, and lower respiratory infections were the three leading causes of second-hand smoke-attributable numbers of deaths and DALYs for both sexes.[26] Smoking during pregnancy poses a risk for the fetus, by altering lung growth and development *in utero*, and possibly priming the immune system by inducing specific epigenetic changes.[27] This is a good example of the GETomics approach discussed above. The fetus exposed to 'passive smoking' is likely to respond differently to a second GxE hit later in life.[13]

Biomass exposure

Tobacco smoking has been recognized as a major risk factor associated with COPD for over five decades, but this was largely because most research was conducted in high income countries. As more studies from LMICs were conducted,[28] it has become apparent that non-smoking risk factors are more important in these parts of the world. Whilst tobacco smoking remains the leading risk factor for COPD in high income countries, accounting for over 70% of the cases, in LMICs tobacco smoking contributes to around 30% to 40% of the total burden.[15] Because the LMICs together contribute to over 85% of the total burden of COPD globally, non-smoking risk factors now contribute to over 50% of the global burden of COPD.[15]

Wood, animal dung, crop residues, and coal, typically burned in open fires or poorly functioning stoves, may lead to very high levels of household air pollution.[29] Household air pollution exposure is associated with an increased risk of developing COPD in LMICs[30] although the extent to which household air pollution versus other poverty-related exposures explain the association is unclear.[31-36] However, there is limited research about household air pollution related COPD or the interventions that could reduce the risk of developing it.[37] Based on a systematic review, the use of gas for heating and cooking reduced the risk of COPD and other respiratory diseases and may be considered as a transitional fuel option in areas where clean fuel (electricity) is not readily available.[38]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Occupational exposures

Occupational exposures, including organic and inorganic dusts, chemical agents and fumes, are an under-appreciated environmental risk factor for COPD.[39,40] Individuals with exposure to inhalation of high doses of pesticides have a higher incidence of respiratory symptoms, airways obstruction and COPD.[41,42] A study of the population-based UK Biobank Cohort identified occupations including sculptors, gardeners and warehouse workers that were associated with an increased COPD risk among never-smokers without asthma.[43] A cross-sectional observational study demonstrated that self-reported exposure to workplace dust and fumes is associated with not only increased airflow obstruction and respiratory symptoms, but also more emphysema and gas trapping, as assessed by computed tomography scan, in both men and women.[44] A cross-sectional study of workers across multiple stone quarries documented spirometric obstruction in 39%; this was more prevalent in smokers (46.7%) compared with non-smokers (30.1%).[45] An analysis of the large US population-based National Health and Nutrition Examination Survey III survey of almost 10,000 adults aged 30-75 years estimated the fraction of COPD attributable to workplace exposures was 19.2% overall, and 31.1% among never-smokers.[46] These estimates are consistent with a statement published by the ATS that concluded that occupational exposures account for 10-20% of either symptoms or functional impairment consistent with COPD.[47] The risk from occupational exposures in less regulated areas of the world is likely to be much higher than reported in studies from Europe and North America.

Air pollution

Air pollution typically consists of particulate matter, ozone, oxides of nitrogen or sulfur, heavy metals, and other greenhouse gases, and is a major worldwide cause of COPD, responsible for approximately 50% of the attributable risk for COPD in LMICs.[48] In never smokers, air pollution is the leading known risk factor for COPD.[49] Data from China from the GBD Study (2021) showed that while smoking was a major risk factor for COPD in men, ambient particulate matter pollution had a greater impact on women and younger adults (30-34 years).[50] The respiratory risk of air pollution to individuals is dose-dependent with no apparent "safe" thresholds. Even in countries with low ambient air pollution levels, chronic exposure to PM2.5 and nitrogen dioxides significantly impairs lung growth in children,[51] accelerates lung function decline in adults and increases the risk for COPD, especially among those with additional risk factors for COPD.[52] Poor air quality from air pollution also increases the risk of exacerbations, hospitalizations and mortality.[53-55] A study among the population residing near a coke plant at the time of its closure found a 19% reduction in the risk of long-term hospitalizations due to COPD and related diseases in the population after closure (annual hospitalization IRR 0.81; 95% CI 0.69,0.94).[56] These results suggest that reducing exposure to fossil fuel-related air pollution produces both short- and long-term respiratory health benefits.[56] Thus, reduction in both indoor and outdoor air pollution is a key goal in the prevention and management of COPD.

Genetic factors

The most relevant (albeit epidemiologically rare) genetic risk factor for COPD identified to date is mutations in the SERPINA1 gene, leading to AATD, but other genetic variants, with a low individual effect size, are associated with reduced lung function and risk of COPD too.[57]

A significant familial risk of airflow obstruction has been observed in people who smoke and are siblings of patients with COPD who had irreversible airflow obstruction with a reduced gas transfer factor,[58] suggesting that genetics (in combination with environmental risk factors) could influence this susceptibility. The best documented genetic risk factor for COPD are mutations in the SERPINA1 gene that leads to the hereditary deficiency of α-1 antitrypsin,[59] a major circulating inhibitor of serine proteases. Although AATD is relevant to only a small part of the world's population, it illustrates the interaction between genes and environmental exposures that predispose an individual to COPD. A systematic review of 20 studies in European populations found AATD PiZZ genotypes in 0.12% of patients with COPD (range 0.08% to 0.24%), and a prevalence ranging from 1 in 408 in Northern Europe to 1 in 1,274 in Eastern Europe.[60]

There has been a long-standing controversy concerning the risk of heterozygotes (MZ and SZ) for the development of

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

COPD. This has largely reflected acquisition bias but is of critical importance due to the large numbers of such individuals worldwide[61] who may potentially benefit from augmentation therapy. Careful sibling studies[62,63] indicated no increased risk in these heterozygotes in the absence of smoking, although lung function was reduced in smokers compared to MM siblings. This likely reflects the presence of low concentrations of the Z AAT protein rather than an absolute lack,[64] and is not an indication for augmentation therapy (discussed in more detail in **Chapter 3**).

To date, hundreds of genetic variants associated with reduced lung function and risk of COPD have been identified (albeit epidemiologically rare), including genes encoding matrix metalloproteinase 12, glutathione S-transferase, the alpha-nicotinic acetylcholine receptor, and the hedgehog interacting protein.[65,66] Yet, their individual effect size is small,[57] and it remains uncertain whether these genes are directly responsible for COPD or are merely markers of other causal genes.[67-71]

Diagnostic criteria

In the appropriate clinical context (See 'Definition' and 'Causes and Risk Factors' above), the presence of non-fully reversible airflow obstruction (FEV1/FVC < 0.7 post-bronchodilation) measured by spirometry confirms the diagnosis of COPD.

Yet, some individuals may present with structural lung lesions (e.g., emphysema) and/or physiological abnormalities (including low FEV1, gas trapping, hyperinflation, reduced lung diffusing capacity and/or rapid FEV1 decline) without airflow obstruction (FEV1/FVC ≥ 0.7 post-bronchodilation). These subjects are labeled 'pre-COPD'. The term 'PRISm' has been proposed to identify those with normal ratio but abnormal spirometry. Subjects with pre-COPD or PRISm are at risk of developing airflow obstruction over time, but not all of them do.[72,73] Research is needed to determine what is the best treatment for these individuals (beyond smoking cessation).

Clinical presentation

Patients with COPD typically complain of dyspnea, wheezing, chest tightness, fatigue, activity limitation, and/or cough with or without sputum production, and may experience acute events characterized by increased respiratory symptoms called exacerbations that influence their health status and prognosis, and require specific preventive and therapeutic measures.

Patients with COPD frequently harbor other comorbid diseases that also influence their clinical condition and prognosis and require specific treatment. These comorbid conditions can mimic and/or aggravate an acute exacerbation.

New opportunities

COPD is a common, preventable, and treatable disease, but extensive under- and misdiagnosis leads to patients receiving no, or incorrect, treatment. The realization that environmental factors other than tobacco smoking can contribute to COPD, that it can start early in life and affect young individuals, and that there are precursor conditions (pre-COPD, PRISm), opens new windows of opportunity for its prevention, early diagnosis, and prompt and appropriate therapeutic intervention.[74]

BURDEN OF COPD

COPD is a leading cause of morbidity and mortality worldwide with an economic and social burden that is both substantial and increasing.[75-79] COPD prevalence, morbidity and mortality vary across countries,[75-78,80] and although it is often directly related to the prevalence of tobacco smoking, in many countries outdoor, occupational and

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

household air pollution (resulting from the burning of wood and other biomass fuels) are important COPD risk factors.

The number of COPD cases globally is projected to increase over the coming decades, approaching nearly 600 million COPD patients by 2050 and the increase will be greater among women and in LMICs.[77] This is due to a combination of continued exposure to COPD risk factors and an increase in both the total number and average age of the world's population.[75,78]

Information on the burden of COPD can be found on international websites, such as the WHO[81] and the World Bank/WHO GBD Study.[75,80]

Prevalence

Existing COPD prevalence data vary widely due to differences in survey methods, diagnostic criteria, and analytical approaches.

In the past two decades, BOLD, PLATINO and GBD collaborators have pioneered efforts to collect country-specific population-based data on prevalence and risk factors for COPD, providing updates on global estimates of deaths, prevalence, and DALYs.[75,78,82-85]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

GBD data include margins of error, are internally consistent with mortality and other health indicators, and help assess trends in COPD and risk factors over time worldwide since 1990, even in countries without adequate health statistics, as well as the potential impact of different prevention and treatment strategies on health outcomes. The GBD collaborators have combined data from various sources in complex statistical models.[75,79] However, GBD COPD burden estimates appear to be inconsistent with other epidemiological studies based on spirometric measurements and may underestimate the true burden of COPD.[78] Disparities between the GBD and other epidemiological surveys or meta-analyses on prevalence may lie primarily in the use of different definitions of COPD, the inclusion of the entire population (people aged ≥ 15 years) in the GBD, and the adoption of different methods for building predictive models.

The 2021 GBD data estimates a total of 213.39 million cases of COPD of all ages, which represents a prevalence of 2.7% (2.5 age-standardized prevalence per 100,000) a change of −1.46% since 1990.[75] A higher total number of female COPD patients and a higher age-standardized prevalence of male COPD patients was observed from 1990 to 2021.[75,78] High-income North America and South Asia had the highest age-standardized prevalence of COPD, with more than 3,000 cases per 100,000 people. The lowest age-standardized prevalence was reported in southern Latin America and high-income Asia Pacific.[75]

A systematic review and modeling study that included data from population-based studies using spirometric measurements for the diagnosis of COPD in 65 countries estimated a global prevalence of COPD in 2019 in people aged 30-79 years of 10.3%, which translates to 392 million people with COPD worldwide, the majority (315 million, 80.5%) living in LMICs.[76] After considering the demographic characteristics (age, sex, and population distribution), the overall prevalence of GOLD-COPD was slightly higher in LMICs (10.3%) than in HICs (10.1%).[76] Worldwide, the COPD prevalence in men was more than double that in women in the same age range (14.1% vs. 6.5%).[76] The overall prevalence of GOLD-COPD was highest in the Western Pacific region (11.7%) and lowest in the Americas (6.8%). The ten countries with the highest number of COPD cases are: China, India, Indonesia, USA, Bangladesh, Japan, Pakistan, Russia, Vietnam, and Germany, accounting for 255 million (65.2%) of global COPD cases in 2019.[76] **Figure 1.1**[75-77,86] shows a summary of COPD prevalence according to different sources.

Of note, the lowest estimates of COPD prevalence are those based on the self-reporting of a diagnosis of COPD, or equivalent condition. For example, most national data show that < 6% of the adult population have been told that they have COPD.[87] This is likely to be a reflection of the widespread under-recognition and under-diagnosis of

COPD.[88] A study using data from 30,874 participants in several epidemiological surveys indicates that COPD underdiagnosis is universally high, estimating that, overall, 81.4% of COPD cases (defined spirometrically) are undiagnosed. Global determinants of COPD underdiagnosis were male sex, younger age, current and never smoking, lower educational, absence of reported symptoms, no previous spirometry, and less severe airflow limitation.[88]

Estimated COPD Prevalence According to Different Sources

Figure 1.1

	GBD 2019[a]	GBD 2021[b]	Population-based study 2019[c]	Other sources 2020[d]
Prevalence (%)	2.6	2.5	10.3	10.6
Number of cases (million)	212	213	392	479

References: [a]Safiri et al. BMJ 2022;378:e069679; [b]Wang et al. Respir Res 2025;26:2; [c]Adeloye et al. Lancet Respir Med 2022;10:447–458; [d]Boers et al. JAMA Netw Open 2023;6:E2346598.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

A number of systematic reviews and meta-analyses provide evidence that the prevalence of COPD is appreciably higher in smokers and ex-smokers compared to non-smokers, in those ≥ 40 years of age compared to those < 40, and in men compared to women.[89-91]

Morbidity

Morbidity measures traditionally include physician visits, emergency department visits, and hospitalizations. Morbidity due to COPD increases with age,[84,87] and in patients with COPD the development of comorbidities is seen at an earlier age than in the general population.[92,93] Morbidity in COPD may also be influenced by concomitant chronic conditions (e.g., cardiovascular disease, musculoskeletal impairment, diabetes mellitus)[94] that are related to smoking, aging and/or COPD.[95]

Mortality

COPD is the third leading cause of death worldwide.[79] Data from the GBD study estimated that the number of COPD-attributable deaths increased from 2.50 million in 1990 to 3.72 million in 2021, with an age-standardized mortality of 45.22 per 100,000, a decrease of 37.1% since 1990.[75] East Asia, South Asia, and Southeast Asia had the highest number of deaths (1.32; 1.23; and 0.23; million, respectively).[75] COPD is associated with reduced life expectancy, with an estimated loss of approximately 2 years on average, rising to as much as 7 years among those with stage 4 disease.[96] Smoking contributes to 35% of the COPD deaths globally (51% in men and 15% in women), followed by outdoor and

household air pollution.[78] Global data also demonstrate reductions in death rates across all leading COPD risk factors. The age-standardized death rate from COPD attributed to smoking has significantly decreased in all countries, with HMICs showing the largest decreases.[78] In LICs household air pollution is the leading risk factor in both sexes for age-standardized death rate.[78]

Although age-standardized COPD mortality rates have decreased globally since 1990, the total number of COPD deaths, people living with the disease (prevalence), and the overall health burden (DALYs) of COPD have increased substantially, with direct effects on health systems worldwide.[75] It is estimated that the increased prevalence of smoking in LMICs coupled with aging populations in high-income countries will result in over 5.4 million annual deaths from COPD and related conditions by 2060.[97]

The WHO publishes mortality statistics for selected causes of death annually for all WHO regions.[98] However, data must be interpreted with caution because of the inconsistent use of COPD terminology. In the ICD-10, deaths from COPD or chronic airways obstruction are included in the broad category of "COPD and allied conditions" (ICD-10 codes J42-46).

Under-recognition and under-diagnosis of COPD reduces the accuracy of mortality data.[99] Furthermore, the accuracy of COPD diagnosis codes recorded in administrative health databases is also uncertain.[100,101] In some jurisdictions, reliance on administrative health data, particularly those that only record hospitalizations, may underestimate the burden of COPD.[102] The reliability of recording of COPD-related deaths in mortality data is also problematic. Although COPD is often a primary cause of death, it is more likely to be listed as a contributory cause of death or omitted from the death certificate entirely.[103]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Economic burden

COPD is associated with a significant economic burden. In the EU, the total direct costs (excluding indirect costs, such as the economic value of care provided by family members) of respiratory disease are estimated to be about 6% of the total annual healthcare budget, with COPD accounting for 56% (38.6 billion Euros) of the cost of respiratory disease.[104] In the US the costs attributable to COPD are expected to increase over the next 20 years, with projected costs of $800.90 billion or $40 billion per year.[105,106] Significant geographic variability has been reported in the direct annual cost of healthcare per patient. The cost per patient in the US is, on average, 1.4 times higher than in Europe. The costs were lower in Asia.[107] Another projections study using the GBD database, WHO, and meta-analysis indicates that globally by 2050, the direct costs related to COPD are estimated to be $24.35 trillion (a relative growth of 526% compared to 2025), indirect costs are estimated to be $15.43 trillion (a relative growth of 518% compared to 2025), and exacerbations are estimated to be $15.60 billion (a relative growth of 584% compared with 2025).[108] Exacerbations account for the greatest proportion of the total COPD burden on the healthcare system.[109] Not surprisingly, there is a striking direct relationship between the severity of COPD and the cost of care, and the cost distribution changes as the disease progresses. For example, hospitalization and ambulatory oxygen costs soar as COPD severity increases. Any estimate of direct medical expenditure for home-based care under-represents the true cost of home-based care to society because it ignores the economic value of the care provided by family members to people with COPD. In high-income countries the average total indirect cost is estimated to be US $7,850 per patient.[107]

In LMICs, both direct and indirect medical costs may be substantial. The WHO and other organizations suggest that inhaled medicines for COPD are poorly available and largely unaffordable in LMICs.[110] Most inhaled medications are still branded and there are few options currently available for generic inhalers. The situation is similar for access to diagnostic spirometry. Because the healthcare sector might not provide long-term supportive care services for severely disabled individuals, COPD may force at least two individuals to leave the workplace – the affected individual and a family member who must now stay home to care for their disabled relative.[111] Since human capital is often the most important national asset for LMICs, the indirect costs of COPD may represent a serious threat to their economy.

Social burden

Since mortality offers only a limited perspective on the human burden of a disease, it is desirable to find other measures of disease burden that are consistent and measurable within and between nations. The GBD study designed a method to estimate the fraction of mortality and disability attributable to major diseases and injuries using a composite measure of the burden of each health problem: the DALY.[112] The DALY for a specific condition is the sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of disability. The GBD 2019 estimated a COPD DALY rate of 926.1 per 100,000, and GBD 2021 estimated it to be 940.7 per 100,000.[75,86] According to the GBD Study, COPD was the primary driver of increased DALYs worldwide, especially in LMICs. Predictions indicated that in 2022, COPD DALYs will rank sixth, but by 2050, are expected to rise to the fourth position.[75,113] In 2021, the number of DALYs for COPD was estimated to be 79.8 million, with an age-standardized DALYs rate of 940.7 per 100,000, a decrease of 36.98% since 1990.[75] East Asia, South Asia, and Southeast Asia had the highest DALYs (24.39, 28.01, and 5.56 million, respectively).[75] Although East Asia had a higher age standardized COPD DALYs from 1990 to 2021, it's important to highlight that this region also had a significant decline in COPD-related deaths and DALYs during the same period. Taking China as an example, the country implemented various measures over the past 30 years to reduce burden due to COPD. These measures included reducing smoking rates, decreasing the use of fossil fuels to improve air quality, promoting clean energy sources, encouraging environmentally friendly practices, and improving access to quality healthcare for early diagnosis and treatment.[75,78] At the same time, the US has experienced an increase in age standardized mortality, driven primarily by an increase in mortality in women, attributed to delayed uptake of smoking among American women relative to men.[114]

PATHOGENESIS

COPD is the end-result of complex, cumulative and dynamic gene-environment interactions over the lifetime that can damage the lungs and/or alter their normal developmental or aging processes.[13] Understanding the relationships and interactions between the genetic (G) background of the host and varied environmental (E) risk factors over the lifetime (T) requires further investigation.[13,115] According to this GETomics proposal, the end result of a given GxE interaction depends not only on G and E, but also on T, as determined by both the age of the individual at which that particular interaction occurs (development vs aging) and the previous history of GxE interactions that the individual has encountered earlier in her/his life (biological memory).[13]

Trajectories of lung function: development and aging

At birth, the lungs are not fully developed. They grow and mature until about 20-25 years of age (earlier in females), when lung function reaches its peak (**Figure 1.2**).[16] This is followed by a short plateau and a final phase of mild lung function decline due to physiological lung aging.[16] This constitutes the normal lung function trajectory in **Figure 1.2**.[116,117] This normal lung function trajectory can be altered by processes occurring during gestation, birth, childhood, and adolescence that affect lung growth (hence, peak lung function) and/or processes shortening the plateau phase and/or accelerating the aging phase (hence accelerating the normal rate of lung function decline with age).[118-120]

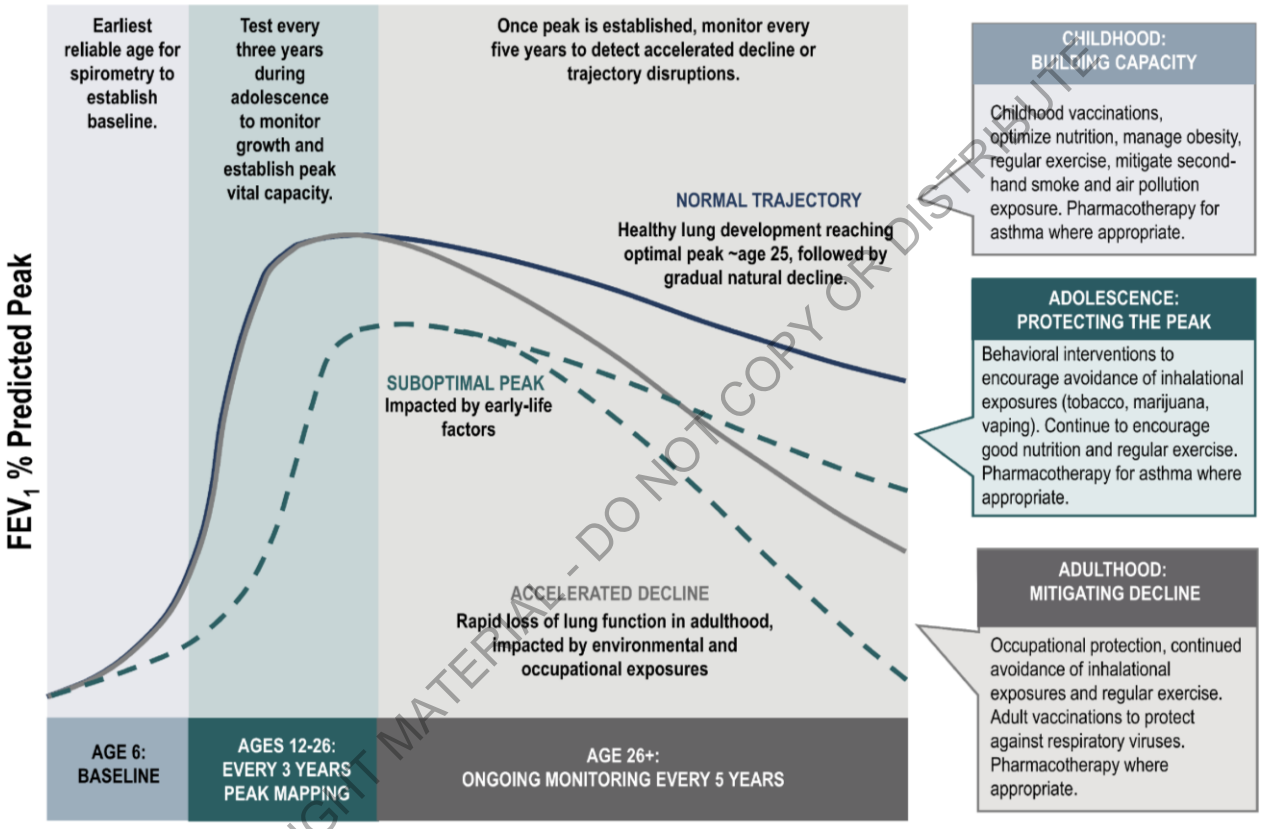
As a result, a given individual may follow one of a range of potential lung function trajectories through her/his lifetime, both below and above the normal one (**Figure 1.2**). It is now well established that those above the normal trajectory are associated with healthier aging[121] whereas those below it have an increased prevalence and incidence of respiratory, cardiovascular and metabolic diseases and premature death.[93,122] From this perspective, spirometry can be considered a marker of global health. In fact, free downloadable software to monitor spirometry over time can now be accessed from the ERS website (gli-calculator.ersnet.org/lung_tracker/).[123,124]
Spirometrically-measured reduced maximal attained lung function can identify individuals who are at increased risk

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

for the development of COPD.[125,126] A large study and meta-analysis confirmed a positive association between birthweight and FEV1 in adulthood.[127] Factors in early life termed "childhood disadvantage factors" are key determinants of lung function in adult life.[127-135] One study in three independent longitudinal cohorts (Framingham, Copenhagen and Lovelace) found that approximately 50% of patients developed COPD due to accelerated decline in FEV1 over time (the traditional Fletcher and Peto model),[136] while the other 50% developed COPD due to abnormal lung growth and development (with normal lung function decline over time; **Figure 1.2**).[116,117]

FEV1 Trajectories (TR) Over the Life Course

Figure 1.2



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

References: Agusti A, Hogg JC. N Engl J Med. 2019;381:1248-56; Han, MK et al. AJRCCM 2026, aamag432.

Age is often listed as a risk factor for COPD because there is a physiological decline in lung function with age. Yet, it is unclear whether healthy aging as such leads to COPD or if age reflects the sum of cumulative exposures throughout life.[137] However, aging of the airways and parenchyma mimic some of the structural changes associated with COPD,[137] and there is evidence of accelerated aging in patients with COPD.[129] A prospective study showed an association between accelerated telomere shortening (a marker of accelerated aging) and progressive worsening of pulmonary gas exchange, lung hyperinflation and extrapulmonary affection in patients with COPD who were followed over 10 years.[138] Further, persistently shorter telomeres over this observation time increase the risk for all-cause mortality.[138] Age-related epigenetic changes in DNA in immune cells are also associated with increased risk of exacerbations and mortality in patients with COPD.[133,139,140]

The term *dysanapsis* refers to an anthropometric mismatch of airway tree caliber relative to lung volume.[141,142] It was

first proposed by Green and colleagues in 1974 from maximal expiratory airflow variation among healthy adults.[128] There are still major gaps in our understanding of the origins and clinical implications of dysanapsis, but recent research using CT has shown that: (1) it is common in the general population;[128,132,143] (2) it is associated with FEV1/FVC from early adulthood;[144] (3) in explanted lungs from adult healthy donors, central airway dysanapsis (detectable by CT) extended to peripheral airways (non-visible on CT);[144] (4) dysanapsis is associated with baseline airflow obstruction and risk of incident COPD independently of age, sex, height and race-ethnicity, but not with lung function decline over time.[132] This observation is consistent with the trajectory of low peak lung function in early adulthood followed by normal lung function decline that accounts for 50% of COPD in older adults;[116] (5) a computational study of airway tree fluid dynamics and an *in vivo* study of regional lung ventilation suggest that dysanapsis may contribute to obstructive lung disease pathophysiology and deposition of aerosolized drugs;[145-147] and, (6) the mechanisms contributing to the development of dysanapsis are not well understood. It is not clear whether it is due to genetic predisposition, *in utero* exposures to noxious particulates or pathogens, premature birth, low birth weight, neonatal lung injury, repeated respiratory infections in early life or a combination of them, but factors affecting airway tree growth early in life[128,130,132] and factors affecting airway tree homeostasis later in life have been implicated.[129,131] Of note, investigating the etiology of dysanapsis earlier in life will require radiation-free (or lower-dose radiation) methods in order to quantify lung structure in children.

The fact that COPD can result from reduced peak lung function in early adulthood and/or accelerated lung function decline later in life[118,148] opens novel opportunities for prevention, and earlier diagnosis and treatment of the disease[74] but, at the same time, has generated several nosological terms that require proper definition to avoid confusion and facilitate future research.[149]

Early COPD

The word “early” means “near the beginning of a process”. Because COPD can start early in life and take a long time to manifest clinically, identifying “early COPD” is difficult. We propose that the term “early COPD” is a useful concept for planning future studies to identify predictive clinical or laboratory biomarkers associated with the initial pathobiological mechanisms that cause COPD. However, the term “early COPD” should not be used to describe patients in a clinical setting because patients present in various stages of disease and the onset of the pathogenetic process in any specific patient is impossible to determine.

Mild COPD

Mild airflow obstruction (GOLD Stage 1) does not necessarily reflect a low disease burden, as many individuals with mild airflow obstruction report symptoms, experience exacerbations, and have structural or functional abnormalities beyond spirometry. Accordingly, the adjective “mild” should only be used to describe the severity of airflow obstruction measured by spirometry.

COPD in young individuals

We propose to operationally consider “COPD in young individuals” in patients with COPD who are less than 50 years of age.[150] Of note, this can include patients who had never achieved normal peak lung function by age 25 and/or those who experienced accelerated lung function decline between ages 30 and 50 years.[151,152] COPD in young individuals is the preferred term to describe these patients, as opposed to “young COPD”. COPD in young individuals may be associated with significant structural and functional lung abnormalities that can have a substantial impact on health. Importantly, COPD is frequently not diagnosed in young individuals and thus not treated. A family history of respiratory diseases and/or early-life events (including hospitalizations for respiratory causes before the age of 5 years) is reported by a significant proportion of young individuals with COPD, further supporting the possibility of early-life origins of COPD. [149,152]

COPYRIGHT MATERIAL- DO NOT COPY OR DISTRIBUTE

Pre-COPD

Pre-COPD is a term used to capture individuals who are at increased future risk of COPD. These individuals have structural lung abnormalities, symptoms, or physiologic impairment but they do not currently meet spirometric criteria for COPD (because their post-bronchodilator FEV1/FVC is ≥ 0.70).[12]

An individual with post-bronchodilator FEV1/FVC ≥ 0.70 may be classified as "pre-COPD" if they have a history of risk factors for COPD (smoking, exposure to biomass fuel, occupational exposure, or history of early-life respiratory events) and they exhibit any of the following:

- Respiratory symptoms
- Structural lung abnormalities (seen on thoracic CT scan)
- Physiologic abnormalities (found on lung function testing)

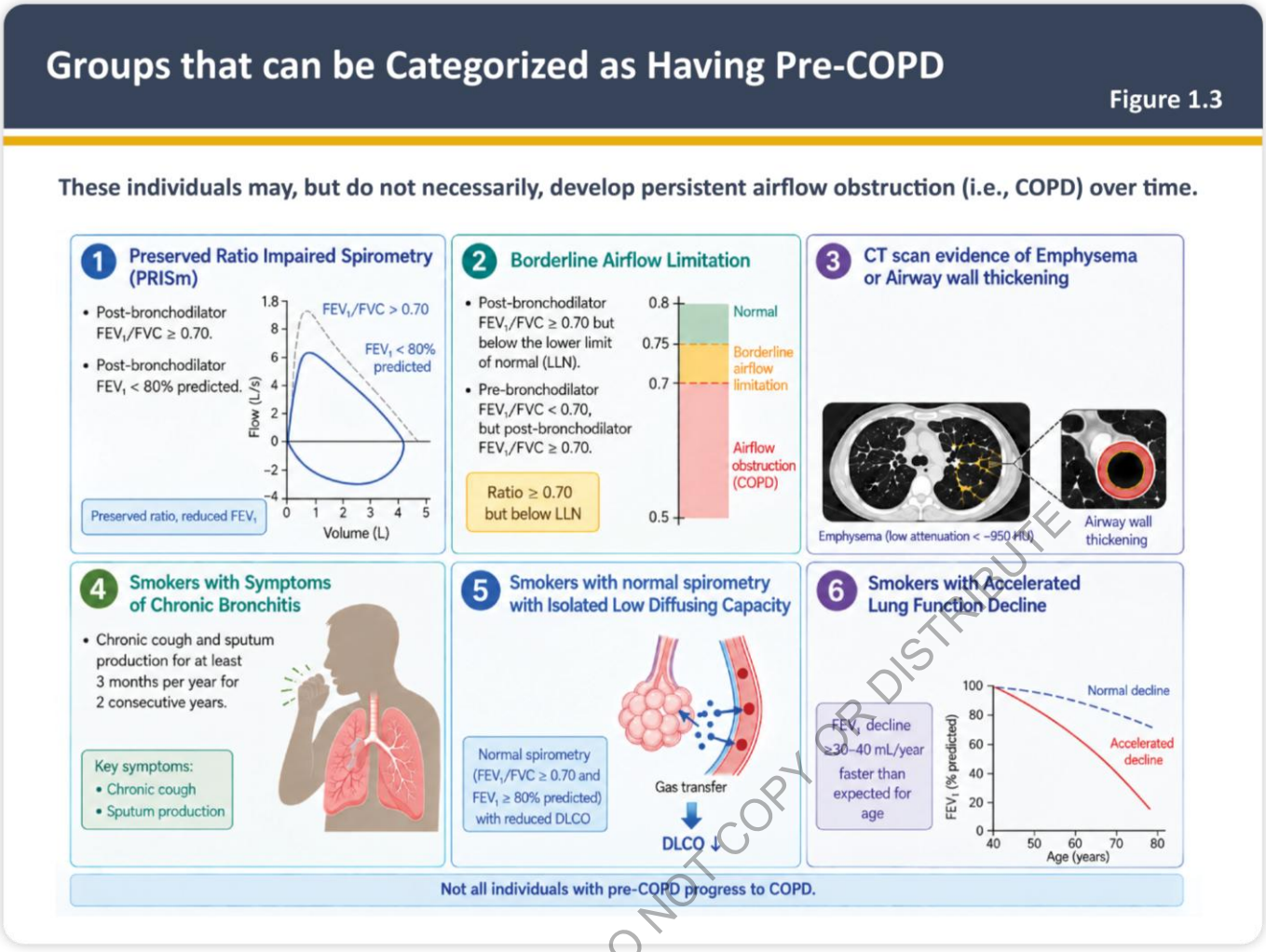
The following groups below can be categorized as having pre-COPD (see **Figure 1.3**). These patients may (or may not) develop persistent airflow obstruction,[153] therefore they should be monitored with clinical assessments and follow-up spirometry:

1. **Preserved ratio impaired spirometry (PRISm)**
    - Post-bronchodilator FEV1/FVC ≥ 0.70 and post-bronchodilator FEV1 < 80% predicted.[154]
2. **Borderline airflow limitation**
    - Post-bronchodilator FEV1/FVC ≥ 0.70 but below the lower limit of normal (LLN)[154] **or**
    - Pre- bronchodilator FEV1/FVC < 0.70, but post-bronchodilator FEV1/FVC ≥ 0.70.[155,156]
3. **CT scan evidence of emphysema or airway wall thickening**
    - Emphysema on CT is typically defined by the percentage of lung voxels with attenuation values less than −950 Hounsfield Units exceeding the upper limit of normal,[157,158] or alternatively may be defined based on visual interpretation by a radiologist.
4. **Smokers or individuals with biomass exposure with symptoms of chronic cough and sputum production**[159]
5. **Smokers or individuals with biomass exposure who have an isolated low diffusing capacity**[160]
6. **Smokers or individuals with biomass exposure with accelerated lung function decline**
    - Excessive decline in FEV1 over time (≥ 30-40 mL/year).[161,162]

Individuals who meet multiple pre-COPD categories may be at highest risk of developing COPD. For example, in the COPDGene study participants with normal spirometry at baseline who reported chronic respiratory symptoms **and** had structural abnormalities on CT scan **and** had borderline airflow limitation exhibited the highest likelihood of developing COPD five years later.[163] More research is needed to appropriately weight these categories and develop risk scores to quantify individuals' probabilities for development of COPD.

It should be noted that no validated treatment, other than smoking cessation, has been shown to alter the trajectory from pre-COPD to COPD; the category currently has more prognostic value than established therapeutic implications. It is unknown whether pre-COPD will eventually fragment into multiple distinct phenotypes/endotypes with different natural histories, rather than functioning as a single unified pre-disease state.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

PRISm

The term PRISm describes individuals with preserved ratio (FEV1/FVC ≥ 0.7 after bronchodilation) but impaired spirometry (FEV1 < 80% of reference, after bronchodilation).[73,164] The prevalence of PRISm in population-based studies ranges from 7.1% to 11%[165-168] and from 10.4% to 11.3% in a selected population of current and former smokers such as the COPDGene cohort.[164] The prevalence of PRISm is particularly high in current and former smokers, and it is associated with both high and low BMI values, female sex, obesity and multimorbidity.[165-168] PRISm is associated with increased risk of: respiratory symptoms; cardiopulmonary disease; all-cause and cardiovascular mortality; hospitalization; and an increased risk of developing airways obstruction.[165,166,168-173]

PRISm is not always a stable phenotype and can transition to both normal and obstructed spirometry over time. It has been reported that around 20% to 30% of PRISm subjects transitioned to obstructed spirometry over time and the most important predictors of transition from PRISm spirometry to COPD are lower baseline FEV1%, and FEV1/FVC, higher age, current smoking, female gender, and a longer forced expiratory time in the second assessment.[164,166,168] Despite an increasing body of literature on PRISm, significant knowledge gaps remain in relation to its pathogenesis and treatment.

Not all individuals with pre-COPD or PRISm will eventually develop fixed airflow obstruction over time (and hence COPD) but they should be considered “patients” (because they already suffer symptoms and/or have functional and/or structural abnormalities) and, as such, they deserve care and treatment. The challenge is that there is no evidence on what the best treatment is for these patients yet.[174]

Asthma and airway hyper-reactivity

Asthma may also be a risk factor for the development of chronic airflow obstruction and COPD. In a report from a longitudinal cohort, adults diagnosed with asthma had a 12-fold higher risk of acquiring COPD compared to those without asthma, after adjusting for smoking.[175] In other longitudinal studies, around 20% of people with asthma developed irreversible airflow obstruction and reduced diffusing lung capacity,[176] and self-reported asthma was associated with excess loss of FEV1.[177] In addition, 11% of children with asthma had lung function impairment consistent with the spirometric classification of COPD by early adulthood.[178-180] The pathology of chronic airflow obstruction in asthmatic non-smokers and non-asthmatic smokers is markedly different, suggesting that the two disease entities may remain different even when presenting with similarly reduced lung function.[175,181,182] However, separating asthma from COPD in adults may be clinically difficult at times. Further, abnormal lung development in childhood and adolescence can cause asthma-like symptoms. Given that poor lung development is associated with COPD in adulthood (**Figure 1.2**), these infants and adolescents may have been mislabeled as having asthma.

On the other hand, airway hyper-responsiveness can exist without a clinical diagnosis of asthma and has been shown to be an independent predictor of COPD and respiratory mortality in population studies[183,184] as well as an indicator of risk of excess decline in lung function in patients with mild COPD.[185]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Chronic bronchitis

Chronic bronchitis is a common, but variable condition in patients with COPD, defined by the presence of cough with expectorated sputum on a regular basis over a defined period. Variability in the prevalence of chronic bronchitis depends upon the definition used, which differ in the regularity or duration of symptoms.[186] The classic description defines chronic bronchitis as chronic cough and sputum production for at least 3 months per year for two consecutive years, in the absence of other conditions that can explain these symptoms (an important caveat that is often ignored). Using this definition, the prevalence of chronic bronchitis ranges from 27-35% in large observational studies in patients with COPD.[187-189] Other factors associated with increased prevalence of chronic bronchitis in COPD includes male sex, younger age, greater pack-years of smoking, more severe airflow obstruction, rural location and increased occupational exposures.[186-192] Although the primary risk for chronic bronchitis is smoking, 4-22% of chronic bronchitis is found in never smokers suggesting other factors are involved.[193,194] Inhalational exposures to dusts, biomass fuels, chemical fumes or domestic heating and cooking fuels may be important.[191,192,195] Gastroesophageal reflux is also associated with an increased incidence of chronic bronchitis.[196,197]

Lung health depends upon effective mucus clearance. In disease states, thick and viscous mucus can lead to airway inflammation and infection, with cough and dyspnea the principal symptoms of impaired mucus clearance.[198,199] Cough and sputum production are predominately associated with mucus production in the large airways. However, increased mucus production also occurs in the smaller conducting airways and is associated with luminal occlusion, hallmarked by dyspnea but less cough and sputum production.[200,201] Radiographic manifestations of mucus plugging may be present and persist in patients with COPD despite a lack of chronic bronchitis symptoms and is associated with greater airflow obstruction, lower oxygen saturation, poorer exercise tolerance, more exacerbations and worsened quality of life[202-204] and all-cause mortality.[179,205,206]

The relationship between chronic mucus production and lung function, exacerbations and mortality has been the subject of multiple investigations. In adults less than 50 years of age, chronic bronchitis without airflow obstruction is an early marker for susceptibility to the long-term risk of COPD and all-cause mortality.[207] In smokers between 36 and 43 years of age with chronic mucus production, there was a significant higher risk of airflow obstruction, however, following smoking cessation, mucus production returned to levels observed amongst never smokers.[159] Importantly, the longer chronic mucus hypersecretion is present, the greater the concurrent decrease in FEV1.[208,209] After adjustment for height, age and smoking history, men with cough or phlegm and women with cough show accelerated

loss of lung function,[210] and there is an association between chronic sputum production and lower lung function, or greater FEV1 decline in patients with COPD.[210-214]

The association between chronic mucus hypersecretion and mortality is unclear. Several studies report no predictive value of mucus production on mortality when controlling for respiratory impairment and smoking;[215-217] other studies state sputum production has an independent role in predicting both overall and COPD-specific mortality.[190,218-220] In the Copenhagen City Heart Study, chronic mucus hypersecretion was associated with pulmonary infection that was implicated in 54% of the deaths.[221] Moreover, chronic mucus hypersecretion was associated with excessive FEV1 decline and increased COPD hospitalizations.[213] In patients with advanced emphysema, chronic bronchitis has been associated with increased hospitalizations and mortality.[222] In patients with non-obstructive chronic bronchitis, increased all-cause and respiratory disease related mortality has been reported.[223,224]

Infections

A history of severe childhood respiratory infections is associated with reduced lung function and increased respiratory symptoms in adulthood.[180] The Medical Research Council National Survey of Health and Development documented a synergistic interaction between smoking and infant respiratory infections as well as early life home overcrowding with lung function at age 43.[225] Chronic bronchial infection, particularly with *Pseudomonas aeruginosa*, is associated with accelerated FEV1 decline.[226] TB is a risk factor for COPD,[227,228] and is both a differential diagnosis for COPD and a potential comorbidity.[229,230] Nontuberculous mycobacterial pulmonary disease is also associated with an increased risk of incident COPD.[231] Finally, patients with HIV are at increased risk of COPD compared to HIV negative controls,[232,233] probably due to methylation disruptions in airway epithelium.[179,234,235]

Sex

Sex-related differences in immune pathways and the pattern of airway damage might be clinically important, although more work in this area is needed. In the past, most studies have reported that COPD prevalence and mortality are greater among men than women, but later data from developed countries has shown that the prevalence of COPD is almost equal in males and females, probably reflecting the changing patterns of tobacco smoking.[236] Although controversial, some studies have suggested that women may be more susceptible to the harmful effects of smoking than men,[91,237-239] leading to more severe disease for the equivalent quantity of cigarettes consumed.[240] The results of a population-based cohort study that selected individuals from a Danish population-based cohort, indicate that females have more severe disease with comparable smoking exposure, manifesting as lower lung function and a higher risk of airway obstruction, chronic bronchitis and dyspnea. Additionally, females exhibit a poorer prognosis with higher smoking exposure, including a higher risk of COPD exacerbations and early death.[241] However, the results regarding mortality have not been consistent and a real-life cohort study from France observed that women had a lower risk of mortality.[242]

A systematic review and meta-analysis of the global prevalence of COPD reported sex-based prevalence differences across WHO GBD sub-regions. In females the highest prevalence of COPD was observed in North America and in urban settings. Using the World Bank's income categories prevalence was highest in upper-middle income countries for males and in high-income countries for females. Multiple female reproductive factors including age at menarche, number of children, miscarriage, stillbirth, and age at natural menopause were associated with the risk of COPD in a large cohort study.[243]

Race and ethnicity

An ATS workshop report[244] has recommended replacing race- and ethnicity-specific equations with race-neutral average reference equations in pulmonary function testing. It also emphasized the importance of further research and education into the clinical and epidemiological consequences of these changes.[54,244]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Socioeconomic status

Poverty is consistently associated with airflow obstruction[245] and lower socioeconomic status is associated with an increased risk of developing COPD.[246,247] It is not clear, however, whether this pattern reflects exposures to household and outdoor air pollutants, crowding, poor nutrition, infections, or other factors related to low socioeconomic status.

Disparities in COPD outcomes between rural and urban populations have been reported worldwide. A systematic review showed that COPD prevalence was higher in rural areas, a pattern that remained consistent across different geographic regions. Likewise, overall exacerbation rates, symptom burden, and mortality were higher in rural settings.[248] These findings reflect the impact of healthcare inequalities, socioeconomic deprivation, and environmental exposures on the burden of COPD in rural areas.

PATHOBIOLOGY

In patients with COPD, pathological changes can be found in the airways, lung parenchyma, and pulmonary vasculature.[249] These include inflammatory and structural changes which increase with the severity of airflow obstruction and can persist on smoking cessation.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Inflammatory changes

The inflammation observed in the lungs of patients with COPD appears to be a modification of the normal inflammatory response to chronic irritants such as cigarette smoke. The mechanisms for this amplified inflammation are not yet fully understood but may, at least in part, be genetically determined.

COPD is characterized by increased numbers of macrophages in peripheral airways, lung parenchyma and pulmonary vessels, together with increased activated neutrophils and increased lymphocytes. These inflammatory cells, together with epithelial cells and other structural cells release multiple inflammatory mediators[250] which attract inflammatory cells from the circulation (chemotactic factors), amplify the inflammatory process (via proinflammatory cytokines), and induce structural changes (via growth factors).[251] Lung inflammation can persist after smoking cessation through as yet unclear mechanisms, although autoantigens and perturbations in the lung microbiome may play a role.[252,253] Systemic inflammation may also be present and could play a role in the comorbid conditions frequently found in patients with COPD.[250] The nature of the inflammatory response in non-smoking related COPD is much less well characterized.

Although both COPD and asthma are associated with chronic inflammation of the respiratory tract, there are differences in the inflammatory cells and mediators involved in the two diseases.[254] albeit some patients with COPD have an inflammatory pattern with increased eosinophils and Type 2 innate lymphoid cells, similar to that of asthma.[255]

Oxidative stress can also contribute to COPD.[250,256] Biomarkers of oxidative stress (e.g., hydrogen peroxide, 8-isoprostane) are increased in the exhaled breath condensate, sputum, and systemic circulation of patients with COPD. Oxidative stress is further increased during exacerbations. Oxidants are both generated by cigarette smoke and other inhaled particulates and released from activated inflammatory cells such as macrophages and neutrophils.[229,257]

Structural changes

There is compelling evidence for an imbalance in the lungs of patients with COPD between proteases derived from inflammatory and epithelial cells that break down connective tissue components and antiproteases that counterbalance this action.[258] Protease-mediated destruction of elastin, a major connective tissue component of the

lung parenchyma, is an important feature of emphysema but its role may be more difficult to establish in airway changes.[259]

Peribronchiolar fibrosis and interstitial opacities have been reported in patients with COPD and in asymptomatic smokers,[252,260-262] and an excessive production of growth factors may be found in smokers and patients with COPD.[263] Inflammation may precede the development of fibrosis or repeated injury of the airway wall itself may lead to excessive production of muscle and fibrous tissue,[264] which may contribute to the development of small airways obstruction.[265]

The lung vasculature can also be altered in patients with COPD, even those with mild disease.[266]

Dysbiosis

Gene sequencing analysis of respiratory samples has been used to describe the lung microbiome. These techniques are markedly more sensitive than traditional cultures used in clinical practice, which detect only live bacteria colonizing the airways or associated with symptoms of infection. Gene sequencing studies provide information about the relative abundance and diversity of microbiota and have shown that the lower respiratory tract is not sterile but permanently contains a diverse array of bacteria.

Dysbiosis refers to disruption of the microbiome and has been observed in several compartments in patients with COPD including the airways. Very diverse risk factors for COPD such as cigarette smoking or prematurity altered mucosal immunity and gut and airway microbiota, which interact in both directions (the 'gut-lung axis') through immune cross-talk and microbial metabolites and peptides.[267] Dysbiosis is cross-sectionally associated with the presence of COPD and different disease characteristics such as frequency of exacerbations,[268] likely through the alteration of mucosal defenses (vicious circle) and stimulation of lung inflammation by immune responses.[269,270] The microbiome profile is modified following viral infections and during exacerbations and is differentially altered by antibiotics and oral or inhaled corticosteroids.[271-273] Overall, these observations suggest a role for dysbiosis in the development and progression of COPD, but the paucity of longitudinal data[274] and interventional studies underline the need for further research to ascertain the direction(s) of causality and possible prognostic, diagnostic or therapeutic applications.[273]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

PATHOPHYSIOLOGY

Airflow obstruction and gas trapping

Airflow obstruction is usually measured by spirometry as this is the most widely available and reproducible test of lung function. In COPD, airflow obstruction is caused by a mixture of small airways disease (which increases airway resistance) and parenchymal destruction (emphysema, that reduces the normal elastic recoil of the lung parenchyma), the relative contributions of which vary from person to person. Further, these changes do not always occur together and may evolve at different rates over time. Chronic inflammation causes structural changes, narrowing of the small airways, luminal exudates in the small airways and destruction of the lung parenchyma that leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil. In turn, these changes diminish the ability of the airways to remain open during expiration. A loss of small airways may also contribute to airflow obstruction and mucociliary dysfunction.[275] The reduced number of small airways identified in patients with COPD[275] may be due to an enhanced loss of airways and/or to deficient lung development (see dysanapsis above; **Figure 1.2**).[148] Collectively, these changes limit emptying of the lungs during forced expiration, decrease FEV1 and the FEV1/FVC ratio, and contribute to gas trapping and lung hyperinflation.[276]

Hyperinflation

Hyperinflation occurs when gas volume in the lungs is increased compared to normal values at the end of spontaneous expiration.[277,278] Hyperinflation is clinically relevant in patients with COPD and contributes to dyspnea,[279-282] impaired exercise tolerance,[283-285] increased number of hospitalizations,[286] development of respiratory failure[287] and increased mortality.[284,286,288] In patients with COPD, hyperinflation arises due to loss of elastic recoil and expiratory flow obstruction.[289] Expiratory flow obstruction occurs when the expiratory flows generated during spontaneous breathing are the maximal flows that can be generated at that operational lung volume.[277] Expiratory flow obstruction is caused by the dual effects of emphysematous parenchymal destruction and airways abnormalities (e.g., mucus obstruction, airway edema, heightened bronchial tone, airway wall remodeling). The lung can be hyperinflated at rest (static hyperinflation due to the loss of elastic lung recoil as a consequence of emphysema) and/or during exercise (dynamic hyperinflation as a consequence of airflow obstruction) when ventilatory demands are increased and expiratory times are reduced.[277,278]

Hyperinflation is common in patients with COPD and can be found in patients with even mild obstruction at rest and even more so during exercise.[290,291] In patients with moderate to severe obstruction, the level of dynamic hyperinflation correlates more closely with the impairment in diffusion capacity and severity of small airways obstruction and higher ventilatory response to exercise than FEV1 measurement.[277,283]

Lung volumes assessed by body plethysmography or gas dilution techniques (helium dilution or nitrogen washout) represent the reference measurements to assess the presence and degree of hyperinflation, however, values may vary due to differences in measuring compressible gas volumes or communicating gas volumes, respectively.[292,293] Measurement of inspiratory capacity at rest and during exercise is an indirect measurement of increased end-expiratory lung volumes and indicates the presence of static and/or dynamic hyperinflation.[294] Hyperinflation can also be detected on chest imaging but standardization is lacking.[277]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Pulmonary gas exchange abnormalities

Structural abnormalities in the airways, alveoli and pulmonary circulation in patients with COPD alter the normal V_A/Q distributions. This is the main mechanism of abnormal pulmonary gas exchange resulting in different degrees of arterial hypoxemia, without or with hypercapnia.[295] Rarely, reduced ventilation may also be due to reduced ventilatory drive (e.g., sedatives and hypnotic drugs), causing hypercapnic respiratory failure and acidosis.[296] Parenchymal destruction due to emphysema also leads to decreased DLco. In general, pulmonary gas exchange worsens as the disease progresses.

Pulmonary hypertension

In smokers with normal spirometry and in patients with COPD who have mild airflow obstruction there may be abnormalities in the pulmonary circulation that include intimal hyperplasia and smooth muscle hypertrophy/hyperplasia.[297-300] Moreover, an inflammatory response in pulmonary blood vessels, similar to that seen in the airways, can be observed in these individuals along with evidence of endothelial cell dysfunction. Yet, severe pulmonary hypertension in COPD is rare.[301,302] It may develop late in the course of COPD and it can be due to a combination of loss of pulmonary capillary bed due to emphysema and/or hypoxic vasoconstriction of the small pulmonary arteries. Progressive pulmonary hypertension may lead to right ventricular hypertrophy and eventually to right-sided heart failure ('*cor pulmonale*'). Severe pulmonary hypertension worsens survival.[303] The diameter of pulmonary artery as measured on CT scans has been shown to relate to the increased risk of suffering exacerbations, independent of previous history of exacerbations.[304]

Exacerbations

Exacerbations of respiratory symptoms in patients with COPD can be triggered by a number of different factors (alone

or in combination), including respiratory infections with bacteria or viruses (which may coexist), environmental pollutants, or unknown factors. During exacerbations there is evidence of increased airway and systemic inflammation, increased gas trapping and hyperinflation with reduced expiratory flow, thus accounting for increased dyspnea,[305] and worsening of V_A/Q abnormalities that can result in arterial hypoxemia with or without hypercapnia.[306] Other conditions, such as pneumonia, pulmonary, and/or heart failure, among others, may mimic or aggravate an exacerbation, and need to be considered in the clinical management of these episodes.[307] See **Chapter 4** for an extended discussion on exacerbations.

Proposed Taxonomy (Etiotypes) for COPD

Figure 1.4

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, HIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Multimorbidity

Most patients with COPD suffer concomitant chronic comorbid diseases linked to the same risk factors i.e., smoking, aging, and inactivity, which may have a major impact on health status and survival.[308,309] The term syndemics has been introduced to describe the co-occurrence of COPD with other conditions that have possible shared mechanisms and risk factors.[310] Airflow obstruction and particularly hyperinflation affect cardiac function.[305] Inflammatory mediators in the circulation may contribute to skeletal muscle wasting and cachexia, and may initiate or worsen comorbidities such as ischemic heart disease, heart failure, osteoporosis, normocytic anemia, diabetes, and metabolic syndrome (see **Chapter 5**).

TAXONOMY

COPD has been traditionally understood as a single "disease" caused by tobacco smoking.[136] Accordingly, most efforts have been devoted to the study of the pathogenetic mechanisms of only one major cause of COPD (tobacco smoking), failing to expand the horizon about the heterogeneity of processes that we know can contribute to its final clinical presentation.[13] It is therefore important to expand the taxonomy (classification) of COPD to include non-smoking related COPD types, so specific studies can be designed and conducted for these different types of COPD or *etiotypes*.[311] **Figure 1.4** combines two recent taxonomic proposals developed independently.[12,312] This proposal has relatively little impact on current clinical practice, other than illuminating this so-far ignored aspect of COPD, but it is of the outmost importance to highlight the need to explore current and future therapies in these other *etiotypes* of COPD.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

CHAPTER 2: DIAGNOSIS, ASSESSMENT AND MONITORING

KEY POINTS:

Diagnosis

- A diagnosis of COPD should be **considered** in any patient who has dyspnea, chronic cough or sputum production, a history of recurrent lower respiratory tract infections and/or a history of exposure to risk factors; **spirometry** with post-bronchodilator FEV1/FVC < 0.7 is **mandatory** to establish the diagnosis of COPD.
- Pre-bronchodilator spirometry can be used to exclude a diagnosis of COPD.

Initial assessment

- The goals of the initial COPD assessment are to determine the severity of airflow obstruction, assess the impact of current symptoms on the patient, and their risk of future events (such as exacerbations, hospital admissions, or death), to guide therapy.

Monitoring and follow-up

- Routine follow-up of lung function, symptoms and exacerbations is essential to determine when to modify management and to identify any complications and/or comorbidities.
- Virtual and hybrid virtual/in-person care models may offer improved healthcare access, outcomes, and affordability, but use should be based on evidence.

Additional investigations

- Additional clinical assessment, including the measurement of lung volumes, diffusion capacity, exercise testing and/or lung imaging may be considered in patients with COPD who have a marked discordance between the level of airflow obstruction and the perceived symptoms.
- Concomitant chronic diseases (multimorbidity) occur frequently in patients with COPD, including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety, and lung cancer. These comorbidities should be actively sought, and treated appropriately when present, because they influence health status, hospitalizations and mortality independently of the severity of airflow obstruction due to COPD.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

DIAGNOSIS

A diagnosis of COPD should be **considered** in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease (**Figure 2.1**) but **forced spirometry** that demonstrates the presence of a post-bronchodilator FEV1/FVC < 0.7 is **mandatory** to establish the diagnosis of COPD.[313] GOLD is aware that other proposals for confirming the diagnosis of COPD, and assessing and categorizing its severity and prognosis, have been made.[314,315] These proposals include criteria derived from CT scans which are not readily available or accessible in many countries. For this reason, GOLD still believes that a definition based on spirometry in the appropriate clinical context (symptoms and risk factors) is more appropriate for global use across primary and secondary care.

CLINICAL PRESENTATION

Symptoms

Chronic dyspnea is the most characteristic symptom of COPD. Cough with sputum production is present in up to 30% of patients. These symptoms may vary from day-to-day[316] and may precede the development of airflow obstruction by many years. Individuals, particularly those with COPD risk factors, presenting with these symptoms should be examined to search for the underlying cause(s). Airflow obstruction may also be present without chronic dyspnea and/or cough and sputum production and *vice versa*.[317] Although COPD is defined on the basis of airflow obstruction, in practice the decision to seek medical help is usually determined by the impact of symptoms on a patient's functional status. A person may seek medical attention either because of chronic respiratory symptoms or because of an acute, transient episode of exacerbated respiratory symptoms.

Clinical Indicators for Considering a Diagnosis of COPD

Figure 2.1

Consider the diagnosis of COPD, and perform spirometry, if any of these clinical indicators are present:
(these indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of the presence of COPD; in any case, spirometry is required to establish a diagnosis of COPD)

Dyspnea that is	Progressive over time Worse with exercise Persistent
Recurrent wheeze	
Chronic cough	May be intermittent and may be non-productive
Recurrent lower respiratory tract infections	
History of risk factors	Tobacco smoke (including popular local preparations) Smoke from home cooking and heating fuels Occupational dusts, vapors, fumes, gases and other chemicals Host factors (e.g., genetic factors, developmental abnormalities, low birthweight, prematurity, childhood respiratory infections etc.)

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Dyspnea

Dyspnea is a cardinal symptom of COPD and a major cause of the disability and anxiety associated with the disease.[318] Dyspnea comprises a sensory and an affective component.[319] Typically, patients with COPD describe their dyspnea as a sense of increased effort to breathe, chest heaviness, air hunger, or gasping.[320] However, the terms used to describe dyspnea may vary both individually and culturally.[320]

Dyspnea is highly prevalent across all stages of airflow obstruction.[321] It occurs particularly during exertion or physical activity. Moderate-to-severe dyspnea has been reported by > 40% of patients diagnosed with COPD in primary care.[322]

Dyspnea is complex and multiple mechanisms can be involved in its pathogenesis, including impaired respiratory mechanics as a consequence of airflow obstruction and lung hyperinflation, gas exchange abnormalities, peripheral muscle dysfunction related to deconditioning (and systemic inflammation in some patients), psychological distress, dysfunctional breathing, cardiovascular or other comorbid diseases.[323,324]

Dyspnea measured by the 5-level mMRC scale is integrated in the GOLD clinical classification scheme (see below) because patients with high dyspnea scores incur higher healthcare resource utilization and costs.[325] Dyspnea in daily life can be measured by a number of detailed questionnaires that are more discriminant and sensitive to change.[326,327]

Chronic cough

Chronic cough is often the first symptom of COPD and is frequently discounted by the patient as an expected consequence of smoking and/or environmental exposures. Initially, the cough may be intermittent, but subsequently it may be present every day, often throughout the day. Chronic cough in COPD may be productive or non-productive.[328] In some cases, significant airflow obstruction may develop without the presence of a cough. Other causes of chronic cough are listed in **Figure 2.2**. Syncope during cough in patients with COPD who have severe airflow obstruction can occur due to rapid increases in intrathoracic pressure during prolonged attacks of coughing. Coughing spells may also cause rib fractures, which are sometimes asymptomatic.

Sputum production

Patients with COPD commonly raise small quantities of tenacious sputum with coughing. Regular production of sputum for three or more months in two consecutive years (in the absence of any other conditions that may explain it) is the classical definition of chronic bronchitis,[329] but this is a somewhat arbitrary definition that does not reflect the entire range of sputum production that occurs in COPD (see detailed discussion in **Chapter 1**). Sputum production is often difficult to evaluate because patients may swallow sputum rather than expectorate it, a habit that is subject to significant cultural and sex variation. Furthermore, sputum production can be intermittent with periods of flare-up interspersed with periods of remission.[159] Patients producing large volumes of sputum may have underlying bronchiectasis.[330,331] The presence of purulent sputum reflects an increase in inflammatory mediators,[332,333] and its development may identify the onset of a bacterial exacerbation, though the association is relatively weak.[333,334]

Wheezing and chest tightness

Inspiratory and/or expiratory wheezes and chest tightness are symptoms that may vary between days, and over the course of a single day. Alternatively, widespread inspiratory or expiratory wheeze can be present on auscultation. Chest tightness often follows exertion, is poorly localized, is muscular in character, and may arise from isometric contraction of the intercostal muscles. An absence of wheezing or chest tightness does not exclude a diagnosis of COPD, nor does the presence of these symptoms confirm a diagnosis of asthma.

Fatigue

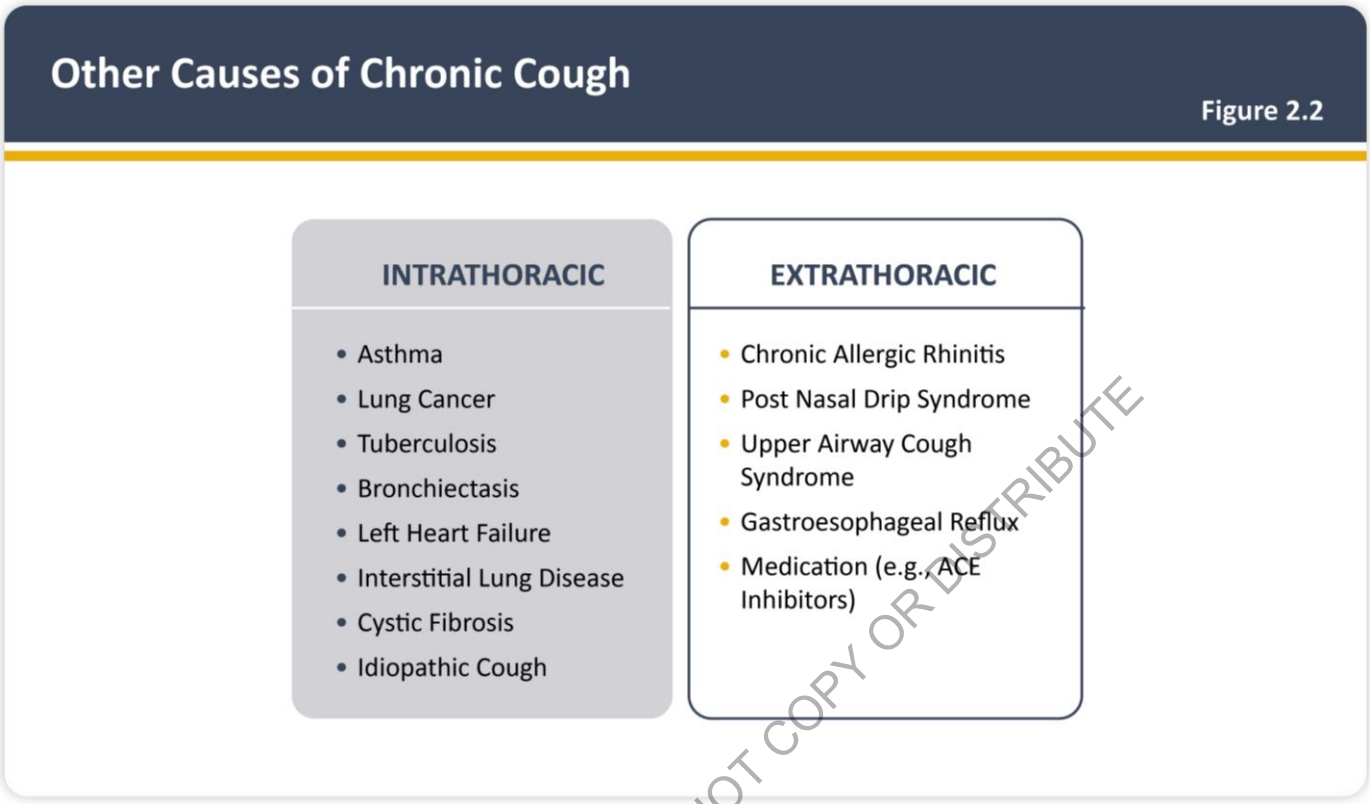
Fatigue is the subjective feeling of tiredness or exhaustion and is one of the most common and distressing symptoms experienced by people with COPD.[335] People with COPD describe their fatigue as a feeling of “general tiredness” or as a feeling of being “drained of energy”.[336,337] Fatigue impacts a patient’s ability to perform activities of daily living and their quality of life.

Additional clinical features in severe disease

Weight loss, muscle mass loss, and anorexia are common problems in patients with COPD who have severe and very severe airflow obstruction.[338-340] They have prognostic importance[341,342] and can also be a sign of other diseases, such as tuberculosis or lung cancer, and therefore should always be investigated. Ankle swelling may indicate the

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

presence of *cor pulmonale*. Symptoms of depression and/or anxiety merit specific enquiry when obtaining the medical history because they are common in COPD,[343] are associated with poorer health status, increased risk of exacerbations, and emergency hospital admission, and are treatable.[344]



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

DIFFERENTIAL DIAGNOSIS OF COPD

In some patients with COPD, a clear distinction from asthma is difficult using current imaging and physiological testing techniques, since the two conditions share common traits and clinical expressions.[345] Most other potential differential diagnoses are easier to distinguish from COPD (**Figure 2.3**).

Differential Diagnosis of COPD

Figure 2.3

Diagnosis	Suggestive Features
COPD	Symptoms slowly progressive History of tobacco smoking or other risk factors
Asthma	Variable airflow obstruction Symptoms vary widely from day to day Symptoms worse at night/early morning Allergy, rhinitis, and/or eczema also present Often occurs in children Family history of asthma
Congestive heart failure	Chest X-ray shows dilated heart, pulmonary edema Pulmonary function tests indicate volume restriction, not airflow obstruction
Bronchiectasis	Large volumes of purulent sputum Commonly associated with bacterial infection Chest X-ray/HRCT shows bronchial dilation
Tuberculosis	Onset at all ages Chest X-ray shows lung infiltrate Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Can occur in children Seen after lung or bone marrow transplantation HRCT on expiration shows hypodense areas
Diffuse panbronchiolitis	Predominantly seen in patients of Asian descent Most patients are male and nonsmokers Almost all have chronic sinusitis Chest X-ray & HRCT show diffuse small centrilobular nodular opacities & hyperinflation

These features tend to be characteristic of the respective diseases, but are not mandatory. For example, a person who has never smoked may develop COPD (especially in LMICs where other risk factors may be more important than cigarette smoking).

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

MEDICAL HISTORY

A detailed medical history of a new patient who is known, or suspected, to have COPD should include:

- *Patient's exposure to risk factors*, such as smoking and environmental exposures (household/outdoor).
- *Past medical history*, including early life events (prematurity, low birthweight, maternal smoking during pregnancy, passive smoking exposure during infancy), asthma, allergy, sinusitis, or nasal polyps;

respiratory infections in childhood; HIV; tuberculosis.

- *Family history of COPD or other chronic respiratory disease.*
- *Pattern of symptom development*: COPD typically develops in adult life and most patients are conscious of increased breathlessness, more frequent or prolonged "winter colds," and some social restriction for a number of years before seeking medical help.
- *History of exacerbations or previous hospitalizations for respiratory disorder.* Patients may be aware of periodic worsening of symptoms even if these episodes have not been identified as exacerbations of COPD.
- *Presence of comorbidities*, such as heart disease, osteoporosis, musculoskeletal disorders, anxiety and depression, and malignancies that may also contribute to restriction of activity.
- *Impact of disease on patient's life*, including limitation of activity, missed work and economic impact, effect on family routines, feelings of depression or anxiety, wellbeing, and sexual activity.
- *Social and family support available to the patient.*
- *Possibilities for reducing risk factors, especially smoking cessation.*

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

PHYSICAL EXAMINATION

Although an important part of patient care, a physical examination is rarely (if ever) diagnostic in COPD. Physical signs of airflow obstruction are usually not present until significant impairment of lung function has occurred,[346,347] and detection based on physical examination has relatively low sensitivity and specificity. A number of physical signs (e.g., lung hyperinflation, cyanosis) may be present in COPD, but their absence does not exclude the diagnosis.

SPIROMETRY

Forced spirometry is the most reproducible and objective measurement of airflow obstruction. It is a noninvasive, reproducible, cheap, and readily available test. Good quality spirometric measurement is possible in any healthcare setting and all healthcare workers who care for people with COPD should have access to spirometry. Some of the factors needed to achieve accurate test results are summarized in **Figure 2.4**.[348,349] Despite its good sensitivity, peak expiratory flow measurement alone cannot be reliably used as the only diagnostic test because of its weak specificity.[350,351]

Considerations in Performing Spirometry

Figure 2.4

PREPARATION	• Spirometers should produce hard copy or have a digital display of the expiratory curve to permit detection of technical errors or have an automatic prompt to identify an unsatisfactory test and the reason for it • The supervisor of the test needs training in optimal technique and quality performance • Maximal patient effort in performing the test is required to avoid underestimation of values and hence errors in diagnosis and management
PERFORMANCE	• Spirometry should be performed following national and/or international recommendations[a] • The expiratory volume/time traces should be smooth and free from irregularities • The pause between inspiration and expiration should be less than one second • The recording should go on long enough for a volume plateau to be reached, which may take more than 15 seconds in severe disease • Both FVC and FEV1 should be the largest value obtained from any of three technically satisfactory curves and the FVC and FEV1 values in these three curves should vary by no more than 5% or 150 mL, whichever is greater • The FEV1/FVC ratio should be calculated using the largest FVC and the largest FEV1 even though they may not come from the same maneuver
BRONCHODILATION	• Possible dosage protocols are 400 mcg short-acting beta$_2$-agonist, 160 mcg short-acting anticholinergic, or the two combined[b]; FEV1 should be measured 10-15 minutes after a short-acting beta$_2$-agonist is given, or 30-45 minutes after a short-acting anticholinergic or a combination of both classes of drugs • Patients already on bronchodilator treatment, in whom spirometry is requested for monitoring purposes do not need to stop their regular treatment for spirometry
EVALUATION	• Spirometry measurements are evaluated by comparison of the results with appropriate reference values based on age, height and sex • The presence of a post-bronchodilator FEV1/FVC < 0.7 confirms the presence of non-fully reversible airflow obstruction

[a]Miller et al. Eur Respir J 2005; **26**(2): 319-38;
[b]Pellegrino et al. Eur Respir J 2005; **26**(5): 948-68.

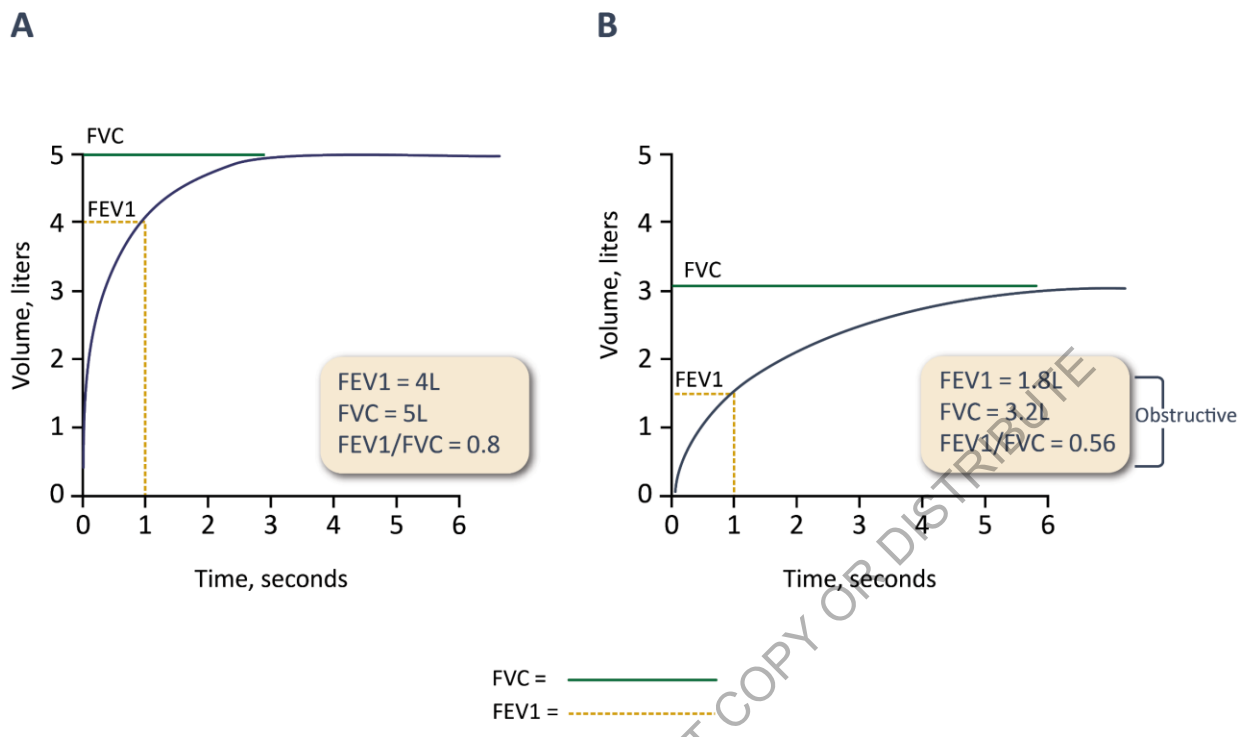
COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

As shown in **Figure 2.5**, forced spirometry measures: (1) the volume of air forcibly exhaled from the point of maximal inspiration (FVC); (2) the volume of air exhaled during the first second of this maneuver (FEV1); and (3) the ratio of these two measurements (FEV1/FVC). Spirometry measurements are evaluated by comparison with reference values[349,352,353] based on age, height and sex (see below).

Figure 2.5A shows a normal spirometry tracing and **Figure 2.5B** shows a tracing obtained in a person with COPD. Patients with COPD typically show a decrease in both FEV1 (due to airflow obstruction) and (to a lesser degree) FVC (due to gas trapping).

A. Spirometry - Normal Trace B. Spirometry - Airflow Obstruction

Figure 2.5



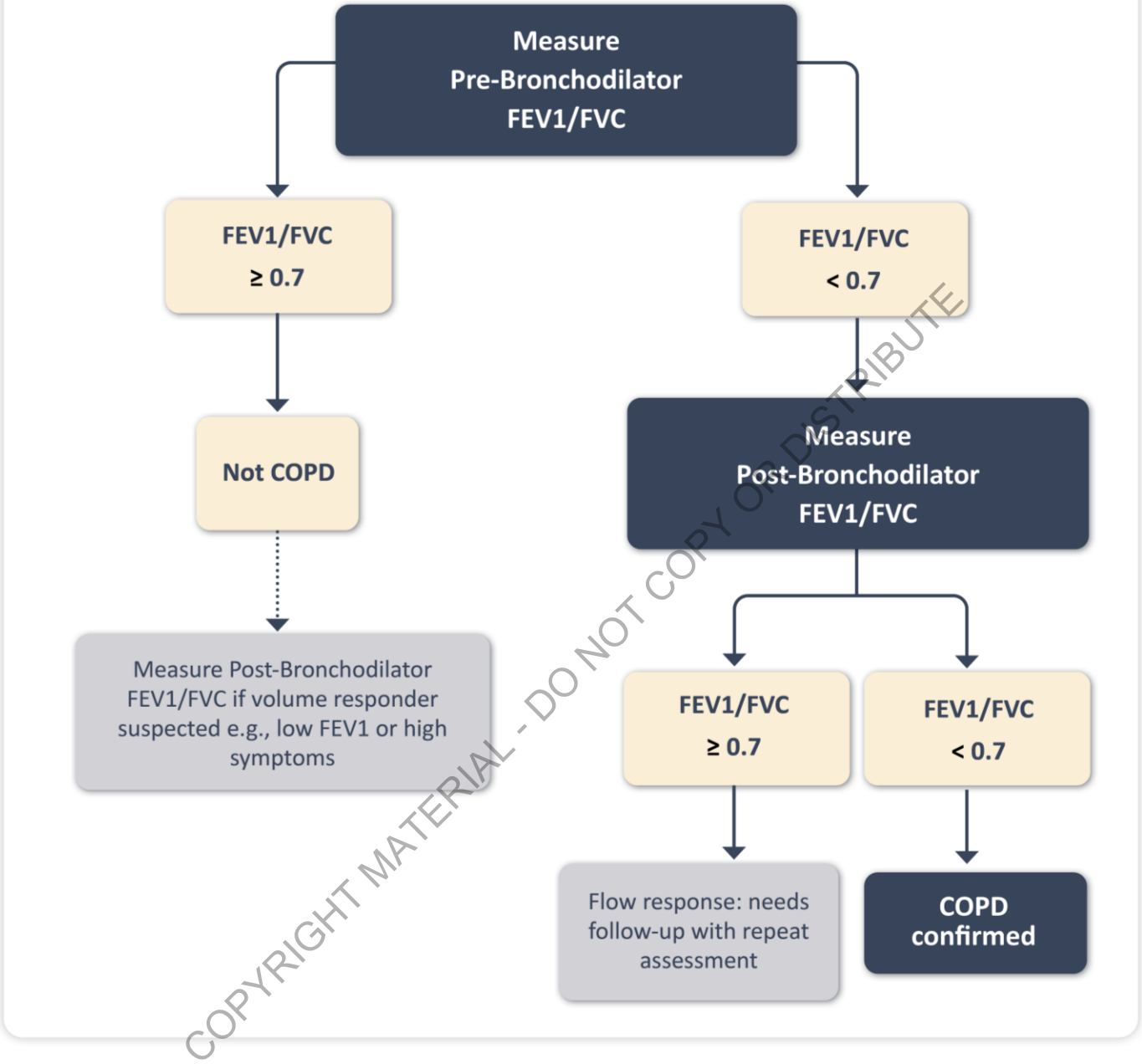
COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Pre- or post-bronchodilator spirometry to confirm the diagnosis of COPD

In line with other national and international guidelines, GOLD recommends using post-bronchodilator values when considering a diagnosis of COPD. Historically, post-bronchodilator values were considered more appropriate for confirming a diagnosis of fixed airflow obstruction as they were thought to be more reproducible, to be useful in excluding asthma and could identify volume responders to bronchodilators in whom the obstruction was revealed by bronchodilator-induced increase in FVC.[354] However, it is now recognized that the bronchodilator response has little value in differentiating asthma from COPD,[355] that pre-bronchodilator values are reproducible[356] and obstruction only on post-bronchodilator measurements is uncommon.[357] Obtaining post-bronchodilator values is more time-consuming and this may deter clinicians from performing spirometry. Pre-bronchodilator spirometry can be used as an initial test to investigate whether symptomatic individuals have airflow obstruction (**Figure 2.6**). If the pre-bronchodilator spirometry does not show obstruction (see below for definition) performing post-bronchodilator spirometry is not necessary unless there is a very high clinical suspicion of COPD, in which case an FVC volume response may reveal obstruction. Further tests to investigate the cause of the patient's symptoms and follow-up, including repeating the spirometry after an interval, may be required. If the pre-bronchodilator values show obstruction the diagnosis of COPD should be confirmed using post-bronchodilator measurements. Individuals with a pre-bronchodilator FEV1/FVC ratio that shows obstruction but a post-bronchodilator ratio that does not show obstruction have been shown to have an increased risk of future development of COPD, and should be followed closely.[155]

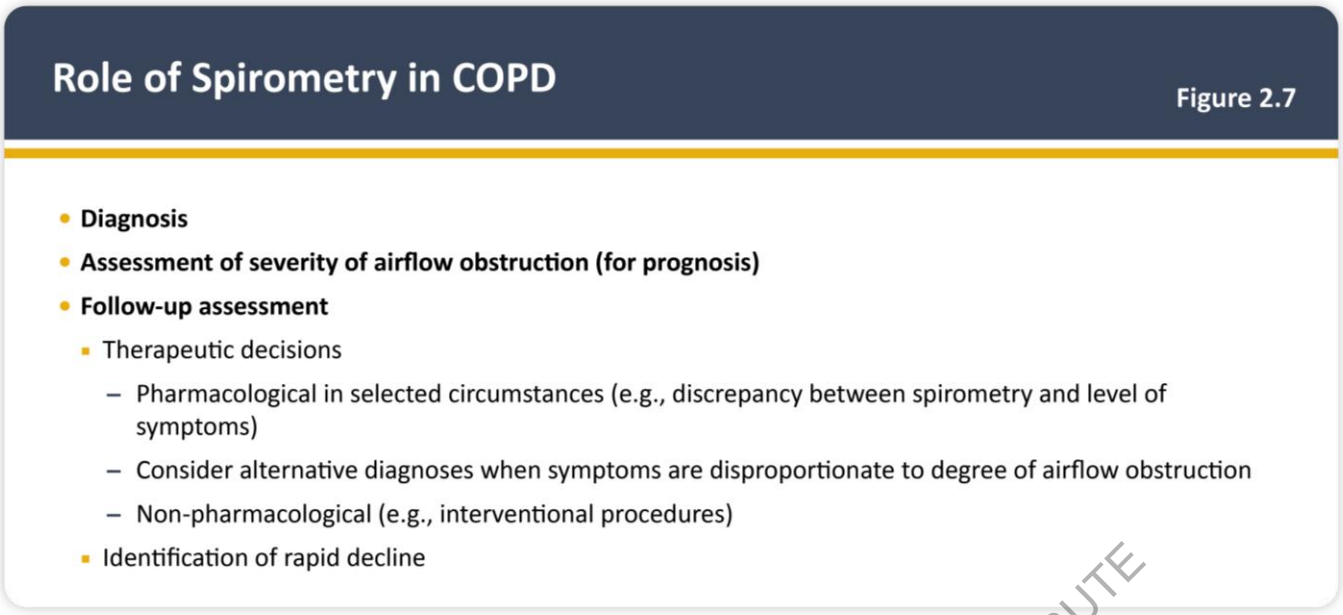
Spirometry to Confirm a COPD Diagnosis

Figure 2.6



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

While post-bronchodilator spirometry is required for the diagnosis and assessment of COPD, using the degree of reversibility of airflow obstruction (e.g., measuring FEV1 before and after bronchodilator or corticosteroids) to inform therapeutic decisions is no longer recommended.[358] The degree of reversibility in a single patient varies over time and has not been shown to differentiate the diagnosis from asthma, or to predict the response to long-term treatment with bronchodilators or corticosteroids.[359] Accordingly, it is not necessary to stop inhaled medication before obtaining spirometry measurements during follow-up of patients. **Figure 2.7** shows the role of spirometry in patients with COPD.



Spirometric criteria to define airflow obstruction

The spirometric criterion for airflow obstruction selected by GOLD for the diagnosis of COPD remains a post-bronchodilator ratio of FEV1/FVC < 0.7. This criterion is simple and independent of reference values because it relates to variables measured in the same individual and has been used in all the clinical trials that form the evidence base from which treatment recommendations are drawn.

In 2026, GOLD and the Global Lung Function Initiative (GLI) issued a joint statement that addressed the question as to whether a fixed ratio of 0.7 or a defined lower limit of normal (LLN) value for the FEV1/FVC ratio should be used to define airflow obstruction.[360] Both groups agreed that neither threshold is intrinsically right or wrong. Each threshold for defining airflow obstruction evolved to solve different problems, and discordance between the criteria reflect fundamentally different goals. The threshold proposed by GOLD was intended to be a pragmatic approach for confirmation of the diagnosis of COPD in everyday practice. The threshold proposed by GLI intends to reflect the variability in lung function measures observed between individuals in populations. The statement acknowledged that both approaches have been criticized. The fixed ratio has the advantage of its simplicity; however, it ignores potential age-related lung function changes and may identify fewer younger and more older individuals as having airflow obstruction.[361,362] The LLN considers age-related changes in lung function, reflecting loss of tissue elasticity, but crucially depends on the characteristics of the reference population and assumes the reference population is 'healthy'. Some individuals included in populations used to define "normal ranges" may have had undiagnosed or sub-clinical disease, leading to distortion of the LLN values. By considering age-related decline as physiologically normal, use of the LLN identifies more younger and fewer older individuals as having airflow obstruction.[361-364] If used without reference to the presence of symptoms or exposure to risk factors for COPD, the LLN will falsely label some healthy younger individuals as having COPD and miss some older individuals with COPD.

GLI predicted values are also based on pre-bronchodilator measurements, but postbronchodilator reference values were more successful at identifying individuals with mild COPD than prebronchodilator reference values in the Swedish CArdioPulmonary bioImage Study (SCAPIS).[365] There are no longitudinal studies available validating the use of the LLN, or studies using reference equations in populations where smoking is not the major cause of COPD. The fixed ratio is not inferior to the LLN, and may provide greater prognostic value.[365,366]

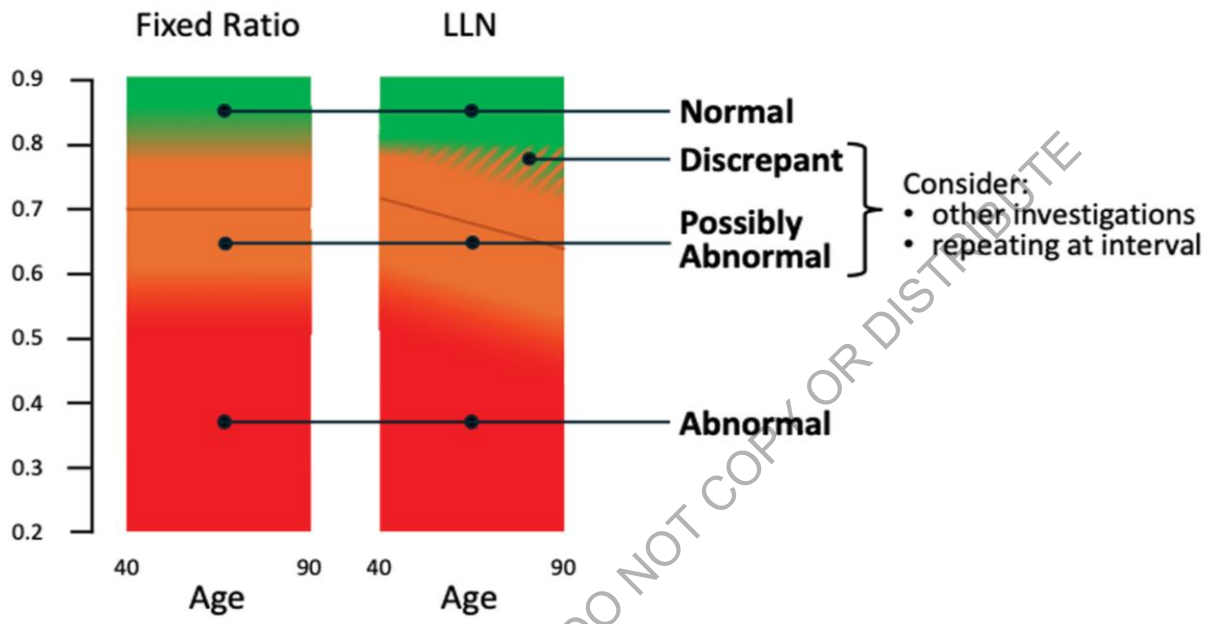
GLI and GOLD agree that the differences in recommendations about thresholds of 'abnormality' are outweighed by shared concerns about the under-use of spirometry. GOLD and GLI agree that COPD is a heterogeneous disease and

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

spirometry measures are prone to measurement errors and biological variability; both contribute to uncertainty when interpreting results. The results of biological measurements used as diagnostic tests cannot always be empirically categorized as “normal” or “abnormal”.

Interpretation of FEV1/FVC Ratio in a Person with Suspected COPD

Figure 2.8



Reproduced with permission of the © ERS 2026: *Halpin et al. European Respiratory Journal 2026 67(4): 2502574; DOI: https://doi.org/10.1183/13993003.02574-2025*

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Unavoidable variation exists in the measurement itself as, at their best, spirometers may show up to 5% variation in repeated test results.[367] In practice, therefore, it makes little difference whether the fixed ratio or LLN is used. Where there is a discrepancy or more commonly where the result lies between 0.6 and 0.8, further investigations or repeat measurements should be performed to confirm or exclude a diagnosis of COPD (**Figure 2.8**). Assessment of the presence or absence of airflow obstruction based on a single measurement of the post-bronchodilator FEV1/FVC ratio should be confirmed by repeat spirometry on a separate occasion if the value is between 0.6 and 0.8, as in some cases the ratio may change as a result of biological variation when measured at a later interval.[366,368] If the initial post-bronchodilator FEV1/FVC ratio is less than 0.6 it is very unlikely to rise spontaneously above 0.7.[366] If COPD is suspected in younger adults (age < 50 years) who have a repeated fixed ratio ≥ 0.7, comparing the ratio to a predicted LLN or using z-scores (see below) may help when deciding how to best manage this small number of patients. The risk of misdiagnosis and over-treatment of individual patients using the fixed ratio as a diagnostic criterion is limited, as spirometry is only one biologic measurement to establish the clinical diagnosis of COPD in the appropriate clinical context (symptoms and risk factors). Diagnostic simplicity and consistency are crucial for the busy clinician.

GOLD and GLI recommend that in the appropriate clinical context (i.e. a symptomatic patient with a medical and exposure history suggestive of COPD) the fixed ratio should be used to identify COPD-related airflow obstruction and

confirm a diagnosis of COPD.[360]

It is important to emphasize that airflow obstruction that is not fully reversible is not specific to COPD; the clinical context and risk factors should also be considered. Airflow obstruction that is not fully reversible may also be found in patients with asthma and other diseases.

Studies in many countries show that most people with a diagnostic label of COPD had not had spirometry performed.[369-376] Lack of access to spirometry, lack of confidence in interpreting the results and patient reluctance to attend and perform spirometry have all been identified as barriers to its use.[377,378] Education programs can help overcome some of these and AI may also help to improve spirometry quality in situations where confidence and understanding is poor.[379]

Assessing the severity of airflow obstruction

Interpretation of the severity of lung function impairment is dependent on having appropriate reference values. Previously reference values have taken account of race, as studies such as the Prospective Urban and Rural Epidemiological study that analyzed pre-bronchodilator spirometry data from 153,996 healthy people with < 5 pack-year smoking histories in 17 countries and observed wide variation by region.[99] Compared with individuals living in North America or Europe, people living in south Asia had FEV1 values that were on average 31% lower, adjusted for age, height and sex. Similarly, those living in southeast Asia, sub-Saharan Africa, East Asia, Middle East and South America had FEV1 values that were on average 24%, 21%, 13%, 11%, and 6% lower than individuals living in North America or Europe, respectively, independent of age, height, sex, and smoking status.[99] However, race-correction may have important consequences for patients from these areas and eliminating race-based reference values has been proposed[353] because they can lead to underestimation of disease severity and normalize the effects of malnutrition and childhood illness on lung development. In 2022, GLI published new race neutral equations (GLI-Global equations)[380] and these are now the only reference equations officially endorsed by ATS and ERS.[244] In a study of 369,077 participants in the National Health and Nutrition Examination Survey, UK Biobank, the Multi-Ethnic Study of Atherosclerosis, and the Organ Procurement and Transplantation Network the use of race-based and race-neutral equations generated similarly accurate predictions of respiratory outcomes in participants with lung diseases, including COPD.[381] However, the study showed that changing to using race-neutral reference would lead to significant changes in occupational eligibility and disability compensation. Questions also remain about the validity of the GLI-Global equations as they are essentially based on a weighted average of racial and ethnic categories, were derived from a population that did not include participants from many countries or global regions, and ignore the observed population differences in body proportions.[382-384] In addition, lung reference values change over time and require periodic revision.[385] Nevertheless, GOLD recommends using the GLI-Global equations as the reference standard for the assessment of lung function impairment in patients with COPD, despite their limitations.

GOLD continues to recommend using the FEV1 as a percentage of the predicted value to stage the severity of airflow obstruction. The ERS and ATS recommend using z-scores rather than percent predicted values to stage severity and have proposed a three-level (four-tier) severity system that considers z-scores > −1.65 as normal, between −1.65 and −2.5 as mild, between −2.51 and −4 as moderate and < −4.1 as severe.[353] Using these thresholds inevitably leads to differences in the classification of some patients compared to using the percentage predicted[386] but whether this has significant implications for management or prognosis remains unclear. The majority of COPD studies that form the evidence base for treatment recommendations, recruited and classified subjects using the GOLD stages based on percentage predicted values, and for the time being GOLD recommends continuing to use this method to assess severity of airflow obstruction. The percentage of the predicted GLI-Global equation value can be determined using the online GLI calculator (gli-calculator.ersnet.org). In patients with airflow obstruction, a low FEV1 or a rapid decline in FEV1 is associated with increased mortality.[387]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Assessing pulmonary function during airborne viral epidemics

Performing spirometry and pulmonary function testing during airborne viral epidemics may lead to viral transmission as a result of coughing and droplet formation during the tests.[388,389] During periods of high prevalence of airborne viral infections in the community, spirometry should be restricted to patients requiring urgent or essential tests for the diagnosis of COPD, and/or to assess lung function status for interventional procedures or surgery. The ATS and ERS have provided recommendations regarding testing and precautions that should be taken.[388,390,391]

When routine spirometry is not available, home measurement of PEF combined with validated patient questionnaires could be used to support or refute a possible diagnosis of COPD.[392-395] However, PEF does not correlate well with the results of spirometry,[396-398] has low specificity,[351] and cannot differentiate obstructive and restrictive lung function abnormalities. When making a diagnosis of COPD, airflow obstruction could also be confirmed by personal electronic portable spirometers,[399,400] and instructing them in their use and observing them in their homes using video conferencing technology.

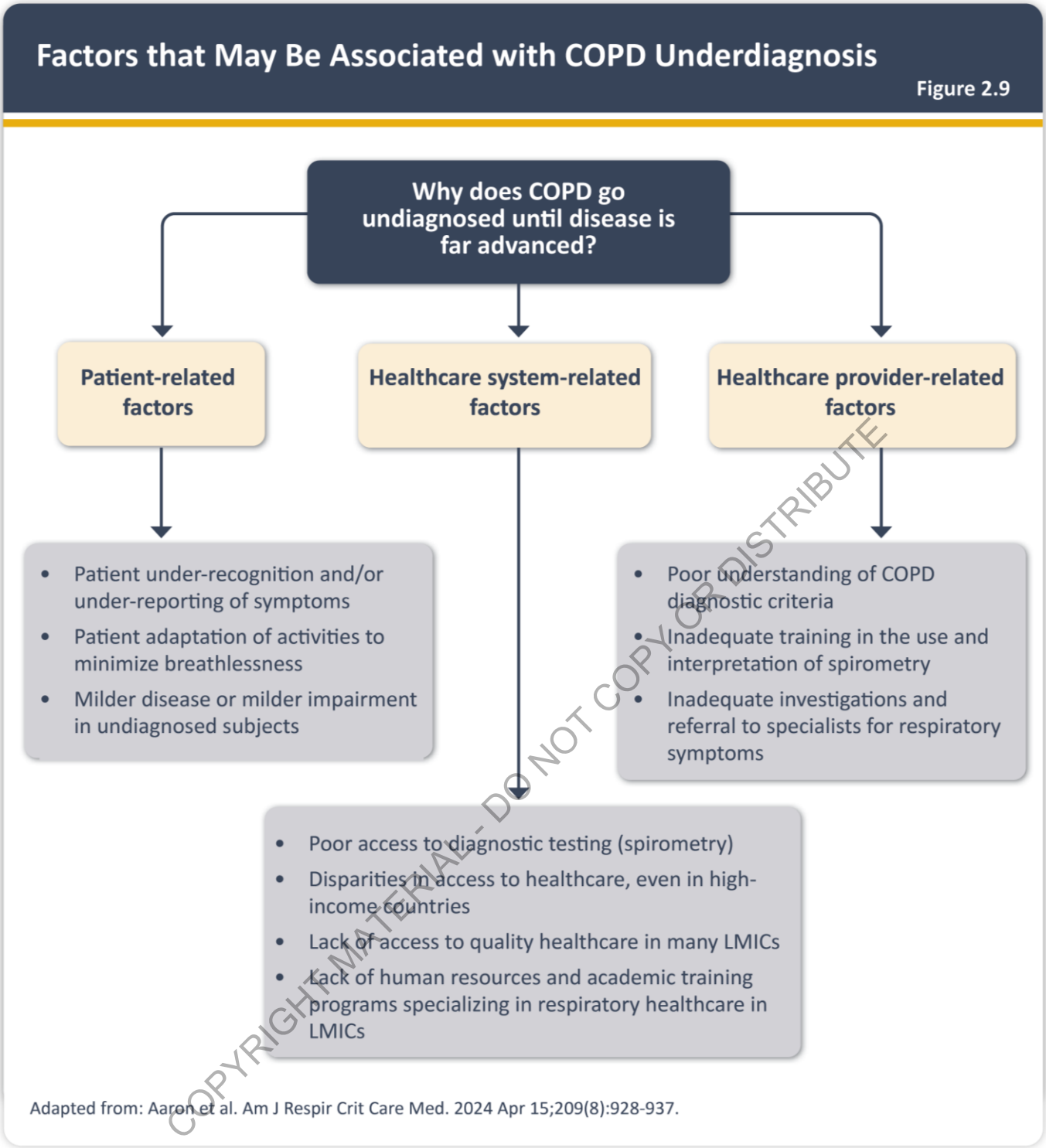
SCREENING AND CASE-FINDING

The impact of undiagnosed COPD

Studies from across the world suggest that up to 70% of adults with COPD remain undiagnosed. The 2007-2012 US National Health and Nutritional Examination Survey found obstructive lung disease in 13.4% of randomly selected American adults who underwent spirometry, however 71% had never received a prior diagnosis of COPD.[401] A 27-country collaborative study found a prevalence of COPD (FEV1/FVC < LLN), of 9.7%, with 81% of COPD cases being undiagnosed.[88] The problem of COPD underdiagnosis was worse in low and middle-income countries, and in these countries more than 90%-95% of COPD cases were undiagnosed.[88] Reasons for under-diagnosis of COPD are complex and are summarized in **Figure 2.9**.

Individuals with undiagnosed COPD are afflicted by poor quality of life and they suffer from exacerbations like those seen in patients with diagnosed disease.[402] A Canadian study of individuals with symptomatic undiagnosed COPD showed that undiagnosed COPD was associated with greater symptom burden, poorer disease-specific quality of life, impaired work productivity, and poorer overall general health status.[403,404] A Danish study showed that individuals with previously undiagnosed COPD had age- and sex-adjusted hazard ratios for exacerbations and pneumonia that were 15.5 and 2.8 times higher than age-matched individuals without COPD.[405] In addition, adults with undiagnosed, symptomatic COPD had a 4.3 times greater risk of death from respiratory causes, and a 2.0 times greater risk of death from any cause, compared to individuals without COPD.[404]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Finding undiagnosed COPD: screening vs case-finding

Earlier diagnosis of COPD is achieved when an individual undergoes targeted assessment for obstructive lung disease, and disease is identified prior to a conventional diagnosis being made by the individual's healthcare professionals. This can be potentially achieved by either: i) screening or ii) case-finding.

i. Screening is performed in the general population and involves testing mostly asymptomatic individuals with spirometry. This approach is expensive and has a relatively low yield, and screening of low-risk, asymptomatic individuals is not recommended by the US Preventive Services Task Force.[406] In asymptomatic individuals without any significant exposures to tobacco or other risk factors, screening spirometry is probably not indicated, and this approach is not recommended by GOLD.

The potential use of screening spirometry in children, adolescents and young adults to identify individuals with poor lung development at risk of COPD and other chronic conditions later in life merits future investigation.[93]

ii. Case-finding targets only those who have unexplained respiratory symptoms, or specific risk factors for COPD, for subsequent testing with spirometry. Case-finding is a potential strategy for identifying undiagnosed individuals at high risk of COPD to allow earlier identification of disease and to direct resources to these individuals. In turn, case-finding approaches can be divided into 1) active case-finding or 2) opportunistic case-finding:

   a. Active case-finding involves proactively searching for individuals at higher risk of the condition, often based on presence of symptoms. In active case-finding, respiratory symptoms and risks for COPD (e.g. unexplained dyspnea, or > 20 pack-years of smoking, or history of recurrent chest infections, or history of early life events) are elicited from the individual via questionnaire and based on positive responses they are targeted to receive spirometry.

      Active case-finding approaches first involve identifying individuals at higher risk for COPD using risk assessment tools such as case finding questionnaires or risk prediction models,[407] and the diagnosis is then confirmed with an objective measure such as pre-/post bronchodilator spirometry. A pragmatic case-finding algorithm (**Figure 2.10**) has been recently proposed to enable accurate COPD diagnoses for most populations.[408]

      Several COPD case-finding questionnaires, including the CDQ and the CAPTURE questionnaire, have been validated in different populations. Hand-held devices, such as the PEF and micro-spirometers (COPD-6 and the Piko-6) have also been widely tested to try to improve identification of people with undiagnosed COPD. Increasingly, it appears that combining questionnaires with simple physiological measurements provided by hand-held devices enhances case-finding performance.[409-411]

   b. Opportunistic case-finding involves identification of individuals when they present themselves for healthcare services for reasons other than the condition being screened for. An example would be performing diagnostic spirometry in individuals who present for lung cancer screening.

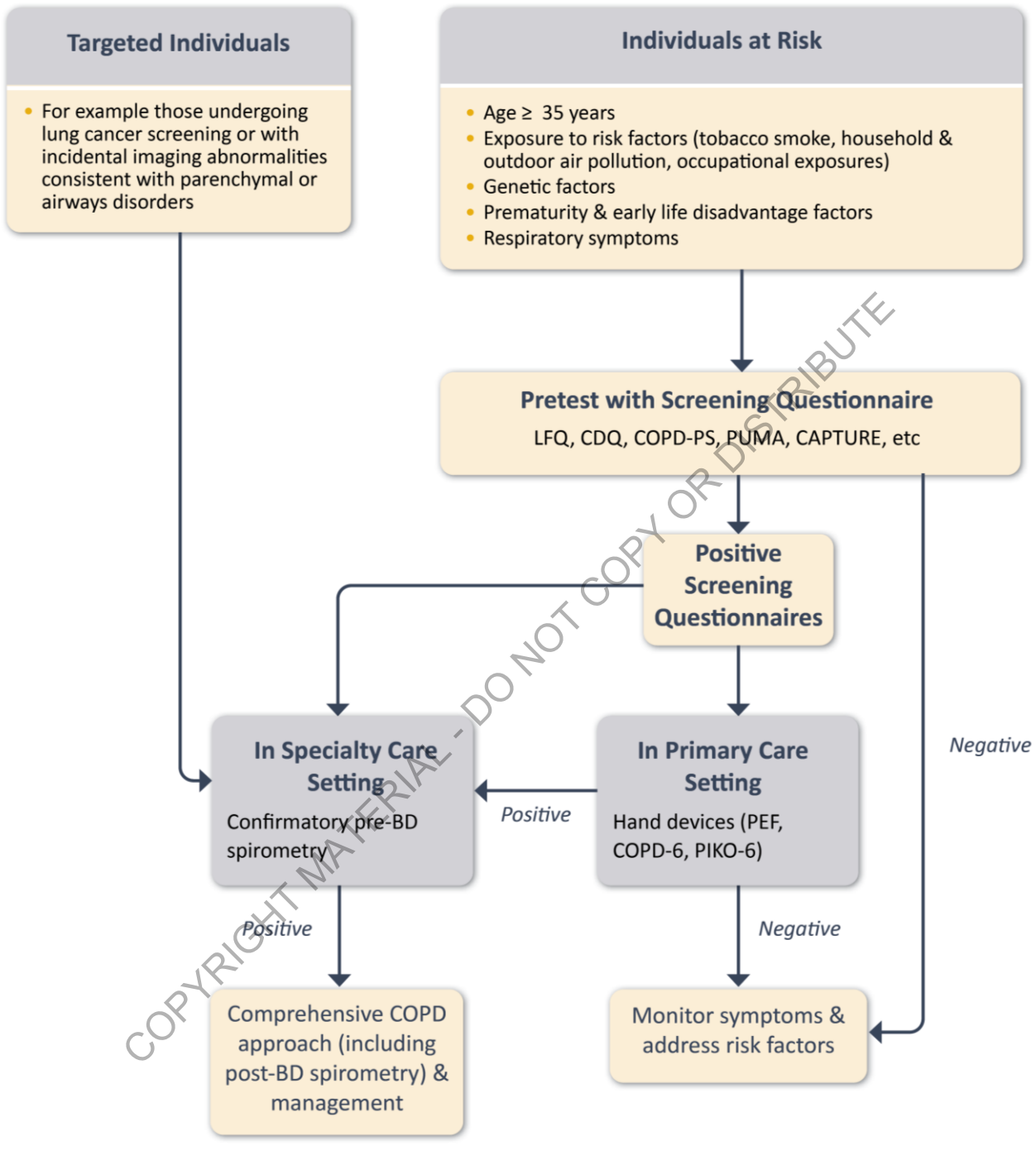
COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Active case-finding in the population

Prior to 2024, multiple studies had demonstrated that earlier identification and diagnosis of adults with previously undiagnosed COPD was feasible, however no studies had coupled earlier diagnosis of COPD with a treatment strategy to demonstrate that such a strategy improves health outcomes. The Undiagnosed COPD and Asthma in the Population Study (UCAP) coupled an active, community-based case-finding study to a randomized, controlled clinical trial.[412] This study was the first to show that identification and diagnosis of COPD via active telephone-based case-finding of symptomatic community-dwelling individuals, coupled to a comprehensive intervention, reduces patients' healthcare utilization and improves quality of life and health outcomes.[412] It has been found that patients identified by case-finding with greater disease burden benefit more from earlier diagnosis and treatment.[413] Based on the above evidence, GOLD advocates for active case finding,[414-416] i.e., performing spirometry in individuals with symptoms and/or risk factors.

An Algorithm for COPD Case-finding

Figure 2.10



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Adapted from: Aaron et al. Am J Respir Crit Care Med. 2024 Apr 15;209(8):928-937.

Opportunistic case-finding in primary care

Systematic active case-finding in a primary care setting via mail-out of a screening questionnaire has been found to be an effective way to identify undiagnosed COPD patients.[417]

Although COPD case-finding in primary care has been demonstrated to have a small but significant impact on

increasing rates of diagnoses and physician's clinical actions, there is limited data suggesting a significant impact on patient outcomes.[417-420] In the Veterans Affairs system, the use of a clinical decision support system algorithm that incorporated case-finding for COPD and alpha-1 antitrypsin deficiency (AATD), improved correct COPD diagnosis rates and improved screening rates for AATD in a primary care setting.[421]

In a prospective study in China the COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE) tool showed a good sensitivity to identify COPD patients who may require treatment because of increased symptoms, risk of exacerbations or hospitalization.[422] However, a recently completed cluster-randomized trial of 100 family practices in the US, which employed the CAPTURE tool to try to identify patients with undiagnosed COPD, was unable to show a significant effect. Randomizing family practices to knowledge of patients' CAPTURE scores did not significantly impact on the process of care nor did patients' CAAT™ scores significantly improve.[423] The trial was affected by the COVID pandemic, and more research is needed to determine if opportunistic case-finding for COPD in primary care will improve patient outcomes.

Opportunistic case-finding for COPD in targeted populations

Leveraging lung cancer imaging for COPD case-finding

Annual LDCT imaging of the chest is recommended by the USPSTF to diagnose lung cancer earlier among individuals aged 50 to 80 years with a ≥ 20 pack-year smoking history. Lung cancer and COPD share common risk factors, and COPD is also an independent risk factor for lung cancer and represents the major comorbidity affecting survival in patients with lung cancer.[424-427] Thoroughly assessing symptoms and performing spirometry in individuals undergoing LDCT for lung cancer screening therefore represents a unique opportunity to simultaneously assess patients for both the presence of unrecognized symptoms of COPD and airflow obstruction.

Studies that have evaluated individuals for COPD symptoms and performed spirometry at lung cancer screening have reported airflow obstruction in 34-57% of individuals, emphysema in 68-73% and no prior diagnosis of COPD in 67%.[425,428,429] Male sex, younger age, lower smoking duration and being asymptomatic were associated with detection of airflow obstruction without a prior diagnosis of COPD.[429,430] Those without a prior diagnosis of COPD were less symptomatic; however, the prevalence of symptoms was still high, being found in over 50% of individuals. The prevalence of the underdiagnosis of COPD in those undergoing lung cancer screening can approach 90% in some reports.[431-437]

In a lung cancer screening cohort, over half of those with visually detected emphysema had airflow obstruction.[438] Quantitative analysis of density can also be used to detect COPD with varying sensitivity and specificity depending on the threshold chosen.[439] Deep learning approaches are also being investigated that could diagnose COPD from lung cancer screening CT scans with results varying depending on the method and cohort analyzed.[440]

Airflow obstruction or emphysema are markers of an increased risk for lung cancer. The severity of airflow obstruction and the presence of emphysema are both independent risk factors and may be useful indicators for triaging patients for more careful lung cancer surveillance.[427,431-433,435-437,441] Reporting of incidental findings such as emphysema on lung cancer screening reports is highly variable.[442] Even 1% emphysema on a CT is associated with increased risk for COPD.[443] Hence GOLD recommends that the presence of any level of emphysema should be highlighted as a key finding in lung cancer screening reports, with a recommendation for further clinical evaluation and spirometry if the patient has no prior diagnosis of COPD.

Leveraging incidental lung imaging abnormalities for COPD case-finding

Factors other than cigarette smoking can increase the risk of COPD (e.g., premature birth, genetic predisposition, environmental exposures, childhood infections, etc.) and these individuals may undergo chest imaging for evaluation of respiratory symptoms. These individuals have no or minimal exposure to cigarette smoking and are usually of

COPYRIGHT MATERIAL-DO NOT COPY OR DISTRIBUTE

younger age and distinct from the population undergoing annual LDCT for lung cancer screening. The CT scans themselves can be used to help identify individuals at increased risk for COPD in the non-lung cancer screened population and prompt consideration for spirometry.

Emphysema is a hallmark of COPD and easily detected on chest imaging, either through visual inspection via a radiologist or through quantitative lung density.[438-440] Lung imaging may also identify other abnormalities that may indicate the presence of COPD including air trapping, airway wall thickening and mucus plugging.[204,430,434,444-446] These abnormalities not only associate with the presence of airflow obstruction but may indicate patients that have a more rapid decline in lung function and worse quality of life.[447-450]

While quantitative analysis of LDCT data is often not available in clinical settings, the presence of emphysema and other airway abnormalities should raise clinical suspicion for COPD and lead to a detailed assessment of symptoms and consideration for pulmonary function testing if not previously performed. The use of spirometry in targeted patients undergoing lung cancer screening, or when incidental imaging abnormalities consistent with airways disorders are found, is recommended by GOLD.[451]

The case for universal spirometry

While case-finding strategies for COPD remain the most immediate actionable approach, emerging evidence supports a broader, life-course approach to lung health. Lung function varies substantially between individuals, both in the level achieved during growth and in the rate of decline during adulthood. COPD may develop not only because of accelerated loss of lung function, but also because an individual never achieves a normal peak lung function in early adulthood. Reduced lung function in early adulthood is also associated with increased risks of asthma, interstitial lung abnormalities, cardiovascular and metabolic disease, and premature death.[452-454]

These observations suggest that spirometry should be considered not only a diagnostic test for established respiratory disease, but also a longitudinal biomarker of lung and overall health.[117] Further, given the challenges of defining "normal," repeated measurements allow an individual to serve as their own control. Tracking lung function trajectories at the individual level may identify abnormal lung development, impaired peak lung function, or accelerated decline earlier than a single measurement. In this respect, longitudinal spirometry is analogous to pediatric growth charts, which monitor an individual's growth over time and compare measurements with population-based standards.[117]

We propose that universal spirometry could begin at approximately 6 years of age, when most children can perform reliable testing, and be repeated at approximately 3-year intervals through adolescence and early adulthood, followed by less frequent testing in adulthood if no abnormality is present. This proposed approach would track FEV1, FVC, and the FEV1/FVC ratio, as these measures provide complementary information regarding airflow obstruction, restrictive patterns, lung growth, and prognosis. Abnormal results or deviations from an established trajectory could prompt further evaluation and targeted interventions, including assessment for asthma, reducing tobacco and vaping exposure, mitigating occupational and environmental exposures, vaccination and infection prevention, and promoting physical activity and a healthy weight.

We acknowledge that adoption of universal spirometry may not yet be feasible for population-wide implementation. Nevertheless, establishing longitudinal lung-function trajectories represents a promising future strategy for prevention and earlier recognition of COPD and other chronic respiratory diseases.

COPYRIGHT MATERIAL- DO NOT COPY OR DISTRIBUTE

INITIAL ASSESSMENT

Once the diagnosis of COPD has been confirmed by spirometry, COPD assessment must focus on the following five fundamental aspects to guide therapy:

- Severity of airflow obstruction
- Nature and magnitude of current symptoms
- Previous history of moderate and severe exacerbations
- Blood eosinophil count
- Presence and type of other diseases (multimorbidity)

Severity of airflow obstruction

In the presence of FEV1/FVC ratio < 0.7 the assessment of **airflow obstruction severity** in COPD (note that this may be different from severity of the *disease*) is based on the post-bronchodilator value of FEV1 % predicted (GLI-Global; see **Spirometry** section). The specific spirometric cut points are proposed for purposes of simplicity (**Figure 2.11**).

Symptoms

Because there is only a weak correlation between the severity of airflow obstruction (**Figure 2.11**) and the symptoms experienced by the patient or the impairment of their health status,[455,456] formal assessment of symptoms using validated questionnaires is required.

Dyspnea questionnaire: the mMRC dyspnea scale

The mMRC scale was the first questionnaire developed to measure breathlessness, which is a key symptom in many patients with COPD, although often unrecognized.[457] (**Figure 2.12**) Of note, the mMRC score relates well to other multidimensional health status measures[458] and predicts future mortality risk.[459,460]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

GOLD Grades and Severity of Airflow Obstruction in COPD (based on post-bronchodilator FEV1) Figure 2.11

In patients with COPD (FEV1/FVC < 0.7):

GOLD 1:	Mild	FEV1 ≥ 80% predicted
GOLD 2:	Moderate	50% ≤ FEV1 < 80% predicted
GOLD 3:	Severe	30% ≤ FEV1 < 50% predicted
GOLD 4:	Very Severe	FEV1 < 30% predicted

Modified MRC Dyspnea Scale

Figure 2.12

PLEASE TICK IN THE BOX THAT APPLIES TO YOU | ONE BOX ONLY | Grades 0 - 4

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

Reference: American Thoracic Society. Am Rev Respir Dis 1982;126(5):952-6.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Multidimensional questionnaires

It is now recognized that COPD impacts patients beyond dyspnea.[461] For this reason, multidimensional questionnaires are recommended. The most comprehensive disease-specific health status questionnaires such as the CRQ[462] and SGRQ[463] are important research tools but they are too complex to use in routine practice. Shorter comprehensive measures, such as the CAAT™ and the CCQ© have been developed and are suitable for use in the clinic. Below we discuss the CAAT™ and the SGRQ.

The CAAT™*/CAT™† is an 8-item questionnaire that assesses health status in patients with COPD (**Figure 2.13**).[464,465] It was developed to be applicable worldwide and validated translations are available in a wide range of languages. The score ranges from 0 to 40, correlates very closely with the SGRQ, and has been extensively documented in numerous publications.[466]

* The COPD Assessment Test was developed by a multi-disciplinary group of international experts in COPD supported by GSK. COPD Assessment Test and the CAT™ logo is a trademark of the GlaxoSmithKline group of companies. © 2009 GlaxoSmithKline. All rights reserved. GSK activities with respect to the COPD Assessment Test™ are overseen by a governance board that includes independent external experts, one of whom chairs the board.

† The COPD Assessment Test CAT™ was designed to assess the impact of COPD on a person's health status. To facilitate its use in other chronic airway diseases, CAT™ has been renamed as the Chronic Airways Assessment Test CAAT™. CAT™ and CAAT™ are equivalent, and the scores are interchangeable.

CAAT™ Assessment

Figure 2.13

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	

Reference: Jones et al. ERJ 2009; 34 (3); 648-54.

TOTAL SCORE: ☐

CAT™ has been renamed as the Chronic Airways Assessment Test CAAT™; CAT™ and CAAT™ are equivalent and the scores are interchangeable.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

The SGRQ is the most widely documented comprehensive measure; scores < 25 are uncommon in diagnosed patients with COPD,[187] and scores ≥ 25 are very uncommon in healthy persons.[467,468] Therefore, it is recommended that a symptom score equivalent to SGRQ score ≥ 25 should be used as the threshold for considering regular treatment for symptoms including breathlessness, particularly since this corresponds to the range of severity seen in patients recruited to the trials that have provided the evidence base for treatment recommendations. The equivalent cut-point for the CAAT™ is 10.[469] An equivalent mMRC score cannot be calculated because a simple breathlessness cut-point cannot equate to a comprehensive symptom score cut-point. The great majority of patients with an SGRQ of ≥ 25 will have an mMRC of ≥ 1; however, patients with mMRC < 1 may also have a number of other COPD symptoms.[470] For this reason, the use of a comprehensive symptom assessment is recommended. However, because use of the mMRC is widespread, an mMRC of ≥ 2 is still included as a threshold for separating "less breathlessness" from "more breathlessness." Nevertheless, users are cautioned that assessment of other symptoms is required.[470]

Exacerbation risk

An exacerbation of COPD is an acute event with symptoms worsening over a few days (up to 14 days) and characterized by increased dyspnea and/or cough and sputum which may be accompanied by tachypnea and/or tachycardia and is

often associated with increased local and systemic inflammation caused by infection, pollution, or other insult to the airways (see **Chapter 4**).[471-474] Even one moderate or severe exacerbation treated with steroids and/or antibiotics is key in the natural history of the disease as these episodes significantly impact the health status of the patient (often for a prolonged period of time), enhance the rate of lung function decline, worsen the prognosis of the patient and are associated with an increased risk of future exacerbations as well as much of the healthcare costs of COPD.[475-477] Exacerbation rates vary greatly between patients[478] and during follow-up.[479] The most commonly used predictor of having an exacerbation is a previous history of an exacerbation event with greater risk seen in those experiencing more than one exacerbation requiring steroids and/or antibiotics, particularly one requiring hospitalization.[478] In the COPDGene and NOVELTY study cohorts, having a moderate or severe exacerbation in the past two years was the best predictor of having of two moderate or one severe exacerbation, or of any exacerbation, in the next 12 months.[480] Even in GOLD 1 patients, a history of exacerbations is the strongest predictor of future exacerbations.[481] Worsening of airflow obstruction is associated with an increasing prevalence of exacerbations, hospitalization[415,482] and risk of death.[187,483]

Blood eosinophil count

There is evidence that on average blood eosinophil counts are higher in patients with COPD, although there is marked overlap with healthy individuals.[484,485] Higher blood eosinophil counts in patients with COPD are associated with increased numbers of eosinophils in the lungs and higher levels of markers of T2 inflammation in the airways, although the concordance between blood and lung/airways T2 biomarkers is not strict.[486,487] These differences in airway inflammation may explain the differential response to ICS treatment according to blood eosinophil counts.[488]

The repeatability of blood eosinophil counts appears reasonable,[489] although greater variability is observed at higher thresholds,[490] with better reproducibility at lower thresholds (e.g., ≤ 100 cells/µL).[491]

Cohort studies have produced differing results with regard to the ability of blood eosinophils to predict future exacerbation outcomes, with either no relationship[492] or a positive relationship reported.[493,494] Differences between studies are likely to be related to different previous exacerbation histories and ICS use. There is insufficient evidence to recommend that blood eosinophils should be used to predict future exacerbation risk on an individual basis in patients with COPD. Greater FEV1 decline was observed in patients with COPD who had mild to moderate airflow obstruction and higher blood eosinophil counts in a population where ICS use was low,[495] highlighting the possible usefulness of blood eosinophil counts as a prognostic biomarker for lung function decline when not confounded by ICS use. In younger individuals without COPD, higher blood eosinophil counts are associated with increased risk of subsequent development of COPD.[496]

A number of studies have shown that blood eosinophil counts predict the magnitude of the effect of ICS (added on top of regular maintenance bronchodilator treatment) in preventing future exacerbations; blood eosinophil counts are recommended by GOLD to guide the use of ICS as part of pharmacological management (see **Chapter 3**, **Figures 3.8, 3.9 and 3.10**).[497-502]

Imaging

Chest CT has become an important tool to understand both disease severity and structural abnormalities. GOLD now recommends a chest CT (non-contrast) with inspiratory and expiratory images as part of the initial evaluation for all patients with COPD where available (**Figure 2.16**). This allows further characterization of airway disease and emphysema, thereby identifying patients who may be candidates for targeted therapies

Multimorbidity

People with COPD often suffer other concomitant chronic diseases (multimorbidity). This can occur in patients with

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

mild, moderate or severe airflow obstruction.[187] Multimorbidity influences mortality and hospitalizations independently of the severity of airflow obstruction,[503] and deserves specific treatment. Therefore, comorbid conditions should be looked for routinely, and treated appropriately if present, in any patient with COPD. Recommendations for the diagnosis, assessment of severity, and management of individual comorbid diseases are the same as for patients without COPD.

Frequent multimorbid diseases in COPD include CVD,[94] metabolic syndrome, osteoporosis, depression, and anxiety, with the coexistence likely due to shared risk factors (e.g., aging, smoking, alcohol, diet, and inactivity).[475,504-506] In addition, COPD itself may increase the risk for other comorbid diseases (e.g., COPD (particularly emphysema) and lung cancer).[507,508] Whether the association between COPD and lung cancer is due to common risk factors (e.g., smoking), involvement of shared susceptibility genes and/or impaired clearance of carcinogens is unclear. COPD can also have significant extrapulmonary (systemic) effects including weight loss, nutritional abnormalities, and skeletal muscle dysfunction. The latter is characterized by both sarcopenia (loss of muscle cells) and abnormal function of the remaining cells.[509] Its causes are likely multifactorial (e.g., inactivity, poor diet, inflammation and/or hypoxia) and it can contribute to exercise intolerance and poor health status in patients with COPD. Importantly, skeletal muscle dysfunction is a modifiable source of exercise intolerance by rehabilitation.[510] A more detailed description of the management of COPD and morbidities is provided in **Chapter 5**.

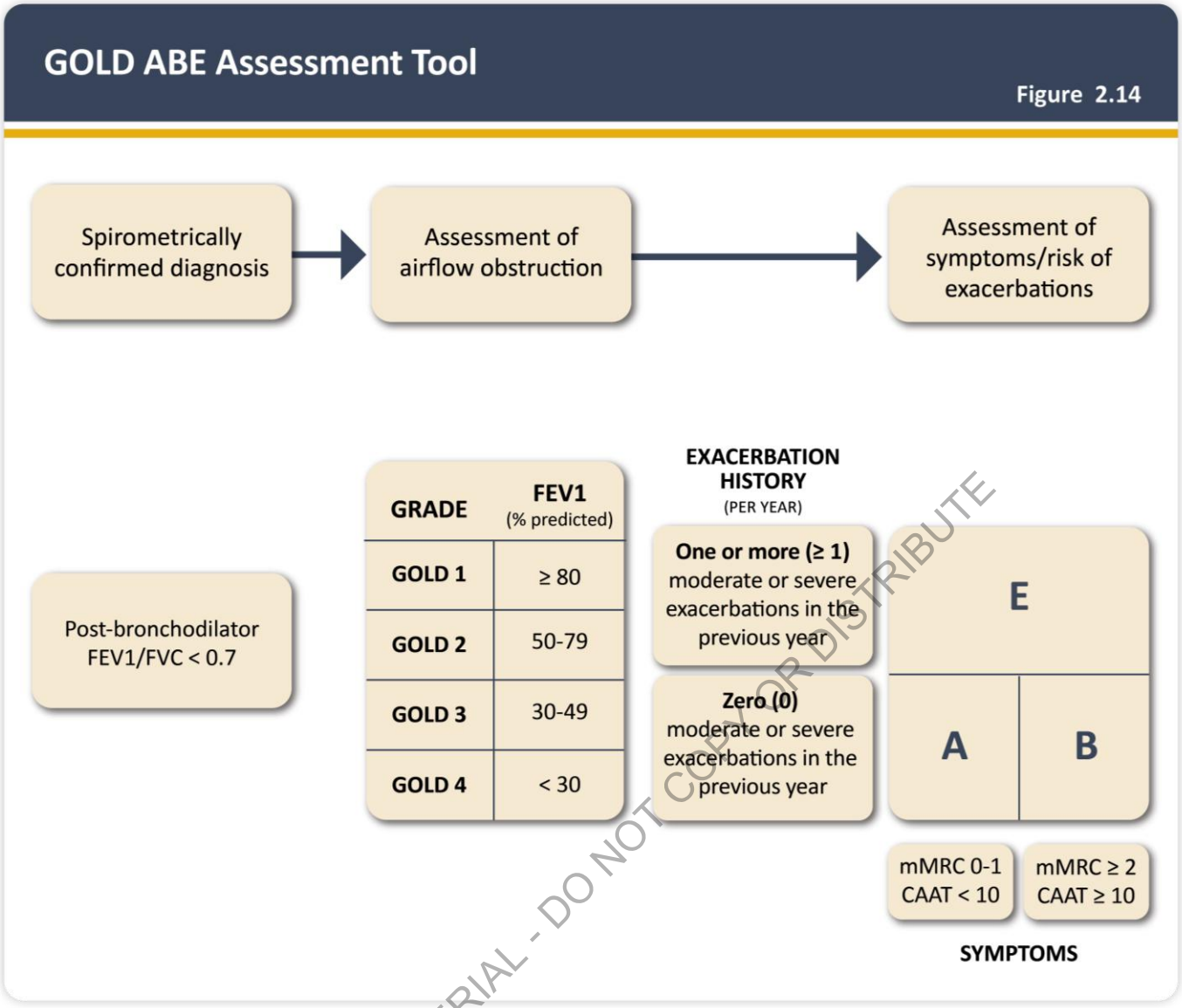
Combined initial COPD assessment

In 2011, GOLD proposed moving from a simple spirometric grading system for disease severity assessment and treatment to a combined assessment strategy based on the level of symptoms (mMRC or CAAT™), the severity of airflow obstruction (GOLD grades 1-4), and the frequency of previous exacerbations. This classification was proposed to guide initial pharmacological treatment. The main step forward achieved by this combined assessment strategy was to incorporate patient-reported outcomes and highlight the importance of exacerbation prevention in the management of COPD. The initial version of the combined assessment relied on both the severity of airflow obstruction (GOLD grades 1-4) and the frequency of previous exacerbations to assess exacerbation risk.

The severity of airflow obstruction was subsequently removed from this combined assessment scheme considering its lower precision at the individual level (versus that at a population level) to predict outcomes and drive treatment decisions, while complexifying the use of the classification by clinicians.[456,483,511,512]

In the 2023 GOLD report, GOLD proposed a further evolution of the ABCD combined assessment tool that recognized the clinical relevance of exacerbations, independently of the level of symptoms of the patient. **Figure 2.14** presents the recommendations for patients who are naïve to pharmacological treatment. The A and B groups remained unchanged, but the C and D groups were merged into a single group termed “E” to highlight the clinical relevance of exacerbations. It was acknowledged that this proposal needs to be validated by appropriate clinical research. Observational studies[513,514] have shown that even one moderate or severe exacerbation prior to initiating maintenance pharmacological therapy increases the risk of subsequent events; this risk is further increased if there are more frequent or severe events.[122,502,515,516] Consequently, Group E has been modified to include individuals with one moderate exacerbation in the previous year.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

MONITORING AND FOLLOW-UP

Routine follow-up of patients with COPD is essential. Lung function may worsen over time, even with the best available care. Symptoms, exacerbations and objective measures of airflow obstruction should be monitored to determine when to modify management and to identify any complications and/or comorbidities that may develop.

Symptoms

At each visit, information on symptoms since the last visit should be collected, including cough and sputum, breathlessness, fatigue, activity limitation, and sleep disturbances, including insomnia. Questionnaires such as the CAAT™[464] can be used; trends and changes are more valuable than single measurements.

Exacerbations

The frequency, severity, type and likely causes of all exacerbations[517] should be monitored. Sputum volume and presence or absence of sputum purulence should be noted. Specific inquiry into response to previous treatment, unscheduled visits to providers, telephone calls for assistance, and use of urgent or emergency care facilities is important. Hospitalizations should be documented, including the facility, duration of stay, and any use of critical care or mechanical ventilatory support.

Adherence and appropriate use of prescribed treatments

This is a key action in the chronic management of patients with COPD that should be mandatory in each clinical visit. Adherence to, effectiveness, and adverse effects of pharmacological and non-pharmacological treatments should be assessed, and adjustments made if necessary.

Assessment of pharmacological treatments

Dosage of prescribed medications

Review the current medications of the person with COPD; prescribed dose, frequency and duration of use; and any recent changes. Assess whether the medication and dosage are appropriate and whether the patient understands how and when to take each medication.

Adherence to the medication regimen

Evaluate how consistently the patient follows the prescribed treatment plan, including missed doses, barriers to adherence (e.g., side effects, lack of perceived efficacy, cost, forgetfulness, complexity of regimen), and strategies used to improve medication compliance. This can be done during the anamnesis, or by using specific questionnaires such as the 'Test of Adherence to Inhalers' (TAI).[518]

Inhaler type and technique

Identify the type of inhaler device being used (e.g., metered-dose inhaler, dry powder inhaler, soft mist inhaler) and assess inhaler technique, including preparation, inhalation method, timing, breath-holding, and device maintenance. Provide education or correction as needed to ensure effective medication delivery.

See **Appendix 2: Pharmacological Treatments - Clinical Checklist.**

Assessment of non-pharmacological treatments

Engagement with prescribed non-pharmacological interventions

Assess whether the individual has participated in recommended non-pharmacological interventions (any healthcare intervention that is not primarily based on medication such as vaccination, pulmonary rehabilitation, exercise programs and physical activity, education sessions and other treatments such as home oxygen). If the patient has not engaged, explore the reasons (e.g., lack of awareness, access barriers, motivation, symptoms, personal circumstances).

Pulmonary rehabilitation and maintenance exercise adherence

For people who have completed pulmonary rehabilitation, assess their adherence to a maintenance exercise training program (formal or informal), including frequency, intensity, type of activity, barriers encountered, and strategies used to maintain long-term participation.

Physical activity promotion and awareness

Evaluate whether the individual understands their current level of physical activity and how it impacts disease management. Assess whether they monitor their activity, set goals, and incorporate regular physical activity at appropriate intensity into their daily routine as well as the symptoms and difficulties experienced.

Integration of self-management skills into daily life

Assess the ability of the patient to apply day-to-day self-management strategies, including:

- Breathing control techniques (e.g., paced breathing, pursed-lip breathing if effective in the individual)
- Stress and anxiety management strategies
- Recognition and early management of symptoms
- Appropriate use of an action plan for prevention and management of exacerbations

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

See **Appendix 3: Non-Pharmacological Treatments - Clinical Checklist.**

Smoking status

At each visit, current smoking status and smoke exposure should be determined followed by appropriate action including, when necessary, referral to a smoking cessation program.

Measurements

Decline in FEV1 can be tracked by spirometry performed at regular intervals (e.g., yearly) to identify patients who are declining quickly, although other lung function parameters reflecting hyperinflation and gas transfer may also be informative.

A timed walking test (6MWD or shuttle-walking test) provides additional information regarding prognosis.[519,520] Measurement of oxygenation at rest in an arterial blood gas sample may help identify patients who will benefit from supplemental oxygen to improve both symptoms and survival in those with severe resting hypoxemia.

Imaging

If there is a clear worsening of symptoms, imaging may be indicated. When exacerbations are repeatedly characterized by purulent sputum, patients should be investigated for bronchiectasis.

Comorbidities

Symptoms that may indicate the development or worsening of a comorbid condition such as lung cancer, obstructive sleep apnea, congestive heart failure, ischemic heart disease, osteoporosis, or depression/anxiety should be recorded. If present, an appropriate diagnostic work-up should follow (see also **Chapter 5**).

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

ADDITIONAL INVESTIGATIONS

In cases where there is a marked discordance between the level of airflow obstruction and the perceived symptoms, a more detailed evaluation should be carried out to better understand lung mechanics (e.g., full lung function tests and exercise testing), lung structure (e.g., CT) and/or comorbidities (e.g., ischemic heart disease) that might impact patient symptoms.

Physiological tests

Lung volumes

Patients with COPD exhibit gas trapping (a rise in residual volume) from the early stages of the disease, where exertional gas trapping (dynamic hyperinflation) is often observed. As airflow obstruction worsens, static hyperinflation (an increase in total lung capacity) occurs. These changes can be documented by body plethysmography, or less accurately by gas dilution lung volume measurement. Lung volumes are helpful in determining the cause of persistent dyspnea, exercise intolerance and in the consideration of lung volume reduction treatments.

Carbon monoxide diffusing capacity of the lungs

The single breath DLco measurement[521] evaluates the gas transfer properties of the respiratory system. DLco is well-standardized, with valid predicted values of practical utility.[352,522-524] The advent of reliable portable systems capable of providing accurate determinations in the field, expands its potential use as a complement to the information provided by spirometry.[525] DLco should be measured in any person with symptoms (dyspnea) disproportionate to the degree of airflow obstruction since reduced DLco values < 60% predicted are associated with increased symptoms,

decreased exercise capacity, worse health status,[526-529] and increased risk of death, independently of the severity of airflow obstruction and other clinical variables.[530-533] Further, DLco has been shown to be a strong predictor of COPD hospitalizations, independent of airflow obstruction and prior hospitalizations.[534] Additionally, in patients with COPD, low DLco values help preclude surgical lung resection in patients with lung cancer[535] while in smokers without airflow obstruction, values < 80% predicted (as a marker of emphysema) signal an increased risk for developing COPD over time.[160]

Over time, people with COPD have an accelerated decline in DLco compared to smokers without the disease, and this decline is significantly greater in women than men.[536,537] However, DLco decline is slow, and years of follow up are often needed before a meaningful change in DLco is detected.

Oximetry and arterial blood gas measurement

Pulse oximetry can be used to evaluate a patient's arterial oxygen saturation and need for supplemental oxygen therapy at the point-of-care and should be used to assess all patients with clinical signs suggestive of respiratory failure or right heart failure. If peripheral oxygen saturation is ≤ 92%, arterial blood gases should be measured due to the imperfect correlation between oxygen saturation detected via pulse oximetry as compared to arterial blood gas.[538] Further, pulse oximetry does not provide information on $PaCO_2$ or pH, which may have potential therapeutic implications (e.g., non-invasive ventilation).

Exercise testing

In some cases, patients may complain of minimal symptoms despite severe airflow obstruction. This may be due to reduced dyspnea perception[539] and/or life-style adaptations (sedentarism) to reduce dyspnea generation. In these cases, exercise tests such as the 6MWD may reveal that the patients are severely constrained and do need more intense treatment (e.g., rehabilitation) than the initial evaluation would have suggested.

Further, exercise capacity should be assessed objectively and compared to normal "reference" values for sex, age and anthropometric characteristics. Exercise tests challenge different organ systems, including the cardiovascular and respiratory system and the skeletal muscles. Objectively measured exercise impairment, assessed by a reduction in self-paced walking distance[540,541] or during incremental exercise testing in a laboratory,[542] is a powerful indicator of health status impairment and predictor of prognosis.[543] **Figure 2.15** presents exercise tests, frequently used in patients with COPD along with setting/equipment, outcome, minimal clinical important difference and useful references.[544-550]

Laboratory testing using cycle or treadmill ergometry can assist in identifying co-existing or alternative conditions e.g., cardiac diagnoses. Walking tests can be useful for assessing disability and risk of mortality[551] and are used to assess the effectiveness of pulmonary rehabilitation. Both the paced shuttle walk test[552] and the self-paced 6MWD test can be used.[547,553] Guidance on the conduct and standardization of these tests is available.[545]

Physical activity assessment

Physical activity (PA) is typically defined as "any bodily movement produced by skeletal muscles that requires energy expenditure."[554] While exercise capacity largely defines the boundaries of the intensity of physical activity in an individual, physical activity itself refers to the behavior of a patient to move for leisure, for transport to get to and from places, or as part of work or domestic activities. As physical activity requires action of skeletal muscles with increases in oxygen consumption, cardiovascular stress and pulmonary ventilation it may result in symptoms comparable to those observed with submaximal exercise. A long-term lack of physical activity has deleterious effects on health in people with COPD and in other chronic conditions.[555] Importantly, acute reductions in physical activity, as experienced during severe exacerbations, have –in combination with other exacerbation related factors such as inflammation- an impact on for example skeletal muscle function.[556,557] Compared to patients with better preserved

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

PA, those with low physical activity have poor prognosis and higher disease burden.[558]

Exercise Tests in COPD Assessment

Figure 2.15

Test	Setting & Equipment	Main Outcome	Minimal Important Difference (MID)
EXERCISE CAPACITY			
Incremental maximal cardiopulmonary exercise test[1,2]	Laboratory: cardiorespiratory and metabolic responses to incremental exercise on ergometer	Peak oxygen consumption and peak work rate	No robust data (approx. 5 watts severe COPD)
6-minute walking test (6MWT)[3,4]	Field (30 m corridor)	Maximal distance walked in 6 minutes (functional walking test)	25-30 m
Incremental shuttle walking test (ISWT)[3,4,5]	Field (10 m track)	Maximal distance covered with incremental pace (functional, incremental walking speed)	35-48 m
1-minute sit-to-stand test[6]	Field/home/primary care	Maximal number of rises in 1 min from chair (functional sit-stand transition)	3 repetitions
EXERCISE ENDURANCE (in submaximal tests)			
Constant work rate cycling test[7]	Cycle at high fraction (75% to 80%) of peak work rate	Bicycle endurance time	Approx. 60 sec
Endurance shuttle walking test[3]	Constant work rate at high fraction of ISWT speed	Walking endurance time	159 sec

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

References: 1. Puente-Maestu et al. Eur Respir J. 2016 Feb;47(2):429-60; **2.** Radtke et al. Eur Respir Rev. 2019 Dec 18;28(154):180101; **3.** Daynes et al. Eur Respir Rev. 2025 May 28;34(176):240198; **4.** Holland et al. Eur Respir J. 2014 Dec;44(6):1428-46; **5.** Evans RA, Singh SJ. Thorax. 2019 Oct;74(10):994-995; **6.** Spence et al. NPJ Prim Care Respir Med. 2023 Mar 15;33(1):11; **7.** Casaburi et al. Ann Am Thorac Soc. 2024 May;21(5):727-739.

Patients with COPD decrease physical activity because of experienced symptoms, and this often happens early in the course of the disease. Given the long-term health consequences, it is of paramount importance that patients remain as active as possible. Assessment of physical activity behavior (amount and intensity) as well as symptom experience with physical activity is therefore important in the context of clinical visits. At a minimum, such assessment can be done during the anamnesis and can be standardized using simple questionnaires or simple, but standardized items that ask patients about their physical activity. An example of such an item is: “How many minutes per day do you engage in brisk walking?” In a Spanish cohort, when patients answered “less than 30 minutes per day,” they were likely to be physically inactive.[559] While these simple questionnaires raise awareness (with patients and clinicians), they are not very reliable[560] and should not be used to follow up physical activity behavior. Activity monitors and wearables or even smartphone applications can be used to track physical activity over time or to assess the effects of interventions.[561] Symptom experience with physical activity can be assessed with dedicated patient reported outcomes as these symptoms constitute an important aspect of the burden of COPD in individual patients.[562] The CAAT questionnaire captures to some extent symptoms during activities of daily life in some of the items. Dedicated

Patient Reported Outcomes (PROs) are the PROactive Physical Activity questionnaires,[562] London Chest Activity of Daily Living (LCADL) scale,[563] or the Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ).[564]

Imaging

Chest X-ray

A chest X-ray is not useful to establish a diagnosis in COPD, but it is valuable in excluding alternative diagnoses and establishing the presence of significant comorbidities such as concomitant respiratory (pulmonary fibrosis, bronchiectasis, pleural diseases), skeletal (e.g., kyphoscoliosis), and cardiac diseases (e.g., cardiomegaly). Radiological changes associated with COPD may include signs of lung hyperinflation (flattened diaphragm and an increase in the volume of the retrosternal air space), hyperlucency of the lungs, and tapering of the vascular markings.

Computed tomography

CT provides insights into the structural and pathophysiologic abnormalities present in COPD. This has improved understanding of disease phenotypes, severity, and outcomes. Because many of these features, including emphysema, bronchiectasis, mucus plugging, and interstitial lung abnormalities, may not be reliably identified from symptoms alone,[204,261,565,566] and because CT also identifies common comorbidities,[567] GOLD suggests considering non-contrast chest CT with inspiratory and expiratory images at least once in all patients with COPD, where available. CT does not replace spirometry for diagnosis. CT is also recommended in patients with frequent exacerbations or persistent symptoms and as part of lung volume reduction evaluation and lung cancer screening.

CT and emphysema

Emphysema distribution and severity can be readily assessed and can assist with decision making for LVRS or endobronchial valve placement. While historically this has been performed based on expert radiologist visual analysis, particularly for LVRS, increasingly quantitative analysis for emphysema extent, location and fissure integrity is now commonly used to assist with endobronchial valve therapy decision making. Endobronchial valve therapy has also expanded the pool of patients where CT evaluation is used more routinely as patients with post-bronchodilator FEV1 between 15%-45% and evidence of marked hyperinflation on plethysmography may benefit.[567,568] The percentage of lung with low attenuation area defined as percentage of voxels with density ≤ −950 Hounsfield Units is the most common way to objectively quantify emphysema on CT and correlates with presence of emphysema on lung pathology and physiological measurements of airflow obstruction as well as increased risk for symptoms, exacerbations, risk of lung cancer, disease progression and death.[439,450,533,569,570] Additionally there is evidence to indicate that upper lobe emphysema, in particular, may also help identify individuals most at risk for rapid lung function decline[571] and emphysema progression.[572]

CT and lung nodules

While chest CT is not required for COPD diagnosis, more patients with COPD are now undergoing CT as part of evaluation of pulmonary nodules detected on chest X-ray or assessment for concurrent lung disease. Recently, the number of patients who would potentially benefit from chest CT has also expanded. The American Cancer Society now suggests individuals aged 50-80 with 20 pack years smoking history regardless of years since quitting should be considered for lung cancer with CT imaging, although access to such screening varies widely across the world.

CT and airways

Additional CT features relevant to COPD include airway abnormalities. This includes both small and large airways. Evidence suggests small airway abnormalities, including narrowing, fibrosis, and loss, are early lesions in COPD and can be detected before emphysema develops.[573] It is these small airways that are thought to be the primary site for airflow obstruction in COPD.[574] Although small airways (<2mm in diameter) cannot be directly visualized, CT can detect nonemphysematous air trapping, which has been validated to correlate with histologic small airway

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

abnormality in human COPD lung samples.[575] Various methodologies for detection have been developed to indirectly assess small airway disease in COPD.[576-579] This is important because data suggests that areas of lung impacted by small airway disease transitions into emphysema over time, and CT small airway disease metrics are associated with increased risk for exacerbations and lung function decline.[479,576,580] Large airway thickening can be detected via visual inspection or quantitative metrics[581] and has been associated with increased symptoms.[582] Another well-described airway abnormality present in COPD is bronchiectasis, although the reported prevalence varies widely, likely based upon the amount of radiographic abnormality required to describe "presence" vs "absence." Bronchiectasis is associated with increased exacerbation frequency and mortality,[583] although it is not yet known whether treatment according to bronchiectasis guidelines influences these outcomes.

Airway mucus plugging is increasingly recognized as an important imaging phenotype in COPD, with an accumulating body of evidence that it can be altered by treatment. Mucus plugs can be identified on CT and visually quantified, most commonly by the number of bronchopulmonary segments impacted by plugs.[584] Importantly, mucus plugging may occur without chronic cough or sputum production, such that symptoms of chronic bronchitis do not reliably identify patients with intraluminal mucus obstruction.[203] Across cohort studies including COPDGene, SPIROMICS, and ECLIPSE, greater mucus plug burden has been associated with worse airflow obstruction, more rapid decline in FEV1, health status, reduced exercise capacity, increased risk of moderate and severe exacerbations, and higher mortality.[585] Mucus plugging likely occurs in multiple inflammatory endotypes. Some data show an association between blood eosinophilia and mucus plugging in COPD. Further research is needed to understand the strength and implications of this association.[586] Recent data in COPD demonstrate that biologic therapy targeting IL-33 may mitigate mucus plugging in COPD.[587] This body of evidence, together with data showing mucus plug regression on CT paralleling improved FEV1 in interventional studies of biologic therapies (e.g., tozorakimab in a phase 2a COPD trial),[583,587] has led many to regard mucus plugging as a potential treatable trait in COPD, though it is not yet recommended for routine clinical scoring outside research settings.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

CT and COPD related morbidities

It should also be noted that CT imaging of the chest can provide additional information about COPD comorbidities including coronary artery calcium, pulmonary artery enlargement, bone density, muscle mass, interstitial lung abnormalities, hiatal hernias, and liver steatosis. Such CT extracted features have been shown to be independently associated with all-cause mortality.[567] As technology advances, such information is likely to become increasingly available to clinicians to enhance patient management.

In summary, while we advocate for CT imaging at the time of diagnosis, additional chest CT imaging should be considered for patients with persistent exacerbations, symptoms out of proportion to disease severity on lung function testing, or those not responsive to medical management. Those with FEV1 between 15% and 45% of predicted, with hyperinflation and gas trapping, may also meet criteria for lung volume reduction procedures, for which a high-resolution CT scan can help determine eligibility. For those who meet criteria for lung cancer screening, annual low dose CT imaging should also be conducted (**Figure 2.16**).[533,567,568,575,576,583,588]

Use of CT in COPD

Figure 2.16

Chest CT (non-contrast) with inspiratory and expiratory images should be considered as part of the initial evaluation for all patients with COPD at least once, where available, and is additionally recommended for patients with persistent symptoms or exacerbations, for lung volume reduction evaluation, and lung cancer screening.

Initial Evaluation	• **Characterize emphysema:** assess its extent and distribution. • **Assess airway disease:** identify bronchiectasis, mucus plugging, and airway wall thickening. • **Identify interstitial abnormalities:** assess for interstitial lung abnormalities and coexisting pulmonary fibrosis. • **Assess comorbidities:** identify coronary artery calcification, pulmonary artery enlargement, low bone density or vertebral fractures, and low muscle mass.
Frequent Exacerbations	• **Identify potential contributors to exacerbations:** evaluate for bronchiectasis, mucus plugging, or findings suggestive of atypical infection, including nontuberculous mycobacterial infection, particularly in patients with purulent sputum or before initiating long-term macrolide therapy.
Persistent Symptoms Despite Optimized Treatment	• **Evaluate structural abnormalities and alternative or coexisting causes of symptoms,** particularly when symptoms are disproportionate to the degree of airflow limitation.
Lung Volume Reduction Evaluation	• **Assess suitability for bronchoscopic or surgical lung volume reduction based on emphysema severity and distribution.** • **Endobronchial valve therapy** may be a therapeutic option for patients if they demonstrate postbronchodilator FEV1 15% to 45% and evidence of hyperinflation. • **Lung volume reduction surgery** may be a therapeutic option for patients with hyperinflation, severe upper lobe predominant emphysema and low exercise capacity after pulmonary rehabilitation.
Lung Cancer Screening	• **Detect lung cancer:** perform repeated low-dose CT in patients who meet lung cancer screening eligibility criteria, according to recommendations for the general population.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Interstitial lung abnormalities

Findings suggestive of parenchymal lung fibrosis or inflammation are common on chest CT imaging of both smokers and nonsmokers, and have been termed ILA when discovered incidentally in patients without known ILD.[589] The prevalence of ILA ranges from 4% to 9% among older (over 60 years) adults, and spans the spectrum from subclinical findings to clinical disease.[589] Among 4,360 COPDGene participants, ILA was present in 8% of individuals, with half meeting criteria for suspected ILD, which was defined as definite fibrosis on CT, FVC < 80% predicted or DLco < 70% predicted.[261,590] Individuals with suspected ILD had increased respiratory symptoms and mortality.[590] Fibrotic ILA (i.e., those with traction bronchiectasis, architectural distortion and honeycombing) are more likely to progress and

are associated with poor outcomes, especially when combined with emphysema.[591,592] Given the clinical relevance of ILA, multiple studies support clinical evaluation, risk stratification and follow up monitoring of individuals with these findings.

Alpha-1 antitrypsin deficiency

GOLD recommends that all patients with a diagnosis of COPD should be tested for AATD.[593,594] Although the classical patient at the time of diagnosis is young (< 45 years) with panlobular basal emphysema, it has become recognized that delay in diagnosis has led to identification of some AATD patients when they are older and have a more typical distribution of emphysema (centrilobular apical).[595] A low concentration (< 20% normal) is highly suggestive of homozygous deficiency. Family members should also be tested and, together with the patient, referred to specialist centers for advice and management (see **Chapter 3**).

Composite scores

Several variables identify patients at increased risk for mortality including FEV1, exercise tolerance assessed by walking distance or peak oxygen consumption, weight loss, and reduction of arterial oxygenation. The BODE method gives a composite score that is a better predictor of subsequent survival than any single component.[596,597] Simpler alternatives that do not include an exercise test have been suggested but need validation across a wide range of disease severities and clinical settings to confirm that they are suitable for routine clinical use.[598,599]

Biomarkers

There is rapidly increasing interest in the use of biomarkers in COPD. Biomarkers are characteristics (either clinical, functional, biologic and/or imaging) that are objectively measured and evaluated as an indicator of normal biological or pathogenic processes or pharmacological responses to therapeutic interventions. In general, such data has proven difficult to interpret, largely as a result of weak associations and lack of reproducibility between large patient cohorts.[600]

At present blood eosinophil counts provide guidance to identify patients with COPD who are more likely to benefit from preventive treatment with ICSs (see **Chapter 3**).[600]

Treatable traits

To address the heterogeneity and complexity of COPD in clinical practice, a strategy based on so-called 'treatable traits' has been proposed.[601] Treatable traits can be identified based on phenotypic recognition and/or on deep understanding of critical causal pathways (endotypes) through validated biomarkers (e.g., high circulating eosinophil levels (a biomarker) identify patients with COPD who are at risk of exacerbations (a treatable trait) in whom treatment with ICS is most effective).[602] Treatable traits can co-exist in the same patient[345] and change with time (spontaneously or because of treatment). GOLD highlights the role of two key treatable traits (persistent dyspnea and exacerbations) in the follow-up algorithm of pharmacological (**Figure 3.9**) and non-pharmacological treatment (**Figure 3.16**) but there are many more pulmonary and extra-pulmonary traits, as well as behavioral/social risk factors, that merit individual attention and treatment if present.[345] These can be addressed with pulmonary rehabilitation (e.g., skeletal muscle dysfunction, respiratory muscle weakness, depression, anxiety, cognitive dysfunction, abnormalities in body composition).[603]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

CHAPTER 3: PREVENTION & MANAGEMENT OF COPD

KEY POINTS:

Risk reduction, lifestyle and patient education

- All individuals who smoke should be strongly encouraged and supported to quit. Nicotine replacement and pharmacotherapy reliably increase long-term smoking abstinence rates. Legislative smoking bans and counseling, delivered by healthcare professionals, improve quit rates. There is no evidence to support the effectiveness and safety of e-cigarettes as a smoking cessation aid at present.
- People with COPD should receive all recommended vaccinations in line with the relevant local guidelines.
- COVID-19 vaccines are highly effective against SARS-CoV-2 infection and people with COPD should have the COVID-19 vaccination in line with local recommendations.
- Influenza, pneumococcal and RSV vaccines have been shown to decrease the incidence of lower respiratory tract infections.
- The immunization committees recommend Tdap vaccination (dTaP/dTPa; pertussis, tetanus and diptheria) for people with COPD who were not vaccinated in adolescence; and routine use of herpes zoster (shingles) vaccine.

Pharmacological maintenance treatment of COPD

- Initial pharmacological treatment of COPD should be individualized and guided by the severity of symptoms, risk of exacerbations, side-effects, comorbidities, drug availability and cost, and the patient's preference, and ability to use various drug delivery devices.
- Patients should be reviewed after a suitable interval (shorter in patients with more severe disease, and longer in patients with less severe disease) and reassessed for attainment of treatment goals and identification of any barriers for successful treatment.
- Inhaler technique and adherence need to be assessed regularly.

Non-pharmacological treatment of COPD

- Non-pharmacological treatment of COPD is complementary to pharmacological maintenance treatment and should form part of comprehensive management as it addresses lifestyle modifications, disease-specific self-management, and psychological interventions targeting daily symptoms, which cannot be resolved by medication alone.
- Pulmonary rehabilitation, including exercise training combined with disease-specific education, and interventions addressing other treatable traits, improves patient function (physical and mental), exercise capacity, symptoms, and quality of life across all grades of COPD severity. Physical activity coaching can be added for patients with low physical activity levels.
- LTOT should not be prescribed routinely for patients with stable COPD and resting or exercise-induced moderate desaturation, but it may improve survival in patients with severe resting chronic hypoxemia ($PaO_2 \leq 55$ mmHg or < 60 mmHg if there is *cor pulmonale* or secondary polycythemia).
- Long-term NIV may be of some use in a selected group of patients, particularly those with pronounced daytime hypercapnia and recent hospitalization.

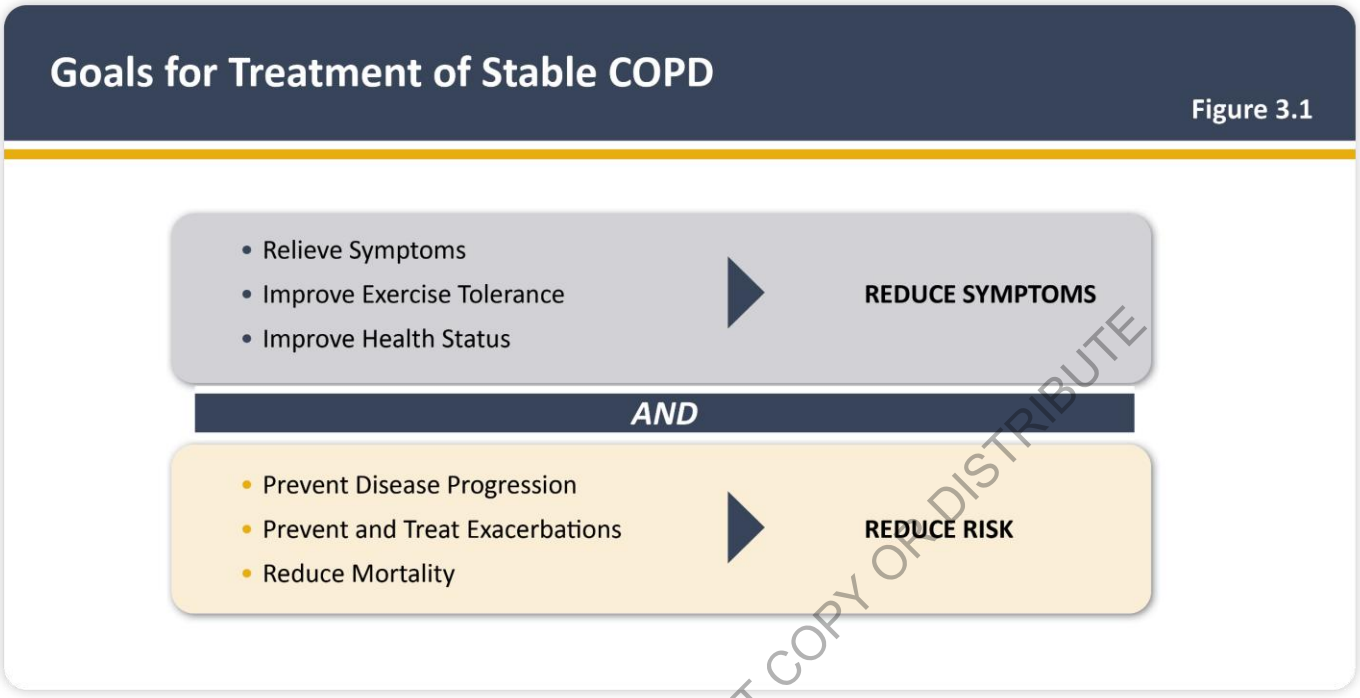
Palliative, interventional and surgical therapies

- In select patients with advanced emphysema refractory to optimized medical care, surgical or bronchoscopic interventional treatments may be beneficial.
- Palliative approaches are effective in controlling symptoms in advanced COPD.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

INTRODUCTION

The aim of COPD management is to reduce symptoms and future risk (**Figure 3.1**). Patients with COPD should have an assessment of the severity of their airflow obstruction, symptoms, history of exacerbations, exposure to risk factors and comorbidities (see **Chapter 2**) to guide management.



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Pharmacological and non-pharmacological therapy should be adjusted as necessary (see below) and further reviews undertaken (**Figure 3.2**). This chapter contains recommendations on how to manage patients with COPD in clinical practice and summarizes the evidence about the effectiveness and safety of maintenance and prevention strategies in COPD on which the recommendations are based.

Disease activity

In chronic inflammatory diseases, the term "disease activity" is often used to refer to biological pathways that (1) cause the pathological outcomes of the disease and (2) are potentially reversible (or controllable) with treatment. If left untreated or if treatment is ineffective, disease activity processes can lead to disease progression with permanent organ damage and dysfunction. Pharmacological treatment with anti-inflammatory drugs can reduce disease activity and therefore potentially prevent organ damage in COPD, while some non-pharmacological interventions (e.g., smoking cessation, pulmonary rehabilitation and volume reduction in hyperinflated emphysematous patients) can also reduce disease activity.

Assessing disease activity and its modulation by interventions generally requires the monitoring of biomarkers that are related to the reversible or modifiable biological processes. In COPD, there has been progress using biomarkers (blood eosinophil counts) to identify individuals with type 2 inflammation, but there is a need to identify and validate other biomarkers of disease activity. Clinical features such as exacerbations, chronic worsening of respiratory symptoms or disease progression (e.g. lung function decline that is greater than the anticipated normal age-related loss or progression of radiological evidence of emphysematous destruction) are all measurable indicators of disease activity.

Low disease activity is manifested clinically by having no exacerbations and no worsening of symptoms over a period of time accompanied by no accelerated loss of lung function. Achieving low disease activity is a treatment target in COPD with the aim to prevent any exacerbations over both the short and long term. GOLD recommends that a key

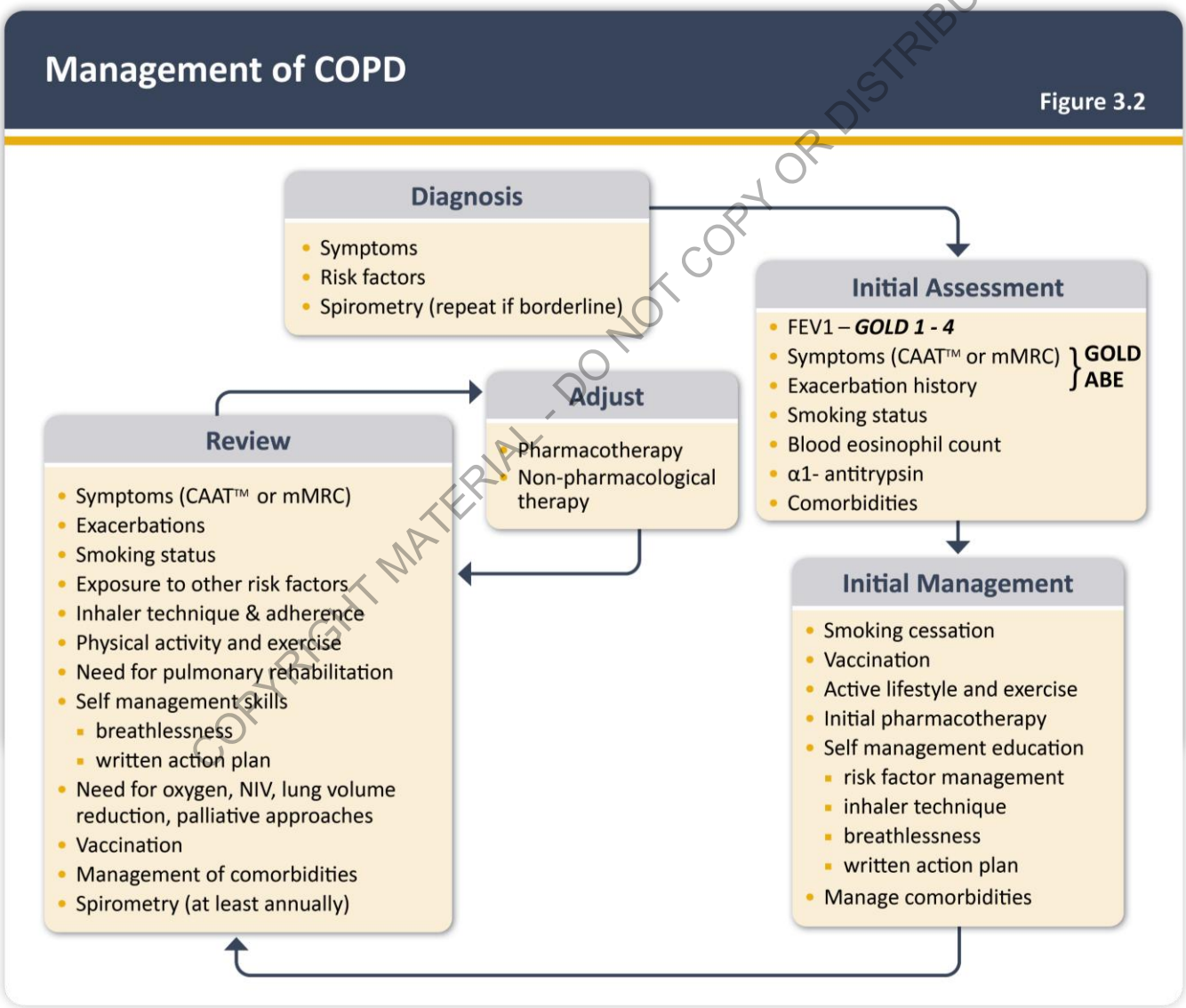
objective of COPD management should be to reduce disease activity with the aim that patients have:

- no exacerbations
- no worsening of symptoms
- no accelerated loss of lung function.

While reducing disease activity can prevent symptom worsening and may improve symptoms, additional interventions to further optimize symptom relief may be required. Two terms with similar, but importantly different definitions, have been proposed to describe the clinical state achieved when considering these outcomes over time:

- disease stability – a low disease activity state with no exacerbations, no worsening of symptoms and no accelerated loss of lung function[604]
- disease control – a state of low disease activity, defined by no exacerbations and no worsening of symptoms, plus low impact on the patient defined as symptoms below a threshold value.[605]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE



While aiming for control may appear more ambitious than stability, control is unachievable for individuals with extensive end-organ damage causing a high symptom burden. Although disease control may be more difficult to achieve in patients with later stage disease due to structural damage, improvements in disease activity may be achieved with combined pharmacological and non-pharmacological interventions.

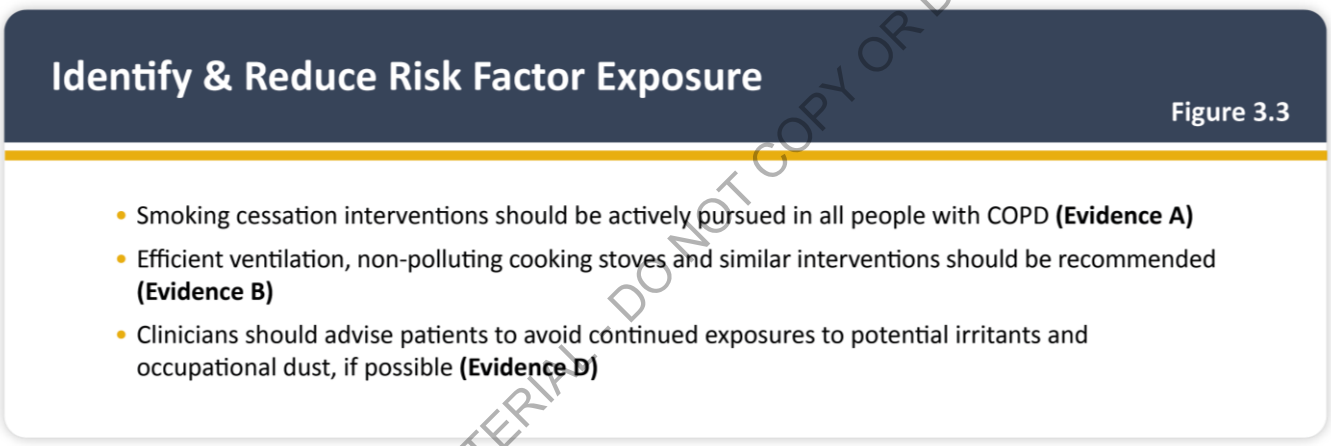
Late diagnosis of COPD contributes to a high symptom burden due to the severity of lung pathology with structural damage at the time of diagnosis. Targeting disease activity at earlier stages of the natural history of COPD has the potential to minimize disease progression and associated structural damage, thereby resulting in lower levels of symptoms and disability. This paradigm requires earlier diagnoses, disease activity evaluation using biomarkers and therapy that suppresses disease activity.

RISK REDUCTION, LIFESTYLE, AND PATIENT EDUCATION

Risk reduction

Identification and reduction of exposure to risk factors is important not only for the primary prevention of COPD but also as part of the management of a patient with COPD. Cigarette smoking is the most commonly encountered and easily identifiable risk factor for COPD, and smoking cessation should be continually encouraged for all individuals who smoke. Reduction of total personal exposure to occupational dusts, fumes, and gases, and to household and outdoor air pollutants, should also be addressed (**Figure 3.3**).

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE



Smoking cessation

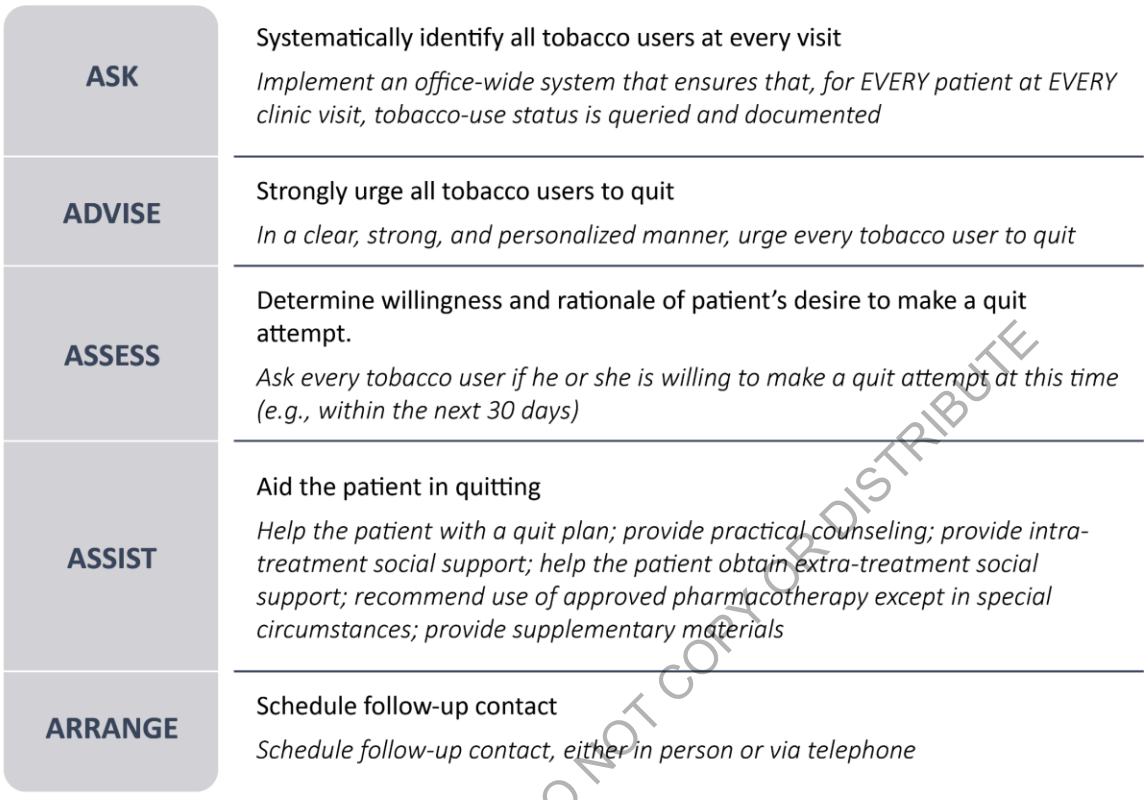
Smoking cessation is a key intervention for all patients with COPD who continue to smoke. Healthcare providers are pivotal in delivering smoking cessation messages and interventions and should encourage patients to quit at every available opportunity (**Figure 3.4**).

A significant proportion of people with COPD continue to smoke despite knowing they have the disease (approximately 40% of those with COPD are current smokers), and continued smoking has a negative impact on prognosis and progression of the disease.[606] Smoking cessation has the greatest capacity to influence the natural history of COPD, it also improves daily symptoms,[607] and decreases the frequency of exacerbations.[608]

For smokers with COPD, the quitting may be more challenging than for smokers without COPD due to greater nicotine dependence, lower self-efficacy and lower self-esteem.[609-611] In addition, it has been reported that depression is more common in smokers with COPD[612] and this could contribute to failed attempts to quit.[612,613] Despite these adverse conditions, if effective time and resources are dedicated to smoking cessation, long-term quit rates of 14% to 27% have been reported.[613]

Brief Strategies to Help the Patient Willing to Quit

Figure 3.4



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

As for all smokers, smoking cessation treatment for people with COPD should be adapted to the individual's needs and according to the level of tobacco dependence. There is evidence that a combination of counseling and pharmacotherapy is the most effective smoking cessation treatment for people with COPD.[613-615] The complexity of the smoking cessation process is largely determined by nicotine addiction. An accurate assessment of nicotine dependence should therefore be carried out for all patients. Some indicators of high nicotine dependence are: smoking within 30 min of waking up, smoking at night, consuming ≥ 20 cigarettes per day, a score of 7 to 10 on the Fagerström scale or 5 to 6 on the Heaviness of Smoking Index.[616,617]

In addition to individual approaches to smoking cessation, legislative smoking bans are effective in increasing quit rates and reducing harm from second-hand smoke exposure.[618]

Advice and counseling interventions

A five-step program for intervention (**Figure 3.4**)[619-621] provides a helpful strategic framework to guide healthcare providers interested in helping their patients stop smoking.[619,621,622] When possible, the patient should be referred to a comprehensive smoking cessation program that incorporates behavioral techniques that enhance patient motivation and confidence, patient education, and pharmacological and non-pharmacological interventions. Recommendations for treating tobacco use and dependence are summarized in **Figure 3.5**.[619] Because tobacco dependence is a chronic disease,[619,621] clinicians should recognize that relapse is common and reflects the chronic nature of dependence and addiction, and does not represent failure on the part of the patient or the clinician.

Treating Tobacco Use and Dependence

Figure 3.5

Major Findings & Recommendations from the Tobacco Use & Dependence Clinical Practice Guideline Panel:

- Tobacco dependence is a chronic condition that warrants repeated treatment until long-term or permanent abstinence is achieved
- Effective treatments for tobacco dependence exist and all tobacco users should be offered these treatments
- Clinicians and health care delivery systems must operationalize the consistent identification, documentation, and treatment of every tobacco user at every visit
- Brief smoking cessation counseling is effective and every tobacco user should be offered such advice at every contact with health care providers
- There is a strong dose-response relation between the intensity of tobacco dependence counseling and its effectiveness
- Three types of counseling have been found to be especially effective: practical counseling, social support of family and friends as part of treatment, and social support arranged outside of treatment
- First-line pharmacotherapies for tobacco dependence — varenicline, nortriptyline, bupropion sustained release, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch— are effective and at least one of these medications should be prescribed in the absence of contraindications
- Financial incentive programs for smoking cessation may facilitate smoking cessation
- Tobacco dependence treatments are cost effective interventions

Reference: The Tobacco Use and Dependence Clinical Practice Guideline Panel. *JAMA* 2000; **283**(24): 3244-54

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Counseling delivered by physicians and other health professionals significantly increases quit rates over self-initiated strategies.[623] Even brief (3-minute) periods of counseling urging a smoker to quit improve smoking cessation rates.[623]

In patients with COPD a network meta-analysis showed a trend for smoking cessation counseling alone to be superior than usual care.[624] Another study reported a continuous one-year abstinence rate of 1.4% for usual care, 2.6% for minimal counseling (< 90 min), 6% for intensive counseling (≥ 90 min), and 12.3% for intensive counseling plus pharmacotherapy.[614] However, controversy remains as to whether more intensive individual counseling is more effective when combined with pharmacotherapy.[624]

Household and outdoor air pollution

Reducing exposure to household and outdoor air pollution requires a combination of public policy, local and national resources, cultural changes, and protective steps taken by individual patients. Reduction of exposure to smoke from biomass fuel is a crucial goal to reduce the prevalence of COPD worldwide. Efficient ventilation, non-polluting cooking stoves and similar interventions are feasible and should be recommended.[14,15]

Occupational exposures

There are no studies that demonstrate whether interventions that reduce occupational exposure also reduce the burden of COPD, but it seems logical to advise patients to avoid ongoing exposures to potential irritants e.g., dusts, fumes and gases, if possible.

Climate change and COPD

Climate change has increased the frequency, intensity and geographic distribution of extreme weather events such as heatwaves, severe winter conditions, floods, droughts, hurricanes, thunderstorms, wildfires and dust storms. Excess deaths have been reported during heatwaves in all regions of the world,[625-631] and during periods of cold weather.[632-635] Epidemiological studies confirm the association between exposure to extreme, but not moderate, heat and mortality,[636-638] with the mortality impact of extreme high temperatures increasing with the length of the heat episode.[639] Temperature thresholds for given health impacts are unique to particular locations, with greater effects of heat in large cities and colder regions where extreme temperatures were not previously common, and greater effects of falls in temperature in warmer regions that were unused to cold.[632,638] The effects of heat also vary with levels of atmospheric humidity and air pollution.[626,640,641]

Population studies have consistently found that people with COPD are at increased risk of death as a consequence of exposure to both heat and cold,[642-644] with cold leading to a greater risk than heat.[645,646] As well as the effects on mortality, higher outdoor temperatures are associated with an increased risk of hospitalization for COPD[644,647-649] and lower outdoor temperatures are associated with an increased risk of exacerbations.[650]

Most studies have examined the effect of outdoor air temperature on mortality and morbidity in COPD; however, many patients, particularly those with more severe disease, spend much of their time indoors. Indoor temperature and humidity vary significantly between dwellings despite similar outdoor conditions, and are influenced by the building type, insulation, presence of heating, sun shades and ventilation, socioeconomic factors including the ability to afford heating, and behavioral factors such as cooking and bathing.[651-653] Indoor temperatures are often higher than outdoor including during heatwaves,[654,655] and high indoor humidity can exacerbate the adverse effects of heat by impeding natural evaporative cooling. Lower indoor temperatures during cold periods are found in older properties, in those lacking heating systems and those that are expensive to heat.[656] Even if heating is available, patients with COPD may not heat their bedrooms at night and may keep windows open overnight even in winter.[657,658]

Studies of the relationship between temperature, symptoms and lung function in COPD at an individual patient level have shown higher outdoor temperature is associated with increased dyspnea[659] particularly on days that patients go outside.[660] Higher indoor temperatures are associated with increased symptoms and SABA use[660] and colder indoor and outdoor temperatures are also associated with increased cough and sputum, increased SABA use and a fall in FEV1.[657,659-661] Over an autumn, winter and spring period (with average minimum outdoor temperature of 2.9°C and maximum of 10.1°C) health status was better in patients with at least 9 hours of indoor temperature ≥ 21°C.[662]

Weather also has a significant impact on air quality. Ozone levels strongly correlate with temperature, as its generation depends on high temperatures and sunlight,[663] and the generation and dispersion of air pollutants may be influenced by local patterns of wind, solar radiation and precipitation, especially in urban areas.[664] Some studies have shown synergistic effects between heat and air pollution exposure on all-cause mortality, and hospital admissions in general populations;[644,665,666] however, there are also studies showing no interaction.[667,668] A synergistic effect of low temperatures and ozone concentrations on the general population has also been found in some countries (e.g., China and Hong Kong)[669,670] but not in others.[642,665] Although not widely studied, there is conflicting evidence regarding the interactive effects of outdoor heat and pollution on respiratory outcomes.[644,671,672] Several studies have looked at the interactive effects of pollution and temperature in people with COPD. There appears to be a greater effect of pollutants on COPD hospital admissions and emergency visits at low temperatures or during winter.[673-676] Outdoor air pollutants,

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

including PM2.5, NO_2, and ozone do not appear to worsen the effect of outdoor temperature on symptoms,[677] but the detrimental effect of higher indoor temperatures on symptoms appears to be potentiated by higher indoor concentrations of PM2.5 and NO_2.[677] The conflicting findings regarding interactions between temperature and pollutants on symptoms and exacerbations in people with COPD may, in part, reflect differences in behaviors that affect exposure, such as avoiding going out, opening windows and using air conditioning.

The mechanisms by which heat exposure and cold adversely impact COPD are not well understood. However, on the basis of the evidence showing a relationship between high and low temperatures and morbidity and mortality, patients with COPD living in temperate and colder climates should, in line with WHO recommendations,[678] ensure they keep bedroom temperatures above 18°C during cold weather. During heatwaves and periods of high temperature patients should ensure they keep adequately hydrated, keep out of the heat and try to keep living spaces < 32°C and sleeping spaces < 24°C as recommended by WHO.[679] Prior identification and management of cardiovascular comorbidities is also important to reduce adverse outcomes.

There are significant differences in the carbon footprint of inhaler devices reflecting whether they contain a propellant gas, what they are made from, how they are manufactured and transported, and whether they can be reused or recycled. Selection and correct use and disposal of inhalers by patients can have important implications for global warming and climate change. There were no safety concerns with budesonide/glycopyrronium/formoterol fumarate delivered from a pMDI with the new propellant hydrofluoroolefin-1234ze (HFO-1234ze) which has near zero global warming potential, compared with HFA-134a.[680] The safety, tolerability and pharmacokinetics of combined beclometasone dipropionate/formoterol fumarate, and of beclometasone dipropionate/formoterol fumarate/ glycopyrronium, delivered by a pMDI containing the new propellant HFA-152a were similar to those of the pMDI containing HFA-134a.[681,682]

Models of care should consider the environmental impact of healthcare facilities and the need for patients to travel.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Vaccinations

People with COPD should receive all recommended vaccinations in line with the relevant local guidelines (**Figure 3.6**).

Influenza vaccine

Routine annual influenza vaccination is recommended for all people aged ≥ 6 months who do not have contraindications, and should be prioritized in individuals with chronic conditions like COPD.[683] Influenza vaccination can reduce serious illness (such as lower respiratory tract infections requiring hospitalization),[684] stroke,[685] and death in people with COPD.[686-689] Only a few studies have evaluated exacerbations; they have shown a significant reduction in the total number of exacerbations per vaccinated subject compared with those who received placebo.[686] Vaccines containing either killed or live inactivated viruses are recommended[690] as they are more effective in elderly people with COPD.[691] The FDA approved the first mRNA seasonal influenza vaccine (mFLUSIVA®) in August 2026.[692] The CDC recommends high-dose inactivated (HD-IIV3) and adjuvanted inactivated (aIIV3) influenza vaccines as acceptable options for influenza vaccination in older adults.[683] Findings from a population-based study suggested that people with COPD, particularly the elderly, had decreased risk of ischemic heart disease when they were vaccinated with influenza vaccine over many years.[693] Influenza vaccination during a hospital admission in patients with acute heart failure can improve their survival and reduce likelihood of readmission to hospital over the subsequent 12 months.[694] The occurrence of adverse reactions is generally mild and transient.

Pneumococcal vaccines

Pneumococcal vaccinations, pneumococcal conjugated vaccine (PCV21, PCV20, PCV15 or PCV13) and pneumococcal polysaccharide vaccine (PPSV23), are indicated for all adults aged ≥ 50 years, and adults aged 19-49 years with an underlying medical condition such as chronic lung disease (including COPD, emphysema, cystic fibrosis, and asthma)

or solid organ transplant etc.[695] The PCV21[695] covers 11 unique serotypes not included in PCV20; notably many cases of adult disease are caused by subtypes not covered by other FDA-approved pneumococcal vaccines.[696] Pneumococcal vaccination is universally recommended for adults in these age groups, if they have never received a pneumococcal conjugate vaccine previously, or if their previous pneumococcal vaccination history is unknown. The current recommendation is PCV13 or PCV15 followed by PPSV23 or one-dose PCV20,[697] or one-dose PCV21[695] in adults who have an indication for the vaccine (**Figure 3.6**).[697,698] We recommend the use of PCV20 or PCV21 in patients with COPD.

Vaccination for People with COPD

Figure 3.6

People with COPD should receive all recommended vaccinations in line with the relevant local guidelines:

- Yearly influenza vaccination **(Evidence B)**
- SARS-CoV-2 (COVID-19) vaccination based on WHO and CDC updated recommendations **(Evidence B)**
- We recommend either one dose of 21-valent pneumococcal conjugate vaccine (PCV21) or one dose of PCV20 **(Evidence B)**. Pneumococcal vaccination has been shown to reduce the incidence of community-acquired pneumonia and exacerbations for people with COPD **(Evidence B)**
- Respiratory syncytial virus (RSV) vaccination for individuals aged ≥ 50 years and/or with chronic heart or lung disease, as recommended by the CDC **(Evidence A)**
- Tdap (dTaP/dTPa) vaccination to protect against pertussis (whooping cough), in addition to tetanus and diphtheria, for people with COPD that were not vaccinated in adolescence, as recommended by the CDC **(Evidence B)**
- Zoster vaccine to protect against herpes zoster (shingles) for people with COPD aged > 50 years, as recommended by the CDC **(Evidence B)**

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Specific data on the effects of PPSV and PCV in people with COPD are limited.[699] A systematic review of injectable vaccines in patients with COPD identified twelve randomized studies for inclusion and observed injectable polyvalent pneumococcal vaccination provides significant protection against community-acquired pneumonia, although there was no evidence that vaccination reduced the risk of confirmed pneumococcal pneumonia, which was a relatively rare event. Vaccination reduced the likelihood of an exacerbation, and moderate-quality evidence suggested the benefits of pneumococcal vaccination in patients with COPD. Evidence was insufficient for comparison of different pneumococcal vaccine types.[700] PPSV23 has been shown to reduce the incidence of community-acquired pneumonia in patients with COPD who are < 65 years, with an FEV1 < 40% predicted, or have comorbidities (especially cardiac comorbidities).[701] The PCV13 has been shown to exhibit at least the same or greater immunogenicity than the PPSV23 up to 2 years after vaccination in patients with COPD.[702] In a large RCT PCV13 demonstrated significant efficacy for the prevention of vaccine-type community-acquired pneumonia (45.6%) and vaccine-type invasive pneumococcal disease (75%) among adults ≥ 65 years and the efficacy persisted for at least 4 years.[703] PCV20 covers up to 58% of those strains, while PCV21 covers up to 84% of strains responsible for invasive disease in adults.[696,698]

A study that compared the effectiveness of PPSV23 and PCV13 in patients with COPD over a 5-year follow-up cohort study found that although both vaccines have comparable clinical effects during the first year after vaccination, PCV13 showed persistent clinical effectiveness during the 5-year follow-up period. Pneumonia by year 5 after vaccination was registered in 47% of patients in the PPSV23 group, versus 3.3% of patients in the PCV13 group ($p < 0.001$). Similar effects were shown in the reduction of exacerbations.[704]

Pneumococcal vaccine can be co-administered with influenza vaccine in an adult immunization program, as concomitant administration (PCV15 or PPSV23 and QIV [Fluarix], PCV20 and adjuvanted QIV [Fluad]) has been demonstrated to be immunogenic and safe.[705]

Respiratory syncytial virus vaccine

The CDC estimates that every year, RSV causes approximately 60,000-160,000 hospitalizations and 6,000-10,000 deaths among older adults in the US.[706,707] RSV infection in adults may have a significant impact not only in the respiratory system but also on other organs. In a cross-sectional study over five RSV seasons, nearly one-quarter of hospitalized adults aged ≥ 60 years with RSV infection experienced an acute cardiac event (most frequently acute heart failure), including one in 12 adults (8.5%) with no documented underlying CVD.[708] In a report from the UK, RSV was associated with 8.7% of outpatient managed exacerbations.[709]

The Advisory Committee on Immunization Practices and the European Commission recommend use of RSV bivalent prefusion F protein-based vaccine,[710] adjuvanted prefusion F protein vaccine,[711] and mRNA RSV based vaccine in adults aged ≥ 50 years.[712] For adults aged ≥75 years, the vaccination is universally recommended for those who have not been previously vaccinated. For adults aged 50-74 years, vaccination is recommended if they have a risk factor or other indication that increases their risk for severe RSV disease such as chronic heart or lung disease, immune compromise, or living in a nursing home or long-term care facility.[697] Follow-up demonstrated that one dose of adjuvanted prefusion F protein-based vaccine was efficacious in preventing RSV-related disease in participants aged ≥ 60 years during three full RSV seasons.[713,714] In other studies RSV vaccination reduced the likelihood of RSV-associated hospitalization.[715,716] The safety of RSV vaccinations has been demonstrated in a CDC publication.[717] RSV vaccines can be co-administered with other adult vaccines during the same visit.[718]

Other vaccines

Patients with COPD are at increased risk of pertussis (whooping cough).[719] As such, in adults with COPD the CDC recommends the Tdap vaccination (also called dTaP/dTPa) to protect against pertussis, in addition to tetanus and diphtheria, in those who were not vaccinated in adolescence.[697] Adults with COPD have an increased risk of herpes zoster (shingles) and associated complications, with higher risks in those on corticosteroids. Routine herpes zoster vaccination is recommended.[720]

People with COPD should have the COVID-19 vaccinations in line with national recommendations.[697,721] COVID-19 vaccines are highly effective against SARS-CoV-2 infection requiring hospitalization, ICU admission, or an ED or urgent care clinic visit, including those with chronic respiratory disease.[205,722,723] Recently the EMA approved the first combination influenza and COVID-19 mRNA vaccine, giving protection against both respiratory viruses in a single shot (mCOMBRIAX®).[724]

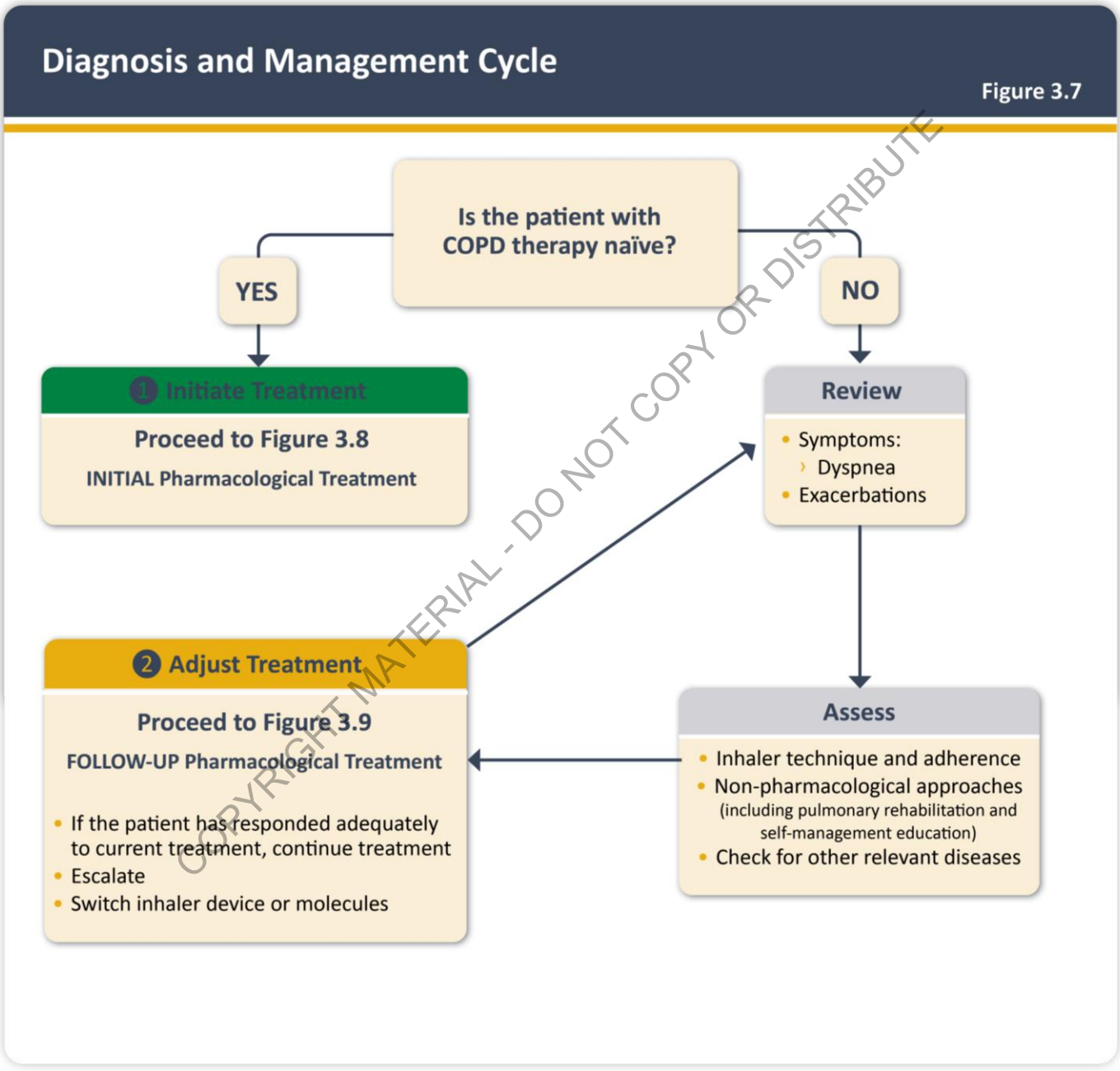
COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

PHARMACOLOGICAL MAINTENANCE TREATMENT OF COPD

We propose a tailored approach to initiate treatment based on the level of symptoms and risk for exacerbations. Treatment can be escalated based on the presence of the predominant symptoms (treatable traits) of breathlessness and exercise limitation, and the continued occurrence of exacerbations whilst on maintenance therapy. Studies comparing LABA+ICS versus LABA or triple inhaled therapy (LABA+LAMA+ICS) versus either LABA+ICS or LABA+LAMA, confirmed a significant decrease in exacerbation rate with the addition of an ICS in patients who experienced one moderate or severe exacerbation in the prior year. This recommendation is derived from evidence generated by RCTs. Observational and interventional studies suggest that one moderate or severe exacerbation increases the risk of

subsequent events; this risk is further increased if there are more frequent or severe events.[502,515,725,726] Our therapeutic recommendations are intended to support clinician decision-making; they also incorporate expert advice based on clinical experience.

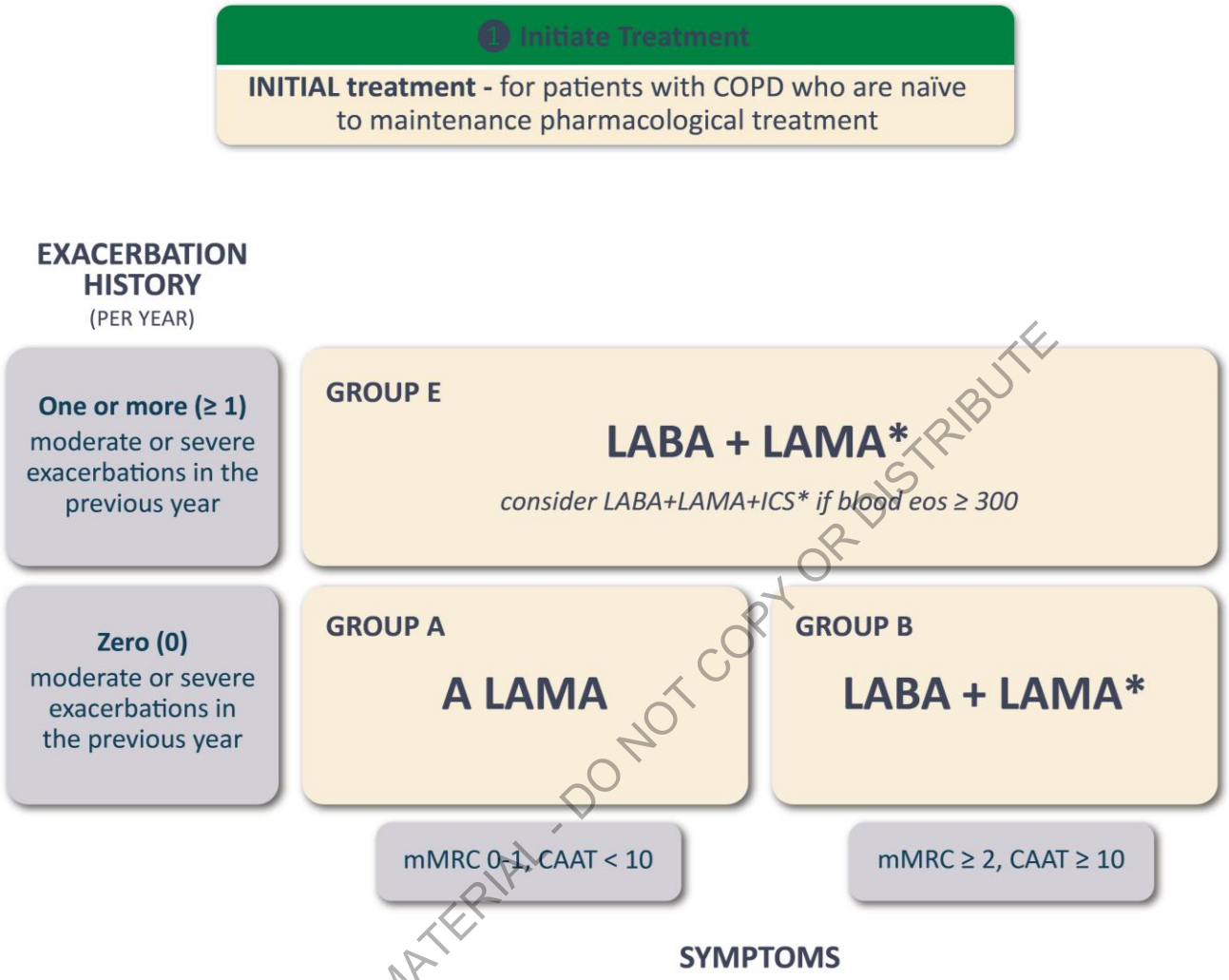
Figure 3.7 gives an overview of the diagnosis and management cycle. **Initial pharmacotherapy** should be based on the patient's GOLD group (**Figure 3.8**). Patients should be offered guidance and follow-up on self-management of breathlessness, and stress management, and be given a written action plan. Comorbidities should be managed as per specific guidelines, irrespective of the presence of COPD (**Chapter 5**). **Follow-up pharmacotherapy** should be based on the patient's symptoms (dyspnea or exacerbations) at review (**Figure 3.9**).



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Initial Pharmacological Treatment

Figure 3.8



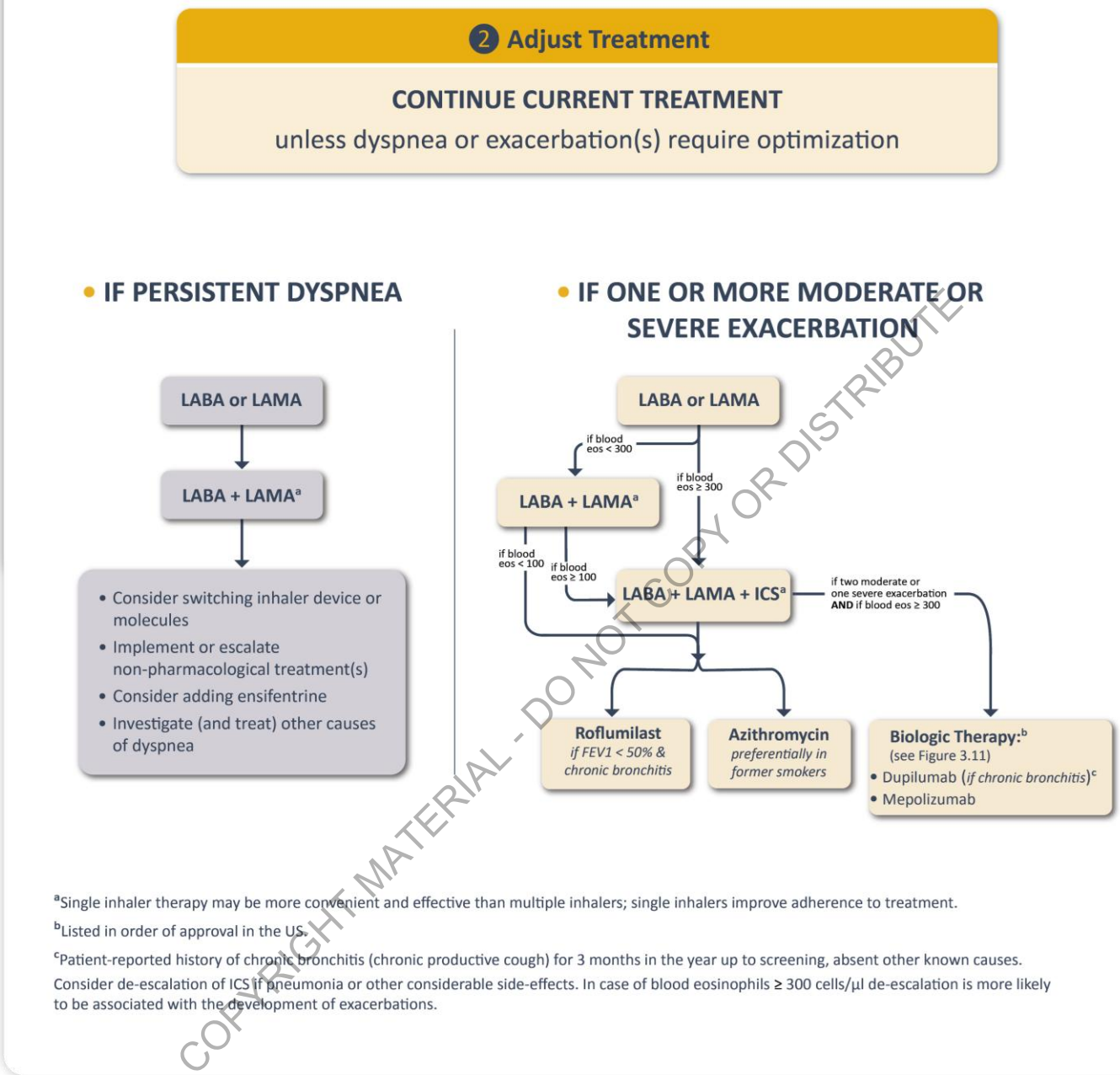
*Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment.

Exacerbations refers to the number of exacerbations per year; eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAAT™: Chronic Airways Assessment Test™.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Follow-up Pharmacological Treatment

Figure 3.9



[a]Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment.

[b]Listed in order of approval in the US.

[c]Patient-reported history of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening, absent other known causes.

Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eosinophils ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Patients should be reviewed after a suitable interval (shorter in patients with more severe disease, and longer in patients with less severe disease) and their current level of symptoms (using either the CAAT™ or mMRC scores) and exacerbation frequency assessed. The effect of treatment and possible adverse effects should be evaluated, and comorbidities reassessed.

Inhaler technique, adherence to prescribed therapy (both pharmacological and non-pharmacological), smoking status and continued exposure to risk factors should be regularly checked. Physical activity should be encouraged and referral for pulmonary rehabilitation considered in severe patients. The need for oxygen therapy, non-invasive ventilatory support, lung volume reduction and palliative approaches should be considered individually, and the action plan should be updated accordingly. Spirometry should be repeated at least annually. If the patient is already receiving bronchodilator treatment, the latter should not be interrupted for performing spirometry.

We no longer refer to asthma and COPD overlap, instead we emphasize that asthma and COPD are different disorders, although they may share some common treatable traits and clinical features (e.g., eosinophilia, some degree of reversibility). Asthma and COPD may coexist in an individual patient. If a concurrent diagnosis of asthma is suspected, pharmacotherapy should primarily follow asthma guidelines.

Algorithms for initial and follow-up pharmacological treatment

Further information on the evidence that underpins these recommendations is given later in **Appendix 5 "Overview of the evidence: Pharmacotherapy"**.

Initial pharmacological management

A proposal for the **INITIATION** of pharmacological management of COPD according to the individualized assessment of symptoms and exacerbation risk following the ABE scheme, and also accounting for blood eosinophil count, is shown in **Figure 3.8**. It is an attempt to provide clinical guidance. There is no high-quality evidence such as RCTs to support initial pharmacological treatment strategies in newly diagnosed individuals with COPD.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Group A

► All patients in group A should be offered initial treatment with a LAMA based on its effect on breathlessness in patients with GOLD stage 1 or 2 airflow obstruction. If LAMAs are unavailable and/or unaffordable then a short-acting bronchodilator may be substituted instead.[727]

► This should be continued if benefit is documented.

Group B

► Treatment should be initiated with a LABA+LAMA combination. It has been shown in a RCT that in patients with ≤ 1 moderate exacerbation in the year before the study and a CAAT™ ≥ 10 LABA+LAMA is superior to a LAMA with regard to several endpoints.[728] Therefore, providing there are no issues regarding availability, cost and side-effects LABA+LAMA is the recommended initial pharmacological choice.

► If a LABA+LAMA combination is not considered appropriate, there is no evidence to recommend one class of long-acting bronchodilators over another (LABA or LAMA) for initial relief of symptoms in this group of patients. In the individual patient, the choice should depend on the patient's perception of symptom relief.

► Patients in group B are likely to have comorbidities that may add to their symptomatology and impact their prognosis, and these possibilities should be investigated and treated, if present, by following national and international guidelines.[729,730]

Group E

► A Cochrane systematic review and network meta-analysis comparing dual combination therapy versus mono long-acting bronchodilators showed that the LABA+LAMA combination was the highest ranked treatment group to reduce exacerbations.[731] Therefore, provided there are no issues regarding availability, cost and side-effects LABA+LAMA is the preferred choice for initial therapy of patients in group E.

► Use of LABA+ICS in COPD is not encouraged. If there is an indication for an ICS, then LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice.[502,515]

► Consider LABA+LAMA+ICS as initial therapy in group E if blood eosinophil counts are ≥ 300 cells/µL (practical recommendation). As detailed later in this chapter, the effect of ICS on exacerbation prevention is correlated to blood eosinophil count (**Figure 3.10**). There are no direct data in the literature concerning initiation of triple therapy in newly

diagnosed patients. However, we think available studies performed mostly in treated patients provide a rationale for considering this treatment option as initial therapy for patients with a high eosinophil count (≥ 300 cells/µL).

► If patients with COPD have concomitant asthma they should be treated like patients with asthma. Under these circumstances the use of an ICS is mandatory.

Rescue short-acting bronchodilators should be prescribed to all patients for immediate symptom relief.

Follow-up pharmacological management

Following implementation of therapy, patients should be reassessed for attainment of treatment goals and identification of any barriers for successful treatment (**Figure 3.7**). Following review of the patient's response to treatment initiation, adjustments may be needed.

This is guided by the principles of first ***review*** and ***assess***, then ***adjust*** if necessary (**Figure 3.7**):

► **Review**
- Review symptoms (dyspnea) and exacerbation risk (previous history, blood eosinophils).

► **Assess**
- Assess inhaler technique and adherence, and the role of non-pharmacological approaches (covered later in this chapter).

► **Adjust**
- Adjust pharmacological treatment, including escalation or de-escalation. Switching inhaler device or molecules within the same class (e.g., using a different long-acting bronchodilator) may be considered as appropriate. Any change in treatment requires a subsequent ***review*** of the clinical response, including side effects.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

A separate algorithm is provided for **FOLLOW-UP** treatment, where the management is based on two key treatable traits: persistence of dyspnea and occurrence of exacerbations (**Figure 3.9**).[488,732-734] These follow-up recommendations are designed to facilitate management of patients taking maintenance treatment(s), whether early after initial treatment or after years of follow-up. These recommendations incorporate the evidence from clinical trials and the use of peripheral blood eosinophil counts as a biomarker to guide the use of ICS therapy for exacerbation prevention (see more detailed information regarding blood eosinophil counts as a predictor of ICS effects in **Appendix 5**).

Figure 3.9 presents suggested escalation and de-escalation strategies based on available efficacy and safety data. The response to treatment escalation should always be reviewed. Patients in whom treatment modification is considered, in particular de-escalation, should be under close medical supervision. We are fully aware that treatment escalation has not been systematically tested; trials of de-escalation are also limited and only include ICS. This follow-up pharmacological treatment algorithm (**Figure 3.9**) can be applied to any patient who is already taking maintenance treatment(s) **irrespective of the GOLD group allocated at treatment initiation**. If response to initial treatment is appropriate, maintain it. If not:

- Check adherence, inhaler technique and possible interfering comorbidities.
- The need to primarily target dyspnea/activity limitation or to prevent further exacerbations should be evaluated in each patient. Consider the predominant treatable trait to target (dyspnea or exacerbations).
  - Use the exacerbation pathway if both exacerbations and dyspnea need to be targeted.
- If a change in treatment is considered necessary, then select the corresponding algorithm for dyspnea (**Figure 3.9** left column) or exacerbations (**Figure 3.9** right column)

- Identify which box corresponds to the patient's current treatment and follow the suggested algorithm.

Dyspnea

► For patients with persistent breathlessness or exercise limitation on ***bronchodilator*** monotherapy,[735] the use of a LABA plus a LAMA is recommended.

► If the addition of a second long-acting bronchodilator does not improve symptoms, we suggest:

- Considering switching inhaler device or molecules.
- Implementing or escalating non-pharmacological treatment(s) e.g., pulmonary rehabilitation.
- Considering adding ensifentrine if available.

► At all stages, dyspnea due to other causes (not COPD) should be investigated and treated appropriately. Inhaler technique and adherence should be considered as causes of inadequate treatment response. Rehabilitation should also be considered.

Exacerbations

► For patients who have an exacerbation on ***bronchodilator*** monotherapy, escalation to LABA+LAMA is recommended.

► In patients who have a moderate or severe exacerbation on **LABA+LAMA** therapy we suggest escalation to **LABA+LAMA+ICS** (**Figure 3.10**). A beneficial response after the addition of ICS may be observed at blood eosinophil counts ≥ 100 cells/µL, with a greater magnitude of response more likely with higher eosinophil counts.[502]

► If patients treated with **LABA+LAMA** still have exacerbations and ICS are not indicated because the eosinophil count is < 100 cells/µL, the following options may be considered:

- Among those who are not currently smoking, consider adding azithromycin.[736,737] Consideration to the development of resistant organisms should be factored into decision-making.
- Among those with FEV1 < 50%, symptoms of chronic bronchitis and history of a prior severe exacerbation, consider adding roflumilast.[738-740]

► If patients treated with **LABA+LAMA+ICS** still have exacerbations the following options may be considered:

- Among patients with blood eosinophils ≥ 300 cells/µL, consider adding dupilumab (if chronic bronchitis) or mepolizumab (with and without chronic bronchitis) (**Figure 3.11**).[732,733,741,742]
- Among those who are not currently smoking, consider adding azithromycin.[736,737] Consideration to the development of resistant organisms should be factored into decision-making.
- Among those with FEV1 < 50%, symptoms of chronic bronchitis and history of prior severe exacerbation, consider adding roflumilast.[738-740]

► Patients treated with **LABA+LAMA+ICS** should not have the ICS component withdrawn unless the ICS was started inappropriately, there has been no response to ICS or they experience significant side-effects or severe or recurrent pneumonia. The risks and benefits of discontinuing ICS should be considered. If blood eosinophils are ≥ 300 cells/µL de-escalation is more likely to be associated with the development of exacerbations.[743,744]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Factors to Consider when Initiating ICS Treatment

Figure 3.10

Factors to consider when adding ICS to long-acting bronchodilators:

(note the scenario is different when considering ICS withdrawal)

STRONGLY FAVORS USE	History of hospitalization(s) for exacerbations of COPD[#]
	≥ 2 moderate exacerbations of COPD per year[#]
	Blood eosinophils ≥ 300 cells/μL
	History of, or concomitant asthma
FAVORS USE	1 moderate exacerbation of COPD per year[#]
	Blood eosinophils 100 to < 300 cells/μL
AGAINST USE	Repeated pneumonia events
	Blood eosinophils < 100 cells/μL
	History of mycobacterial infection

[#]despite appropriate long-acting bronchodilator maintenance therapy (see Figures 3.8 & A5.1 for recommendations); *note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

Adapted from & reproduced with permission of the © ERS 2019: *European Respiratory Journal 52 (6) 1801219; DOI: 10.1183/13993003.01219-2018 Published 13 December 2018*

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Evidence Supporting Use of Biologics Registered for the Treatment of COPD

Figure 3.11

Molecule/RCT*	Key inclusion criteria[a]	Annualized rate of moderate/severe exacerbations	Lung function improvement (pre-BD FEV1)[d]	Quality of life improvement (SGRQ)
Dupilumab (300 mg/2 weeks)				
BOREAS[1] (n=939)	FEV1 post-BD 30-70% chronic bronchitis[b] eos ≥ 300 (screen)	RR 0.70; P < 0.001 (95% CI: 0.58, 0.86)	83mL; P < 0.001 (95% CI: 42, 125)	-3.4; P = 0.002 (95% CI: -5.5, -1.3)
NOTUS[2] (n=935)	FEV1 post-BD 30-70% chronic bronchitis[b] eos ≥ 300 (screen)	RR 0.66; P < 0.001 (95% CI: 0.54, 0.82)	62mL; P = 0.02 (95% CI: 11, 113)	-3.4[e] (95% CI: -5.8, -0.9)
Mepolizumab (100 mg/4 weeks)				
METREO[3] (n=674)	FEV1 post-BD 20-80% eos ≥ 150 (screen) or eos ≥ 300 (previous year)	RR 0.80 (100 mg); NS RR 0.86 (300 mg); NS	19mL; NS (95% CI: -29, 67)	-1.8; NS (95% CI: -4.5, 0.8)
METREX[3] (n=836)	FEV1 post-BD 20-80% eos ≥ 150 (screen) or eos ≥ 300 (previous year)[c]	RR 0.82; P = 0.04 (95% CI: 0.68, 0.98)	-10mL; NS (95% CI: -54, 33)	0.2; NS (95% CI: -2.8, 3.2)
MATINEE[4] (n=804)	FEV1 post-BD 20-80% eos ≥ 300 (screen) and eos ≥ 150 (previous year)	RR 0.79; P = 0.01 (95% CI: 0.66, 0.94)	-9.0mL; NS (95% CI: -60.1, 42.1)	-2.3; NS (95% CI: -4.6, 0.1)

*Molecules are listed in order of approval in the US.

These results cannot be directly compared across trials as there were different patient populations included.

a: all studies recruited patients with exacerbations in the previous year while receiving inhaled triple therapy
b: patient-reported history of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening, absent other known causes
c: pre-defined eosinophilic population
d: at 52 weeks
e: significance not tested according to hierarchical testing procedure

NS: not statistically significant; eos: blood eosinophils (cells/μL); SGRQ: St George's Respiratory Questionnaire; BD: bronchodilator; RR: risk ratio.

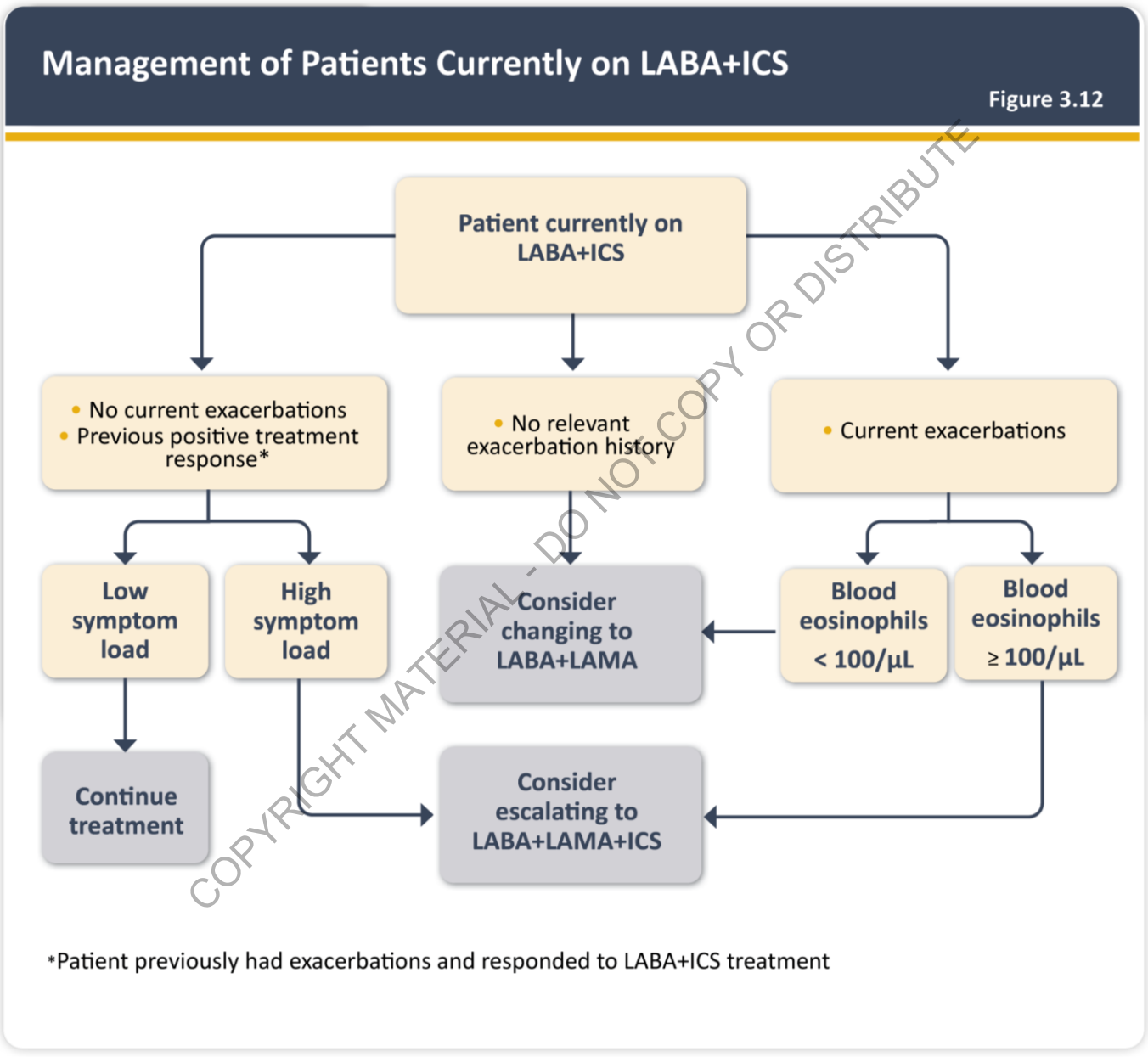
References: [1]Bhatt et al. N Engl J Med 2023;389:205-214; [2]Bhatt et al. N Engl J Med 2024;390:2274-2283; [3]Pavord et al. N Engl J Med 2017;377:1613-1629; [4]Sciurba et al. N Engl J Med 2025;392:1710-1720; .

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

Patients on treatment with LABA+ICS

► If a patient with COPD and **no features of asthma** has been treated – for whatever reason – with LABA+ICS and is well controlled in terms of symptoms and exacerbations, continuation with LABA+ICS is an option (**Figure 3.12**). However, if the patient has:

- **Further exacerbations:** treatment should be escalated to LABA+LAMA+ICS if the blood eosinophil count is ≥ 100 cells/µL or switched to LABA+LAMA if it is < 100 cells/µL.[502,745]
- **Major symptoms:** change to LABA+LAMA or LABA+LAMA+ICS depending on previous treatment response to ICS (**Figure 3.12**).[746]



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Managing inhaled therapy

Most of the drugs used to treat COPD are inhaled. Thus, appropriate use of inhaler devices is crucial to optimize the benefit-risk ratio of inhaled therapy. Achieving this goal requires choosing the appropriate device, providing education, checking inhaler use regularly and, whenever necessary, adapting education and device (**Figure 3.13**).

Key Points for Inhalation of Drugs

Figure 3.13

- When a treatment is given by the inhaled route, the importance of education and training in inhaler device technique cannot be over-emphasized
- The choice of inhaler device has to be individually tailored and will depend on access, cost, prescriber, and most importantly, patient's ability and preference
- It is essential to provide instructions and to demonstrate the proper inhalation technique when prescribing a device, to ensure that inhaler technique is adequate and to re-check at each visit that patients continue to use their inhaler correctly
- Inhaler technique (and adherence to therapy) should be assessed before concluding that the current therapy is insufficient

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

There are currently more than 30 different inhaled therapies containing different bronchodilators (both short- and long-acting) and ICS alone or in combinations (**Figure A3.1**). In addition, more than 20 different inhaler devices are available,[747] including nebulizers, pMDIs used with or without VHC/spacers, BAIs, SMIs, and DPIs.[748] In multi-dose DPIs, the powder is contained in a reservoir or in individual blisters.[748] More information about inhalation devices is available on the Asthma + Lung UK website.[749]

Devices differ in their size and portability. They also differ in the number of steps required to prepare them,[750] in the force needed to load or actuate them,[751] in the time taken to deliver the drug, and in the need for cleaning and maintenance, as well as in the inspiratory maneuver required to use them effectively.[748] Increased steps reduces the ease of use and likelihood that patients use the inhaler correctly.[752] There may also be quite significant differences in the carbon footprint of devices reflecting whether or not they contain a propellant gas, what they are made from, how they are manufactured and transported, and whether they can be reused or recycled.[753] The proper use of an inhaler has a positive environmental impact through the reduction of exacerbations and their CO_2 footprint (especially when hospitalization is required).[753] Smart inhalers incorporate sensors that detect the date and time of use, and for some inspiratory flow and inspired volume. These allow the identification of problems and feedback in real time[754] and can provide objective data on adherence and technique.[755,756]

Particles > 5 µm are most likely to be deposited in the oropharynx. For drug delivery to the lower respiratory tract and lungs, particle size (mass-median aerodynamic diameter) can be fine (2-5 µm) or extra-fine (< 2 µm), which influences the total respirable fraction (particles < 5 µm) and the amount and site of drug deposition (more peripheral deposition with extra-fine particles).[748] Inspiratory flow, flow acceleration, and inhaled volume are important factors for patients to successfully inhale drug particles from handheld devices into the lower respiratory tract.[748,757] pMDIs and SMIs require a slow and deep inspiration while DPIs require forceful inspiration. Each DPI has a unique internal resistance, and patients must create turbulent energy within the device during inhalation to disaggregate the powder into fine particles. Prescribers should check visually that the patient can inhale forcefully through the device and, if there is doubt, either check the inspiratory flow objectively[758,759] or switch to a pMDI+/-spacer/VHC or SMI depending on drug availability and patient's characteristics. Suboptimal peak inspiratory flow and inhalation technique errors were associated with higher COPD-related healthcare utilization and costs in patients on DPI maintenance therapy.[760]

RCTs have not identified superiority of one device/formulation and there is no evidence for superiority of nebulized therapy over hand-held devices in patients who are able to use these devices properly.[748] However, patients included

in these trials are usually those who master inhalation technique and receive proper education and follow-up regarding this issue, and therefore may not be reflective of normal clinical practice. Fixed-dose triple inhaled combination therapy in one inhaler may help improve health status compared to treatment using multiple inhalers.[761]

Ability to use delivery system correctly

Specific instructions are available for each type of device.[748,749] On average more than two thirds of patients make at least one error in using an inhalational device.[762-765] Observational studies in these patients show that, although the type and frequency of inhalation errors vary between devices depending on their characteristics, there is no device obviating the need to explain, demonstrate and regularly check inhalation technique.[766-772] The main errors in delivery device use relate to problems with inspiratory flow, inhalation duration, coordination, dose preparation, exhalation maneuver prior to inhalation and breath-holding following dose inhalation.[773]

Patients' ability to use inhalers correctly is affected by their cognitive ability, manual dexterity and coordination skills, the inspiratory flow that they can achieve, the use of different types of device, and previous education on inhaler technique.[763,774] Poor inhaler technique and errors using devices are more common with advancing age,[775] but this is likely to be mainly due to cofounders such as cognitive impairment or reduced manual dexterity.[776,777] pMDIs require sufficient hand strength to actuate the inhaler, and although BAIs are triggered by inhalation they still require priming which needs a degree of strength.[751] Patients with poor dexterity may struggle to load a DPI, particularly if capsules require extraction from foil, insertion into the device or puncturing prior to administration.[751] Tremor may result in shaking of the device and loss of the dose.[778]

If there is any doubt that the patient will not be able to use a pMDI correctly they should be prescribed a VHC/spacer; however, these are not a panacea and there is evidence that few older patients using a pMDI and VHC find them easy to use compared to a pMDI alone.[779] Currently available VHCs range in volume from < 50 mL to 750 mL[780] but VHC with volumes from 150 mL to 250 mL have been shown to be as effective as those with larger volumes[781] and are more portable. As well as reducing difficulties caused by poor co-ordination and inspiratory maneuvers with pMDIs, VHCs increase pulmonary and reduce oropharyngeal deposition, which is particularly important to minimize the risk of oropharyngeal candidiasis with corticosteroid containing pMDIs.[748]

Leaflets included in device packages are insufficient to provide proper education of patients regarding inhaler use. Other strategies and tools including physical training and use of video or web-based education have proven effective to improve inhaler technique in some but not all patients on the short-term, but effects appear to wane over time.[752] Using the "teach-back" approach (patients being asked to show how the device has to be used) appears to be particularly effective.[782] Pharmacist-, physician-, physiotherapist- and nurse-led interventions[783] as well as lay health coaching[784] can improve inhalation technique and adherence in patients with COPD. As in asthma, digital inhalers could contribute to improved adherence and inhaler technique in patients with COPD.[785]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

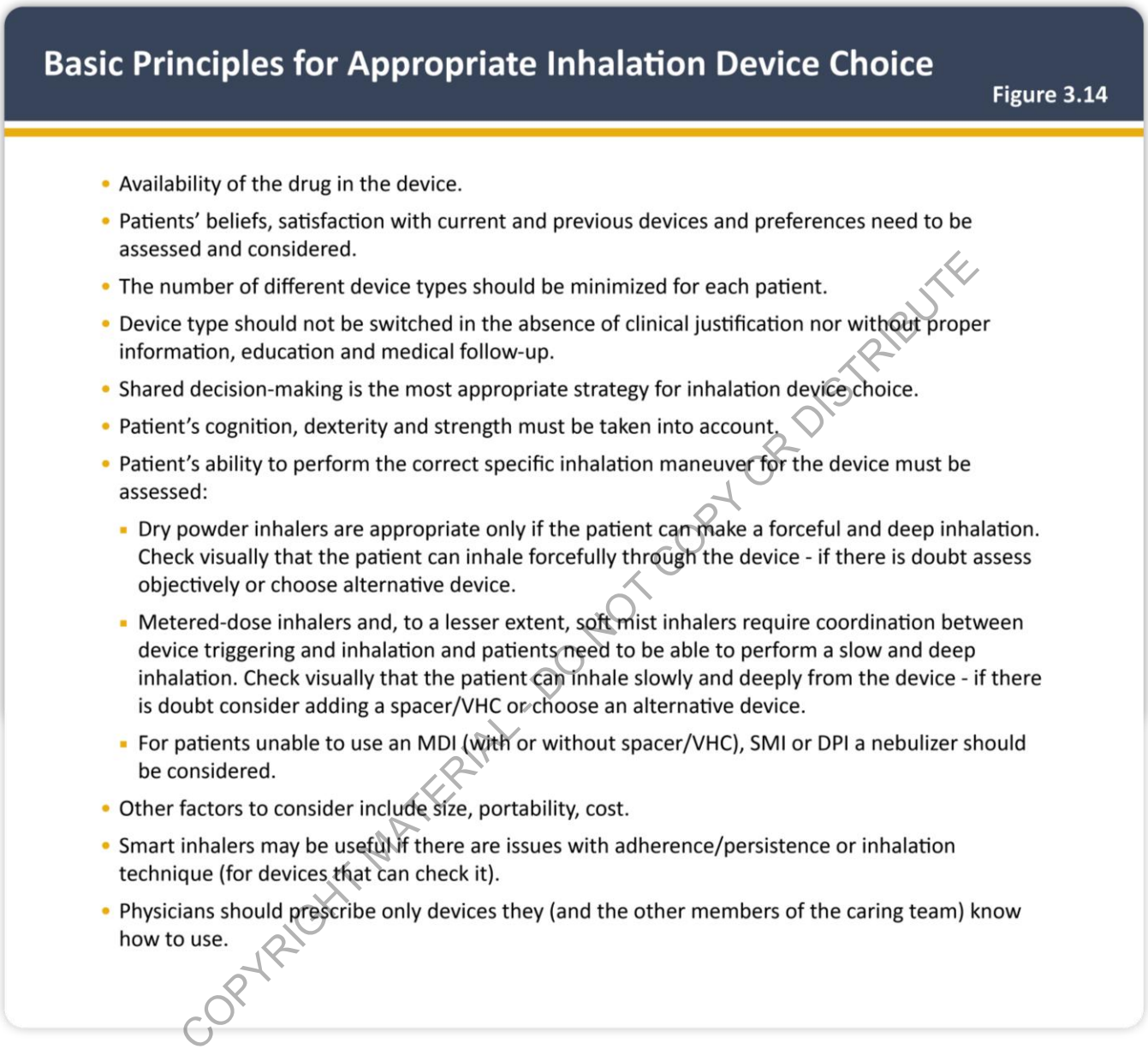
Choice of inhaler device

If a patient is currently taking inhaled therapy and able to use their current device correctly, new therapy is best prescribed in the same device. If a new device is required, either because the patient is not using their current device correctly or the drug is not available in the same device, a systematic iterative process should be used to select a delivery system and ensure the patient can use it.

The choice of an inhaler device depends on drug availability, characteristics of the device, the patient's abilities and preferences, and the knowledge of healthcare professionals caring for the patient about devices and their correct usage. The final choice should be made jointly by the prescriber and the patient using a shared decision-making approach. Once a device has been selected and prescribed it should not be changed without clinical justification. Mass switching of devices for cost or supply reasons driven by payors, or even for perceived impact of particular devices on

the environment, without retraining patients to use the new device and ensuring that they can do so, has led to increased prednisolone use and higher healthcare utilization.[786]

Figure 3.14 summarizes the main principles that should be considered to guide the individualized selection of the appropriate device for a given patient.



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Appropriate education must be provided by healthcare professionals, including physical, or video-based demonstration of the proper technique and live verification that the patient masters this technique. It is crucial to check regularly (ideally, at each visit) that patients continue to use their device correctly. Lack of placebo devices within clinical areas is often a limitation and barrier to providing quality inhaler technique instruction to patients. Encouraging a patient to bring their own devices to clinic is a useful alternative.

NON-PHARMACOLOGICAL TREATMENT OF COPD

Non-pharmacological treatment is complementary to pharmacological maintenance treatment and should form part of the comprehensive management of COPD.

After receiving a diagnosis of COPD, a patient should be given further information about the condition with education and individualized self-management support. Physicians and healthcare professionals should emphasize the importance of a smoke free environment, promote physical activity, prescribe vaccinations, and consider referring patients to pulmonary rehabilitation (see **Chapter 2: Monitoring and Follow-up**). Further information on the evidence that underpins these recommendations is given in **Appendix 6 "Overview of the evidence: Non-pharmacological therapy"**.

Algorithms for the initiation and follow-up of non-pharmacological treatment

Some relevant non-pharmacological measures based on the patient's GOLD A, B, or E group **AT DIAGNOSIS** are summarized in **Figure 3.15**.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Non-Pharmacological Management of COPD*

Figure 3.15

Patient Group	Essential	Recommended	
A	• Smoking cessation (can include pharmacological treatment)	• Physical activity • Education, self-management personalized on patient needs	• Influenza vaccination • COVID-19 vaccination • Pneumococcal vaccination • Pertussis vaccination • Zoster (shingles) vaccination • RSV vaccination
B and E	• Smoking cessation (can include pharmacological treatment) • Pulmonary rehabilitation	• Physical activity • Education, self-management personalized on patient needs	• Influenza vaccination • COVID-19 vaccination • Pneumococcal vaccination • Pertussis vaccination • Zoster (shingles) vaccination • RSV vaccination

*Can include pharmacological treatment

Recommendations for the **FOLLOW-UP** of non-pharmacological treatments are based on treatable traits e.g., symptoms and exacerbations (**Figure 3.16**).

Follow-up of Non-Pharmacological Treatment

Figure 3.16

1. If response to initial treatment is appropriate, maintain it and offer:

- Influenza vaccination every year and other recommended vaccinations according to guidelines
- Self-management education
- Assessment of behavioral risk factors such as smoking cessation (if applicable) and environmental exposures

Ensure

- Maintenance of exercise program and physical activity
- Adequate sleep and a healthy diet

2. If not, consider the predominant treatable trait to target

DYSPNEA	EXACERBATIONS
• Self-management education (written action plan) with integrated self-management regarding: ▪ Breathlessness, energy conservation techniques, and stress management strategies • Pulmonary rehabilitation (PR) program and/or maintenance exercise program post PR	• Self-management education (written action plan) that is personalized with respect to: ▪ Avoidance of aggravating factors ▪ How to monitor/manage worsening of symptoms ▪ Contact information in the event of an exacerbation • Pulmonary rehabilitation (PR) program and/or maintenance exercise program post PR

All patients with advanced COPD should be considered for end of life and palliative care support to optimize symptom control and allow patients and their families to make informed choices about future management.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Education, self-management and integrative care

Traditional patient education often focuses on providing information and advice, with the assumption that better knowledge will automatically lead to healthier behaviors. While knowledge is necessary, information alone rarely produces sustained behavior change. Passive approaches, such as lectures or didactic group sessions, are not enough to help patients develop the practical skills needed to manage their health conditions.

Self-management interventions go beyond simply teaching facts. They provide personalized education, skills training, and support tailored to each patient's needs, abilities, and circumstances. These interventions help patients make decisions, solve problems, recognize changes in their condition, and take appropriate action.

Education

Patient education is an integral component of comprehensive COPD management and pulmonary rehabilitation. Education may be delivered through individual sessions, group-based programs, or a combination of both approaches. Within pulmonary rehabilitation, group education commonly incorporates active, participatory learning strategies that encourage patient engagement and the application of disease-management skills.

Individualized education should incorporate motivational communication techniques that support patient autonomy, enhance self-efficacy, and promote active participation in health-related decision-making. In this approach, healthcare professionals serve as facilitators and coaches, supporting patients in developing the knowledge, confidence, and skills required for effective self-management.

Educational interventions should be tailored according to disease severity, exacerbation risk, patient needs, preferences, and personal goals.

Appropriate topics include:

- Smoking cessation and relapse prevention strategies
- Basic information about COPD, symptoms, and progression
- Principles of COPD treatment and individualized management approaches, including:
  - Respiratory medications and correct inhaler use
  - Non-pharmacological therapies such as pulmonary rehabilitation
- Strategies to reduce and manage dyspnea
- Recognition of worsening symptoms and guidance regarding when to seek medical assistance
- Development of action plan and decision-making strategies during exacerbations
- Advance care planning, advance directives, and end-of-life considerations

Education should be integrated with individualized self-management support, which includes the strategies, skills, and techniques used by healthcare professionals to help patients manage their disease effectively. Self-management interventions should be patient-centered and informed by an assessment of exacerbation risk, functional status, health literacy, psychosocial factors, treatment preferences, and individual goals.

Although education is a fundamental component of pulmonary rehabilitation, the independent contribution of education alone to clinical improvements observed after pulmonary rehabilitation remains uncertain. Therefore, pulmonary rehabilitation programs should continue to refine educational strategies and evaluate their impact on patient knowledge, self-management behaviors, adherence, and clinically meaningful outcomes, including symptoms, quality of life, and healthcare utilization.[787]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Self-management

Self-management education and coaching by healthcare professionals should be a major component of the "Chronic Care Model" within the context of the healthcare delivery system.

The aim of self-management interventions is to motivate, engage and coach patients to positively adapt their health behavior(s) and develop skills to better manage their COPD on a day-to-day basis.[788] Physicians and healthcare providers need to go beyond pure education/advice-giving (didactic) approaches to help patients learn and adopt sustainable self-management skills. The basis of enabling patients to become active partners in their ongoing care is to build knowledge and skills. It is important to recognize that patient education alone does not itself change behavior or even motivate patients, and it has had no impact on improving exercise performance or lung function,[789,790] but it can play a role in improving skills, ability to cope with illness, and health status.[791]

For COPD, self-management has focused on an action plan centering on the early recognition and early treatment of exacerbations to prevent further deterioration, reduce impact on patient health status, and hospital admissions.[792] There is also evidence that the early recognition and prompt treatment of exacerbations is associated with more accelerated recovery time, reduced morbidity and health care utilization[793,794] suggesting that a collaborative, self-management action plan should be incorporated into COPD care.

However, it is one thing to have an action plan and to convey this information to the patient; it is another to ensure that the patient puts it into practice effectively. It has been shown that to be successful, action plan delivery should be combined with the coaching of a healthcare professional, case manager or navigator.[795]

Comprehensive COPD self-management interventions should address multiple domains, including smoking cessation, physical activity and exercise, medication adherence and inhaler technique, nutritional management, symptom monitoring, exacerbation prevention, and strategies to manage the psychological impact of COPD. These interventions should be integrated into routine COPD care and delivered through a partnership between patients and healthcare providers, with the aim of improving health outcomes and supporting patients' ability to live well with COPD.

Pulmonary Rehabilitation

Definition and description of pulmonary rehabilitation

Pulmonary rehabilitation is defined as "a comprehensive intervention based on thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, self-management intervention aiming at behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors."[791,796] In 2023 the WHO described a package of interventions for rehabilitation for patients with cardiopulmonary disease .[797] This document follows a resolution of WHO that advocates to make pulmonary rehabilitation (as well as other forms of rehabilitation) universally available for patients with COPD.[798] In this package, the WHO recommends the inclusion of a diverse rehabilitation workforce comprising dietitians/nutritionists, nursing professionals, occupational therapists, physiotherapists, psychologists, social work and counseling professionals, and specialist medical practitioners, including physicians specializing in physical or rehabilitation medicine (PRM). This collaborative model supports a comprehensive approach to pulmonary rehabilitation by addressing the complex physical, psychological, nutritional, and social and/or environmental factors that influence patient outcomes. Unfortunately, access to such healthcare teams is still low and needs to be further improved as (pulmonary) rehabilitation is an essential part of universal health coverage (WHO resolution 76.6 30th May 2023). The package of care developed by the WHO may provide guidance to governments and clinicians who want to implement pulmonary rehabilitation.[797]

Figure 3.17 provides a summary of the main components, setting and anticipated effects of three types of interventions which are often confused in clinical practice and even in research publications: pulmonary rehabilitation, exercise training and physical activity coaching.[799,800] These interventions overlap in some respects, but they differ in purpose, structure, and delivery. Pulmonary rehabilitation is a broad comprehensive intervention; exercise training, a core component of pulmonary rehabilitation targets physical capacity and physical activity coaching targets everyday engagement with physical activity and movement behavior.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Non-pharmacological Programs in COPD

Figure 3.17

Program	Components	Setting	Anticipated effect
Physical activity coaching	Counseling, telemonitoring using wearables	In-person or tele-coaching	Improved physical activity
Exercise training*	Whole body exercise training (endurance/interval) Resistance training	Monitored exercise training (in-person or tele-supervised; synchronous or asynchronous)	Improved exercise tolerance, skeletal muscle function, nutritional status (FFM), symptoms and health-related quality of life
Pulmonary rehabilitation	Exercise training (aerobic & resistance) is the cornerstone plus education/ self-management plus multidisciplinary support: dietitians & nutritionists, nursing professionals, occupational therapists, physiotherapists, psychologists, social work and counselling professionals and specialist medical practitioners/physical & rehabilitation medicine physicians	Center-based (outpatient or inpatient), community-based, home-based. In-person or tele-rehabilitation (supervised remotely)	Improved exercise tolerance, health-related quality of life, respiratory and non-respiratory symptoms, utilization of healthcare resources, self-efficacy, physical activity

*Exercise training can be culturally adapted to include exercise modalities that are appropriate in specific populations. Examples are yoga, Tai Chi, dancing and water-based exercises.[1,2] The frequency, intensity, and duration (time) and type of exercise needs to be appropriate, progressed, and is best monitored.

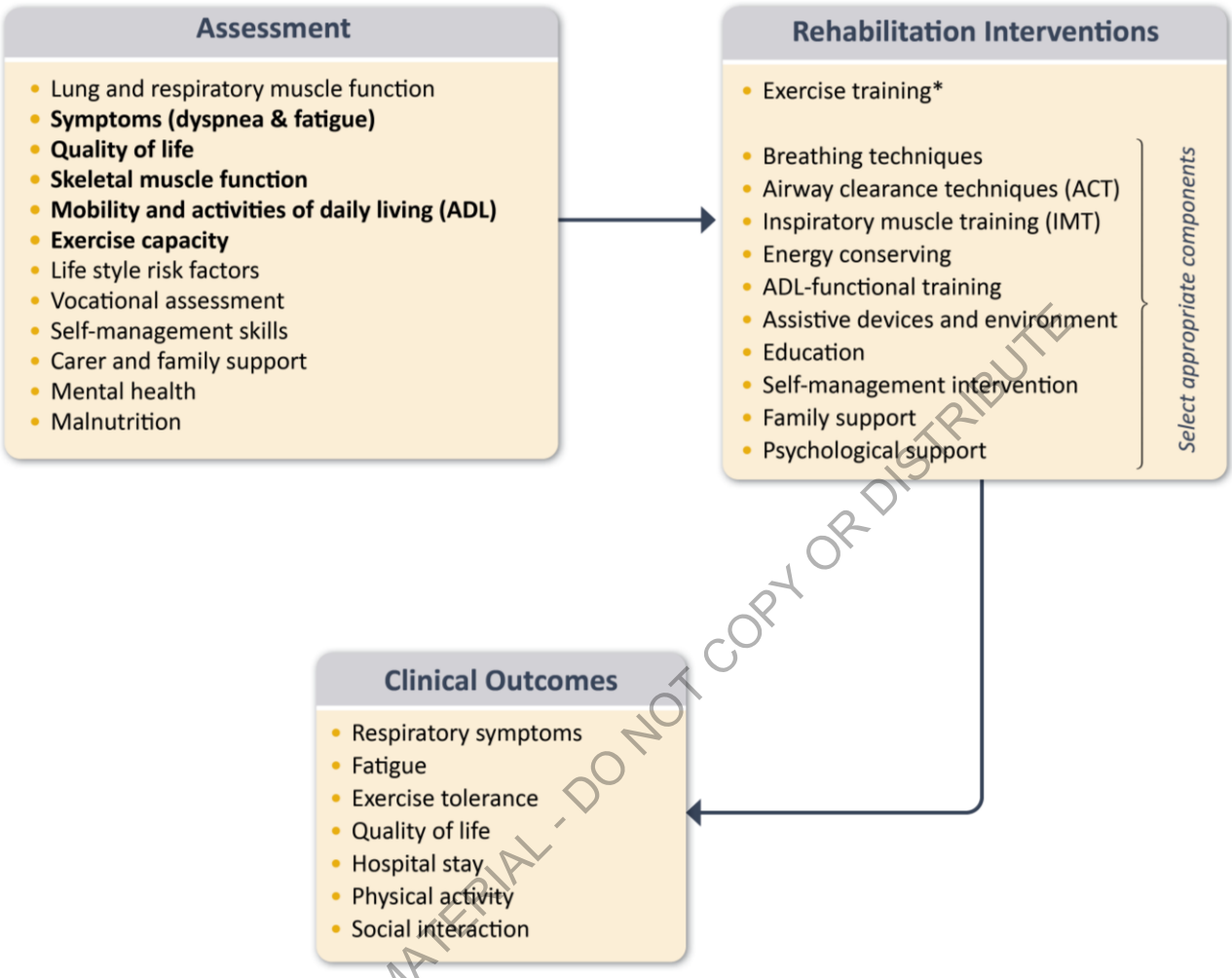
References: 1. Sánchez Romero et al. NPJ Prim Care Respir Med. 2026 Apr 11;36(1):52; **2.** Zhang et al. Thorax. 2023 Jan;78(1):69-75.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Rehabilitation interventions, assessments to guide the selection of interventions, and the anticipated benefits have been summarized from the WHO package in **Figure 3.18**.[801] The package recommends a multidisciplinary, patient-centered rehabilitation program comprising assessment, exercise training, education and self-management, breathing and airway clearance techniques, nutritional management, psychological support, and occupational therapy to improve function, quality of life, and participation while reducing symptoms and healthcare utilization. A minimal set of core outcomes for rehabilitation was recently identified by an international panel of experts using the Delphi method (**Figure 3.18**).[801]

Assessment and Rehabilitation Interventions

Figure 3.18



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

*Default component; assessment allows for proper prescription (frequency, intensity, type and time). The assessment items in bold type are also outcomes identified in the domains of a 'Core Outcome Set' for pulmonary rehabilitation according to Souto-Miranda et al. Thorax. 2023 Dec;78(12):1240-1247.

Adapted from the WHO Package of Interventions for Rehabilitation Module 4: Cardiopulmonary Conditions.

Pulmonary rehabilitation should be considered as part of integrated patient management and usually includes a range of healthcare professionals to ensure optimum coverage of the many aspects involved.[802] Optimum benefits are achieved from programs lasting 6 to 12 weeks and at least two supervised sessions per week to allow for changes to occur in the cardiorespiratory, metabolic and muscular systems. The British Thoracic Society recommends a minimum of 12 supervised sessions over 6 weeks. In a Cochrane systematic review by McCarthy et al. (2010), highly regarded as evidence for the efficacy of pulmonary rehabilitation, a median of 24 sessions (IQR 14 to 24) was reported in outpatient programs.[803]

Exercise training is recommended, and this can include endurance training, interval training, resistance/strength training; upper and lower limbs can be included as well as walking exercise; flexibility, inspiratory muscle training and

neuromuscular electrical stimulation can also be incorporated. In all cases the rehabilitation intervention (content, scope, frequency, and intensity) should be individualized to maximize personal functional gains.[804] If a center based pulmonary rehabilitation program is complimented with a physical activity promotion program, clinically significant improvements in physical activity are observed.[805,806] The importance of long-term behavior change to improve physical functionality, and reduce the psychological impact of COPD, should be emphasized to the patient.[807]

Programs can be organized in dedicated centers, but also in the community, in primary care and even in the home setting. Programs can be supervised in-person or via tele-rehabilitation, synchronous (where there is real-time supervision by a health professional during the program that may be offered on a one-on-one or group basis) or asynchronous (where a health care provider receives data, monitors progression through the program, and provides feedback off-line). A recent guideline of the American Thoracic Society provides a strong recommendation to consider tele-rehabilitation as an alternative for center-based rehabilitation. A Cochrane systematic review also found similar, positive outcomes following tele-rehabilitation.[808] Patients, however, may have a strong preference for either of both modalities[809] and it is important to see both options as alternatives for a patient, rather than as a single option in a dedicated site. Also, it is important that, regardless of where rehabilitation is offered, it should fulfil the principles of multidisciplinary rehabilitation outlined in recommendations from Respiratory Societies.[791,810-812]

Patient selection for pulmonary rehabilitation

Patients with high symptom burden and risk of exacerbations at initial evaluation (Groups B and E), and those with dyspnea at follow-up, should be encouraged to take part in a formal rehabilitation program that includes setting patient goals and is designed and delivered in a structured manner, taking into account the individual's COPD characteristics (including extra-pulmonary features such as skeletal muscle dysfunction and exercise intolerance) and comorbidities.[791,802,813] This includes patients who are older, female, more deprived, or have a comorbidity of diabetes, asthma, or a painful condition, who currently appear less likely to be referred for pulmonary rehabilitation.[814]

Expected benefits of pulmonary rehabilitation

Pulmonary rehabilitation is designed to improve the non-respiratory physiological (muscle, nutrition, exercise), social and mental health treatable traits in patients with COPD that receive optimal pharmacotherapy but remain symptomatic. Pulmonary rehabilitation has well established evidence to produce clinically meaningful improvements in exercise capacity, dyspnea, and health-related quality of life in people with COPD, without necessarily improving lung function. Pulmonary rehabilitation is strongly recommended both for patients with stable COPD and following a hospital admission for an exacerbation.[796] **Figure 3.19** presents outcomes of pulmonary rehabilitation in COPD.[803,805,815-817]

Assessment and follow-up of pulmonary rehabilitation

Baseline and outcome assessments are essential to design an individual rehabilitation program. A core outcome set (COS) for pulmonary rehabilitation was designed by international global experts.[801] To ascertain the safety of high intensity exercise, an incremental cardiopulmonary exercise test can be performed. Nutritional assessment did not reach sufficient consensus to be included in the COS but might be important to decide on the need for nutritional interventions e.g., to enhance fat free mass (FFM) or optimize weight. Assessments recommended by the WHO at baseline, and at follow-up after pulmonary rehabilitation, are provided in **Figure 3.18**.[797] In settings where frailty is more common (e.g., nursing homes, or following exacerbations),[818] assessment of frailty (physical, cognitive and social) may be advised.[819] A thorough anamnesis and needs assessment for each participant referred to a pulmonary rehabilitation program should be made to specify individual maladaptive behaviors (including motivation), physical and mental health impediments to training, goals, barriers and capabilities and to quantify gains and to target areas for improvement.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Pulmonary Rehabilitation Outcomes in COPD

Figure 3.19

Outcome	Evidence in COPD Pulmonary Rehabilitation	Effect Estimate	Clinical Interpretation
Exercise capacity (6MWD)[1]	Improves walking	44 m increase (95% CI: 33, 55)	MCID 25 m to 30 m
ISWT[1]	Improves walking	40 m increase (95% CI: 22, 57)	MCID 35 m to 48 m
SGRQ[1]	Improves respiratory quality of life	6.89 unit decrease (95% CI: -9.26, -4.52)	MCID -4 points
Physical activity[2]	Improves physical activity	CBRP increase of 680 steps per day (95% CI: 12, 1,348) CBRP + coaching increase of 1,376 steps per day (95% CI: 608, 2,144)	MCID 600 to 1,000 steps per day
Dyspnea (CRQ)[1]	Improves dyspnea	0.79 unit increase (95% CI: 0.56, 1.03)	MCID 0.5 units
Depression/ anxiety[3]	Improves symptoms of anxiety & depression	Depression SMD -0.35 (95% CI: -0.58, -0.12) Anxiety SMD -0.27 (95% CI: -0.53, -0.01)	Clinically relevant
Hospital admissions[4]	Reduces hospital admissions/ readmissions	RR 0.60 (95% CI: 0.32, 0.95)	Significant reduction
Mortality[5]	Not conclusive	OR 0.68 (95% CI: 0.28, 1.67) Non-randomized US-based VA cohort study suggests HR 0.74 (95% CI: 0.65, 0.84)	Prospective trials cannot be conducted

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Abbreviations: CRQ: chronic respiratory disease questionnaire; MCID: mean clinically important difference; 6MWD: 6-minute walking distance; ISWT: incremental shuttle walk test; PR: pulmonary rehabilitation; RR: relative risk; SGRQ: St George's Respiratory Questionnaire; SMD: symptoms of major depressive disorder scale.

References: 1. McCarthy et al. Cochrane Database Syst Rev. 2015 Feb 23;2015(2):CD003793; **2.** Manifield et al. Eur Respir Rev. 2024 Apr 10;33(172):230225; **3.** Chen et al. Int J Chron Obstruct Pulmon Dis. 2026 May 6;21:578054; **4.** Jia et al. BMC Med. 2026 Mar 16;24(1):260; **5.** Robinson et al. Am J Respir Crit Care Med. 2026 Jun 1;212(6):1227-1236.

Several detailed questionnaires for assessing health status are available, including some specifically designed for patients with respiratory disease. Health status can also be assessed by generic instruments, although these are less sensitive to change than the disease specific questionnaires such as the CAAT™, CRQ or SGRQ. The HADS[820] and the PRIME-MD patient questionnaire[821] have been used to improve identification and treatment of anxious and depressed patients. All these instruments are responsive to pulmonary rehabilitation interventions.

It is important not to limit assessment only to these outcome measures but gather information on each patient's ultimate goal (relevant or valued outcomes), such as their desired achievements in work, home and leisure by the end of the program.

Acute exacerbations and pulmonary rehabilitation

Following acute exacerbation, key principles of rehabilitation include early resumption of physical activity, gradual progression of exercise, close monitoring of symptoms, and individualized adjustment of exercise intensity to facilitate safe and effective recovery. For patients who have not yet been referred to pulmonary rehabilitation, referral to a multidisciplinary program is recommended after an exacerbation, although the best timing may need further investigation. Such programs should incorporate exercise training and address other treatable traits, including anxiety, weight loss or gain, occupational difficulties, and challenges with self-management.[796,812] **Figure 3.20** gives recommendations for gradual return to exercise training following exacerbation.[822]

Exercise training during an acute respiratory exacerbation focuses primarily on preventing further functional decline, maintaining mobility, and promoting safe recovery rather than restoring fitness to the pre-exacerbation state. Effectiveness is not shown in all trials,[823] but several trials have shown that resistance training can be used during acute exacerbations to prevent acute loss of skeletal muscle function.[824,825]

After stabilization (typically within 3-4 weeks), pulmonary rehabilitation aims to restore the physical function that was lost, improve exercise tolerance, reduce symptoms, and prevent future exacerbations. In this phase, particularly after a hospital admission, inclusion in pulmonary rehabilitation is highly recommended[796] and significantly reduces the risk for readmission (OR 0.48, 95% CI 0.30, 0.77).[826]

Integrative care

Integrated care refers to the development of coordinated programs designed to improve patient outcomes and satisfaction, enhance the efficiency of care delivery, and minimize fragmentation across the healthcare system. [827] Different terms for integrative care may be used, including ''shared care'', ''disease management'', ''integrated care pathways'' and ''integrated care". Although all strategies the common aim of improving coordination and integration of services, some strategies also consider overcoming professional and departmental boundaries as well as boundaries of lines of care (primary to specialized).

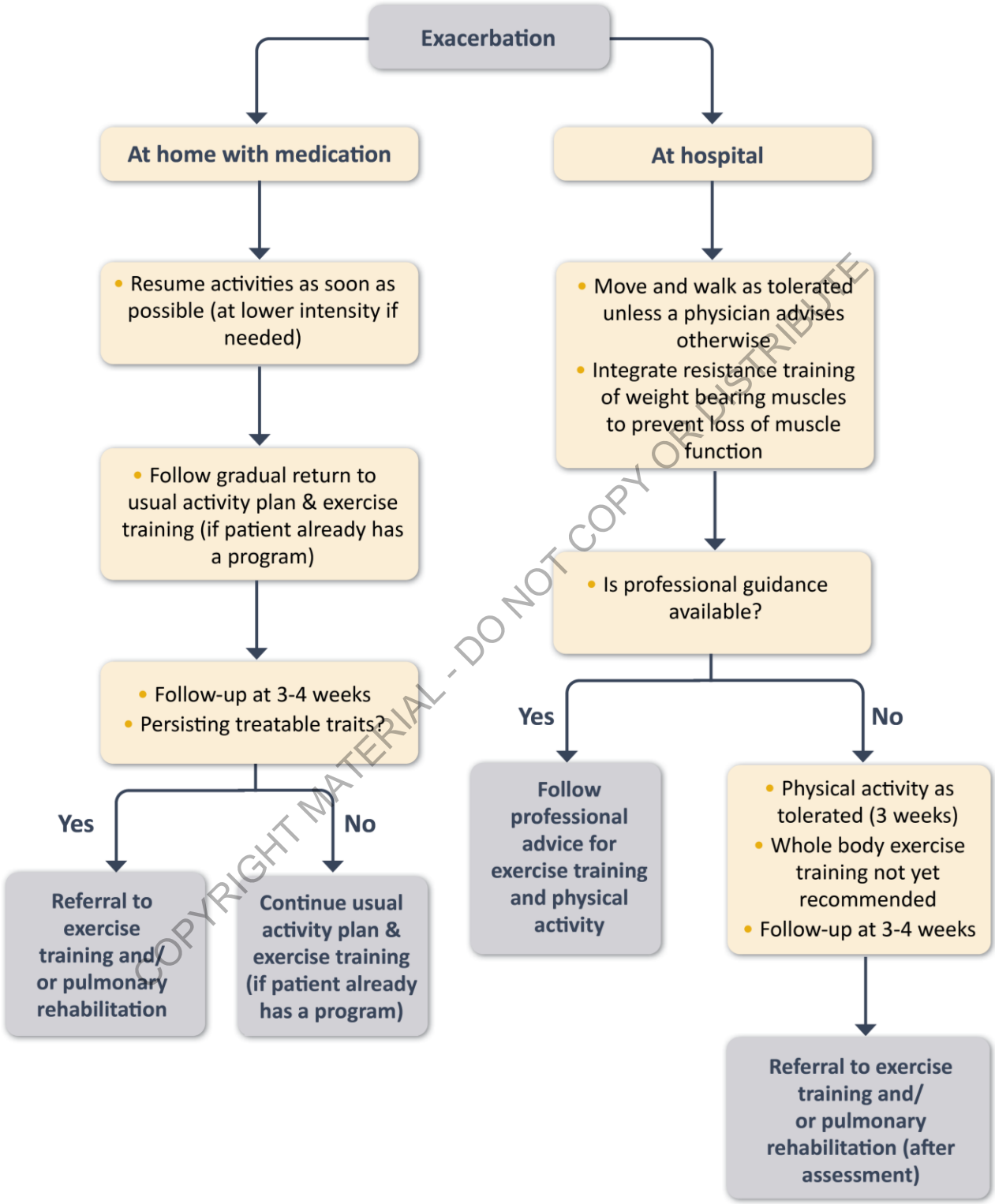
It remains unclear which components or interventions need to be prioritized in integrated care programs and how they should be best structured to maximize their benefit. A Cochrane systematic review investigating integrative care in COPD reported decreased hospitalizations, and improved quality of life and exercise capacity.[828] The impact of a new integrated care program versus usual care is less apparent when usual care already routinely contains several of the components.

Integrated care programs with different dominant components will often have different beneficial effects for specific outcomes. For example, exercise tolerance is improved by an integrated care program with a dominant component of exercise training, whereas respiratory-related admissions are improved by self-management with the implementation of an action plan and communication with a coach or navigator. Integrated care programs should consist of several different components to reach maximum potential to improve clinical outcomes.[827]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Physical Activity and Exercise Training After COPD Exacerbation

Figure 3.20



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Oxygen therapy and ventilatory support

Oxygen therapy

The long-term administration of oxygen (> 15 hours per day; LTOT) is indicated for patients with stable COPD who have:

- PaO_2 at or below 55 mmHg (7.3 kPa) or SaO_2 at or below 88%, with or without hypercapnia confirmed twice over a three-week period; or
- PaO_2 between 55 mmHg (7.3 kPa) and 60 mmHg (8.0 kPa), or SaO_2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%).

LTOT has been shown to increase survival in patients with severe resting hypoxemia.[829]

Ekström and colleagues[830] reported that among patients with severe hypoxemia agreeing to participate in a study, LTOT used for 24 hours per day did not result in a lower risk of hospitalization or death within one year compared to therapy for 15 hours per day. Thus, the recommendation to use oxygen > 15 hours per day is not supported by newer evidence.

In patients with moderate resting or exercise-induced arterial oxygen desaturation LTOT does not lengthen time to death or first hospitalization, or provide sustained benefit for any of the measured outcomes.[831] Breathlessness may be relieved in patients with COPD who are either mildly hypoxemic, or non-hypoxemic but do not otherwise qualify for home oxygen therapy, when oxygen is given during exercise training; however, studies have shown no improvement of breathlessness in daily life and no benefit on health-related quality of life (**Figure 3.21**).[831-833] There are contradictory studies although the majority do not demonstrate changes.[834]

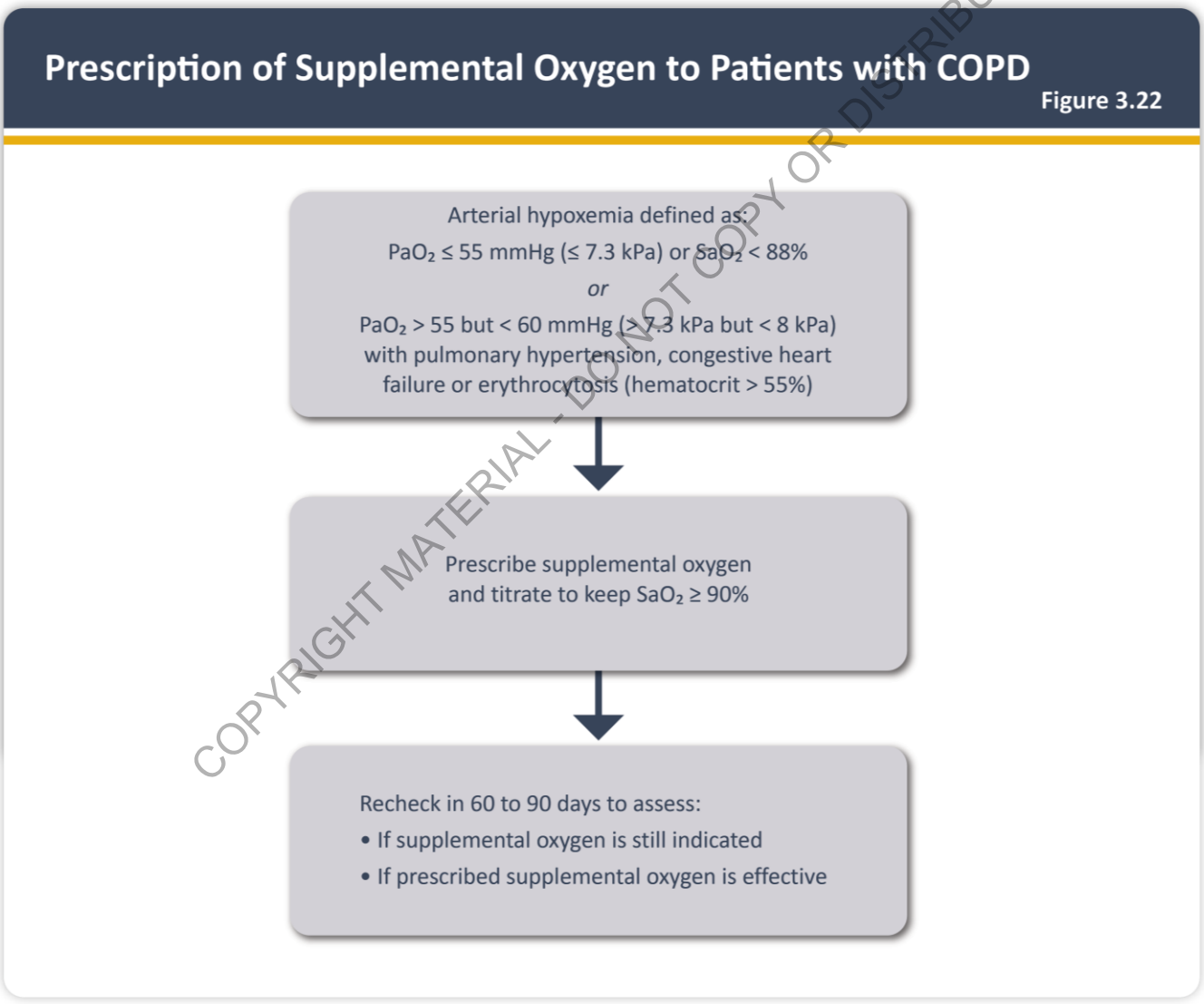
COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Oxygen Therapy and Ventilatory Support in Stable COPD — Figure 3.21

Oxygen Therapy	• The long-term administration of oxygen increases survival in patients with severe chronic resting arterial hypoxemia **(Evidence A)** • In patients with stable COPD and moderate resting or exercise-induced arterial desaturation, prescription of long-term oxygen does not lengthen time to death or first hospitalization or provide sustained benefit in health status, lung function and 6-minute walk distance **(Evidence A)** • Sufficient resting oxygenation at sea level does not exclude the development of severe hypoxemia when traveling by air **(Evidence C)**
Ventilatory Support	• NPPV may improve hospitalization-free survival in selected patients after recent hospitalization, particularly in those with pronounced daytime persistent hypercapnia **(Evidence B)** • In patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure, long-term noninvasive ventilation may be considered **(Evidence B)**

Although air travel is safe for most patients with chronic respiratory failure who are on LTOT,[835] patients should ideally maintain an in-flight PaO_2 of at least 6.7 kPa (50 mmHg). Studies indicate that this can be achieved in those with moderate to severe hypoxemia at sea level by supplementary oxygen at 3 liters/min by nasal cannula or 31% by Venturi facemask.[836] Those with a resting oxygen saturation > 95% and 6MWD oxygen saturation > 84% may travel without further assessment,[837] although it is important to emphasize that resting oxygenation at sea level does not exclude the development of severe hypoxemia when travelling by air.[835] Careful consideration should be given to any comorbidity that may impair oxygen delivery to tissues (e.g., cardiac impairment, anemia). Also, walking along the aisle of the airplane may profoundly aggravate hypoxemia.[838]

Once placed on LTOT the patient should be re-evaluated after 60 to 90 days with repeat ABG or oxygen saturation measurements while inspiring room air and the level of oxygen flow that had been prescribed to determine if oxygen is still indicated and if so, therapeutic. An appropriate algorithm for the prescription of oxygen to patients with COPD is shown in **Figure 3.22**.



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Ventilatory support

Chronic NIV may be of some use in a selected group of patients, particularly in those with pronounced daytime hypercapnia and recent hospitalization. In patients with both COPD and obstructive sleep apnea there are clear indications for CPAP.[839,840]

In patients with comorbid COPD and obstructive sleep apnea there are clear benefits associated with the use of CPAP to improve both survival and the risk of hospital admissions.[839,840]

Whether to use NPPV chronically at home to treat patients with acute or chronic respiratory failure following hospitalization remains undetermined and outcome may be affected by persistent hypercapnia.[841] A multicenter prospective RCT of patients with COPD who had persistent hypercapnia ($PaCO_2$ > 53 mmHg) 2-4 weeks after hospital discharge following an acute exacerbation compared the effects of home NIV plus oxygen versus home oxygen alone on time to readmission or death.[841] Adding home NIV to oxygen therapy significantly prolonged the time to readmission or death within 12 months.[841] A systematic review and meta-analysis of these studies confirms that NIV decreases mortality and risk of hospitalization. The best candidate subgroups (by recent hospitalization history or $PaCO_2$) remain unclear.[842]

Two retrospective studies[843,844] and two of three RCTs[841,845-848] reported reductions in re-hospitalization and improved survival with using NPPV post-hospitalization. Two of these studies reported decreases in mortality and hospitalization rates while another showed no benefit of NPPV for survival.[846] Several factors may account for these discrepancies: differences in patient selection, underpowered studies, NPPV settings incapable of achieving adequate ventilation, and poor adherence with NPPV therapy.[849] NPPV when indicated should be instituted and monitored by personnel familiar with the process and the devices utilized.[850,851]

A meta-analysis suggested that in patients with chronic hypercapnic respiratory failure long-term treatment with HFNT may reduce acute exacerbations and improve SGRQ scores compared to standard care, but its effect on mortality and hospitalizations is uncertain.[852,853]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

THERAPEUTIC INTERVENTIONS THAT REDUCE COPD MORTALITY

As we move towards targeting subgroups of patients with COPD for specific therapy, it is important to know which modifiable factors (treatable traits) are associated with mortality. A large clinical database study of COPD in primary care has demonstrated that the highest magnitude of risk of all-cause mortality, COPD- and CVD-related mortality, was in individuals with increased severity and frequency of exacerbations, and those with lower FEV1 (particularly FEV1 < 50% predicted).[854] We are still learning about the mechanisms that cause death in patients with COPD. Demonstrating benefits of therapeutic modalities on mortality in RCTs has been difficult, requiring large populations and/or long follow-up duration and/or highly selected populations with a high but preventable risk of death during follow-up. In addition, the low number of events makes the analysis of disease specific mortality (e.g., respiratory or cardiovascular) in most trials difficult. **Figure 3.23** presents a summary of pharmacological and non-pharmacological therapies with evidence of efficacy in reducing the mortality of patients with COPD.

Non-pharmacological therapy

Smoking cessation. From the Lung Health Study, an RCT that included patients with asymptomatic or mildly symptomatic COPD treated with a 10-week smoking cessation intervention program and followed up to 14.5 years, the overall mortality rate was reduced in the smoking cessation intervention group compared to the usual care group.[855]

Pulmonary rehabilitation. A systematic review of RCTs reported a reduction in mortality for patients who had pulmonary rehabilitation initiated during hospitalization or 4 weeks after discharge compared to those who did not

have pulmonary rehabilitation.[856-859] These results have been corroborated by real-world evidence, from a large population-based cohort of 190,000 patients hospitalized for COPD, in whom initiation of pulmonary rehabilitation within 90 days of discharge, while rare, was associated with a statistically significant reduced mortality.[860]

Long term oxygen therapy. The survival benefit of LTOT in COPD demonstrated in two studies in the early 1980s laid the foundation for long-term domiciliary management of hypoxemia. The Nocturnal Oxygen Therapy Trial (≥ 19 hours of continuous oxygen compared to ≤ 13 hours)[861] and a Medical Research Council trial (≥ 15 hours compared to no oxygen),[862] two RCTs in patients with COPD with resting $PaO_2 \leq 55$ mmHg or < 60 mmHg with *cor pulmonale* or secondary polycythemia showed a survival benefit. No significant benefit of LTOT was found in patients with moderate desaturation.[863]

Evidence Supporting a Reduction in Mortality with Pharmacotherapy and Non-pharmacotherapy in COPD Patients

Figure 3.23

Therapy	RCT*	Treatment effect on mortality	Patient characteristics
Pharmacotherapy			
LABA+LAMA+ICS[1]	Yes	Single inhaler triple therapy compared to dual LABD therapy relative risk reduction: IMPACT: HR 0.72 (95% CI: 0.53, 0.99)[1a] ETHOS: HR 0.51 (95% CI: 0.33, 0.80)[1b]	Symptomatic people with a history of frequent and/or severe exacerbations
Non-pharmacological Therapy			
Smoking cessation[2]	Yes	HR for usual care group compared to intervention group (smoking cessation) HR 1.18 (95% CI: 1.02, 1.37)[2]	Asymptomatic or mildly symptomatic
Pulmonary rehabilitation[3#]	Yes	Old trials: RR 0.28 (95% CI 0.10, 0.84)[3a] New trials: RR 0.68 (95% CI 0.28, 1.67)[3b]	Hospitalized for exacerbations of COPD (during or ≤ 4 weeks after discharge)
Long-term oxygen therapy[4]	Yes	NOTT: ≥ 19 hours of continuous oxygen vs ≤ 13 hours: 50% reduction[4a] MRC: ≥ 15 hours vs no oxygen: 50% reduction[4b]	$PaO_2 \leq 55$ mmHg or < 60 mmHg with *cor pulmonale* or secondary polycythemia
Noninvasive positive pressure ventilation[5]	Yes	12% in NPPV (high IPAP level) and 33% in control HR 0.24 (95% CI 0.11, 0.49)[5]	Stable COPD with marked hypercapnia
Lung volume reduction surgery[6]	Yes	0.07 deaths/person-year (LVRS) vs 0.15 deaths/person-year (UC) RR for death 0.47 (p = 0.005)[6]	Upper lobe emphysema and low exercise capacity

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

*RCT with pre-specified analysis of the mortality outcome (primary or secondary outcome); #Inconclusive results likely due to differences in pulmonary rehabilitation across a wide range of participants and settings.

1. a) IMPACT trial (Lipson et al. 2020) and b) ETHOS trials (Martinez et al. 2021); 2.Lung Health Study (Anthonisen et al. 2005); 3. a) Puhan et al. (2011) and b) Puhan et al. 2016; 4. a) NOTT (NOTT, 1980) and b) MRC (MRC, 1981); 5. Kohlein trial (Kohlein et al. 2014); 6. NETT trial (Fishman et al. 2003).

ICS: inhaled corticosteroid; IPAP: inspiratory positive airway pressure; LABA: long-acting beta$_2$-agonist; LABD: long-acting bronchodilator; LAMA: long-acting muscarinic antagonist; LTOT: long-term oxygen therapy; NPPV: noninvasive positive pressure ventilation; LVRS: lung volume reduction surgery; UC: usual treatment control group.

Non-invasive positive pressure ventilation. Meta-analyses[842,864] have shown positive results of long-term NPPV in patients with stable COPD. Although RCT results have been inconsistent on survival, larger trials with mortality as the primary outcome that enrolled patients with marked hypercapnia and applying higher IPAP levels demonstrated a reduction of mortality.[846,865]

Lung transplantation and lung volume reduction surgery. Due to the absence of randomized trials, observational data have been used to estimate the survival benefit of lung transplantation, relative to remaining "untransplanted." The survival benefit of transplantation varied by disease group, with a 2-year expected benefit in 40% of patients with COPD following transplantation.[866]

LVRS has been shown to prolong survival compared to medical therapy in a very select group of patients with severe emphysema, predominantly upper lobe emphysema, and low exercise capacity post-rehabilitation.[867] Among patients with non-upper-lobe emphysema and high exercise capacity post-rehabilitation, mortality was higher in the surgery group than in the medical-therapy group.

Pharmacological therapy

Previous studies such as TORCH[868] and SUMMIT[869] failed to provide evidence for the efficacy of a LABA+ICS combination compared to placebo in reducing mortality (primary outcome) in patients with COPD. These trials had no requirement for a history of previous exacerbations. In the largest LAMA treatment trial UPLIFT, the intention to treat analysis, i.e., 30 days after completion of the study period, did not demonstrate a reduction in mortality (secondary outcome) compared to placebo. The majority of patients included in this study utilized an ICS.

Evidence has emerged from two large randomized clinical trials, IMPACT[502] and ETHOS,[515] that fixed-dose inhaled triple combinations (LABA+LAMA+ICS) reduce all-cause mortality compared to dual inhaled LABD therapy. Together these results suggest a beneficial effect of fixed-dose triple inhaled therapy versus fixed-dose LABA+LAMA combinations on mortality in patients with symptomatic COPD who have a history of frequent and/or severe exacerbations, and who were previously receiving maintenance therapy with triple therapy, LABA+ICS or single or dual long-acting bronchodilators. These trials were enriched for symptomatic patients (CAAT™ ≥ 10) with a history of frequent (≥ 2 moderate exacerbations) and/or severe exacerbations (≥ 1 exacerbation requiring a hospital admission) (**Figure 3.23**).

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

SUPPORTIVE, PALLIATIVE, END-OF-LIFE & HOSPICE CARE

Symptom control and palliative care

Palliative care is a broad term that encompasses approaches to symptom control as well as management of terminal patients close to death. The goal of palliative care is to prevent and relieve suffering, and to support the best possible quality of life for patients and their families, regardless of the stage of disease or the need for other therapies.[870] COPD is a highly symptomatic disease and has many elements such as fatigue, dyspnea, depression, anxiety, insomnia that require symptom-based palliative treatments. There is evidence that people with COPD are less likely to receive such services compared to patients with lung cancer.[871,872] Palliative care expands traditional disease-model medical treatment to increase the focus on the goals of enhancing quality of life, optimizing function, helping with decision-making about end-of-life care, and providing emotional and spiritual support to patients and their families.[870] Palliative approaches are essential in the context of end-of-life care as well as hospice care (a model for delivery of end-of-life care for patients who are terminally ill and predicted to have less than 6 months to live). Increasingly, palliative care teams are available for consultation for hospitalized patients.[873] Availability for outpatient palliative care consultation is less common, and has been shown to improve quality of life, reduce symptoms and even prolong survival for patients with advanced lung cancer.[872] Key points for palliative, end-of-life and hospice care in COPD are summarized in **Figure 3.24**.

Palliative Care, End of Life and Hospice Care in COPD

Figure 3.24

- All clinicians managing patients with COPD should be aware of the effectiveness of palliative approaches to symptom control and use these in their practice **(Evidence D)**
- End of life care should include discussions with patients and their families about their views on resuscitation, advance directives and place of death preferences **(Evidence D)**
- Opiates, neuromuscular electrical stimulation (NMES), oxygen and fans blowing air onto the face can relieve breathlessness **(Evidence C)**
- Nutritional supplementation should be considered in malnourished patients with COPD (**Evidence B**) as it may improve respiratory muscle strength and overall health status **(Evidence B)**
- Fatigue can be improved by self-management education, pulmonary rehabilitation, nutritional support and mind-body interventions **(Evidence B)**

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Therapy relevant to all people with COPD

Even when receiving optimal medical therapy many people with COPD continue to experience distressing breathlessness, impaired exercise capacity, fatigue, and suffer panic, anxiety and depression.[874] Some of these symptoms can be improved by wider use of palliative therapies that in the past have often been restricted to end-of-life situations.

Palliative treatment of dyspnea

Relieving dyspnea during daily life activities to limit disability, improve quality of life, and reduce medical resource use is a major goal of COPD care. Multiple therapeutic approaches can be considered to target the variety of involved mechanisms; they are dominated by inhaled bronchodilators, self-management education (where patients learn breathing techniques) and pulmonary rehabilitation that includes exercise training. The roles of oxygen therapy, HFNT and NIV for palliation of dyspnea are debated.[875]

Opiates,[876-878] neuromuscular electrical stimulation,[878,879] chest wall vibration,[878] and fans blowing air onto the face[878,880,881] can relieve breathlessness. Morphine may improve health status in patients with COPD,[325] and no worsening in sleepiness was reported in one study when used for breathlessness in COPD.[882] Immediate-release morphine extended exercise endurance time in over half of the patients with advanced COPD in one study.[325] However, in another RCT oral extended-release morphine (8 mg/day or 16 mg/day for one week) did not improve dyspnea compared with placebo in patients with mMRC scores of 3 or 4;[883] withdrawal symptoms were rare on opioid discontinuation in this trial.[884] Further research is required to determine what patient characteristics predict response to opioid therapy,[885] however one cross-sectional study found greater benefit in those with worse baseline dyspnea and higher BMI.[886] The optimal formulation and administration route remain under discussion.[878,887]

Oxygen may offer some benefit even if the patient is not hypoxemic (SpO_2 > 92%) (**Figure 3.21**).[888] Pulmonary rehabilitation is effective and in severe cases NIV can also reduce daytime breathlessness. Acupuncture and acupressure are other non-pharmacological approaches in patients with advanced COPD that may improve breathlessness and quality of life.[429,889] Refractory dyspnea may be more effectively managed with a multidisciplinary integrated palliative and respiratory care service.[890]

There is no evidence for a beneficial effect of benzodiazepines[891] and there are not enough data to recommend distractive auditory stimuli (music), relaxation, counseling and support, with or without breathing relaxation training, or psychotherapy.[892]

Nutritional support

Low BMI and particularly low fat-free mass is associated with worse outcomes in people with COPD.[893] In malnourished people with COPD, nutritional supplementation promotes significant weight gain and leads to significant improvements in respiratory muscle strength and overall health-related quality of life.[894] Nutritional antioxidant supplementation (vitamin C and E, zinc, and selenium) has been shown to improve antioxidant deficits, quadriceps strength, and serum total protein, without further improvement in quadriceps endurance. Only in malnourished patients has nutritional supplementation demonstrated significant improvements for 6MWD, respiratory muscle strength and health status.[895] A 12-month nutritional intervention in muscle wasted patients had no effect on physical capacity but physical activity was significantly higher.[896]

Panic, anxiety & depression

The causes of depression and anxiety symptoms in people with COPD are multifactorial and include behavioral, social and biological factors.[897] Pulmonary rehabilitation may help reduce anxiety symptoms. The efficacy of antidepressants in people with COPD has been inconclusive, possibly as a result of methodological issues in the published trials. Cognitive behavioral therapy and mind-body interventions (e.g., mindfulness-based therapy, yoga, and relaxation) can reduce anxiety and depression; mind-body interventions also improve physical outcomes such as lung function, dyspnea, exercise capacity and fatigue in people with COPD and psychological problems.[898]

Fatigue

Fatigue in people with COPD can be improved by self-management education, pulmonary rehabilitation, nutritional support and mind-body interventions.[899]

End-of-life and hospice care

In many patients, the disease trajectory in COPD is marked by a gradual decline in health status and increasing symptoms, punctuated by acute exacerbations that are associated with an increased risk of dying.[900] Although mortality rates following hospitalization for an acute exacerbation are declining,[901] reported rates still vary from 23%[902] to 80%.[903] Progressive respiratory failure, cardiovascular diseases, malignancies and other diseases are the primary cause of death in people with COPD hospitalized for an exacerbation.[903] In qualitative studies, as well as describing the high symptom burden, people with COPD and their families describe a need for a better understanding of their condition and the psychological impact of living and dying with COPD.[904] Palliative care is a broad term that includes approaches to symptom control as well as management of terminal patients close to death. Palliative care, end-of-life care, and hospice care are important components of the care of patients with advanced COPD.

End-of-life care should also include discussions with patients and their families about their views on resuscitation, advance directives and place of death preferences.[905] At an individual level, prediction of 6-month survival in people with COPD is unreliable and therefore early discussion of these issues is important together with phased introduction of supportive care.[906] Hospitalization may be a trigger to initiate discussion of advance care planning. Patients and their families live with uncertainty about the timing of death and fear of death will result from worsening dyspnea and suffocation.[907] Good advance care planning can reduce anxiety for patients and their families by talking about death and dying and offering emotional support. It can also ensure that care is consistent with their wishes and avoids unnecessary, unwanted and costly invasive approaches.[908,909]

For patients with very advanced or terminal illness, hospice services may provide additional benefit. Hospice services often focus on patients with severe disability or symptom burden and may provide these services within the patient's

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

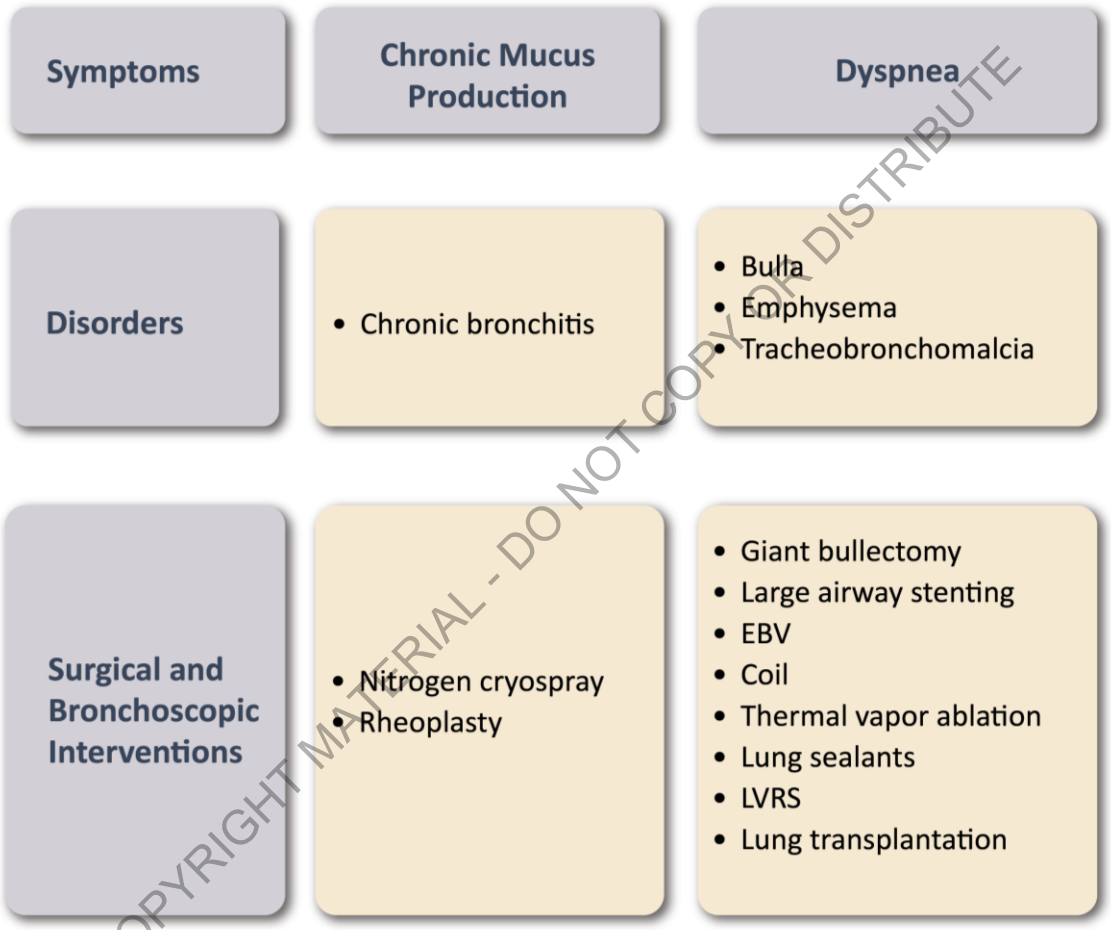
home or in hospice beds in dedicated hospice units or other institutions such as hospitals or nursing homes. Organizations such as the National Hospice and Palliative Care Organization[910] provide guidance for selecting patients with non-cancer diseases like COPD for access to hospice services (for example, disabling dyspnea at rest that is poorly responsive to bronchodilators and progression of advanced disease demonstrated by increasing hospitalizations or emergency department visits).[871,872] These guidelines discuss the difficulties in accurately predicting the prognosis of patients with advanced COPD, but recognize the appropriateness of providing hospice services for some of these patients.[870]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

INTERVENTIONAL & SURGICAL TREATMENTS FOR COPD

COPD is associated with airway and lung parenchyma structural changes that provide potential targets for interventional and surgical treatments to alleviate dyspnea, reduce cough and mucus production, and improve quality of life (**Figure 3.25**).

Overview of Current and Proposed Surgical and Bronchoscopic Interventions for People with COPD Figure 3.25



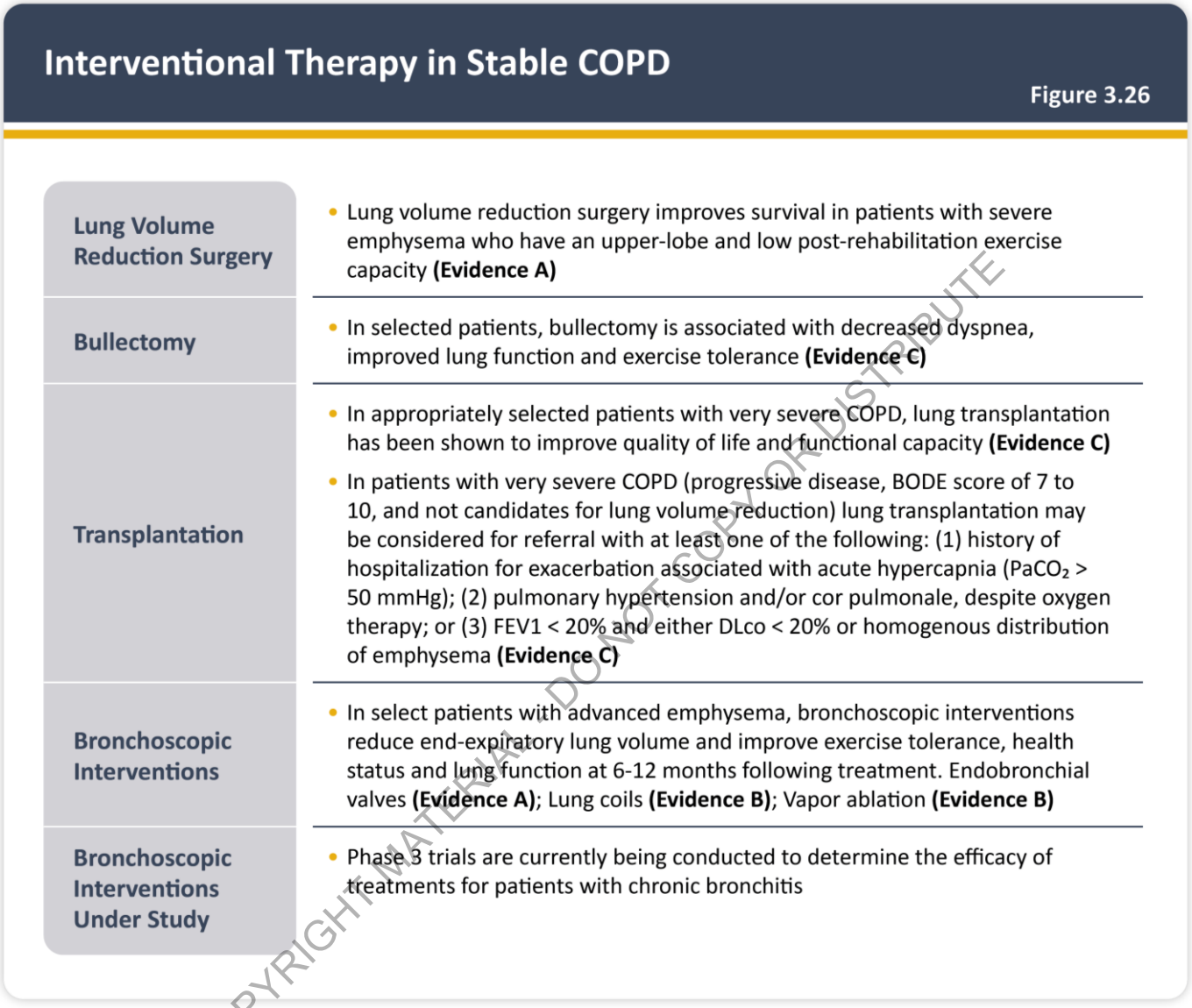
COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Lung structural related therapies include airway and emphysematous predominant treatments. Phenotyping patients with clinical, physiological, and imaging tests is critical to select appropriate candidates and in assessing the benefits, timing, and type of intervention to be performed. Multidisciplinary collaboration of pulmonology, thoracic surgery and imaging disciplines are necessary to ensure quality outcomes.

Airway predominant treatments are currently the subject of phase 3 clinical trials; emphysematous based treatments include bullectomy, lung volume reduction surgery, bronchoscopic lung reduction and in select cases, lung transplantation. Each of these therapies are reviewed below.

Surgical and interventional treatments for patients with emphysema depends upon the severity of patient symptoms despite optimized medical treatment, the specific structural abnormalities and features of the lung seen on CT imaging, the presence of pulmonary and non-pulmonary comorbid conditions, physiological assessment, and the balance of benefits and risks for the individual patient.

Key points for interventional therapy in stable COPD are summarized in **Figure 3.26**.



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Lung surgical treatments for patients with emphysema

Bullectomy

Giant bullectomy is a rare, but effective procedure for surgical resection of bulla that occupies more than one-third of a hemithorax and compresses adjacent viable lung tissue. Reductions in dyspnea, and improvements in lung, respiratory muscle, and cardiac performance, as well as exercise tolerance have been reported.[911-913] Blood or thrombin instillation may be effective in those unfit for resection.[914-916]

Lung volume reduction surgery

Lung hyperinflation is a major contributor to impaired respiratory function and is associated with increased hospitalization and mortality. Hyperinflation increases the sensation of breathlessness and causes a reduction in exercise due to increased chest wall elastance and reduced respiratory muscle and cardiac mechanics. Hyperinflation is most pronounced in those patients with COPD that have an emphysematous predominant phenotype.

With LVRS, the most emphysematous portions of the lungs are resected to reduce hyperinflation,[917] and increase lung elastic recoil pressure and density.[918] The structural changes that result from LVRS can significantly improve expiratory flow and chest wall, respiratory muscle and cardiac mechanics.[919,920] This results in improvements in FEV1, walking distance and quality of life.[921-924] LVRS can be performed unilaterally or bilaterally. In NETT, a RCT that included patients with severe emphysema, bilateral LVRS improved survival in patients with upper-lobe emphysema and low post-rehabilitation exercise capacity.[867] In similar patients with high post-pulmonary rehabilitation exercise capacity, no difference in survival was noted after LVRS, although health status and exercise capacity improved. A reinterpretation of the NETT data at 5 years post treatment showed sustained improvements in lung function, exercise, shortness of breath and quality of life.[925]

LVRS has been demonstrated to result in higher mortality than medical management in patients with severe emphysema who have FEV1 ≤ 20% predicted and either homogeneous emphysema on HRCT or a DLco ≤ 20% of predicted.[926] In addition to a lower DLco, a lower FEV1 and BMI values have also been reported to increase mortality.[927] Decreasing to a lower postoperative BODE is a predictor of improved survival following LVRS.[928] Successful outcomes with LVRS have been reported in select patients with severely impaired DLco when hyperinflation is severe, and associated with approachable emphysematous targets for resection.[929] Identification of target zones using three-dimensional computed tomographic imaging is beneficial in selecting resectable target zones.[930] A prospective economic analysis in NETT indicated that LVRS is costly relative to healthcare programs that do not include surgery.[931]

Post NETT, experienced centers have reported substantial physiological and functional improvements with LVRS, accompanied by reduced morbidity and mortality.[932,933] However, the numbers of patients undergoing LVRS remain low worldwide.[933,934] Several patient factors such as difficulty in obtaining referrals, the perception of increased surgical complications, and limited continuity of care are reasons why the numbers of patients undergoing LVRS remain low despite its reported benefits.[935] Additionally, respiratory physicians are reluctant to refer patients for LVRS because of the uncertainty about the associated complications, or lack of access to a multidisciplinary team to discuss patient candidates.[936] To achieve successful outcomes, a multidisciplinary team is key to select potential patients for LVRS and coordinate postoperative care.[937]

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

Lung volume reduction surgery

- In selected patients with heterogeneous or homogenous emphysema and significant hyperinflation refractory to optimized medical care, surgical or bronchoscopic modes of lung volume reduction (e.g., endobronchial one-way valves, lung coils or thermal ablation) may be considered.[938] Some of these therapies (vapor ablation and lung coils) are not widely available for clinical care in many countries.
- In selected patients with a large bulla, surgical bullectomy may be considered.
- In selected patients with COPD who have very severe airflow obstruction, and who do not have relevant contraindications, lung transplantation may be considered.

Bronchoscopic interventions to reduce hyperinflation in severe emphysema

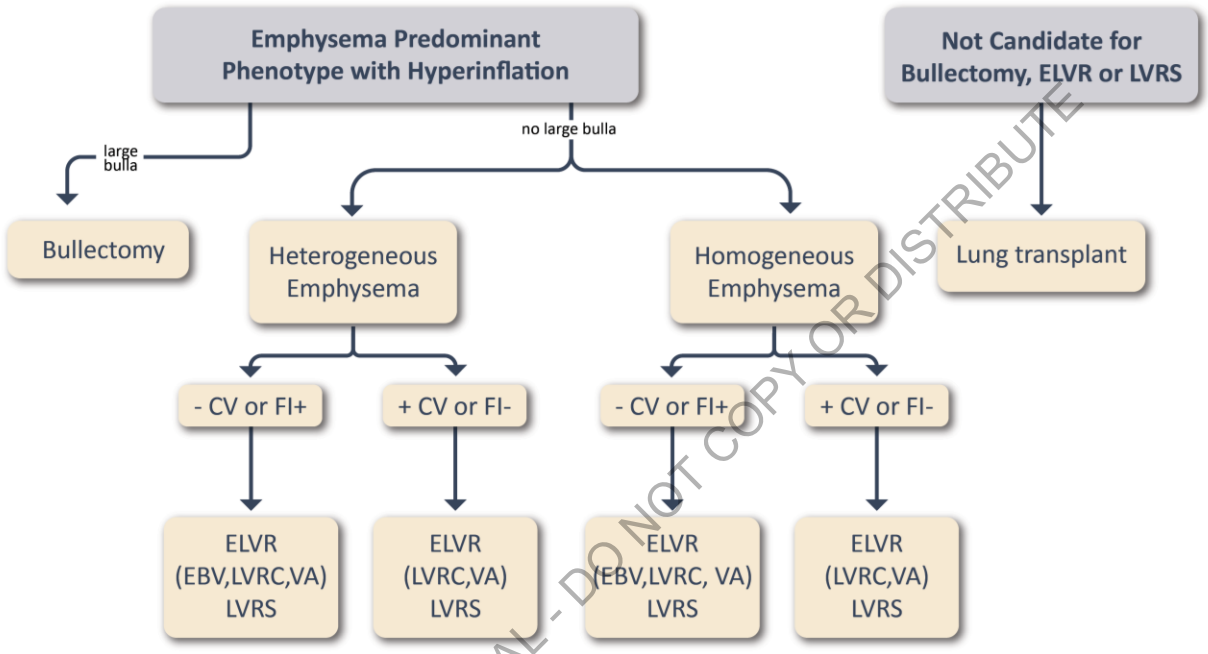
Due to the morbidity and mortality associated with LVRS, less invasive bronchoscopic approaches to lung reduction have been examined.[939] These include a variety of different bronchoscopic procedures to perform lung volume reduction (i.e., ELVR) including airway bypass stents, EBV, self-activating coils, sealants and thermal ablative techniques.[939] Although these techniques differ markedly from one another they are similar in their objective to decrease thoracic volume to improve lung, chest wall and respiratory muscle mechanics.

Choosing bronchoscopic lung reduction (EBV, coil placement or thermal ablation) or surgical resection (LVRS) to treat hyperinflation in a patient with emphysema depends on a number of factors. These include: the extent and pattern of emphysema identified on HRCT; the presence of interlobar collateral ventilation measured by fissure integrity on HRCT

or physiological assessment (endoscopic balloon occlusion and flow assessment); regional availability of the various therapies for clinical care, local proficiency in the performance of the procedures; and patient and provider preferences. Bronchoscopic techniques depend upon the presence of an intact fissure between the treated and non-treated lobe for EBV to be successful, but not for the other techniques. Vapor ablation therapy is the only lung reduction therapy that has been reported to be successfully performed at the segmental rather than lobar level.[940] **Figure 3.27** provides an overview of the various interventional and surgical options for patients with emphysema.

Surgical and Interventional Therapies in Advanced Emphysema

Figure 3.27



Note: not all therapies are clinically available in all countries. Long term ELVR outcomes or direct comparisons to LVRS are unknown.

Definition of abbreviations: CV, collateral ventilation measure by Chartis; FI + fissure integrity > 90% by HRCT; FI-, fissure integrity < 90% by HRCT; ELVR, Endoscopic Lung Volume Reduction, EBV, Endobronchial Valve; VA, Vapor Ablation; LVRC, Lung Volume Reduction Coil; LVRS, Lung Volume Reduction Surgery. Modified from Vogelmeier, AJRCCM, 2017.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Endobronchial one-way valves

EBV are the most well studied therapy of all the ELVR techniques. RCTs showed significant increases in FEV_1 and 6MWD as well as health status in subjects selected for the absence of interlobar collateral ventilation compared to the control group at 6 and 12 months.[568,941] Adverse effects in the endobronchial valve treatment group in both studies included pneumothorax, valve removal or valve replacement.[568] Pneumothorax was seen in 26.6% of subjects treated with the endobronchial valve usually within the first 72 hours of the procedure (76%).[941-943] But benefits have also been shown in patients with heterogeneous compared to those with homogenous emphysema in one study.[568]

Early-onset pneumothorax in the EBV treated group likely results from lung structural changes due to acute volume reduction in the emphysematous targeted lobe by valve therapy that triggers rapid ipsilateral non-targeted lobe expansion, a recognized indicator of successful target lobe occlusion in patients with intact fissures or absence of collateral ventilation.[944] Pleural adhesions may also be a contributing factor to the development of a pneumothorax.[945] The occurrence of pneumothorax highlights the need for physicians performing this procedure to have expertise in the management of procedural complications.[944]

After the post-procedural period, patients treated with EBV tend to have a lower number of exacerbations and episodes of respiratory failure compared to usual care. A comparison of treatment benefits and complications associated with EBV compared to LVRS show comparable benefits with endobronchial valve treatment but with fewer complications.[941] Additionally, ELVR has similar beneficial effects whether it is performed in the upper or lower lobes.[941,944]

Improved survival has been associated with post procedural atelectasis of the treated lobe post EBV.[946-948] Improved survival has also been reported in patients with severe hyperinflation undergoing EBV compared to a matched population not undergoing ELVR.[949]

When preferences for medical treatment for patients with severe emphysema are elicited, the majority chose treatments with EBV over LVRS or continued medial therapy.[950] ELVR with EBV is clinically available and approved for treatment in many countries in the treatment of patients who have intact fissures or lack collateral ventilation.[941,951,952]

The following bronchoscopic lung volume reduction techniques do not depend upon the presence of intact fissures or absence of collateral ventilation.

Airway bypass stents

Airway bypass stents are transbronchial passages that are created through the walls of the central airways into the emphysematous parenchyma to facilitate the emptying of trapped gas. In a prospective randomized controlled clinical trial, patients had short term improvements, but no durable improvements were found in lung function, 6MWD or quality of life.[953]

Sealants

A multicenter study examining the effects of a lung sealant to create lung reduction was discontinued prematurely; while the study reported significant benefits in some physiologic parameters, the intervention was associated with significant morbidity and mortality.[954]

Vapor ablation

In a prospective RCT, targeted thermal vapor ablation of more diseased emphysematous segments to produce fibrosis and atelectasis resulted in clinically meaningful and statistically significant improvements in lung function and health status at 6 months. COPD exacerbation was the most common serious adverse event. Durability of these changes was subsequently reported at 12 months follow-up.[940,955] This therapy has limited clinical availability.

Self-activating coils

Multicenter trials have examined nitinol coils implanted into the lung compared to usual care on changes in 6MWD, lung function and health status in patients with advanced homogenous and heterogeneous emphysema. Studies reported an increase in 6MWD with coil treatment compared to control and smaller improvements in FEV_1, and quality of life measured by SGRQ.[956-958] Patients with baseline residual volume > 200% predicted, emphysema score > 20% low attenuation area, and absence of airway disease are more likely to have clinically meaningful improvements in lung function and quality of life.[959] Major complications included pneumonia, pneumothorax, hemoptysis and exacerbations occurring more frequently in the coil group.[957] This therapy has limited clinical availability.

Additional data are needed to define the optimal bronchoscopic lung volume technique to produce bronchoscopic lung volume reduction in patients who lack fissure integrity, or exhibit collateral ventilation, and to refine the procedure to reduce complications and improve longer term clinical outcomes.[957]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Sequential performance of LVRS or ELVR and lung transplantation

Because COPD is a progressive disease, LVRS or ELVR may be followed by lung transplantation. Conversely, patients who undergo single lung transplantation may subsequently undergo LVRS or ELVR to treat the hyperinflated native lung. In patients with advanced emphysema who are hyperinflated, LVRS or ELVR might be effective treatments to either delay the need for lung transplantation or optimize the condition of patients who may eventually require lung transplantation.[960-962] In some patients following single lung transplantation, the performance of LVRS or ELVR to decrease native lung hyperinflation may improve lung function and performance status.[963-968] The incidence of postoperative bleeding requiring re-exploration and renal dysfunction requiring dialysis or the use of extracorporeal membrane oxygenation may be higher in patients undergoing lung transplantation following LVRS.[969,970] Previous ELVR has been reported to have no impact on morbidity or survival post subsequent lung transplantation but may affect microbial colonization.[970,971]

Airway predominant treatments

Abnormalities that predominantly involve the airways, such as excessive dynamic collapse of the large airways (tracheobronchomalacia) chronic bronchitis and frequent and severe exacerbations not responsive to optimal medical treatment pose significant clinical challenges.

Excessive dynamic airway collapse

Excessive dynamic airway collapse or tracheobronchomalacia is a disorder of the large airways where abnormal collapsibility occurs with expiration. Commons symptoms are dyspnea, cough and wheezing with inability to expectorate phlegm. In a cross-sectional analysis of smokers, the presence of excessive dynamic airway collapse observed on CT imaging was 5% and associated with worsened quality of life and more frequent and severe exacerbations.[972] Airway stenting and tracheoplasty may be beneficial in select patients.[973,974]

Nitrogen cryospray

Chronic bronchitis is a common and significant contributor to a worsening of patient's symptoms of cough and sputum production and cause worsened quality of life and increased mortality. No specific medical intervention significantly and consistently alleviates chronic bronchitis. Newer interventions have been proposed to reduce mucus hypersecretion by eliminating airway goblet cell hyperplasia and submucosal glands.

Liquid nitrogen metered cryospray is delivered to the central airways and ablates the epithelium to a depth of 0.1 to 0.5 mm.[975] After treatment, rapid regeneration of normal epithelium occurs without scarring and may potentially treat chronic bronchitis.[976,977] A prospective multicenter RCT reported that metered dose nitrogen cyrospray therapy in patients with COPD and chronic bronchitis improved SGRQ and CAAT score and decreased the occurrence of severe exacerbations compared to a sham-controlled group at 52 weeks.[978]

Another novel treatment for chronic bronchitis is rheoplasty,[979] which delivers short bursts of high frequency electrical energy to the airway epithelium targeting submucosal tissues and goblet cells to facilitate their replacement with healthier tissue. An ongoing phase 3 RCT is evaluating the efficacy of this therapy.[980]

Lung denervation

Targeted lung denervation intends to disrupt parasympathetic nerve transmission to and from the lungs.[981,982] In patients with COPD, basal parasympathetic tone is elevated and increases acetylcholine levels and mucus production and airway contraction. The treatment uses a water-cooled catheter with radiofrequency energy to disrupt parasympathetic nerve transmission while protecting the airway surface.[982-985] A Phase 3 multicenter sham-controlled RCT reported that lung denervation did not reduce the annualized rate of moderate and severe exacerbations compared to sham but did show an improvement in dyspnea and less decline in FVC and FEV1 and increase in residual volume.[986] Post-hoc analyses identified a subgroup with greater hyperinflation (residual volume ≥ 175% pred) and

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

less emphysema (≤ 20% low attenuation area −950 HU) who had improvements in FEV1, CAAT™, mMRC, and TDI, together with a reduction in moderate and severe exacerbations.[986] A further study is planned in that subgroup.

Lung transplantation

Over 1,000 patients with COPD annually undergo lung transplantation, or about 30.6% of all patients that undergo transplantation.[987] Since implementation of the LAS scoring system, the numbers of patients undergoing lung transplantation for COPD has been exceeded by the numbers of patients receiving transplantation for interstitial lung diseases. Patients with COPD should be referred for consideration of lung transplantation when they have progressive disease despite maximal medical treatment, are not candidates for lung volume reduction surgery, have a BODE index of 5 to 6, a $PaCO_2$ > 50 mmHg (6.6 kPa) and/or PaO_2 < 60 mmHg (8 kPa) and FEV1 < 25%.[988] They should be considered for listing for lung transplantation when: the BODE index is ≥ 7; FEV1 is < 15% to 20%; they have had three or more severe exacerbations during the previous year; one severe exacerbation with hypercapnic respiratory failure; or have moderate to severe pulmonary hypertension.[988] In the last decade, lung transplant has been increasingly performed in patients of older age, higher BMI, prior chest surgery, poor nutritional status, prior evidence of chronic infection, cardiovascular disease, or extrapulmonary comorbid conditions.[989]

Lung transplantation in patients with COPD has been predominately associated with an improvement in quality of life, although not an increase in survival except for patients with COPD who have severe AATD or those severely impaired with high BODE scores.[911,990-996] The median survival following lung transplantation for COPD is 5.9 years.[987] Over 70% of lung transplants conducted in patients with COPD are double lung transplants; the remainder are single lung transplants.[997] Bilateral lung transplantation leads to longer survival in patients with COPD especially in those < 60 years of age.[998,999]

In general, lung transplantation has limited availability due to the shortage of donor organs and cost, thus single vs. double lung transplantation is balanced between individual patient factors vs. societal demands to increase the donor pool for eligible recipients.[1000] The most frequent complications in patients with COPD after lung transplantation are acute rejection, bronchiolitis obliterans, opportunistic infections and lymphoproliferative disease.[1001]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

CHAPTER 4: MANAGEMENT OF EXACERBATIONS

KEY POINTS:

- An exacerbation of COPD is an acute event with symptoms worsening over a few days (up to 14 days) and characterized by increased dyspnea and/or cough and sputum that may be accompanied by tachypnea and/or tachycardia. Exacerbations are often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insults to the lungs.
- Although COPD exacerbations are most frequently caused by infections (viral, bacteria) or environmental pollutants, other conditions can mimic or worsen exacerbation-like symptoms. These include pneumonia, pulmonary embolism, acute heart failure, and pneumothorax. In many patients the exact cause of an exacerbation is unknown.
- Exacerbation severity is classified as mild, moderate or severe based on the clinical characteristics of the patient, according to the Rome proposal.
- Pharmacological therapy should be started as soon as possible to prevent both complications and subsequent events. It includes:
    - SABAs, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat moderate/severe exacerbations.
    - Systemic corticosteroids are recommended for up to 5 days in patients with moderate/severe exacerbations.
    - Antibiotics are recommended for a total of 5 days in patients with purulent sputum, prior history of lung infections, etc.
    - Methylxanthines are not recommended due to increased side effect profiles.
- High flow oxygen systems and mechanical NIV are indicated for patients with COPD and acute respiratory failure because they improve gas exchange, reduce work of breathing and the need for intubation. They also decrease hospitalization duration and improve survival.
- Maintenance therapy with LABDs should be initiated as soon as possible. In patients with ≥ 1 moderate or severe exacerbation and elevated blood eosinophil levels, the addition of ICSs to a dual bronchodilator regimen should be considered at discharge.
- Exacerbation recovery time varies, taking up to 4-6 weeks, with some patients failing to return to their pre-exacerbation functional state.
- Following an exacerbation (of any severity) there is an increased risk of severe cardiovascular events.
- Following an exacerbation, the management of COPD and its comorbidities should be reviewed and appropriate measures for exacerbation prevention should be implemented (see **Chapter 3**).

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

DEFINITION

An exacerbation of COPD is an acute event with symptoms worsening over a few days (up to 14 days) and characterized by increased dyspnea and/or cough and sputum that may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by infection, pollution, or other insult to the airways.[307]

Impact

Exacerbations of COPD are important events because they negatively impact health status, worsen airflow obstruction,[1002] disease progression, rates of hospitalization and readmission, and risk of death.[473,475,1003-1005] COPD exacerbations are associated with increased airway inflammation, increased mucus production and marked gas trapping.[305,1006] These changes contribute to increased dyspnea that is the key symptom of an exacerbation. Other important symptoms include increased sputum purulence and volume, together with worsened cough, wheeze and difficulty sleeping due to symptoms.[1007] Many exacerbations are not reported to healthcare professionals, and yet these events, although often shorter in duration, also have a significant impact on health status.[1008,1009] The WHO has defined a minimum set of interventions for the management of exacerbations that are of use in most settings.[1010]

Assessing the patient and confirming the diagnosis

The diagnosis and assessment at the point of contact with a person with COPD can be confirmed by applying a systematic approach as proposed by the Rome classification of severity and outlined in **Figure 4.1**.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Exacerbations: Diagnosis and Assessment — Figure 4.1

1.	Complete a thorough clinical assessment for evidence of COPD and potential respiratory and non-respiratory conditions, including patient's symptoms, and signs of pneumonia, cardiovascular conditions, and pulmonary embolism.
2.	**Assess:** a. Symptoms, severity of dyspnea that can be determined by using a VAS, and documentation of the presence of cough. b. Signs (tachypnea, tachycardia), sputum volume and color, and respiratory distress (accessory muscle use).
3.	Perform additional investigations, if needed and available, to evaluate severity such as pulse oximetry, laboratory assessments such as blood eosinophils, CRP, viral and bacterial studies, and arterial blood gases.
4.	Evaluate for underlying conditions such as viral or bacterial infections, environmental or cardiovascular events that mimic the exacerbation.
5.	Consider appropriate place of care.

Abbreviations: COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; VAS = visual analog scale.

COPD exacerbation severity classification

Over the last two decades, the severity of an exacerbation has been classified *post hoc* primarily based on healthcare resource utilization and the treatment implemented.[502,515,732,868,1011,1012] This is probably adequate in clinical trials but useless at the point of care. We are **NOW** proposing that the severity of an exacerbation (as well as its treatment and place of care) be determined based on the clinical characteristics of the patient. The Rome classification of exacerbation severity[1013] is based on a thorough review of the available literature and a modified Delphi method to determine the variables and thresholds included. We propose that the severity of COPD exacerbations should be classified as mild, moderate or severe as summarized in **Figure 4.2**:

- **Mild**
  - Dyspnea VAS < 5
  - Respiratory rate < 24 breaths/min
  - Heart rate < 95 bpm
  - Resting SaO_2 ≥ 92% breathing ambient air (or patient's usual oxygen prescription) AND change ≤ 3% (when known)
  - CRP < 10 mg/L (if available)
- **Moderate** (meets at least three of five*)
  - Dyspnea VAS ≥ 5
  - Respiratory rate ≥ 24 breaths/min
  - Heart rate ≥ 95 bpm
  - Resting SaO_2 < 92% breathing ambient air (or patient's usual oxygen prescription) AND/OR change > 3% (when known)
  - CRP ≥ 10 mg/L (if available)

  *If obtained, ABG may show hypoxemia (PaO_2 70-80 mmHg)
- **Severe**
  - Dyspnea, respiratory rate, heart rate, SaO_2 and CRP same as moderate
  - If obtained, ABG may show hypoxemia (PaO_2 ≤ 60 mmHg) and/or hypercapnia and acidosis ($PaCO_2$ > 45 mmHg and pH < 7.35)

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

When evaluating a patient with COPD who is complaining of acute worsening of respiratory symptoms, it is desirable to systematically evaluate the severity of the event using clinical, physiological and laboratory variables that can reflect organ decompensation and potential outcomes (**Figure 4.2**).

In hospitalized patients, the severity of the exacerbation should be based on the patient's clinical signs, and we recommend the following classification:[1014]

No respiratory failure: Respiratory rate: ≤ 24 breaths per minute; heart rate ≤ 95 bpm, no use of accessory respiratory muscles; no changes in mental status; hypoxemia improved with supplemental oxygen given via Venturi mask 24-35% FiO_2; no increase in $PaCO_2$.

Respiratory failure: Respiratory rate: > 24 breaths per minute; heart rate > 95 bpm, using accessory respiratory muscles; appropriate mental status; hypoxemia improved with supplemental oxygen via Venturi mask > 35% FiO_2; hypercapnia i.e., $PaCO_2$ increased compared with baseline or elevated 50-60 mmHg.

Ventilatory Failure: Respiratory rate: > 24 breaths per minute; heart rate > 95 bpm, using accessory respiratory muscles; acute changes in mental status; hypoxemia not improved with supplemental oxygen via Venturi mask or requiring FiO_2 > 40%; hypercapnia i.e., $PaCO_2$ increased compared with baseline or elevated > 60 mmHg

and the presence of acidosis (pH ≤ 7.25).

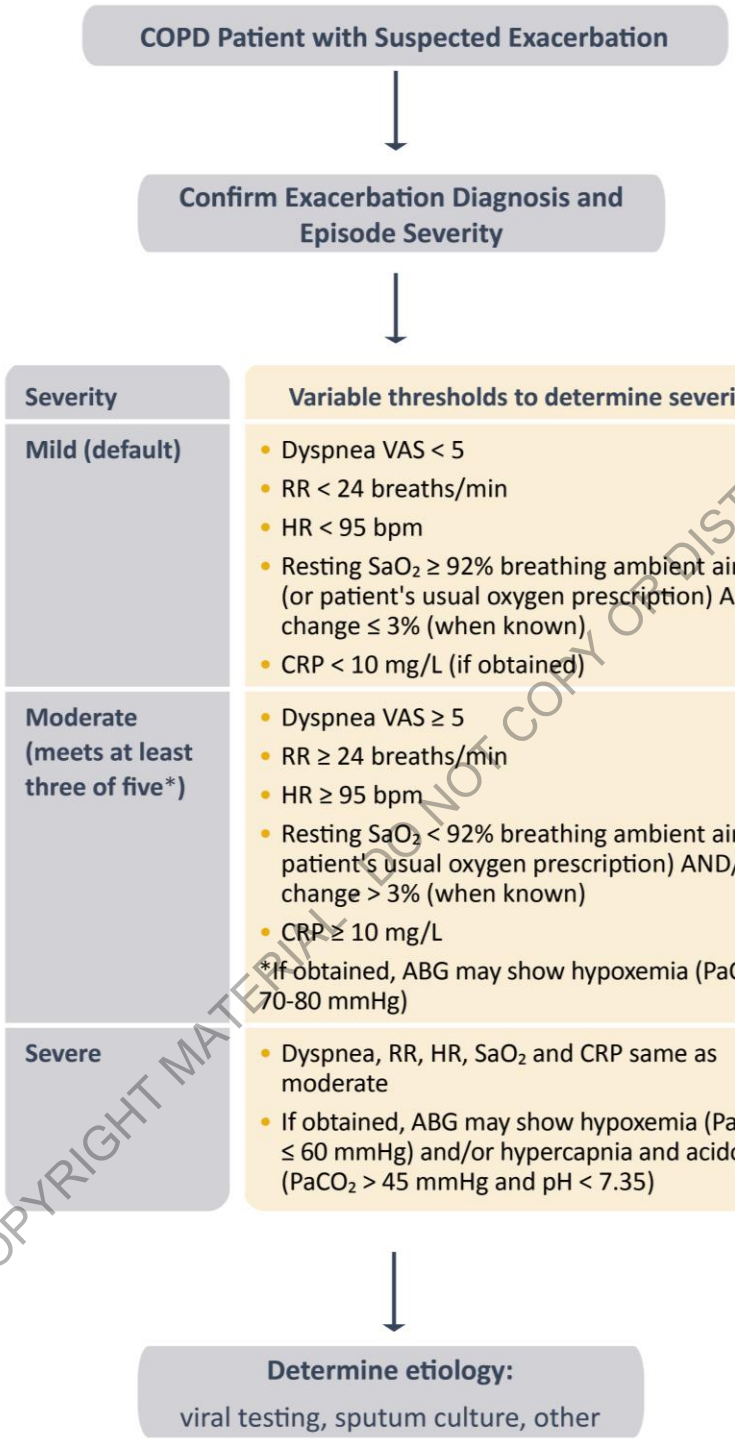
Several studies conducted in different countries have shown that the variables included in the Rome classification are routinely available in the hospital setting.[1015,1016] Importantly, these studies have shown that using the Rome classification 15-30% of people admitted for a COPD exacerbation classify as having a mild event, whereas using a severity classification based on healthcare resource use they would have been classified as having had a severe event. Around 50% of those admitted had a moderate episode and close to 10% a severe episode.[1015-1018] Data suggest that severity of exacerbations using the Rome grading scheme correlates with prognosis, including need for intensive care admission and mortality.[1015-1019]

In settings where laboratory variables are not available, such as primary care, the severity of an exacerbation can be determined by quantification of dyspnea intensity using the VAS 0 to 10 dyspnea scale (where zero equates to not short of breath at all and 10 is the worst shortness of breath ever experienced), respiratory rate, heart rate and SaO_2 (**Figure 4.2**). Worsening of dyspnea in a patient with COPD, particularly if associated with cough, purulent sputum, and difficulty sleeping due to these symptoms, but no other symptoms or signs may be diagnosed as a COPD exacerbation. However, some patients may have worsening of respiratory symptoms, particularly dyspnea, but without other COPD exacerbation symptoms; this should prompt careful consideration of concomitant conditions.[1020] Where available, measuring blood CRP level is also recommended.[1021] To move from mild to moderate severity, three of the variables need to exceed the established thresholds. It is hoped that prospective validation will help better define exacerbations and their severity at point of contact, and that documented validation may confirm, or help modify, the thresholds of included factors. It is proposed that prospective research will help determine a more specific marker of lung injury than the more generic CRP, as has been true for other organs and acute events.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Classification of the Severity of COPD Exacerbations

Figure 4.2



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Adapted from: The Rome Proposal, Celli et al. (2021) Am J Respir Crit Care Med. 204(11): 1251-8.

Abbreviations: VAS visual analog dyspnea scale; RR respiratory rate; HR heart rate; SaO_2 oxygen saturation; CRP C-reactive protein; ABG arterial blood gases; PaO_2 arterial pressure of oxygen; $PaCO_2$ arterial pressure of carbon dioxide.

Conditions to be considered

Patients with COPD are at increased risk of respiratory viral infections;[1022,1023] bacterial infections;[1024] pneumonia;[1025-1029] decompensated heart failure;[1030,1031] myocardial infarction and arrhythmias;[1032-1034] and pulmonary embolism.[1035-1037] These conditions may mimic or worsen exacerbations, particularly those requiring hospitalization, and are associated with increased risk of developing a fatal or non-fatal cardiovascular event such as heart failure, cardiac arrhythmias and/or stroke. Furthermore, the major adverse cardiovascular event risk remains elevated up to one year after the exacerbation.[1033,1034] In some patients, one or more conditions may contribute to the clinical presentation and should be addressed appropriately, as outlined in **Figure 4.3**.

Conditions That May Mimic or Worsen Exacerbation-like Symptoms

Figure 4.3

Tools available to address potential confounders:

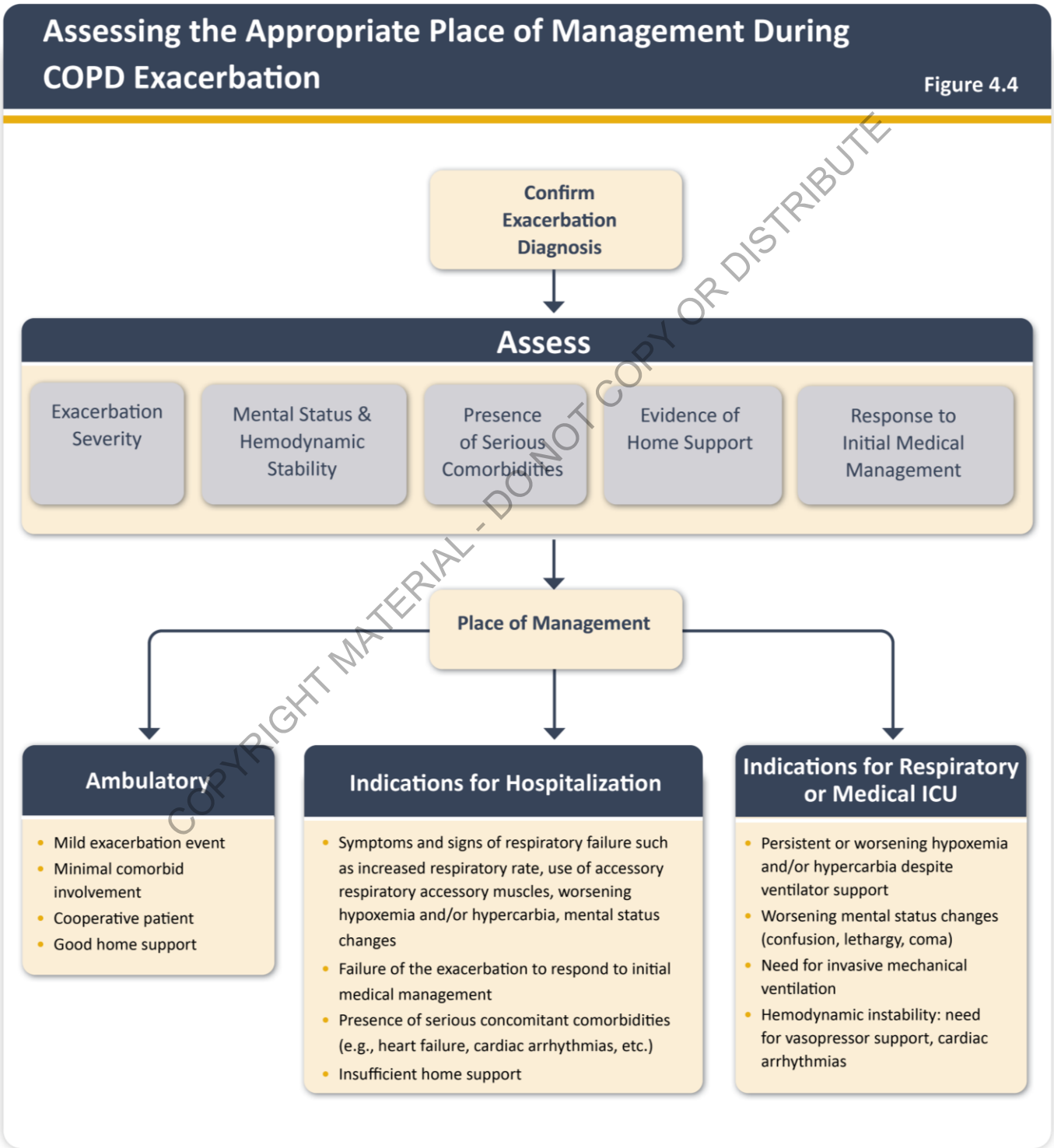
Most frequent	**Acute viral or bacterial bronchitis** • Viral and bacterial microbiological assessment • Chest X-ray
	Heart failure • Chest X-ray or chest CT scan • NT pro-brain natriuretic peptide (NT proBNP) and BNP • Cardiac ultrasound (echocardiogram)
	Myocardial infarction and/or cardiac arrhythmias (atrial flutter/fibrillation) • Electrocardiography • Troponin
	Pulmonary embolism • Clinical probability assessment (hemoptysis, deep vein thrombosis, history of cancer, surgery, bone fracture) • D-dimer • CT angiography for pulmonary embolism
	Pneumonia • Viral and bacterial microbiological assessment • Chest X-ray or chest CT scan • Lung ultrasound
Less frequent	**Pneumothorax** • Chest X-ray or chest CT scan • Thoracic ultrasound

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Echocardiography will help to detect heart changes in patients with COPD exacerbations including heart failure and pulmonary hypertension despite challenges like poor acoustic windows.[1038] Hospitalized patients with severe exacerbations demonstrate significant echocardiographic abnormalities across the left and right sides of the heart even if they have no history of heart disease.[1039,1040]

Decision-making about the management setting

When deciding on the setting in which a patient with an exacerbation should be managed, it is important to determine not only the severity of the exacerbation *per se*, as detailed in the Rome proposal, if possible, but also assess how compromised the patient is. This assessment should include underlying COPD severity, presence and severity of comorbidities, mental status, and social and environmental factors, particularly the availability of home support. In practice, most exacerbations are managed on an outpatient basis, however even patients with a mild exacerbation may need hospital admission if there are other underlying problems. A guide to help assess the appropriate place of management is given in **Figure 4.4**.



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

In patients with exacerbations who have no signs of respiratory distress or indications for hospitalization (**Figure 4.4**) management can be ambulatory. Ambulatory patients should be closely followed up to ensure improvement, and they should be instructed to seek medical care if there is acute worsening of their condition. When a person having a COPD exacerbation comes to the ED, it is necessary to determine whether the exacerbation is life-threatening and consider whether the increased work of breathing or impaired gas exchange requires high flow oxygen or NIV. To determine the need for ventilator support (usually in the ED or hospital setting) blood gases should be measured. If high flow oxygen or ventilator support is required healthcare providers should consider admission to an area where proper monitoring and care by well-trained personnel can be provided. In less severe cases, the patient may be managed in the ED and if the clinical response is good, the patient may be discharged to be treated at home with clear instructions and a follow-up appointment.

If the patient is hospitalized, the severity of the exacerbation should be monitored based on their clinical signs including the variables mentioned in the Rome proposal and mental status changes. Particularly important is the monitoring of gas exchange variables. In this regard, the gold standard continues to be determination of ABGs[1041,1042] in more severe cases, while venous blood gases can be helpful in less severe COPD exacerbations.[1043] The use of transcutaneous capnography[1044,1045] can be helpful in less severe cases, while oxygen saturation, a universally useful tool as the fifth vital sign, has been shown to be less accurate in individuals with darker skin tone.[1046]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

RISK FACTORS AND SYMPTOMS

Triggers

Given many exacerbations are not reported to healthcare professionals, people with COPD need to receive education about the importance of understanding exacerbation symptoms and when to seek professional healthcare.

Exacerbations are mainly triggered by respiratory viral infections, although bacterial infections and environmental factors such as ambient air pollution, excess heat and cold, wildfire smoke and dust-storms may also initiate and/or amplify these events.[650,1047-1050] The most common viruses isolated are human rhinovirus (the cause of the common cold), influenza, para-influenza and metapneumovirus which can be detected for up to a week after an exacerbation onset.[1051,1052] A report from the UK showed RSV was associated with 8.7% of outpatient managed COPD exacerbations.[709] Exacerbations associated with viral infections are often more severe, last longer and precipitate more hospitalizations, as seen during winter. Short-term exposure to ambient NO_2, PM2.5, and PM10 is associated with increased hospitalizations, ED visits, and outpatient visits,[1053] as well as increased mortality from COPD exacerbations.[53,1054-1056] A 2025 cohort study found that long term exposure to air pollution is also associated with increased risk of COPD exacerbations.[115]

Filamentous fungi, particularly Aspergillus species, may be identified in sputum samples of patients during moderate or severe exacerbations[1057-1059] although their clinical relevance remains unclear. Invasive pulmonary aspergillosis is rare (1.3-3.9%)[1060] and more frequent in patients with more severe baseline airflow obstruction, recent use of broad-spectrum antibiotics or parenteral steroids, and hypoalbuminemia.[1061] The diagnostic approach to invasive aspergillosis in this setting remains challenging.[1062] Aspergillus sensitization is also a marker of increased risk of exacerbations.[1063]

Symptoms

Exacerbations can be associated with increased dyspnea, difficulty breathing, fever and sputum production that, if purulent, may indicate bacterial infection.[1007,1022,1051] There is evidence that viral infections are associated with a persistent, non-productive cough, worsening dyspnea and wheeze, with significant impact on quality of life.[1064-1066]

During a COPD exacerbation, increased symptoms are usually present for 7-10 days, but some events may last longer. At 8 weeks up to 20% of patients will not have recovered to their pre-exacerbation state.[1067] COPD exacerbations contribute to disease progression,[1068] which is more likely if recovery from exacerbations is slow.[1069] Exacerbations can also cluster in time and once they occur there is increased likelihood of another event[478,1070] (see **Chapter 2**).

Exacerbations in patients with COPD with biomass exposure are clinically similar to smoking-related COPD but markers of inflammation (T2) may be enhanced in these patients during exacerbations.[1071]

Risk factors and scores for future events

Risk of occurrence

Several scores and factors can help predict COPD exacerbations. The most significant predictors include a history of previous exacerbations, impaired lung function (particularly FEV1), and the number of COPD maintenance medications. Other factors include female sex, higher daily reliever medication use, eosinophil count, and the presence of comorbidities, such as a history of gastro-esophageal reflux. However, the strongest predictor of future exacerbation frequency remains the number of exacerbations in the prior year.[478] This includes exacerbations prior to diagnosis, with even one exacerbation in the prior year increasing the risk of exacerbations in the next 12 months,[478,513,1072,1073] although the risk is greater if there have been two or more previous exacerbations. It is recognized that these patients form a moderately stable phenotype, even if some studies have shown that a significant proportion of patients change their exacerbation frequency especially with worsening FEV1.[1074]

Other factors associated with an increased risk of acute exacerbations and/or severity of exacerbations include an increase in the ratio of the pulmonary artery to aorta cross sectional dimension (i.e., ratio > 1),[304] a greater percentage of emphysema or airway wall thickness[570] measured by chest CT imaging, dynamic hyperinflation,[1075] the presence of chronic bronchitis,[188,1076] high symptom burden (as measured by mMRC scale and CAAT™) and GERD.[1077]

Risk of poor short-term outcomes

Several factors are associated with an increased risk of readmission, including age, male sex, markers of health status, disease burden (including previous exacerbation history), exacerbation severity (e.g., acidotic respiratory failure, need for mechanical ventilation, length of hospital stay), multimorbidity (e.g., CVDs, anxiety and depression), socio-familial context, and some biomarkers.[1078-1080] Receiving intubation with positive pressure ventilation or NIV are independent risk factors for rehospitalization and higher mortality.[1081] In addition, predictive scores have been developed to predict the risk of readmission.[1082] Deficiencies in management have also been identified in large-scale audits: the lack of healthcare resources such as respiratory specialists is associated with re-hospitalization and mortality.[1083]

Vitamin D has an immune-modulating role and has been implicated in the pathophysiology of exacerbations.[1084] As with many chronic diseases, vitamin D levels are lower in people with COPD than in healthy individuals. Some, but not all studies have shown that supplementation in people with severe deficiency results in a 50% reduction in episodes and hospital admission.[1084,1085] Therefore it is recommended that all patients hospitalized for exacerbations should be assessed and investigated for severe deficiency (< 10 ng/ml or < 25 nM) followed by supplementation if required.

Cohort studies have produced differing results regarding the ability of blood eosinophils to predict future exacerbation outcomes, reporting either no relationship[492] or a positive relationship.[493,494] Differences between studies are likely due to different exacerbation histories and ICS use. The presence of sputum eosinophilia has been related to susceptibility to viral infection.[1022] There is insufficient evidence to recommend that blood eosinophils should be used to predict future exacerbation risk on an individual basis in patients with COPD. It has been suggested that exacerbations associated with an increase in sputum or blood eosinophils may be more responsive to systemic steroids[1086] although more prospective trials are needed to test this hypothesis.[1086] Recent prospective analysis of SPIROMICS suggests that serum IgG levels are associated with increased risk of exacerbation.[1087]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Risk of poor long-term prognosis

Long-term prognosis following hospitalization for a COPD exacerbation is poor, with a five-year mortality rate of about 50%.[1088] Factors independently associated with poor outcome include older age, lower BMI, comorbidities (e.g., CVD or lung cancer), previous hospitalizations for COPD exacerbations, clinical severity of the index exacerbation, and need for LTOT at discharge.[1089-1091] Patients characterized by a higher prevalence and severity of respiratory symptoms, poorer quality of life, worse lung function, lower exercise capacity, lower lung density and thickened bronchial walls on CT-scan are also at increased risk of mortality following an acute COPD exacerbation.[1092] COPD exacerbations increase the risk of adverse cardiovascular events, with heightened risk in the first 30 days persisting for up to 1–2 years.[1093] Mortality risk may be heightened during spells of cold weather.[1094]

A Cochrane review concluded that the use of COPD exacerbation action plans with a single, short educational component, in conjunction with ongoing support, reduced in-hospital healthcare utilization. Such educational interventions were also found to increase the treatment of COPD exacerbations with corticosteroids and antibiotics.[1095]

Cardiopulmonary interactions during and following an exacerbation of COPD

During an exacerbation of COPD, cardiopulmonary interactions may be aggravated with the consequence of a deterioration of both cardiovascular and lung function. The mechanisms underlying these interactions are discussed in **Chapter 5**.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Risk of Severe Cardiovascular Event or All-Cause Death following COPD Exacerbation of any Severity Figure 4.5

Exposure (days after exacerbation)	Pooled Hazard Ratio*
1-7 days	10.22 (95% CI: 5.34, 19.57)
8-14 days	4.00 (95% CI: 2.58, 6.18)
15-30 days	2.93 (95% CI: 2.13, 4.02)
31-180 days	1.70 (95% CI: 1.45, 2.00)
181-365 days	1.24 (95% CI: 1.08, 1.40)
> 365 days	1.18 (95% CI: 0.93, 1.50)

*Random effects meta-analysis of adjusted hazard ratio; HR: hazard ratio; CI: confidence interval; adapted from Nordon et al.ERJ Open Res. 2025 Jun 16;11(3):01091-2024.

As a result, during an exacerbation of COPD the risk of an acute cardiovascular event, such as myocardial infarction, heart failure, arrhythmias and stroke, increases further,[1096] particularly in those with severe exacerbations that require hospitalization.[1034,1097] Recent research has shown that the risk of suffering a serious cardiovascular event remains high during the first few weeks after hospital discharge following an exacerbation of COPD, and it can still remain significantly increased for up to one year.[1033,1096,1098-1100] A multi-country real-world analysis of studies based on a common protocol reported significant increased risk of severe cardiovascular events following both moderate and severe exacerbations (**Figure 4.5**).[1101]

These considerations have clinical implications: (1) It may be advisable to measure markers of CVD, such as troponin and brain-natriuretic peptides, *routinely during* exacerbations.[1098,1102] The evidence supporting this proposal is still weak, but the observations discussed above support it.[1096,1097] If any of these markers are abnormal *during* the exacerbation, appropriate further investigations and treatment are required following CVD recommendations; (2) Currently, however, there is no evidence to support the routine use of preventive cardiovascular treatment (e.g., aspirin) *during* or *following* an exacerbation, but this merits research. Beta-blockers and statins should be prescribed according to their CVD indication.

Scores

Several scoring systems have been developed to quantify the risk of future COPD exacerbations. The most used tools are SCOPEX (Score to Predict Short-Term Risk of COPD Exacerbations), which considers factors such as the number of COPD maintenance medications prior to the trial, higher average daily reliever use, a greater number of previous year exacerbations, lower FEV1/FVC ratio, and female sex. The score was validated to predict the likelihood of exacerbation within 6 months.[1103] CEX-HScore (CopdEX-Health Search Score) assesses the risk of COPD exacerbation, with a focus on the primary care setting and uses predictive factors that were developed using 16 determinants. The score showed fair accuracy for predicting exacerbations over a 6-month period.[1104] The DECAF Score (Dyspnea, Eosinopenia, Consolidation, Acidemia, and Atrial Fibrillation) was developed to identify in-hospital mortality in patients experiencing acute exacerbations.[1105] A modification of the DECAF score (mDECAF) replaces atrial fibrillation with history of exacerbations in the previous year. The main limitation of these scores is the lack of validation, poor sensitivity and specificity. GOLD does not recommend the routine use of any of these scores.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

TREATMENT OPTIONS

Treatment setting

The goals of treatment for COPD exacerbations are to minimize the negative impact of the current exacerbation and prevent the development of subsequent events.[1106] Depending on the severity of an exacerbation and/or the severity of the underlying disease, an exacerbation can be managed in either the outpatient or inpatient setting. More than 80% of exacerbations are managed on an outpatient basis with pharmacological therapies including bronchodilators, corticosteroids, and antibiotics.[478,1012,1107]

The indications for assessing the need for hospitalization during a COPD exacerbation are shown in **Figure 4.4**. When patients with a COPD exacerbation come to the ED, if hypoxemic they should be started on controlled oxygen therapy and undergo assessment to determine whether the exacerbation is life-threatening and if increased work of breathing or impaired gas exchange requires consideration for NIV. If so, healthcare providers should consider admission to an area where proper monitoring and care can be provided. In less severe cases, the patient may be managed in the ED or hospital ward unit. In addition to pharmacological therapy, hospital management of exacerbations includes respiratory support (oxygen therapy, ventilation). The management of severe, but not life-threatening, exacerbations is outlined in **Figure 4.6**. Key points for the management of all exacerbations are given in **Figure 4.7**.

Management of Severe but not Life-threatening Exacerbations*

Figure 4.6

Assess severity of symptoms, blood gases, chest radiograph

Bronchodilators:

- Increase doses and/or frequency of short-acting bronchodilators
- Combine short-acting beta$_2$-agonists and anticholinergics
- Consider use of long-acting bronchodilators when patient becomes stable
- Use spacers or air-driven nebulizers when appropriate

Consider oral corticosteroids

Consider antibiotics (oral) in patients with purulent oral secretions, prior positive sputum bacteria culture or requiring mechanical ventilation (invasive or noninvasive)

Consider high flow oxygen (HFNT) or noninvasive ventilation (NIV), obtain serial blood gas, venous blood gas and pulse oximetry measurements

At all times:

- Monitor fluid balance
- Consider subcutaneous heparin or low molecular weight heparin for thromboembolism prophylaxis
- Identify and treat associated conditions (e.g., heart failure, arrhythmias, pulmonary embolism etc.)

*Local resources need to be considered

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Key Points for the Management of Exacerbations

Figure 4.7

- Short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation **(Evidence C)**
- Systemic corticosteroids can improve lung function (FEV1), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy 5 days **(Evidence A)**
- Antibiotics are indicated in patients with purulent sputum, prior positive sputum bacteria culture, or requiring mechanical ventilation (invasive or noninvasive) **(Evidence A)**
- Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy 5 days **(Evidence B)**
- High flow oxygen (HFNT) is the first mode of ventilation used in COPD patients with acute hypoxemic respiratory failure. For patients with hypercarbic respiratory failure or those who do not respond to HFNT, use non-invasive mechanical ventilation (NIV) unless absolutely contraindicated. NIV has been shown to: improve gas exchange, reduce breathing work and need for intubation, decrease hospitalization duration and improve survival **(Evidence A)**

PHARMACOLOGICAL TREATMENT

The three classes of medications commonly used for COPD exacerbations are bronchodilators, glucocorticoids, and antibiotics.

Bronchodilators

Although there is no high-quality evidence from RCTs, it is recommended that inhaled SABAs, with or without short-acting anticholinergics, are the initial bronchodilators for acute treatment of a COPD exacerbation.[1108,1109] A systematic review of the route of delivery of SABAs found no significant differences in FEV1 between using pMDIs (with or without a spacer device) or nebulizers to deliver the agent,[613,1110] although the latter may be an easier delivery method for sicker patients. If a nebulizer is chosen to deliver the bronchodilator agent, air-driven bronchodilator nebulization is preferable to oxygen-driven in acute exacerbations of COPD to avoid the potential risk of increasing the $PaCO_2$ associated with oxygen-driven bronchodilator administration.[1111] It is recommended that patients do not receive high doses of SABA due to possible side effects. Patients can receive one dose of nebulized medication every hour for 2-3 doses or use a pMDI one or two puffs every one hour for two or three doses and then every 2-4 hours based on the patient's response. Although there are limited clinical studies that have evaluated the use of inhaled LABDs (either $beta_2$-agonists or anticholinergics or combinations) with or without ICS during an exacerbation, we recommend continuing these treatments during the exacerbation or to start these medications as soon as possible before hospital discharge.[1112,1113] In several countries nebulized LABDs are available, such as arformoterol, formoterol, or revefenacin. These medications have an onset of action similar to albuterol but have a longer duration of action. These nebulized solutions might be effective bronchodilators during exacerbations and could reduce the required frequency of treatments. However, there have not been any trials comparing nebulized LABA with nebulized SABA for COPD exacerbations, although this approach has been used in some hospital settings. One retrospective case-control study that compared hospitalized subjects treated with a nebulized LABA versus a nebulized SABA found that there was a reduction in 30-day readmissions with the LABA.[1114]

Intravenous methylxanthines (theophylline or aminophylline) **are not recommended** in these patients due to significant side effects.[1115,1116]

Glucocorticoids

Data from studies (mostly hospital-based) indicate that systemic glucocorticoids in COPD exacerbations shorten recovery time and improve lung function (FEV1). They also improve oxygenation,[1117-1120] the risk of early relapse, treatment failure,[1121] and the length of hospitalization.[1117,1119,1122] A dose of 40 mg prednisone-equivalent per day for 5 days is recommended.[1123] A systematic literature review concluded that a 5-day course of glucocorticoids is likely to be sufficient in patients with mild-to-moderate exacerbations, with the recognition that the quality of the evidence behind this recommendation is moderate.[1124] One observational study suggested that longer courses of oral glucocorticoids for COPD exacerbations are associated with an increased risk of pneumonia and mortality.[1125] Therapy with oral prednisolone is equally effective to intravenous administration.[1126] Nebulized budesonide alone may be a suitable alternative for treatment of exacerbations in some patients,[1118,1127,1128] and provides similar benefits to intravenous methylprednisolone, although the choice between these options may depend on local cost issues.[1129,1130] Even short bursts of glucocorticoids are associated with subsequent increased risk of pneumonia, sepsis and death[1131] and use should be confined to patients with significant exacerbations. Recent studies suggest that glucocorticoids are more efficacious when treating acute COPD exacerbations in patients based on blood eosinophil levels.[478,1023,1086,1132] A double-blind, placebo-controlled RCT (STARR2) of prednisolone therapy guided by blood eosinophil count during an acute COPD exacerbation suggested that prednisone could be safely avoided in some patients with COPD exacerbations and low eosinophil levels in primary care settings.[1133] However, there is a need for further prospective studies in hospitalized patients to validate these findings.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Antibiotics

Although the infectious agents in COPD exacerbations can be viral or bacterial,[1052,1134] the use of antibiotics in exacerbations remains controversial. A Cochrane review concluded that there is a strong beneficial effect of antibiotic treatment during an exacerbation requiring intensive care, in terms of mortality and treatment failure.[1135] In other exacerbations requiring hospitalization the benefit is significant only when trials using antibiotics no longer in use are included.[1135] A large retrospective study showed that the administration of antibiotics in the first 2 hospital days was associated with improved outcomes compared with later initiation or no antibiotic treatment during the hospitalization.[1136] The benefit of using antibiotics in moderate, ambulatory exacerbations is less clear. In an RCT, the addition of doxycycline to oral corticosteroids in an outpatient setting did not prolong the time to next exacerbation.[1137] Systematic reviews of placebo-controlled studies have shown the benefits of antibiotic treatment in moderately or severely ill patients with COPD exacerbations with increased cough and sputum purulence.[1138,1139] These data are supported by more RCTs in patients with diagnoses of moderate COPD.[1140]

Identifying markers to help determine which patients will benefit from the use of antibiotics for the treatment of exacerbations is key. In general, there is evidence supporting the use of antibiotics when patients have clinical signs of a bacterial infection e.g., increased sputum purulence.[334,1141] Indeed, observed sputum purulence has 94.4% sensitivity and 52% specificity for high bacterial load.[334] Unfortunately, in the outpatient setting, sputum cultures are not feasible as they take at least 2 days and frequently do not give reliable results for technical reasons.

Several biomarkers of airway infection are being studied in exacerbations of COPD. Earlier studies of CRP reported contradictory findings.[1142,1143] One RCT found a marked reduction in antibiotic prescriptions without impaired outcomes in UK primary care outpatients with an exacerbation in whom antibiotics prescriptions were guided by point-of-care CRP testing.[1144] Another trial in patients hospitalized for exacerbations of COPD in The Netherlands found similar results (reduced antibiotic use with no increase in treatment failure).[1144] A double-blind, placebo-controlled study in exacerbations in patients with COPD who had mild to moderate airflow limitation and who were being managed in primary care showed that purulence of sputum and elevated point-of-care CRP were the two factors that identified patients with increased risk of failure without antibiotics.[1145]

Procalcitonin is an acute phase reactant that increases in response to bacterial infection and has been studied to determine the use of antibiotics in COPD exacerbations.[1146] The efficacy of this biomarker is controversial. Several studies, conducted mainly in the outpatient setting, suggested that procalcitonin-guided antibiotic treatment reduces antibiotic exposure and side effects with the same clinical efficacy.[1147-1149] A systematic review and meta-analysis on the use of procalcitonin in hospitalized patients with a COPD exacerbation found no significant reduction in overall antibiotic exposure.[1150] In patients with COPD exacerbations treated in an ICU setting, the use of a procalcitonin-based algorithm for initiating or stopping antibiotics was associated with a higher mortality rate when compared to those receiving standard antibiotic regimens.[1151] Based on these conflicting results at this time we cannot recommend the use of procalcitonin-based protocols to make the decision on using antibiotics in patients with COPD exacerbations.[1152]

In summary, during an exacerbation antibiotics should be given to patients with COPD who:

- Have these at least two of these symptoms: increase in dyspnea, fever, sputum volume, and sputum purulence, if increased purulence of sputum is one of these symptoms
- Prior positive sputum culture during prior exacerbation
- Require mechanical ventilation (invasive or noninvasive).[1007,1052]

The choice of the antibiotic should be based on local bacterial resistance patterns. Usually, initial empirical treatment is an aminopenicillin with clavulanic acid, a macrolide, a tetracycline or, in selected patients, a quinolone. In patients

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

with frequent exacerbations, severe airflow obstruction,[1153,1154] and/or exacerbations requiring mechanical ventilation,[1155] cultures from sputum or other materials from the lung should be performed, as gram-negative bacteria (e.g., *Pseudomonas* species) or resistant pathogens that are not sensitive to the above-mentioned antibiotics may be present. The route of administration (oral or intravenous) depends on the condition of the patient and pharmacokinetics of the antibiotic.

Shorter exposure to antibiotics may decrease the risk of developing antimicrobial resistance and complications associated with this therapy. A meta-analysis demonstrated that ≤ 5 days of antibiotic treatment had the same clinical and bacteriological efficacy to longer conventional treatment in outpatients with COPD exacerbations.[1156] The recommended length of antibiotic therapy is 5-7 days.[1157] We recommend a duration of ≤ 5 days of antibiotic treatment for outpatient treatment of COPD exacerbations.[1151,1156]

Other pharmacotherapy

Antioxidants

Mucolytics have been shown to have anti-inflammatory and antioxidant activity in addition to their classical mucolytic actions.[1158] Although mucolytics have been studied and used for COPD exacerbation prevention, there has been less investigation of mucolytics during acute exacerbations, even though the properties of mucolytics make them suitable for use during acute decompensations. Trials have shown that N-acetylcysteine is not effective in improving recovery of FEV1, although it reduces symptoms of cough and phlegm, and reduces inflammatory biomarkers during exacerbations.[1158,1159] Thus, N-acetylcysteine may be a useful adjunct to drug therapy in patients with difficulty clearing airway secretions. A meta-analysis of 24 studies and 2172 patients has shown with moderate certainty that mucolytics increase the rate of treatment success by 37%, while they also exert benefits on overall symptom scores, presence of cough at follow-up and ease of expectoration. Further adequately powered clinical trials are needed.[1160]

Adjunct therapies

Depending on the clinical condition of the patient, an appropriate fluid balance, use of diuretics when clinically indicated, anticoagulants, and the treatment of comorbidities and nutritional aspects should be considered. Hospitalized patients with COPD are at an increased risk of deep vein thrombosis and pulmonary embolism; up to 5.9% were found to have pulmonary embolism.[1035,1161,1162] Prophylactic measures for thromboembolism should be instituted in these patients.[1163,1164] At all times, healthcare providers should strongly enforce the need for smoking cessation.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

MANAGEMENT OF RESPIRATORY FAILURE

Oxygen therapy

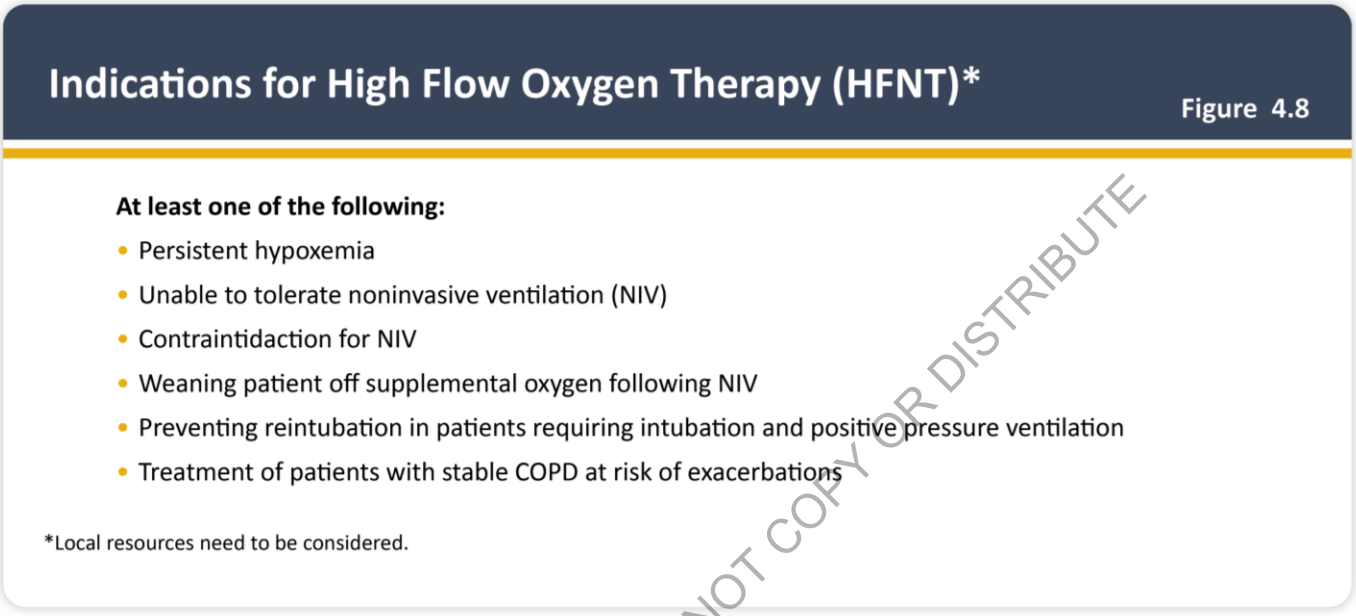
High-flow nasal therapy

Oxygen therapy has been considered first line respiratory support in patients suffering an exacerbation. However, in patients with COPD who remain hypoxemic despite the use of conventional oxygen therapy, hypercapnic, or unable to tolerate NIV, HFNT has been used to deliver heated and humidified air-oxygen blends from 10 to 60 lpm via specialized nasal cannulas.[1165-1167] In uncontrolled, observational and retrospective studies, HFNT is associated with a range of improvements in physiological measurements; decreased respiratory rate and effort, reduction in hypercapnia, and improvements in thoracoabdominal synchrony.[1168-1170]

HFNT has been utilized in the treatment of exacerbations in patients with COPD in three distinct scenarios: 1) treatment during hospitalized exacerbation, 2) to prevent reintubation in patients requiring intubation and positive

pressure ventilation during an exacerbation, and 3) treatment of patients with stable COPD who are at risk for exacerbations to prevent future moderate or severe exacerbations (**Figure 4.8**).

In a prospective RCT conducted in hospitalized hypoxemic exacerbations, patients who received HFNT developed less treatment failure that required switching to NIV, or intubation and mechanical ventilation than those who received conventional oxygen therapy.[1171] However, another prospective RCT in patients hospitalized with exacerbations reported no differences in the need for intubation or switch to NIV when comparing HFNT to conventional oxygen therapy.[1172] Furthermore, in subjects with a chronic hypercapnia those receiving HFNT had longer hospital stays and used less NIV compared to those receiving conventional oxygen therapy.[1173]



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Several prospective RCTs have compared HFNT to NIV as first-line therapy in patients presenting with hospitalized exacerbations and respiratory acidosis. Patients who received HFNT had similar improvements in gas exchange at 12 hours and 5 days, hospitalization duration, and days of respiratory support to those receiving NIV, but patients who received HFNT had fewer complications and reported it more comfortable than NIV.[1174] A multicenter RCT of patients hospitalized with exacerbations reported HFNT to be non-inferior to NIV in lowering $PaCO_2$; however, approximately 30% of patients randomized to HFNT switched to NIV at 6 hours post-randomization due to a lack of improvement in gas exchange.[1174] In another prospective noninferiority RCT of patients hospitalized with exacerbations, the intubation rate was higher in the HFNT group compared to the NIV group; however, treatment switch rates, hospital length of stay, and 28-day mortality rates were similar between groups.[1175] In patients with hypercapnic respiratory failure, HFNT was noninferior to NIV for the primary outcome of endotracheal intubation or death within 7 days.[1176,1177]

HFNT has also been used post-extubation to prevent reintubation in patients hospitalized with exacerbation and acute respiratory failure that required intubation and mechanical ventilation. Small, single-centered trials have shown that HFNT is non-inferior to NIV in reducing carbon dioxide levels and respiratory rate, and HFNT was better tolerated than NIV post-extubation in patients with COPD after receiving positive pressure ventilation to treat acute on chronic respiratory failure.[1175,1178] The effect of post extubation HFNT vs. NIV on reintubation and development of post-extubation respiratory failure was evaluated in a large, prospective, multicenter RCT in high-risk patients, of whom approximately 18-22% had underlying COPD as the cause of respiratory failure.[1179] HFNT was non-inferior to NIV in preventing reintubation or post-extubation respiratory failure, but the rates of post-extubation respiratory failure and reintubation were high at 22% and 27%, respectively. In a subsequent study, post-extubation HFNT with NIV was again non-inferior to HFNT alone in patients at high risk of extubation failure (e.g., age > 65 years or underlying cardiopulmonary disease; approximately 21-25% of subjects had underlying COPD),[1179] whereas in a further study in

similar patients, the rates of reintubation (11.8% vs. 18.2%) were significantly lower in those who received HFNT and NIV vs. HFNT alone, as were the rates of post-extubation respiratory failure (21% vs. 29%).[1180] ERS Clinical Practice Guidelines currently recommend the use of NIV over HFNT for patients at high risk of extubation failure post-mechanical ventilation for exacerbations unless there are contraindications to NIV use. They also recommend the use of NIV over HFNT in patients hospitalized with exacerbations and hypercapnic respiratory failure.[1181]

Chronic use of home HFNT in addition to LTOT has been reported to decrease the frequency of moderate and severe exacerbations in select patients with COPD in comparison to LTOT.[1182-1184] However, there was no impact on mortality, together with inconsistent effects on quality of life, gas exchange, lung function and 6MWD, potentially because baseline patient characteristics varied in terms of degree of airflow obstruction and severity of hypercapnia between studies. No obvious adverse effects were attributable to the use of chronic home HFNT. The home use of chronic nocturnal HFNT to prevent moderate or severe exacerbations of COPD is currently the focus of several large, multicenter international trials (NCT05204888, EpIC-HFT, HiLOT and HiFAE), which should provide results to definitively assess appropriate parameters of patient selection, the efficacy of home HFNT on patient outcomes, and the technical aspects of optimal application.

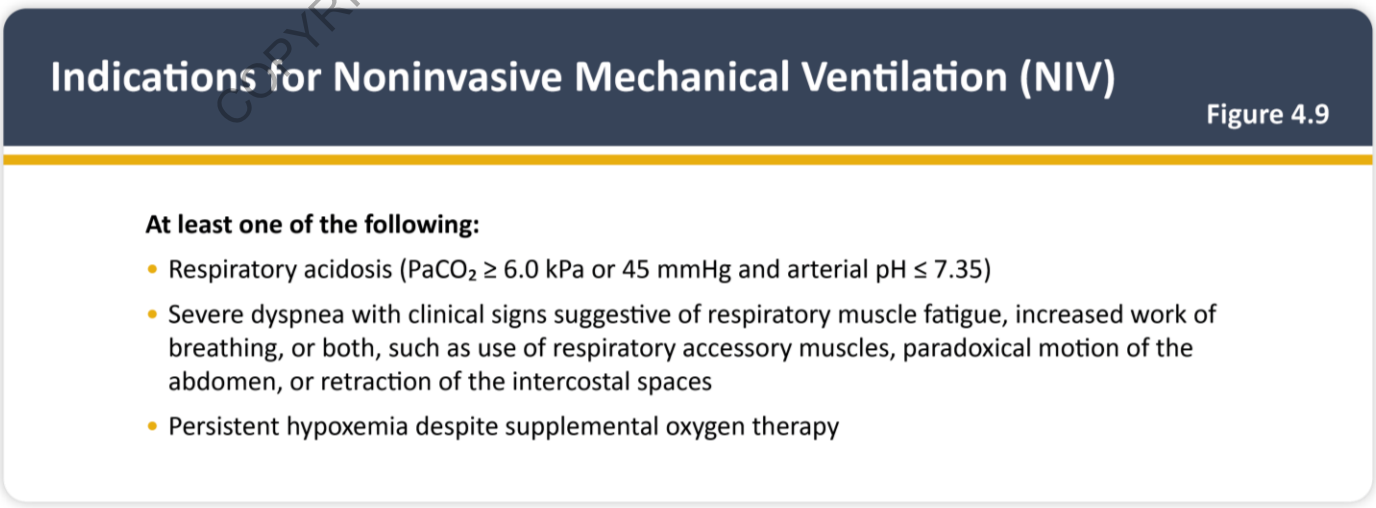
COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Ventilatory support

Some patients need immediate admission to a specialist respiratory care unit or ICU (**Figure 4.4**). In particular, the admission of patients with severe exacerbations to intermediate or specialist respiratory care units may be appropriate if adequate personnel skills and equipment exist to identify and manage acute respiratory failure. Ventilatory support in an exacerbation can be provided by either noninvasive (nasal or facial mask) or invasive (orotracheal tube or tracheostomy) ventilation. Respiratory stimulants are not recommended for acute respiratory failure.[1108]

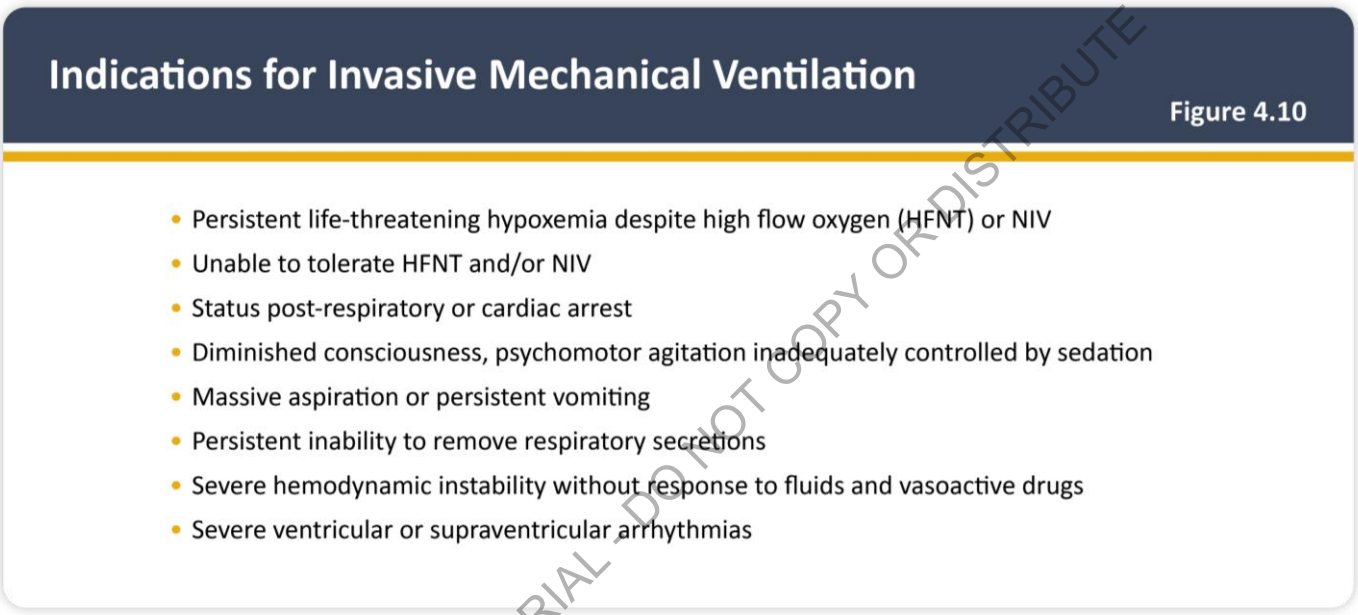
Noninvasive mechanical ventilation (NIV)

NIV is the initial mode of ventilation to treat acute respiratory failure in patients hospitalized for acute exacerbations of COPD. NIV has been studied in RCTs showing a success rate of 80-85%,[1185-1189] and has been shown to improve oxygenation and acute respiratory acidosis, i.e., increasing pH and decreasing $PaCO_2$. It also decreases respiratory rate, work of breathing and severity of breathlessness, and also decreases complications such as ventilator associated pneumonia, and length of hospital stay. More importantly, mortality and intubation rates are reduced by this intervention.[1186,1190-1192] Once patients improve and can tolerate at least 4 hours of unassisted breathing, NIV can be directly discontinued without any need for a "weaning" period.[1193] The indications for NIV[1189] are summarized in **Figure 4.9**.



Invasive mechanical ventilation

The indications for initiating invasive mechanical ventilation during an exacerbation are shown in **Figure 4.10**, and include failure of an initial trial of NIV.[1194] As experience is gained with the generalized clinical use of NIV in COPD, a number of indications for invasive mechanical ventilation are being successfully treated with NIV, thus eliminating invasive mechanical ventilation as first line treatment of acute respiratory failure during hospitalization for COPD exacerbation.[1194] In patients who fail NIV as initial therapy and receive invasive ventilation as subsequent rescue therapy, morbidity, hospital length of stay and mortality are greater.[1187] The use of invasive ventilation in patients with very severe COPD is influenced by the likely reversibility of the precipitating event, the patient's wishes, and the availability of intensive care facilities.[1187] When possible, a clear statement of the patient's own treatment wishes, such as an advance directive or "living will", makes these difficult decisions easier to resolve. Major hazards include the risk of ventilator-acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma and volutrauma, the need for tracheostomy and consequential prolonged ventilation.



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

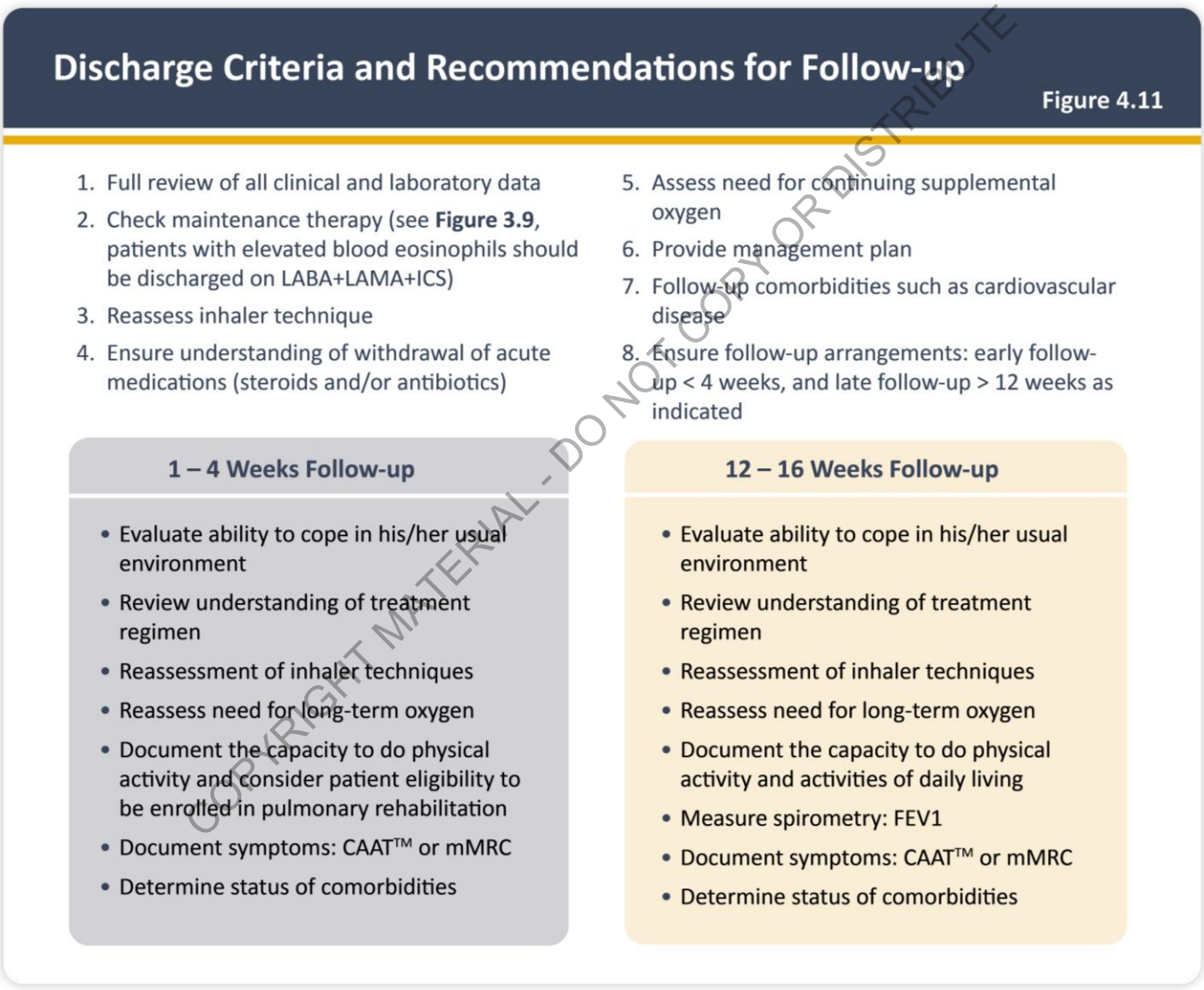
Acute mortality among patients with COPD and respiratory failure is lower than among patients ventilated for non-COPD causes.[1195] Despite this, patients who might otherwise survive are frequently denied admission to ICUs for intubation because of unwarranted prognostic pessimism.[1196] A large study of patients with COPD and acute respiratory failure reported in-hospital mortality of 17% to 49%.[1197] Further risk of mortality was reported over the next 30 days up to 12 months, particularly among those patients who had poor lung function before invasive ventilation (FEV1 < 30% predicted), had underlying cardiovascular disease, or were housebound. Patients who did not have a previously diagnosed comorbidity, had respiratory failure due to a potentially reversible cause (such as an infection), or were relatively mobile and not using long-term oxygen, did well after ventilator support.[1097,1198]

HOSPITAL DISCHARGE AND FOLLOW-UP

Readmissions occur in 30%-50% of patients within 30 days of discharge after hospitalization for COPD exacerbation, and are associated with increased mortality. Prevention of readmission is a major goal of post-discharge care, together with treatment optimization and stabilization of health status, prevention of comorbidity-related events, and prolongation of survival. Reaching these goals requires planning discharge properly in terms of both timing and post-discharge follow-up, and to implement appropriate long-term pharmacological and non-pharmacological therapy.

Early supported discharge and at-home programs have provided inconclusive results, despite trends towards a

reduction of readmission and costs.[1199] The introduction of care bundles on hospital discharge that include education, optimization of medication, supervision and correction of inhaler technique, adherence reinforcement, the assessment and optimal management of comorbidities, pulmonary rehabilitation, supported self-management, early visit to specialists, telemonitoring and continued patient contact have also been investigated (**Figure 4.11**). Several observational studies analyzing retrospective claims for early (0 to 30 days) vs delayed (> 30 days) initiation of LABA+LAMA+ICS fixed combination following patients' first COPD exacerbation showed 20%-30% reduction in first moderate or severe COPD exacerbation and a reduction in re-hospitalizations.[1200-1202] A large real-world observational study of patients hospitalized for COPD exacerbation demonstrated that the maintenance therapy received at discharge impacted the future risk of exacerbation, readmission and mortality. It was also shown that most patients were discharged on inappropriate therapy. Only 17.5% of patients were prescribed triple therapy at discharge, or during the 2-week post-discharge period, with over one quarter of patients prescribed SABA only, or no inhaled medication at all.[1203]



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

The impact of transitioning from hospital to home on patient outcomes and readmissions is impacted by patient education and transitional care services.[1204] Early rehabilitation post hospital discharge (i.e., < 4 weeks) is associated with improved quality of life and increased exercise capacity and may be associated with decreased readmission rate and improved survival,[1205] although the evidence regarding these two outcomes is heterogeneous.[1206,1207]

Further, early follow-up (within one month) following discharge to review patient status and therapy should be

undertaken when possible, as this has been related to fewer readmissions.[1207,1208] Lack of early follow-up may reflect both patient compliance, limited access to medical care, poor social and medical support, and/or the presence of more severe disease. Additional follow-up at three months is recommended to ensure a return to the stable clinical state and to permit a review of the patient's symptoms, lung function (by spirometry), and where possible the assessment of prognosis using multiple scoring systems such as BODE. In addition, arterial oxygen saturation and blood gas assessment will more accurately determine the need for LTOT at prolonged follow-up compared to shortly after discharge.[1209]

CT assessment to determine the presence of bronchiectasis and emphysema should be done in patients with recurrent exacerbations and/or hospitalizations.[1210] A further detailed assessment of the presence and management of comorbidities should also be undertaken (**Figure 4.11**).

PREVENTION OF FURTHER EXACERBATIONS

After an acute exacerbation, appropriate measures for prevention of further exacerbations should be initiated (**Figure 4.12**). The use of a LABA+LAMA+ICS, smoking cessation, immunization against influenza, pneumonia, RSV and pulmonary rehabilitation have been shown to improve function and reduce subsequent COPD exacerbations.[686,1211-1213] The use of a LABA+LAMA+ICS fixed combination following hospitalization showed a significant reduction in first moderate or severe COPD exacerbation and in the rate of re-hospitalizations.[1200,1201,1214] Alerting patients in real time to high levels of outdoor air pollution can also reduce the risk of exacerbations.[1215] The treatment interventions that significantly impact exacerbation risk and/or frequency are shown in **Figure 4.12** and **Chapter 3**.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Interventions that Reduce the Frequency of COPD Exacerbations

Figure 4.12

Intervention Class	Intervention
Bronchodilators	LABAs LAMAs LABA + LAMA
Corticosteroid-containing regimens	LABA + LAMA + ICS
Anti-inflammatory (non-steroid)	Roflumilast Dupilumab Mepolizumab
Anti-infectives	Vaccines Long term macrolides
Mucoregulators	N-acetylcysteine Carbocysteine Erdosteine
Various others	Smoking cessation Rehabilitation Lung volume reduction Vitamin D Shielding measures (e.g., mask wearing, minimizing social contact, frequent hand washing) Exposure avoidance (e.g., avoiding exposure to outdoor air pollution)

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

CHAPTER 5: COPD AND MULTIMORBIDITY

KEY POINTS:

- Patients with COPD often have other chronic conditions (multimorbidity) that increase the risk of poor outcomes.
- Multimorbidity is often underdiagnosed and undertreated, and should be actively searched for in each patient with COPD.
- The presence of those morbidities should not alter COPD treatment; comorbid disease should be treated as per usual standards, despite the presence of COPD.
- CVDs, particularly hypertension, ischemic heart disease, heart failure and atrial fibrillation, are common in COPD. The risk of a major cardiovascular event is significantly increased during and up to one year after a moderate or severe exacerbation.
- Lung cancer is a major cause of death in patients with COPD. An annual LDCT scan is recommended for lung cancer screening in patients with a smoking history, similar to recommendations for the general population. Screening for lung cancer in patients with COPD not associated with tobacco smoking is not recommended due to lack of evidence.
- Bronchiectasis is frequently present in patients with COPD, and when associated with infections impacts disease progression, exacerbations and risk of death.
- Depression/anxiety are frequent and important morbidities in COPD. They are often under-diagnosed and under-treated and are associated with poor health status and increased risk of death.
- In COPD, low BMI (< 21 kg/m^2) is associated with increased risk of death. Obesity (> 30 kg/m^2) is associated with metabolic syndrome and OSA. If OSA is present, CPAP treatment decreases risk of death.
- GERD is associated with an increased risk of exacerbations and poor health status.
- Multiple organ loss of tissue (MOLT) manifested by osteoporosis, sarcopenia, anemia and emphysema is associated with poor outcomes. Adequate nutrition, pulmonary rehabilitation and management of MOLT can improve outcomes.
- When COPD is part of a multimorbidity care plan, a goal should be simplicity of treatment, minimizing polypharmacy.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

INTRODUCTION

Multimorbidity (defined as more than two additional chronic medical conditions) is common in patients with COPD.[308,503,504,1216-1222] Hypertension, ischemic heart disease (IHD), heart failure (HF), atrial fibrillation, lung cancer, depression and anxiety, bronchiectasis, GERD, morbid obesity, frailty, and malnutrition are among the most common morbid conditions in patients with COPD. These chronic conditions complicate the management of COPD and have a

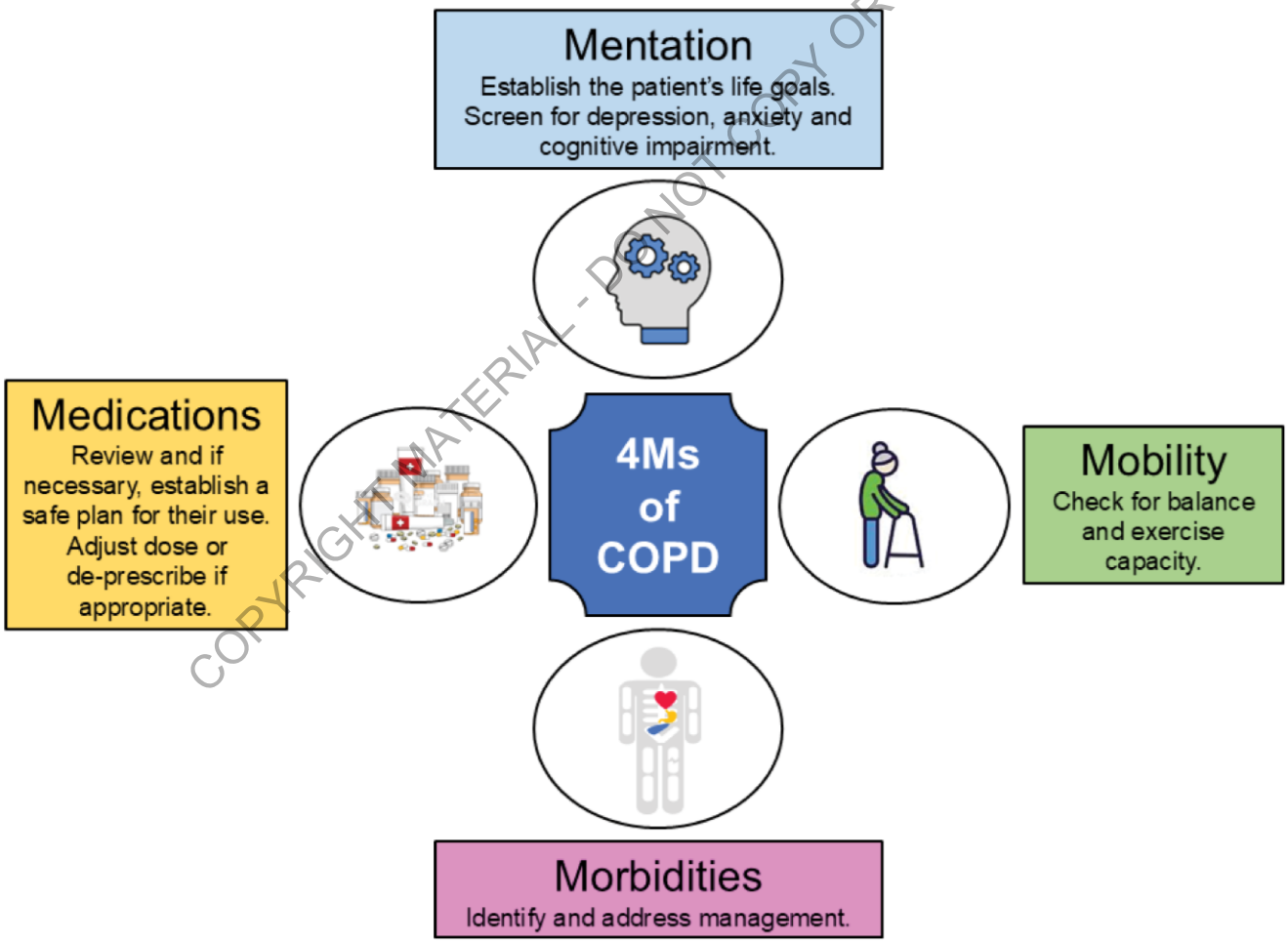
significant impact on its prognosis. Providing specific recommendations for many of these conditions in the setting of COPD is challenging given the current state of evidence and the lack of guidelines addressing multimorbidity.

In patients with COPD, some of these morbidities arise independently of COPD. However, many are causally related, either sharing pathobiological pathways or one disease increasing the poor outcome risk of the other. This concept, known as "syndemics" represents a link between COPD and some of its comorbidities.[310,1223,1224] Importantly, comorbidities that are characterized by symptoms usually associated with COPD may be overlooked e.g., heart failure and lung cancer (breathlessness) or depression (fatigue and reduced physical activity).

Although COPD is negatively impacted by multiple comorbid diseases, COPD itself is also one of the most important conditions that adversely affects the outcomes of other disorders. For example, patients with congestive heart failure, ischemic heart disease,[1225] or those undergoing cardiac procedures such as coronary artery bypass grafting have greater morbidity and mortality when COPD is present compared to when it is absent.[1226,1227]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Summary of the Modified 4Ms Person-centered Approach to Multimorbid Patients with COPD Figure 5.1



Adapted from: Celli BR, Fabbri LM, Yohannes AM, Hawkins NM, Criner GJ, Bon J, Humbert M, Jenkins CR, Pantoni L, Papi A, Quint JK, Sethi S, Stolz D, Agusti A, Sin DD. A person-centred clinical approach to the multimorbid patient with COPD. Eur J Intern Med. 2025 Aug 12:106424. doi: 10.1016/j.ejim.2025.07.020.

It is important to provide patients who have COPD with optimal evidence-based management for their respiratory disease. Any encounter between a healthcare practitioner and an individual with COPD offers an opportunity to manage not only their lung disease, but other prevalent morbidities.[506,1228] To maximize this opportunity, the Institute for Healthcare Improvement[1229] has proposed a systematic approach based on the '4Ms' for elderly patients with chronic non-communicable diseases: Mentation, Mobility, Medications, and Morbidities, all of which are important drivers of outcomes in this population.[1230,1231] In the context of patients with COPD, the 4Ms approach has been modified (**Figure 5.1**).[1232] Evaluating **Mentation** is important to define health goals,[1231] with a particular focus on depression and dementia[1233] as well as more severe psychiatric pathologies including bipolarity and schizophrenia. The patient should also be evaluated for **Mobility**, with particular attention to balance and frailty,[1234] and exercise capacity tested with the 6MWD test, an excellent predictor of survival in patients with COPD.[551,1235] It is important to review all **Medications** used by the patient, as more than 90% receive polypharmacy, inappropriate use of which results in poor clinical outcomes.[1236] Finally, **Morbidities,** the focus of this chapter, need to be identified, since appropriate diagnosis and management (in addition to specific treatment for COPD) improves outcomes. It is important to remember that in this population, active smoking should be considered a disease by itself,[1237] and needs to be addressed with a smoking cessation program.

COPD, FRAILTY AND MULTIMORBIDITY

Frailty can be defined as a decline in multiple physiological systems, usually associated with aging. Practically, it can be determined by the presence of five components: weakness, slowness, exhaustion, low physical activity, and unintentional weight loss.[1238] Frailty is linked to conditions like cognitive impairment, cardiovascular disease, and with multimorbidity, compounding health risks.[1239] In a cohort study, the prevalence of frailty among individuals with COPD was higher than in individuals without COPD and may help identify people with COPD at risk of poor outcomes.[1240] A meta-analysis reported that frailty and pre-frailty were associated with all-cause mortality, acute exacerbation, and hospitalization in patients with COPD.[1241] Frailty is a predictor of outcomes in people with COPD.[1242] The ERS has published a review of current evidence on treating frailty in adults with chronic respiratory disease and includes clinical management options such as geriatric care, rehabilitation, nutrition, pharmacological and psychological therapies.[819]

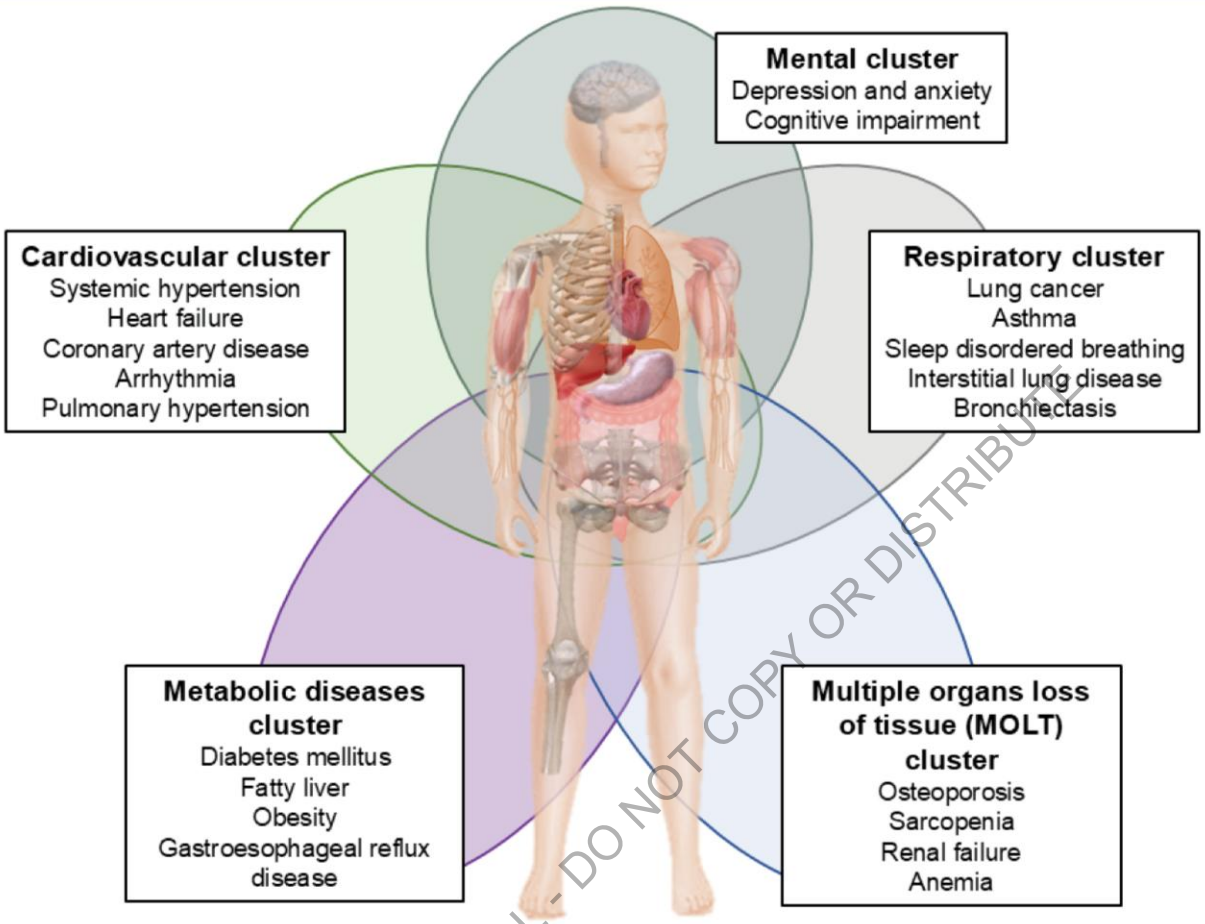
Once the general evaluation of Mentation, Medication and Mobility is complete, it is important to consider the most frequent morbidities potentially affecting the patient. These morbidities have been clustered by system organs using a modified Delphi methodology as shown in **Figure 5.2**.[1232]

Together with respiratory failure, some CVDs (arterial hypertension, heart failure, coronary artery disease, atrial fibrillation-flutter and pulmonary hypertension) and lung cancer are the most frequent causes of death in patients with COPD and therefore require close attention. However, other morbidities such as osteoporosis, depression, anxiety, sarcopenia, anemia, sleep-related disorders and renal failure negatively impact health-related quality of life, exacerbations and hospitalizations. Many are readily treatable and therefore, if identified, should be reviewed and monitored over time to optimize management. We recognize that the recommendations presented below may be insufficient for the management of all the morbidities patients with COPD may have and are not a substitute for the use of specific guidelines for the management of each individual comorbid condition. However, they contain practical information of use to healthcare providers caring for these patients.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

Morbidity Clusters Frequently Present in Patients with COPD that Independently Impact Outcomes

Figure 5.2



Adapted from: Celli BR, Fabbri LM, Yohannes AM, Hawkins NM, Criner GJ, Bon J, Humbert M, Jenkins CR, Pantoni L, Papi A, Quint JK, Sethi S, Stolz D, Agusti A, Sin DD. A person-centred clinical approach to the multimorbid patient with COPD. Eur J Intern Med. 2025 Aug 12:106424. doi: 10.1016/j.ejim.2025.07.020.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

CARDIOVASCULAR DISEASES

Cardiovascular diseases (CVD) are highly prevalent in COPD and contribute substantially to mortality. Incidence rates of CVD are higher in COPD than in the general population across all age and sex groups, with approximately 3.5 events per 100 person-years in UK primary care. When coexisting with COPD, CVD increases unscheduled hospital visits by 62%. Around 20% of patients with COPD die from CVD, representing a two- to 4-fold higher risk than matched controls at three years.

CVD in COPD most commonly presents as heart failure (HF), and atrial fibrillation (AF). Hypertension affects approximately 50% of individuals with COPD, and the incidence of ischemic heart disease is about 70% higher than in those without COPD. A meta-analysis of case-control studies showed increased risks of HF (RR 2.33; 95% CI 1.78, 3.06), myocardial infarction (RR 1.47; 95% CI 1.28, 1.68), stroke (RR 1.38; 95% CI 1.18, 1.62), AF (RR 1.38; 95% CI 1.19, 1.61), and cardiovascular death (RR 1.55; 95% CI 1.33–1.82) in COPD compared with controls.[1243] Conversely, in a large real-world population of people with established CVDs, COPD was associated with a higher rate of cardiovascular events but patients with COPD were given less preventive therapy.[1244] Pre-COPD and Preserved Ratio Impaired Spirometry

(PRISm, a particular case of pre-COPD) are also associated with increased all-cause and cardiovascular mortality, and a higher burden of cardiometabolic comorbidity, conferring increased risk of incident CVD.[1243]

The mechanisms underlying the frequent co-existence of COPD and CVD are multiple. First, CVD and COPD share risk factors (e.g., aging, smoking), a concept that is now recognized as a *syndemic* occurrence.[310] Second, several abnormalities characteristic of COPD can contribute to CVD, including: 1) COPD is often associated with persistent systemic inflammation which, in turn, can cause endothelial dysfunction, platelet activation and coagulation disorders, all of which can then contribute to CVD;[1245] 2) abnormal pulmonary gas exchange in patients with COPD can cause arterial hypoxemia and myocardial hypoxia, with impaired contractility and increased risk of arrhythmias; 3) lung hyperinflation in COPD reduces venous return and compresses the lung vessels, thus limiting cardiac output and oxygen delivery to tissues; 4) COPD-related exertional dyspnea results in decreased physical activity (which can be aggravated by anxiety/depression that are other frequent COPD comorbidities), a well-established cardiovascular risk factor. On the other hand, CVD can also contribute to worsening health status in patients with established COPD through several potential mechanisms, including: 1) alveolar and bronchial edema due to abnormal myocardial contractility; 2) post-capillary pulmonary hypertension; 3) reduced skeletal muscle oxygen delivery, further contributing to reduced physical activity in these patients.

From the above it follows that the presence of major CVD (arterial hypertension, coronary artery disease, heart failure, arrhythmia) needs to be investigated in any patient with COPD,[1098,1102] and if present treated according to available guidelines.[1246] Of note, the use of established CV risk scores in the general population, such as Framingham or QRisk, may underestimate CVD in patients with COPD, and merits further research.[1102,1247] Likewise, the inclusion of spirometric variables (e.g., FEV1) and coronary artery calcium scores may augment the predictive value of the standard cardiovascular risk scores in use.[1102,1247,1248] This also merits research.

Below, we discuss how to manage the main CVDs that occur in COPD patients (**Figure 5.3**).

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Cardiovascular Diseases in COPD: Burden & Management

Figure 5.3

Systemic Hypertension	• Approximately 50% of people with COPD have systemic hypertension • Systemic hypertension increases the risk of heart failure, myocardial infarction and stroke • Blood pressure (BP) should be recorded at every medical evaluation • BP over 130/80 is abnormal and warrants treatment
Heart Failure	• Approximately 30% of people with COPD have heart failure • Overlapping symptoms can make the diagnosis of heart failure challenging • Evaluate natriuretic peptide (NTproBNP) levels in all cases of suspected heart failure • Cardioselective beta-blockers are recommended and safe in COPD • SGLT2 inhibitors are indicated in all heart failure types • Treatment with ACEi/ARB/ARNI plus BB+MRA+SGLT2i is indicated in heart failure with reduced ejection fraction • Continue heart failure therapies during a COPD exacerbation
Coronary Artery Disease	• Approximately 20% of people with COPD have coronary artery disease • Cardiovascular risk for primary prevention of CVD can be estimated using calculators, but these underestimate risk in COPD • The use of troponins should be reserved for cases of suspected acute coronary syndrome • Treatment of coronary artery disease should follow standard cardiovascular guidelines irrespective of COPD • Beta-blockers should not be withheld in COPD when indicated for coronary artery disease
Arrhythmias	• Common in people with COPD • COPD should not preclude guideline-directed arrhythmia management • For atrial fibrillation, there is no contraindication to any specific rate or rhythm control medication or strategy in patients with COPD, including beta-blockers • For supraventricular and ventricular arrhythmias, follow guideline recommendations, with caution regarding bronchoconstriction risk and use of atrioventricular nodal agents
Valvular Heart Disease	• Up to 50% of people with COPD have valvular heart disease • Diagnostic evaluation of valvular heart disease is similar in patients with and without COPD • Additional imaging, including CT coronary angiography and cardiac magnetic resonance, may be necessary to assess valve anatomy, function, and suitability for transcatheter interventions

Abbreviations: ACEi (ACE inhibitor); ARB (Angiotensin Receptor Blocker); ARNI (Angiotensin Receptor-Neprilysin Inhibitor); BB (Beta-Blocker); MRA (Mineralocorticoid Receptor Antagonist); NTproBNP (N-terminal prohormone of brain natriuretic peptide test); SGLT2i (Sodium-Glucose Co-transporter 2 Inhibitor).

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Systemic hypertension

Close to 50% of patients with COPD have high blood pressure.[1221,1223] Uncontrolled hypertension is associated with reduced health-related quality of life and an increased risk of heart failure, myocardial infarction, and stroke.[1249] All patients should have their blood pressure measured at each medical evaluation, potentially complemented with home monitoring, with values > 130/80 mmHg abnormal and meriting treatment.[1249] Correcting poor diet, physical inactivity, and excessive alcohol consumption is crucial for hypertension control, either alone or with pharmacological therapy.[1250] The pharmacological treatment of COPD should be optimized because such treatment has not been associated with alterations in blood pressure levels. Systemic arterial hypertension should be managed according to guidelines.[1251,1252]

Heart failure

Heart failure is defined as a clinical syndrome (symptoms and signs) caused by a structural or functional cardiac abnormality corroborated by elevated natriuretic peptide levels or objective clinical or laboratory evidence of congestion. The prevalence of heart failure in patients with COPD ranges from 20%-30%,[1253,1254] with annual incidence of 3%-4%, although it is frequently under-diagnosed and should be proactively searched for since it is easily identified. The reduced (HFrEF) and preserved (HFpEF) ejection fraction phenotypes of heart failure occur with similar frequency (10% each) in patients with COPD. Close to 40% of patients with COPD who are mechanically ventilated due to hypercapnic respiratory failure have evidence of left ventricular dysfunction.[1255,1256] The presence of heart failure is an independent predictor of all-cause mortality.[1257]

Diagnosis of HF in patients with COPD is challenging due to overlapping symptoms (dyspnea, wheeze, exercise limitation) and technical echocardiographic limitations from lung hyperinflation. International guidelines recommend the measurement of natriuretic peptides in patients with suspected heart failure, followed by echocardiography if abnormal. However, specific natriuretic peptides thresholds are not established. In patients with COPD, natriuretic peptides demonstrate high negative predictive values (0.80-0.98) to exclude left ventricular dysfunction in both stable state and during COPD exacerbations. However, they have relatively lower positive predictive values in patients with COPD than in the general population.[1258,1259]

Cardiovascular guidelines provide specific recommendations guided by HF phenotype.[1258] For HFrEF this includes ACE inhibitors or angiotensin receptor blockers or sacubitril-valsartan, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose transport protein 2 inhibitors. In chronic heart failure with reduced ejection fraction (HFrEF), cardioselective beta-blockers are recommended and are safe in COPD, improving outcomes without increasing exacerbation risk. ACE inhibitors or ARNI are also appropriate; ACE inhibitor–related cough may necessitate switching to and angiotensin II receptor blockers (ARB) and angiotensin receptor–neprilysin inhibitors (ARNI) according to HF type. For HFpEF this includes sodium-glucose transport protein 2 inhibitors, sacubitril-valsartan and mineralocorticoid receptor antagonists. Treatment with $beta_1$-blockers improves survival in heart failure and is recommended in patients who also have COPD. Selective $beta_1$-blockers should be used only for approved cardiovascular indications and not for preventing exacerbations of COPD.[1260] Sodium-glucose co-transporter 2 (SGLT2) inhibitors are indicated across HF phenotypes and may reduce exacerbations and mortality in COPD. Finerenone may reduce HF hospitalization in heart failure with mildly reduced ejection fraction and heart failure with preserved ejection fraction (HFmrEF/HFpEF).

During exacerbations of COPD, HF therapies should generally be continued, as withdrawal may worsen outcomes. Acute heart failure should be treated according to usual heart failure guidelines. Oxygen and loop diuretics are indicated in pulmonary oedema with hypoxemia; caution is required to avoid metabolic alkalosis in hypercapnic patients. Noninvasive ventilation added to conventional therapy improves outcomes for patients with heart failure with acute pulmonary edema,[1261] but may increase right ventricular (RV) afterload in selected patients.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Coronary artery disease

Coronary artery disease (CAD) occurs in 10%-20% of patients with COPD, and its presence is associated with increased morbidity and mortality of these patients.[1262,1263] Cardiovascular risk may be assessed by the global risk calculator that can be found on the US NHLBI website.[1264] The diagnosis of coronary artery disease is made in patients with different clinical presentations, including patients with symptoms (angina) or as a result of tests (ECG, high sensitivity troponin or coronary artery calcification seen in a CT scan).[1265]

The thoracic CT-derived coronary artery calcium (CAC) score, obtainable from standard non-ECG-gated chest CTs that COPD patients frequently undergo, is an effective screening tool, with an **area-under-the-curve (AUC) of 0.98 for detecting any CAD** and 0.89 for obstructive CAD.[1266] This represents a practical opportunity for opportunistic screening.

We recommend screening with high-sensitivity troponin at COPD diagnosis and at any unexplained change in symptoms (dyspnea, chest pain, worsened exercise limitation) if there is a suspicion of acute coronary syndrome (ACS). Notably, approximately 29%–39% of stable COPD patients have elevated high-sensitivity troponin (hs-troponin) above the moderate cardiovascular risk threshold of 5–6 ng/L.[1267,1268] Thus, troponin elevation should be interpreted as ACS only when accompanied by consistent clinical features, including symptoms of ischemia, dynamic changes on serial testing, ECG abnormalities, or imaging evidence of new myocardial dysfunction. Isolated minor elevations may reflect supply-demand mismatch (type 2 myocardial infarction) or non-ischemic myocardial injury.[1269]

Combining CAC score with a cardiovascular risk score (CVRS) improves MACE prediction in COPD. In a cohort study patients with both elevated CVRS (≥10%) and elevated CACS had a **hazard ratio of 7.6** for MACE compared to those with low scores on both measures.[1248]

Treatment of coronary artery disease should follow standard cardiovascular guidelines irrespective of COPD. Key management principles include:

- **Lipid lowering therapy** guided by CAC burden: the 2026 ACC/AHA Dyslipidemia Guideline recommends high-intensity statins for moderate or severe CAC found incidentally on non-cardiac CT scans, and moderate-intensity statins for mild CAC. For CAC ≥ 300, LDL-C goals align with secondary prevention targets (< 55 mg/dL), and for CAC ≥ 1000, a ≥ 50% LDL-C reduction with a goal < 55 mg/dL is advised.[1270]
- Standard cardiovascular risk factor modification (blood pressure control, smoking cessation, diabetes management) remains essential.
- Beta-blockers, often underused in COPD due to concerns about bronchospasm, are generally safe and should not be withheld when indicated for cardiovascular disease.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Arrhythmias

Cardiac arrhythmias are common in patients with COPD,[1271] although they often remain underdiagnosed and undertreated. Up to 30% of individuals with COPD develop arrhythmias, most commonly atrial fibrillation (in about one in five), with risk increasing with a lower FEV1.[1272] Concomitant COPD and atrial fibrillation is associated with more than a two-fold higher risk of all-cause mortality and of cardiovascular death compared with atrial fibrillation alone.[1273] The results of a systematic review and meta-analysis showed that cardiac arrhythmias are common among hospitalized patients during and after an acute exacerbation.[1274]

Airflow limitation, hyperinflation and hypoxemia contribute to pulmonary hypertension, right ventricular hypertrophy and atrial remodeling (including atrial functional mitral regurgitation), providing a substrate for arrhythmia. Chronic hypoxemia, systemic inflammation, sympathetic activation and comorbidities further increase susceptibility to arrythmias, particularly during exacerbations. Additional triggers include impaired gas exchange, elevated intrathoracic pressure, autonomic imbalance, and bronchodilator therapy. Long-acting inhaled agents are generally safe; however, arrhythmic risk with beta$_2$-agonists is highest early after initiation, particularly with short-acting agents. Excess short-acting beta-agonist use increases arrhythmic risk and should prompt optimization of COPD management. Oral corticosteroids and theophylline increase arrhythmic risk, whereas inhaled corticosteroids appear neutral.

For diagnosis, it is recommended that an ECG be obtained in all COPD at initial diagnosis and at unexplained change in symptoms. Symptom overlap (e.g. dyspnea, fatigue) complicates diagnosis, especially AF. Use of Holter monitoring may be indicated in patients with intermittent complaints of dizziness or fainting episodes because the prevalence of atrial fibrillation rises with extended monitoring duration.

COPD should not preclude guideline-directed arrhythmia management. Rhythm control (pharmacological or catheter ablation) should be considered in appropriate patients, particularly those symptomatic or with heart failure. The cornerstones of atrial fibrillation management are oral anticoagulation combined with rate or rhythm control strategies.[1275] There is no contraindication to any specific rate or rhythm control medication or strategy in patients with COPD, including beta-blockers. Catheter ablation should be considered for atrial fibrillation according to standard eligibility criteria. The presence of atrial fibrillation does not alter the treatment of COPD, as although bronchodilators have been previously described as potentially pro-arrhythmic agents;[1276,1277] available evidence suggests an overall acceptable safety profile for LABAs,[1278] anticholinergic drugs (and ICSs).[1012,1279-1285] Nevertheless, caution is advised when using SABAs[1278,1286] and theophylline, which may precipitate atrial fibrillation and make control of the ventricular response rate difficult.[1287-1289]

Management of supraventricular and ventricular arrhythmias should follow guideline recommendations, with caution regarding bronchoconstriction risk and use of atrioventricular nodal agents. Hemodynamically unstable patients require urgent direct current cardioversion.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Valvular heart disease

The prevalence of COPD in clinically significant valvular heart disease varies by population. In severe aortic stenosis, COPD prevalence ranges from 22%-50%, and is approximately 15% in severe mitral regurgitation. Data for other valve lesions are limited.

Aortic and mitral valve disease may exacerbate COPD through elevated pulmonary pressures, while COPD-related precapillary pulmonary hypertension can contribute to tricuspid regurgitation and right heart failure. COPD also increases the risk of AF, and atrial functional mitral regurgitation may further worsen tricuspid regurgitation. Diagnostic evaluation of valvular heart disease is similar in patients with and without COPD; however, pulmonary pressures may be underestimated on echocardiography, particularly in severe tricuspid regurgitation, and right heart catheterization may be required. Additional imaging, including CT coronary angiography and cardiac magnetic resonance, may be necessary to assess valve anatomy, function, and suitability for transcatheter interventions.

Pulmonary hypertension

The presence of pulmonary hypertension (PH) in patients with COPD (PH-COPD) is clinically relevant, as it is associated with increased healthcare resource utilization, more hospitalizations and a poor prognosis.[303]

PH is classified in five distinct groups, based on their different pathophysiological mechanisms, clinical presentation and therapeutic management: PAH (group 1), PH associated with left heart disease (group 2), PH associated with lung

diseases and/or hypoxia (group 3), chronic thromboembolic PH (group 4) and PH associated with unclear and/or multifactorial mechanisms (group 5). COPD is typically associated with group 3 PH, but all groups of PH can be diagnosed in patients with COPD.[301]

PH is hemodynamically defined by an elevated mPAP > 20 mmHg, as assessed by right heart catheterization.[1290,1291] A diagnosis of PH in a patient with COPD requires a careful analysis of the possible mechanisms leading to elevated mPAP. This is critical in order to identify treatable traits of PH. For example, chronic thromboembolic PH is a treatable cause of PH occurring more frequently in patients above the age of 40 years, which may be detected in patients with COPD.[1292]

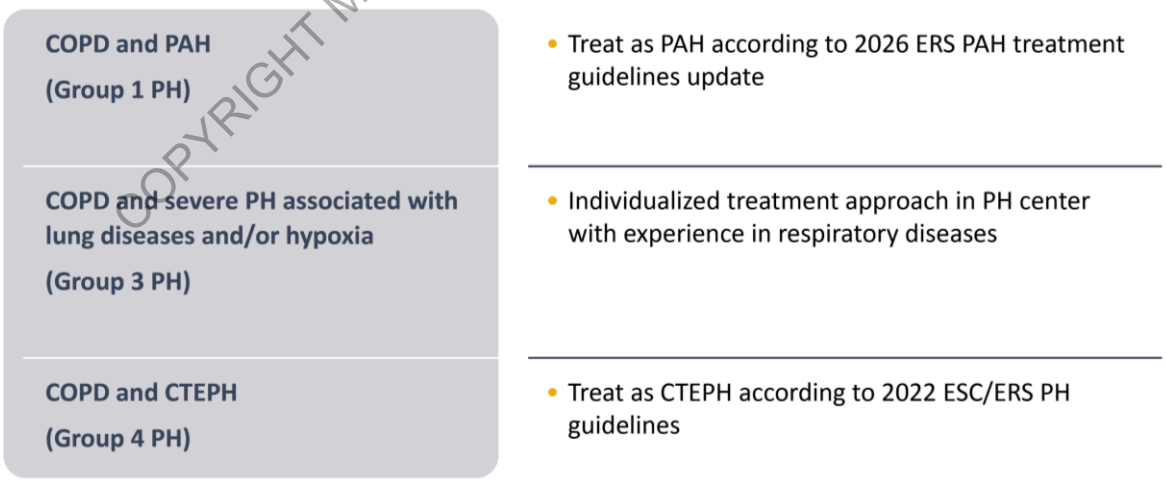
Around 25-30% of all patients with COPD present with mildly elevated mPAP.[1290,1291,1293] A subgroup (approximately 5%) of patients with COPD have severe PH.[1290,1291,1294] The 2022 ESC/ERS PH guidelines define severe PH associated with COPD by an increased peripheral vascular resistance > 5 Wood Units.[1290,1291,1295] The severity of PH is an independent predictor of prognosis,[303] and patients with severe PH-COPD frequently present with mild-to-moderate airflow limitation, no or very mild hypercapnia, a low DLco (< 45% predicted) and circulatory exercise limitation. For this group of patients the term "pulmonary vascular phenotype" has been suggested.[301] Pulmonary pressure increases during a COPD exacerbation, but its consequences remain unclear.[1296]

Echocardiography is the best non-invasive tool to estimate the probability and severity of PH.[303,1290,1291] In addition, elevated N-terminal pro B-type natriuretic peptide and an increased ratio of the diameter of the pulmonary artery and the aorta on HRCT are associated with the presence of PH-COPD. Of note, the diameter of the pulmonary artery has also been associated with the risk of COPD exacerbations.[304] Detailed parenchymal analysis and vessel segmentation by chest CT is a novel tool that allows identification of imaging-based subgroups with different mortality risks, stressing the central role of CT for refined clinical phenotyping in patients with COPD and pulmonary vascular disease.[1297,1298]

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

Treatable Traits in Pulmonary Hypertension-COPD (PH-COPD) & Suggested Management

Figure 5.4



Abbreviations: PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; ESC/ERS, European Society of Cardiology/European Respiratory Society; CTEPH, chronic thromboembolic PH.

Reference: Kovacs et al. European Respiratory Society clinical practice guidelines update for the treatment of pulmonary arterial hypertension. Eur Respir J. 2026 Sep 7:2601178.

Patients with COPD and PH should be referred to a PH center with experience in respiratory diseases to undergo right heart catheterization, if clinically indicated, and subsequent multidisciplinary assessment to guide treatment decision-making (**Figure 5.4**).[1299] Long-term oxygen therapy is recommended in hypoxemic patients.

In patients with non-severe (group 3) PH associated with COPD the use of drugs approved for PAH is not recommended due to lack of benefit and potential harm. Patients with severe (group 3) PH associated with COPD require an individualized approach.[1290,1291] Right ventricular dysfunction is common and prognostically significant. Management includes reducing right ventricular afterload, ensuring adequate oxygenation, treating arrhythmias and using non-invasive ventilation where appropriate.

Ongoing and future RCTs may further advise for or against the use of drugs targeting the pulmonary vasculature in PH associated with COPD.[1300] The INSIGNIA-PH-COPD trial has been recently completed. This is a phase 2a study, examining the safety and efficacy of frespaciguat, an inhaled soluble guanylate cyclase stimulator in PH associated with COPD. Detailed results are expected by the end of 2026. ERASE PH-COPD is a prospective, double-blind RCT evaluating the use of the phosphodiesterase-5 inhibitor tadalafil in patients with severe PH associated with COPD. The results are expected by the end of 2027.

Peripheral artery disease

PAD frequently coexists with COPD but is often under-recognised. PAD in COPD is associated with reduced exercise capacity, impaired quality of life and increased mortality. In a large cohort of patients with COPD of all degrees of severity, 8.8% were diagnosed with PAD – a prevalence that is higher than in non-COPD controls (1.8%).[1301] Patients with COPD and PAD reported worse functional capacity and health status compared to those without PAD. The management of PAD depends on its severity, with surgery to be considered in patients with severe limitations.[1302] COPD is also linked to a higher risk of thoracic aortic aneurysm rupture and adverse outcomes.

There is no evidence that the diagnosis or management of PAD should differ in individuals with COPD. Identification and treatment should follow established guidelines. Screening for PAD may be appropriate in patients with COPD, particularly those with additional cardiovascular risk factors or established CVD. Clinical vigilance for symptoms such as exertional leg pain or claudication is recommended, with further investigation as indicated. Screening for aortic aneurysm or carotid artery disease should also follow guideline-directed approaches.

Management should include lifestyle modification, antithrombotic therapy and optimization of comorbidities. Cardio selective beta-blockers may be used when indicated, with caution in advanced limb ischemia. Although COPD is associated with worse outcomes following revascularization, there is no evidence to support alternative revascularization strategies.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Stroke

COPD is independently associated with increased stroke risk, mediated in part by systemic inflammation, hypoxemia and a higher prevalence of AF. AECOPD are associated with a transient increase in stroke risk, likely reflecting a prothrombotic state. Optimal COPD and risk factor management is essential for primary prevention.

Management of stroke in COPD should follow standard guidelines. Acute therapies (thrombolysis, thrombectomy, anti-thrombotic) and secondary prevention should not be modified solely due to COPD. In selected cases, specialist input (e.g., intensive care) may support safe delivery of reperfusion therapies. AF management and blood pressure control remain central to secondary prevention.

Respiratory assessment is important in acute stroke, particularly where hypoventilation is suspected. Oxygen therapy should be guided by standard targets, with caution to avoid hypercapnia. COPD is associated with increased risk of

post-stroke complications, including pneumonia; close monitoring is required given reduced respiratory reserve and impaired airway protection.

Secondary prevention should align with international guidelines, including smoking cessation and vaccination. Influenza vaccination reduces both respiratory and vascular events. Inhaler technique should be reassessed post-stroke due to potential functional or communication impairments.

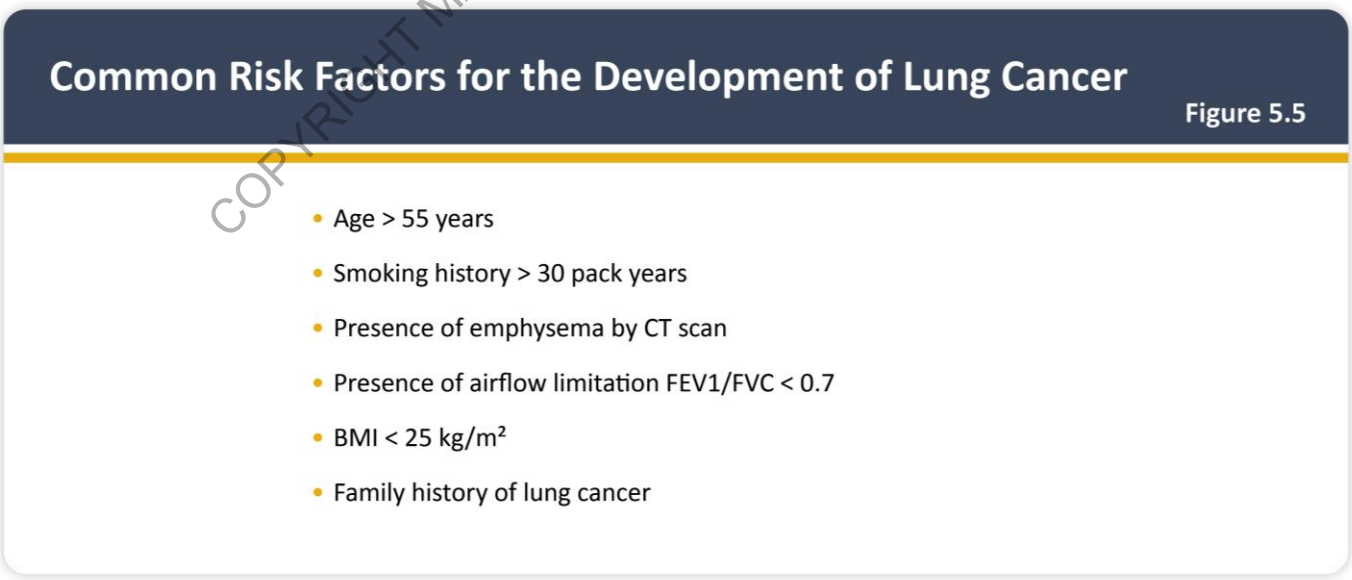
Rehabilitation is essential and integration with pulmonary rehabilitation may improve outcomes, although evidence for optimal combined approaches is limited.

RESPIRATORY DISEASES

Lung cancer

Lung cancer is the leading cause of death from malignant disease worldwide, with more deaths from lung cancer than from colon, breast and prostate cancer combined, causing an estimated 1.6 million deaths worldwide each year.[1303] Unfortunately, the great majority of lung cancers are diagnosed at an advanced stage, resulting in poor overall survival.[1304] Therefore, primary and secondary prevention and early detection are important to improve survival. The association between COPD and lung cancer has been systematically confirmed in several epidemiological and observational cohort studies.[1223,1305-1308] These two diseases appear to share more than tobacco smoke exposure as their common origin (**Figure 5.5**). Genetic susceptibility, epigenetic changes in DNA methylation, local pulmonary chronic inflammation and abnormal lung repair mechanisms present in COPD are also thought to be the most important potential contributors to lung cancer development.[1309-1311] Whether the spirometric severity of airflow obstruction is directly or inversely associated with a greater risk for lung cancer development remains controversial.[1307,1312] The association between lung cancer and the degree of emphysema is stronger than that existing between lung cancer and degree of airflow obstruction, and the greatest risk is observed in people with the combination of emphysema diagnosed by CT and airflow obstruction determined by spirometry.[1313,1314] The best preventive measures for lung cancer (as for COPD) are smoking prevention and cessation.[1315]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE



Several studies involving the use of low-dose chest CT screening have shown improved survival.[427,1316,1317] The USPSTF updated its recommendation for lung cancer screening in 2021,[1318] based on a systematic review that examined the

accuracy of screening for lung cancer, and that considered the benefits and harms associated with lung cancer screening. USPSTF also commissioned collaborative modeling studies from the National Cancer Institute CISNET to provide the optimal age to begin and end lung cancer screening, the optimal screening interval, and to assess the relative benefits and harms of different screening strategies. The USPSTF now recommends annual screening for lung cancer with low-dose CT in adults aged 50-80 years who have a 20-pack year smoking history and currently smoke, or who quit smoking within the past 15 years. They recommend stopping screening once either the person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. Additionally, the CISNET modelling analysis supports screening at a younger age with a lower smoking burden to address current racial and gender disparities that exist with lung cancer screening.[1318-1322] COPD has also been reported to be an independent risk factor for lung cancer incidence in never smokers,[1323,1324] with risk factors including biomass fuel exposure, second-hand smoke, radon exposure, air pollution, a family history of lung cancer, and asbestos exposure. However, routine annual screening with LDCT has not been conducted in people with COPD who are never smokers, and annual LDCT screening is not currently recommended for these individuals since the possible harms of screening seem to outweigh the possible benefit of finding early lung cancer.[1325] Although the USPSTF recommendations are supported by several major medical societies, important questions still remain. Several studies have suggested that the yield of CT screening would improve if additional variables such as age, smoking history, BMI, presence of airflow obstruction and or emphysema and family history of lung cancer were added to the current screening criteria.[426,1326]

The implementation of a screening program, where available, could be useful, but has to be implemented in the appropriate environment to avoid over-diagnosis, increased morbidity and mortality due to needless diagnostic procedures for benign abnormalities, and anxiety and incomplete follow-up.[1327] However, one Danish study suggested that being part of a lung cancer screening program significantly promotes smoking abstinence,[1328] and a review of different studies concluded that smoking cessation during LDCT screening results in improved spirometry as well as a decrease in micronodules seen on the baseline CT, thus beneficially affecting lung cancer and COPD.[1315] Smoking cessation interventions as part of CT scan screening programs could be of use.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Inhaled corticosteroids and lung cancer incidence

ICSs are recommended in selected people with COPD, although their potential impact on the development of lung cancer has been the subject of conflicting reports.[1329-1331] Based on the available data, ICSs do not appear to increase or decrease the risk of lung cancer – although this is pending studies adequately planned to clarify these important questions.

Asthma

Patients with asthma have a high risk of developing COPD, even after adjusting for smoking status.[175] Furthermore, airflow limitation that persists after bronchodilator administration may be present in 5-21% of patients with asthma.[1332,1333] Patients with comorbid asthma and COPD have increased dyspnea, worse health-related quality of life, an increased risk of exacerbation and hospitalization, greater lung function decline, and a reduced life expectancy compared to those with COPD alone.[1334-1337] In patients with COPD, the coexistence of asthma should be considered in those with a family history of asthma, previous childhood diagnosis of asthma/bronchitis, wheezing, atopic manifestations, childhood respiratory infections, and use of inhaled medications.[1338]

Bronchodilator responsiveness and blood eosinophil levels do not differentiate between asthma, COPD, or comorbid asthma and COPD, even though blood eosinophil and fractional exhaled nitric oxide levels tend to be higher in those with comorbid asthma and COPD.[1339,1340] We recommend the close examination of a lung CT, as patients with comorbid asthma and COPD tend to have greater airway thickness and less emphysema than those with COPD alone. Furthermore, mucus plugging is more prevalent in patients with asthma or comorbid asthma and COPD than COPD alone, and the extent of mucus plugging is associated with increased mortality.[202,205,1341]

All asthma preventive measures and treatments should be employed, particularly maintenance ICS, if asthma is identified in a patient with COPD. Some patients with COPD and T2 inflammation without a diagnosis of asthma benefit from biologic therapy.[732,742,1342]

Pulmonary tuberculosis

Pulmonary TB and COPD are two prevalent respiratory diseases in LMICs. Increasing evidence has shown that a history of pulmonary TB is associated with the development of chronic airflow obstruction,[229,1343] while patients with COPD have a three times increased risk of developing active TB compared with the general population.[1344] Pulmonary TB can cause permanent structural abnormalities in both the airways and lung parenchyma, such as calcification, cavitation, traction bronchiectasis, and fibrosis, leading to post-TB lung damage. Besides, TB may induce a particular form of inflammatory response with small airway and perivascular involvement which may further contribute to gas trapping, airflow limitation, and impaired diffusion capacity.[227,1345] Given these pathophysiological features, TB-associated COPD is increasingly recognized as a distinct cause of COPD. Cigarette smoking and *Mycobacterium tuberculosis* infection may act synergistically to exacerbate lung destruction, and patients with TB who smoke often present with more severe disease, increased cavitation, delayed response to anti-TB therapy, and worse outcomes.

The use of ICS, especially at higher doses, may increase the risk of TB reactivation or development in patients with COPD,[1346,1347] and in patients with underlying risk factors, such as those living in TB-endemic regions, patients with radiologic sequelae of TB, and patients who are immunocompromised or have comorbidities such as diabetes or low bodyweight.[1348,1349] In such settings, ICS should be used with caution and active TB must be excluded before initiation of this therapy. Patients should be closely monitored during treatment.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Bronchiectasis

With increasing use of CT in the assessment of COPD, previously unrecognized bronchiectasis is often being identified,[1350] although it is unclear at present whether a diagnosis based on radiological criteria has the same impact as a clinical diagnosis of bronchiectasis. The prevalence of bronchiectasis in patients with COPD has been reported in several studies with varied results ranging from 20-69%.[331,1351] Bronchiectasis is probably caused by an interplay between chronic airways infection and inflammation in COPD.[1352] A continuum may exist between chronic bacterial infection without radiological changes and overt radiological bronchiectasis.[583,1353] Comorbid bronchiectasis in COPD tends to be cylindrical or tubular, bilateral and lower lobe dominant, and is associated with increased exacerbation frequency, increased risk of pneumonia, airflow obstruction, and mortality.[330,1354,1355] If bronchiectasis is diagnosed (usually with imaging), tests to determine etiology should be individualized, such as immunoglobulin deficiency, cystic fibrosis transmembrane conductance regulator mutation, ciliary dysfunction, and fungal or mycobacterial infection.

In patients with COPD and bronchiectasis, ICS use should be carefully evaluated because such individuals are prone to pneumonia and nontuberculous mycobacteria infections.[1356] A blood eosinophil threshold of 300 cells/µL could be used to support ICS use, although if lower respiratory tract infections are frequent, ICS cessation should be considered. Macrolide therapy may benefit both the COPD and bronchiectasis by reducing exacerbations. Measures to enhance secretion clearance and chronic inhaled antibiotics can prevent exacerbations.[1357] Sputum culture is indicated, because its results may help guide antibiotic therapy. The anti-inflammatory dipeptidyl peptidase-1 inhibitor brensocatib, which has been evaluated in bronchiectasis and approved by the FDA, might also be effective in patients with combined bronchiectasis and COPD.[1358]

Interstitial lung disease / interstitial lung abnormalities

ILDs are conditions hallmarked by fibrotic changes of the lung.[1359-1361] COPD and ILDs may coexist as they share common risks (e.g., older age, male sex, and occupational and toxic inhaled exposures). Patients with ILDs typically report dyspnea as their main symptom due to similar mechanisms as COPD despite marked differences in respiratory

mechanics.[1362,1363] When patients with comorbid ILDs and COPD experience an acute exacerbation it may be due to either disease, with important implications for treatment and prognosis.[1364] ILAs, an imaging finding of early ILDs that occurs in 7-10% of patients with COPD, are associated with worsening dyspnea, health-related quality of life and exercise capacity, and increased mortality risk.[262] A smaller subset of patients may present with combined pulmonary fibrosis (usually in lower lobes) and emphysema in the upper zones, with lung function tests that indicate a marked reduction in diffusing capacity but lung volumes within the normal range.[1365]

A careful examination of thoracic imaging, preferably chest HRCT, may help exclude the presence of ILAs or ILDs. Lung function testing at diagnosis and sequential measurements help define disease progression. Patients with combined COPD and ILD require a multidisciplinary approach, involving specialists in COPD, ILD, pathology and radiology. Although there are no specific trials of anti-fibrotic treatments in patients with COPD and ILDs, we recommend intermittent follow-up, including assessment of DLco every 6-12 months to define disease progression. In this context, patients with some emphysema (< 30%) and pulmonary fibrosis treated with antifibrotics have a lung function decline similar to treated patients with pulmonary fibrosis without COPD.[1366]

Obstructive sleep apnea

OSA is a sleep disorder hallmarked by repeated episodes of upper airway closure that affects 9-26% of the US adult population.[1367] Both COPD and OSA frequently coexist, particularly in obese men and obese post-menopausal women.[1368-1370]

Patients with both COPD and OSA have a worse prognosis compared with either condition alone.[1371] During sleep, they experience more frequent episodes of oxygen desaturation and have more total sleep time with hypoxemia and hypercapnia than patients who have OSA without COPD.[1372] Their apneic events involve more profound hypoxemia and more cardiac arrhythmias,[1373] and they are more likely to develop daytime pulmonary hypertension[1374,1375] and other cardiovascular outcomes including heart failure and myocardial infarction[1376] than patients with just OSA or COPD alone. A systematic review and meta-analysis of 29 studies in COPD patients found a prevalence of OSA of 38%.[1377]

If there is a clinical suspicion of OSA (e.g., obesity, snoring, daytime somnolence, hypertension) a formal sleep study is indicated.

For patients with COPD and OSA, a program should be implemented that includes weight loss for obese patients, reduced alcohol intake, and sleep hygiene interventions. CPAP or bi-level positive airway pressure should be initiated in patients with COPD and sleep disordered breathing as it improves health-related quality of life and decreases the risk of death.[840] Further, in patients with COPD and OSA, CPAP has been reported to reduce all-cause hospitalizations, emergency room visits, moderate and severe exacerbations and associated healthcare costs.[840,1378] Weight reduction medications, such as glucagon-like peptide receptor agonists could help in selected obese patients.[1379,1380]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

MENTAL CONDITIONS

Anxiety, depression and psychosis

Anxiety and depression are important and underdiagnosed morbidities in patients with COPD,[343,1381-1383] and both are associated with poor prognosis.[1382,1384] The prevalence of anxiety alone and combined anxiety and depression is similar in men and women with COPD (all approximately 34%). Furthermore, younger age is associated with more severe symptoms of depression and anxiety.[94,343,1383,1385] COPD is very common in patients with other psychiatric

illnesses, particularly schizophrenia,[1386-1388] and people with COPD are twice as likely to commit suicide as those without COPD.[1389]

Untreated depression and anxiety are associated with social isolation, increased healthcare utilization, premature mortality, and increased disease burden for patients and their caregivers. Depression, anxiety and psychosis (including schizophrenia and substance abuse, both alcohol and drugs) are independently associated with elevated 30-day readmission rates in patients with COPD, and are important determinants of death in younger patients with COPD.[1388,1390-1393] People with severe mental illness tend to receive medical care intermittently, often with a lack of continuity of care and infrequent use of primary and preventive services. Physical symptoms may be viewed as "psychosomatic" leading to under-diagnosis. People with COPD and schizophrenia are less likely to receive adequate general medical care, including investigation and treatment, in line with guidelines.[1388]

The Patient Health Questionnaire-2 for depression, with scores less than three suggesting no important depression,[1394] and the Generalized Anxiety Disorder-2 for anxiety, with the same score threshold,[1395] can be used as screening tools to detect clinically significant depression or anxiety.

COPD should be treated as usual in patients with psychological disorders. The potential impact of pulmonary rehabilitation should be stressed as studies have found that physical exercise has a beneficial effect on depression in general.[1396,1397] Combining pulmonary rehabilitation and cognitive behavioral therapy are effective in alleviating anxiety and depressive symptoms.[1398,1399] Anti-depressant drug therapy needs to be managed with caution, and patients with severe depression and suicidal ideation or attempts must be referred promptly for specialist treatment.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Cognitive impairment and dementia

Cognitive impairment is common in people with COPD,[1400] with an estimated average prevalence of 32%,[1401] although prevalence and severity vary by the type of assessment,[1402] and extensive neuropsychological testing suggests that up to 56% of patients with COPD may have cognitive impairment.[1403,1404] Longitudinal studies suggest a greater risk of developing cognitive impairment in patients with COPD that is diagnosed in midlife,[1400,1405] and associate COPD with the development of dementia.[1406] In a systematic review, age-matched patients with COPD had a 24% increased risk of dementia and a 30% elevated risk of cognitive impairment compared to individuals without COPD, with no differences by sex, although the risk of both increased with age.[1407]

Cognitive impairment has been associated with impairment in basic activities of daily living,[1408,1409] and variably associated with impaired health status.[1410,1411] The coexistence of cognitive impairment and COPD is associated with an increased risk of hospitalization, longer hospital stay during acute exacerbation hospitalization, worse health-related quality of life, and increased risk of death.[1408,1409,1412,1413]

Patients with cognitive impairment are more likely to make errors when using inhalers.[1408] The relatively easy to use Mini Mental State Examination can help screen for cognitive impairment,[1414] with the Montreal Cognitive Assessment test being a potential alternative.[1415]

Patients with COPD who have mild cognitive impairment should be enrolled in pulmonary rehabilitation programs with or without cognitive training.[1416] Addressing potential underlying risk factors such as sleep deprivation, hypoxemia, frequent exacerbations and atherosclerosis is important. Patients with dementia should be referred to mental healthcare specialists for further neuropsychological assessment and treatment.

METABOLIC DISEASE

Diabetes mellitus

Studies have shown that metabolic syndrome and manifest diabetes are frequent in patients with COPD.[503,1417] Type 2 DM is present in approximately 20% of patients with COPD, increasing morbidity and mortality, and complicating the management of both.[1418] Type 2 DM is associated with a restrictive lung function profile, independent of race, age, sex, country of origin, bodyweight, smoking history, or history of lung disease,[1419,1420] although insulin resistance is associated with an increased risk of COPD in women but not in men.[1421] When patients are treated with systemic corticosteroids during exacerbations, hyperglycemia worsens, enhancing the risk of infection and prolonging the duration of the episode. ICS, especially in high doses, are associated with worsening DM control and increased risk of glaucoma and cataracts.[1422]

Measurement of hemoglobin A1c and fasting blood glucose for patients who have not had these tests in more than a year can help verify a diagnosis and monitor disease control. COPD should be treated as usual, although efforts should be made not to use systemic corticosteroids. If indicated, they should be used at the lowest possible dose for the shortest possible time. The use of novel DM therapies such as glucagon-like peptide agonists and sodium-glucose cotransporter-2 inhibitors are promising, but further trials in COPD specific populations are needed before clear recommendations can be made.[1423,1424]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Obesity

The relationship between weight and COPD outcomes is complex. Extensive data in multiple cohorts show that there is increased mortality risk at BMI extremes,[1091,1425-1427] such that values < 21 kg/m^2 or > 30 kg/m^2 contribute to a poor prognosis. Obesity is associated with airflow limitation, increased symptoms such as dyspnea, and an elevated risk of cardiovascular complications, although it appears protective for COPD progression and respiratory-related mortality. Very obese patients with COPD are more likely to decompensate and require non-invasive or mechanical ventilation, and have a higher tracheostomy rate and odds of being discharged on domiciliary oxygen.[1428] However, a low BMI also carries a poor prognosis, being a phenotype of COPD with a higher mortality risk than patients of normal weight. Thus, the most beneficial BMI for patients with COPD appears to be one that is within the 'normal' or 'overweight' categories.

BMI should be measured at all visits, and changes monitored over time. Optimization of BMI includes lifestyle management implementing regular exercise, adequate nutrition to attain and maintain BMI 21-30 kg/m^2. The recent introduction of weight control medications with important beneficial systemic effects should be considered by providers knowledgeable of their use.[1429,1430]

Gastroesophageal reflux

GERD is an independent risk factor for COPD exacerbations, and is associated with worse health status in patients with COPD,[478,1431,1432] although the mechanisms responsible for the increased risk of exacerbations are not yet fully established.

GERD should be minimized through weight loss (if obese) and avoiding late-night meals or specific food and drink that might aggravate reflux. In addition, a semi-recumbent sleeping posture may be helpful, and an empiric trial of a proton-pump inhibitor may improve GERD symptoms and decrease the risk of exacerbation,[1433] In patients with severe reflux and in whom conservative therapy has failed, surgical fundoplication has been effective.[1434,1435]

Liver steatosis

NAFLD, also known as metabolic dysfunction-associated steatotic liver disease, affects 30-60% of patients with COPD,[1436] linked through common risk factors (e.g., chronic inflammation, obesity, inactivity) or causal mechanisms such as hypoxemia. It can be detected using low-dose chest CT,[567,1437] and although most cases are benign, 20-30% can progress to MASH (metabolic dysfunction-associated steatohepatitis), which can in turn progress to liver cirrhosis and hepatocellular carcinoma.[1438] Although NAFLD prevalence is slightly increased in patients with COPD it does not seem to worsen the prognosis of COPD.[1439]

Liver function testing and checking the CT for evidence of NAFLD can help establish the diagnosis. These patients should be advised to lose weight, exercise regularly, control risk factors such as hyperglycemia, hypertension and hypercholesterolemia, and avoid alcohol. Resmetirom, a thyroid hormone receptor β-agonist, has been approved in some countries for the treatment of metabolic dysfunction-associated steatohepatitis,[1440,1441] while glucagon-like peptide-1 receptor agonists may also be of use in this disease.

DISEASES WITH MULTIPLE ORGANS LOSS OF TISSUE

The term 'multiple organs loss of tissue' (MOLT) has been proposed for patients with emphysema, low BMI, osteoporosis and sarcopenia.[1442] These characteristics frequently co-occur in patients with COPD, and are associated with poor exercise capacity, compromised health-related quality of life, and an increased risk of exacerbations, hospitalizations and mortality.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Osteoporosis

Osteoporosis is an important and common comorbidity in patients with COPD,[504,1224] which is often under-diagnosed[1443] and is associated with poor health status and prognosis. The prevalence may be as high as 30% in women and 18% in men, with the prevalence increased by the presence of COPD.[1444] Osteoporosis is often associated with emphysema,[1445] decreased BMI[1446] and low fat-free mass.[1447] Low bone mineral density and fractures are common in people with COPD even after adjustment for steroid use, age, pack-years of smoking, current smoking, and exacerbations.[1448,1449] Systemic corticosteroids significantly increase the risk of osteoporosis, and repeated courses for COPD exacerbations should be avoided if possible. An association between ICS use and fractures has been found in pharmaco-epidemiological studies;[1450] however, these studies have not fully taken severity of COPD or exacerbations and their treatment into consideration.

Clinically, chest CT scans can help identify individuals with low bone mineral density and muscle mass who should undergo more detailed assessment. Dual energy X-ray absorptiometry scanning can establish bone mineral density with excellent precision.

COPD should be treated as usual despite the presence of osteoporosis. Given the complicated landscape of anabolic and antiresorptive agents for the treatment of osteoporosis, these patients should be managed by providers familiar with the treatments or referred to an osteoporosis specialist.[1451]

Renal failure

The prevalence of renal failure, defined as GFR < 60 mL/min/1.73 m^2, is three-times higher in patients with COPD than in matched controls (approximately 7% in patients aged < 65 years; 17-20% in those > 70 years).[1452,1453] Because sarcopenia is frequent in patients with COPD, serum creatinine levels may be normal in patients with renal failure. Low estimated GFR values are associated with decreased health-related quality of life and 6MWD, and increased hospitalizations and mortality.[1454] Importantly, glomeruli number and size are decreased in patients with COPD, who

also frequently have microalbuminuria.[1455,1456]

Estimated GFR should be measured, and the use of medication should be checked, since patients with COPD frequently receive potentially nephrotoxic drugs, such as non-steroidal anti-inflammatory drugs, or treatments that are eliminated via the kidney. Furthermore, many patients with COPD receive an ACE inhibitor, angiotensin II receptor blocker or β-blocker that can decrease erythropoietin production. With renal failure, it is important to adjust medications that can injure the kidney or where renal elimination of the drugs may result in relevant side effects.[1457]

Anemia

Anemia is frequent in people with COPD, with a reported prevalence of 7.5-34%.[1458] Those with combined COPD and anemia are generally older, have more frequent cardiometabolic comorbidities, greater dyspnea, worse health-related quality of life and airflow obstruction, reduced exercise capacity, an increased risk of severe exacerbations and higher mortality than patients with COPD alone.[1458-1464]

Anemia due to chronic disease is the most common type seen in COPD, followed by iron deficiency anemia,[1465,1466] mainly related to chronic systemic inflammation and impaired iron utilization. However, other possible reversible factors should be investigated including use of long-term oxygen, theophylline, ACE inhibitors, angiotensin II receptor inhibitors, renal dysfunction, and androgens.[1453,1467-1474]

Although anemia has been established as an important comorbidity in COPD, optimal hemoglobin and hematocrit levels in these patients have not yet been defined, and it is also unclear whether the correction of anemia alters outcomes. However, hemoglobin assessment is advisable, particularly in more severely affected patients. If anemia is diagnosed, a systematic search for a treatable cause is recommended in accordance with appropriate clinical guidelines.

Polycythemia

Smoking causes an increase in carboxyhemoglobin, thereby increasing red blood cell mass and the risk of secondary polycythemia in patients with COPD.[1475,1476] Indeed, secondary polycythemia has long been recognized as a common comorbidity in COPD, with a reported prevalence of 6-10.2% in patients with COPD in an outpatients department (when defined as hemoglobin ≥ 17g/dL in males and ≥ 15g/dL in females),[1460,1462,1477] and 9.2% of men and 3.5% of women in the COPDGene cohort.[1478]

Male sex, current smoking, living at high altitude (e.g., Denver, Colorado, USA), impaired DLco, and severe hypoxemia are associated with an increased risk for secondary polycythemia, whereas LTOT use is associated with a decreased risk.[1478,1479] The coexistence of OSA is also associated with an increased risk of polycythemia in patients with COPD.[1480]

Secondary polycythemia in COPD may be associated with PH,[1481,1482] venous thromboembolism,[1482] and increased mortality.[1483,1484] However, these findings should be interpreted with caution, since secondary polycythemia may be related to the presence of severe uncorrected hypoxemia, which is a predictor of mortality in COPD, as well as to the presence of concomitant interstitial lung disease or pulmonary vascular disease.

In patients with COPD, if secondary polycythemia is present a careful evaluation should be performed to determine uncorrected hypoxemia or to rule out the presence of any comorbidities that require a specific intervention.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

POSTOPERATIVE RISK OF COPD ON GENERAL AND THORACIC SURGERY OUTCOMES

General surgery

Postoperative pulmonary complications are as important and common as postoperative cardiac complications and, consequently, are a key component of the increased risk posed by general surgery in patients with COPD.[1485] The key factors that can contribute to the risk include smoking, poor general health status, age, obesity, and COPD severity. A comprehensive definition of postoperative pulmonary complications should include only major pulmonary respiratory complications, namely lung infections, atelectasis and/or increased airflow obstruction, which all potentially result in acute respiratory failure and aggravation of COPD.[1109,1486,1487]

The risk of postoperative pulmonary complications in patients with COPD may vary with the severity of COPD, although the surgical site is the most important predictor and risk increases as the incision approaches the diaphragm.[1487] Most reports conclude that epidural or spinal anesthesia have a lower risk than general anesthesia, although the results are not totally uniform. Some studies conducted in patients undergoing sham bronchoscopic procedures have reported acute exacerbation rates as high as 8.4%.[953] These data suggest that intubation and/or simple airway manipulation may increase the risk of exacerbation in select patients with COPD.

To prevent postoperative pulmonary complications, patients with COPD who are clinically symptomatic and/or have limited exercise capacity should be treated medically intensively before surgery, with all the measures already well established for such patients who are not about to have surgery. The presence of comorbid conditions, especially cardiac abnormalities, should be systemically assessed and treated before any major surgical intervention.

Resection for lung cancer treatment

For lung resection, the individual patient's risk factors should be identified by careful history taking including physical examination, chest radiography, and pulmonary function tests. Although the value of pulmonary function tests remains contentious, there is consensus that all COPD candidates for lung resection should undergo a complete battery of tests, including spirometry with bronchodilator response, static lung volumes, diffusing capacity, and arterial blood gases at rest.[1488,1489] Patients with COPD who are at high risk for surgical complications due to poor lung function should undergo further assessment, for example, tests of regional distribution of perfusion and exercise capacity.[1488,1489]

The risk of postoperative complications from lung resection appears to be increased in patients with decreased predicted postoperative pulmonary function (FEV1 or DLco < 30-40% predicted) or exercise capacity (peak VO_2 < 10 mL/kg/min or 35% predicted). The final decision to pursue surgery should be made after discussion with the surgeon, pulmonary specialist, primary clinician, and the patient. Surgery should be postponed if an exacerbation is present.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

OTHER CONSIDERATIONS

Periodontitis and dental hygiene

The association between COPD and periodontitis has been mainly reported in the dental literature, although whether this reflects common causative factors such as age, smoking, and socioeconomic circumstances remains speculative.

Both conditions have a common (neutrophilic) relationship; whether this reflects cause or effect is difficult to elucidate,[1490] although one study suggested a shared pathophysiology between periodontitis and COPD, with similar aberrant neutrophil function, especially when associated with AATD.[1491]

The risk of developing periodontitis is proportional to COPD control, with prevalence increasing with the number of emergency department visits for COPD.[1492] High antibody levels to common periodontal pathogens is associated with fewer exacerbations of COPD.[1493] In a recent systematic review, low to moderate quality evidence suggests that periodontal treatment is associated with slower lung function decline, reduced frequency of exacerbations, and less healthcare resource use in patients with COPD and chronic periodontitis.[1494] In the absence of an effective curative treatment for COPD it is difficult to prove the reverse is also true. Nevertheless, periodontitis is common in COPD, and often requires treatment in its own right, which may lead to a reduction in exacerbations.

Vitamin D deficiency

Patients with COPD may have low vitamin D levels due to reduced sunlight exposure (COPD symptoms keep patients indoors) and poor dietary intake. In addition, long-term use of corticosteroids impairs vitamin D absorption and some studies have shown that very low vitamin D levels are linked to increased risk of lung infections, which can trigger exacerbations and worsen COPD.[1495] A meta-analysis of RCTs found that vitamin D supplementation significantly reduced moderate/severe exacerbations in patients with very low baseline levels (< 25 nmol/L).[1084] Thus, consider checking for vitamin D deficiency in people with COPD, particularly if the patient has a history of frequent exacerbations.

Guide to the practical tools available to evaluate and monitor multimorbid patients with COPD

A useful grouping of testing that could be used to evaluate multimorbid patients with COPD is presented in **Figures 5.6** and **5.7**. Although not all need to be used in every patient, a systematic approach considering these tools could help organize care in complex cases.[1232]

COPD as part of multimorbidity

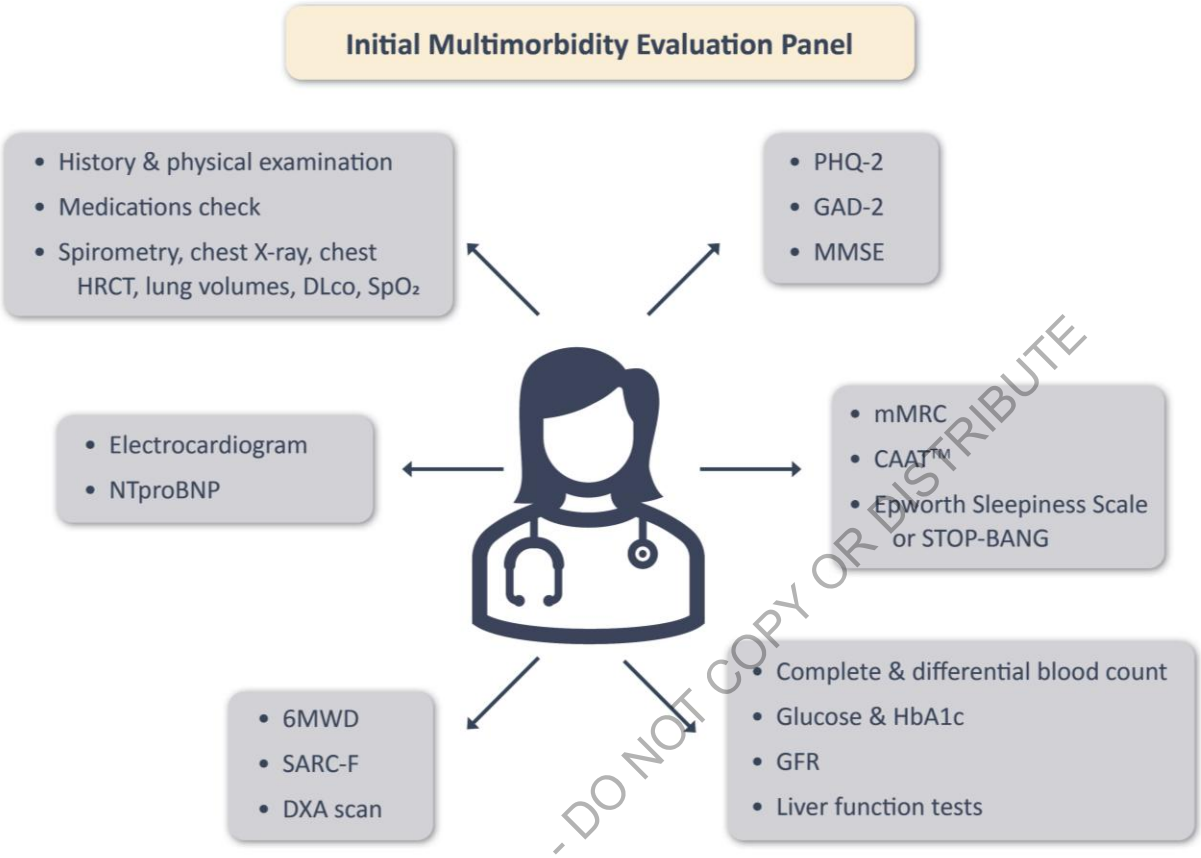
As expected, multimorbid patients have symptoms from multiple diseases and thus symptoms and signs are complex and most often attributable to several causes in the chronic state as well as during acute events. GOLD does not aim to turn the specialist into a generalist, but we propose that healthcare providers managing patients with COPD should integrate clinical information to help maximize the interaction with the patient to the benefit of the latter. A proactive, holistic rather than a siloed approach can decrease the fragmented care so prevalent in today's healthcare systems. Simple and practical clinical tools are available to most clinicians that help identify and grade the severity of the most important morbidities affecting individual patients, and that determine whether the problem is being properly addressed. If it is not, either treat it according to best practice or help direct the patient to the appropriate specialist care and resources to achieve optimal management. As a rule, there is no evidence that COPD should be treated differently when part of multimorbidity; however, it should be kept in mind that most evidence comes from trials in people with COPD as the only significant disease.[505]

Finally, treatments should be kept simple in the light of the unbearable polypharmacy that these patients are often exposed to. It is likely that a holistic approach in the management of patients with COPD might help reverse the effects of different diseases on overall health, prevent exacerbations, improve health-related quality of life and hopefully reduce hospitalizations and the risk of death.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Potential Complementary Approach for the Detection of Frequent Morbidities in all Patients with COPD – Initial Evaluation

Figure 5.6



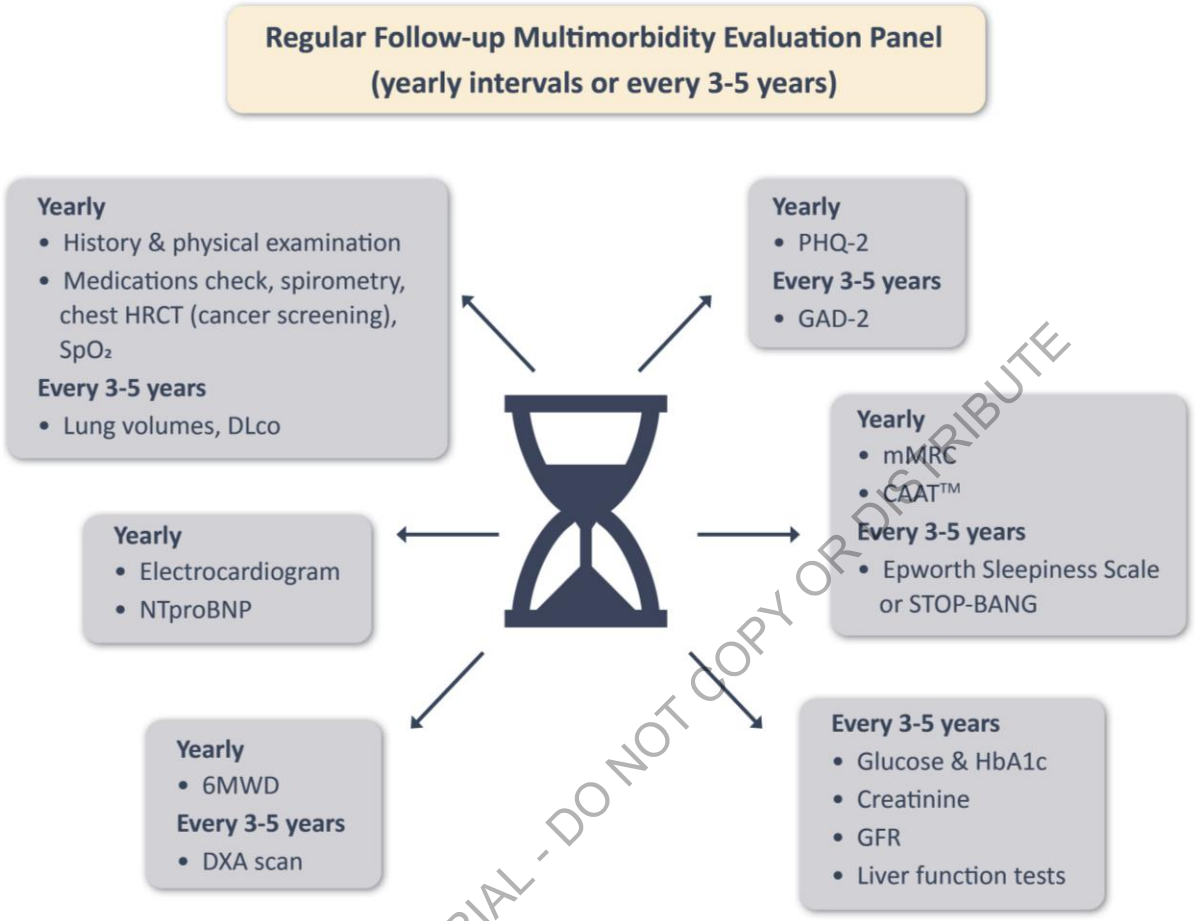
Abbreviations: HRCT, high-resolution computerized tomography; DLco, diffusing capacity for carbon monoxide; SpO_2, oxygen saturation; SARC-F, Strength, Assistance walking, Rising from chair, Climbing stairs and Falls; DXA, dual energy X-ray absorptiometry; mMRC, modified Medical Research Council dyspnea scale; CAAT™, Chronic Airways Assessment Test; GFR, glomerular filtration rate; NTproBNP, N-terminal prohormone of brain natriuretic peptide; 6MWD, 6-minute walking distance test; HbA1c, glycated hemoglobin A1c test; PHQ-2, Patient Health Questionnaire-2; GAD-2, Generalized Anxiety Disorder-2; MMSE, Mini Mental State Examination.

Adapted from: Celli BR, Fabbri LM, Yohannes AM, Hawkins NM, Criner GJ, Bon J, Humbert M, Jenkins CR, Pantoni L, Papi A, Quint JK, Sethi S, Stolz D, Agusti A, Sin DD. A person-centred clinical approach to the multimorbid patient with COPD. Eur J Intern Med. 2025 Aug 12:106424. doi: 10.1016/j.ejim.2025.07.020.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Potential Complementary Approach for the Detection of Frequent Morbidities in all Patients with COPD – Regular Follow-up

Figure 5.7



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Abbreviations: HRCT, high-resolution computerized tomography; DLco, diffusing capacity for carbon monoxide; SpO_2, oxygen saturation; SARC-F, Strength, Assistance walking, Rising from chair, Climbing stairs and Falls; DXA, dual energy X-ray absorptiometry; mMRC, modified Medical Research Council dyspnea scale; CAAT™, Chronic Airways Assessment Test; GFR, glomerular filtration rate; NTproBNP, N-terminal prohormone of brain natriuretic peptide; 6MWD, 6-minute walking distance test; HbA1c, glycated hemoglobin A1c test; Patient Health Questionnaire-2; GAD-2, Generalized Anxiety Disorder-2.

Adapted from: Celli BR, Fabbri LM, Yohannes AM, Hawkins NM, Criner GJ, Bon J, Humbert M, Jenkins CR, Pantoni L, Papi A, Quint JK, Sethi S, Stolz D, Agusti A, Sin DD. A person-centred clinical approach to the multimorbid patient with COPD. Eur J Intern Med. 2025 Aug 12:106424. doi: 10.1016/j.ejim.2025.07.020.

CHAPTER 6: ARTIFICIAL INTELLIGENCE AND EMERGING TECHNOLOGIES IN COPD

KEY POINTS:

- Artificial intelligence can help in the diagnosis, assessment, clinical management, and prediction of prognosis of COPD.
- Yet, AI comes with risks and limitations that need careful consideration before deployment in clinical practice.
- Telehealth includes virtual, hybrid virtual and in-person care models.
- Telehealth may offer improved healthcare access, outcomes, and affordability.
- Pulmonary rehabilitation and self-management may be delivered virtually.
- Evidence is still emerging regarding the effectiveness of virtual compared to in-person delivery.

COPYRIGHT MATERIAL- DO NOT COPY OR DISTRIBUTE

ARTIFICAL INTELLIGENCE IN COPD

The term artificial intelligence refers to a set of rules (algorithms) that enable computers to learn, analyze data and make decisions based on that knowledge.[1496,1497] AI has many potential clinical benefits in the diagnosis and management of COPD (**Figure 6.1**).[1498] The common "*AI models*" differ in the way they are trained and analyze data,[1499] and AI comes with risks and limitations that need careful consideration before deployment in clinical practice (**Figure 6.2**).[1500] Below we discuss briefly some areas where AI can be helpful in COPD and we refer the interested reader to a recent manuscript that extends these concepts further.[1498]

Diagnosis

Underdiagnosis, misdiagnosis and late diagnosis are very prevalent in COPD.[408,1501,1502] They are clinically relevant because underdiagnosis implies no treatment, misdiagnosis can lead to wrong treatment, and late diagnosis likely supposes less effective treatment. AI can help address these three domains.

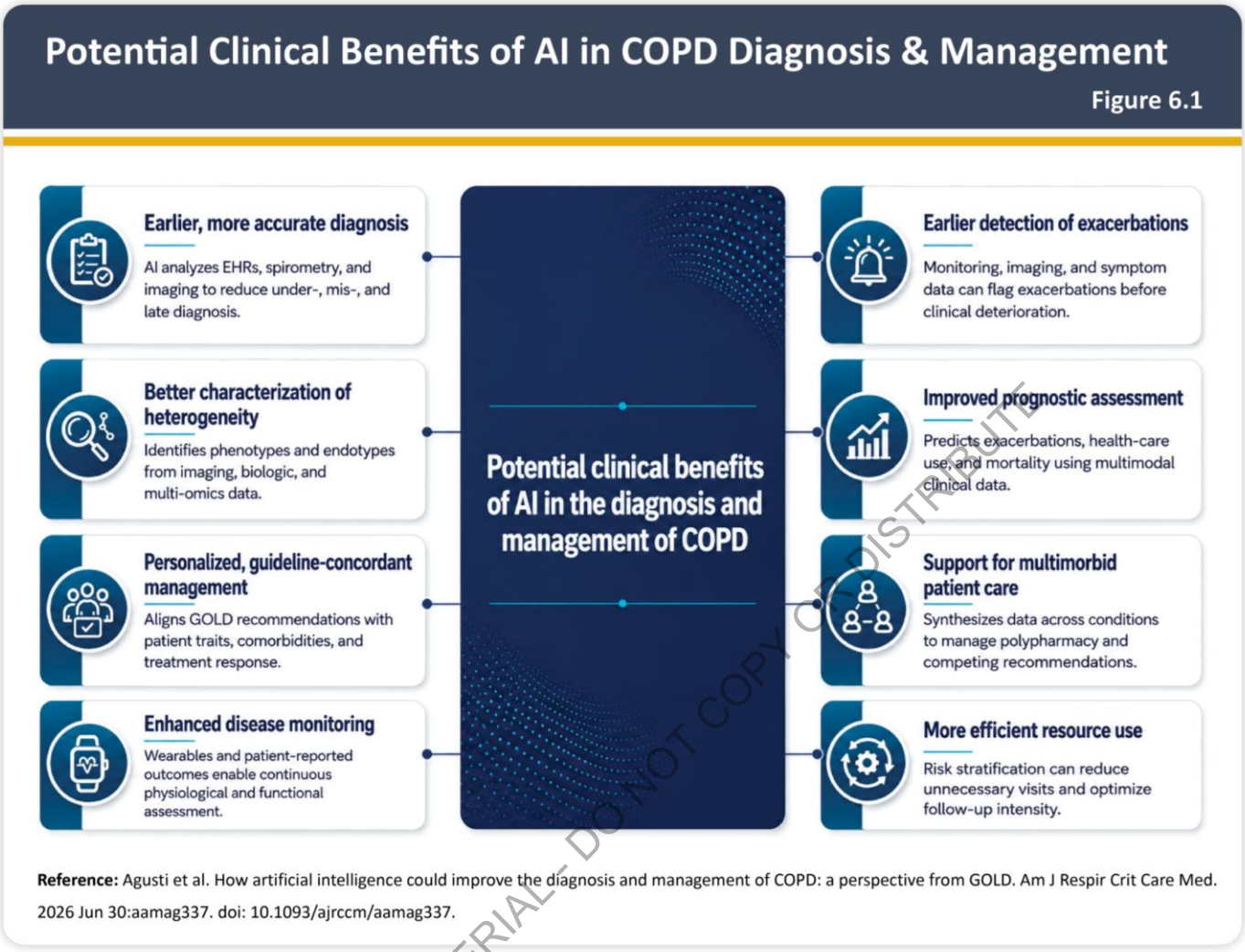
Underdiagnosis

AI can potentially help identify individuals at risk in electronic health records, both in primary and specialized care. This can also be done in the community, as shown in Canada.[412] There may even be the opportunity to identify undiagnosed patients with COPD in lung cancer screening programs.[412,1503] However, currently the quality and interoperability of the data included in the EHR, together with the legal framework on data access and medical devices, may limit its practical implementation.

Misdiagnosis

AI based interpretation strategies can reduce misdiagnosis by providing automated interpretations and diagnostic

suggestions.[1504-1506] Likewise, AI may be able to extract novel, hidden, high-dimensional features from the flow-volume spirometry loops.[1505,1507]



Reference: Agusti et al. How artificial intelligence could improve the diagnosis and management of COPD: a perspective from GOLD. Am J Respir Crit Care Med. 2026 Jun 30:aamag337. doi: 10.1093/ajrccm/aamag337.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Late diagnosis

The diagnosis of COPD is often established (if it is at all) in the 7th decade. By then the disease is frequently far advanced and less responsive to treatment.[1508] As discussed above, AI can facilitate earlier diagnosis by searching EHRs.[1509,1510] Further, several studies used AI to predict lung function trajectories and risk of COPD in individuals in the general population requiring intervention.[1511,1512]

AI-assisted diagnostic alternatives to spirometry

There are several AI-assisted novel diagnostic alternatives to spirometry being explored in relatively small populations, so they require validation in larger cohorts:[1513]

- Analysis of respiratory sound attributes[1514]
- Analysis of voice features[1515]
- Oscillometry (FOT, IOS, AOS)[1516]
- Motion sensors[1517]
- E-nose signals / volatile organic compounds (VOC)[1518,1519]
- Photoplethysmography[1520]
- Chest computed tomography (CT)[312,1521-1523]
- Electrical Impedance Tomography (EIT)[1521]

Heterogeneity of COPD

COPD is a heterogeneous disease, and clinical management can be improved if a personalized and precise approach to care is used. Biomarkers can potentially be used to address this heterogeneity.

Imaging biomarkers

The use of AI imaging is the most developed AI platform currently utilized in COPD. AI can be used to quantify the extent and the pattern of emphysema and to analyze fissure integrity, mucus plugs, bronchiectasis and/or pulmonary vessels.[1524] Likewise, using AI-assisted analysis of nodules may avoid overuse of invasive procedures and a more accurate and rapid classification of patients at risk of lung cancer.[1525]

Biologic biomarkers

Several studies used AI on omics data to identify biologic biomarkers of potential use in COPD.[1526-1528] Most of them require validation in large cohorts with longitudinal data[1529] but clearly pave the way for a better characterization of COPD patients and, potentially, the identification of novel therapeutic targets.

Multimodal models

Multimodal models that integrate biological and imaging data may offer better insights into COPD risk and progression. Emerging foundation models such as *Merlin* extends this concept further by integrating imaging and text but also structured clinical and laboratory data.[1525,1530] This highlights the potential of AI to address the complex, multi-domain nature of COPD risk stratification and management.[1531]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Potential Risks and Mitigation Strategies of AI in Medicine Figure 6.2

	Potential Risks	Mitigation Strategies
Clinical Risks	• Misdiagnosis, overreliance on AI, biased outcomes	• Rigorous validation, human oversight, bias testing
Data-Related Risks	• Poor data quality, biased training data, privacy breaches	• Data cleaning, diverse datasets, strong security protocols
Technical Limitations	• Black-box models, poor generalizability, data drift	• Use interpretable models, retraining, external validation
Ethical & Legal Risks	• Unclear accountability, informed consent issues, inequity	• Clear liability frameworks, transparent patient communication, equitable access
Operational Challenges	• Workflow integration problems, regulatory complexity, high maintenance costs	• User-centered design, regulatory alignment, ongoing monitoring and funding

Management guidelines, multimorbidity and AI

The concept of evidence-based medicine (EBM) has been widely adopted by the medical community since its proposal, back in 1992.[1532] As a result, a large number of evidence-based clinical practice guidelines are now available. Yet, to be fully and appropriately implemented in clinical practice, any clinical practice guideline needs to be read, memorized and applied wisely by the practicing physician. Many patients with chronic diseases, including COPD, often suffer from other diseases.[310] So, many different guidelines need to be considered in everyday practice.[1232] This is an herculean process where AI can be of great help, since algorithms could be embedded in current EHR systems to summarize the current clinical status of the multimorbid patient who has been seen by different (often many) specialties and/or to advise the practicing physicians of potential problems with the management of that patient (e.g., polypharmacy, inappropriate treatment of a multimorbid disease, tests missing, vaccination needed and others). As a side note, in order to get AI collecting the appropriate information included in the EHRs, the use of acronyms (which often vary between specialties and even between physicians) should be banned. An alternative, already in place in some institutions, is that the conversation between the patient and the doctor is continuously recorded ("keyboard zero"). Then, AI can produce a summary of the visit (without acronyms) for the doctor (and the patient using a user-friendly, not technical language) that, after being approved by the attending physician, can be stored in the EHR and printed or sent e.g., via e-mail, text message, SMS, WhatsApp etc) to the patient. As a side effect, this keyboard zero strategy is likely to improve eye contact (and empathy) with the patient. Finally, given that guidelines are written by "human consensus based on best available evidence by experts in the field", they constitute an invaluable source of input data for AI, and should continue to be produced by "human expert consensus".

Remote patient monitoring

When combined with wearable sensor technologies, AI can also allow RPM by facilitating transmission of patient-reported outcomes and physiological data directly to healthcare professionals. Yet, there is still limited evidence that RPM in COPD impacts on relevant clinical outcomes.[1533] A key issue in this setting is how healthcare systems will be able to efficiently review this data and respond to it.[1534]

On the other hand, given that inhaled therapy is a cornerstone of COPD treatment and that adherence and correct inhalation is often poor, the potential of digital smart inhalers to improve adherence and inhaler technique is large.[1534-1536] Likewise, AI-supported home rehabilitation is a potential alternative when face to face programs are not available.[1537]

Finally, AI can be potentially used at the home of the patient. A chatbot is a computer program designed to simulate conversation with human users, either through text or voice, to provide information, answer questions, or complete tasks. If appropriately trained and validated, a chatbot in the home of the patient can potentially be the first interface to contact the healthcare system[1538] and answer questions the patient may have about her/his health at home and recommend specific actions, including automatically seeking healthcare, either remotely or in person.[1539]

Prognosis

In a systematic review and meta-analysis Smith *et al* concluded that there is still limited evidence that conventional machine learning and deep learning prognostic models demonstrate superior performance to pre-existing disease severity scores in COPD patients.[1540] Likewise, AI can also help identifying patients at higher risk of exacerbations.[1528] Most of these studies require validation in large cohorts with longitudinal data[1529] but clearly pave the way for a better assessment of risk in COPD patients.[1541]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

TELEHEALTH, REMOTE MONITORING AND FOLLOW-UP

The COVID-19 pandemic dramatically changed how outpatient care is delivered in healthcare practices. Telehealth may offer a bridge to care, and now offers a chance to consider virtual and hybrid virtual/in-person care models, with a goal of improved healthcare access, outcomes, and affordability.[822] However, incorporation of virtual care into ambulatory care should be based on evidence.

A Cochrane review[1542] on telehealth for remote monitoring and consultations for patients with COPD included three main different models that have been studied in RCTs:[1542]

- Remote monitoring (linked to a healthcare professional) plus usual care versus usual care alone (as reported by trialists).
- Remote consultation (e.g., real-time contact with a health professional) plus usual care versus usual care alone (e.g., face-to- face visit for a check-up in a health service with a health professional, or as reported by trialists).
- Remote monitoring or remote consultation versus usual care (e.g., where tele healthcare has replaced an element of usual face-to-face care).

For most of the studies included in the review (24 RCTs) remote monitoring interventions required participants to transfer measurements using a remote device for subsequent health professional review (asynchronous) as opposed to only five RCTs that transferred data and allowed review by health professionals in real time (synchronous).[1542] The results of this systematic review demonstrate the paucity of evidence of superiority of these models compared to usual care, i.e., exacerbations, hospitalization, health status and mortality. While there was no evidence of harm, it is still unclear which COPD severity subgroups would benefit, or possibly be harmed, by telehealth interventions. Telehealth interventions may be beneficial as an additional health resource based on professional assessment, and depending on individual needs, although the long-term effects remain unknown.

Information is provided on how i) to prepare for the remote visit; ii) to set up the visit agenda with the patient; and a standardized checklist is provided for follow-up of patients with COPD, whether in-person, by phone or in a virtual/online setting, in **Appendix 4** at the end of the GOLD report.

The principles of good record keeping and clinical practice should always apply: i) treat patients with dignity; ii) respect people's right to privacy and confidentiality; iii) listen to the patient's needs and act in their best interest; and iv) base your recommendations on the best available evidence.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Triage and prioritizing process

The process of triage should help decide: i) whether to offer an in-person as opposed to a remote (telephone or virtual/online) consultation, and ii) who to prioritize.

Remote follow-up could be considered in the following situations:

- Patient or caregiver can understand the process and provide information clearly;
- Regular COPD follow-up or patient followed for a known condition;
- Medical records and laboratory test results are accessible to the healthcare professionals;
- Prescription and access to medication is possible and follow-up to the prescription can be arranged if necessary.

In-person follow-up should be prioritized in these situations:

- Patient and caregiver have difficulty providing information;
- Patient needs immediate attention due to the presence of severe medical symptoms;
- Changes in patient's symptoms require a differential diagnosis work-up with the need for a physical exam and/or laboratory testing;
- Patient treatment can only be given in person and cannot be given at home.

Prioritization of in-person visits should take into consideration disease severity (symptom burden and risk of exacerbations), recent emergency department visit and/or hospital admission, associated significant comorbidities, age, and/or living alone at home.

Consideration and instruction for remote COPD follow-up

Ensure documentation of the whole visit (in writing) as you would normally do for an in-person follow-up. The documentation should reflect that this is a remote follow-up (telephone or virtual/online) and should be specific about how the information was obtained.

1. Start the call by
    a. Introducing yourself and, if necessary, any other healthcare professional(s) who may be with you (e.g., case manager, student, resident, etc.);
    b. Verifying who you are speaking with (patient name and date of birth), and patient consent to receive remote follow-up;
    c. If applicable, informing the patient that the speakerphone is on;

2. Welcome the patient to the call
    a. Verify technical issues;
    b. Ask the patient if (s)he can hear you well;
    c. Describe what to do if the connection fails;

3. Explain that this is a remote visit and give the reason why;

4. ***Check if there are others listening*** to the conversation, and if patient consents to all those present;

5. ***Set the agenda*** (agree on elements to be discussed, time allotted, etc.);

6. ***Conduct the follow-up visit*** using the instructions below in the COPD Follow-up Checklist and remember to keep the focus on the main issues raised by the patient;

7. End and summarize the visit
    a. Ask the patient to summarize what the discussion and main issues have been, reinforce any action plan or intervention you have agreed upon (if any homework);
    b. Set up a date for follow-up;
    c. Agree upon ending the meeting.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

DELIVERY OF PULMONARY REHABILITATION: IN-PERSON VERSUS VIRTUAL

The COVID-19 pandemic and resulting need for social distancing forced the healthcare system to implement remote solutions and telehealth to ensure delivery of appropriate care. However, the use and acceptance of telehealth solutions in the post-pandemic context is still being elucidated. To date the most studied telehealth modalities in COPD are pulmonary rehabilitation and self-management interventions.

Pulmonary rehabilitation has the highest quality studies in the COPD-telehealth field with well-defined and reported exercise training programs, and comparing telerehabilitation with usual care and/or center-based rehabilitation, which was established as the gold-standard in a 2021 Cochrane review.[808] A clinical practice guideline reported that telerehabilitation can achieve similar clinical outcomes as face-to-face, center-based pulmonary rehabilitation, and recommended that adults with stable chronic respiratory disease, particularly COPD, should be offered the choice of a center-based pulmonary rehabilitation or telerehabilitation (strong recommendation, moderate quality evidence).[796]

Key to the delivery of an effective pulmonary rehabilitation program, with demonstrated proven benefits for COPD, is the inclusion of lower extremity endurance exercise training. For most people telerehabilitation still involves a face-to-face, center-based assessment to complete a comprehensive pre-rehabilitation evaluation. Telerehabilitation does create a means to provide pulmonary rehabilitation services, and like center-based rehabilitation, it requires appropriately trained staff and adequate infrastructure. However, considering issues such as lack of trained medical personnel, and the appeal of technology, there is a need to ensure that telehealth pulmonary rehabilitation is not misused.

DELIVERY OF SELF-MANAGEMENT: IN-PERSON VERSUS VIRTUAL

A 2022 Cochrane review reported that a self-management intervention both improved quality of life and reduced hospital admissions.[1543] Tele-education and self-management using information communication technology could have the potential to ease the working life of health practitioners and transform the way patients are monitored, and healthcare is delivered.

Despite the many advances in self-management, delivering self-management at a distance using digital technology still raises many unanswered questions and important limitations. No studies to date have been designed to demonstrate whether there is any additional benefit of telehealth-supported self-management compared to self-management interventions not using information communication technologies.[1544]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

APPENDICES

APPENDIX 1: ABBREVIATIONS

6MWD, 6-minute walking distance
6MWT, 6-minute walking test
AATD, α-1 antitrypsin deficiency
ABG, arterial blood gas
ACE, angiotensin converting enzyme
ACEi, angiotensin converting enzyme inhibitor
ACS, acute coronary syndrome
ACT, airway clearance technique(s)
ADL, activities of daily living
AF, atrial fibrillation
AI, artificial intelligence
ARB, angiotensin receptor blocker
ARNI, angiotensin receptor-neprilysin inhibitor
ATS, American Thoracic Society
BAI, breath-actuated metered-dose inhaler
BB, beta-blocker
BD, bronchodilator
BMI, body mass index
BODE, Body mass index, Obstruction, Dyspnea, and Exercise
BOLD, Burden of Obstructive Lung Diseases
CAT™, COPD Assessment Test
CAAT™, Chronic Airways Assessment Test
CAC, coronary artery calcium
CAD, coronary artery disease
CAPTURE, COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk
CCQ©, Clinical COPD Questionnaire
CDC, US Centers for Disease Control
CDQ, COPD Diagnostic Questionnaire
CI, confidence interval
CISNET, Cancer Intervention and Surveillance Modeling Network
COPD, chronic obstructive pulmonary disease
COPD-PS, COPD Population Screener
COS, core outcome set
COVID-19, coronavirus disease 2019
CPAP, continuous positive airway pressure
CRP, C-reactive protein
CRQ, Chronic Respiratory Questionnaire
CT, computed tomography
CVD, cardiovascular disease
CVRS, cardiovascular risk score
DALY, disability-adjusted life years
DLco, carbon monoxide diffusing capacity of the lungs
DM, diabetes mellitus
DNA, deoxyribonucleic acid
DPI, dry powder inhaler
ED, emergency department
EBV, endobronchial one-way valves
ECG, electrocardiogram
EHR, electronic health record
ELVR, endoscopic lung volume reduction
ERS, European Respiratory Society
ESC, European Society of Cardiology
EU, European Union
EVALI, e-cigarette or vaping product use-associated lung injury
FDA, US Food and Drug Administration
FEV1, forced expiratory volume in 1 second
FFM, fat free mass
FiO_2, fraction of inspired oxygen
FVC, forced vital capacity
GBD, Global Burden of Disease
GERD, gastroesophageal reflux disease
GETomics, gene(G)-environment(E) interactions occurring over the lifetime(T) of the individual
GFR, glomerular filtration rate
GLI, Global Lung Initiative
GOLD, Global Initiative for Chronic Obstructive Lung Disease
HADS, Hospital Anxiety and Depression Scale
HFNT, high-flow nasal therapy
HFpEF, heart failure with preserved ejection fraction
HFrEF, heart failure with reduced ejection fraction
HICs, high-income countries
HIV, human immunodeficiency virus
HMICs, high- and middle-income countries
HRCT, high-resolution computed tomography
hs troponin, high sensitivity troponin
ICD, International Statistical Classification of Diseases and Related Health Problems
ICS, inhaled corticosteroid
ICU, intensive care unit
ILA, interstitial lung abnormalities

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

ILD, interstitial lung disease
Ig, immunoglobulin
IL, interleukin
IMP, inspiratory muscle training
IPAP, inspiratory positive airway pressure
IRR, incidence rate ratio
ISWT, incremental shuttle walking test
LABA, long-acting beta$_2$-agonist
LABD, long-acting bronchodilator
LAMA, long-acting muscarinic antagonist
LAS, lung allocation severity
LDCT, low-dose computed tomography
LFQ, Lung Function Questionnaire
LICs, low-income countries
LLN, lower limit of normal
LMICs, low- and middle-income countries
LTOT, long-term oxygen therapy
LVRS, lung volume reduction surgery
MCID, mean clinically important difference
mmHG, millimeters of mercury
mMRC scale, modified Medical Research Council dyspnea scale
MOLT, multiple organ loss of tissue
mPAP, mean pulmonary arterial pressure
MRA, mineralocorticoid receptor antagonist
NAFLD, non-alcoholic fatty liver disease
NETT, National Emphysema Treatment Trial
NHLBI, National Heart, Lung, and Blood Institute
NIH, National Institutes of Health
NIV, noninvasive ventilation
NPPV, noninvasive positive pressure ventilation
NS, not statistically significant
NTproBNP, N-terminal prohormone of brain natriuretic peptide test
OSA, obstructive sleep apnea
$PaCO_2$ partial pressure of carbon dioxide
PAD, peripheral artery disease
PAH, pulmonary arterial hypertension
PaO_2 partial pressure of oxygen
PCV, pneumococcal conjugate vaccine
PDE, phosphodiesterase
PEF, peak expiratory flow
PH, pulmonary hypertension
PLATINO, Project for the Investigation of Obstructive Lung Disease
PM2.5 or PM10, particulate matter of 2.5 or 10 µm or less in diameter
pMDI, pressurized metered-dose inhaler
PPSV, pneumococcal polysaccharide vaccine
PR, pulmonary rehabilitation
PRIME-MD, Primary Care Evaluation of Mental Disorders
PRISm, preserved ratio impaired spirometry
PROs, patient reported outcomes
PUMA, PUMA COPD questionnaire
RCT, randomized controlled trial
RPM, remote patient monitoring
RSV, respiratory syncytial virus
SABA, short-acting beta$_2$-agonist
SABD, short acting bronchodilator
SaO_2, oxygen saturation of arterial blood
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
SE, standard error
SGLT2i, sodium-glucose co-transporter 2 inhibitor
SGRQ, St. George's Respiratory Questionnaire
SMI, soft mist inhaler
T2, type 2 (referring to inflammation)
TB, pulmonary tuberculosis
TDI, Translational Dyspnea Index
UC, Usual treatment control group
UK, United Kingdom
USPSTF, United States Preventative Service Task Force
US, United States of America
VAS, visual analog scale
V_A/Q, ventilation-perfusion
VHC, valved holding chamber
VHD, valvular heart disease
WHO, World Health Organization

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

APPENDIX 2: PHARMACOLOGICAL THERAPY CHECKLIST

Patient Name: _____
Date: _____
Clinician: _____

Inhaler Treatment Summary Checklist

☐ **Inhaler prescribed:** Medication name and device type documented
☐ **Purpose of inhaler:** Controller/preventer or reliever/rescue confirmed
☐ **Dose and schedule:** Dose, frequency, and timing reviewed
☐ **Adherence:** Regular use and missed doses assessed
☐ **Inhaler technique:** Patient demonstrates correct use
☐ **Spacer use:** Assessed and technique reviewed (if applicable)
☐ **Mouth rinsing:** Reviewed after inhaled corticosteroids (if applicable)
☐ **Device care:** Cleaning, storage, and dose counter checked
☐ **Symptom control:** Effectiveness of treatment assessed
☐ **Reliever use:** Frequency of rescue inhaler use reviewed
☐ **Side effects:** Assessed and documented
☐ **Patient education:** Technique and treatment plan reinforced
☐ **Follow-up:** Need for reassessment or treatment adjustment identified

Overall inhaler treatment assessment:
☐ Effective and well tolerated
☐ Technique requires correction
☐ Adherence support required
☐ Treatment review/change recommended

Follow-Up Plan

Identified barriers:

_____

Interventions planned:

_____

Next review date: _____

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

APPENDIX 3: NON-PHARMACOLOGICAL THERAPY CHECKLIST

Patient Name: _____
Date: _____
Clinician: _____

1. Engagement with Prescribed Non-Pharmacological Interventions

☐ Patient has been referred to non-pharmacological interventions
☐ Patient has participated in recommended interventions
☐ Patient has not participated in recommended interventions

If not engaged, reasons identified:
☐ Lack of awareness/understanding
☐ Lack of motivation or confidence
☐ Symptom limitations (dyspnea, fatigue, pain)
☐ Access barriers (transportation, cost, availability)
☐ Other: _____

Interventions completed:
☐ Pulmonary rehabilitation
☐ Exercise training program
☐ Patient education/self-management program
☐ Smoking cessation support
☐ Nutritional counseling
☐ Other: _____

---

2. Pulmonary Rehabilitation and Maintenance Exercise Program

Has the patient completed pulmonary rehabilitation?
☐ Yes
☐ No
☐ Currently participating

If completed:

☐ Patient continues maintenance exercise program
☐ Patient follows recommended exercise frequency
☐ Patient follows recommended exercise intensity/duration
☐ Patient monitors symptoms during exercise
☐ Patient understands strategies to manage breathlessness during exercise

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Adherence barriers identified:
☐ Increased symptoms
☐ Lack of motivation
☐ Lack of support
☐ Time constraints
☐ Other: _____

Maintenance exercise plan reviewed:
☐ Yes
☐ No

---

3. Physical Activity Assessment and Promotion

Patient awareness of current physical activity level:
☐ Aware
☐ Partially aware
☐ Not aware

Physical activity assessment completed:
☐ Daily activity level reviewed
☐ Sedentary behavior assessed
☐ Activity goals discussed
☐ Exercise recommendations reviewed

Patient currently engages in:
☐ Walking
☐ Strength training
☐ Breathing exercises
☐ Other: _____

Physical activity goals:

---

4. Self-Management Skills Integration

Breathing Control Techniques
☐ Patient understands breathing control strategies
☐ Patient demonstrates appropriate technique
☐ Patient uses breathing control technique
☐ Techniques reviewed/reinforced

Examples:
☐ Pursed-lip breathing
☐ Pacing techniques
☐ Diaphragmatic breathing

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Stress and Anxiety Management

☐ Patient identifies stress/anxiety triggers
☐ Patient uses coping strategies
☐ Relaxation techniques discussed
☐ Referral/support offered if needed

Exacerbation Prevention and Management

☐ Patient recognizes early warning signs of exacerbation
☐ Patient understands when to seek medical advice
☐ Written action plan reviewed
☐ Patient demonstrates appropriate use of action plan

Written action plan available:

☐ Yes
☐ No
☐ Needs updating

Follow-Up Plan

Identified barriers:

_____

Interventions planned:

_____

Next review date: _____

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

APPENDIX 4: COPD FOLLOW-UP CHECKLIST

In-person follow-up □ **Phone follow-up** □ **Virtual/online follow-up** □

Date: YYYY / MM / DD	**Diagnosis:**

1. BASELINE SYMPTOMS – Breathlessness on a regular day: mMRC /4

Daily sputum production: □ no □ yes, color: Regular cough □ no □ yes

Recent change in symptoms □ no □ yes

If yes, since when:

□ Sputum color: □ Sputum volume ↑ = ↓

□ Dyspnea ↑ = ↓ □ Fatigue ↑ = ↓

□ Cough ↑ = ↓ □ Other

□ Signs of hypercapnia **CAAT™: /40**

Maintenance medication and adherence:

□ SABA □ LABA+LAMA

□ LABA □ LABA+ICS

□ LAMA □ LABA+LAMA+ICS

□Other:

Non pharmacological Rx:

O2: CPAP: BIPAP :

2. AIRBORNE VIRUS – If patient is feeling unwell, check other symptoms: □ Fever____ □ Sore throat □ Anosmia □ Others_____

Contact with someone positive for airborne virus? □ no □ yes Tested for airborne virus? □ no □ yes If yes □ positive □ negative

3. WRITTEN ACTION PLAN – no □ yes □

Instruction and any additional treatment: _____

Last time it has been used (date):

4. RECENT ADMISSIONS AND EMERGENCY VISITS

Hospital/ED	Where	Date	Length	Reason (Dx)

Comments:

5. COPD Self-management (healthy behaviors) – Integrated (patient has used it in their daily life)?

Smoke-free environment	yes	no	cannot tell
Medication adherence	yes	no	cannot tell
Prevention/management of exacerbations	yes	no	cannot tell
Breathing control	yes	no	cannot tell
Stress management	yes	no	cannot tell
Physical activity and exercise	yes	no	cannot tell
Other _____	yes	no	

Comments and what patient should prioritize based on his/her needs:

6. MAIN ISSUES

1.	*2.*	*3.*

7. SUMMARY, INTERVENTIONS & PLAN

(healthcare professional name & signature)

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Instructions for using the COPD follow-up checklist

1. **Introduction**
    a. Identify dates, Dx and whether this follow-up is being done in-person, by phone or remotely.
2. **Section 1 – Baseline symptoms**
    a. Go over the patient symptoms and whether there have been changes in dyspnea, cough, sputum volume and color (from least to most purulent: mucus; mucopurulent; purulent).
    b. Identify maintenance pharmacological and non-pharmacological treatment and whether the patient is observing treatment as prescribed.
3. **Section 2 – Airborne virus**
    a. Assess whether the patient has any symptoms of airborne virus infection and would need to be tested. Have at hand local numbers where the patient can be referred to for testing and treatment.
    b. If the patient has already been tested identify when the results will be obtained, or whether the result was positive or negative. If positive, is there a follow-up test planned, and dates.
    c. Verify patient is practicing precautions (face masks, hand washing, social distancing, or shielding if necessary).
4. **Section 3 – Action plan**
    a. Describe if the patient already has a written action plan. See example of an action plan from the Living well with COPD program.[822] Describe if the education for this action plan has already been done. Describe if the written action plan includes a prescription to be self-administered at home or whether the patient need to call his contact person / physician to obtain the prescription. Describe when it was used the last time and if used appropriately.
5. **Section 4 – Recent admissions and ED visits**
    a. Write down recent admissions and ED visits, dates and where they took place.
6. **Section 5 – COPD self-management behaviors**
    a. Go over each of the self-management behaviors described in the list. You should cover what is pertinent to the patient treatable traits (dyspnea and/or exacerbation). Describe whether the patient has integrated these strategies in their daily life (yes), not at all (e.g., it has not been discussed or not applicable), and whether the patient is unsure “cannot tell”.
7. **Section 6 – Main issues**
    a. Identify with the patient the main issues of the call. Up to a maximum of 3 items that can be covered for the duration of the call. Avoid covering too many issues in one visit.
8. **Section 7 – Summary, intervention and plan**
    a. Finalize by describing the interventions done during the remote visit, the ones to be put in place, and agreed by the patient, the plan, including whether the patient needs to be referred to other services, healthcare professionals, etc. and when the next follow-up will take place (describe whether will it be in-person or remote).

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

APPENDIX 5: OVERVIEW OF THE EVIDENCE: PHARMACOTHERAPY

Pharmacotherapies for smoking cessation

Pharmacological treatments for smoking cessation include controller medications aimed at achieving long-term abstinence (nicotine patch, bupropion, and varenicline) and those that rapidly relieve acute withdrawal symptoms (short-acting nicotine).

Nicotine replacement products

Nicotine replacement therapy (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge) reliably increases long-term smoking abstinence rates[619,621,623,1545,1546] and is significantly more effective than placebo. Nicotine replacement therapy often causes irritation at the site through which it is administered, and can cause non-ischemic chest pain and palpitations, therefore medical contraindications to nicotine replacement therapy include recent myocardial infarction or stroke.[623,1547,1548] The contraindication to nicotine replacement therapy after acute coronary syndrome remains unclear and the evidence suggests that this treatment can and should be started > 2 weeks after a cardiovascular event.[1549] Continuous chewing of nicotine gum produces secretions that are swallowed rather than absorbed through the buccal mucosa resulting in little absorption and potentially causing nausea.

Vaping/E-cigarettes

There is a perception that vaping with electronic cigarettes (e-cigarettes, vapes) is safer than smoking and therefore an effective nicotine replacement therapy for smoking cessation. The efficacy of vaping with regard to smoking cessation remains controversial.[1550-1554] E-cigarettes provide a vaporized and doseable method of nicotine inhalation and have increased in usage as an alternative to cigarettes for those wishing to quit, but also as a rising trend in younger individuals who have never smoked. E-cigarettes may contain not only nicotine but also other chemicals, such as vegetable glycine, propylene glycol, various flavoring agents, volatile carbonyls, diacetyl, reactive oxygen species, furones and metals. The long-term health effects in general smokers, but more importantly in high-risk populations such as COPD, are largely unknown although preliminary evidence suggests that e-cigarette use could be associated with COPD.[1555-1557]

What is known has been reported mainly as individual, or series' of case reports of the acute effects of e-cigarettes, including vaping-associated lung injury. Severe acute lung injury, eosinophilic pneumonia, alveolar hemorrhage, respiratory bronchiolitis and other forms of lung abnormalities have been reportedly linked to e-cigarette use, and occasionally death.[1558-1561] A review of studies on the pulmonary effects of e-cigarettes reported that e-cigarette aerosol is cytotoxic to pulmonary cells, induces acute and chronic inflammation, impairs immune responses against viral and bacterial pathogens, impairs mucociliary clearance, induces oxidative stress, causes DNA damage and increases airway hyperresponsiveness *in vitro* and *in vivo*. Adding nicotine to the e-liquid increased mucociliary dysfunction, oxidative stress, emphysema and airway hyperreactivity.[1562]

The CDC and FDA investigated an outbreak of EVALI. Laboratory data showed that vitamin E acetate, an additive in some THC-containing e-cigarettes, was strongly linked to the EVALI outbreak.[1563] Following the identification of vitamin E acetate as a primary cause of EVALI there was a decline in new cases.

Neutrophilic inflammation of the airways, airways irritability, ciliary paresis and increased mucus hypersecretion are seen in animal models and *in vitro* human airway studies and are similar to changes induced by cigarette smoke and recognized features of COPD.[1564-1568] These data are summarized in a review by Gotts and colleagues,[1569] although it

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

is likely to be many years before the long-term risks of vaping, including risks of cancer, are clarified, particularly in people with COPD and/or whether vaping is an independent risk factor for developing COPD.[1558-1561] In a large prospective cohort study, an increased risk of respiratory disease among former and current e-cigarette users was observed even when adjusted for cigarette and other combustible tobacco product use, demographic characteristics, and chronic health conditions.[1570] There is additional evidence that in older adults at risk of or with COPD, e-cigarette users have greater nicotine dependence, poorer lung-related health outcomes (more chronic bronchitis and exacerbations), and are less likely to reduce or quit smoking conventional cigarettes.[1571]

A meta-analysis of five RCTs has suggested that e-cigarettes are superior to nicotine replacement therapy for achieving 6 months continuous abstinence from smoking tobacco.[1572] Nevertheless, based on the available evidence and the lack of knowledge about the long-term effects of e-cigarettes on respiratory health, it is not possible to recommend this intervention for smoking cessation in patients with COPD.[1573]

Pharmacological products

Results of a meta-analysis comparing simple controller pharmacotherapy (nicotine replacement therapy, bupropion, nortriptyline and varenicline) with placebo in smokers with COPD showed that all pharmacotherapy groups (except nortriptyline) increased the chances of smoking cessation compared with placebo.[613] Prolonged abstinence rates in the pharmacotherapy groups ranged from 14% to 27%, and in the placebo group from 5% to 9%.[613]

A study in patients with COPD showed higher continuous abstinence rates during weeks 9 to 24 with varenicline (58.3%) and bupropion (55.6%) compared with nicotine patch (38.2%).[1574] Varenicline and bupropion showed similar efficacy, however, the group receiving varenicline compared with bupropion smoked more cigarettes per day.[1574]

Maintenance therapy for stable COPD

Pharmacotherapy for COPD is currently focused on symptoms and exacerbations. FEV1 decline has been considered a surrogate for the natural course of the disease. In this context, studies have been performed to evaluate if pharmacotherapy may have an impact on the change of FEV1 over time. Individual clinical trials have not been sufficiently conclusive to show that pharmacotherapy can reduce the rate of FEV1 decline.[1012,1575-1578] However, a systematic review combining data from nine studies demonstrated a reduction in the rate of FEV1 decline of 5.0 mL/year in active treatment arms compared with placebo arms.[1579] The difference between long-acting bronchodilator containing treatment arms and placebo arms was 4.9 mL/year. The difference between ICS containing treatment arms and placebo arms was 7.3 mL/year. Although we need to be aware of the potential benefit of pharmacotherapy in reducing the rate of lung function decline, further research is needed to know which patients are likely to benefit.

The classes of medications commonly used to treat COPD are shown in **Figure A5.1**. The choice within each class depends on the availability and cost of medication, and the clinical response balanced against side effects. One caveat is that most trials of COPD maintenance therapy have been conducted in high or middle-income countries and have included an over-representation of men and white individuals.[1580,1581] Future studies should include and report results from more diverse populations. Each treatment regimen needs to be individualized as the relationship between severity of symptoms, airflow obstruction, and severity of exacerbations can differ between patients. The WHO has defined a minimum set of interventions for the management of stable COPD in primary care.[1010]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Maintenance Medications Registered for the Treatment of COPD*

Figure A5.1

Generic Drug Name	Inhaler Type	Nebulizer	Oral/Injectable Delivery	Duration of Action
BETA$_2$-Agonists				
Short-acting (SABA)				
Fenoterol	MDI	✓	tablet, solution	variable
Levalbuterol	MDI	✓		variable
Salbutamol (albuterol)	MDI, DPI	✓	syrup, tablet	variable
Terbutaline	DPI		tablet	variable
Long-acting (LABA)				
Arformoterol		✓		12 hours
Formoterol	DPI	✓		12 hours
Indacaterol	DPI			24 hours
Olodaterol	SMI			24 hours
Salmeterol	MDI, DPI			12 hours
Anticholinergics				
Short-acting (SAMA)				
Ipratropium bromide	MDI	✓		6-8 hours
Oxitropium bromide	MDI	✓		7-9 hours
Long-acting (LAMA)				
Aclidinium bromide	DPI			12 hours
Glycopyrronium bromide	DPI	✓	solution	variable
Tiotropium	DPI, SMI, MDI			24 hours
Umeclidinium	DPI			24 hours
Revefenacin		✓		24 hours
Combination Short-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (SABA+SAMA)				
Fenoterol/ipratropium	SMI	✓		6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓		variable
Combination Long-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (LABA+LAMA)				
Formoterol/aclidinium	DPI			12 hours
Formoterol/glycopyrronium	MDI			12 hours
Indacaterol/glycopyrronium	DPI			12-24 hours
Vilanterol/umeclidinium	DPI			24 hours
Olodaterol/tiotropium	SMI			24 hours
Methylxanthines				
Aminophylline			solution, injectable	variable
Theophylline (SR)			tablet, capsule, elixir, solution, injectable	variable
Combination of Long-Acting Beta$_2$-Agonist Plus Corticosteroid in One Device (LABA+ICS)				
Formoterol/beclometasone	MDI, DPI			12 hours
Formoterol/budesonide	MDI, DPI			12 hours
Formoterol/mometasone	MDI			12 hours
Salmeterol/fluticasone propionate	MDI, DPI			12 hours
Vilanterol/fluticasone furoate	DPI			24 hours
Triple Combination in One Device (LABA+LAMA+ICS)				
Fluticasone/umeclidinium/vilanterol	DPI			24 hours
Beclometasone/formoterol/glycopyrronium	MDI, DPI			12 hours
Budesonide/formoterol/glycopyrrolate	MDI			12 hours
Phosphodiesterase-3 and/or -4 Inhibitors				
Roflumilast			tablet	24 hours
Ensifentrine		✓		12 hours
Mucolytic Agents				
Erdosteine			capsule, suspension	12 hours
Carbocysteine†			capsule, packet, solution, syrup	6-8 hours
N-acetylcysteine†		✓	solution, tablet	2-6 hours
Biologics				
Dupilumab			injectable	2 weeks
Mepolizumab			injectable	4 weeks

*This list is not exhaustive. Not all formulations are available in all countries. In some countries other formulations and dosages may be available. †Dosing regimens are under discussion. MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler. Note that glycopyrrolate & glycopyrronium are the same compound.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Bronchodilators

Bronchodilators are medications that increase FEV1 and/or change other spirometric variables (**Figure A5.2**). They act by altering airway smooth muscle tone, and the improvements in expiratory flow reflect widening of the airways rather than changes in lung elastic recoil. Bronchodilators tend to reduce dynamic hyperinflation at rest and during exercise,[1582,1583] and improve exercise performance. The extent of these changes, especially in patients with severe and very severe COPD, is not easy to predict from the improvement in FEV1 measured at rest.[1584,1585]

Bronchodilator dose-response (FEV1 change) curves are relatively flat with all classes of bronchodilators.[1586-1592] Increasing the dose of either a beta$_2$-agonist or an anticholinergic by an order of magnitude, especially when given by a nebulizer, appears to provide subjective benefit in acute episodes[1593] but is not necessarily helpful in stable disease.[1594] Bronchodilator medications in COPD are most often given on a regular basis to prevent or reduce symptoms. Toxicity is also dose-related (**Figure A5.1**). Use of short-acting bronchodilators on a regular basis is not generally recommended.

Beta$_2$-agonists

The principal action of beta$_2$-agonists is to relax airway smooth muscle by stimulating beta$_2$-adrenergic receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. There are short-acting (SABA) and long-acting (LABA) beta$_2$-agonists. The effect of SABAs usually wears off within 4 to 6 hours.[1588,1589] Regular and as-needed use of SABAs improve FEV1 and symptoms.[1595] LABAs show duration of action of 12 or more hours and do not preclude additional benefit from as-needed SABA therapy.[1596]

Formoterol and salmeterol are twice-daily LABAs that significantly improve FEV1 and lung volumes, dyspnea, health status, exacerbation rate and number of hospitalizations,[1597] but have no effect on mortality or rate of decline of lung function. Indacaterol is a once daily LABA that improves breathlessness,[1598,1599] health status[1599] and exacerbation rate.[1599] Some patients experience cough following the inhalation of indacaterol. Olodaterol and vilanterol are additional once daily LABAs that improve lung function and symptoms.[1600,1601]

Adverse effects

Stimulation of beta$_2$-adrenergic receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in susceptible patients. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of beta$_2$-agonists, regardless of route of administration. Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics,[1602] and oxygen consumption can be increased under resting conditions in patients with chronic heart failure,[1603] these metabolic effects decrease over time (i.e., show tachyphylaxis). Mild falls in PaO_2 can occur after administration of both SABAs and LABAs[1604] but the clinical significance of these changes is uncertain. Despite prior concerns related to the use of beta$_2$-agonists in the management of asthma, no association between beta$_2$-agonist use and loss of lung function or increased mortality has been reported in COPD.[1597,1605,1606]

Antimuscarinic drugs

Antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle.[1607] SAMAs, namely ipratropium and oxitropium, also block the inhibitory neuronal receptor M2, which potentially can cause vagally induced bronchoconstriction.[1608] LAMAs, such as tiotropium, aclidinium, glycopyrronium bromide (also known as glycopyrrolate), umeclidinium and revefenacin, have prolonged binding to M3 muscarinic receptors, with faster dissociation from M2 muscarinic receptors, thus prolonging the duration of bronchodilator effect.[1607]

A systematic review of RCTs concluded that ipratropium, a short acting muscarinic antagonist, alone provided small

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

benefits over short-acting beta$_2$-agonist in terms of lung function, health status and requirement for oral steroids.[1609] Among LAMAs, some are administered once a day (tiotropium, umeclidinium, revefenacin), others twice a day (aclidinium), and some are approved for once daily dosing in some countries and twice daily dosing in others (glycopyrrolate).[1607,1610] LAMA treatments improve symptoms, including cough and sputum and health status.[1607,1611,1612] They also improve the effectiveness of pulmonary rehabilitation[1613,1614] and reduce exacerbations and related hospitalizations.[1611] Clinical trials have shown a greater effect on exacerbation rates for LAMA treatment (tiotropium) versus LABA treatment.[1615,1616]

Bronchodilators in Stable COPD

Figure A5.2

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**
- Inhaled bronchodilators are recommended over oral bronchodilators (**Evidence A**)
- Regular and as-needed use of SABA or SAMA improves FEV1 and symptoms **(Evidence A)**
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV1 and symptoms **(Evidence A)**
- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea (**Evidence A**), and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**
- When initiating treatment with long acting bronchodilators the preferred choice is a combination of a LABA and a LAMA. In patients with persistent dyspnea on a single long-acting bronchodilator treatment should be escalated to two (**Evidence A**).
- Combination treatment with a LABA and a LAMA increases FEV1 and reduces symptoms compared to monotherapy **(Evidence A)**
- Combination treatment with a LABA+LAMA reduces exacerbations compared to monotherapy **(Evidence B)**
- Combinations can be given as single inhaler or multiple inhaler treatment. Single inhaler therapy may be more convenient and effective than multiple inhalers
- Ensifentrine significantly improves lung function **(Evidence A)**, dyspnea **(Evidence A)** and health status **(Evidence B)**
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Adverse effects

Inhaled anticholinergic drugs are poorly absorbed which limits the troublesome systemic effects observed with atropine.[1607,1617] Extensive use of this class of agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of mouth.[1608,1618] Although occasional urinary symptoms have been reported, there are no data to prove a true causal relationship.[1619] Some patients using ipratropium report a bitter,

metallic taste. An unexpected small increase in cardiovascular events in those patients with COPD regularly treated with ipratropium bromide has been reported.[1620,1621] In a large, long-term clinical trial in patients with COPD, tiotropium added to other standard therapies had no effect on cardiovascular risk.[1012] Although there were some initial concerns regarding the safety of tiotropium delivery via the Respimat® inhaler,[1622] the findings of a large trial observed no difference in mortality or exacerbation rates when comparing tiotropium in a dry-powder inhaler and the Respimat® inhaler.[1279] There are less safety data available for the other LAMAs, but the rate of anti-cholinergic side effects for drugs in this class appears to be low and generally similar. Use of solutions with a facemask can precipitate acute glaucoma, probably as a direct result of the contact between the solution and the eye.[1623-1625]

Methylxanthines

Controversy remains about the exact effects of xanthine derivatives. They may act as non-selective phosphodiesterase inhibitors, but have also been reported to have a range of non-bronchodilator actions, the significance of which is disputed.[1626-1628] Data on duration of action for conventional, or even slow-release, xanthine preparations are lacking in COPD.

Theophylline, the most commonly used methylxanthine, is metabolized by cytochrome P450 mixed function oxidases. Clearance of the drug declines with age. Many other physiological variables and drugs modify theophylline metabolism. Enhanced inspiratory muscle function has been reported in patients treated with methylxanthines,[1626] but whether this reflects a reduction in gas trapping or a primary effect on the respiratory skeletal muscles is not clear. All studies that have shown efficacy of theophylline in COPD were performed with sustained-release preparations.

There is evidence for a modest bronchodilator effect compared with placebo in stable COPD,[1629] including patients with mild-to-moderate airflow limitation.[1630] Addition of theophylline to salmeterol produces a greater improvement in FEV1 and breathlessness than salmeterol alone.[1631,1632] Earlier studies reported contradictory evidence regarding the effect of low-dose theophylline on exacerbation rates.[1633,1634] A study that investigated the effectiveness of adding low-dose theophylline to ICS in patients with COPD who were at increased risk of exacerbation showed no difference compared with placebo in the number of COPD exacerbations over a one-year period.[1635] A large placebo-controlled trial in patients with COPD who had moderate to very severe airflow obstruction (FEV1 < 70%) showed no effect of oral theophylline alone or in combination with prednisolone 5 mg daily on exacerbations of COPD.[1636]

Adverse effects

Toxicity is dose-related, which is a particular problem with xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given.[1627,1629] Methylxanthines are non-specific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include atrial and ventricular arrhythmias (which can prove fatal) and *grand mal* convulsions (which can occur irrespective of prior epileptic history). Other side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum levels of theophylline. These medications have significant interactions with commonly used medications such as erythromycin (but not azithromycin), certain quinolone antibiotics (ciprofloxacin, but not ofloxacin), allopurinol, cimetidine (but not ranitidine), serotonin uptake inhibitors (fluvoxamine) and the 5-lipoxygenase inhibitor zileuton.

Combination bronchodilator therapy

Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation with a lower risk of side-effects compared to increasing the dose of a single bronchodilator.[1637,1638] Combinations of SABAs and SAMAs are superior compared to either medication alone in improving FEV1 and symptoms.[1639] Treatment with formoterol and tiotropium in *separate inhalers* has a bigger impact on FEV1 than either component alone.[1640] There are numerous combinations of a LABA and LAMA in a *single inhaler* available (**Figure**

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

A5.1). These combinations improve lung function compared to placebo;[1637] this improvement is consistently greater than long-acting bronchodilator monotherapy effects although the magnitude of improvement is less than the fully additive effect predicted by the individual component responses.[1641] Single inhalers improve adherence to treatment[1642] and are more cost-effective.[1643] In studies where PROs are the primary endpoint or in pooled analyses, combination bronchodilators have a greater impact on PROs compared to monotherapies.[1644-1647] In one clinical trial, combination LABA+LAMA treatment had the greatest improvement in quality of life compared to placebo or its individual bronchodilator components in patients with a greater baseline symptom burden.[1648] A clinical trial showed that LABA+LAMA improved lung function and symptoms versus long-acting bronchodilator monotherapy in symptomatic patients with low exacerbation risk and not receiving inhaled corticosteroids.[728] The LABA+LAMA combination demonstrated favorable improvements compared with the monotherapies for the majority of outcomes irrespective of baseline health-related quality of life.[1649] These clinical trials deal with group mean data, but symptom responses to LABA+LAMA combinations are best evaluated on an individual patient basis. A lower dose, twice daily regimen for a LABA+LAMA has also been shown to improve symptoms and health status in patients with COPD [1650] (**Figure A5.2**). These findings have been shown in people across different ethnic groups (Asian as well as European).[1651]

Most studies with LABA+LAMA combinations have been performed in patients with a low rate of exacerbations. One study in patients with a history of exacerbations indicated that a combination of long-acting bronchodilators is more effective than long-acting bronchodilator monotherapy for preventing exacerbations.[1652] Another large study found that combining a LABA with a LAMA did not reduce exacerbation rate as much as expected compared with a LAMA alone.[1653] Another study in patients with a history of exacerbations showed that a combination LABA+LAMA decreased exacerbations to a greater extent than an LABA+ICS combination.[1654] However, another study in a population with high exacerbation risk (≥ 2 exacerbations and/or 1 hospitalization in the previous year) reported that LABA+ICS decreased exacerbations to a greater extent than a LABA+LAMA combination at higher blood eosinophil concentrations.[502] A large observational pharmaco-epidemiological study found similar effectiveness of LABA+LAMA and LABA+ICS but a significantly higher risk of pneumonia in those treated with LABA+ICS.[1655]

Anti-inflammatory agents

To date, exacerbations (e.g., exacerbation rate, patients with at least one exacerbation, time-to-first exacerbation) represent the main clinically relevant endpoint used for efficacy assessment of drugs with anti-inflammatory effects (**Figure A5.3**).

Inhaled corticosteroids

General considerations

In vitro evidence suggests that COPD-associated inflammation has limited responsiveness to corticosteroids. Moreover, some drugs including beta$_2$-agonists, theophylline or macrolides may partially facilitate corticosteroid sensitivity in COPD.[1656,1657] The clinical relevance of this effect has not yet been fully established.

In vivo data suggest that the dose-response relationships and long-term (> 3 years) safety of ICS in people with COPD are unclear and require further investigation.[1654] Because the effects of ICS in COPD can be modulated by the concomitant use of long-acting bronchodilators, these two therapeutic options are discussed separately.

Both current and ex-smokers with COPD benefit from ICS use in terms of lung function and exacerbation rates, although the magnitude of the effect is lower in heavy or current smokers compared to light or ex-smokers.[502,1658]

Efficacy of ICS (alone)

Most studies have found that regular treatment with ICS alone does not modify the long-term decline of FEV1 nor

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

mortality in people with COPD.[1659] Studies and meta-analyses assessing the effect of regular treatment with ICS alone on mortality in people with COPD have not provided conclusive evidence of benefit.[1659] In the TORCH trial, a trend toward higher mortality was observed for patients treated with fluticasone propionate alone compared to those receiving placebo or salmeterol plus fluticasone propionate combination.[868] However, an increase in mortality was not observed in patients with COPD who were treated with fluticasone furoate in the SUMMIT trial.[1285] In patients with COPD who had moderate airflow obstruction, fluticasone furoate alone or in combination with vilanterol was associated with slower decline in FEV1 compared with placebo or vilanterol alone by on average 9 mL/year.[1660] A number of studies have investigated whether there is a relationship between ICS treatment and risk of lung cancer with conflicting results.[1661]

ICS in combination with long-acting beta$_2$-agonist (LABA+ICS)

In patients with COPD who have moderate to very severe airflow obstruction and a history of exacerbations, an ICS combined with a LABA is more effective than either component alone in improving lung function, health status and reducing exacerbations.[1662,1663] Clinical trials powered on all-cause mortality as the primary outcome failed to demonstrate a statistically significant effect of LABA+ICS combination therapy on survival.[868,1285]

Blood eosinophil count

A number of studies have shown that blood eosinophil counts predict the magnitude of the effect of ICS (added on top of regular maintenance bronchodilator treatment) in preventing future exacerbations.[497-502] There is a continuous relationship between blood eosinophil counts and ICS effects; no and/or small effects are observed at lower eosinophil counts, with incrementally increasing effects observed at higher eosinophil counts.[488] Data modeling indicates that ICS containing regimens have little or no effect at a blood eosinophil count < 100 cells/µL,[497] therefore, this threshold can be used to identify patients with a low likelihood of treatment benefit with ICS. In addition, lower blood and sputum eosinophils are associated with greater presence of proteobacteria,[268,273,1664] notably haemophilus, and increased bacterial infections and pneumonia.[1665] Lower blood eosinophil counts therefore may identify individuals with microbiome profiles associated with increased risk of clinical worsening due to pathogenic bacterial species. The threshold of a blood eosinophil count ≥ 300 cells/µL identifies the top of the continuous relationship between eosinophils and ICS, and can be used to identify patients with the greatest likelihood of treatment benefit with ICS.

Sources of evidence include: 1) *post-hoc* analyses comparing LABA+ICS versus LABA;[497,498,500] 2) pre-specified analyses comparing triple therapy versus LABA+LAMA or LAMA;[499,501,502] and 3) other analyses comparing LABA+ICS versus LABA+LAMA[1666] or studying ICS withdrawal.[743,744,1667]

The treatment effect of ICS containing regimens (LABA+LAMA+ICS and LABA+ICS vs LABA+LAMA) is higher in patients with high exacerbation risk (≥ 2 exacerbations and / or 1 hospitalization in the previous year).[499,502,1654] Thus, the use of blood eosinophil counts to predict ICS effects should always be combined with clinical assessment of exacerbation risk (as indicated by the previous history of exacerbations). Other factors (smoking status, ethnicity, geographical location) could influence the relationship between ICS effect and blood eosinophil count but remains to be further explored.

Factors to consider when initiating ICS treatment in combination with long-acting bronchodilators are shown in **Figure 3.10**.[602]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Anti-Inflammatory Maintenance Therapy Registered for the Treatment of COPD

Figure A5.3

Inhaled Corticosteroids	• Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)** • An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)** • We do not encourage the use of a LABA+ICS combination in COPD. If there is an indication for an ICS the combination LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice • Triple inhaled therapy of LABA+LAMA+ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA+ICS, LABA+LAMA or LAMA monotherapy **(Evidence A)**. Recent data suggesta beneficial effect of triple inhaled therapy versus fixed-dose LABA+LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations • If patients with COPD have features of asthma, treatment should always contain an ICS • Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of pneumonia **(Evidence C)** • Combinations can be given as single or multiple inhaler therapy. Single inhaler therapy may be more convenient and effective than multiple inhalers
Oral Glucocorticoids	• Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**
PDE Inhibitors	• In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations: ▪ Roflumilast improves lung function and reduces moderate and severe exacerbations **(Evidence A)** • Ensifentrine improves lung function **(Evidence A)** but an effect on exacerbations has not been evaluated in patients at increased exacerbation risk
Antibiotics	• Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)** • Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, azithromycin can be considered (**Evidence B**) • Treatment with azithromycin is associated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**
Mucoregulators & Antioxidant Agents	• Regular treatment with mucolytics such as erdosteine, carbocysteine and N-acetylcysteine reduces the risk of exacerbations in select populations **(Evidence B)** • Antioxidant mucolytics are recommended only in selected patients **(Evidence A)**

Biologics	• In patients with moderate to severe COPD with a history of exacerbations despite triple therapy and higher blood eosinophils (≥ 300 cells/µL):
	  ▪ Dupilumab reduces exacerbations, improves lung function and quality of life in patients with chronic bronchitis **(Evidence A)**
	  ▪ Mepolizumab reduces exacerbations in patients with and without chronic bronchitis **(Evidence A)**

Other Anti-Inflammatory Agents	• Statin therapy is not recommended for prevention of exacerbations (**Evidence A**) • Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy **(Evidence A)**. However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications **(Evidence C)** • Leukotriene modifiers have not been tested adequately in COPD patients

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Adverse effects

There is high quality evidence from RCTs that ICS use modifies the airway microbiome[1668] and is associated with higher prevalence of oral candidiasis, hoarse voice, skin bruising and pneumonia.[1659] This excess risk has been confirmed in ICS studies using fluticasone furoate, even at low doses.[1669] Patients at higher risk of pneumonia include those who currently smoke, are aged ≥ 55 years, have a history of prior exacerbations or pneumonia, a BMI < 25 kg/m^2, a poor mMRC dyspnea grade and/or severe airflow obstruction.[1670,1671] Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of developing pneumonia.[1672] In studies of patients with COPD who had moderate airflow obstruction, ICS by itself or in combination with a LABA did not increase the risk of pneumonia.[1285,1671]

Results from RCTs have yielded varied results regarding the risk of decreased bone density and fractures with ICS treatment, which may be due to differences in study designs and/or differences between ICS compounds.[1577,1669,1673-1675] Results of observational studies suggest that ICS treatment could also be associated with increased risk of diabetes/poor control of diabetes,[1422] cataracts,[1676] and mycobacterial infection.[1677] An increased risk of tuberculosis has been found in both observational studies and a meta-analysis of RCTs.[1346,1348,1678] In the absence of RCT data on these issues, it is not possible to draw firm conclusions.[1679] ICS and lung cancer incidence is discussed in **Chapter 5**.

Triple therapy (LABA+LAMA+ICS)

The step up in inhaled treatment to LABA plus LAMA plus ICS (triple therapy) can occur by various approaches[1680] and has been shown to improve lung function, patient reported outcomes and reduce exacerbations when compared to LAMA alone, LABA+LAMA and LABA+ICS.[499,501,502,1681-1688] A *post-hoc* analysis of one of the RCTs that evaluated the effects of LABA+LAMA+ICS showed that triple therapy improved clinical outcomes versus dual therapy regardless of smoking status.[1689]

A *post-hoc* pooled analysis of three triple therapy RCTs in patients with COPD who had severe airflow obstruction and a history of exacerbations showed a non-significant trend for lower mortality (assessed as a safety outcome) with triple inhaled therapy compared to non-ICS based treatments.[1690] Two large one-year RCTs (IMPACT and ETHOS) were reviewed in **Chapter 3** (see 'Therapeutic interventions that reduce COPD mortality') and provide new evidence on mortality reduction with fixed-dose inhaled triple combinations compared to dual bronchodilation.[515,1691]

New propellants for pMDI with lower global warming potential

There were no safety concerns with budesonide/glycopyrronium/formoterol fumarate delivered from a pMDI with the new propellant hydrofluoroolefin-1234ze (HFO-1234ze) compared with HFA-134a.[680] The safety, tolerability and pharmacokinetics of combined beclometasone dipropionate/formoterol fumarate, and of beclometasone dipropionate/formoterol fumarate/glycopyrronium, delivered by a pMDI containing the new propellant HFA-152a were similar to those of the pMDI containing HFA-134a.[681,682]

Oral glucocorticoids

Oral glucocorticoids have numerous side effects, including steroid myopathy[1692] which can contribute to muscle weakness, decreased functionality, and respiratory failure. Systemic glucocorticoids for treating acute exacerbations in hospitalized patients, or during emergency department visits, have been shown to reduce the rate of treatment failure, the rate of relapse and to improve lung function and breathlessness.[1693] Conversely, prospective studies on the long-term effects of oral glucocorticoids in stable COPD are limited.[1694,1695] Therefore, while oral glucocorticoids play a role in the acute management of exacerbations, they have no role in the chronic daily treatment in COPD because of a lack of benefit balanced against a high rate of systemic complications.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Phosphodiesterase-4 inhibitors

The principal action of PDE4 inhibitors is to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP.[1696] Roflumilast is a once daily oral medication with no direct bronchodilator activity. Roflumilast reduces moderate and severe exacerbations treated with systemic corticosteroids in patients with chronic bronchitis, severe to very severe airflow obstruction, and a history of exacerbations.[1697] The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators,[1698] and in patients who are not controlled on fixed-dose LABA+ICS combinations.[738] The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation.[740] There has been no study directly comparing roflumilast with an ICS.

Adverse effects

Roflumilast has more adverse effects than inhaled medications for COPD.[1699] The most frequent are diarrhea, nausea, reduced appetite, weight loss, abdominal pain, sleep disturbance, and headache. Adverse effects have led to increased withdrawal rates from clinical trials. Adverse effects seem to occur early during treatment, are reversible, and diminish over time with continued treatment. In controlled studies an average unexplained weight loss of 2 kg has been seen and weight monitoring during treatment is advised, in addition to avoiding roflumilast treatment in underweight patients. Roflumilast should also be used with caution in patients with depression.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Antibiotics

In older studies prophylactic, *continuous* use of antibiotics had no effect on the frequency of exacerbations in COPD,[1700,1701] and a study that examined the efficacy of chemoprophylaxis undertaken in winter months over a period of 5 years concluded that there was no benefit.[1702] Later studies have shown that regular use of some antibiotics may reduce exacerbation rate.[1703,1704]

Azithromycin (250 mg/day or 500 mg three times per week) or erythromycin (250 mg two times per day) for one year in patients prone to exacerbations reduced the risk of exacerbations compared to usual care.[736,1705,1706] Azithromycin use was associated with an increased incidence of bacterial resistance, prolongation of QTc interval, and impaired hearing tests.[736] A *post-hoc* analysis suggests lesser benefit in active smokers.[737] There are no data showing the efficacy or safety of chronic azithromycin treatment to prevent COPD exacerbations beyond one-year of treatment.

Pulse therapy with moxifloxacin (400 mg/day for 5 days every 8 weeks) in patients with chronic bronchitis and frequent exacerbations had no beneficial effect on the exacerbation rate overall.[1707] Long-term doxycycline did not reduce exacerbations, although there may be responder subgroups.[1708]

Mucolytic (mucokinetics, mucoregulators) and antioxidant agents (N-acetylcysteine, carbocysteine, erdosteine)

In patients with COPD who are not receiving ICS, regular treatment with mucolytics such as carbocysteine and N-acetylcysteine may reduce exacerbations and modestly improve health status.[1709-1712] Long-term treatment of mild to moderate COPD with high-dose N-acetylcysteine (600 mg twice daily) neither significantly reduced the annual rate of total exacerbations nor improved lung function.[1713] In contrast, it has been shown that erdosteine may have a significant effect on (mild) exacerbations irrespective of concurrent treatment with ICS. Due to the heterogeneity of studied populations, treatment dosing and concomitant treatments, currently available data do not allow precise identification of the potential target population for antioxidant agents in COPD.[1714]

Phosphodiesterase-3 and -4 inhibitors

Ensifentrine is a novel, first-in-class, inhaled dual inhibitor of PDE3 and PDE4 with both anti-inflammatory activity and bronchodilator effects. PDE3 inhibition, through modulation of cyclic guanosine monophosphate levels, causes

smooth muscle relaxation.[1715] In parallel phase 3 RCTs, ensifentrine, delivered via standard jet nebulizer, significantly improved lung function[1715] and dyspnea but had inconsistent effects on quality of life. A reduction in exacerbation rate was suggested but the patient populations were not enriched for exacerbation risk. In addition, the studies were not designed to assess the impact of ensifentrine on top of LABA+LAMA or LABA+LAMA+ICS making it difficult to fully position this agent in our treatment algorithm.[488,732-734] Studies did not find safety or tolerability issues.[1716] Ensifentrine is currently only available in the US.

Biologic therapy

Dupilumab is a fully human monoclonal antibody that blocks the shared receptor component for IL-4 and IL-13. In two phase 3, double-blind, randomized trials, patients with COPD, chronic bronchitis, a history of two or more moderate exacerbations or one or more severe exacerbation(s) in the last year despite treatment with LABA+LAMA+ICS, from GOLD 2-3, and blood eosinophil count of ≥ 300 cells/µL who received dupilumab had fewer exacerbations, better lung function and improved health status at 52 weeks (**Figure 3.11**).[732,733]

Mepolizumab is a humanized monoclonal antibody that targets IL-5. Across three phase 3, double-blind, randomized, placebo-controlled trials, patients with COPD, a history of two or more moderate exacerbations or one or more severe exacerbation(s) in the last year despite treatment with LABA+LAMA+ICS, from GOLD 2-4, with and without chronic bronchitis, and blood eosinophil count of ≥ 300 cells/µL who received mepolizumab for 52 to 104 weeks and had fewer moderate or severe exacerbations and a reduction in exacerbations leading to ED visits or hospitalizations (**Figure 3.11**).[741,742]

Benralizumab is a humanized monoclonal antibody directed against the alpha chain of the IL-5 receptor. Two phase 3, double-blind, randomized, placebo-controlled trials, of patients with COPD, a history of two or more moderate exacerbations or one or more severe exacerbation(s) in the last year despite treatment with LABA+ICS, LABA+LAMA or LABA+LAMA+ICS, from GOLD 2-4, found that add-on benralizumab was not associated with a lower annualized rate of COPD exacerbations.[1717]

Astegolimab is an IgG2 human monoclonal antibody directed against ST2 the receptor for IL-33 which blocks ST2-mediated IL-33 activity. Two double-blind, randomized, placebo-controlled trials (one phase 2b and one phase 3), enrolled symptomatic (mMRC ≥ 2) current or former smokers with COPD, from GOLD 2-4 who had a history of frequent exacerbations despite treatment with LABA+ICS, LABA+LAMA or LABA+LAMA+ICS. Patients were enrolled irrespective of their blood eosinophil counts and chronic bronchitis status. The annualized rate of COPD moderate or severe exacerbations was significantly reduced in one study but not in the other.[1718]

Tozorakimab is a human monoclonal antibody that inhibits the activity of both the reduced form and the oxidized form of IL-33. Two phase 3, double-blind, randomized, placebo-controlled trials, enrolled symptomatic (CAAT ≥ 10 and ≥ 2 for cough and phlegm/mucus) current or former smokers with COPD from GOLD 1-4, with and without chronic bronchitis, who had a history of least two moderate or at least one severe exacerbation, including at least one treated with systemic corticosteroids, in the previous 12 months despite treatment with LABA+LAMA+ICS (or LABA+ICS, LABA+LAMA if triple therapy was not tolerated). Patients were enrolled irrespective of blood eosinophil counts. Patients who received tozorakimab had fewer moderate or severe exacerbations over 52 weeks. The reduction was observed across all blood eosinophil categories.[1719]

Other drugs with potential to reduce exacerbations

Nedocromil and leukotriene modifiers have not been tested adequately in patients with COPD and the available evidence does not support their use. [1720,1721]

There was no evidence of benefit, and some evidence of harm, including malignancy and pneumonia, following

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

treatment with an anti-tumor necrosis factor-alpha antibody (infliximab) in patients with COPD.[1722]
A recent Cochrane meta-analysis did not show sufficient evidence to support the use of immunostimulants.[1723]

An RCT of the selective β_1 receptor blocker metoprolol in patients with COPD who had moderate or severe airflow obstruction, and who did not have an established indication for beta-blocker use, showed it did not delay the time until the first COPD exacerbation compared to the placebo group and hospitalization for exacerbation was more common among the patients treated with metoprolol.[1260,1724] There is no evidence that beta-blockers should be used in people with COPD who do not have a cardiovascular indication for their use.[1725]

Simvastatin did not prevent exacerbations in people with COPD who had no metabolic or cardiovascular indication for statin treatment.[1726] An association between statin use and improved outcomes (including decreased exacerbations and mortality) has been reported in observational studies of people with COPD who received them for cardiovascular and metabolic indications.[1727]

There is no evidence that supplementation with vitamin D has a positive impact on exacerbations in unselected patients.[1728] In a meta-analysis vitamin D supplementation reduced exacerbation rates in patients with low baseline vitamin D levels,[1084] but a more recent study has shown no effect.[1085]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Adherence to inhaled COPD medications

Adherence is defined as the process by which a person takes their medication as prescribed by a healthcare provider.[1729] Adherence to therapy is a challenging issue in any chronic condition including COPD.

Non-adherence to COPD medication has been associated with poor symptom control, increased risk of exacerbation, increased healthcare utilization and costs, decreased health-related quality of life and higher mortality risk.[1730-1740]

Although inhaled therapy is a key component in the management of COPD, the adherence to inhaled medication is generally low, even in very severe disease. One systematic review reported non-adherence rates to COPD medication of 22% to 93%, with over half of the included studies reporting non-adherence in > 50% of subjects.[1741] Most studies included were conducted in high-income countries and many used pharmacy claims data to assess adherence.[1741] Self-reported non-adherence to COPD medication varies between 28% and 74% (mean 50.9%) in HICs[1732,1741,1742] and between 46% and 93% (mean 61.7%) in LMICs.[1743-1746] However, when compared with data obtained through electronic monitoring, studies have consistently demonstrated that self-reports are inaccurate as people generally over-report medication use.[1747,1748]

Adherence is a complex concept, influenced by multiple factors including social/environmental, person-related and treatment-related factors.[1749] Several studies have explored the variables associated with medication adherence in people with COPD.[1741,1743] Factors such as the presence of co-morbidities, in particular depression, smoking status, schooling level, disease severity, and drug regimen factors such as dosage complexity, polypharmacy and side effects of therapy, are the main factors associated with low adherence.[1740,1741,1743,1744,1750,1751] In addition, socioeconomic factors, including unemployment, low-income status, immigration status, living alone and poor medication availability[110] have been shown to negatively influence inhaled medication adherence and to be related to the non-use of medication.[1750,1752,1753]

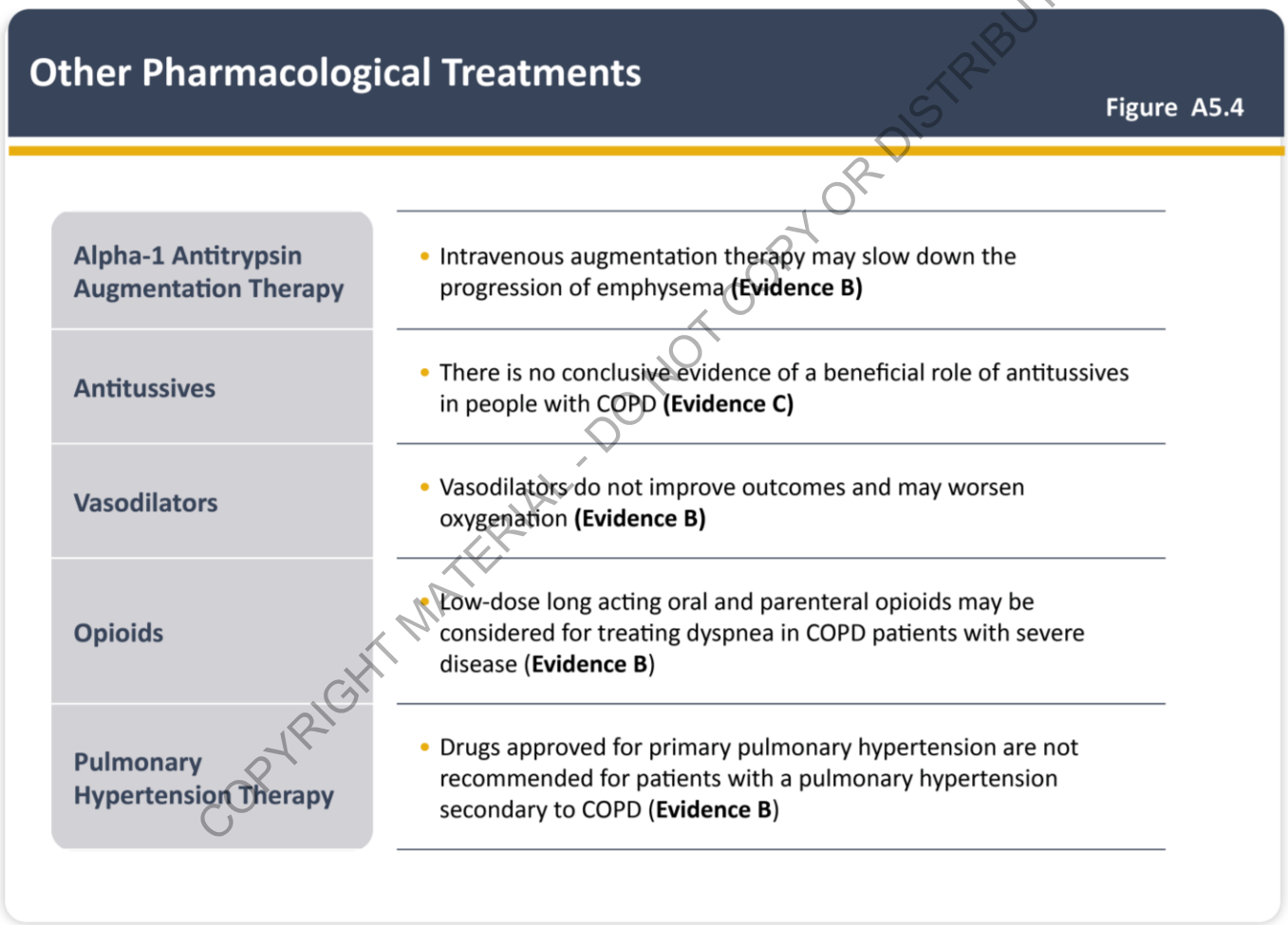
Although patient preferences may vary, prescribing strategies that could help improve adherence often include selecting devices with a similar inhalation technique (in the case of multiple inhalers) and combination therapy.[761,1754]

Healthcare provider and caregiver factors can also contribute to perception of disease, healthcare, medication and ultimately adherence. A better understanding of the disease and drug therapy, as well as greater trust in healthcare

professionals and pharmacist-led interventions have been shown to improve COPD medication adherence.[783,1741] Self-management education can help a person understand their disease and the benefits of proper use of medication. Prescribing behavioral components that are tailored to the individual barriers of each person (e.g., keeping medications in one place, self-monitoring of symptoms, medication reminders, etc.) is more effective in changing behavior than offering general suggestions. A study assessing interventions intended to improve adherence to pharmacological therapy showed that multi-component interventions with education, motivational or behavioral components delivered by health professionals may improve adherence.[1542,1755] Involving a person in establishing an individually tailored treatment plan has been shown to improve adherence.[1756] Further research on medication adherence in COPD is needed to gain insight into the effectiveness of different self-management education and health behavior change strategies.

Other pharmacological treatments

Other pharmacological treatments for COPD are summarized in **Figure A5.4**.



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Alpha-1 antitrypsin augmentation therapy

The logical approach to minimize the development and progression of lung disease in patients with AATD is alpha-1-antitrypsin augmentation. Such therapy has been available in many, though not all, countries since the 1980s. Because AATD is rare, few clinical trials to assess efficacy with conventional spirometric outcome have been undertaken. However, a wealth of observational studies suggest a reduction in spirometric progression in treated versus non-treated patients[1757] and that this reduction is most effective for patients with FEV1 35% to 49% predicted.[1758] Never- or ex-smokers with an FEV1 of 35% to 60% predicted have been suggested as those most suitable for AATD augmentation therapy (**Evidence B**).

The available clinical trial and registry data have almost exclusively been focused on patients with the ZZ (ZZ-AATD/PiZZ) genotype. Risks to other genotypes have not been explored in clinical trials although people with the Z/null or null/null genotypes have even lower levels of plasma AAT and are usually assessed for augmentation therapy. Other genotypes are not considered at risk or likely to benefit from augmentation therapy. Recent studies have suggested an increased risk of developing COPD in heterozygotes for the Z gene[62,63] although unlike ZZ neither develop COPD in the absence of smoking, so smoking cessation is thought to prevent progression and hence augmentation is not necessary or appropriate.

Studies using sensitive parameters of emphysema progression determined by CT scans have provided evidence for an effect on preserving lung tissue compared to placebo.[1759-1761] Based on the last trial the indications for therapy have been extended to include "those patients with evidence of progressive lung disease despite other optimal therapy." However, not all patients with AATD develop or persist with rapid spirometric progression especially following smoking cessation.[1762] Since the purpose of augmentation therapy is to preserve lung function and structure it seems logical to reserve such expensive therapy for those with evidence of continued and rapid progression following smoking cessation.[1762]

The indication for augmentation therapy is emphysema although there are no fixed criteria for diagnosis or confirmation. The evidence for augmentation therapy efficacy varies according to the outcome studied.[1763] Intravenous augmentation therapy has been recommended for individuals with AATD and an FEV1 ≤ 65% predicted based on previous observational studies. However, one study powered on CT scan as an outcome recommended that all patients with evidence of progressive lung disease related to AATD, and an FEV1 > 65% should be considered for augmentation. Individual discussion is recommended with consideration of the cost of therapy and lack of evidence for much benefit,[1764] although recent studies comparing mortality in patients with AATD-associated COPD and severe airflow obstruction have observed a survival advantage of augmentation.[1765] The main limitation for this therapy is the very high cost and lack of availability in many countries.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Antitussives

The role of antitussives in people with COPD is inconclusive.[1766]

Vasodilators

Vasodilators have not been properly assessed in patients with COPD who have severe/disproportionate pulmonary hypertension. Inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation-perfusion balance and is contraindicated in stable COPD.[1767] Studies have shown that sildenafil does not improve the results of rehabilitation in people with COPD and moderately increases pulmonary artery pressure.[1768] Tadalafil does not appear improve exercise capacity or health status in patients with COPD who have mild pulmonary hypertension.[1769]

Management of mucus hypersecretion

Treatment goals for patients with chronic bronchitis include: 1) reducing the overproduction of mucus; 2) decreasing mucus hypersecretion by reducing inflammation; 3) facilitating elimination of mucus by increasing ciliary transport; 4) decreasing mucus viscosity; and 5) facilitating cough mechanisms. Smoking cessation can improve cough by improving mucociliary function and decreasing goblet cell hyperplasia.[1770] Smoking cessation may decrease airway injury by limiting immune mechanisms that cause persistent inflammation and abnormal epithelial cell gene expression.[1771]

Mucus clearance treatments that promote mechanical movement through the airway such as oscillating positive expiratory pressure therapy may improve mucus mobilization, symptoms and quality of life in people with COPD who produce sputum daily or most days.[1772,1773] The use of nebulized hypertonic saline for copious mucus has been used

in obstructive lung disease and cystic fibrosis with beneficial effects. However, in patients with COPD, current studies are limited, and results are inconsistent.[1774-1778]

LAMAs, predominantly tiotropium and aclidinium, can improve sputum production and decrease cough in patients with COPD who have moderate to severe airflow obstruction.[1779-1782] Triple therapy with dual LABDs combined with an ICS may be effective in reducing exacerbations and improving lung function and quality of life regardless of the presence of mucus hypersecretion.

Use of mucolytics was associated with a reduction of 0.03 exacerbations per participant per month compared with placebo, that is, about 0.36 per year, or one exacerbation every three years. Very high heterogeneity was noted for this outcome, so results need to be interpreted with caution.[1710] Nevertheless, in participants with chronic bronchitis or COPD, we are moderately confident that treatment with mucolytics may produce a small reduction in acute exacerbations and a small effect on overall quality of life.[1710] Recombinant human DNase has similarly shown lack of benefit in mucopurulent patients with COPD.[1783,1784] New classes of mucolytics agents are being developed.[1785] In a small double-blind placebo-controlled study, patients randomized to receive a cystic fibrosis transmembrane conductance regulator potentiator icenticaftor had improvements in FEV1 and sputum bacterial colonization compared to placebo.[1786] New bronchoscopic interventions have been proposed to reduce mucus hypersecretion by eliminating airway goblet cell hyperplasia and submucosal glands. Liquid nitrogen metered cryospray, rheoplasty, and targeted lung denervation are currently under evaluation.[975,983,985,1787]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

APPENDIX 6: OVERVIEW OF THE EVIDENCE: NON-PHARMACOLOGICAL THERAPY

Self-management

A Delphi process has resulted in a conceptual definition for COPD self-management interventions: "A COPD self-management intervention is structured but personalized and often multi-component, with goals of motivating, engaging and supporting the patients to positively adapt their health behavior(s) and develop skills to better manage their disease."[788] The process requires iterative interactions between patients and healthcare professionals who are competent in delivering self-management interventions. Behavior change techniques are used to elicit patient motivation, confidence and competence. Literacy sensitive approaches are used to enhance comprehensibility.[788]

Systematic reviews have provided evidence that self-management interventions improve outcomes in COPD. A 2022 Cochrane review included 27 studies, involving 6008 participants, that evaluated the effectiveness and safety of COPD self-management interventions over two-and-a-half to 24 months.[1543] Studies were conducted on four different continents (15 in Europe, 8 in North America, one in Asia, and 4 in Oceania; with one study conducted in both Europe and Oceania). Self-management interventions had to include at least two intervention components and include an iterative process between participant and healthcare provider(s) in which goals were formulated and feedback was given on self-management actions by the participant. All studies had control groups of participants who received usual care – that is, care typical for people with COPD. The Cochrane review reported that interventions for people with COPD are associated with improvements in health-related quality of life, a lower probability of respiratory-related hospital admissions, and no excess respiratory-related and all-cause mortality risks. This strengthens the view that self-management interventions are unlikely to cause harm. There had previously been concerns that health benefits from self-management programs in COPD could be counterbalanced by increased mortality.[1788,1789] Furthermore, two independent, well-designed studies, the COMET[1790] and the PIC-COPD,[1791] have shown the potential for reduction in mortality from integrated case management with self-management interventions. The program in these two studies may have promoted earlier appropriate treatment for exacerbations, which could have prevented some fatal complications. These data, in conjunction with the most recently published Cochrane review, confirm the benefit of self-management interventions that provides people to develop the skills and behaviors they need to successfully manage their disease, and also strengthens the view that the interventions are unlikely to cause harm.[1543]

There remain problems with heterogeneity among interventions, consistency of their application, specifics of the intervention, patient populations, follow-up times and outcome measures that make generalization difficult in real life. It is also challenging to formulate clear recommendations regarding the most effective form and content of a self-management intervention in COPD given the range of heterogeneity across studies, and lack of precise definitions of self-management components (e.g., skills taught) and fidelity measures. The recent conceptual definition should help redress these deficiencies. For example, in the definition it is mentioned that: "The process requires iterative interactions between patients and healthcare professionals who are competent in delivering self-management interventions." Having proper health coaching is important to improve self-management abilities. In people with COPD admitted for an exacerbation, a study has reported the positive effect of health coaching, commencing at the time of hospital discharge, on reducing risk of re-hospitalization and emergency department visits.[1792] Furthermore, this randomized study indicated that health coaching delivered by a respiratory therapist or nurse may improve self-management abilities as demonstrated by meaningful improvements in Chronic Respiratory Disease Questionnaire mastery scores.[1793]

In summary, RCTs prove that self-management interventions benefit COPD patients by lowering hospital admissions and improving health. However, real-world application remains difficult due to inconsistencies across study

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

populations, follow-up times, and intervention methods. To succeed, these interventions must drive behavioral change by providing proper case-manager support, boosting patients' intrinsic motivation through client-centered communication, and carefully evaluating the patient, case manager, and quality assurance systems.[1794]

Physical activity

Physical activity is behavior that requires skeletal muscle activity and results in meaningful movement that allows patients to participate in daily life. It was observed that physical activity in patients with COPD, objectively assessed as steps per day, was only 64% of that in matched control subjects when 17 studies were pooled.[1795] This may lead to a downward spiral of inactivity which predisposes patients to deconditioning, social isolation,[1796] reduced quality of life, increased rates of hospitalization and mortality.[558,1797,1798] As such, there has been tremendous interest in implementing behavior-targeted interventions with the aim of improving physical activity[1799] and these should be encouraged.[558] Behavior change techniques can be combined to enhance physical activity and a scoping review identified that interventions typically combine 7 to 8 techniques.[1800] The most popular techniques are self-monitoring (for example using wearables) and dynamic or fixed goal setting. [1800] Studies using these techniques in combination also showed superior and clinically meaningful effects in improving physical activity compared to those using other strategies.[1801]

Technology-based interventions have the potential to provide convenient and accessible means to enhance physical activity self-efficacy, and to educate and motivate people in their efforts to make healthy lifestyle changes.[1537] However, published studies to date are heterogeneous and inconsistent in the techniques used. They often lack the necessary details (e.g., type, quantity, timing and method of delivery; tools used; quality-assurance methods) to replicate the study or adapt the interventions for clinical care. Effects of coaching interventions, not combined with other interventions such as exercise training or pulmonary rehabilitation, are mainly seen on physical activity, but fall short of meeting benchmarks for clinical improvements in exercise tolerance and quality of life.[1802] In addition, long term success, even with continued use of wearables or interfaces is not guaranteed.[1803,1804] One RCT that evaluated the long-term effectiveness of a community-based physical activity coaching intervention in people with COPD exacerbation history showed no benefits in acute care use or survival.[1805] Another pedometer-based physical activity interventional study (pedometer alone or pedometer plus a website with feedback) showed an association between the intervention and reduced risk for acute exacerbations over 12-15 months of follow-up.[1806]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Exercise training

Exercise training is a monodisciplinary intervention where planned and structured regular exercises of appropriate intensity are provided to patients with COPD with the aim to improve skeletal muscle and cardiovascular and respiratory function with downstream effects on symptoms, health-related quality of life, mental health and the treatable traits that are related to deconditioning. Exercise training can be offered as a single intervention or can be combined with other interventions like physical activity coaching. Often exercise training is embedded as the cornerstone of pulmonary rehabilitation (see below). A meta-analysis of RCTs found that exercise training alone, or with the addition of activity counseling, significantly improved physical activity levels in patients with COPD.[1807] A combination of constant load or interval training with resistance training provides better outcomes than either method alone.[1808]

Broad consensus exist on the frequency of exercise (three times per week, with two supervised sessions). Where possible, lower limb endurance exercise training of at least moderate intensity increases peak oxygen uptake with the greatest improvement seen at high intensity.[1809] Typically whole body exercise training is prescribed at 60%-80% of the symptom-limited maximum work,[1810] or to a Borg-rated dyspnea or fatigue score of 4 to 6 (moderate to severe).[1811] Aerobic training can be accomplished through either continuous or interval exercise programs using bicycle, treadmill or regular walking exercises. Interval training involves the patient doing the same total work but divided into briefer periods of high-intensity exercise, a useful strategy when performance is limited by ventilatory

capacity, dynamic hyperinflation or other comorbidities.[1812] Upper extremities exercise training improves arm strength and endurance, and results in improved functional capacity for upper extremity activities.[1813] Exercise capacity may also be improved by whole-body vibration training[1814] or neuromuscular electrical stimulation,[1815] although these are not first line therapies for patients with COPD.

Cultural adaptation to conventional 'gym based' exercise is possible and can be effective. In some cultures alternatives such as Tai Chi practice, emphasizing the use of 'mind' or concentration for control of breathing and circular body movement, have been shown to improve exercise capacity in comparison to usual care in patients with COPD. Tai Chi alone, or in combination with pulmonary rehabilitation, reduced dyspnea and improved quality of life.[1816] Other forms of mind body exercises have also been utilized in COPD patients, particularly in Asian countries.

Exercise training intensity and effectiveness is enhanced by optimizing bronchodilators,[1614] since both LAMAs and LABAs have shown reduced resting and dynamic hyperinflation. These changes contribute to better training effects.[1582,1817] Similarly, adding exercise training to a dual bronchodilator regimen led to the larger improvements in exercise tolerance than bronchodilator therapy alone.[1818]

When needed, it is common practice to supplement oxygen during exercise training with the aim of facilitating higher exercise intensity. There was little support for oxygen supplementation during exercise training for individuals with COPD from a 2007 systematic review,[1819] but most evidence was limited by low study quality. A large RCT,[834] with blinding of participants, trainers and assessors, demonstrated that patients with COPD training with either supplemental oxygen or medical air had significantly improved exercise capacity and health-related quality of life; no greater benefit with oxygen was observed. The incidence and severity of adverse events were similar in both groups. In patients with COPD who have severe airflow obstruction, are on LTOT, and in whom exercise training is done with oxygenation systems, there has been increased interest in using an alternative tool, namely nasally administered mixtures of humidified air-oxygen blends at flow rates of 20-60 L/min. While potentially interesting, clinical benefits are not consistently shown and more studies are needed to identify possible candidates for its addition to regular exercise training.[1820]

Inspiratory muscle training increases strength of inspiratory muscles.[1821] The intervention reduces dyspnea and can lead to improvements in functional exercise tolerance (6MWD) and health-related quality of life compared to usual care.[1822] When added to comprehensive pulmonary rehabilitation, effects are more modest and the therapy is likely best restricted to patients with disabling dyspnea and respiratory muscle weakness. Studies in Asia showed that breathing techniques such as pursed lip breathing, diaphragmatic breathing and Ba Duan Jin exercise improve pulmonary function and exercise capacity in patients with COPD.[1823,1824]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

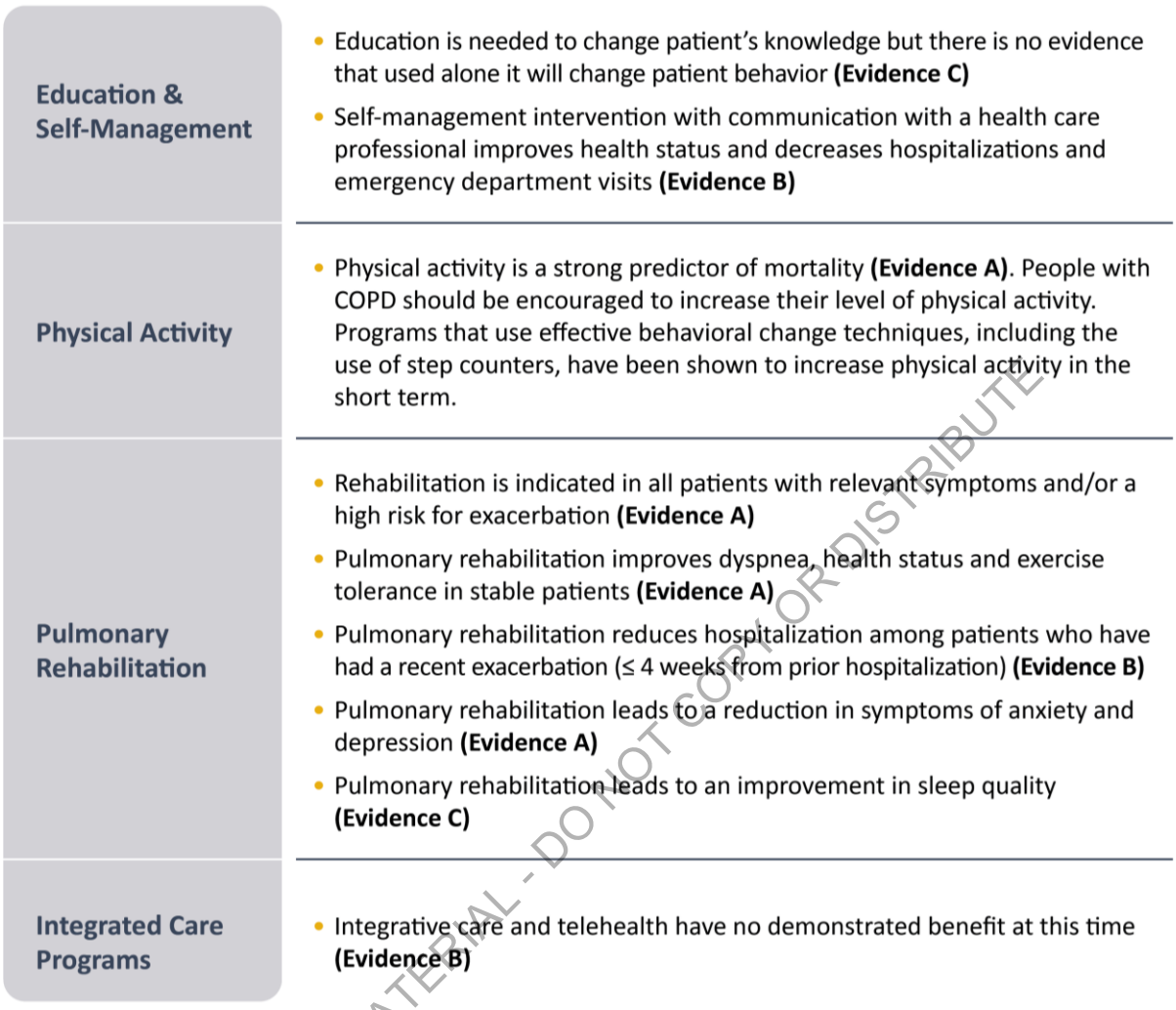
Pulmonary rehabilitation

Pulmonary rehabilitation is an individualised and comprehensive multidisciplinary intervention that is tailored to the treatable traits of patients with COPD.[1825] The benefits of pulmonary rehabilitation for COPD patients are considerable (**Figure A6.1**) and rehabilitation has been shown to be the most effective therapeutic strategy to improve shortness of breath, health status, exercise tolerance and sleep quality.[803,1826] Pulmonary rehabilitation is appropriate for most people with COPD; improved functional exercise capacity and health-related quality of life have been demonstrated across all grades of COPD severity, although the evidence is especially strong in patients with moderate to severe disease. Even patients with chronic hypercapnic failure show benefit.[1827,1828]

Pulmonary rehabilitation also improves aspects of mental[1829] and cognitive function[1830] although evidence is still limited. Because of its clear benefits the WHO,[797] the American Thoracic Society[796] and the British Thoracic Society[811] all strongly advocate for pulmonary rehabilitation.

Education, Self-Management, Physical Activity, Pulmonary Rehabilitation & Integrated Care in COPD

Figure A6.1



COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Exercise training is the cornerstone of pulmonary rehabilitation programs, but a multidisciplinary team should have access to a dietitian, a nurse, an occupational therapist, physiotherapist, psychologist social workers and counseling professionals and medical doctors with know-how in rehabilitation medicine and respiratory disease according to the package of rehabilitation care designed by the WHO (WHO package of rehabilitation care for cardiopulmonary conditions).[797] While the access to a multidisciplinary team is advised, many programs lack this multidisciplinary input.[603]

There are data from large RCTs regarding the effectiveness of pulmonary rehabilitation after hospitalization for an acute exacerbation. A systematic review that included 13 RCTs reported reduced mortality, and number of readmissions among patients who had pulmonary rehabilitation initiated during hospitalization or within 4 weeks of discharge.[826,857] Long-term effects on mortality were not statistically significant, but improvements in health-related quality of life and exercise capacity appeared to be maintained for at least 12 months. These results have been corroborated by real world evidence, from a large population-based cohort of more than 190,000 patients hospitalized for COPD in the US, in whom initiation of pulmonary rehabilitation within 90 days of discharge, while rare, was significantly associated with lower risk of mortality[860] and fewer rehospitalizations at one year.[1831] Furthermore, in a meta-analysis pulmonary rehabilitation initiated before hospital discharge with endurance training alone was found

to reduce readmission rate and improve 6MWT distance.[1832] One study has reported that initiating pulmonary rehabilitation before the patient's discharge may compromise survival through unknown mechanisms.[823] Pulmonary rehabilitation ranks as one of the most cost-effective treatment strategies.[802]

There are many challenges with pulmonary rehabilitation. Referral of patients who might benefit, uptake and completion of pulmonary rehabilitation is frequently limited, partly through provider ignorance as well as patients' lack of awareness of availability or benefits. The recommended length of pulmonary rehabilitation (minimum of 6 weeks) could also be a limitation in many countries due to funding constraints of insurance companies and/or national health funds. Tele pulmonary rehabilitation (see below) could be an alternative, combined with traditional exercise training or not; this may be a valid alternative in remote settings or where the length of pulmonary rehabilitation programs is limited to less than 4 weeks.[796,1833] Another challenge is encouraging sustained long-term physical activity. Although the approach may need to be personalized, a behavioral lifestyle physical activity intervention has shown promising results i.e., the potential to decrease sedentarity and increase physical activity in patients with COPD who have moderate to severe airflow obstruction.[1834] A major barrier to full participation is access, which is particularly limited by geography, culture, finances, transport and other logistics.[520,791,874,1835]

Pulmonary rehabilitation can be conducted at a range of sites.[1836] Community-based and home-based programs have been shown to be as effective as hospital-based programs in randomized controlled trials,[1837,1838] as long as the frequency and intensity are equivalent.[1839] In countries where there is economic limitation or those with challenges because patients live in rural or remote regions, home-based programs that deliver exercise training using a stationary bicycle[1837] or a walking program[1838] could be considered as alternative to traditional hospital pulmonary rehabilitation training programs. There is also evidence that standardized home-based pulmonary rehabilitation programs improve dyspnea in patients with COPD.[1840] However, in real life, traditional pulmonary rehabilitation with supervision remains the standard of care and first-line option, with home-based exercise likely to be a less effective alternative for people with COPD who are unable to attend pulmonary rehabilitation.[1841] If needed, hybrid programs combining center-based and home-based telerehabilitation,[1838] center-based and primary care-based rehabilitation[1842] or other combinations may be valid alternatives to conventional strictly center based pulmonary rehabilitation.

Another challenge, although not surprising, is that the benefits of pulmonary rehabilitation tend to wane over time. When the exercise stimulus is stopped the effects dilute, even when physical activity remains improved.[807] There is insufficient evidence, with conflicting research findings in the 21 available RCTs, to recommend continuation of maintenance exercise programs with the aim of maintaining benefit long-term.[796] However, if such programs are available, they should target health behavior taking into account the patient's own preferences, needs and personal goals.[804,1843] Pulmonary rehabilitation may help reduce anxiety and depression symptoms.[1399]

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Tele-rehabilitation

Telerehabilitation is defined as the delivery of rehabilitation services using information and communication technologies. However, there are many challenges encountered in the delivery of pulmonary rehabilitation, which include systemic barriers integral to some healthcare systems leading to a scarcity of in-person pulmonary rehabilitation programs and facilities. In many regions, the programs that do exist tend to be located in urban areas. Hence attending pulmonary rehabilitation is challenging for many patients with COPD. Even for those patients residing in urban areas, availability of frequent transportation that is required for out-patient pulmonary rehabilitation may still be a challenge.

Tele-rehabilitation has been proposed as an alternative to the traditional approaches. However, it is important to distinguish between evidence-based tele-rehabilitation models and pandemic-adapted models. Most of the available evidence regarding tele-rehabilitation was analyzed in a Cochrane review.[808] When data across all modalities of

telerehabilitation delivery was pooled, it was possible to show clinical noninferiority of telerehabilitation compared to center-based pulmonary rehabilitation for exercise capacity (6 studies; 700 participants; SMD 0.02; 95% CI -0.13, 0.17), dyspnea (5 studies; 628 participants; SMD 0.09; 95%CI -0.06, 0.25) or quality of life (5 studies; 651 participants; SMD -0.02; 95% CI -0.18, 0.13).[1844]

Across multiple trials performed in groups and individuals with a large variety of tele-rehabilitation delivery platforms (videoconferencing, telephone only, website with telephone support, mobile application with feedback, centralized "hub" for people to come together), the reported results suggest that tele-rehabilitation is safe and has similar benefits to those of center-based pulmonary rehabilitation across a range of outcomes. The evidence-based models from the Cochrane review were published before the COVID-19 pandemic, and have all included an in-person exercise test at the center prior to commencement, for the purposes of assessing the full extent of desaturation during exercise training[1845] and accurately prescribing exercise capacity.[1846]

Telerehabilitation can be considered an effective alternative, or adjunct, to center-based pulmonary rehabilitation. Clinical practice guidelines recommend that adults with stable chronic respiratory disease, particularly COPD, should be offered the choice of a center-based pulmonary rehabilitation or telerehabilitation (strong recommendation, moderate quality evidence).[796] A recent viewpoint provides important insight: *"Telehealth PR is here to stay, and we welcome innovations in this space. We do, however, need checks and balances to ensure that the appeal and benefits of telehealth PR are not misused by inexperienced or unscrupulous providers"*.[1847]

In the field of tele-rehabilitation, the evidence base is still evolving and best practices are not yet established at this time due to a lack of: i) standardization of delivery platform, e.g., no one single best mode of tele-rehabilitation delivery; ii) tests performed remotely allowing for accurate exercise prescription (e.g., there is still a need for in person evaluation to be able to prescribe the exercise training program); iii) information on suitable variations in components and timing of interventions (e.g., no data are available regarding post-exacerbation rehabilitation); and iv) evidence about duration of benefit (beyond immediate post pulmonary rehabilitation). Furthermore, it is unclear what types of patients were recruited to these studies or their level of familiarity with the technology used. In order to ensure that pulmonary rehabilitation is accessible to all, we must understand the barriers that might be unique to tele-rehabilitation.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Nutritional support

In people with COPD, weight loss and malnutrition develop as disease severity progresses and indicates a poor prognosis. Malnutrition in COPD is associated with impaired lung function, increased hospitalizations, poor exercise tolerance, worsened quality of life and increased mortality.[342,1848-1852] Malnutrition has been reported in 30-60% of patients hospitalized with COPD;[1853] up to 50% of people with COPD weigh less than 90% of ideal bodyweight.[1854] Weight loss occurs when energy expenditure exceeds energy supply; in people with COPD decreases in appetite and oral intake often coincide with elevated systemic levels of pro-inflammatory cytokines and the appetite suppressant hormone, leptin.[1855,1856] The severity of airflow obstruction correlates with the presence of malnutrition[1857] since ventilator inefficiency increases daily energy requirements.[1858] The imbalance of decreased oral intake and increased energy expenditure can lead to a negative nitrogen balance and decreases in skeletal muscle mass and function.[1859-1861]

Nutritional repletion in people with COPD should be coupled with optimization of lung function, regular exercise, and improvement of tissue oxygenation. Dietary advice and oral supplementation have been reported to improve bodyweight, quality of life, respiratory muscle strength and 6MWD.[894,1853] However, nutritional support has not been consistently shown to improve lung function.[894,1862-1864] Multimodality treatment that incorporates rehabilitation with nutritional support and protein supplementation may improve fat free mass, BMI and exercise performance.[1865] Among malnourished, hospitalized people with COPD, a protein enriched supplementation decreased mortality and

improved handgrip strength, bodyweight and nutritional biomarkers 90 days post hospital discharge.[1866]

Integrated care programs

COPD is a complex disease that requires the input of multiple care providers who need to work together closely. In principle, use of a formal structured program that determines how each component is delivered should make care more efficient and effective, but the evidence for this is divided. Currently available evidence is conflicting regarding the benefits of integrated care/disease management programs in terms of quality of life, exercise capacity, and use of healthcare resources.[828,1867,1868] Besides, delivering integrated interventions by telemedicine did not show a significant effect.[1869,1870] The pragmatic conclusion is that well organized care is important, but there may be no advantage in structuring it tightly into a formalized program. A Cochrane review on integrated care has shown results in decreased hospitalizations and increased quality of life and exercise capacity. The contrast of a new integrated care program versus usual care becomes smaller when usual care itself already routinely contains several of the components.[828] Furthermore, integrated care needs to be individualized to the stage of the person's illness and health literacy.

A comprehensive review recommends transitioning COPD management from fragmented acute care to continuous, patient-centered models that emphasize early diagnosis, personalized therapies, and collaborative self-management.[827] The framework also stresses the importance of multidisciplinary coordination across care settings to optimize long-term health outcomes and improve healthcare efficiency. It is highlighted that different dominant components of integrated care programs might typically produce beneficial effects for specific outcomes. It appears that integrated care programs should consist of several different components to reach the highest potential of improving different clinical outcomes.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

TABLE OF FIGURES

Figure Title	Number
Global challenges for COPD & asthma	Figure A
Description of levels of evidence	Figure B
Estimated COPD prevalence according to different sources	Figure 1.1
FEV1 trajectories (TR) over the life course	Figure 1.2
Groups that can be categorized as having pre-COPD	Figure 1.3
Proposed taxonomy (etiotypes) for COPD	Figure 1.4
Clinical indicators for considering a diagnosis of COPD	Figure 2.1
Other causes of chronic cough	Figure 2.2
Differential diagnosis of COPD	Figure 2.3
Considerations in performing spirometry	Figure 2.4
A. Spirometry - normal trace; B. Spirometry – airflow obstruction	Figure 2.5
Spirometry to confirm a diagnosis of COPD	Figure 2.6
Role of spirometry in COPD	Figure 2.7
Interpretation of FEV1/FVC ratio in a person with suspected COPD	Figure 2.8
Factors that may be associated with COPD underdiagnosis	Figure 2.9
An algorithm for COPD case-finding	Figure 2.10
GOLD grades and severity of airflow obstruction in COPD (based on post-bronchodilator FEV1)	Figure 2.11
Modified MRC dyspnea scale	Figure 2.12
CAAT™ assessment	Figure 2.13
GOLD ABE assessment tool	Figure 2.14
Exercise tests in COPD assessment	Figure 2.15
Use of CT in COPD	Figure 2.16
Goals for treatment of stable COPD	Figure 3.1
Management of COPD	Figure 3.2
Identify & reduce risk factor exposure	Figure 3.3
Brief strategies to help the patient willing to quit	Figure 3.4
Treating tobacco use and dependence	Figure 3.5
Vaccination for people with COPD	Figure 3.6
Diagnosis and management cycle	Figure 3.7
Initial pharmacological treatment	Figure 3.8
Follow-up pharmacological treatment	Figure 3.9
Factors to consider when initiating ICS treatment	Figure 3.10
Evidence supporting the use of biologics registered for the treatment of COPD	Figure 3.11
Management of patients currently on LABA+ICS	Figure 3.12
Key points for inhalation of drugs	Figure 3.13
Basic principles for appropriate inhalation device choice	Figure 3.14
Non-pharmacological management of COPD	Figure 3.15
Follow-up of non-pharmacological treatment	Figure 3.16
Non-pharmacological programs in COPD	Figure 3.17
Assessment and rehabilitation interventions	Figure 3.18
Pulmonary rehabilitation outcomes in COPD	Figure 3.19
Physical activity and exercise training after COPD exacerbation	Figure 3.20
Oxygen therapy and ventilatory support in stable COPD	Figure 3.21

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

Prescription of supplemental oxygen to COPD patients	Figure 3.22
Evidence supporting a reduction in mortality with pharmacotherapy and non-pharmacotherapy in COPD patients	Figure 3.23
Palliative care, end of life and hospice care in COPD	Figure 3.24
Overview of current and proposed surgical and bronchoscopic interventions for people with COPD	Figure 3.25
Interventional therapy in stable COPD	Figure 3.26
Surgical and interventional therapies in advanced emphysema	Figure 3.27
Exacerbations: Diagnosis and Assessment	Figure 4.1
Classification of the severity of COPD exacerbations	Figure 4.2
Conditions that may mimic or worsen exacerbation-like symptoms	Figure 4.3
Assessing the appropriate place of management during COPD exacerbation	Figure 4.4
Risk of severe cardiovascular event or all-cause death following COPD exacerbation of any severity	Figure 4.5
Management of severe but not life-threatening exacerbations	Figure 4.6
Key points for the management of exacerbations	Figure 4.7
Indications for high flow oxygen therapy (HFNT)	Figure 4.8
Indications for noninvasive mechanical ventilation (NIV)	Figure 4.9
Indications for invasive mechanical ventilation	Figure 4.10
Discharge criteria and recommendations for follow-up	Figure 4.11
Interventions that reduce the frequency of COPD exacerbations	Figure 4.12
Summary of the modified 4Ms person-centered approach to multimorbid patients with COPD	Figure 5.1
Morbidity clusters frequently present in patients with COPD that independently impact outcomes	Figure 5.2
Cardiovascular diseases in COPD: burden and management	Figure 5.3
Treatable traits in pulmonary hypertension-COPD (PH-COPD) & suggested management	Figure 5.4
Common risk factors for development of lung cancer	Figure 5.5
Potential complementary approach for the detection of frequent morbidities in all patients with COPD - initial evaluation	Figure 5.6
Potential complementary approach for the detection of frequent morbidities in all patients with COPD - regular follow-up	Figure 5.7
Potential clinical benefits of AI in COPD diagnosis & management	Figure 6.1
Potential risks and mitigation strategies of AI in medicine	Figure 6.2
Appendices	
Maintenance medications registered for the treatment of COPD	Figure A5.1
Bronchodilators in stable COPD	Figure A5.2
Anti-inflammatory maintenance therapy registered for the treatment of COPD	Figure A5.3
Other pharmacological treatments	Figure A5.4
Education, self-management, physical activity, pulmonary rehabilitation & integrated care in COPD	Figure A6.1

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

REFERENCES

1. Halpin DMG, Celli BR, Criner GJ, et al. The GOLD Summit on chronic obstructive pulmonary disease in low- and middle-income countries. *Int J Tuberc Lung Dis* 2019; **23**(11): 1131-41 **https://pubmed.ncbi.nlm.nih.gov/31718748**.
2. Meghji J, Mortimer K, Agusti A, et al. Improving lung health in low-income and middle-income countries: from challenges to solutions. *Lancet* 2021; **397**(10277): 928-40 **https://pubmed.ncbi.nlm.nih.gov/33631128**.
3. World Health Organization (WHO). Chronic obstructive pulmonary disease (COPD)Fact Sheet 10 June 2026 Available here: **https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)** [accessed Oct 2026].
4. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; **3**(11): e442 **https://pubmed.ncbi.nlm.nih.gov/17132052**.
5. Halpin DMG, Celli BR, Criner GJ, et al. It is time for the world to take COPD seriously: a statement from the GOLD board of directors. *Eur Respir J* 2019; **54**(1): 1900914 **https://pubmed.ncbi.nlm.nih.gov/31273036**.
6. United Nations. Sustainable Development Goals, online information available here: **https://www.un.org/sustainabledevelopment/sustainable-development-goals/** [accessed Oct 2026].
7. Halpin DMG, Masekela R, Vogelmeier CF, et al. Addressing the global challenges of COPD and asthma: a shared vision from the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) and the Global Initiative for Asthma (GINA). *Eur Respir J* 2026; **67**(2): **https://pubmed.ncbi.nlm.nih.gov/41198399**.
8. Halpin DMG, Masekela R, Vogelmeier CF, et al. Addressing the global challenges of chronic obstructive pulmonary disease and asthma: a shared vision from the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) and the Global Initiative for Asthma (GINA). *Am J Respir Crit Care Med* 2026; **212**(2): 297-302 **https://pubmed.ncbi.nlm.nih.gov/41104909**.
9. Halpin DMG, Masekela R, Vogelmeier CF, et al. Addressing the Global Challenges of COPD and Asthma: A Shared Vision From the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) and the Global Initiative for Asthma (GINA). *Respirology* 2026; **31**(2): 135-40 **https://pubmed.ncbi.nlm.nih.gov/41620839**.
10. Halpin DMG, Masekela R, Vogelmeier CF, et al. Addressing the Global Challenges of COPD and Asthma: A Shared Vision from the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) and the Global Initiative for Asthma (GINA). *Arch Bronconeumol* 2026; **62**(2): 113-7 **https://pubmed.ncbi.nlm.nih.gov/41628954**.
11. Halpin DMG, Masekela R, Vogelmeier CF, et al. Addressing the global challenges of COPD and Asthma: A shared vision from the Global Initiative for Chronic Obstructive Pulmonary Disease and the Global Initiative for Asthma. *J Pan Afr Thorac Soc* 2025; **6**: 33-8
12. Celli B, Fabbri L, Criner G, et al. Definition and Nomenclature of Chronic Obstructive Pulmonary Disease: Time for Its Revision. *Am J Respir Crit Care Med* 2022; **206**(11): 1317-25 **https://pubmed.ncbi.nlm.nih.gov/35914087**.
13. Agusti A, Melen E, DeMeo DL, Breyer-Kohansal R, Faner R. Pathogenesis of chronic obstructive pulmonary disease: understanding the contributions of gene-environment interactions across the lifespan. *Lancet Respir Med* 2022; **10**(5): 512-24 **https://pubmed.ncbi.nlm.nih.gov/35427533**.
14. Sin DD, Doiron D, Agusti A, et al. Air pollution and COPD: GOLD 2023 committee report. *Eur Respir J* 2023; **61**(5): 2202469 **https://pubmed.ncbi.nlm.nih.gov/36958741**.
15. Yang IA, Jenkins CR, Salvi SS. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. *Lancet Respir Med* 2022; **10**(5): 497-511 **https://pubmed.ncbi.nlm.nih.gov/35427530**.
16. Kohansal R, Martinez-Camblor P, Agusti A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit Care Med* 2009; **180**(1): 3-10 **https://pubmed.ncbi.nlm.nih.gov/19342411**.
17. Ozga JE, Sargent JD, Steinberg AW, Tang Z, Stanton CA, Paulin LM. Childhood Cigarette Smoking and Risk of COPD in Older United States Adults: A Nationally Representative Replication Study. *Chronic Obstr Pulm Dis* 2024; **11**(6): 549-57 **https://pubmed.ncbi.nlm.nih.gov/39413254**.
18. Colak Y, Lokke A, Marott JL, et al. Low smoking exposure and development and prognosis of COPD over four decades: a population-based cohort study. *Eur Respir J* 2024; **64**(3): **https://pubmed.ncbi.nlm.nih.gov/38936967**.
19. Rennard SI, Vestbo J. COPD: the dangerous underestimate of 15%. *Lancet* 2006; **367**(9518): 1216-9 **https://pubmed.ncbi.nlm.nih.gov/16631861**.
20. Bardsen T, Roksund OD, Benestad MR, et al. Tracking of lung function from 10 to 35 years after being born extremely preterm or with extremely low birth weight. *Thorax* 2022; **77**(8): 790-8 **https://pubmed.ncbi.nlm.nih.gov/35410959**.
21. Raad D, Gaddam S, Schunemann HJ, et al. Effects of water-pipe smoking on lung function: a systematic review and meta-analysis. *Chest* 2011; **139**(4): 764-74 **https://pubmed.ncbi.nlm.nih.gov/20671057**.
22. She J, Yang P, Wang Y, et al. Chinese water-pipe smoking and the risk of COPD. *Chest* 2014; **146**(4): 924-31 **https://pubmed.ncbi.nlm.nih.gov/24557573**.
23. Gunen H, Tarraf H, Nemati A, Al Ghobain M, Al Mutairi S, Aoun Bacha Z. Waterpipe tobacco smoking. *Tuberk Toraks* 2016; **64**(1): 94-6 **https://pubmed.ncbi.nlm.nih.gov/27266294**.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

24. Yin P, Jiang CQ, Cheng KK, et al. Passive smoking exposure and risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. *Lancet* 2007; **370**(9589): 751-7 https://pubmed.ncbi.nlm.nih.gov/17765524.
25. 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 https://pubmed.ncbi.nlm.nih.gov/37309392.
26. Su Z, Xie Y, Huang Z, et al. Second hand smoke attributable disease burden in 204 countries and territories, 1990-2021: a systematic analysis from the Global Burden of Disease Study 2021. *Respir Res* 2025; **26**(1): 174 https://pubmed.ncbi.nlm.nih.gov/40336093.
27. Tager IB, Ngo L, Hanrahan JP. Maternal smoking during pregnancy. Effects on lung function during the first 18 months of life. *Am J Respir Crit Care Med* 1995; **152**(3): 977-83 https://pubmed.ncbi.nlm.nih.gov/7663813.
28. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 2009; **374**(9691): 733-43 https://pubmed.ncbi.nlm.nih.gov/19716966.
29. Orozco-Levi M, Garcia-Aymerich J, Villar J, Ramirez-Sarmiento A, Anto JM, Gea J. Wood smoke exposure and risk of chronic obstructive pulmonary disease. *Eur Respir J* 2006; **27**(3): 542-6 https://pubmed.ncbi.nlm.nih.gov/16507854.
30. Mortimer K, Montes de Oca M, Salvi S, et al. Household air pollution and COPD: cause and effect or confounding by other aspects of poverty? *Int J Tuberc Lung Dis* 2022; **26**(3): 206-16 https://pubmed.ncbi.nlm.nih.gov/35197160.
31. Gan WQ, FitzGerald JM, Carlsten C, Sadatsafavi M, Brauer M. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. *Am J Respir Crit Care Med* 2013; **187**(7): 721-7 https://pubmed.ncbi.nlm.nih.gov/23392442.
32. Ezzati M. Indoor air pollution and health in developing countries. *Lancet* 2005; **366**(9480): 104-6 https://pubmed.ncbi.nlm.nih.gov/16005317.
33. Zhou Y, Zou Y, Li X, et al. Lung function and incidence of chronic obstructive pulmonary disease after improved cooking fuels and kitchen ventilation: a 9-year prospective cohort study. *PLoS Med* 2014; **11**(3): e1001621 https://pubmed.ncbi.nlm.nih.gov/24667834.
34. Sana A, Somda SMA, Meda N, Bouland C. Chronic obstructive pulmonary disease associated with biomass fuel use in women: a systematic review and meta-analysis. *BMJ Open Respir Res* 2018; **5**(1): e000246 https://pubmed.ncbi.nlm.nih.gov/29387422.
35. Assad NA, Balmes J, Mehta S, Cheema U, Sood A. Chronic obstructive pulmonary disease secondary to household air pollution. *Semin Respir Crit Care Med* 2015; **36**(3): 408-21 https://pubmed.ncbi.nlm.nih.gov/26024348.
36. Sherrill DL, Lebowitz MD, Burrows B. Epidemiology of chronic obstructive pulmonary disease. *Clin Chest Med* 1990; **11**(3): 375-87 https://pubmed.ncbi.nlm.nih.gov/2205437.
37. Ramirez-Venegas A, Velazquez-Uncal M, Aranda-Chavez A, et al. Bronchodilators for hyperinflation in COPD associated with biomass smoke: clinical trial. *Int J Chron Obstruct Pulmon Dis* 2019; **14**: 1753-62 https://pubmed.ncbi.nlm.nih.gov/31496674.
38. Puzzolo E, Fleeman N, Lorenzetti F, et al. Estimated health effects from domestic use of gaseous fuels for cooking and heating in high-income, middle-income, and low-income countries: a systematic review and meta-analyses. *Lancet Respir Med* 2024; **12**(4): 281-93 https://pubmed.ncbi.nlm.nih.gov/38310914.
39. Paulin LM, Diette GB, Blanc PD, et al. Occupational exposures are associated with worse morbidity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015; **191**(5): 557-65 https://pubmed.ncbi.nlm.nih.gov/25562375.
40. Eisner MD, Anthonisen N, Coultas D, et al. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; **182**(5): 693-718 https://pubmed.ncbi.nlm.nih.gov/20802169.
41. Lytras T, Kogevinas M, Kromhout H, et al. Occupational exposures and 20-year incidence of COPD: the European Community Respiratory Health Survey. *Thorax* 2018; **73**(11): 1008-15 https://pubmed.ncbi.nlm.nih.gov/29574416.
42. Faruque MO, Boezen HM, Kromhout H, Vermeulen R, Bultmann U, Vonk JM. Airborne occupational exposures and the risk of developing respiratory symptoms and airway obstruction in the Lifelines Cohort Study. *Thorax* 2021; **76**(8): 790-7 https://pubmed.ncbi.nlm.nih.gov/33653936.
43. De Matteis S, Jarvis D, Darnton A, 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 https://pubmed.ncbi.nlm.nih.gov/31248951.
44. Marchetti N, Garshick E, Kinney GL, et al. Association between occupational exposure and lung function, respiratory symptoms, and high-resolution computed tomography imaging in COPDGene. *Am J Respir Crit Care Med* 2014; **190**(7): 756-62 https://pubmed.ncbi.nlm.nih.gov/25133327.
45. Rahman S, Das A, Islam AN, et al. Prevalence and risk factors for the development of COPD among workers in stone quarries: a cross-sectional study. *BMC Pulm Med* 2025; **25**(1): 384 https://pubmed.ncbi.nlm.nih.gov/40790194.
46. Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2002; **156**(8): 738-46 https://pubmed.ncbi.nlm.nih.gov/12370162.
47. Balmes J, Becklake M, Blanc P, et al. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003; **167**(5): 787-97 https://pubmed.ncbi.nlm.nih.gov/12598220.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

48. Institute for Health Metrics and Evaluation (IHME). GBD Compare Viz Hub Website: https://vizhub.healthdata.org/gbd-compare/ [accessed Oct 2026].
49. GBD Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396**(10258): 1223-49 https://pubmed.ncbi.nlm.nih.gov/33069327.
50. Liao J, Zeng L, Huang X, et al. Burden of Chronic Obstructive Pulmonary Disease in China: A Global Burden of Disease Study on Temporal Trends, Risk Factor Contributions, and Projected Disease Burden from 1990 to 2030. *COPD* 2025; **22**(1): 2531016 https://pubmed.ncbi.nlm.nih.gov/40658101.
51. Guo C, Zhang Z, Lau AKH, et al. Effect of long-term exposure to fine particulate matter on lung function decline and risk of chronic obstructive pulmonary disease in Taiwan: a longitudinal, cohort study. *Lancet Planet Health* 2018; **2**(3): e114-e25 https://pubmed.ncbi.nlm.nih.gov/29615226.
52. Bourbeau J, Doiron D, Biswas S, et al. Ambient Air Pollution and Dysanapsis: Associations with Lung Function and Chronic Obstructive Pulmonary Disease in the Canadian Cohort Obstructive Lung Disease Study. *Am J Respir Crit Care Med* 2022; **206**(1): 44-55 https://pubmed.ncbi.nlm.nih.gov/35380941.
53. Ross BA, Doiron D, Benedetti A, et al. Short-term air pollution exposure and exacerbation events in mild to moderate COPD: a case-crossover study within the CanCOLD cohort. *Thorax* 2023; **78**(10): 974-82 https://pubmed.ncbi.nlm.nih.gov/37147124.
54. Regan EA, Lowe ME, Make BJ, et al. Early Evidence of Chronic Obstructive Pulmonary Disease Obscured by Race-Specific Prediction Equations. *Am J Respir Crit Care Med* 2024; **209**(1): 59-69 https://pubmed.ncbi.nlm.nih.gov/37611073.
55. Robichaux CE, Baldomero AK, Gravely AA, Wendt CH, Berman JD. Fine Particulate Matter and Mortality in Chronic Obstructive Pulmonary Disease with Multimorbidity. *Ann Am Thorac Soc* 2025; **22**(9): 1335-42 https://pubmed.ncbi.nlm.nih.gov/40315387.
56. Yu W, Thurston GD. Reductions in Respiratory Hospital Visits after a Coal Coking Plant Closure: A Natural Experiment. *Am J Respir Crit Care Med* 2025; **211**(11): 2072-85 https://pubmed.ncbi.nlm.nih.gov/40691837.
57. Cho MH, Hobbs BD, Silverman EK. Genetics of chronic obstructive pulmonary disease: understanding the pathobiology and heterogeneity of a complex disorder. *Lancet Respir Med* 2022; **10**(5): 485-96 https://pubmed.ncbi.nlm.nih.gov/35427534.
58. McCloskey SC, Patel BD, Hinchliffe SJ, Reid ED, Wareham NJ, Lomas DA. Siblings of patients with severe chronic obstructive pulmonary disease have a significant risk of airflow obstruction. *Am J Respir Crit Care Med* 2001; **164**(8 Pt 1): 1419-24 https://pubmed.ncbi.nlm.nih.gov/11704589.
59. Stoller JK, Aboussouan LS. Alpha1-antitrypsin deficiency. *Lancet* 2005; **365**(9478): 2225-36 https://pubmed.ncbi.nlm.nih.gov/15978931.
60. Blanco I, Diego I, Bueno P, Perez-Holanda S, Casas-Maldonado F, Miravitlles M. Prevalence of alpha(1)-antitrypsin PiZZ genotypes in patients with COPD in Europe: a systematic review. *Eur Respir Rev* 2020; **29**(157): 200014 https://pubmed.ncbi.nlm.nih.gov/32699024.
61. Martinez-Gonzalez C, Blanco I, Diego I, Bueno P, Miravitlles M. Estimated Prevalence and Number of PiMZ Genotypes of Alpha-1 Antitrypsin in Seventy-Four Countries Worldwide. *Int J Chron Obstruct Pulmon Dis* 2021; **16**: 2617-30 https://pubmed.ncbi.nlm.nih.gov/34556982.
62. Franciosi AN, Hobbs BD, McElvaney OJ, et al. Clarifying the Risk of Lung Disease in SZ Alpha-1 Antitrypsin Deficiency. *Am J Respir Crit Care Med* 2020; **202**(1): 73-82 https://pubmed.ncbi.nlm.nih.gov/32197047.
63. Molloy K, Hersh CP, Morris VB, et al. Clarification of the risk of chronic obstructive pulmonary disease in alpha1-antitrypsin deficiency PiMZ heterozygotes. *Am J Respir Crit Care Med* 2014; **189**(4): 419-27 https://pubmed.ncbi.nlm.nih.gov/24428606.
64. Stockley RA. Alpha-1 Antitrypsin Deficiency: The Learning Goes On. *Am J Respir Crit Care Med* 2020; **202**(1): 6-7 https://pubmed.ncbi.nlm.nih.gov/32343597.
65. Hunninghake GM, Cho MH, Tesfaigzi Y, et al. MMP12, lung function, and COPD in high-risk populations. *N Engl J Med* 2009; **361**(27): 2599-608 https://pubmed.ncbi.nlm.nih.gov/20018959.
66. Ding Z, Wang K, Li J, Tan Q, Tan W, Guo G. Association between glutathione S-transferase gene M1 and T1 polymorphisms and chronic obstructive pulmonary disease risk: A meta-analysis. *Clin Genet* 2019; **95**(1): 53-62 https://pubmed.ncbi.nlm.nih.gov/29704242.
67. Cho MH, Boutaoui N, Klanderman BJ, et al. Variants in FAM13A are associated with chronic obstructive pulmonary disease. *Nat Genet* 2010; **42**(3): 200-2 https://pubmed.ncbi.nlm.nih.gov/20173748.
68. Pillai SG, Ge D, Zhu G, et al. A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci. *PLoS Genet* 2009; **5**(3): e1000421 https://pubmed.ncbi.nlm.nih.gov/19300482.
69. Soler Artigas M, Wain LV, Repapi E, et al. Effect of five genetic variants associated with lung function on the risk of chronic obstructive lung disease, and their joint effects on lung function. *Am J Respir Crit Care Med* 2011; **184**(7): 786-95 https://pubmed.ncbi.nlm.nih.gov/21965014.
70. Repapi E, Sayers I, Wain LV, et al. Genome-wide association study identifies five loci associated with lung function. *Nat Genet* 2010; **42**(1): 36-44 https://pubmed.ncbi.nlm.nih.gov/20010834.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

71. Cho MH, McDonald ML, Zhou X, et al. Risk loci for chronic obstructive pulmonary disease: a genome-wide association study and meta-analysis. *Lancet Respir Med* 2014; **2**(3): 214-25 https://pubmed.ncbi.nlm.nih.gov/24621683.
72. Martinez FJ, Agusti A, Celli BR, et al. Treatment Trials in Young Patients with Chronic Obstructive Pulmonary Disease and Pre-Chronic Obstructive Pulmonary Disease Patients: Time to Move Forward. *Am J Respir Crit Care Med* 2022; **205**(3): 275-87 https://pubmed.ncbi.nlm.nih.gov/34672872.
73. Wan ES, Castaldi PJ, Cho MH, et al. Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry (PRISm) in COPDGene. *Respir Res* 2014; **15**(1): 89 https://pubmed.ncbi.nlm.nih.gov/25096860.
74. Agusti A, Faner R. COPD beyond smoking: new paradigm, novel opportunities. *Lancet Respir Med* 2018; **6**(5): 324-6 https://pubmed.ncbi.nlm.nih.gov/29496484.
75. Wang Z, Lin J, Liang L, et al. Global, regional, and national burden of chronic obstructive pulmonary disease and its attributable risk factors from 1990 to 2021: an analysis for the Global Burden of Disease Study 2021. *Respir Res* 2025; **26**(1): 2 https://pubmed.ncbi.nlm.nih.gov/39748260.
76. Adeloye D, Song P, Zhu Y, et al. 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): 447-58 https://pubmed.ncbi.nlm.nih.gov/35279265.
77. Boers E, Barrett M, Su JG, et al. Global Burden of Chronic Obstructive Pulmonary Disease Through 2050. *JAMA Netw Open* 2023; **6**(12): e2346598 https://pubmed.ncbi.nlm.nih.gov/38060225.
78. de Oca MM, Perez-Padilla R, Celli B, et al. The global burden of COPD: epidemiology and effect of prevention strategies. *Lancet Respir Med* 2025; **13**(8): 709-24 https://pubmed.ncbi.nlm.nih.gov/40684784.
79. GBD Causes of Death Collaborators. Global burden of 292 causes of death in 204 countries and territories and 660 subnational locations, 1990-2023: a systematic analysis for the Global Burden of Disease Study 2023. *Lancet* 2025; **406**(10513): 1811-72 https://pubmed.ncbi.nlm.nih.gov/41092928.
80. Cao W, Zheng J, Li Q, et al. Global, regional, and national temporal trends in prevalence, deaths and disability-adjusted life years for chronic pulmonary disease, 1990-2021: an age-period-cohort analysis based on the global burden of disease study 2021. *Front Med (Lausanne)* 2025; **12**: 1554442 https://pubmed.ncbi.nlm.nih.gov/40103794.
81. World Health Organization. World Health Organization (WHO) Website [accessed Oct 2026]. http://www.who.int.
82. Burney P, Jarvis D, Perez-Padilla R. The global burden of chronic respiratory disease in adults. *Int J Tuberc Lung Dis* 2015; **19**(1): 10-20 https://pubmed.ncbi.nlm.nih.gov/25519785.
83. Marshall DC, Al Omari O, Goodall R, et al. Trends in prevalence, mortality, and disability-adjusted life-years relating to chronic obstructive pulmonary disease in Europe: an observational study of the global burden of disease database, 2001-2019. *BMC Pulm Med* 2022; **22**(1): 289 https://pubmed.ncbi.nlm.nih.gov/35902833.
84. Menezes AM, Perez-Padilla R, Jardim JR, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet* 2005; **366**(9500): 1875-81 https://pubmed.ncbi.nlm.nih.gov/16310554.
85. Burney P, Patel J, Minelli C, et al. Prevalence and Population-Attributable Risk for Chronic Airflow Obstruction in a Large Multinational Study. *Am J Respir Crit Care Med* 2021; **203**(11): 1353-65 https://pubmed.ncbi.nlm.nih.gov/33171069.
86. Safiri S, Carson-Chahhoud K, Noori M, et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. *BMJ* 2022; 10.1136/bmj-2021-069679: e069679.
87. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006; **28**(3): 523-32 https://pubmed.ncbi.nlm.nih.gov/16611654.
88. Lamprecht B, Soriano JB, Studnicka M, et al. Determinants of underdiagnosis of COPD in national and international surveys. *Chest* 2015; **148**(4): 971-85 https://pubmed.ncbi.nlm.nih.gov/25950276.
89. Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. *J Glob Health* 2015; **5**(2): 020415 https://pubmed.ncbi.nlm.nih.gov/26755942.
90. Varmaghani M, Dehghani M, Heidari E, Sharifi F, Moghaddam SS, Farzadfar F. Global prevalence of chronic obstructive pulmonary disease: systematic review and meta-analysis. *East Mediterr Health J* 2019; **25**(1): 47-57 https://pubmed.ncbi.nlm.nih.gov/30919925.
91. Ntritsos G, Franek J, Belbasis L, et al. Gender-specific estimates of COPD prevalence: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2018; **13**: 1507-14 https://pubmed.ncbi.nlm.nih.gov/29785100.
92. Divo MJ, Celli BR, Poblador-Plou B, et al. Chronic Obstructive Pulmonary Disease (COPD) as a disease of early aging: Evidence from the EpiChron Cohort. *PLoS One* 2018; **13**(2): e0193143 https://pubmed.ncbi.nlm.nih.gov/29470502.
93. Agusti A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *Lancet Respir Med* 2017; **5**(12): 935-45 https://pubmed.ncbi.nlm.nih.gov/29150410.
94. 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): 631-9 https://pubmed.ncbi.nlm.nih.gov/26208998.
95. Mannino DM, Higuchi K, Yu TC, et al. Economic Burden of COPD in the Presence of Comorbidities. *Chest* 2015; **148**(1): 138-50 https://pubmed.ncbi.nlm.nih.gov/25675282.
96. Bhatt SP, Sun Y, Wang Y, et al. Life Expectancy in Chronic Obstructive Pulmonary Disease. *JAMA Intern Med* 2026; **186**(7): 852-60 https://pubmed.ncbi.nlm.nih.gov/42143630.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

97. World Health Organization. Projections of mortality and causes of death, 2016 and 2060, online information available here: https://colinmathers.com/2022/05/10/projections-of-global-deaths-from-2016-to-2060/ [accessed Oct 2026].
98. World Health Organization. Evidence-Informed Policy Network: EVIPnet in Action [accessed Oct 2026]. https://www.who.int/initiatives/evidence-informed-policy-network.
99. Duong M, Islam S, Rangarajan S, et al. Global differences in lung function by region (PURE): an international, community-based prospective study. *Lancet Respir Med* 2013; **1**(8): 599-609 https://pubmed.ncbi.nlm.nih.gov/24461663.
100. Schneider A, Gantner L, Maag I, Borst MM, Wensing M, Szecsenyi J. Are ICD-10 codes appropriate for performance assessment in asthma and COPD in general practice? Results of a cross sectional observational study. *BMC Health Serv Res* 2005; **5**(1): 11 https://pubmed.ncbi.nlm.nih.gov/15683548.
101. Cooke CR, Joo MJ, Anderson SM, et al. The validity of using ICD-9 codes and pharmacy records to identify patients with chronic obstructive pulmonary disease. *BMC Health Serv Res* 2011; **11**: 37 https://pubmed.ncbi.nlm.nih.gov/21324188.
102. Stein BD, Bautista A, Schumock GT, et al. The validity of International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes for identifying patients hospitalized for COPD exacerbations. *Chest* 2012; **141**(1): 87-93 https://pubmed.ncbi.nlm.nih.gov/21757568.
103. Jensen HH, Godtfredsen NS, Lange P, Vestbo J. Potential misclassification of causes of death from COPD. *Eur Respir J* 2006; **28**(4): 781-5 https://pubmed.ncbi.nlm.nih.gov/16807258.
104. Forum of International Respiratory Societies (FIRS). The global impact of respiratory disease. Third Edition. ERS, 2021 available at: https://firsnet.org/wp-content/uploads/2025/01/FIRS_Master_09202021.pdf [accessed Oct 2026].
105. Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *Clinicoecon Outcomes Res* 2013; **5**: 235-45 https://pubmed.ncbi.nlm.nih.gov/23818799.
106. Zafari Z, Li S, Eakin MN, Bellanger M, Reed RM. Projecting Long-term Health and Economic Burden of COPD in the United States. *Chest* 2021; **159**(4): 1400-10 https://pubmed.ncbi.nlm.nih.gov/33011203.
107. Gutiérrez-Villegas C, Herrero-Montes M, Fernández Cacho LM, et al. Global Economic and Social Burden of Chronic Obstructive Pulmonary Disease: A Systematic Review (2020-2024). *Int J Chron Obstruct Pulmon Dis* 2026; **21**: 608107 https://pubmed.ncbi.nlm.nih.gov/42292532.
108. Boers E, Allen A, Barrett M, et al. Forecasting the Global Economic and Health Burden of COPD From 2025 Through 2050. *Chest* 2025; **168**(4): 880-9 https://pubmed.ncbi.nlm.nih.gov/40254152.
109. Gutierrez Villegas C, Paz-Zulueta M, Herrero-Montes M, Paras-Bravo P, Madrazo Perez M. Cost analysis of chronic obstructive pulmonary disease (COPD): a systematic review. *Health Econ Rev* 2021; **11**(1): 31 https://pubmed.ncbi.nlm.nih.gov/34403023.
110. Stolbrink M, Thomson H, Hadfield RM, et al. The availability, cost, and affordability of essential medicines for asthma and COPD in low-income and middle-income countries: a systematic review. *Lancet Glob Health* 2022; **10**(10): e1423-e42 https://pubmed.ncbi.nlm.nih.gov/36113528.
111. Sin DD, Stafinski T, Ng YC, Bell NR, Jacobs P. The impact of chronic obstructive pulmonary disease on work loss in the United States. *Am J Respir Crit Care Med* 2002; **165**(5): 704-7 https://pubmed.ncbi.nlm.nih.gov/11874818.
112. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997; **349**(9064): 1498-504 https://pubmed.ncbi.nlm.nih.gov/9167458.
113. GBD Forecasting Collaborators. Burden of disease scenarios for 204 countries and territories, 2022-2050: a forecasting analysis for the Global Burden of Disease Study 2021. *Lancet* 2024; **403**(10440): 2204-56 https://pubmed.ncbi.nlm.nih.gov/38762325.
114. Deng Y, Zhu Y, Chen C, Xu W, Yao W. Divergent Trajectories and Risk Factor Attribution of Chronic Obstructive Pulmonary Disease Burden in China and the United States, 1990-2023: An Age-Period-Cohort Analysis with Projections to 2035 Based on the Global Burden of Disease Study 2023. *Int J Chron Obstruct Pulmon Dis* 2026; **21**: 581670 https://pubmed.ncbi.nlm.nih.gov/41853750.
115. Herrera Lopez AB, Torres-Duque CA, Casas Herrera A, et al. Frequency of Exacerbations of Chronic Obstructive Pulmonary Disease Associated with the Long-Term Exposure to Air Pollution in the AIREPOC Cohort. *Int J Chron Obstruct Pulmon Dis* 2025; **20**: 425-35 https://pubmed.ncbi.nlm.nih.gov/40012686.
116. Lange P, Celli B, Agusti A, et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2015; **373**(2): 111-22 https://pubmed.ncbi.nlm.nih.gov/26154786.
117. Han MK, Aaron SD, Bui D, et al. A GOLD Science Committee Report on Universal Longitudinal Spirometry: A New Paradigm. *American Journal of Respiratory and Critical Care Medicine* 2026; 10.1093/ajrccm/aamag432:
118. Agusti A, Faner R. Lung function trajectories in health and disease. *Lancet Respir Med* 2019; **7**(4): 358-64 https://pubmed.ncbi.nlm.nih.gov/30765254.
119. Bertels X, Ross JC, Faner R, et al. Clinical relevance of lung function trajectory clusters in middle-aged and older adults. *ERJ Open Res* 2024; **10**(1): https://pubmed.ncbi.nlm.nih.gov/38333649.
120. Odling M, Andersson Franko M, Backman H, Vanfleteren L, Stridsman C, Konradsen JR. Gestational Age and Birthweight Predict Airflow Obstruction: A Study from the Swedish National Airway Register. *Ann Am Thorac Soc* 2025; **22**(10): 1522-30 https://pubmed.ncbi.nlm.nih.gov/40466046.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

121. Colak Y, Nordestgaard BG, Vestbo J, Lange P, Afzal S. Relationship between supernormal lung function and long-term risk of hospitalisations and mortality: a population-based cohort study. *Eur Respir J* 2021; **57**(4): 2004055 https://pubmed.ncbi.nlm.nih.gov/33243848.
122. Agusti A, Fabbri LM, Baraldi E, et al. Spirometry: A practical lifespan predictor of global health and chronic respiratory and non-respiratory diseases. *Eur J Intern Med* 2021; **89**: 3-9 https://pubmed.ncbi.nlm.nih.gov/34016514.
123. Melen E, Faner R, Allinson JP, et al. Lung-function trajectories: relevance and implementation in clinical practice. *Lancet* 2024; **403**(10435): 1494-503 https://pubmed.ncbi.nlm.nih.gov/38490231.
124. ERS CADSET collaboration. Lungtracker website: Lung Function Tracker. 2024. https://gli-calculator.ersnet.org/lung_tracker/ [accessed Oct 2026].
125. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007; **370**(9589): 758-64 https://pubmed.ncbi.nlm.nih.gov/17765525.
126. Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and Radiologic Disease in Smokers With Normal Spirometry. *JAMA Intern Med* 2015; **175**(9): 1539-49 https://pubmed.ncbi.nlm.nih.gov/26098755.
127. Lawlor DA, Ebrahim S, Davey Smith G. Association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis. *Thorax* 2005; **60**(10): 851-8 https://pubmed.ncbi.nlm.nih.gov/16055617.
128. Green M, Mead J, Turner JM. Variability of maximum expiratory flow-volume curves. *J Appl Physiol* 1974; **37**(1): 67-74 https://pubmed.ncbi.nlm.nih.gov/4836570.
129. Ito K, Barnes PJ. COPD as a disease of accelerated lung aging. *Chest* 2009; **135**(1): 173-80 https://pubmed.ncbi.nlm.nih.gov/19136405.
130. Martin TR, Feldman HA, Fredberg JJ, Castile RG, Mead J, Wohl ME. Relationship between maximal expiratory flows and lung volumes in growing humans. *J Appl Physiol (1985)* 1988; **65**(2): 822-8 https://pubmed.ncbi.nlm.nih.gov/3170432.
131. Rawlins EL, Okubo T, Xue Y, et al. The role of Scgb1a1+ Clara cells in the long-term maintenance and repair of lung airway, but not alveolar, epithelium. *Cell Stem Cell* 2009; **4**(6): 525-34 https://pubmed.ncbi.nlm.nih.gov/19497281.
132. Smith BM, Kirby M, Hoffman EA, et al. Association of Dysanapsis With Chronic Obstructive Pulmonary Disease Among Older Adults. *JAMA* 2020; **323**(22): 2268-80 https://pubmed.ncbi.nlm.nih.gov/32515814.
133. Dharmage SC, Bui DS, Walters EH, et al. Lifetime spirometry patterns of obstruction and restriction, and their risk factors and outcomes: a prospective cohort study. *Lancet Respir Med* 2023; **11**(3): 273-82 https://pubmed.ncbi.nlm.nih.gov/36244396.
134. Bose S, Pascoe C, McEvoy C. Lifetime lung function trajectories and COPD: when the train derails. *Lancet Respir Med* 2023; **11**(3): 221-2 https://pubmed.ncbi.nlm.nih.gov/36244395.
135. Lilleboe HL, Engeset MS, Clemm HH, et al. Expiratory airflow limitation in adults born extremely preterm: A systematic review and meta-analysis. *Paediatr Respir Rev* 2024; **50**: 2-22 https://pubmed.ncbi.nlm.nih.gov/38490917.
136. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977; **1**(6077): 1645-8 https://pubmed.ncbi.nlm.nih.gov/871704.
137. Mercado N, Ito K, Barnes PJ. Accelerated ageing of the lung in COPD: new concepts. *Thorax* 2015; **70**(5): 482-9 https://pubmed.ncbi.nlm.nih.gov/25739910.
138. Cordoba-Lanus E, Cazorla-Rivero S, Garcia-Bello MA, et al. Telomere length dynamics over 10-years and related outcomes in patients with COPD. *Respir Res* 2021; **22**(1): 56 https://pubmed.ncbi.nlm.nih.gov/33608013.
139. Hernandez Cordero AI, Yang CX, Li X, et al. Epigenetic marker of telomeric age is associated with exacerbations and hospitalizations in chronic obstructive pulmonary disease. *Respir Res* 2021; **22**(1): 316 https://pubmed.ncbi.nlm.nih.gov/34937547.
140. Hernandez Cordero AI, Yang CX, Milne S, et al. Epigenetic blood biomarkers of ageing and mortality in COPD. *Eur Respir J* 2021; **58**(6): https://pubmed.ncbi.nlm.nih.gov/34561282.
141. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ* 1991; **303**(6804): 671-5 https://pubmed.ncbi.nlm.nih.gov/1912913.
142. Todisco T, de Benedictis FM, Iannacci L, et al. Mild prematurity and respiratory functions. *Eur J Pediatr* 1993; **152**(1): 55-8 https://pubmed.ncbi.nlm.nih.gov/8444206.
143. Smith BM, Traboulsi H, Austin JHM, et al. Human airway branch variation and chronic obstructive pulmonary disease. *Proc Natl Acad Sci U S A* 2018; **115**(5): E974-E81 https://pubmed.ncbi.nlm.nih.gov/29339516.
144. Vameghestahbanati M, Kirby M, Tanabe N, et al. Central Airway Tree Dysanapsis Extends to the Peripheral Airways. *Am J Respir Crit Care Med* 2021; **203**(3): 378-81 https://pubmed.ncbi.nlm.nih.gov/33137261.
145. Leary D, Bhatawadekar SA, Parraga G, Maksym GN. Modeling stochastic and spatial heterogeneity in a human airway tree to determine variation in respiratory system resistance. *J Appl Physiol (1985)* 2012; **112**(1): 167-75 https://pubmed.ncbi.nlm.nih.gov/21998266.
146. Tawhai MH, Hunter P, Tschirren J, Reinhardt J, McLennan G, Hoffman EA. CT-based geometry analysis and finite element models of the human and ovine bronchial tree. *J Appl Physiol (1985)* 2004; **97**(6): 2310-21 https://pubmed.ncbi.nlm.nih.gov/15322064.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

147. Young HM, Guo F, Eddy RL, Maksym G, Parraga G. Oscillometry and pulmonary MRI measurements of ventilation heterogeneity in obstructive lung disease: relationship to quality of life and disease control. *J Appl Physiol (1985)* 2018; **125**(1): 73-85 https://pubmed.ncbi.nlm.nih.gov/29543132.
148. Agusti A, Hogg JC. Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2019; **381**(13): 1248-56 https://pubmed.ncbi.nlm.nih.gov/31553836.
149. Celli BR, Agusti A. COPD: time to improve its taxonomy? *ERJ Open Res* 2018; **4**(1): 00132-2017 https://pubmed.ncbi.nlm.nih.gov/29707563.
150. Martinez FJ, Han MK, Allinson JP, et al. At the Root: Defining and Halting Progression of Early Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2018; **197**(12): 1540-51 https://pubmed.ncbi.nlm.nih.gov/29406779.
151. Colak Y, Afzal S, Nordestgaard BG, Lange P, Vestbo J. Importance of Early COPD in Young Adults for Development of Clinical COPD: Findings from the Copenhagen General Population Study. *Am J Respir Crit Care Med* 2021; **203**(10): 1245-56 https://pubmed.ncbi.nlm.nih.gov/33142077.
152. Cosio BG, Pascual-Guardia S, Borras-Santos A, et al. Phenotypic characterisation of early COPD: a prospective case-control study. *ERJ Open Res* 2020; **6**(4): 00047-2020 https://pubmed.ncbi.nlm.nih.gov/33043045.
153. Han MK, Agusti A, Celli BR, et al. From GOLD 0 to Pre-COPD. *Am J Respir Crit Care Med* 2021; **203**(4): 414-23 https://pubmed.ncbi.nlm.nih.gov/33211970.
154. Colak Y, Lange P, Vestbo J, Nordestgaard BG, Afzal S. Susceptible Young Adults and Development of Chronic Obstructive Pulmonary Disease Later in Life. *Am J Respir Crit Care Med* 2024; **210**(5): 607-17 https://pubmed.ncbi.nlm.nih.gov/38364200.
155. Buhr RG, Barjaktarevic IZ, Quibrera PM, et al. Reversible Airflow Obstruction Predicts Future Chronic Obstructive Pulmonary Disease Development in the SPIROMICS Cohort: An Observational Cohort Study. *Am J Respir Crit Care Med* 2022; **206**(5): 554-62 https://pubmed.ncbi.nlm.nih.gov/35549640.
156. Pérez-Padilla R, de Oca MM, Thirion-Romero I, et al. Prognostic impact of pre- and post-bronchodilator airflow obstruction and post-bronchodilator reference values in a population-based study. On behalf of the PLATINO group. *Respir Res Clin Pract* 2026; **52**(2): e20250275 https://pubmed.ncbi.nlm.nih.gov/42781375.
157. Charbonnier JP, Pompe E, Moore C, et al. Airway wall thickening on CT: Relation to smoking status and severity of COPD. *Respir Med* 2019; **146**: 36-41 https://pubmed.ncbi.nlm.nih.gov/30665516.
158. Oelsner EC, Smith BM, Hoffman EA, et al. Associations between emphysema-like lung on CT and incident airflow limitation: a general population-based cohort study. *Thorax* 2018; **73**(5): 486-8 https://pubmed.ncbi.nlm.nih.gov/29074811.
159. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. The Presence of Chronic Mucus Hypersecretion across Adult Life in Relation to Chronic Obstructive Pulmonary Disease Development. *Am J Respir Crit Care Med* 2016; **193**(6): 662-72 https://pubmed.ncbi.nlm.nih.gov/26695373.
160. Harvey BG, Strulovici-Barel Y, Kaner RJ, et al. Risk of COPD with obstruction in active smokers with normal spirometry and reduced diffusion capacity. *Eur Respir J* 2015; **46**(6): 1589-97 https://pubmed.ncbi.nlm.nih.gov/26541521.
161. Petersen H, Sood A, Meek PM, et al. Rapid lung function decline in smokers is a risk factor for COPD and is attenuated by angiotensin-converting enzyme inhibitor use. *Chest* 2014; **145**(4): 695-703 https://pubmed.ncbi.nlm.nih.gov/24008986.
162. Petersen H, Sood A, Polverino F, et al. The Course of Lung Function in Middle-aged Heavy Smokers: Incidence and Time to Early Onset of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2018; **198**(11): 1449-51 https://pubmed.ncbi.nlm.nih.gov/30114375.
163. Zhang N, Gargurevich N, Murray S, et al. Mapping the trajectory from pre-COPD to COPD: predictive value of symptoms, imaging, and physiologic abnormalities. *Ann Am Thorac Soc* 2026; **23**(3): 468-71 https://pubmed.ncbi.nlm.nih.gov/41842738.
164. Wan ES. The Clinical Spectrum of PRISm. *Am J Respir Crit Care Med* 2022; **206**(5): 524-5 https://pubmed.ncbi.nlm.nih.gov/35612910.
165. Higbee DH, Granell R, Davey Smith G, Dodd JW. Prevalence, risk factors, and clinical implications of preserved ratio impaired spirometry: a UK Biobank cohort analysis. *Lancet Respir Med* 2022; **10**(2): 149-57 https://pubmed.ncbi.nlm.nih.gov/34739861.
166. Perez-Padilla R, Montes de Oca M, Thirion-Romero I, et al. Trajectories of Spirometric Patterns, Obstructive and PRISm, in a Population-Based Cohort in Latin America. *Int J Chron Obstruct Pulmon Dis* 2023; **18**: 1277-85 https://pubmed.ncbi.nlm.nih.gov/37366430.
167. Wan ES, Balte P, Schwartz JE, et al. Association Between Preserved Ratio Impaired Spirometry and Clinical Outcomes in US Adults. *JAMA* 2021; **326**(22): 2287-98 https://pubmed.ncbi.nlm.nih.gov/34905031.
168. Wijnant SRA, De Roos E, Kavousi M, et al. Trajectory and mortality of preserved ratio impaired spirometry: the Rotterdam Study. *Eur Respir J* 2020; **55**(1): https://pubmed.ncbi.nlm.nih.gov/31601717.
169. Washio Y, Sakata S, Fukuyama S, et al. Risks of Mortality and Airflow Limitation in Japanese Individuals with Preserved Ratio Impaired Spirometry. *Am J Respir Crit Care Med* 2022; **206**(5): 563-72 https://pubmed.ncbi.nlm.nih.gov/35549659.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

170. Marott JL, Ingebrigtsen TS, Colak Y, Vestbo J, Lange P. Trajectory of Preserved Ratio Impaired Spirometry: Natural History and Long-Term Prognosis. *Am J Respir Crit Care Med* 2021; **204**(8): 910-20 https://pubmed.ncbi.nlm.nih.gov/34233141.
171. Zheng J, Zhou R, Zhang Y, et al. Preserved Ratio Impaired Spirometry in Relationship to Cardiovascular Outcomes: A Large Prospective Cohort Study. *Chest* 2023; **163**(3): 610-23 https://pubmed.ncbi.nlm.nih.gov/36372304.
172. Kogo M, Sato S, Muro S, et al. Longitudinal Changes and Association of Respiratory Symptoms with Preserved Ratio Impaired Spirometry (PRISm): The Nagahama Study. *Ann Am Thorac Soc* 2023; **20**(11): 1578-86 https://pubmed.ncbi.nlm.nih.gov/37560979.
173. Phillips DB, James MD, Vincent SG, et al. Physiological Characterization of Preserved Ratio Impaired Spirometry in the CanCOLD Study: Implications for Exertional Dyspnea and Exercise Intolerance. *Am J Respir Crit Care Med* 2024; **209**(11): 1314-27 https://pubmed.ncbi.nlm.nih.gov/38170674.
174. Han MK, Ye W, Wang D, et al. Bronchodilators in Tobacco-Exposed Persons with Symptoms and Preserved Lung Function. *N Engl J Med* 2022; **387**(13): 1173-84 https://pubmed.ncbi.nlm.nih.gov/36066078.
175. Silva GE, Sherrill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. *Chest* 2004; **126**(1): 59-65 https://pubmed.ncbi.nlm.nih.gov/15249443.
176. Vonk JM, Jongepier H, Panhuysen CI, Schouten JP, Bleecker ER, Postma DS. Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. *Thorax* 2003; **58**(4): 322-7 https://pubmed.ncbi.nlm.nih.gov/12668795.
177. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; **339**(17): 1194-200 https://pubmed.ncbi.nlm.nih.gov/9780339.
178. McGeachie MJ, Yates KP, Zhou X, et al. Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma. *N Engl J Med* 2016; **374**(19): 1842-52 https://pubmed.ncbi.nlm.nih.gov/27168434.
179. Silva J, Hipolito N, Machado P, Flora S, Cruz J. Technological features of smartphone apps for physical activity promotion in patients with CxsOPD: A systematic review. *Pulmonology* 2025; **31**(1): 2416796 https://pubmed.ncbi.nlm.nih.gov/37394341.
180. de Marco R, Accordini S, Marcon A, et al. Risk factors for chronic obstructive pulmonary disease in a European cohort of young adults. *Am J Respir Crit Care Med* 2011; **183**(7): 891-7 https://pubmed.ncbi.nlm.nih.gov/20935112.
181. Fabbri LM, Romagnoli M, Corbetta L, et al. Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; **167**(3): 418-24 https://pubmed.ncbi.nlm.nih.gov/12426229.
182. To T, Zhu J, Larsen K, et al. Progression from Asthma to Chronic Obstructive Pulmonary Disease. Is Air Pollution a Risk Factor? *Am J Respir Crit Care Med* 2016; **194**(4): 429-38 https://pubmed.ncbi.nlm.nih.gov/26950751.
183. Rijcken B, Schouten JP, Weiss ST, Speizer FE, van der Lende R. The relationship of nonspecific bronchial responsiveness to respiratory symptoms in a random population sample. *Am Rev Respir Dis* 1987; **136**(1): 62-8 https://pubmed.ncbi.nlm.nih.gov/3605843.
184. Hospers JJ, Postma DS, Rijcken B, Weiss ST, Schouten JP. Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study. *Lancet* 2000; **356**(9238): 1313-7 https://pubmed.ncbi.nlm.nih.gov/11073020.
185. Tashkin DP, Altose MD, Connett JE, Kanner RE, Lee WW, Wise RA. Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. The Lung Health Study Research Group. *Am J Respir Crit Care Med* 1996; **153**(6 Pt 1): 1802-11 https://pubmed.ncbi.nlm.nih.gov/8665038.
186. de Oca MM, Halbert RJ, Lopez MV, et al. The chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. *Eur Respir J* 2012; **40**(1): 28-36 https://pubmed.ncbi.nlm.nih.gov/22282547.
187. Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010; **11**(1): 122 https://pubmed.ncbi.nlm.nih.gov/20831787.
188. Kim V, Han MK, Vance GB, et al. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. *Chest* 2011; **140**(3): 626-33 https://pubmed.ncbi.nlm.nih.gov/21474571.
189. Lu M, Yao W, Zhong N, et al. Chronic obstructive pulmonary disease in the absence of chronic bronchitis in China. *Respirology* 2010; **15**(7): 1072-8 https://pubmed.ncbi.nlm.nih.gov/20723142.
190. Speizer FE, Fay ME, Dockery DW, Ferris BG, Jr. Chronic obstructive pulmonary disease mortality in six U.S. cities. *Am Rev Respir Dis* 1989; **140**(3 Pt 2): S49-55 https://pubmed.ncbi.nlm.nih.gov/2782760.
191. Trupin L, Earnest G, San Pedro M, et al. The occupational burden of chronic obstructive pulmonary disease. *Eur Respir J* 2003; **22**(3): 462-9 https://pubmed.ncbi.nlm.nih.gov/14516136.
192. Matheson MC, Benke G, Raven J, et al. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. *Thorax* 2005; **60**(8): 645-51 https://pubmed.ncbi.nlm.nih.gov/16061705.
193. Pelkonen M, Notkola IL, Nissinen A, Tukiainen H, Koskela H. Thirty-year cumulative incidence of chronic bronchitis and COPD in relation to 30-year pulmonary function and 40-year mortality: a follow-up in middle-aged rural men. *Chest* 2006; **130**(4): 1129-37 https://pubmed.ncbi.nlm.nih.gov/17035447.
194. Miravitlles M, de la Roza C, Morera J, et al. Chronic respiratory symptoms, spirometry and knowledge of COPD among general population. *Respir Med* 2006; **100**(11): 1973-80 https://pubmed.ncbi.nlm.nih.gov/16626950.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

195. Ehrlich RI, White N, Norman R, et al. Predictors of chronic bronchitis in South African adults. *Int J Tuberc Lung Dis* 2004; **8**(3): 369-76 https://pubmed.ncbi.nlm.nih.gov/15139477.
196. Barish CF, Wu WC, Castell DO. Respiratory complications of gastroesophageal reflux. *Arch Intern Med* 1985; **145**(10): 1882-8 https://pubmed.ncbi.nlm.nih.gov/2864025.
197. Smyrnios NA, Irwin RS, Curley FJ. Chronic cough with a history of excessive sputum production. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Chest* 1995; **108**(4): 991-7 https://pubmed.ncbi.nlm.nih.gov/7555175.
198. Mullen JB, Wright JL, Wiggs BR, Pare PD, Hogg JC. Reassessment of inflammation of airways in chronic bronchitis. *Br Med J (Clin Res Ed)* 1985; **291**(6504): 1235-9 https://pubmed.ncbi.nlm.nih.gov/3933614.
199. Saetta M, Turato G, Facchini FM, et al. Inflammatory cells in the bronchial glands of smokers with chronic bronchitis. *Am J Respir Crit Care Med* 1997; **156**(5): 1633-9 https://pubmed.ncbi.nlm.nih.gov/9372687.
200. Hogg JC, Chu FS, Tan WC, et al. Survival after lung volume reduction in chronic obstructive pulmonary disease: insights from small airway pathology. *Am J Respir Crit Care Med* 2007; **176**(5): 454-9 https://pubmed.ncbi.nlm.nih.gov/17556723.
201. Caramori G, Di Gregorio C, Carlstedt I, et al. Mucin expression in peripheral airways of patients with chronic obstructive pulmonary disease. *Histopathology* 2004; **45**(5): 477-84 https://pubmed.ncbi.nlm.nih.gov/15500651.
202. Okajima Y, Come CE, Nardelli P, et al. Luminal Plugging on Chest CT Scan: Association With Lung Function, Quality of Life, and COPD Clinical Phenotypes. *Chest* 2020; **158**(1): 121-30 https://pubmed.ncbi.nlm.nih.gov/32017932.
203. Dunican EM, Elicker BM, Henry T, et al. Mucus Plugs and Emphysema in the Pathophysiology of Airflow Obstruction and Hypoxemia in Smokers. *Am J Respir Crit Care Med* 2021; **203**(8): 957-68 https://pubmed.ncbi.nlm.nih.gov/33180550.
204. Mettler SK, Nath HP, Grumley S, et al. Silent Airway Mucus Plugs in COPD and Clinical Implications. *Chest* 2024; **166**(5): 1010-9 https://pubmed.ncbi.nlm.nih.gov/38013161.
205. Diaz AA, Orejas JL, Grumley S, et al. Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease. *JAMA* 2023; **329**(21): 1832-9 https://pubmed.ncbi.nlm.nih.gov/37210745.
206. Burgel PR, Martin C. Mucus hypersecretion in COPD: should we only rely on symptoms? *Eur Respir Rev* 2010; **19**(116): 94-6 https://pubmed.ncbi.nlm.nih.gov/20956176.
207. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Chronic bronchitis before age 50 years predicts incident airflow limitation and mortality risk. *Thorax* 2009; **64**(10): 894-900 https://pubmed.ncbi.nlm.nih.gov/19581277.
208. Radicioni G, Ceppe A, Ford AA, et al. Airway mucin MUC5AC and MUC5B concentrations and the initiation and progression of chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med* 2021; **9**(11): 1241-54 https://pubmed.ncbi.nlm.nih.gov/34058148.
209. Kesimer M, Ford AA, Ceppe A, et al. Airway Mucin Concentration as a Marker of Chronic Bronchitis. *N Engl J Med* 2017; **377**(10): 911-22 https://pubmed.ncbi.nlm.nih.gov/28877023.
210. Sherman CB, Xu X, Speizer FE, Ferris BG, Jr., Weiss ST, Dockery DW. Longitudinal lung function decline in subjects with respiratory symptoms. *Am Rev Respir Dis* 1992; **146**(4): 855-9 https://pubmed.ncbi.nlm.nih.gov/1416410.
211. Vestbo J, Lange P. Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 2002; **166**(3): 329-32 https://pubmed.ncbi.nlm.nih.gov/12153965.
212. Dowson LJ, Guest PJ, Stockley RA. The relationship of chronic sputum expectoration to physiologic, radiologic, and health status characteristics in alpha(1)-antitrypsin deficiency (PiZ). *Chest* 2002; **122**(4): 1247-55 https://pubmed.ncbi.nlm.nih.gov/12377849.
213. Vestbo J, Prescott E, Lange P. Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group. *Am J Respir Crit Care Med* 1996; **153**(5): 1530-5 https://pubmed.ncbi.nlm.nih.gov/8630597.
214. Stanescu D, Sanna A, Veriter C, et al. Airways obstruction, chronic expectoration, and rapid decline of FEV1 in smokers are associated with increased levels of sputum neutrophils. *Thorax* 1996; **51**(3): 267-71 https://pubmed.ncbi.nlm.nih.gov/8779129.
215. Peto R, Speizer FE, Cochrane AL, et al. The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease. Results from 20 years of prospective observation. *Am Rev Respir Dis* 1983; **128**(3): 491-500 https://pubmed.ncbi.nlm.nih.gov/6614643.
216. Ebi-Kryston KL. Respiratory symptoms and pulmonary function as predictors of 10-year mortality from respiratory disease, cardiovascular disease, and all causes in the Whitehall Study. *J Clin Epidemiol* 1988; **41**(3): 251-60 https://pubmed.ncbi.nlm.nih.gov/3339378.
217. Ebi-Kryston KL. Predicting 15 year chronic bronchitis mortality in the Whitehall Study. *J Epidemiol Community Health* 1989; **43**(2): 168-72 https://pubmed.ncbi.nlm.nih.gov/2592906.
218. Wiles FJ, Hnizdo E. Relevance of airflow obstruction and mucus hypersecretion to mortality. *Respir Med* 1991; **85**(1): 27-35 https://pubmed.ncbi.nlm.nih.gov/2014356.
219. Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Relation of ventilatory impairment and of chronic mucus hypersecretion to mortality from obstructive lung disease and from all causes. *Thorax* 1990; **45**(8): 579-85 https://pubmed.ncbi.nlm.nih.gov/2402719.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

220. Annesi I, Kauffmann F. Is respiratory mucus hypersecretion really an innocent disorder? A 22-year mortality survey of 1,061 working men. *Am Rev Respir Dis* 1986; **134**(4): 688-93 https://pubmed.ncbi.nlm.nih.gov/3767125.
221. Prescott E, Lange P, Vestbo J. Chronic mucus hypersecretion in COPD and death from pulmonary infection. *Eur Respir J* 1995; **8**(8): 1333-8 https://pubmed.ncbi.nlm.nih.gov/7489800.
222. Kim V, Sternberg AL, Washko G, et al. Severe chronic bronchitis in advanced emphysema increases mortality and hospitalizations. *COPD* 2013; **10**(6): 667-78 https://pubmed.ncbi.nlm.nih.gov/23978192.
223. Wu F, Fan H, Liu J, et al. Association Between Non-obstructive Chronic Bronchitis and Incident Chronic Obstructive Pulmonary Disease and All-Cause Mortality: A Systematic Review and Meta-Analysis. *Front Med (Lausanne)* 2021; **8**: 805192 https://pubmed.ncbi.nlm.nih.gov/35145979.
224. Fortis S, Shannon ZK, Garcia CJ, et al. Association of Nonobstructive Chronic Bronchitis With All-Cause Mortality: A Systematic Literature Review and Meta-analysis. *Chest* 2022; **162**(1): 92-100 https://pubmed.ncbi.nlm.nih.gov/35150657.
225. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. Combined Impact of Smoking and Early-Life Exposures on Adult Lung Function Trajectories. *Am J Respir Crit Care Med* 2017; **196**(8): 1021-30 https://pubmed.ncbi.nlm.nih.gov/28530117.
226. Martinez-Garcia MA, Faner R, Oscullo G, et al. Chronic Bronchial Infection Is Associated with More Rapid Lung Function Decline in Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2022; **19**(11): 1842-7 https://pubmed.ncbi.nlm.nih.gov/35666811.
227. Fan H, Wu F, Liu J, 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 https://pubmed.ncbi.nlm.nih.gov/33842611.
228. Byrne AL, Marais BJ, Mitnick CD, Lecca L, Marks GB. Tuberculosis and chronic respiratory disease: a systematic review. *Int J Infect Dis* 2015; **32**: 138-46 https://pubmed.ncbi.nlm.nih.gov/25809770.
229. Menezes AM, Hallal PC, Perez-Padilla R, et al. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. *Eur Respir J* 2007; **30**(6): 1180-5 https://pubmed.ncbi.nlm.nih.gov/17804445.
230. Jordan TS, Spencer EM, Davies P. Tuberculosis, bronchiectasis and chronic airflow obstruction. *Respirology* 2010; **15**(4): 623-8 https://pubmed.ncbi.nlm.nih.gov/20409028.
231. Kim BG, Shin SH, Lee SK, Kim SH, Lee H. Risk of incident chronic obstructive pulmonary disease during longitudinal follow-up in patients with nontuberculous mycobacterial pulmonary disease. *Respir Res* 2024; **25**(1): 333 https://pubmed.ncbi.nlm.nih.gov/39252048.
232. 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 https://pubmed.ncbi.nlm.nih.gov/29254748.
233. Thudium RF, Ronit A, Afzal S, et al. Faster lung function decline in people living with HIV despite adequate treatment: a longitudinal matched cohort study. *Thorax* 2023; **78**(6): 535-42 https://pubmed.ncbi.nlm.nih.gov/36639241.
234. Hernandez Cordero AI, Yang CX, Obeidat M, et al. DNA methylation is associated with airflow obstruction in patients living with HIV. *Thorax* 2021; **76**(5): 448-55 https://pubmed.ncbi.nlm.nih.gov/33443234.
235. Lee H, Kovacs C, Mattman A, et al. The impact of IgG subclass deficiency on the risk of mortality in hospitalized patients with COPD. *Respir Res* 2022; **23**(1): 141 https://pubmed.ncbi.nlm.nih.gov/35641962.
236. Landis SH, Muellerova H, Mannino DM, et al. Continuing to Confront COPD International Patient Survey: methods, COPD prevalence, and disease burden in 2012-2013. *Int J Chron Obstruct Pulmon Dis* 2014; **9**: 597-611 https://pubmed.ncbi.nlm.nih.gov/24944511.
237. Foreman MG, Zhang L, Murphy J, et al. Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGene Study. *Am J Respir Crit Care Med* 2011; **184**(4): 414-20 https://pubmed.ncbi.nlm.nih.gov/21562134.
238. Lopez Varela MV, Montes de Oca M, Halbert RJ, et al. Sex-related differences in COPD in five Latin American cities: the PLATINO study. *Eur Respir J* 2010; **36**(5): 1034-41 https://pubmed.ncbi.nlm.nih.gov/20378599.
239. Silverman EK, Weiss ST, Drazen JM, et al. Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; **162**(6): 2152-8 https://pubmed.ncbi.nlm.nih.gov/11112130.
240. Amaral AFS, Strachan DP, Burney PGJ, Jarvis DL. Female Smokers Are at Greater Risk of Airflow Obstruction Than Male Smokers. UK Biobank. *Am J Respir Crit Care Med* 2017; **195**(9): 1226-35 https://pubmed.ncbi.nlm.nih.gov/28075609.
241. Çolak Y, Nordestgaard BG, Lange P, Afzal S. Sex differences in COPD in relation to smoking exposure: a population-based cohort study. *Thorax* 2025; **80**(8): 512-9 https://pubmed.ncbi.nlm.nih.gov/40185636.
242. Jestin-Guyon N, Ouaalaya EH, Bernady A, et al. Sex Differences and Survival Among COPD Patients in France: The Palomb Cohort. *Int J Chron Obstruct Pulmon Dis* 2026; **21**: 531894 https://pubmed.ncbi.nlm.nih.gov/41847336.
243. Liang C, Chung HF, Dobson A, Sandin S, Weiderpass E, Mishra GD. Female reproductive histories and the risk of chronic obstructive pulmonary disease. *Thorax* 2024; **79**(6): 508-14 https://pubmed.ncbi.nlm.nih.gov/38350732.
244. Bhakta NR, Bime C, Kaminsky DA, et al. Race and Ethnicity in Pulmonary Function Test Interpretation: An Official American Thoracic Society Statement. *Am J Respir Crit Care Med* 2023; **207**(8): 978-95 https://pubmed.ncbi.nlm.nih.gov/36973004.
245. Townend J, Minelli C, Mortimer K, et al. The association between chronic airflow obstruction and poverty in 12 sites of the multinational BOLD study. *Eur Respir J* 2017; **49**(6): https://pubmed.ncbi.nlm.nih.gov/28572124.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

246. Beran D, Zar HJ, Perrin C, Menezes AM, Burney P, Forum of International Respiratory Societies working group c. Burden of asthma and chronic obstructive pulmonary disease and access to essential medicines in low-income and middle-income countries. *Lancet Respir Med* 2015; **3**(2): 159-70 https://pubmed.ncbi.nlm.nih.gov/25680912.
247. Gershon AS, Warner L, Cascagnette P, Victor JC, To T. Lifetime risk of developing chronic obstructive pulmonary disease: a longitudinal population study. *Lancet* 2011; **378**(9795): 991-6 https://pubmed.ncbi.nlm.nih.gov/21907862.
248. Patel S, Marchant J, Bhatt SP, Hurst JR. Rural versus urban living and COPD: a systematic review. *Eur Respir Rev* 2026; **35**(180): https://pubmed.ncbi.nlm.nih.gov/42055591.
249. Hogg JC, Timens W. The pathology of chronic obstructive pulmonary disease. *Annu Rev Pathol* 2009; **4**: 435-59 https://pubmed.ncbi.nlm.nih.gov/18954287.
250. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2016; **138**(1): 16-27 https://pubmed.ncbi.nlm.nih.gov/27373322.
251. Barnes PJ. Cellular and molecular mechanisms of chronic obstructive pulmonary disease. *Clin Chest Med* 2014; **35**(1): 71-86 https://pubmed.ncbi.nlm.nih.gov/24507838.
252. Sze MA, Dimitriu PA, Suzuki M, et al. Host Response to the Lung Microbiome in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015; **192**(4): 438-45 https://pubmed.ncbi.nlm.nih.gov/25945594.
253. Lee SH, Goswami S, Grudo A, et al. Antielastin autoimmunity in tobacco smoking-induced emphysema. *Nat Med* 2007; **13**(5): 567-9 https://pubmed.ncbi.nlm.nih.gov/17450149.
254. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol* 2008; **8**(3): 183-92 https://pubmed.ncbi.nlm.nih.gov/18274560.
255. Global Initiative for Asthma (GINA). 2017 Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS) available here: https://ginasthma.org/wp-content/uploads/2019/11/GINA-GOLD-2017-overlap-pocket-guide-wms-2017-ACO.pdf [accessed Oct 2026].
256. Domej W, Oettl K, Renner W. Oxidative stress and free radicals in COPD--implications and relevance for treatment. *Int J Chron Obstruct Pulmon Dis* 2014; **9**: 1207-24 https://pubmed.ncbi.nlm.nih.gov/25378921.
257. Malhotra D, Thimmulappa R, Vij N, et al. Heightened endoplasmic reticulum stress in the lungs of patients with chronic obstructive pulmonary disease: the role of Nrf2-regulated proteasomal activity. *Am J Respir Crit Care Med* 2009; **180**(12): 1196-207 https://pubmed.ncbi.nlm.nih.gov/19797762.
258. Stockley RA. Neutrophils and protease/antiprotease imbalance. *Am J Respir Crit Care Med* 1999; **160**(5 Pt 2): S49-52 https://pubmed.ncbi.nlm.nih.gov/10556170.
259. Johnson SR. Untangling the protease web in COPD: metalloproteinases in the silent zone. *Thorax* 2016; **71**(2): 105-6 https://pubmed.ncbi.nlm.nih.gov/26769014.
260. Katzenstein AL, Mukhopadhyay S, Myers JL. Diagnosis of usual interstitial pneumonia and distinction from other fibrosing interstitial lung diseases. *Hum Pathol* 2008; **39**(9): 1275-94 https://pubmed.ncbi.nlm.nih.gov/18706349.
261. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. *N Engl J Med* 2011; **364**(10): 897-906 https://pubmed.ncbi.nlm.nih.gov/21388308.
262. Putman RK, Hatabu H, Araki T, et al. Association Between Interstitial Lung Abnormalities and All-Cause Mortality. *JAMA* 2016; **315**(7): 672-81 https://pubmed.ncbi.nlm.nih.gov/26881370.
263. Churg A, Tai H, Coulthard T, Wang R, Wright JL. Cigarette smoke drives small airway remodeling by induction of growth factors in the airway wall. *Am J Respir Crit Care Med* 2006; **174**(12): 1327-34 https://pubmed.ncbi.nlm.nih.gov/17008639.
264. Rennard SI, Wachenfeldt K. Rationale and emerging approaches for targeting lung repair and regeneration in the treatment of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2011; **8**(4): 368-75 https://pubmed.ncbi.nlm.nih.gov/21816994.
265. Hogg JC, McDonough JE, Gosselink JV, Hayashi S. What drives the peripheral lung-remodeling process in chronic obstructive pulmonary disease? *Proc Am Thorac Soc* 2009; **6**(8): 668-72 https://pubmed.ncbi.nlm.nih.gov/20008873.
266. Peinado VI, Barbera JA, Ramirez J, et al. Endothelial dysfunction in pulmonary arteries of patients with mild COPD. *Am J Physiol* 1998; **274**(6): L908-13 https://pubmed.ncbi.nlm.nih.gov/9609729.
267. Song Z, Meng Y, Fricker M, et al. The role of gut-lung axis in COPD: Pathogenesis, immune response, and prospective treatment. *Heliyon* 2024; **10**(9): e30612 https://pubmed.ncbi.nlm.nih.gov/38742057.
268. Dicker AJ, Huang JTJ, Lonergan M, et al. The sputum microbiome, airway inflammation, and mortality in chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2021; **147**(1): 158-67 https://pubmed.ncbi.nlm.nih.gov/32353489.
269. Kayongo A, Robertson NM, Siddharthan T, et al. Airway microbiome-immune crosstalk in chronic obstructive pulmonary disease. *Front Immunol* 2022; **13**: 1085551 https://pubmed.ncbi.nlm.nih.gov/36741369.
270. Sulaiman I, Wu BG, Chung M, et al. Lower Airway Dysbiosis Augments Lung Inflammatory Injury in Mild-to-Moderate Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2023; **208**(10): 1101-14 https://pubmed.ncbi.nlm.nih.gov/37677136.
271. Lea S, Higham A, Beech A, Singh D. How inhaled corticosteroids target inflammation in COPD. *Eur Respir Rev* 2023; **32**(170): https://pubmed.ncbi.nlm.nih.gov/37852657.
272. Wang Z, Bafadhel M, Haldar K, et al. Lung microbiome dynamics in COPD exacerbations. *Eur Respir J* 2016; **47**(4): 1082-92 https://pubmed.ncbi.nlm.nih.gov/26917613.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

273. Wang Z, Locantore N, Haldar K, et al. Inflammatory Endotype-associated Airway Microbiome in Chronic Obstructive Pulmonary Disease Clinical Stability and Exacerbations: A Multicohort Longitudinal Analysis. *Am J Respir Crit Care Med* 2021; **203**(12): 1488-502 https://pubmed.ncbi.nlm.nih.gov/33332995.
274. Opron K, Begley LA, Erb-Downward JR, et al. Loss of Airway Phylogenetic Diversity Is Associated with Clinical and Pathobiological Markers of Disease Development in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2024; **210**(2): 186-200 https://pubmed.ncbi.nlm.nih.gov/38261629.
275. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med* 2011; **365**(17): 1567-75 https://pubmed.ncbi.nlm.nih.gov/22029978.
276. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004; **350**(26): 2645-53 https://pubmed.ncbi.nlm.nih.gov/15215480.
277. O'Donnell DE, Laveneziana P. The clinical importance of dynamic lung hyperinflation in COPD. *COPD* 2006; **3**(4): 219-32 https://pubmed.ncbi.nlm.nih.gov/17361503.
278. Gagnon P, Guenette JA, Langer D, et al. Pathogenesis of hyperinflation in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2014; **9**: 187-201 https://pubmed.ncbi.nlm.nih.gov/24600216.
279. O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; **160**(2): 542-9 https://pubmed.ncbi.nlm.nih.gov/10430726.
280. O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation. *Am Rev Respir Dis* 1993; **148**(5): 1351-7 https://pubmed.ncbi.nlm.nih.gov/8239175.
281. O'Donnell DE, Laveneziana P. Dyspnea and activity limitation in COPD: mechanical factors. *COPD* 2007; **4**(3): 225-36 https://pubmed.ncbi.nlm.nih.gov/17729066.
282. O'Donnell DE, Webb KA. The major limitation to exercise performance in COPD is dynamic hyperinflation. *J Appl Physiol (1985)* 2008; **105**(2): 753-5; discussion 5-7 https://pubmed.ncbi.nlm.nih.gov/18678624.
283. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; **164**(5): 770-7 https://pubmed.ncbi.nlm.nih.gov/11549531.
284. Ozgur ES, Nayci SA, Ozge C, Tasdelen B. An integrated index combined by dynamic hyperinflation and exercise capacity in the prediction of morbidity and mortality in COPD. *Respir Care* 2012; **57**(9): 1452-9 https://pubmed.ncbi.nlm.nih.gov/22348294.
285. Albuquerque AL, Nery LE, Villaca DS, et al. Inspiratory fraction and exercise impairment in COPD patients GOLD stages II-III. *Eur Respir J* 2006; **28**(5): 939-44 https://pubmed.ncbi.nlm.nih.gov/16870665.
286. Casanova C, Cote C, de Torres JP, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; **171**(6): 591-7 https://pubmed.ncbi.nlm.nih.gov/15591470.
287. Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1997; **155**(3): 906-15 https://pubmed.ncbi.nlm.nih.gov/9117025.
288. Tantucci C, Donati P, Nicosia F, et al. Inspiratory capacity predicts mortality in patients with chronic obstructive pulmonary disease. *Respir Med* 2008; **102**(4): 613-9 https://pubmed.ncbi.nlm.nih.gov/18083020.
289. Hyatt RE. Expiratory flow limitation. *J Appl Physiol Respir Environ Exerc Physiol* 1983; **55**(1 Pt 1): 1-7 https://pubmed.ncbi.nlm.nih.gov/6350246.
290. Gagnon P, Saey D, Provencher S, et al. Walking exercise response to bronchodilation in mild COPD: a randomized trial. *Respir Med* 2012; **106**(12): 1695-705 https://pubmed.ncbi.nlm.nih.gov/22999808.
291. Deesomchok A, Webb KA, Forkert L, et al. Lung hyperinflation and its reversibility in patients with airway obstruction of varying severity. *COPD* 2010; **7**(6): 428-37 https://pubmed.ncbi.nlm.nih.gov/21166631.
292. O'Donnell CR, Bankier AA, Stiebellehner L, Reilly JJ, Brown R, Loring SH. Comparison of plethysmographic and helium dilution lung volumes: which is best for COPD? *Chest* 2010; **137**(5): 1108-15 https://pubmed.ncbi.nlm.nih.gov/20022972.
293. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; **26**(3): 511-22 https://pubmed.ncbi.nlm.nih.gov/16135736.
294. Tantucci C, Duguet A, Similowski T, Zelter M, Derenne JP, Milic-Emili J. Effect of salbutamol on dynamic hyperinflation in chronic obstructive pulmonary disease patients. *Eur Respir J* 1998; **12**(4): 799-804 https://pubmed.ncbi.nlm.nih.gov/9817148.
295. Rodriguez-Roisin R, Drakulovic M, Rodriguez DA, Roca J, Barbera JA, Wagner PD. Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity. *J Appl Physiol (1985)* 2009; **106**(6): 1902-8 https://pubmed.ncbi.nlm.nih.gov/19372303.
296. Elbehairy AF, Ciavaglia CE, Webb KA, et al. Pulmonary Gas Exchange Abnormalities in Mild Chronic Obstructive Pulmonary Disease. Implications for Dyspnea and Exercise Intolerance. *Am J Respir Crit Care Med* 2015; **191**(12): 1384-94 https://pubmed.ncbi.nlm.nih.gov/25826478.
297. Sakao S, Voelkel NF, Tatsumi K. The vascular bed in COPD: pulmonary hypertension and pulmonary vascular alterations. *Eur Respir Rev* 2014; **23**(133): 350-5 https://pubmed.ncbi.nlm.nih.gov/25176971.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

298. Iyer KS, Newell JD, Jr., Jin D, et al. Quantitative Dual-Energy Computed Tomography Supports a Vascular Etiology of Smoking-induced Inflammatory Lung Disease. *Am J Respir Crit Care Med* 2016; **193**(6): 652-61 https://pubmed.ncbi.nlm.nih.gov/26569033.
299. Alford SK, van Beek EJ, McLennan G, Hoffman EA. Heterogeneity of pulmonary perfusion as a mechanistic image-based phenotype in emphysema susceptible smokers. *Proc Natl Acad Sci USA* 2010; **107**(16): 7485-90 https://pubmed.ncbi.nlm.nih.gov/20368443.
300. Peinado VI, Pizarro S, Barbera JA. Pulmonary vascular involvement in COPD. *Chest* 2008; **134**(4): 808-14 https://pubmed.ncbi.nlm.nih.gov/18842913.
301. Kovacs G, Agusti A, Barbera JA, et al. Pulmonary Vascular Involvement in Chronic Obstructive Pulmonary Disease. Is There a Pulmonary Vascular Phenotype? *Am J Respir Crit Care Med* 2018; **198**(8): 1000-11 https://pubmed.ncbi.nlm.nih.gov/29746142.
302. Zhang L, Liu Y, Zhao 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**: 1365-79 https://pubmed.ncbi.nlm.nih.gov/35711174.
303. Kovacs G, Avian A, Bachmaier G, et al. Severe Pulmonary Hypertension in COPD: Impact on Survival and Diagnostic Approach. *Chest* 2022; **162**(1): 202-12 https://pubmed.ncbi.nlm.nih.gov/35092746.
304. Wells JM, Washko GR, Han MK, et al. Pulmonary arterial enlargement and acute exacerbations of COPD. *N Engl J Med* 2012; **367**(10): 913-21 https://pubmed.ncbi.nlm.nih.gov/22938715.
305. Parker CM, Voduc N, Aaron SD, Webb KA, O'Donnell DE. Physiological changes during symptom recovery from moderate exacerbations of COPD. *Eur Respir J* 2005; **26**(3): 420-8 https://pubmed.ncbi.nlm.nih.gov/16135722.
306. Barbera JA, Roca J, Ferrer A, et al. Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease. *Eur Respir J* 1997; **10**(6): 1285-91 https://pubmed.ncbi.nlm.nih.gov/9192930.
307. Celli BR, Fabbri LM, Aaron SD, et al. An Updated Definition and Severity Classification of COPD Exacerbations: The Rome Proposal. *American Journal of Respiratory and Critical Care Medicine* 2021; **204**(11): 1251-8 https://pubmed.ncbi.nlm.nih.gov/34570991.
308. Miller J, Edwards LD, Agusti A, et al. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. *Respir Med* 2013; **107**(9): 1376-84 https://pubmed.ncbi.nlm.nih.gov/23791463.
309. Joo H, Yoon HK, Hwang YI, et al. Application of the Lancet Commission COPD classification to COPD Cohort Population in South Korea. *Respir Med* 2024; **230**: 107679 https://pubmed.ncbi.nlm.nih.gov/38797345.
310. Fabbri LM, Celli BR, Agusti A, et al. COPD and multimorbidity: recognising and addressing a syndemic occurrence. *Lancet Respir Med* 2023; **11**(11): 1020-34 https://pubmed.ncbi.nlm.nih.gov/37696283.
311. Dharmage S, Agusti A. Personal communication. 2022.
312. Stolz D, Mkorombindo T, Schumann DM, et al. Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. *Lancet* 2022; **400**(10356): 921-72 https://pubmed.ncbi.nlm.nih.gov/36075255.
313. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007; **370**(9589): 741-50 https://pubmed.ncbi.nlm.nih.gov/17765523.
314. COPDGene Diagnosis Working Group, CanCold Investigators, Bhatt SP, et al. A Multidimensional Diagnostic Approach for Chronic Obstructive Pulmonary Disease. *JAMA* 2025; **333**(24): 2164-75 https://pubmed.ncbi.nlm.nih.gov/40382791.
315. Lowe KE, Regan EA, Anzueto A, et al. COPDGene((R)) 2019: Redefining the Diagnosis of Chronic Obstructive Pulmonary Disease. *Chronic Obstr Pulm Dis* 2019; **6**(5): 384-99 https://pubmed.ncbi.nlm.nih.gov/31710793.
316. Kessler R, Partridge MR, Miravitlles M, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *Eur Respir J* 2011; **37**(2): 264-72 https://pubmed.ncbi.nlm.nih.gov/21115606.
317. Montes de Oca M, Perez-Padilla R, Talamo C, et al. Acute bronchodilator responsiveness in subjects with and without airflow obstruction in five Latin American cities: the PLATINO study. *Pulm Pharmacol Ther* 2010; **23**(1): 29-35 https://pubmed.ncbi.nlm.nih.gov/19818867.
318. Miravitlles M, Worth H, Soler Cataluna JJ, et al. Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. *Respir Res* 2014; **15**(1): 122 https://pubmed.ncbi.nlm.nih.gov/25331383.
319. Laviolette L, Laveneziana P, Faculty ERSRS. Dyspnoea: a multidimensional and multidisciplinary approach. *Eur Respir J* 2014; **43**(6): 1750-62 https://pubmed.ncbi.nlm.nih.gov/24525437.
320. Elliott MW, Adams L, Cockcroft A, MacRae KD, Murphy K, Guz A. The language of breathlessness. Use of verbal descriptors by patients with cardiopulmonary disease. *Am Rev Respir Dis* 1991; **144**(4): 826-32 https://pubmed.ncbi.nlm.nih.gov/1928956.
321. Phillips DB, Elbehairy AF, James MD, et al. Impaired Ventilatory Efficiency, Dyspnea, and Exercise Intolerance in Chronic Obstructive Pulmonary Disease: Results from the CanCOLD Study. *Am J Respir Crit Care Med* 2022; **205**(12): 1391-402 https://pubmed.ncbi.nlm.nih.gov/35333135.
322. Mullerova H, Lu C, Li H, Tabberer M. Prevalence and burden of breathlessness in patients with chronic obstructive pulmonary disease managed in primary care. *PLoS One* 2014; **9**(1): e85540 https://pubmed.ncbi.nlm.nih.gov/24427316.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

323. Lapperre T, Bodtger U, Kjærsgaard Klein D, et al. Dysfunctional breathing impacts symptom burden in Chronic Obstructive Pulmonary Disease (COPD). *European Respiratory Journal* 2020; **56**(suppl 64): 124
324. Vidotto LS, Carvalho CRF, Harvey A, Jones M. Dysfunctional breathing: what do we know? *J Bras Pneumol* 2019; **45**(1): e20170347 https://pubmed.ncbi.nlm.nih.gov/30758427.
325. 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): 1306-14 https://pubmed.ncbi.nlm.nih.gov/32804188.
326. Lewthwaite H, Jensen D, Ekstrom M. How to Assess Breathlessness in Chronic Obstructive Pulmonary Disease. *Int J Chron Obstruct Pulmon Dis* 2021; **16**: 1581-98 https://pubmed.ncbi.nlm.nih.gov/34113091.
327. O'Donnell DE, Milne KM, James MD, de Torres JP, Neder JA. Dyspnea in COPD: New Mechanistic Insights and Management Implications. *Adv Ther* 2020; **37**(1): 41-60 https://pubmed.ncbi.nlm.nih.gov/31673990.
328. Cho SH, Lin HC, Ghoshal AG, et al. Respiratory disease in the Asia-Pacific region: Cough as a key symptom. *Allergy Asthma Proc* 2016; **37**(2): 131-40 https://pubmed.ncbi.nlm.nih.gov/26802834.
329. Medical Research Council Committee on the Aetiology of Chronic Bronchitis. Definition and classification of chronic bronchitis for clinical and epidemiological purposes. A report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis. *Lancet* 1965; **1**(7389): 775-9 https://pubmed.ncbi.nlm.nih.gov/4165081.
330. 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 https://pubmed.ncbi.nlm.nih.gov/26978269.
331. Ni Y, Shi G, Yu Y, Hao J, Chen T, Song H. Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: a systemic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2015; **10**: 1465-75 https://pubmed.ncbi.nlm.nih.gov/26251586.
332. Soler N, Esperatti M, Ewig S, Huerta A, Agusti C, Torres A. Sputum purulence-guided antibiotic use in hospitalised patients with exacerbations of COPD. *Eur Respir J* 2012; **40**(6): 1344-53 https://pubmed.ncbi.nlm.nih.gov/22523352.
333. Brusse-Keizer MG, Grotenhuis AJ, Kerstjens HA, et al. Relation of sputum colour to bacterial load in acute exacerbations of COPD. *Respir Med* 2009; **103**(4): 601-6 https://pubmed.ncbi.nlm.nih.gov/19027281.
334. Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest* 2000; **117**(6): 1638-45 https://pubmed.ncbi.nlm.nih.gov/10858396.
335. Goertz YMJ, Looijmans M, Prins JB, et al. Fatigue in patients with chronic obstructive pulmonary disease: protocol of the Dutch multicentre, longitudinal, observational FAntasTIGUE study. *BMJ Open* 2018; **8**(4): e021745 https://pubmed.ncbi.nlm.nih.gov/29643168.
336. Ream E, Richardson A. Fatigue in patients with cancer and chronic obstructive airways disease: a phenomenological enquiry. *Int J Nurs Stud* 1997; **34**(1): 44-53 https://pubmed.ncbi.nlm.nih.gov/9055120.
337. Small SP, Lamb M. Measurement of fatigue in chronic obstructive pulmonary disease and in asthma. *Int J Nurs Stud* 2000; **37**(2): 127-33 https://pubmed.ncbi.nlm.nih.gov/10684954.
338. von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. *J Cachexia Sarcopenia Muscle* 2010; **1**(1): 1-5 https://pubmed.ncbi.nlm.nih.gov/21475699.
339. Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993; **147**(5): 1151-6 https://pubmed.ncbi.nlm.nih.gov/8484624.
340. Attaway AH, Welch N, Hatipoglu U, Zein JG, Dasarathy S. Muscle loss contributes to higher morbidity and mortality in COPD: An analysis of national trends. *Respirology* 2021; **26**(1): 62-71 https://pubmed.ncbi.nlm.nih.gov/32542761.
341. Rutten EP, Calverley PM, Casaburi R, et al. Changes in body composition in patients with chronic obstructive pulmonary disease: do they influence patient-related outcomes? *Ann Nutr Metab* 2013; **63**(3): 239-47 https://pubmed.ncbi.nlm.nih.gov/24216978.
342. Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2005; **82**(1): 53-9 https://pubmed.ncbi.nlm.nih.gov/16002800.
343. Hanania NA, Mullerova H, Locantore NW, et al. Determinants of depression in the ECLIPSE chronic obstructive pulmonary disease cohort. *Am J Respir Crit Care Med* 2011; **183**(5): 604-11 https://pubmed.ncbi.nlm.nih.gov/20889909.
344. Blakemore A, Dickens C, Chew-Graham CA, et al. Depression predicts emergency care use in people with chronic obstructive pulmonary disease: a large cohort study in primary care. *Int J Chron Obstruct Pulmon Dis* 2019; **14**: 1343-53 https://pubmed.ncbi.nlm.nih.gov/31388297.
345. Agusti A, Rapsomaniki E, Beasley R, et al. Treatable traits in the NOVELTY study. *Respirology* 2022; **27**(11): 929-40 https://pubmed.ncbi.nlm.nih.gov/35861464.
346. Holleman DR, Jr., Simel DL. Does the clinical examination predict airflow limitation? *JAMA* 1995; **273**(4): 313-9 https://pubmed.ncbi.nlm.nih.gov/7815660.
347. Kesten S, Chapman KR. Physician perceptions and management of COPD. *Chest* 1993; **104**(1): 254-8 https://pubmed.ncbi.nlm.nih.gov/8325079.
348. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005; **26**(2): 319-38 https://pubmed.ncbi.nlm.nih.gov/16055882.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

349. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005; **26**(5): 948-68 https://pubmed.ncbi.nlm.nih.gov/16264058.
350. Colak Y, Nordestgaard BG, Vestbo J, Lange P, Afzal S. Prognostic significance of chronic respiratory symptoms in individuals with normal spirometry. *Eur Respir J* 2019; **54**(3): 1900734 https://pubmed.ncbi.nlm.nih.gov/31248954.
351. Jackson H, Hubbard R. Detecting chronic obstructive pulmonary disease using peak flow rate: cross sectional survey. *BMJ* 2003; **327**(7416): 653-4 https://pubmed.ncbi.nlm.nih.gov/14500437.
352. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; **40**(6): 1324-43 https://pubmed.ncbi.nlm.nih.gov/22743675.
353. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J* 2022; **60**(1): https://pubmed.ncbi.nlm.nih.gov/34949706.
354. Walker PP, Calverley PM. The volumetric response to bronchodilators in stable chronic obstructive pulmonary disease. *COPD* 2008; **5**(3): 147-52 https://pubmed.ncbi.nlm.nih.gov/18568838.
355. Calverley PM, Albert P, Walker PP. Bronchodilator reversibility in chronic obstructive pulmonary disease: use and limitations. *Lancet Respir Med* 2013; **1**(7): 564-73 https://pubmed.ncbi.nlm.nih.gov/24461617.
356. Enright PL, Beck KC, Sherrill DL. Repeatability of spirometry in 18,000 adult patients. *Am J Respir Crit Care Med* 2004; **169**(2): 235-8 https://pubmed.ncbi.nlm.nih.gov/14604836.
357. Fortis S, Eberlein M, Georgopoulos D, Comellas AP. Predictive value of prebronchodilator and postbronchodilator spirometry for COPD features and outcomes. *BMJ Open Respir Res* 2017; **4**(1): e000213 https://pubmed.ncbi.nlm.nih.gov/29435342.
358. Albert P, Agusti A, Edwards L, et al. Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. *Thorax* 2012; **67**(8): 701-8 https://pubmed.ncbi.nlm.nih.gov/22696176.
359. Hansen JE, Porszasz J. Counterpoint: Is an increase in FEV(1) and/or FVC >/= 12% of control and >/= 200 mL the best way to assess positive bronchodilator response? No. *Chest* 2014; **146**(3): 538-41 https://pubmed.ncbi.nlm.nih.gov/25180718.
360. Halpin DMG, Stanojevic S, McCormack MC, et al. Joint statement from GOLD/GLI regarding the use of spirometry to define airflow obstruction and diagnose COPD. *Eur Respir J* 2026; **67**(4): https://pubmed.ncbi.nlm.nih.gov/41748283.
361. Guder G, Brenner S, Angermann CE, et al. "GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study". *Respir Res* 2012; **13**(1): 13 https://pubmed.ncbi.nlm.nih.gov/22309369.
362. Bhatt SP, Sieren JC, Dransfield MT, et al. Comparison of spirometric thresholds in diagnosing smoking-related airflow obstruction. *Thorax* 2014; **69**(5): 409-14 https://pubmed.ncbi.nlm.nih.gov/23525095.
363. Colak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. Young and middle-aged adults with airflow limitation according to lower limit of normal but not fixed ratio have high morbidity and poor survival: a population-based prospective cohort study. *Eur Respir J* 2018; **51**(3): https://pubmed.ncbi.nlm.nih.gov/29449425.
364. Vaz Fragoso CA, McAvay G, Van Ness PH, et al. Phenotype of Spirometric Impairment in an Aging Population. *Am J Respir Crit Care Med* 2016; **193**(7): 727-35 https://pubmed.ncbi.nlm.nih.gov/26540012.
365. Bhatt SP, Balte PP, Schwartz JE, et al. Discriminative Accuracy of FEV1:FVC Thresholds for COPD-Related Hospitalization and Mortality. *JAMA* 2019; **321**(24): 2438-47 https://pubmed.ncbi.nlm.nih.gov/31237643.
366. Aaron SD, Tan WC, Bourbeau J, et al. Diagnostic Instability and Reversals of Chronic Obstructive Pulmonary Disease Diagnosis in Individuals with Mild to Moderate Airflow Obstruction. *Am J Respir Crit Care Med* 2017; **196**(3): 306-14 https://pubmed.ncbi.nlm.nih.gov/28267373.
367. Graham BL, Steenbruggen I, Miller MR, 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 https://pubmed.ncbi.nlm.nih.gov/31613151.
368. Schermer TR, Robberts B, Crockett AJ, et al. Should the diagnosis of COPD be based on a single spirometry test? *NPJ Prim Care Respir Med* 2016; **26**: 16059 https://pubmed.ncbi.nlm.nih.gov/27684728.
369. Arne M, Lisspers K, Ställberg B, et al. How often is diagnosis of COPD confirmed with spirometry? *Respir Med* 2010; **104**(4): 550-6 https://pubmed.ncbi.nlm.nih.gov/19931443.
370. Bourbeau J, Sebaldt RJ, Day A, et al. Practice patterns in the management of chronic obstructive pulmonary disease in primary practice: the CAGE study. *Can Respir J* 2008; **15**(1): 13-9 https://pubmed.ncbi.nlm.nih.gov/18292848.
371. Fisk M, McMillan V, Brown J, et al. Inaccurate diagnosis of COPD: the Welsh National COPD Audit. *Br J Gen Pract* 2019; **69**(678): e1-e7 https://pubmed.ncbi.nlm.nih.gov/30559109.
372. Halpin DMG, Dickens AP, Skinner D, et al. Identification of key opportunities for optimising the management of high-risk COPD patients in the UK using the CONQUEST quality standards: an observational longitudinal study. *Lancet Reg Health Eur* 2023; **29**: 100619 https://pubmed.ncbi.nlm.nih.gov/37131493.
373. Kim KY, Yoo KH, Choi HS, et al. Nationwide quality assessment of treatment for chronic obstructive pulmonary disease. *J Thorac Dis* 2020; **12**(12): 7174-81 https://pubmed.ncbi.nlm.nih.gov/33447406.
374. Koefoed MM, dePont Christensen R, Søndergaard J, Jarbøl DE. Lack of spirometry use in Danish patients initiating medication targeting obstructive lung disease. *Respir Med* 2012; **106**(12): 1743-8 https://pubmed.ncbi.nlm.nih.gov/23044193.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

375. Nishi SP, Wang Y, Kuo YF, Goodwin JS, Sharma G. Spirometry use among older adults with chronic obstructive pulmonary disease: 1999-2008. *Ann Am Thorac Soc* 2013; **10**(6): 565-73 https://pubmed.ncbi.nlm.nih.gov/24053440.
376. Walters JA, Walters EH, Nelson M, et al. Factors associated with misdiagnosis of COPD in primary care. *Prim Care Respir J* 2011; **20**(4): 396-402 https://pubmed.ncbi.nlm.nih.gov/21687918.
377. Lim R, Smith T, Usherwood T. Barriers to spirometry in Australian general practice: A systematic review. *Aust J Gen Pract* 2023; **52**(9): 585-93 https://pubmed.ncbi.nlm.nih.gov/37666778.
378. Shahaj O, Meiwald A, Puri Sudhir K, et al. Mapping the Common Barriers to Optimal COPD Care in High and Middle-Income Countries: Qualitative Perspectives from Clinicians. *Int J Chron Obstruct Pulmon Dis* 2024; **19**: 1207-23 https://pubmed.ncbi.nlm.nih.gov/38831892.
379. Sunjaya A, Edwards GD, Harvey J, et al. Validation of artificial intelligence spirometry diagnostic support software in primary care: a blinded diagnostic accuracy study. *ERJ Open Res* 2025; **11**(5): https://pubmed.ncbi.nlm.nih.gov/41031099.
380. Bowerman C, Bhakta NR, Brazzale D, et al. A Race-neutral Approach to the Interpretation of Lung Function Measurements. *Am J Respir Crit Care Med* 2023; **207**(6): 768-74 https://pubmed.ncbi.nlm.nih.gov/36383197.
381. Diao JA, He Y, Khazanchi R, et al. Implications of Race Adjustment in Lung-Function Equations. *N Engl J Med* 2024; **390**(22): 2083-97 https://pubmed.ncbi.nlm.nih.gov/38767252.
382. Pomeroy E, Stock JT, Wells JCK. Population history and ecology, in addition to climate, influence human stature and body proportions. *Sci Rep* 2021; **11**(1): 274 https://pubmed.ncbi.nlm.nih.gov/33431970.
383. Wang RJ. Beyond Race-Specific Spirometry Reference Equations: What Comes Next? *Am J Respir Crit Care Med* 2024; **209**(1): 117-8 https://pubmed.ncbi.nlm.nih.gov/37595271.
384. Burton RF, Nevill AM, Stewart AD, Daniell N, Olds T. Statistical approaches to relationships between sitting height and leg length in adults. *Ann Hum Biol* 2013; **40**(1): 64-9 https://pubmed.ncbi.nlm.nih.gov/23301801.
385. Allinson JP, Afzal S, Colak Y, et al. Changes in lung function in European adults born between 1884 and 1996 and implications for the diagnosis of lung disease: a cross-sectional analysis of ten population-based studies. *Lancet Respir Med* 2022; **10**(1): 83-94 https://pubmed.ncbi.nlm.nih.gov/34619103.
386. Schiavi E, Ryu MH, Martini L, et al. Application of the European Respiratory Society/American Thoracic Society Spirometry Standards and Race-Neutral Equations in the COPDGene Study. *Am J Respir Crit Care Med* 2024; **210**(11): 1317-28 https://pubmed.ncbi.nlm.nih.gov/38607551.
387. Backman H, Blomberg A, Lundquist A, et al. Lung Function Trajectories and Associated Mortality among Adults with and without Airway Obstruction. *Am J Respir Crit Care Med* 2023; **208**(10): 1063-74 https://pubmed.ncbi.nlm.nih.gov/37460250.
388. European Respiratory Society. Recommendation from ERS Group 9.1 (Respiratory function technologists /Scientists). Lung function testing during COVID-19 pandemic and beyond; online document available here: https://10.13140/RG.2.2.28428.67207 [accessed Oct 2026].
389. American Thoracic Society. Pulmonary Function Laboratories: Advice Regarding COVID-19; online article available here: https://www.thoracic.org/professionals/clinical-resources/disease-related-resources/pulmonary-function-laboratories.php [accessed Oct 2026].
390. Borg BM, Osadnik C, Adam K, et al. Pulmonary function testing during SARS-CoV-2: An ANZSRS/TSANZ position statement. *Respirology* 2022; **27**(9): 688-719 https://pubmed.ncbi.nlm.nih.gov/35981737.
391. Wilson KC, Kaminsky DA, Michaud G, et al. Restoring Pulmonary and Sleep Services as the COVID-19 Pandemic Lessens. From an Association of Pulmonary, Critical Care, and Sleep Division Directors and American Thoracic Society-coordinated Task Force. *Ann Am Thorac Soc* 2020; **17**(11): 1343-51 https://pubmed.ncbi.nlm.nih.gov/32663071.
392. Martinez FJ, Mannino D, Leidy NK, et al. A New Approach for Identifying Patients with Undiagnosed Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017; **195**(6): 748-56 https://pubmed.ncbi.nlm.nih.gov/27783539.
393. Jithoo A, Enright PL, Burney P, et al. Case-finding options for COPD: results from the Burden of Obstructive Lung Disease study. *Eur Respir J* 2013; **41**(3): 548-55 https://pubmed.ncbi.nlm.nih.gov/22743668.
394. Mahboub B, Alzaabi A, Soriano JB, et al. Case-finding of chronic obstructive pulmonary disease with questionnaire, peak flow measurements and spirometry: a cross-sectional study. *BMC Res Notes* 2014; **7**: 241 https://pubmed.ncbi.nlm.nih.gov/24739210.
395. Perez-Padilla R, Vollmer WM, Vazquez-Garcia JC, et al. Can a normal peak expiratory flow exclude severe chronic obstructive pulmonary disease? *Int J Tuberc Lung Dis* 2009; **13**(3): 387-93 https://pubmed.ncbi.nlm.nih.gov/19275802.
396. Aggarwal AN, Gupta D, Jindal SK. The relationship between FEV1 and peak expiratory flow in patients with airways obstruction is poor. *Chest* 2006; **130**(5): 1454-61 https://pubmed.ncbi.nlm.nih.gov/17099024.
397. Pothirat C, Chaiwong W, Phetsuk N, et al. Peak expiratory flow rate as a surrogate for forced expiratory volume in 1 second in COPD severity classification in Thailand. *Int J Chron Obstruct Pulmon Dis* 2015; **10**: 1213-8 https://pubmed.ncbi.nlm.nih.gov/26150713.
398. Llewellin P, Sawyer G, Lewis S, et al. The relationship between FEV1 and PEF in the assessment of the severity of airways obstruction. *Respirology* 2002; **7**(4): 333-7.
399. Carpenter DM, Jurdi R, Roberts CA, Hernandez M, Horne R, Chan A. A Review of Portable Electronic Spirometers: Implications for Asthma Self-Management. *Curr Allergy Asthma Rep* 2018; **18**(10): 53 https://pubmed.ncbi.nlm.nih.gov/30145683.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

400. Ramos Hernandez C, Nunez Fernandez M, Pallares Sanmartin A, et al. Validation of the portable Air-Smart Spirometer. *PLoS One* 2018; **13**(2): e0192789 https://pubmed.ncbi.nlm.nih.gov/29474502.
401. Martinez CH, Mannino DM, Jaimes FA, et al. Undiagnosed Obstructive Lung Disease in the United States. Associated Factors and Long-term Mortality. *Ann Am Thorac Soc* 2015; **12**(12): 1788-95 https://pubmed.ncbi.nlm.nih.gov/26524488.
402. Labonte LE, Tan WC, Li PZ, et al. Undiagnosed Chronic Obstructive Pulmonary Disease Contributes to the Burden of Health Care Use. Data from the CanCOLD Study. *Am J Respir Crit Care Med* 2016; **194**(3): 285-98 https://pubmed.ncbi.nlm.nih.gov/26836958.
403. Gerstein E, Bierbrier J, Whitmore GA, et al. Impact of Undiagnosed Chronic Obstructive Pulmonary Disease and Asthma on Symptoms, Quality of Life, Healthcare Use, and Work Productivity. *Am J Respir Crit Care Med* 2023; **208**(12): 1271-82 https://pubmed.ncbi.nlm.nih.gov/37792953.
404. Siddharthan T, Pollard SL, Quaderi SA, et al. Discriminative Accuracy of Chronic Obstructive Pulmonary Disease Screening Instruments in 3 Low- and Middle-Income Country Settings. *JAMA* 2022; **327**(2): 151-60 https://pubmed.ncbi.nlm.nih.gov/35015039.
405. Çolak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. Prognosis of asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark: a prospective cohort study. *Lancet Respir Med* 2017; **5**(5): 426-34 https://pubmed.ncbi.nlm.nih.gov/28389225.
406. Webber EM, Lin JS, Thomas RG. Screening for Chronic Obstructive Pulmonary Disease: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2022; **327**(18): 1812-6 https://pubmed.ncbi.nlm.nih.gov/35536261.
407. Perret JL, Vicendese D, Simons K, et al. Ten-year prediction model for post-bronchodilator airflow obstruction and early detection of COPD: development and validation in two middle-aged population-based cohorts. *BMJ Open Respir Res* 2021; **8**(1): e001138 https://pubmed.ncbi.nlm.nih.gov/34857526.
408. Aaron SD, Montes de Oca M, Celli B, et al. Early Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease: The Costs and Benefits of Case Finding. *Am J Respir Crit Care Med* 2024; **209**(8): 928-37 https://pubmed.ncbi.nlm.nih.gov/38358788.
409. Pan Z, Dickens AP, Chi C, et al. Accuracy and cost-effectiveness of different screening strategies for identifying undiagnosed COPD among primary care patients (>/=40 years) in China: a cross-sectional screening test accuracy study: findings from the Breathe Well group. *BMJ Open* 2021; **11**(9): e051811 https://pubmed.ncbi.nlm.nih.gov/34556515.
410. Zhou J, Li X, Wang X, Yu N, Wang W. Accuracy of portable spirometers in the diagnosis of chronic obstructive pulmonary disease A meta-analysis. *NPJ Prim Care Respir Med* 2022; **32**(1): 15 https://pubmed.ncbi.nlm.nih.gov/35440665.
411. Du D, He S, Guo S, et al. Performance of multiple case-finding approaches in detecting chronic obstructive pulmonary disease: a systematic review and network meta-analysis. *Public Health* 2026; **257**: 106349 https://pubmed.ncbi.nlm.nih.gov/42214892.
412. Aaron SD, Vandemheen KL, Whitmore GA, et al. Early Diagnosis and Treatment of COPD and Asthma - A Randomized, Controlled Trial. *N Engl J Med* 2024; **390**(22): 2061-73 https://pubmed.ncbi.nlm.nih.gov/38767248.
413. Tardif A, Whitmore GA, Vandemheen KL, et al. Patient Factors and Clinical Efficacy of Early Identification and Treatment of Chronic Obstructive Pulmonary Disease and Asthma. *Am J Respir Crit Care Med* 2025; **211**(11): 2053-9 https://pubmed.ncbi.nlm.nih.gov/41056133.
414. Dirven JA, Tange HJ, Muris JW, van Haaren KM, Vink G, van Schayck OC. Early detection of COPD in general practice: implementation, workload and socioeconomic status. A mixed methods observational study. *Prim Care Respir J* 2013; **22**(3): 338-43 https://pubmed.ncbi.nlm.nih.gov/23966213.
415. Le Rouzic O, Roche N, Cortot AB, et al. Defining the "Frequent Exacerbator" Phenotype in COPD: A Hypothesis-Free Approach. *Chest* 2018; **153**(5): 1106-15 https://pubmed.ncbi.nlm.nih.gov/29054347.
416. Hill K, Goldstein RS, Guyatt GH, et al. Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care. *CMAJ* 2010; **182**(7): 673-8 https://pubmed.ncbi.nlm.nih.gov/20371646.
417. Jordan RE, Adab P, Sitch A, et al. Targeted case finding for chronic obstructive pulmonary disease versus routine practice in primary care (TargetCOPD): a cluster-randomised controlled trial. *Lancet Respir Med* 2016; **4**(9): 720-30 https://pubmed.ncbi.nlm.nih.gov/27444687.
418. Bertens LC, Reitsma JB, van Mourik Y, et al. COPD detected with screening: impact on patient management and prognosis. *Eur Respir J* 2014; **44**(6): 1571-8 https://pubmed.ncbi.nlm.nih.gov/24925924.
419. Yawn BP, Duvall K, Peabody J, et al. The impact of screening tools on diagnosis of chronic obstructive pulmonary disease in primary care. *Am J Prev Med* 2014; **47**(5): 563-75 https://pubmed.ncbi.nlm.nih.gov/25241196.
420. Yawn BP, Martinez FJ. POINT: Can Screening for COPD Improve Outcomes? Yes. *Chest* 2020; **157**(1): 7-9 https://pubmed.ncbi.nlm.nih.gov/31916966.
421. Campos M, Hagenlocker B, Lascano J, Riley L. Impact of a Computerized Clinical Decision Support System to Improve Chronic Obstructive Pulmonary Disease Diagnosis and Testing for Alpha-1 Antitrypsin Deficiency. *Ann Am Thorac Soc* 2023; **20**(8): 1116-23 https://pubmed.ncbi.nlm.nih.gov/36989247.
422. Li Y, Wen F, Ma Q, et al. Use of CAPTURE to Identify Individuals Who May or May Not Require Treatment for Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2023; **208**(4): 435-41 https://pubmed.ncbi.nlm.nih.gov/37315325.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

423. Martinez FJ, Yawn BP, Angulo D, et al. Impact of the CAPTURE Chronic Obstructive Pulmonary Disease Screening Tool in U.S. Primary Care: A Cluster-Randomized Trial. *Am J Respir Crit Care Med* 2025; **211**(5): 789-802 https://pubmed.ncbi.nlm.nih.gov/39715575.
424. Perrotta F, D'Agnano V, Scialo F, et al. Evolving concepts in COPD and lung cancer: a narrative review. *Minerva Med* 2022; **113**(3): 436-48 https://pubmed.ncbi.nlm.nih.gov/35156786.
425. Ruparel M, Quaife SL, Dickson JL, et al. Prevalence, Symptom Burden, and Underdiagnosis of Chronic Obstructive Pulmonary Disease in a Lung Cancer Screening Cohort. *Ann Am Thorac Soc* 2020; **17**(7): 869-78 https://pubmed.ncbi.nlm.nih.gov/32164439.
426. Young RP, Hopkins RJ. Diagnosing COPD and targeted lung cancer screening. *Eur Respir J* 2012; **40**(4): 1063-4 https://pubmed.ncbi.nlm.nih.gov/23024333.
427. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. *N Engl J Med* 2020; **382**(6): 503-13 https://pubmed.ncbi.nlm.nih.gov/31995683.
428. Hopkins RJ, Duan F, Chiles C, et al. Reduced Expiratory Flow Rate among Heavy Smokers Increases Lung Cancer Risk. Results from the National Lung Screening Trial-American College of Radiology Imaging Network Cohort. *Ann Am Thorac Soc* 2017; **14**(3): 392-402 https://pubmed.ncbi.nlm.nih.gov/28076701.
429. Yu Y, Xiao W, Du LY, et al. Acupuncture for dyspnea and breathing physiology in chronic respiratory diseases: A systematic review and meta-analysis of randomized controlled trials. *Heliyon* 2024; **10**(10): e31176 https://pubmed.ncbi.nlm.nih.gov/38813170.
430. Balata H, Harvey J, Barber PV, et al. Spirometry performed as part of the Manchester community-based lung cancer screening programme detects a high prevalence of airflow obstruction in individuals without a prior diagnosis of COPD. *Thorax* 2020; **75**(8): 655-60 https://pubmed.ncbi.nlm.nih.gov/32444437.
431. Maldonado F, Bartholmai BJ, Swensen SJ, Midthun DE, Decker PA, Jett JR. Are airflow obstruction and radiographic evidence of emphysema risk factors for lung cancer? A nested case-control study using quantitative emphysema analysis. *Chest* 2010; **138**(6): 1295-302 https://pubmed.ncbi.nlm.nih.gov/20348193.
432. Carr LL, Jacobson S, Lynch DA, et al. Features of COPD as Predictors of Lung Cancer. *Chest* 2018; **153**(6): 1326-35 https://pubmed.ncbi.nlm.nih.gov/29452098.
433. Kishi K, Gurney JW, Schroeder DR, Scanlon PD, Swensen SJ, Jett JR. The correlation of emphysema or airway obstruction with the risk of lung cancer: a matched case-controlled study. *Eur Respir J* 2002; **19**(6): 1093-8 https://pubmed.ncbi.nlm.nih.gov/12108862.
434. Undrunas A, Kasprzyk P, Rajca A, Kuziemski K, Rzyman W, Zdrojewski T. Prevalence, symptom burden and under-diagnosis of chronic obstructive pulmonary disease in Polish lung cancer screening population: a cohort observational study. *BMJ Open* 2022; **12**(4): e055007 https://pubmed.ncbi.nlm.nih.gov/35410926.
435. de-Torres JP, Wilson DO, Sanchez-Salcedo P, et al. Lung cancer in patients with chronic obstructive pulmonary disease. Development and validation of the COPD Lung Cancer Screening Score. *Am J Respir Crit Care Med* 2015; **191**(3): 285-91 https://pubmed.ncbi.nlm.nih.gov/25522175.
436. Sanchez-Salcedo P, Wilson DO, de-Torres JP, et al. Improving selection criteria for lung cancer screening. The potential role of emphysema. *Am J Respir Crit Care Med* 2015; **191**(8): 924-31 https://pubmed.ncbi.nlm.nih.gov/25668622.
437. Wilson DO, Weissfeld JL, Balkan A, et al. Association of radiographic emphysema and airflow obstruction with lung cancer. *Am J Respir Crit Care Med* 2008; **178**(7): 738-44 https://pubmed.ncbi.nlm.nih.gov/18565949.
438. Balkan A, Bulut Y, Fuhrman CR, et al. COPD phenotypes in a lung cancer screening population. *Clin Respir J* 2016; **10**(1): 48-53 https://pubmed.ncbi.nlm.nih.gov/24989058.
439. Labaki WW, Xia M, Murray S, et al. Quantitative Emphysema on Low-Dose CT Imaging of the Chest and Risk of Lung Cancer and Airflow Obstruction: An Analysis of the National Lung Screening Trial. *Chest* 2021; **159**(5): 1812-20 https://pubmed.ncbi.nlm.nih.gov/33326807.
440. Tang LYW, Coxson HO, Lam S, Leipsic J, Tam RC, Sin DD. Towards large-scale case-finding: training and validation of residual networks for detection of chronic obstructive pulmonary disease using low-dose CT. *Lancet Digit Health* 2020; **2**(5): e259-e67 https://pubmed.ncbi.nlm.nih.gov/33328058.
441. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; **365**(5): 395-409 https://pubmed.ncbi.nlm.nih.gov/21714641.
442. Colucci RL, Garshick E, White J, et al. Identification and management of incidental findings in a Veteran's lung cancer screening program. *Respir Res* 2025; **27**(1): 24 https://pubmed.ncbi.nlm.nih.gov/41421986.
443. Labaki WW, Xia M, Murray S, et al. Quantitative Emphysema on Low-Dose CT Imaging of the Chest and Risk of Lung Cancer and Airflow Obstruction: An Analysis of the National Lung Screening Trial. *Chest* 2021; **159**(5): 1812-20 https://pubmed.ncbi.nlm.nih.gov/33326807.
444. Bradley C, Boland A, Clarke L, et al. Diagnosis and treatment outcomes from prebronchodilator spirometry performed alongside lung cancer screening in a Lung Health Check programme. *Thorax* 2023; **78**(6): 543-50 https://pubmed.ncbi.nlm.nih.gov/36972979.
445. Crosbie PA, Balata H, Evison M, et al. Implementing lung cancer screening: baseline results from a community-based 'Lung Health Check' pilot in deprived areas of Manchester. *Thorax* 2019; **74**(4): 405-9 https://pubmed.ncbi.nlm.nih.gov/29440588.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

446. Tisi S, Creamer AW, Dickson J, et al. Prevalence and clinical characteristics of non-malignant CT detected incidental findings in the SUMMIT lung cancer screening cohort. *BMJ Open Respir Res* 2023; **10**(1): e001664 https://pubmed.ncbi.nlm.nih.gov/37321665.
447. Koo HK, Jin KN, Kim DK, Chung HS, Lee CH. Association of incidental emphysema with annual lung function decline and future development of airflow limitation. *Int J Chron Obstruct Pulmon Dis* 2016; **11**: 161-6 https://pubmed.ncbi.nlm.nih.gov/26893550.
448. Mohamed Hoesein FA, de Hoop B, Zanen P, et al. CT-quantified emphysema in male heavy smokers: association with lung function decline. *Thorax* 2011; **66**(9): 782-7 https://pubmed.ncbi.nlm.nih.gov/21474499.
449. Roberts HR, Wells AU, Milne DG, et al. Airflow obstruction in bronchiectasis: correlation between computed tomography features and pulmonary function tests. *Thorax* 2000; **55**(3): 198-204 https://pubmed.ncbi.nlm.nih.gov/10679538.
450. Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med* 2011; **365**(13): 1184-92 https://pubmed.ncbi.nlm.nih.gov/21991892.
451. Halpin DM. Do the 'missing millions' of COPD patients want to be found? *Thorax* 2023; **78**(6): 531-2 https://pubmed.ncbi.nlm.nih.gov/36972980.
452. Agustí A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *The Lancet Respiratory Medicine* 2017; **5**(12): 935-45
453. Liu GY, Colangelo LA, San Jose Estepar R, et al. Low-Normal FVC Trajectory Starting in Early Adulthood and Risk of Future Interstitial Abnormalities. *Am J Respir Crit Care Med* 2023; **208**(7): 816-8 https://pubmed.ncbi.nlm.nih.gov/37490649.
454. Bui DS, Lodge CJ, Burgess JA, et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *The Lancet Respiratory Medicine* 2018; **6**(7): 535-44
455. Jones PW. Health status and the spiral of decline. *COPD* 2009; **6**(1): 59-63 https://pubmed.ncbi.nlm.nih.gov/19229709.
456. Han MK, Muellerova H, Curran-Everett D, et al. GOLD 2011 disease severity classification in COPDGene: a prospective cohort study. *Lancet Respir Med* 2013; **1**(1): 43-50 https://pubmed.ncbi.nlm.nih.gov/24321803.
457. American Thoracic Society (ATS). Surveillance for respiratory hazards in the occupational setting *Am Rev Respir Dis* 1982; **126**: 952-6
458. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; **54**(7): 581-6 https://pubmed.ncbi.nlm.nih.gov/10377201.
459. Sundh J, Janson C, Lisspers K, Stallberg B, Montgomery S. The Dyspnoea, Obstruction, Smoking, Exacerbation (DOSE) index is predictive of mortality in COPD. *Prim Care Respir J* 2012; **21**(3): 295-301 https://pubmed.ncbi.nlm.nih.gov/22786813.
460. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002; **121**(5): 1434-40 https://pubmed.ncbi.nlm.nih.gov/12006425.
461. Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax* 2001; **56**(11): 880-7 https://pubmed.ncbi.nlm.nih.gov/11641515.
462. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987; **42**(10): 773-8 https://pubmed.ncbi.nlm.nih.gov/3321537.
463. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; **145**(6): 1321-7 https://pubmed.ncbi.nlm.nih.gov/1595997.
464. 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): 648-54 https://pubmed.ncbi.nlm.nih.gov/19720809.
465. Jones PW, Tomaszewski EL, Belton L, et al. Validity of the Chronic Airways Assessment Test (CAAT) in asthma, asthma+COPD and COPD in NOVELTY. *ERJ Open Res* 2025; **11**(4): https://pubmed.ncbi.nlm.nih.gov/40692841.
466. 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): 413-25 https://pubmed.ncbi.nlm.nih.gov/26513112.
467. Nishimura K, Mitsuma S, Kobayashi A, et al. COPD and disease-specific health status in a working population. *Respir Res* 2013; **14**(1): 61 https://pubmed.ncbi.nlm.nih.gov/23725096.
468. Miravitlles M, Soriano JB, Garcia-Rio F, et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. *Thorax* 2009; **64**(10): 863-8 https://pubmed.ncbi.nlm.nih.gov/19553233.
469. 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 https://pubmed.ncbi.nlm.nih.gov/21835018.
470. Jones PW, Adamek L, Nadeau G, Banik N. Comparisons of health status scores with MRC grades in COPD: implications for the GOLD 2011 classification. *Eur Respir J* 2013; **42**(3): 647-54 https://pubmed.ncbi.nlm.nih.gov/23258783.
471. Hurst JR, Wedzicha JA. What is (and what is not) a COPD exacerbation: thoughts from the new GOLD guidelines. *Thorax* 2007; **62**(3): 198-9 https://pubmed.ncbi.nlm.nih.gov/17329557.
472. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet* 2007; **370**(9589): 786-96 https://pubmed.ncbi.nlm.nih.gov/17765528.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

473. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; **157**(5 Pt 1): 1418-22 https://pubmed.ncbi.nlm.nih.gov/9603117.
474. Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. *Eur Respir J Suppl* 2003; **41**: 46s-53s https://pubmed.ncbi.nlm.nih.gov/12795331.
475. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; **60**(11): 925-31 https://pubmed.ncbi.nlm.nih.gov/16055622.
476. Choi JY, Yoon HK, Moon JY, et al. Prognostic Impact of Single Moderate Exacerbation in Patients With COPD: Analysis of 12-Year Mortality and Future Exacerbation Risk. *Chest* 2026; 10.1016/j.chest.2026.07.5219: https://pubmed.ncbi.nlm.nih.gov/42526633.
477. Wu F, Wan Q, Tian H, et al. Prognostic Significance of Mild Exacerbations or 1 Moderate Exacerbation in COPD: A Prospective Community-Based Cohort Study. *Chest* 2026; **170**(3): 725-38 https://pubmed.ncbi.nlm.nih.gov/42026000.
478. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; **363**(12): 1128-38 https://pubmed.ncbi.nlm.nih.gov/20843247.
479. Han MK, Quibrera PM, Carretta EE, et al. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med* 2017; **5**(8): 619-26 https://pubmed.ncbi.nlm.nih.gov/28668356.
480. Bhatt SP, Adibi A, Bodduluri S, et al. Discriminative performance and clinical utility of chronic obstructive pulmonary disease exacerbation categories for predicting future exacerbations. *Am J Respir Crit Care Med* 2026; **212**(8): 1721-9 https://pubmed.ncbi.nlm.nih.gov/42085195.
481. Lan Y, Chen R, Zheng J, et al. Predictors of COPD exacerbations differ between grades of airflow limitation. *ERJ Open Res* 2026; **12**(1): https://pubmed.ncbi.nlm.nih.gov/41668878.
482. Mullerova H, Maselli DJ, Locantore N, et al. Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort. *Chest* 2015; **147**(4): 999-1007 https://pubmed.ncbi.nlm.nih.gov/25356881.
483. Soriano JB, Lamprecht B, Ramirez AS, et al. Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data. *Lancet Respir Med* 2015; **3**(6): 443-50 https://pubmed.ncbi.nlm.nih.gov/25995071.
484. Hartl S, Breyer MK, Burghuber OC, et al. Blood eosinophil count in the general population: typical values and potential confounders. *Eur Respir J* 2020; **55**(5): 1901874 https://pubmed.ncbi.nlm.nih.gov/32060069.
485. Kolsum U, Southworth T, Jackson N, Singh D. Blood eosinophil counts in COPD patients compared to controls. *Eur Respir J* 2019; **54**(4): 1900633 https://pubmed.ncbi.nlm.nih.gov/31221811.
486. George L, Taylor AR, Esteve-Codina A, et al. Blood eosinophil count and airway epithelial transcriptome relationships in COPD versus asthma. *Allergy* 2020; **75**(2): 370-80 https://pubmed.ncbi.nlm.nih.gov/31506971.
487. Higham A, Beech A, Wolosianka S, et al. Type 2 inflammation in eosinophilic chronic obstructive pulmonary disease. *Allergy* 2021; **76**(6): 1861-4 https://pubmed.ncbi.nlm.nih.gov/33206402.
488. Singh D, Agusti A, Martinez FJ, et al. Blood Eosinophils and Chronic Obstructive Pulmonary Disease: A Global Initiative for Chronic Obstructive Lung Disease Science Committee 2022 Review. *Am J Respir Crit Care Med* 2022; **206**(1): 17-24 https://pubmed.ncbi.nlm.nih.gov/35737975.
489. Landis SH, Suruki R, Hilton E, Compton C, Galwey NW. Stability of Blood Eosinophil Count in Patients with COPD in the UK Clinical Practice Research Datalink. *COPD* 2017; **14**(4): 382-8 https://pubmed.ncbi.nlm.nih.gov/28569614.
490. Oshagbemi OA, Burden AM, Braeken DCW, et al. Stability of Blood Eosinophils in Patients with Chronic Obstructive Pulmonary Disease and in Control Subjects, and the Impact of Sex, Age, Smoking, and Baseline Counts. *Am J Respir Crit Care Med* 2017; **195**(10): 1402-4 https://pubmed.ncbi.nlm.nih.gov/28165763.
491. Southworth T, Beech G, Foden P, Kolsum U, Singh D. The reproducibility of COPD blood eosinophil counts. *Eur Respir J* 2018; **52**(1): https://pubmed.ncbi.nlm.nih.gov/29724922.
492. Casanova C, Celli BR, de-Torres JP, et al. Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD. *Eur Respir J* 2017; **50**(5): https://pubmed.ncbi.nlm.nih.gov/29167301.
493. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. *Am J Respir Crit Care Med* 2016; **193**(9): 965-74 https://pubmed.ncbi.nlm.nih.gov/26641631.
494. Yun JH, Lamb A, Chase R, et al. Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2018; **141**(6): 2037-47 e10 https://pubmed.ncbi.nlm.nih.gov/29709670.
495. Tan WC, Bourbeau J, Nadeau G, et al. High eosinophil counts predict decline in FEV(1): results from the CanCOLD study. *Eur Respir J* 2021; **57**(5): https://pubmed.ncbi.nlm.nih.gov/33303555.
496. Park HY, Chang Y, Kang D, et al. Blood eosinophil counts and the development of obstructive lung disease: the Kangbuk Samsung Health Study. *Eur Respir J* 2021; **58**(4): https://pubmed.ncbi.nlm.nih.gov/33737406.
497. Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med* 2018; **6**(2): 117-26 https://pubmed.ncbi.nlm.nih.gov/29331313.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

498. Siddiqui SH, Guasconi A, Vestbo J, et al. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015; **192**(4): 523-5 https://pubmed.ncbi.nlm.nih.gov/26051430.
499. Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018; **391**(10125): 1076-84 https://pubmed.ncbi.nlm.nih.gov/29429593.
500. 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): 435-42 https://pubmed.ncbi.nlm.nih.gov/25878028.
501. Vestbo J, Papi A, Corradi M, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2017; **389**(10082): 1919-29 https://pubmed.ncbi.nlm.nih.gov/28385353.
502. Lipson DA, Barnhart F, Brealey N, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *N Engl J Med* 2018; **378**(18): 1671-80 https://pubmed.ncbi.nlm.nih.gov/29668352.
503. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008; **32**(4): 962-9 https://pubmed.ncbi.nlm.nih.gov/18579551.
504. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005; **128**(4): 2099-107 https://pubmed.ncbi.nlm.nih.gov/16236861.
505. National Institute for Health and Care Excellence. Multimorbidity: clinical assessment and management; NICE guideline [NG56]Published date: 21 September 2016 [accessed Oct 2026]. https://www.nice.org.uk/guidance/ng56.
506. Vanfleteren LE, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; **187**(7): 728-35 https://pubmed.ncbi.nlm.nih.gov/23392440.
507. Brenner DR, Boffetta P, Duell EJ, et al. Previous lung diseases and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium. *Am J Epidemiol* 2012; **176**(7): 573-85 https://pubmed.ncbi.nlm.nih.gov/22986146.
508. Fry JS, Hamling JS, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating FEV1 decline to lung cancer risk. *BMC Cancer* 2012; **12**: 498 https://pubmed.ncbi.nlm.nih.gov/23101666.
509. Wagner PD. Possible mechanisms underlying the development of cachexia in COPD. *Eur Respir J* 2008; **31**(3): 492-501 https://pubmed.ncbi.nlm.nih.gov/18310396.
510. Maltais F, Decramer M, Casaburi R, et al. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2014; **189**(9): e15-62 https://pubmed.ncbi.nlm.nih.gov/24787074.
511. Goossens LM, Leimer I, Metzdorf N, Becker K, Rutten-van Molken MP. Does the 2013 GOLD classification improve the ability to predict lung function decline, exacerbations and mortality: a post-hoc analysis of the 4-year UPLIFT trial. *BMC Pulm Med* 2014; **14**: 163 https://pubmed.ncbi.nlm.nih.gov/25326750.
512. Kim J, Yoon HI, Oh YM, et al. Lung function decline rates according to GOLD group in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2015; **10**: 1819-27 https://pubmed.ncbi.nlm.nih.gov/26379432.
513. Halpin DMG, Healey H, Skinner D, Carter V, Pullen R, Price D. Exacerbation history and blood eosinophil count prior to diagnosis of COPD and risk of subsequent exacerbations. *Eur Respir J* 2024; **64**(4): https://pubmed.ncbi.nlm.nih.gov/39147410.
514. Sadatsafavi M, McCormack J, Petkau J, Lynd LD, Lee TY, Sin DD. Should the number of acute exacerbations in the previous year be used to guide treatments in COPD? *Eur Respir J* 2021; **57**(2): https://pubmed.ncbi.nlm.nih.gov/32855228.
515. Rabe KF, Martinez FJ, Ferguson GT, et al. Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. *N Engl J Med* 2020; **383**(1): 35-48 https://pubmed.ncbi.nlm.nih.gov/32579807.
516. Ferguson GT, Rabe KF, Martinez FJ, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med* 2018; **6**(10): 747-58 https://pubmed.ncbi.nlm.nih.gov/30232048.
517. Kessler R, Stahl E, Vogelmeier C, et al. Patient understanding, detection, and experience of COPD exacerbations: an observational, interview-based study. *Chest* 2006; **130**(1): 133-42 https://pubmed.ncbi.nlm.nih.gov/16840393.
518. Plaza V, Fernández-Rodríguez C, Melero C, et al. Validation of the 'Test of the Adherence to Inhalers' (TAI) for Asthma and COPD Patients. *J Aerosol Med Pulm Drug Deliv* 2016; **29**(2): 142-52 https://pubmed.ncbi.nlm.nih.gov/26230150.
519. Johnson-Warrington V, Mitchell KE, Singh SJ. Is a practice incremental shuttle walk test needed for patients with chronic obstructive pulmonary disease admitted to hospital for an acute exacerbation? *Respiration* 2015; **90**(3): 206-10 https://pubmed.ncbi.nlm.nih.gov/26406442.
520. Rochester CL, Vogiatzis I, Holland AE, et al. An Official American Thoracic Society/European Respiratory Society Policy Statement: Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation. *Am J Respir Crit Care Med* 2015; **192**(11): 1373-86 https://pubmed.ncbi.nlm.nih.gov/26623686.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

521. Blakemore WS, Forster RE, Morton JW, Ogilvie CM. A standardized breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. *J Clin Invest* 1957; **36**(1 Part 1): 1-17 https://pubmed.ncbi.nlm.nih.gov/13398477.
522. American Thoracic Society (ATS). Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. *Am Rev Respir Dis* 1991; **144**(5): 1202-18 https://pubmed.ncbi.nlm.nih.gov/1952453.
523. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005; **26**(4): 720-35 https://pubmed.ncbi.nlm.nih.gov/16204605.
524. Stanojevic S, Graham BL, Cooper BG, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J* 2017; **50**(3): https://pubmed.ncbi.nlm.nih.gov/28893868.
525. Gochicoa-Rangel L, Perez-Padilla R, Vazquez-Garcia JC, et al. Long-Term Stability of a Portable Carbon Monoxide Single-Breath Diffusing Capacity Instrument. *Respir Care* 2017; **62**(2): 231-5 https://pubmed.ncbi.nlm.nih.gov/27677305.
526. Balasubramanian A, MacIntyre NR, Henderson RJ, et al. Diffusing Capacity of Carbon Monoxide in Assessment of COPD. *Chest* 2019; **156**(6): 1111-9 https://pubmed.ncbi.nlm.nih.gov/31352035.
527. Elbehairy AF, O'Donnell CD, Abd Elhameed A, et al. Low resting diffusion capacity, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *J Appl Physiol (1985)* 2019; **127**(4): 1107-16 https://pubmed.ncbi.nlm.nih.gov/31369329.
528. Farkhooy A, Janson C, Arnardottir RH, Malinovschi A, Emtner M, Hedenstrom H. Impaired carbon monoxide diffusing capacity is the strongest predictor of exercise intolerance in COPD. *COPD* 2013; **10**(2): 180-5 https://pubmed.ncbi.nlm.nih.gov/23547629.
529. Collins SE, Kirby M, Smith BM, et al. Relationship of Pulmonary Vascular Structure and Function With Exercise Capacity in Health and COPD. *Chest* 2025; **167**(2): 402-13 https://pubmed.ncbi.nlm.nih.gov/39368737.
530. Balasubramanian A, Putcha N, MacIntyre NR, et al. Diffusing Capacity and Mortality in Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2023; **20**(1): 38-46 https://pubmed.ncbi.nlm.nih.gov/35969416.
531. Boutou AK, Shrikrishna D, Tanner RJ, et al. Lung function indices for predicting mortality in COPD. *Eur Respir J* 2013; **42**(3): 616-25 https://pubmed.ncbi.nlm.nih.gov/23349449.
532. de-Torres JP, O'Donnell DE, Marin JM, et al. Clinical and Prognostic Impact of Low Diffusing Capacity for Carbon Monoxide Values in Patients With Global Initiative for Obstructive Lung Disease I COPD. *Chest* 2021; **160**(3): 872-8 https://pubmed.ncbi.nlm.nih.gov/33901498.
533. Haruna A, Muro S, Nakano Y, et al. CT scan findings of emphysema predict mortality in COPD. *Chest* 2010; **138**(3): 635-40 https://pubmed.ncbi.nlm.nih.gov/20382712.
534. Balasubramanian A, Gearhart AS, Putcha N, et al. Diffusing Capacity as a Predictor of Hospitalizations in a Clinical Cohort of Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2024; **21**(2): 243-50 https://pubmed.ncbi.nlm.nih.gov/37870393.
535. Ferguson MK, Gaissert HA, Grab JD, Sheng S. Pulmonary complications after lung resection in the absence of chronic obstructive pulmonary disease: the predictive role of diffusing capacity. *J Thorac Cardiovasc Surg* 2009; **138**(6): 1297-302 https://pubmed.ncbi.nlm.nih.gov/19783010.
536. Casanova C, Gonzalez-Davila E, Martinez-Gonzalez C, et al. Natural Course of the Diffusing Capacity of the Lungs for Carbon Monoxide in COPD: Importance of Sex. *Chest* 2021; **160**(2): 481-90 https://pubmed.ncbi.nlm.nih.gov/33878339.
537. Kang J, Oh YM, Lee JH, et al. Distinctive patterns of pulmonary function change according to baseline lung volume and diffusing capacity. *Int J Tuberc Lung Dis* 2020; **24**(6): 597-605 https://pubmed.ncbi.nlm.nih.gov/32553011.
538. Lacasse Y, Theriault S, St-Pierre B, et al. Oximetry neither to prescribe long-term oxygen therapy nor to screen for severe hypoxaemia. *ERJ Open Res* 2021; **7**(4): https://pubmed.ncbi.nlm.nih.gov/34671670.
539. Scioscia G, Blanco I, Arismendi E, et al. Different dyspnoea perception in COPD patients with frequent and infrequent exacerbations. *Thorax* 2017; **72**(2): 117-21 https://pubmed.ncbi.nlm.nih.gov/27586869.
540. Durheim MT, Smith PJ, Babyak MA, et al. Six-minute-walk distance and accelerometry predict outcomes in chronic obstructive pulmonary disease independent of Global Initiative for Chronic Obstructive Lung Disease 2011 Group. *Ann Am Thorac Soc* 2015; **12**(3): 349-56 https://pubmed.ncbi.nlm.nih.gov/25568929.
541. 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 https://pubmed.ncbi.nlm.nih.gov/14738227.
542. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med* 2003; **167**(4): 544-9 https://pubmed.ncbi.nlm.nih.gov/12446268.
543. Polkey MI, Spruit MA, Edwards LD, et al. Six-minute-walk test in chronic obstructive pulmonary disease: minimal clinically important difference for death or hospitalization. *Am J Respir Crit Care Med* 2013; **187**(4): 382-6 https://pubmed.ncbi.nlm.nih.gov/23262518.
544. Daynes E, Barker RE, Jones AV, et al. Determining the minimum important differences for field walking tests in adults with long-term conditions: a systematic review and meta-analysis. *Eur Respir Rev* 2025; **34**(176): https://pubmed.ncbi.nlm.nih.gov/40436612.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

545. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014; **44**(6): 1428-46 https://pubmed.ncbi.nlm.nih.gov/25359355.
546. Casaburi R, Merrill D, Leidy NK, et al. Validation of Constant Work Rate Cycling Endurance Time for Use in Chronic Obstructive Pulmonary Disease Clinical Trials. *Ann Am Thorac Soc* 2024; **21**(5): 727-39 https://pubmed.ncbi.nlm.nih.gov/38109693.
547. Puente-Maestu L, Palange P, Casaburi R, et al. Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. *Eur Respir J* 2016; **47**(2): 429-60 https://pubmed.ncbi.nlm.nih.gov/26797036.
548. Radtke T, Crook S, Kaltsakas G, et al. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *Eur Respir Rev* 2019; **28**(154): https://pubmed.ncbi.nlm.nih.gov/31852745.
549. Spence JG, Brincks J, Løkke A, Neustrup L, Østergaard EB. One-minute sit-to-stand test as a quick functional test for people with COPD in general practice. *NPJ Prim Care Respir Med* 2023; **33**(1): 11 https://pubmed.ncbi.nlm.nih.gov/36922535.
550. Evans RA, Singh SJ. Minimum important difference of the incremental shuttle walk test distance in patients with COPD. *Thorax* 2019; **74**(10): 994-5 https://pubmed.ncbi.nlm.nih.gov/31147399.
551. Celli B, Tetzlaff K, Criner G, 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): 1483-93 https://pubmed.ncbi.nlm.nih.gov/27332504.
552. Revill SM, Morgan MD, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. *Thorax* 1999; **54**(3): 213-22 https://pubmed.ncbi.nlm.nih.gov/10325896.
553. Casanova C, Cote CG, Marin JM, et al. The 6-min walking distance: long-term follow up in patients with COPD. *Eur Respir J* 2007; **29**(3): 535-40 https://pubmed.ncbi.nlm.nih.gov/17107991.
554. World Health Organization. WHO Guidelines Approved by the Guidelines Review Committee, Global Recommendations on Physical Activity for Health. *World Health Organization, Geneva* 2010: https://pubmed.ncbi.nlm.nih.gov/26180873.
555. Geidl W, Schlesinger S, Mino E, Miranda L, Pfeifer K. Dose-response relationship between physical activity and mortality in adults with noncommunicable diseases: a systematic review and meta-analysis of prospective observational studies. *Int J Behav Nutr Phys Act* 2020; **17**(1): 109 https://pubmed.ncbi.nlm.nih.gov/32843054.
556. Alahmari AD, Kowlessar BS, Patel AR, et al. Physical activity and exercise capacity in patients with moderate COPD exacerbations. *Eur Respir J* 2016; **48**(2): 340-9 https://pubmed.ncbi.nlm.nih.gov/27126688.
557. Spruit MA, Gosselink R, Troosters T, et al. Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax* 2003; **58**(9): 752-6 https://pubmed.ncbi.nlm.nih.gov/12947130.
558. Watz H, Pitta F, Rochester CL, et al. An official European Respiratory Society statement on physical activity in COPD. *Eur Respir J* 2014; **44**(6): 1521-37 https://pubmed.ncbi.nlm.nih.gov/25359358.
559. Ramon MA, Esteban C, Ortega F, et al. Discriminant Validity of a Single Clinical Question for the Screening of Inactivity in Individuals Living with COPD. *Int J Chron Obstruct Pulmon Dis* 2022; **17**: 3033-44 https://pubmed.ncbi.nlm.nih.gov/36483675.
560. Cruz J, Jácome C, Oliveira A, et al. Construct validity of the brief physical activity assessment tool for clinical use in COPD. *Clin Respir J* 2021; **15**(5): 530-9 https://pubmed.ncbi.nlm.nih.gov/33484059.
561. Demeyer H, Mohan D, Burtin C, et al. Objectively Measured Physical Activity in Patients with COPD: Recommendations from an International Task Force on Physical Activity. *Chronic Obstr Pulm Dis* 2021; **8**(4): 528-50 https://pubmed.ncbi.nlm.nih.gov/34433239.
562. Garcia-Aymerich J, Puhan MA, Corriol-Rohou S, et al. Validity and responsiveness of the Daily- and Clinical visit-PROactive Physical Activity in COPD (D-PPAC and C-PPAC) instruments. *Thorax* 2021; **76**(3): 228-38 https://pubmed.ncbi.nlm.nih.gov/33479044.
563. Garrod R, Bestall JC, Paul EA, Wedzicha JA, Jones PW. Development and validation of a standardized measure of activity of daily living in patients with severe COPD: the London Chest Activity of Daily Living scale (LCADL). *Respir Med* 2000; **94**(6): 589-96 https://pubmed.ncbi.nlm.nih.gov/10921765.
564. Lareau SC, Carrieri-Kohlman V, Janson-Bjerklie S, Roos PJ. Development and testing of the Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ). *Heart Lung* 1994; **23**(3): 242-50 https://pubmed.ncbi.nlm.nih.gov/8039994.
565. de Torres JP, Bastarrika G, Zagaceta J, et al. Emphysema presence, severity, and distribution has little impact on the clinical presentation of a cohort of patients with mild to moderate COPD. *Chest* 2011; **139**(1): 36-42 https://pubmed.ncbi.nlm.nih.gov/20705800.
566. Kahnert K, Jörres RA, Kauczor HU, et al. Relationship between clinical and radiological signs of bronchiectasis in COPD patients: Results from COSYCONET. *Respir Med* 2020; **172**: 106117 https://pubmed.ncbi.nlm.nih.gov/32891937.
567. Ezponda A, Casanova C, Divo M, et al. Chest CT-assessed comorbidities and all-cause mortality risk in COPD patients in the BODE cohort. *Respirology* 2022; **27**(4): 286-93 https://pubmed.ncbi.nlm.nih.gov/35132732.
568. Klooster K, ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, Slebos DJ. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. *N Engl J Med* 2015; **373**(24): 2325-35 https://pubmed.ncbi.nlm.nih.gov/26650153.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

569. Gu S, Leader J, Zheng B, et al. Direct assessment of lung function in COPD using CT densitometric measures. *Physiol Meas* 2014; **35**(5): 833-45 https://pubmed.ncbi.nlm.nih.gov/24710855.
570. Han MK, Kazerooni EA, Lynch DA, et al. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes. *Radiology* 2011; **261**(1): 274-82 https://pubmed.ncbi.nlm.nih.gov/21788524.
571. Makimoto K, Virdee S, Koo M, et al. Upper-lobe CT imaging features improve prediction of lung function decline in COPD. *ERJ Open Res* 2025; **11**(3): https://pubmed.ncbi.nlm.nih.gov/40589906.
572. Labaki WW, Gu T, Murray S, et al. Voxel-Wise Longitudinal Parametric Response Mapping Analysis of Chest Computed Tomography in Smokers. *Acad Radiol* 2019; **26**(2): 217-23 https://pubmed.ncbi.nlm.nih.gov/30055897.
573. Hogg JC, Paré PD, Hackett TL. The Contribution of Small Airway Obstruction to the Pathogenesis of Chronic Obstructive Pulmonary Disease. *Physiol Rev* 2017; **97**(2): 529-52 https://pubmed.ncbi.nlm.nih.gov/28151425.
574. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet* 2004; **364**(9435): 709-21 https://pubmed.ncbi.nlm.nih.gov/15325838.
575. Vasilescu DM, Martinez FJ, Marchetti N, et al. Noninvasive Imaging Biomarker Identifies Small Airway Damage in Severe Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2019; **200**(5): 575-81 https://pubmed.ncbi.nlm.nih.gov/30794432.
576. Bhatt SP, Soler X, Wang X, et al. Association between Functional Small Airway Disease and FEV1 Decline in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2016; **194**(2): 178-84 https://pubmed.ncbi.nlm.nih.gov/26808615.
577. Jain N, Covar RA, Gleason MC, Newell JD, Jr., Gelfand EW, Spahn JD. Quantitative computed tomography detects peripheral airway disease in asthmatic children. *Pediatr Pulmonol* 2005; **40**(3): 211-8 https://pubmed.ncbi.nlm.nih.gov/16015663.
578. Matsuoka S, Kurihara Y, Yagihashi K, Hoshino M, Watanabe N, Nakajima Y. Quantitative assessment of air trapping in chronic obstructive pulmonary disease using inspiratory and expiratory volumetric MDCT. *AJR Am J Roentgenol* 2008; **190**(3): 762-9 https://pubmed.ncbi.nlm.nih.gov/18287450.
579. O'Donnell RA, Peebles C, Ward JA, et al. Relationship between peripheral airway dysfunction, airway obstruction, and neutrophilic inflammation in COPD. *Thorax* 2004; **59**(10): 837-42 https://pubmed.ncbi.nlm.nih.gov/15454648.
580. Ritchie AI, Donaldson GC, Hoffman EA, et al. Structural Predictors of Lung Function Decline in Young Smokers with Normal Spirometry. *Am J Respir Crit Care Med* 2024; **209**(10): 1208-18 https://pubmed.ncbi.nlm.nih.gov/38175920.
581. Grydeland TB, Dirksen A, Coxson HO, et al. Quantitative computed tomography: emphysema and airway wall thickness by sex, age and smoking. *Eur Respir J* 2009; **34**(4): 858-65 https://pubmed.ncbi.nlm.nih.gov/19324952.
582. Grydeland TB, Dirksen A, Coxson HO, et al. Quantitative computed tomography measures of emphysema and airway wall thickness are related to respiratory symptoms. *Am J Respir Crit Care Med* 2010; **181**(4): 353-9 https://pubmed.ncbi.nlm.nih.gov/19926869.
583. Martinez-Garcia MA, de la Rosa-Carrillo D, Soler-Cataluna JJ, et al. Bronchial Infection and Temporal Evolution of Bronchiectasis in Patients With Chronic Obstructive Pulmonary Disease. *Clin Infect Dis* 2021; **72**(3): 403-10 https://pubmed.ncbi.nlm.nih.gov/31967312.
584. Bosma CB, Aaron SD, Celli BR, et al. Airway mucus plugs in asthma and chronic obstructive pulmonary disease: pathobiology, imaging, and implications for clinical trials. *Am J Respir Crit Care Med* 2026; **212**(9): 1947-61 https://pubmed.ncbi.nlm.nih.gov/42330343.
585. Wan E, Yen A, Elalami R, et al. Airway Mucus Plugs on Chest Computed Tomography Are Associated with Exacerbations in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2025; **211**(5): 814-22 https://pubmed.ncbi.nlm.nih.gov/39470402.
586. Diaz AA, Grumley S, Yen A, et al. Eosinophils, mucus plugs and clinical outcomes: findings from two COPD cohorts. *Eur Respir J* 2024; **64**(6): https://pubmed.ncbi.nlm.nih.gov/39572219.
587. Singh D, Guller P, Reid F, et al. A phase 2a trial of the IL-33 monoclonal antibody tozorakimab in patients with COPD: FRONTIER-4. *Eur Respir J* 2025; **66**(1): https://pubmed.ncbi.nlm.nih.gov/40154559.
588. Galban CJ, Han MK, Boes JL, et al. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nat Med* 2012; **18**(11): 1711-5 https://pubmed.ncbi.nlm.nih.gov/23042237.
589. Hatabu H, Hunninghake GM, Richeldi L, et al. Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. *Lancet Respir Med* 2020; **8**(7): 726-37 https://pubmed.ncbi.nlm.nih.gov/32649920.
590. Rose JA, Menon AA, Hino T, et al. Suspected Interstitial Lung Disease in COPDGene Study. *Am J Respir Crit Care Med* 2023; **207**(1): 60-8 https://pubmed.ncbi.nlm.nih.gov/35930450.
591. Ash SY, Choi B, Oh A, Lynch DA, Humphries SM. Deep Learning Assessment of Progression of Emphysema and Fibrotic Interstitial Lung Abnormality. *Am J Respir Crit Care Med* 2023; **208**(6): 666-75 https://pubmed.ncbi.nlm.nih.gov/37364281.
592. Putman RK, Gudmundsson G, Axelsson GT, et al. Imaging Patterns Are Associated with Interstitial Lung Abnormality Progression and Mortality. *Am J Respir Crit Care Med* 2019; **200**(2): 175-83 https://pubmed.ncbi.nlm.nih.gov/30673508.
593. WHO meeting participants. Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. *Bull World Health Organ* 1997; **75**(5): 397-415 https://pubmed.ncbi.nlm.nih.gov/9447774.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

594. Miravitlles M, Dirksen A, Ferrarotti I, et al. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in alpha(1)-antitrypsin deficiency. *Eur Respir J* 2017; **50**(5): https://pubmed.ncbi.nlm.nih.gov/29191952.
595. Parr DG, Stoel BC, Stolk J, Stockley RA. Pattern of emphysema distribution in alpha1-antitrypsin deficiency influences lung function impairment. *Am J Respir Crit Care Med* 2004; **170**(11): 1172-8 https://pubmed.ncbi.nlm.nih.gov/15306534.
596. Guerra B, Haile SR, Lamprecht B, et al. Large-scale external validation and comparison of prognostic models: an application to chronic obstructive pulmonary disease. *BMC Med* 2018; **16**(1): 33 https://pubmed.ncbi.nlm.nih.gov/29495970.
597. Celli BR, Cote CG, Marin JM, 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): 1005-12 https://pubmed.ncbi.nlm.nih.gov/14999112.
598. Jones RC, Donaldson GC, Chavannes NH, 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): 1189-95 https://pubmed.ncbi.nlm.nih.gov/19797160.
599. Puhan MA, Garcia-Aymerich J, Frey M, 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): 704-11 https://pubmed.ncbi.nlm.nih.gov/19716962.
600. 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): 1195-204 https://pubmed.ncbi.nlm.nih.gov/30592902.
601. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016; **47**(2): 410-9 https://pubmed.ncbi.nlm.nih.gov/26828055.
602. Agusti A, Fabbri LM, Singh D, et al. Inhaled corticosteroids in COPD: friend or foe? *Eur Respir J* 2018; **52**(6): 1801219 https://pubmed.ncbi.nlm.nih.gov/30190269.
603. Holland AE, Wageck B, Hoffman M, Lee AL, Jones AW. Does pulmonary rehabilitation address treatable traits? A systematic review. *Eur Respir Rev* 2022; **31**(165): https://pubmed.ncbi.nlm.nih.gov/36002168.
604. Singh D, Han MK, Bhatt SP, et al. Is Disease Stability an Attainable Chronic Obstructive Pulmonary Disease Treatment Goal? *Am J Respir Crit Care Med* 2025; **211**(3): 452-63 https://pubmed.ncbi.nlm.nih.gov/39680953.
605. Soler-Cataluna JJ, Villagrasa M, Catalan P, Alcazar-Navarrete B, Calle Rubio M, Miravitlles M. Risk validation of a new quantitative score for clinical control of chronic obstructive pulmonary disease: The RADAR score. *Arch Bronconeumol* 2025; 10.1016/j.arbres.2025.06.003: https://pubmed.ncbi.nlm.nih.gov/40592678.
606. Montes de Oca M. Smoking Cessation/Vaccinations. *Clin Chest Med* 2020; **41**(3): 495-512 https://pubmed.ncbi.nlm.nih.gov/32800202.
607. 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): 464-76 https://pubmed.ncbi.nlm.nih.gov/15065840.
608. Bauer CMT, Morissette MC, Stampfli MR. The influence of cigarette smoking on viral infections: translating bench science to impact COPD pathogenesis and acute exacerbations of COPD clinically. *Chest* 2013; **143**(1): 196-206 https://pubmed.ncbi.nlm.nih.gov/23276842.
609. Crowley TJ, Macdonald MJ, Walter MI. Behavioral anti-smoking trial in chronic obstructive pulmonary disease patients. *Psychopharmacology (Berl)* 1995; **119**(2): 193-204 https://pubmed.ncbi.nlm.nih.gov/7659767.
610. Jimenez-Ruiz CA, Masa F, Miravitlles M, et al. Smoking characteristics: differences in attitudes and dependence between healthy smokers and smokers with COPD. *Chest* 2001; **119**(5): 1365-70 https://pubmed.ncbi.nlm.nih.gov/11348940.
611. 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): 1043-7 https://pubmed.ncbi.nlm.nih.gov/17040932.
612. Wagena EJ, Arrindell WA, Wouters EF, van Schayck CP. Are patients with COPD psychologically distressed? *Eur Respir J* 2005; **26**(2): 242-8 https://pubmed.ncbi.nlm.nih.gov/16055871.
613. 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 https://pubmed.ncbi.nlm.nih.gov/27545342.
614. Hoogendoorn M, Feenstra TL, Hoogenveen RT, Rutten-van Molken MP. Long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD. *Thorax* 2010; **65**(8): 711-8 https://pubmed.ncbi.nlm.nih.gov/20685746.
615. Wei X, Guo K, Shang X, et al. Effects of different interventions on smoking cessation in chronic obstructive pulmonary disease patients: A systematic review and network meta-analysis. *Int J Nurs Stud* 2022; **136**: 104362 https://pubmed.ncbi.nlm.nih.gov/36206617.
616. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict* 1991; **86**(9): 1119-27 https://pubmed.ncbi.nlm.nih.gov/1932883.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

617. John U, Meyer C, Schumann A, et al. A short form of the Fagerstrom Test for Nicotine Dependence and the Heaviness of Smoking Index in two adult population samples. *Addict Behav* 2004; **29**(6): 1207-12 https://pubmed.ncbi.nlm.nih.gov/15236824.
618. Frazer K, Callinan JE, McHugh J, 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 https://pubmed.ncbi.nlm.nih.gov/26842828.
619. The Tobacco Use and Dependence Clinical Practice Guideline Panel. A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. *JAMA* 2000; **283**(24): 3244-54 https://pubmed.ncbi.nlm.nih.gov/10866874.
620. The tobacco use and dependence clinical practice guideline panel s, and consortium representatives,. A clinical practice guideline for treating tobacco use and dependence. *JAMA* 2000; **28**: 3244-54
621. Clinical Practice Guideline Treating Tobacco U, Dependence Update Panel L, Staff. 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): 158-76 https://pubmed.ncbi.nlm.nih.gov/18617085.
622. Glynn TJ, Manley M, Smoking T, Cancer P. How to help your patients stop smoking: a National Cancer Institute manual for physicians. [Bethesda, Md.]: Smoking, Tobacco, and Cancer Program, Division of Cancer Prevention and Control, National Cancer Institute, U.S. Dept. of Health and Human Services, Public Health Service, National Institutes of Health; 1990.
623. Stead LF, Buitrago D, Preciado N, Sanchez G, Hartmann-Boyce J, Lancaster T. Physician advice for smoking cessation. *Cochrane Database Syst Rev* 2013; **2013**(5): CD000165 https://pubmed.ncbi.nlm.nih.gov/23728631.
624. Strassmann R, Bausch B, Spaar A, Kleijnen J, Braendli O, Puhan MA. Smoking cessation interventions in COPD: a network meta-analysis of randomised trials. *Eur Respir J* 2009; **34**(3): 634-40 https://pubmed.ncbi.nlm.nih.gov/19357145.
625. Semenza JC, Rubin CH, Falter KH, et al. Heat-related deaths during the July 1995 heat wave in Chicago. *N Engl J Med* 1996; **335**(2): 84-90 https://pubmed.ncbi.nlm.nih.gov/8649494.
626. Tan J, Zheng Y, Song G, Kalkstein LS, Kalkstein AJ, Tang X. Heat wave impacts on mortality in Shanghai, 1998 and 2003. *Int J Biometeorol* 2007; **51**(3): 193-200 https://pubmed.ncbi.nlm.nih.gov/17039379.
627. Robine JM, Cheung SL, Le Roy S, et al. Death toll exceeded 70,000 in Europe during the summer of 2003. *C R Biol* 2008; **331**(2): 171-8 https://pubmed.ncbi.nlm.nih.gov/18241810.
628. Azhar GS, Mavalankar D, Nori-Sarma A, et al. Heat-related mortality in India: excess all-cause mortality associated with the 2010 Ahmedabad heat wave. *PLoS One* 2014; **9**(3): e91831 https://pubmed.ncbi.nlm.nih.gov/24633076.
629. Mazdiyasni O, AghaKouchak A, Davis SJ, et al. Increasing probability of mortality during Indian heat waves. *Sci Adv* 2017; **3**(6): e1700066 https://pubmed.ncbi.nlm.nih.gov/28630921.
630. Yoon L, Richardson GRA, Gorman M. Reflections on a Century of Extreme Heat Event-Related Mortality Reporting in Canada. *Geohealth* 2024; **8**(2): e2023GH000895 https://pubmed.ncbi.nlm.nih.gov/38371353.
631. Green H, Bailey J, Schwarz L, Vanos J, Ebi K, Benmarhnia T. Impact of heat on mortality and morbidity in low and middle income countries: A review of the epidemiological evidence and considerations for future research. *Environ Res* 2019; **171**: 80-91 https://pubmed.ncbi.nlm.nih.gov/30660921.
632. The Eurowinter Group. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. The Eurowinter Group. *Lancet* 1997; **349**(9062): 1341-6 https://pubmed.ncbi.nlm.nih.gov/9149695.
633. Curriero FC, Heiner KS, Samet JM, Zeger SL, Strug L, Patz JA. Temperature and mortality in 11 cities of the eastern United States. *Am J Epidemiol* 2002; **155**(1): 80-7 https://pubmed.ncbi.nlm.nih.gov/11772788.
634. Braga AL, Zanobetti A, Schwartz J. The effect of weather on respiratory and cardiovascular deaths in 12 U.S. cities. *Environ Health Perspect* 2002; **110**(9): 859-63 https://pubmed.ncbi.nlm.nih.gov/12204818.
635. Analitis A, Katsouyanni K, Biggeri A, et al. Effects of cold weather on mortality: results from 15 European cities within the PHEWE project. *Am J Epidemiol* 2008; **168**(12): 1397-408 https://pubmed.ncbi.nlm.nih.gov/18952849.
636. Basu R, Samet JM. Relation between elevated ambient temperature and mortality: a review of the epidemiologic evidence. *Epidemiol Rev* 2002; **24**(2): 190-202 https://pubmed.ncbi.nlm.nih.gov/12762092.
637. Ye X, Wolff R, Yu W, Vaneckova P, Pan X, Tong S. Ambient temperature and morbidity: a review of epidemiological evidence. *Environ Health Perspect* 2012; **120**(1): 19-28 https://pubmed.ncbi.nlm.nih.gov/21824855.
638. Gasparrini A, Guo Y, Hashizume M, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet* 2015; **386**(9991): 369-75 https://pubmed.ncbi.nlm.nih.gov/26003380.
639. Rocklov J, Ebi K, Forsberg B. Mortality related to temperature and persistent extreme temperatures: a study of cause-specific and age-stratified mortality. *Occup Environ Med* 2011; **68**(7): 531-6 https://pubmed.ncbi.nlm.nih.gov/20962034.
640. Fischer PH, Brunekreef B, Lebret E. Air pollution related deaths during the 2003 heat wave in the Netherlands. *Atmospheric Environment* 2004; **38**(8): 1083-5
641. Stedman JR. The predicted number of air pollution related deaths in the UK during the August 2003 heatwave. *Atmospheric Environment* 2004; **38**(8): 1087-90
642. Schwartz J. Who is sensitive to extremes of temperature?: A case-only analysis. *Epidemiology* 2005; **16**(1): 67-72 https://pubmed.ncbi.nlm.nih.gov/15613947.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

643. Davie GS, Baker MG, Hales S, Carlin JB. Trends and determinants of excess winter mortality in New Zealand: 1980 to 2000. *BMC Public Health* 2007; **7**: 263 https://pubmed.ncbi.nlm.nih.gov/17892590.
644. Hansel NN, McCormack MC, Kim V. The Effects of Air Pollution and Temperature on COPD. *COPD* 2016; **13**(3): 372-9 https://pubmed.ncbi.nlm.nih.gov/26683097.
645. Burkart KG, Brauer M, Aravkin AY, et al. Estimating the cause-specific relative risks of non-optimal temperature on daily mortality: a two-part modelling approach applied to the Global Burden of Disease Study. *Lancet* 2021; **398**(10301): 685-97 https://pubmed.ncbi.nlm.nih.gov/34419204.
646. Bai J, Cui J, Yu C. Burden of chronic obstructive pulmonary disease attributable to non-optimal temperature from 1990 to 2019: a systematic analysis from the Global Burden of Disease Study 2019. *Environ Sci Pollut Res Int* 2023; **30**(26): 68836-47 https://pubmed.ncbi.nlm.nih.gov/37129808.
647. Lin S, Luo M, Walker RJ, Liu X, Hwang SA, Chinery R. Extreme high temperatures and hospital admissions for respiratory and cardiovascular diseases. *Epidemiology* 2009; **20**(5): 738-46 https://pubmed.ncbi.nlm.nih.gov/19593155.
648. Anderson GB, Dominici F, Wang Y, McCormack MC, Bell ML, Peng RD. Heat-related emergency hospitalizations for respiratory diseases in the Medicare population. *Am J Respir Crit Care Med* 2013; **187**(10): 1098-103 https://pubmed.ncbi.nlm.nih.gov/23491405.
649. Gronlund CJ, Zanobetti A, Schwartz JD, Wellenius GA, O'Neill MS. Heat, heat waves, and hospital admissions among the elderly in the United States, 1992-2006. *Environ Health Perspect* 2014; **122**(11): 1187-92 https://pubmed.ncbi.nlm.nih.gov/24905551.
650. Tseng CM, Chen YT, Ou SM, et al. The effect of cold temperature on increased exacerbation of chronic obstructive pulmonary disease: a nationwide study. *PLoS One* 2013; **8**(3): e57066 https://pubmed.ncbi.nlm.nih.gov/23554858.
651. Teare J, Mathee A, Naicker N, et al. Dwelling Characteristics Influence Indoor Temperature and May Pose Health Threats in LMICs. *Ann Glob Health* 2020; **86**(1): 91 https://pubmed.ncbi.nlm.nih.gov/32832385.
652. Tamerius J, Perzanowski M, Acosta L, et al. Socioeconomic and Outdoor Meteorological Determinants of Indoor Temperature and Humidity in New York City Dwellings. *Weather Clim Soc* 2013; **5**(2): 168-79 https://pubmed.ncbi.nlm.nih.gov/24077420.
653. Wallace LA, Emmerich SJ, Howard-Reed C. Continuous measurements of air change rates in an occupied house for 1 year: the effect of temperature, wind, fans, and windows. *J Expo Anal Environ Epidemiol* 2002; **12**(4): 296-306 https://pubmed.ncbi.nlm.nih.gov/12087436.
654. White-Newsome JL, Sanchez BN, Jolliet O, et al. Climate change and health: indoor heat exposure in vulnerable populations. *Environ Res* 2012; **112**: 20-7 https://pubmed.ncbi.nlm.nih.gov/22071034.
655. Franck U, Krüger M, Schwarz N, Grossmann K, Röder S, Schlink U. Heat stress in urban areas: Indoor and outdoor temperatures in different urban structure types and subjectively reported well?being during a heat wave in the city of Leipzig. *Meteorol Z* 2013; **22**(2): 167-77
656. Wilkinson P, Landon M, Armstrong B, Stevenson S, McKee M. Cold comfort: the social and environmental determinants of excess winter death in England, 1986-1996. York: Joseph Rowntree Foundation; 2001.
657. Donaldson GC, Seemungal T, Jeffries DJ, Wedzicha JA. Effect of temperature on lung function and symptoms in chronic obstructive pulmonary disease. *Eur Respir J* 1999; **13**(4): 844-9 https://pubmed.ncbi.nlm.nih.gov/10362051.
658. Viggers H, Howden-Chapman P, Ingham T, et al. Warm homes for older people: aims and methods of a randomised community-based trial for people with COPD. *BMC Public Health* 2013; **13**: 176 https://pubmed.ncbi.nlm.nih.gov/23442368.
659. Scheerens C, Nurhussien L, Aglan A, et al. The impact of personal and outdoor temperature exposure during cold and warm seasons on lung function and respiratory symptoms in COPD. *ERJ Open Res* 2022; **8**(1): https://pubmed.ncbi.nlm.nih.gov/35295231.
660. McCormack MC, Paulin LM, Gummerson CE, Peng RD, Diette GB, Hansel NN. Colder temperature is associated with increased COPD morbidity. *Eur Respir J* 2017; **49**(6): https://pubmed.ncbi.nlm.nih.gov/28663313.
661. Mu Z, Chen PL, Geng FH, et al. Synergistic effects of temperature and humidity on the symptoms of COPD patients. *Int J Biometeorol* 2017; **61**(11): 1919-25 https://pubmed.ncbi.nlm.nih.gov/28567499.
662. Osman LM, Ayres JG, Garden C, Reglitz K, Lyon J, Douglas JG. Home warmth and health status of COPD patients. *Eur J Public Health* 2008; **18**(4): 399-405 https://pubmed.ncbi.nlm.nih.gov/18367496.
663. Jacob D, Winner D. Effect of climate change on air quality. *Atmos Environ* 2009; **43**: 51-63
664. De Sario M, Katsouyanni K, Michelozzi P. Climate change, extreme weather events, air pollution and respiratory health in Europe. *Eur Respir J* 2013; **42**(3): 826-43 https://pubmed.ncbi.nlm.nih.gov/23314896.
665. Anenberg SC, Haines S, Wang E, Nassikas N, Kinney PL. Synergistic health effects of air pollution, temperature, and pollen exposure: a systematic review of epidemiological evidence. *Environ Health* 2020; **19**(1): 130 https://pubmed.ncbi.nlm.nih.gov/33287833.
666. Stafoggia M, Michelozzi P, Schneider A, et al. Joint effect of heat and air pollution on mortality in 620 cities of 36 countries. *Environ Int* 2023; **181**: 108258 https://pubmed.ncbi.nlm.nih.gov/37837748.
667. Basu R, Feng WY, Ostro BD. Characterizing temperature and mortality in nine California counties. *Epidemiology* 2008; **19**(1): 138-45 https://pubmed.ncbi.nlm.nih.gov/18091422.
668. Zanobetti A, Schwartz J. Temperature and mortality in nine US cities. *Epidemiology* 2008; **19**(4): 563-70 https://pubmed.ncbi.nlm.nih.gov/18467963.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

669. Wong CM, Ma S, Hedley AJ, Lam TH. Effect of air pollution on daily mortality in Hong Kong. *Environ Health Perspect* 2001; **109**(4): 335-40 https://pubmed.ncbi.nlm.nih.gov/11335180.
670. Zhang Y, Huang W, London SJ, et al. Ozone and daily mortality in Shanghai, China. *Environ Health Perspect* 2006; **114**(8): 1227-32 https://pubmed.ncbi.nlm.nih.gov/16882530.
671. Li G, Zhou M, Cai Y, Zhang Y, Pan X. Does temperature enhance acute mortality effects of ambient particle pollution in Tianjin City, China. *Sci Total Environ* 2011; **409**(10): 1811-7 https://pubmed.ncbi.nlm.nih.gov/21376370.
672. Analitis A, Michelozzi P, D'Ippoliti D, et al. Effects of heat waves on mortality: effect modification and confounding by air pollutants. *Epidemiology* 2014; **25**(1): 15-22 https://pubmed.ncbi.nlm.nih.gov/24162013.
673. Qiu H, Tan K, Long F, et al. The Burden of COPD Morbidity Attributable to the Interaction between Ambient Air Pollution and Temperature in Chengdu, China. *Int J Environ Res Public Health* 2018; **15**(3): https://pubmed.ncbi.nlm.nih.gov/29534476.
674. Bell ML, Ebisu K, Peng RD, et al. Seasonal and regional short-term effects of fine particles on hospital admissions in 202 US counties, 1999-2005. *Am J Epidemiol* 2008; **168**(11): 1301-10 https://pubmed.ncbi.nlm.nih.gov/18854492.
675. Ko FW, Tam W, Wong TW, et al. Temporal relationship between air pollutants and hospital admissions for chronic obstructive pulmonary disease in Hong Kong. *Thorax* 2007; **62**(9): 780-5 https://pubmed.ncbi.nlm.nih.gov/17311838.
676. Ren C, Williams GM, Tong S. Does particulate matter modify the association between temperature and cardiorespiratory diseases? *Environ Health Perspect* 2006; **114**(11): 1690-6 https://pubmed.ncbi.nlm.nih.gov/17107854.
677. McCormack MC, Belli AJ, Waugh D, et al. Respiratory Effects of Indoor Heat and the Interaction with Air Pollution in Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2016; **13**(12): 2125-31 https://pubmed.ncbi.nlm.nih.gov/27684429.
678. World Health Organization (WHO). WHO Housing and Health Guidelines. Executive summary. Geneva: World Health Organization; 2018.
679. World Health Organization (WHO). Heat and Health. Geneva: World Health Organisation; 2018.
680. Usmani OS, Martinez FJ, Pandya H, et al. Safety of budesonide/glycopyrronium/formoterol fumarate dihydrate delivered by HFO-1234ze versus HFA-134a in chronic obstructive pulmonary disease: a phase 3, multi-site, randomised, double-blind, parallel-group, active-comparator study. *EClinicalMedicine* 2025; **87**: 103402 https://pubmed.ncbi.nlm.nih.gov/40831469.
681. Almeida M, Salvadori M, Corradi M, et al. Switching to a Low Global Warming Potential Propellant in a Pressurized Metered-Dose Inhaler Does Not Affect the Pharmacokinetics of Combined Beclometasone Dipropionate/Formoterol Fumarate. *Clin Ther* 2026; **48**(8): 757-63 https://pubmed.ncbi.nlm.nih.gov/42120272.
682. Singh D, Mancini L, Melis G, Cortellini M, Rostello C, Mathews KS. Safety and tolerability of the low global warming potential propellant HFA-152a in patients with asthma receiving beclometasone dipropionate/formoterol fumarate/glycopyrronium: The TRECOS study. *Respir Med* 2026; **256**: 108814 https://pubmed.ncbi.nlm.nih.gov/41951188.
683. Grohskopf LA, Ferdinands JM, Blanton LH, Broder KR, Loehr J. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2024-25 Influenza Season. *MMWR Recomm Rep* 2024; **73**(5): 1-25 https://pubmed.ncbi.nlm.nih.gov/39197095.
684. Wongsurakiat P, Maranetra KN, Wasi C, Kositanont U, Dejsomritrutai W, Charoenratanakul S. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study. *Chest* 2004; **125**(6): 2011-20 https://pubmed.ncbi.nlm.nih.gov/15189916.
685. Zahhar JA, Salamatullah HK, Almutairi MB, et al. Influenza vaccine effect on risk of stroke occurrence: a systematic review and meta-analysis. *Front Neurol* 2023; **14**: 1324677 https://pubmed.ncbi.nlm.nih.gov/38269000.
686. Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006; 10.1002/14651858.CD002733.pub2(1): CD002733 https://pubmed.ncbi.nlm.nih.gov/16437444.
687. Wongsurakiat P, Lertakyamanee J, Maranetra KN, Jongriratanakul S, Sangkaew S. Economic evaluation of influenza vaccination in Thai chronic obstructive pulmonary disease patients. *J Med Assoc Thai* 2003; **86**(6): 497-508 https://pubmed.ncbi.nlm.nih.gov/12924797.
688. Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *N Engl J Med* 1994; **331**(12): 778-84 https://pubmed.ncbi.nlm.nih.gov/8065407.
689. Fiore AE, Shay DK, Broder K, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR Recomm Rep* 2009; **58**(RR-8): 1-52 https://pubmed.ncbi.nlm.nih.gov/19644442.
690. Edwards KM, Dupont WD, Westrich MK, Plummer WD, Jr., Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. *J Infect Dis* 1994; **169**(1): 68-76 https://pubmed.ncbi.nlm.nih.gov/8277200.
691. Hak E, van Essen GA, Buskens E, Stalman W, de Melker RA. Is immunising all patients with chronic lung disease in the community against influenza cost effective? Evidence from a general practice based clinical prospective cohort study in

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

Utrecht, The Netherlands. *J Epidemiol Community Health* 1998; **52**(2): 120-5 https://pubmed.ncbi.nlm.nih.gov/9578860.
692. Leroux-Roels I, Huang G, Ferguson M, et al. Efficacy and Safety of an mRNA Seasonal Influenza Vaccine in Adults. *N Engl J Med* 2026; **394**(18): 1803-13 https://pubmed.ncbi.nlm.nih.gov/42090792.
693. Huang CL, Nguyen PA, Kuo PL, Iqbal U, Hsu YH, Jian WS. Influenza vaccination and reduction in risk of ischemic heart disease among chronic obstructive pulmonary elderly. *Comput Methods Programs Biomed* 2013; **111**(2): 507-11 https://pubmed.ncbi.nlm.nih.gov/23769164.
694. Anderson CS, Hua C, Wang Z, et al. Influenza vaccination to improve outcomes for patients with acute heart failure (PANDA II): a multiregional, seasonal, hospital-based, cluster-randomised, controlled trial in China. *Lancet* 2025; **406**(10507): 1020-31 https://pubmed.ncbi.nlm.nih.gov/40897187.
695. Kobayashi M, Leidner AJ, Gierke R, et al. Use of 21-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Recommendations of the Advisory Committee on Immunization Practices - United States, 2024. *MMWR Morb Mortal Wkly Rep* 2024; **73**(36): 793-8 https://pubmed.ncbi.nlm.nih.gov/39264843.
696. Scott P, Haranaka M, Choi JH, et al. A Phase 3 Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-Experienced Adults 50 Years of Age or Older (STRIDE-6). *Clin Infect Dis* 2024; **79**(6): 1366-74 https://pubmed.ncbi.nlm.nih.gov/39082735.
697. Wodi AP, Issa AN, Moser CA, Cineas S. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older - United States, 2025. *MMWR Morb Mortal Wkly Rep* 2025; **74**(2): 30-3 https://pubmed.ncbi.nlm.nih.gov/39820474.
698. Platt H, Omole T, Cardona J, et al. Safety, tolerability, and immunogenicity of a 21-valent pneumococcal conjugate vaccine, V116, in healthy adults: phase 1/2, randomised, double-blind, active comparator-controlled, multicentre, US-based trial. *Lancet Infect Dis* 2023; **23**(2): 233-46 https://pubmed.ncbi.nlm.nih.gov/36116461.
699. Walters JA, Smith S, Poole P, Granger RH, Wood-Baker R. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2010; 10.1002/14651858.CD001390.pub3(11): CD001390 https://pubmed.ncbi.nlm.nih.gov/21069668.
700. 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 https://pubmed.ncbi.nlm.nih.gov/28116747.
701. Alfageme I, Vazquez R, Reyes N, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. *Thorax* 2006; **61**(3): 189-95 https://pubmed.ncbi.nlm.nih.gov/16227328.
702. Dransfield MT, Harnden S, Burton RL, et al. Long-term comparative immunogenicity of protein conjugate and free polysaccharide pneumococcal vaccines in chronic obstructive pulmonary disease. *Clin Infect Dis* 2012; **55**(5): e35-44 https://pubmed.ncbi.nlm.nih.gov/22652582.
703. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med* 2015; **372**(12): 1114-25 https://pubmed.ncbi.nlm.nih.gov/25785969.
704. Ignatova GL, Avdeev SN, Antonov VN. Comparative effectiveness of pneumococcal vaccination with PPV23 and PCV13 in COPD patients over a 5-year follow-up cohort study. *Sci Rep* 2021; **11**(1): 15948 https://pubmed.ncbi.nlm.nih.gov/34354113.
705. Ofori-Anyinam O, Leroux-Roels G, Drame M, et al. Immunogenicity and safety of an inactivated quadrivalent influenza vaccine co-administered with a 23-valent pneumococcal polysaccharide vaccine versus separate administration, in adults >/=50years of age: Results from a phase III, randomized, non-inferiority trial. *Vaccine* 2017; **35**(46): 6321-8 https://pubmed.ncbi.nlm.nih.gov/28987445.
706. Cong B, Dighero I, Zhang T, Chung A, Nair H, Li Y. Understanding the age spectrum of respiratory syncytial virus associated hospitalisation and mortality burden based on statistical modelling methods: a systematic analysis. *BMC Med* 2023; **21**(1): 224 https://pubmed.ncbi.nlm.nih.gov/37365569.
707. Melgar M, Britton A, Roper LE, et al. Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices - United States, 2023. *MMWR Morb Mortal Wkly Rep* 2023; **72**(29): 793-801 https://pubmed.ncbi.nlm.nih.gov/37471262.
708. Woodruff RC, Melgar M, Pham H, et al. Acute Cardiac Events in Hospitalized Older Adults With Respiratory Syncytial Virus Infection. *JAMA Intern Med* 2024; **184**(6): 602-11 https://pubmed.ncbi.nlm.nih.gov/38619857.
709. Wiseman DJ, Thwaites RS, Ritchie AI, et al. Respiratory Syncytial Virus-related Community Chronic Obstructive Pulmonary Disease Exacerbations and Novel Diagnostics: A Binational Prospective Cohort Study. *Am J Respir Crit Care Med* 2024; **210**(8): 994-1001 https://pubmed.ncbi.nlm.nih.gov/38502541.
710. Walsh EE, Perez Marc G, Zareba AM, et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. *N Engl J Med* 2023; **388**(16): 1465-77 https://pubmed.ncbi.nlm.nih.gov/37018468.
711. Papi A, Ison MG, Langley JM, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. *N Engl J Med* 2023; **388**(7): 595-608 https://pubmed.ncbi.nlm.nih.gov/36791160.
712. Wilson E, Goswami J, Baqui AH, et al. Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults. *N Engl J Med* 2023; **389**(24): 2233-44 https://pubmed.ncbi.nlm.nih.gov/38091530.
713. Ison MG, Papi A, Athan E, et al. Efficacy and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Protein Vaccine (RSVPreF3 OA) in Older Adults Over 2 RSV Seasons. *Clin Infect Dis* 2024; **78**(6): 1732-44 https://pubmed.ncbi.nlm.nih.gov/38253338.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

714. Ison MG, Papi A, Athan E, et al. Efficacy, safety, and immunogenicity of the AS01(E)-adjuvanted respiratory syncytial virus prefusion F protein vaccine (RSVPreF3 OA) in older adults over three respiratory syncytial virus seasons (AReSVi-006): a multicentre, randomised, observer-blinded, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2025; **13**(6): 517-29 **https://pubmed.ncbi.nlm.nih.gov/40245915**.
715. Surie D, Self WH, Zhu Y, et al. RSV Vaccine Effectiveness Against Hospitalization Among US Adults 60 Years and Older. *JAMA* 2024; **332**(13): 1105-7 **https://pubmed.ncbi.nlm.nih.gov/39230920**.
716. Surie D, Self WH, Yuengling KA, et al. RSV Vaccine Effectiveness Against Hospitalization Among US Adults Aged 60 Years or Older During 2 Seasons. *JAMA* 2025; **334**(16): 1442-51 **https://pubmed.ncbi.nlm.nih.gov/40884491**.
717. Hause AM, Moro PL, Baggs J, et al. Early Safety Findings Among Persons Aged >/=60 Years Who Received a Respiratory Syncytial Virus Vaccine - United States, May 3, 2023-April 14, 2024. *MMWR Morb Mortal Wkly Rep* 2024; **73**(21): 489-94 **https://pubmed.ncbi.nlm.nih.gov/38814851**.
718. Centers for Disease Control and Prevention. RSV Vaccine Guidance for Adults available at: **https://www.cdc.gov/rsv/hcp/vaccine-clinical-guidance/adults.html** [accessed Oct 2026].
719. 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): 1352-61 **https://pubmed.ncbi.nlm.nih.gov/38128608**.
720. Cruz AA, Mortimer KJ, Sepúlveda-Pachón IT, Vroling H, Williams C. Global herpes zoster burden in adults with COPD: a systematic review and meta-analysis. *Eur Respir Rev* 2026; **35**(179): **https://pubmed.ncbi.nlm.nih.gov/41638875**.
721. UK Health Security Agency. Guidance: A guide to the spring 2026 COVID-19 vaccination campaign. Updated 22 June 2026. Available here: **https://www.gov.uk/government/publications/covid-19-vaccination-spring-booster-resources/a-guide-to-the-covid-19-spring-booster-2023** [accessed Oct 2026].
722. Thompson MG, Stenehjem E, Grannis S, et al. Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings. *N Engl J Med* 2021; **385**(15): 1355-71 **https://pubmed.ncbi.nlm.nih.gov/34496194**.
723. Chalkias S, Dennis P, Petersen D, et al. Efficacy, immunogenicity, and safety of a next-generation mRNA-1283 COVID-19 vaccine compared with the mRNA-1273 vaccine (NextCOVE): results from a phase 3, randomised, observer-blind, active-controlled trial. *Lancet Infect Dis* 2025; **25**(11): 1230-42 **https://pubmed.ncbi.nlm.nih.gov/40639387**.
724. Rudman Spergel AK, Wu I, Deng W, et al. Immunogenicity and Safety of Influenza and COVID-19 Multicomponent Vaccine in Adults ≥50 Years: A Randomized Clinical Trial. *Jama* 2025; **333**(22): 1977-87 **https://pubmed.ncbi.nlm.nih.gov/40332892**.
725. Halpin DMG, Dransfield MT, Han MK, et al. The effect of exacerbation history on outcomes in the IMPACT trial. *Eur Respir J* 2020; **55**(5): **https://pubmed.ncbi.nlm.nih.gov/32299860**.
726. Singh D, Fabbri LM, Corradi M, et al. Extrafine triple therapy in patients with symptomatic COPD and history of one moderate exacerbation. *Eur Respir J* 2019; **53**(5): **https://pubmed.ncbi.nlm.nih.gov/30792343**.
727. Zhou Y, Zhong NS, Li X, et al. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2017; **377**(10): 923-35 **https://pubmed.ncbi.nlm.nih.gov/28877027**.
728. Maltais F, Bjermer L, Kerwin EM, et al. Efficacy of umeclidinium/vilanterol versus umeclidinium and salmeterol monotherapies in symptomatic patients with COPD not receiving inhaled corticosteroids: the EMAX randomised trial. *Respir Res* 2019; **20**(1): 238 **https://pubmed.ncbi.nlm.nih.gov/31666084**.
729. Lange P, Marott JL, Vestbo J, et al. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. *Am J Respir Crit Care Med* 2012; **186**(10): 975-81 **https://pubmed.ncbi.nlm.nih.gov/22997207**.
730. Agusti A, Edwards LD, Celli B, et al. Characteristics, stability and outcomes of the 2011 GOLD COPD groups in the ECLIPSE cohort. *Eur Respir J* 2013; **42**(3): 636-46 **https://pubmed.ncbi.nlm.nih.gov/23766334**.
731. Oba Y, Keeney E, Ghatehorde N, Dias S. Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis. *Cochrane Database Syst Rev* 2018; **12**(12): CD012620 **https://pubmed.ncbi.nlm.nih.gov/30521694**.
732. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation. *N Engl J Med* 2024; **390**(24): 2274-83 **https://pubmed.ncbi.nlm.nih.gov/38767614**.
733. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. *N Engl J Med* 2023; **389**(3): 205-14 **https://pubmed.ncbi.nlm.nih.gov/37272521**.
734. Fieldes M, Bourguignon C, Assou S, et al. Targeted therapy in eosinophilic chronic obstructive pulmonary disease. *ERJ Open Res* 2021; **7**(2): **https://pubmed.ncbi.nlm.nih.gov/33855061**.
735. Karner C, Cates CJ. Long-acting beta(2)-agonist in addition to tiotropium versus either tiotropium or long-acting beta(2)-agonist alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; **4**(4): CD008989 **https://pubmed.ncbi.nlm.nih.gov/22513969**.
736. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; **365**(8): 689-98 **https://pubmed.ncbi.nlm.nih.gov/21864166**.
737. Han MK, Tayob N, Murray S, et al. Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. *Am J Respir Crit Care Med* 2014; **189**(12): 1503-8 **https://pubmed.ncbi.nlm.nih.gov/24779680**.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

738. Martinez FJ, Calverley PM, Goehring UM, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. *Lancet* 2015; **385**(9971): 857-66 https://pubmed.ncbi.nlm.nih.gov/25684586.
739. Martinez FJ, Rabe KF, Sethi S, et al. Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting Beta-2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE2SPOND) A Randomized Clinical Trial. *Am J Respir Crit Care Med* 2016; **194**(5): 559-67
740. Rabe KF, Calverley PMA, Martinez FJ, Fabbri LM. Effect of roflumilast in patients with severe COPD and a history of hospitalisation. *Eur Respir J* 2017; **50**(1): https://pubmed.ncbi.nlm.nih.gov/28679611.
741. Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2017; **377**(17): 1613-29 https://pubmed.ncbi.nlm.nih.gov/28893134.
742. Sciurba FC, Criner GJ, Christenson SA, et al. Mepolizumab to Prevent Exacerbations of COPD with an Eosinophilic Phenotype. *N Engl J Med* 2025; **392**(17): 1710-20 https://pubmed.ncbi.nlm.nih.gov/40305712.
743. Chapman KR, Hurst JR, Frent SM, et al. Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial. *Am J Respir Crit Care Med* 2018; **198**(3): 329-39 https://pubmed.ncbi.nlm.nih.gov/29779416.
744. Calverley PMA, Tetzlaff K, Vogelmeier C, et al. Eosinophilia, Frequent Exacerbations, and Steroid Response in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017; **196**(9): 1219-21 https://pubmed.ncbi.nlm.nih.gov/28306321.
745. Rabe KF, Martinez FJ, Ferguson GT, et al. Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. *New England Journal of Medicine* 2020; **383**(1): 35-48
746. Singh D, Bafadhel M, Arya N, et al. Step up to triple therapy versus switch to dual bronchodilator therapy in patients with COPD on an inhaled corticosteroid/long-acting β(2)-agonist: post-hoc analyses of KRONOS. *Respir Res* 2025; **26**(1): 175 https://pubmed.ncbi.nlm.nih.gov/40340809.
747. Capstick T, Atack K, The Leeds Teaching Hospitals NHS Trust. The Leeds Inhaler Device Guide: Inhaler Technique Instructions for Healthcare Professionals and Patients. 1st Edition. Available at https://cpe.org.uk/wp-content/uploads/2016/02/90445-Inhaler-Device-Guide.pdf [accessed Oct 2026]. 2018:
748. Laube BL, Janssens HM, de Jongh FH, et al. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J* 2011; **37**(6): 1308-31 https://pubmed.ncbi.nlm.nih.gov/21310878.
749. Asthma + Lung UK. Using your inhalers. Available at https://www.asthma.org.uk/advice/inhalers-medicines-treatments/using-inhalers/ [accessed Oct 2026].
750. Janknegt R, Kooistra J, Metting E, Dekhuijzen R. Rational selection of inhalation devices in the treatment of chronic obstructive pulmonary disease by means of the System of Objectified Judgement Analysis (SOJA). *Eur J Hosp Pharm* 2021; **28**(2): e4 https://pubmed.ncbi.nlm.nih.gov/32920532.
751. Ciciliani AM, Langguth P, Wachtel H. Handling forces for the use of different inhaler devices. *Int J Pharm* 2019; **560**: 315-21 https://pubmed.ncbi.nlm.nih.gov/30711617.
752. Klijn SL, Hiligsmann M, Evers S, Roman-Rodriguez M, van der Molen T, van Boven JFM. Effectiveness and success factors of educational inhaler technique interventions in asthma & COPD patients: a systematic review. *NPJ Prim Care Respir Med* 2017; **27**(1): 24 https://pubmed.ncbi.nlm.nih.gov/28408742.
753. Pernigotti D, Stonham C, Panigone S, et al. Reducing carbon footprint of inhalers: analysis of climate and clinical implications of different scenarios in five European countries. *BMJ Open Respir Res* 2021; **8**(1): https://pubmed.ncbi.nlm.nih.gov/34872967.
754. Carpenter DM, Roberts CA, Sage AJ, George J, Horne R. A Review of Electronic Devices to Assess Inhaler Technique. *Curr Allergy Asthma Rep* 2017; **17**(3): 17 https://pubmed.ncbi.nlm.nih.gov/28290015.
755. Chan AH, Harrison J, Black PN, Mitchell EA, Foster JM. Using electronic monitoring devices to measure inhaler adherence: a practical guide for clinicians. *J Allergy Clin Immunol Pract* 2015; **3**(3): 335-49 e1-5 https://pubmed.ncbi.nlm.nih.gov/25840665.
756. Bowler R, Allinder M, Jacobson S, et al. Real-world use of rescue inhaler sensors, electronic symptom questionnaires and physical activity monitors in COPD. *BMJ Open Respir Res* 2019; **6**(1): e000350 https://pubmed.ncbi.nlm.nih.gov/30956796.
757. J WHK, Wouters H, Bosnic-Anticevich S, et al. Factors associated with health status and exacerbations in COPD maintenance therapy with dry powder inhalers. *NPJ Prim Care Respir Med* 2022; **32**(1): 18 https://pubmed.ncbi.nlm.nih.gov/35618739.
758. Clark AR, Weers JG, Dhand R. The Confusing World of Dry Powder Inhalers: It Is All About Inspiratory Pressures, Not Inspiratory Flow Rates. *J Aerosol Med Pulm Drug Deliv* 2020; **33**(1): 1-11 https://pubmed.ncbi.nlm.nih.gov/31613682.
759. Mahler DA, Halpin DMG. Peak Inspiratory Flow as a Predictive Therapeutic Biomarker in COPD. *Chest* 2021; **160**(2): 491-8 https://pubmed.ncbi.nlm.nih.gov/33812852.
760. Leving MT, van Boven JFM, Bosnic-Anticevich SZ, et al. Suboptimal Peak Inspiratory Flow and Critical Inhalation Errors are Associated with Higher COPD-Related Healthcare Costs. *Int J Chron Obstruct Pulmon Dis* 2022; **17**: 2401-15 https://pubmed.ncbi.nlm.nih.gov/36185173.
761. Halpin DMG, Worsley S, Ismaila AS, et al. INTREPID: single- versus multiple-inhaler triple therapy for COPD in usual clinical practice. *ERJ Open Res* 2021; **7**(2): 00950-2020 https://pubmed.ncbi.nlm.nih.gov/34109236.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

762. Souza ML, Meneghini AC, Ferraz E, Vianna EO, Borges MC. Knowledge of and technique for using inhalation devices among asthma patients and COPD patients. *J Bras Pneumol* 2009; **35**(9): 824-31 https://pubmed.ncbi.nlm.nih.gov/19820807.
763. Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med* 2011; **105**(6): 930-8 https://pubmed.ncbi.nlm.nih.gov/21367593.
764. Sanchis J, Gich I, Pedersen S, Aerosol Drug Management Improvement T. Systematic Review of Errors in Inhaler Use: Has Patient Technique Improved Over Time? *Chest* 2016; **150**(2): 394-406 https://pubmed.ncbi.nlm.nih.gov/27060726.
765. Cho-Reyes S, Celli BR, Dembek C, Yeh K, Navaie M. Inhalation Technique Errors with Metered-Dose Inhalers Among Patients with Obstructive Lung Diseases: A Systematic Review and Meta-Analysis of U.S. Studies. *Chronic Obstr Pulm Dis* 2019; **6**(3): 267-80 https://pubmed.ncbi.nlm.nih.gov/31342732.
766. van der Palen J, Klein JJ, Schildkamp AM. Comparison of a new multidose powder inhaler (Diskus/Accuhaler) and the Turbuhaler regarding preference and ease of use. *J Asthma* 1998; **35**(2): 147-52 https://pubmed.ncbi.nlm.nih.gov/9576140.
767. van der Palen J, van der Valk P, Goosens M, Groothuis-Oudshoorn K, Brusse-Keizer M. A randomised cross-over trial investigating the ease of use and preference of two dry powder inhalers in patients with asthma or chronic obstructive pulmonary disease. *Expert Opin Drug Deliv* 2013; **10**(9): 1171-8 https://pubmed.ncbi.nlm.nih.gov/23815552.
768. Van Der Palen J, Eijsvogel MM, Kuipers BF, Schipper M, Vermue NA. Comparison of the Diskus inhaler and the Handihaler regarding preference and ease of use. *J Aerosol Med* 2007; **20**(1): 38-44 https://pubmed.ncbi.nlm.nih.gov/17388751.
769. van der Palen J, Klein JJ, Kerkhoff AH, van Herwaarden CL. Evaluation of the effectiveness of four different inhalers in patients with chronic obstructive pulmonary disease. *Thorax* 1995; **50**(11): 1183-7 https://pubmed.ncbi.nlm.nih.gov/8553275.
770. van der Palen J, Ginko T, Kroker A, et al. Preference, satisfaction and errors with two dry powder inhalers in patients with COPD. *Expert Opin Drug Deliv* 2013; **10**(8): 1023-31 https://pubmed.ncbi.nlm.nih.gov/23745954.
771. Pascual S, Feimer J, De Soyza A, et al. Preference, satisfaction and critical errors with Genuair and Breezhaler inhalers in patients with COPD: a randomised, cross-over, multicentre study. *NPJ Prim Care Respir Med* 2015; **25**: 15018 https://pubmed.ncbi.nlm.nih.gov/25927321.
772. Yawn BP, Colice GL, Hodder R. Practical aspects of inhaler use in the management of chronic obstructive pulmonary disease in the primary care setting. *Int J Chron Obstruct Pulmon Dis* 2012; **7**: 495-502 https://pubmed.ncbi.nlm.nih.gov/22888221.
773. Sulaiman I, Cushen B, Greene G, et al. Objective Assessment of Adherence to Inhalers by Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017; **195**(10): 1333-43 https://pubmed.ncbi.nlm.nih.gov/27409253.
774. Clark B, Wells BJ, Saha AK, et al. Low Peak Inspiratory Flow Rates are Common Among COPD Inpatients and are Associated with Increased Healthcare Resource Utilization: A Retrospective Cohort Study. *Int J Chron Obstruct Pulmon Dis* 2022; **17**: 1483-94 https://pubmed.ncbi.nlm.nih.gov/35791340.
775. Barbara S, Kritikos V, Bosnic-Anticevich S. Inhaler technique: does age matter? A systematic review. *Eur Respir Rev* 2017; **26**(146): https://pubmed.ncbi.nlm.nih.gov/29212836.
776. Gray SL, Williams DM, Pulliam CC, Sirgo MA, Bishop AL, Donohue JF. Characteristics predicting incorrect metered-dose inhaler technique in older subjects. *Arch Intern Med* 1996; **156**(9): 984-8 https://pubmed.ncbi.nlm.nih.gov/8624178.
777. Maricoto T, Santos D, Carvalho C, Teles I, Correia-de-Sousa J, Taborda-Barata L. Assessment of Poor Inhaler Technique in Older Patients with Asthma or COPD: A Predictive Tool for Clinical Risk and Inhaler Performance. *Drugs Aging* 2020; **37**(8): 605-16 https://pubmed.ncbi.nlm.nih.gov/32602039.
778. Barrons R, Pegram A, Borries A. Inhaler device selection: special considerations in elderly patients with chronic obstructive pulmonary disease. *Am J Health Syst Pharm* 2011; **68**(13): 1221-32 https://pubmed.ncbi.nlm.nih.gov/21690428.
779. Ho SF, MS OM, Steward JA, Breay P, Burr ML. Inhaler technique in older people in the community. *Age Ageing* 2004; **33**(2): 185-8 https://pubmed.ncbi.nlm.nih.gov/14960436.
780. Newman SP. Spacer devices for metered dose inhalers. *Clin Pharmacokinet* 2004; **43**(6): 349-60 https://pubmed.ncbi.nlm.nih.gov/15086274.
781. Mitchell JP, Nagel MW. Valved holding chambers (VHCs) for use with pressurised metered-dose inhalers (pMDIs): a review of causes of inconsistent medication delivery. *Prim Care Respir J* 2007; **16**(4): 207-14 https://pubmed.ncbi.nlm.nih.gov/17625786.
782. Dantic DE. A critical review of the effectiveness of "teach-back" technique in teaching COPD patients self-management using respiratory inhalers. *Health Educ J* 2014; **73**: 41-50
783. Jia X, Zhou S, Luo D, Zhao X, Zhou Y, Cui YM. Effect of pharmacist-led interventions on medication adherence and inhalation technique in adult patients with asthma or COPD: A systematic review and meta-analysis. *J Clin Pharm Ther* 2020; **45**(5): 904-17 https://pubmed.ncbi.nlm.nih.gov/32107837.
784. Willard-Grace R, Chirinos C, Wolf J, et al. Lay Health Coaching to Increase Appropriate Inhaler Use in COPD: A Randomized Controlled Trial. *Ann Fam Med* 2020; **18**(1): 5-14 https://pubmed.ncbi.nlm.nih.gov/31937527.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

785. Sulaiman I, Greene G, MacHale E, et al. A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. *Eur Respir J* 2018; **51**(1): https://pubmed.ncbi.nlm.nih.gov/29301919.
786. Rabin AS, Seelye SM, Weinstein JB, et al. Budesonide-Formoterol Metered-Dose Inhaler vs Fluticasone-Salmeterol Dry-Powder Inhaler. *JAMA Intern Med* 2025; **185**(8): 1005-13 https://pubmed.ncbi.nlm.nih.gov/40622686.
787. Blackstock FC, Webster KE, McDonald CF, Hill CJ. Comparable improvements achieved in chronic obstructive pulmonary disease through pulmonary rehabilitation with and without a structured educational intervention: a randomized controlled trial. *Respirology* 2014; **19**(2): 193-202 https://pubmed.ncbi.nlm.nih.gov/24261584.
788. Effing TW, Vercoulen JH, Bourbeau J, et al. Definition of a COPD self-management intervention: International Expert Group consensus. *Eur Respir J* 2016; **48**(1): 46-54 https://pubmed.ncbi.nlm.nih.gov/27076595.
789. Ashikaga T, Vacek PM, Lewis SO. Evaluation of a community-based education program for individuals with chronic obstructive pulmonary disease. *J Rehabil* 1980; **46**(2): 23-7 https://pubmed.ncbi.nlm.nih.gov/7392019.
790. Janelli LM, Scherer YK, Schmieder LE. Can a pulmonary health teaching program alter patients' ability to cope with COPD? *Rehabil Nurs* 1991; **16**(4): 199-202 https://pubmed.ncbi.nlm.nih.gov/1852971.
791. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013; **188**(8): e13-64 https://pubmed.ncbi.nlm.nih.gov/24127811.
792. Lenferink A, Brusse-Keizer M, van der Valk PD, et al. Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2017; **8**: CD011682 https://pubmed.ncbi.nlm.nih.gov/28777450.
793. Farias R, Sedeno M, Beaucage D, et al. Innovating the treatment of COPD exacerbations: a phone interactive telesystem to increase COPD Action Plan adherence. *BMJ Open Respir Res* 2019; **6**(1): e000379 https://pubmed.ncbi.nlm.nih.gov/31178998.
794. Seemungal TA, Wedzicha JA. Acute exacerbations of COPD: the challenge is early treatment. *Copd* 2009; **6**(2): 79-81 https://pubmed.ncbi.nlm.nih.gov/19378218.
795. Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest* 2015; **147**(4): 894-942 https://pubmed.ncbi.nlm.nih.gov/25321320.
796. Rochester CL, Alison JA, Carlin B, et al. Pulmonary Rehabilitation for Adults with Chronic Respiratory Disease: An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med* 2023; **208**(4): e7-e26 https://pubmed.ncbi.nlm.nih.gov/37581410.
797. World Health Organization (WHO). Package of interventions for rehabilitation: module 4: cardiopulmonary conditions. Available at: https://www.who.int/publications/i/item/9789240071162 [accessed October 2026].
798. World Health Organization (WHO). Strengthening rehabilitation in health systems. SEVENTY-SIXTH WORLD HEALTH ASSEMBLY Agenda item 13.4. Online document available here: https://apps.who.int/gb/ebwha/pdf_files/WHA76/A76_R6-en.pdf [accessed October 2026].
799. Sánchez Romero EA, Zubercová AJ, Gran A, et al. Comparative effectiveness of water-based versus land-based rehabilitation in COPD: a systematic review and network meta-analysis of randomized controlled trials. *NPJ Prim Care Respir Med* 2026; **36**(1): https://pubmed.ncbi.nlm.nih.gov/41965361.
800. Zhang T, Zhou R, Wang T, Xin Y, Liu X, Huang H. Effects of traditional mind-body movement therapy on chronic cardiopulmonary dyspnoea: a systematic review and meta-analysis. *Thorax* 2023; **78**(1): 69-75 https://pubmed.ncbi.nlm.nih.gov/35483892.
801. Souto-Miranda S, Saraiva I, Spruit MA, Marques A. Core outcome set for pulmonary rehabilitation of patients with COPD: results of a modified Delphi survey. *Thorax* 2023; **78**(12): 1240-7 https://pubmed.ncbi.nlm.nih.gov/37758457.
802. Vogiatzis I, Rochester CL, Spruit MA, Troosters T, Clini EM, American Thoracic Society/European Respiratory Society Task Force on Policy in Pulmonary R. Increasing implementation and delivery of pulmonary rehabilitation: key messages from the new ATS/ERS policy statement. *Eur Respir J* 2016; **47**(5): 1336-41 https://pubmed.ncbi.nlm.nih.gov/27132269.
803. 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 https://pubmed.ncbi.nlm.nih.gov/25705944.
804. Alison JA, McKeough ZJ, Johnston K, et al. Australian and New Zealand Pulmonary Rehabilitation Guidelines. *Respirology* 2017; **22**(4): 800-19 https://pubmed.ncbi.nlm.nih.gov/28339144.
805. Manifield J, Chaudhry Y, Singh SJ, Ward TJC, Whelan ME, Orme MW. Changes in physical activity, sedentary behaviour and sleep following pulmonary rehabilitation: a systematic review and network meta-analysis. *Eur Respir Rev* 2024; **33**(172): https://pubmed.ncbi.nlm.nih.gov/38599676.
806. Wootton SL, Hill K, Alison JA, et al. Effects of Ongoing Feedback During a 12-Month Maintenance Walking Program on Daily Physical Activity in People with COPD. *Lung* 2019; **197**(3): 315-9 https://pubmed.ncbi.nlm.nih.gov/30982940.
807. Loeckx M, Rodrigues FM, Blondeel A, et al. Sustaining training effects through physical activity coaching (STEP): a randomized controlled trial. *Int J Behav Nutr Phys Act* 2023; **20**(1): 121 https://pubmed.ncbi.nlm.nih.gov/37814266.
808. Cox NS, Dal Corso S, Hansen H, et al. Telerehabilitation for chronic respiratory disease. *Cochrane Database Syst Rev* 2021; **1**(1): CD013040 https://pubmed.ncbi.nlm.nih.gov/33511633.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

809. Candy S, Reeve J, Dobson R, et al. The Impact of Patient Preference on Attendance and Completion Rates at Centre-Based and mHealth Pulmonary Rehabilitation: A Non-Inferiority Pragmatic Clinical Trial. *Int J Chron Obstruct Pulmon Dis* 2023; **18**: 1419-29 https://pubmed.ncbi.nlm.nih.gov/37465821.
810. Holland AE, Cox NS, Houchen-Wolloff L, et al. Defining Modern Pulmonary Rehabilitation. An Official American Thoracic Society Workshop Report. *Ann Am Thorac Soc* 2021; **18**(5): e12-e29 https://pubmed.ncbi.nlm.nih.gov/33929307.
811. Man W, Chaplin E, Daynes E, et al. British Thoracic Society Clinical Statement on pulmonary rehabilitation. *Thorax* 2023; **78**(Suppl 4): s2-s15 https://pubmed.ncbi.nlm.nih.gov/37770084.
812. Singh SJ, Buxton M, Daynes E, et al. British Thoracic Society quality standard for pulmonary rehabilitation. *BMJ Open Respir Res* 2026; **13**(1): https://pubmed.ncbi.nlm.nih.gov/42379641.
813. Garvey C, Bayles MP, Hamm LF, et al. Pulmonary Rehabilitation Exercise Prescription in Chronic Obstructive Pulmonary Disease: Review of Selected Guidelines: AN OFFICIAL STATEMENT FROM THE AMERICAN ASSOCIATION OF CARDIOVASCULAR AND PULMONARY REHABILITATION. *J Cardiopulm Rehabil Prev* 2016; **36**(2): 75-83 https://pubmed.ncbi.nlm.nih.gov/26906147.
814. Stone PW, Hickman K, Steiner MC, Roberts CM, Quint JK, Singh SJ. Predictors of Referral to Pulmonary Rehabilitation from UK Primary Care. *Int J Chron Obstruct Pulmon Dis* 2020; **15**: 2941-52 https://pubmed.ncbi.nlm.nih.gov/33235443.
815. Jia P, Zhang H, Li Y, Yao Z, Wang L. The timing of the commencement of pulmonary rehabilitation in hospitalized patients with acute exacerbation of COPD: a systematic review and network meta-analysis. *BMC Medicine* 2026; **24**(1): 260
816. Chen S, Shang B, Bi Y, et al. Exercise Training Improves Depression and Anxiety in Patients with COPD: A Dose-Response Meta-Analysis of Randomized Controlled Trials. *Int J Chron Obstruct Pulmon Dis* 2026; **21**: 578054 https://pubmed.ncbi.nlm.nih.gov/42117057.
817. Robinson SA, Burns PA, Fitzelle-Jones E, Gagnon DR, Moy ML. Pulmonary rehabilitation is associated with increased 1-year survival in stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2026; **212**(6): 1227-36 https://pubmed.ncbi.nlm.nih.gov/42085209.
818. Esteban C, Gascón M, Tabernero E, et al. Frailty in COPD hospitalized patients: Associated factors from a multicentre cohort study. *Respir Med Res* 2026; **89**: 101239 https://pubmed.ncbi.nlm.nih.gov/41512562.
819. Osadnik CR, Brighton LJ, Burtin C, et al. European Respiratory Society statement on frailty in adults with chronic lung disease. *Eur Respir J* 2023; **62**(2): https://pubmed.ncbi.nlm.nih.gov/37414420.
820. Dowson C, Laing R, Barraclough R, et al. The use of the Hospital Anxiety and Depression Scale (HADS) in patients with chronic obstructive pulmonary disease: a pilot study. *N Z Med J* 2001; **114**(1141): 447-9 https://pubmed.ncbi.nlm.nih.gov/11700772.
821. Kunik ME, Veazey C, Cully JA, et al. COPD education and cognitive behavioral therapy group treatment for clinically significant symptoms of depression and anxiety in COPD patients: a randomized controlled trial. *Psychol Med* 2008; **38**(3): 385-96 https://pubmed.ncbi.nlm.nih.gov/17922939.
822. Bourbeau J, Nault D, Sedeno M. Action Plan from the Living Well with COPD series 2005. Available at https://www.livingwellwithcopd.com/en/copd-treatment.html [accessed Oct 2026].
823. Greening NJ, Williams JE, Hussain SF, et al. An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. *BMJ* 2014; **349**: g4315 https://pubmed.ncbi.nlm.nih.gov/25004917.
824. Borges RC, Carvalho CR. Impact of resistance training in chronic obstructive pulmonary disease patients during periods of acute exacerbation. *Arch Phys Med Rehabil* 2014; **95**(9): 1638-45 https://pubmed.ncbi.nlm.nih.gov/24879965.
825. Troosters T, Probst VS, Crul T, et al. Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; **181**(10): 1072-7 https://pubmed.ncbi.nlm.nih.gov/20133927.
826. Jenkins AR, Burtin C, Camp PG, 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): 438-47 https://pubmed.ncbi.nlm.nih.gov/38350731.
827. Bourbeau J, LeBlanc C. Integrated care in COPD. *Presse Med* 2026; **55**(1): 104320 https://pubmed.ncbi.nlm.nih.gov/41175926.
828. Poot CC, Meijer E, Kruis AL, Smidt N, Chavannes NH, Honkoop PJ. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2021; **9**(9): CD009437 https://pubmed.ncbi.nlm.nih.gov/34495549.
829. Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005; **2005**(4): CD001744 https://pubmed.ncbi.nlm.nih.gov/16235285.
830. Ekstrom M, Andersson A, Papadopoulos S, et al. Long-Term Oxygen Therapy for 24 or 15 Hours per Day in Severe Hypoxemia. *N Engl J Med* 2024; **391**(11): 977-88 https://pubmed.ncbi.nlm.nih.gov/39254466.
831. Long-term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med* 2016; **375**(17): 1617
832. Ekstrom M, Ahmadi Z, Bornefalk-Hermansson A, Abernethy A, Currow D. Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy. *Cochrane Database Syst Rev* 2016; **11**(11): CD006429 https://pubmed.ncbi.nlm.nih.gov/27886372.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

833. Jacobs SS, Krishnan JA, Lederer DJ, 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 https://pubmed.ncbi.nlm.nih.gov/33185464.
834. Alison JA, McKeough ZJ, Leung RWM, et al. Oxygen compared to air during exercise training in COPD with exercise-induced desaturation. *Eur Respir J* 2019; **53**(5): 1802429 https://pubmed.ncbi.nlm.nih.gov/30880289.
835. Ahmedzai S, Balfour-Lynn IM, Bewick T, et al. Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. *Thorax* 2011; **66 Suppl 1**: i1-30 https://pubmed.ncbi.nlm.nih.gov/21856702.
836. Berg BW, Dillard TA, Rajagopal KR, Mehm WJ. Oxygen supplementation during air travel in patients with chronic obstructive lung disease. *Chest* 1992; **101**(3): 638-41 https://pubmed.ncbi.nlm.nih.gov/1541125.
837. Edvardsen A, Akero 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): 964-9 https://pubmed.ncbi.nlm.nih.gov/22767877.
838. 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 https://pubmed.ncbi.nlm.nih.gov/10780752.
839. Srivali N, Thongprayoon C, Tangpanithandee S, Cheungpasitporn W, Won C. The use of continuous positive airway pressure in COPD-OSA overlap syndrome: A systematic review. *Sleep Med* 2023; **108**: 55-60 https://pubmed.ncbi.nlm.nih.gov/37336060.
840. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med* 2010; **182**(3): 325-31 https://pubmed.ncbi.nlm.nih.gov/20378728.
841. Murphy PB, Rehal S, Arbane G, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. *JAMA* 2017; **317**(21): 2177-86 https://pubmed.ncbi.nlm.nih.gov/28528348.
842. Wilson ME, Dobler CC, Morrow AS, et al. Association of Home Noninvasive Positive Pressure Ventilation With Clinical Outcomes in Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis. *JAMA* 2020; **323**(5): 455-65 https://pubmed.ncbi.nlm.nih.gov/32016309.
843. Galli JA, Krahnke JS, James Mamary A, Shenoy K, Zhao H, Criner GJ. Home non-invasive ventilation use following acute hypercapnic respiratory failure in COPD. *Respir Med* 2014; **108**(5): 722-8 https://pubmed.ncbi.nlm.nih.gov/24702885.
844. Coughlin S, Liang WE, Parthasarathy S. Retrospective Assessment of Home Ventilation to Reduce Rehospitalization in Chronic Obstructive Pulmonary Disease. *J Clin Sleep Med* 2015; **11**(6): 663-70 https://pubmed.ncbi.nlm.nih.gov/25766720.
845. Clini E, Sturani C, Rossi A, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002; **20**(3): 529-38 https://pubmed.ncbi.nlm.nih.gov/12358325.
846. Kohnlein T, Windisch W, Kohler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014; **2**(9): 698-705 https://pubmed.ncbi.nlm.nih.gov/25066329.
847. Struik FM, Sprooten RT, Kerstjens HA, et al. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax* 2014; **69**(9): 826-34 https://pubmed.ncbi.nlm.nih.gov/24781217.
848. Casanova C, Celli BR, Tost L, et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. *Chest* 2000; **118**(6): 1582-90 https://pubmed.ncbi.nlm.nih.gov/11115443.
849. White DP, Criner GJ, Dreher M, et al. The role of noninvasive ventilation in the management and mitigation of exacerbations and hospital admissions/readmissions for the patient with moderate to severe COPD (multimedia activity). *Chest* 2015; **147**(6): 1704-5 https://pubmed.ncbi.nlm.nih.gov/26033131.
850. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *BMJ* 2003; **326**(7382): 185 https://pubmed.ncbi.nlm.nih.gov/12543832.
851. Kolodziej MA, Jensen L, Rowe B, Sin D. Systematic review of noninvasive positive pressure ventilation in severe stable COPD. *Eur Respir J* 2007; **30**(2): 293-306 https://pubmed.ncbi.nlm.nih.gov/17459893.
852. Pitre T, Abbasi S, Kachkovski GV, et al. Home Respiratory Strategies in Patients With COPD With Chronic Hypercapnic Respiratory Failure. *Respir Care* 2024; **69**(11): 1457-67 https://pubmed.ncbi.nlm.nih.gov/38569922.
853. Fu C, Liu X, Zhu Q, et al. Efficiency of High-Flow Nasal Cannula on Pulmonary Rehabilitation in COPD Patients: A Meta-Analysis. *Biomed Res Int* 2020; **2020**: 7097243 https://pubmed.ncbi.nlm.nih.gov/33083481.
854. Whittaker H, Rothnie KJ, Quint JK. Cause-specific mortality in COPD subpopulations: a cohort study of 339 647 people in England. *Thorax* 2024; **79**(3): 202-8 https://pubmed.ncbi.nlm.nih.gov/37328279.
855. Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005; **142**(4): 233-9 https://pubmed.ncbi.nlm.nih.gov/15710956.
856. Lu HY, Chen CF, Lee DL, Tsai YJ, Lin PC. Effects of Early Pulmonary Rehabilitation on Hospitalized Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *Int J Chron Obstruct Pulmon Dis* 2023; **18**: 881-93 https://pubmed.ncbi.nlm.nih.gov/37215744.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

857. Ryrso CK, Godtfredsen NS, Kofod LM, et al. Lower mortality after early supervised pulmonary rehabilitation following COPD-exacerbations: a systematic review and meta-analysis. *BMC Pulm Med* 2018; **18**(1): 154 https://pubmed.ncbi.nlm.nih.gov/30219047.
858. Puhan MA, Gimeno-Santos E, Scharplatz M, Troosters T, Walters EH, Steurer J. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011; 10.1002/14651858.CD005305.pub3(10): CD005305 https://pubmed.ncbi.nlm.nih.gov/21975749.
859. Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2016; **12**(12): CD005305 https://pubmed.ncbi.nlm.nih.gov/27930803.
860. Lindenauer PK, Stefan MS, Pekow PS, et al. Association Between Initiation of Pulmonary Rehabilitation After Hospitalization for COPD and 1-Year Survival Among Medicare Beneficiaries. *JAMA* 2020; **323**(18): 1813-23 https://pubmed.ncbi.nlm.nih.gov/32396181.
861. NOTT Nocturnal Oxygen Therapy Trial Group. 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): 391-8 https://pubmed.ncbi.nlm.nih.gov/6776858.
862. MRC Working Party. 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 https://pubmed.ncbi.nlm.nih.gov/6110912.
863. Lacasse Y, Casaburi R, Sliwinski 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): 1029-37 https://pubmed.ncbi.nlm.nih.gov/35817074.
864. Park SY, Yoo KH, Park YB, et al. The Long-term Efficacy of Domiciliary Noninvasive Positive-Pressure Ventilation in Chronic Obstructive Pulmonary Disease: A Meta-Analysis of Randomized Controlled Trials. *Tuberc Respir Dis (Seoul)* 2022; **85**(1): 47-55 https://pubmed.ncbi.nlm.nih.gov/34775737.
865. McEvoy RD, Pierce RJ, Hillman D, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. *Thorax* 2009; **64**(7): 561-6 https://pubmed.ncbi.nlm.nih.gov/19213769.
866. Vock DM, Durheim MT, Tsuang WM, et al. Survival Benefit of Lung Transplantation in the Modern Era of Lung Allocation. *Ann Am Thorac Soc* 2017; **14**(2): 172-81 https://pubmed.ncbi.nlm.nih.gov/27779905.
867. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; **348**(21): 2059-73 https://pubmed.ncbi.nlm.nih.gov/12759479.
868. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; **356**(8): 775-89 https://pubmed.ncbi.nlm.nih.gov/17314337.
869. Vestbo J, Anderson J, Brook RD, et al. The Study to Understand Mortality and Morbidity in COPD (SUMMIT) study protocol. *Eur Respir J* 2013; **41**(5): 1017-22 https://pubmed.ncbi.nlm.nih.gov/23018908.
870. American Academy of H, Palliative M, Center to Advance Palliative C, et al. National Consensus Project for Quality Palliative Care: Clinical Practice Guidelines for quality palliative care, executive summary. *J Palliat Med* 2004; **7**(5): 611-27 https://pubmed.ncbi.nlm.nih.gov/15588352.
871. Au DH, Udris EM, Fihn SD, McDonell MB, Curtis JR. Differences in health care utilization at the end of life among patients with chronic obstructive pulmonary disease and patients with lung cancer. *Arch Intern Med* 2006; **166**(3): 326-31 https://pubmed.ncbi.nlm.nih.gov/16476873.
872. Levy MH, Adolph MD, Back A, et al. Palliative care. *J Natl Compr Canc Netw* 2012; **10**(10): 1284-309 https://pubmed.ncbi.nlm.nih.gov/23054879.
873. Morrison RS, Maroney-Galin C, Kralovec PD, Meier DE. The growth of palliative care programs in United States hospitals. *J Palliat Med* 2005; **8**(6): 1127-34 https://pubmed.ncbi.nlm.nih.gov/16351525.
874. Han MK, Martinez CH, Au DH, et al. Meeting the challenge of COPD care delivery in the USA: a multiprovider perspective. *Lancet Respir Med* 2016; **4**(6): 473-526 https://pubmed.ncbi.nlm.nih.gov/27185520.
875. Ambrosino N, Fracchia C. Strategies to relieve dyspnoea in patients with advanced chronic respiratory diseases. A narrative review. *Pulmonology* 2019; **25**(5): 289-98 https://pubmed.ncbi.nlm.nih.gov/31129045.
876. 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): 1079-92 https://pubmed.ncbi.nlm.nih.gov/25803110.
877. Rocker GM, Simpson AC, Joanne Young B, et al. Opioid therapy for refractory dyspnea in patients with advanced chronic obstructive pulmonary disease: patients' experiences and outcomes. *CMAJ Open* 2013; **1**(1): E27-36 https://pubmed.ncbi.nlm.nih.gov/25077099.
878. Marciniuk DD, Goodridge D, Hernandez P, et al. Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: a Canadian Thoracic Society clinical practice guideline. *Can Respir J* 2011; **18**(2): 69-78 https://pubmed.ncbi.nlm.nih.gov/21499589.
879. Vieira PJ, Chiappa AM, Cipriano G, Jr., Umpierre D, Arena R, Chiappa GR. Neuromuscular electrical stimulation improves clinical and physiological function in COPD patients. *Respir Med* 2014; **108**(4): 609-20 https://pubmed.ncbi.nlm.nih.gov/24418570.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

880. Galbraith S, Fagan P, Perkins P, Lynch A, Booth S. Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. *J Pain Symptom Manage* 2010; **39**(5): 831-8 https://pubmed.ncbi.nlm.nih.gov/20471544.
881. Marchetti N, Lammi MR, Travaline JM, Ciccolella D, Civic B, Criner GJ. Air Current Applied to the Face Improves Exercise Performance in Patients with COPD. *Lung* 2015; **193**(5): 725-31 https://pubmed.ncbi.nlm.nih.gov/26255060.
882. Altree TJ, Toson B, Loffler KA, Ekstrom M, Currow DC, Eckert DJ. Low-Dose Morphine Does Not Cause Sleepiness in Chronic Obstructive Pulmonary Disease: A Secondary Analysis of a Randomized Clinical Trial. *Am J Respir Crit Care Med* 2024; **210**(9): 1113-22 https://pubmed.ncbi.nlm.nih.gov/38477675.
883. Ekstrom M, Ferreira D, Chang S, 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): 2022-32 https://pubmed.ncbi.nlm.nih.gov/36413230.
884. Currow D, Chang S, Fazekas B, et al. The Subjective Experiences of Ceasing Regular, Low-Dose, Sustained-Release Morphine when Treating Moderate to Severe Chronic Breathlessness. *J Palliat Med* 2026; **29**(5): 651-8 https://pubmed.ncbi.nlm.nih.gov/41472644.
885. Abdallah SJ, Wilkinson-Maitland C, Saad N, et al. Effect of morphine on breathlessness and exercise endurance in advanced COPD: a randomised crossover trial. *Eur Respir J* 2017; **50**(4): 1701235 https://pubmed.ncbi.nlm.nih.gov/29051274.
886. Verberkt CA, van den Beuken-Everdingen MHJ, Schols J, Wouters EFM, Janssen DJA. Morphine for chronic breathlessness in COPD: improvement predictors-cross-sectional study. *BMJ Support Palliat Care* 2024; **13**(e3): e829-e32 https://pubmed.ncbi.nlm.nih.gov/35850961.
887. Nici L, Mammen MJ, Charbek E, et al. Pharmacologic Management of Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med* 2020; **201**(9): e56-e69 https://pubmed.ncbi.nlm.nih.gov/32283960.
888. 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): 492-4 https://pubmed.ncbi.nlm.nih.gov/25472664.
889. von Trott P, Oei SL, Ramsenthaler C. Acupuncture for Breathlessness in Advanced Diseases: A Systematic Review and Meta-analysis. *J Pain Symptom Manage* 2020; **59**(2): 327-38 e3 https://pubmed.ncbi.nlm.nih.gov/31539602.
890. Higginson IJ, Bausewein C, Reilly CC, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *Lancet Respir Med* 2014; **2**(12): 979-87 https://pubmed.ncbi.nlm.nih.gov/25465642.
891. Simon ST, Higginson IJ, Booth S, Harding R, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev* 2010; 10.1002/14651858.CD007354.pub2(1): CD007354 https://pubmed.ncbi.nlm.nih.gov/20091630.
892. Bausewein C, Booth S, Gysels M, Higginson I. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. *Cochrane Database Syst Rev* 2008; 10.1002/14651858.CD005623.pub2(2): CD005623 https://pubmed.ncbi.nlm.nih.gov/18425927.
893. Putcha N, Anzueto AR, Calverley PMA, 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): 204-13 https://pubmed.ncbi.nlm.nih.gov/34406915.
894. Ferreira IM, Brooks D, White J, Goldstein R. Nutritional supplementation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; **12**(12): CD000998 https://pubmed.ncbi.nlm.nih.gov/23235577.
895. Gouzi F, Maury J, Heraud N, et al. Additional Effects of Nutritional Antioxidant Supplementation on Peripheral Muscle during Pulmonary Rehabilitation in COPD Patients: A Randomized Controlled Trial. *Oxid Med Cell Longev* 2019; **2019**: 5496346 https://pubmed.ncbi.nlm.nih.gov/31178967.
896. van Beers M, Rutten-van Molken M, van de Bool C, et al. Clinical outcome and cost-effectiveness of a 1-year nutritional intervention programme in COPD patients with low muscle mass: The randomized controlled NUTRAIN trial. *Clin Nutr* 2020; **39**(2): 405-13 https://pubmed.ncbi.nlm.nih.gov/30954363.
897. Yohannes AM, Alexopoulos GS. Depression and anxiety in patients with COPD. *Eur Respir Rev* 2014; **23**(133): 345-9 https://pubmed.ncbi.nlm.nih.gov/25176970.
898. 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 https://pubmed.ncbi.nlm.nih.gov/25547641.
899. Payne C, Wiffen PJ, Martin S. Interventions for fatigue and weight loss in adults with advanced progressive illness. *Cochrane Database Syst Rev* 2012; **1**: CD008427 https://pubmed.ncbi.nlm.nih.gov/22258985.
900. Murray SA, Kendall M, Boyd K, Sheikh A. Illness trajectories and palliative care. *BMJ* 2005; **330**(7498): 1007-11 https://pubmed.ncbi.nlm.nih.gov/15860828.
901. Eriksen N, Vestbo J. Management and survival of patients admitted with an exacerbation of COPD: comparison of two Danish patient cohorts. *Clin Respir J* 2010; **4**(4): 208-14 https://pubmed.ncbi.nlm.nih.gov/20887343.
902. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest* 2003; **124**(2): 459-67 https://pubmed.ncbi.nlm.nih.gov/12907529.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

903. Gudmundsson G, Ulrik CS, Gislason T, et al. Long-term survival in patients hospitalized for chronic obstructive pulmonary disease: a prospective observational study in the Nordic countries. *Int J Chron Obstruct Pulmon Dis* 2012; **7**: 571-6 https://pubmed.ncbi.nlm.nih.gov/23055707.
904. Disler RT, Green A, Luckett T, et al. Experience of advanced chronic obstructive pulmonary disease: metasynthesis of qualitative research. *J Pain Symptom Manage* 2014; **48**(6): 1182-99 https://pubmed.ncbi.nlm.nih.gov/24780181.
905. Halpin DMG, Seamark DA, Seamark CJ. Palliative and end-of-life care for patients with respiratory diseases. *Eur Respir Monograph* 2009; **43**: 327-53
906. Patel K, Janssen DJ, Curtis JR. Advance care planning in COPD. *Respirology* 2012; **17**(1): 72-8 https://pubmed.ncbi.nlm.nih.gov/22008225.
907. Pinnock H, Kendall M, Murray SA, et al. Living and dying with severe chronic obstructive pulmonary disease: multi-perspective longitudinal qualitative study. *BMJ* 2011; **342**: d142 https://pubmed.ncbi.nlm.nih.gov/21262897.
908. Weber C, Stirnemann J, Herrmann FR, Pautex S, Janssens JP. Can early introduction of specialized palliative care limit intensive care, emergency and hospital admissions in patients with severe and very severe COPD? a randomized study. *BMC Palliat Care* 2014; **13**: 47 https://pubmed.ncbi.nlm.nih.gov/25927907.
909. Ek K, Andershed B, Sahlberg-Blom E, Ternestedt BM. "The unpredictable death"-The last year of life for patients with advanced COPD: Relatives' stories. *Palliat Support Care* 2015; **13**(5): 1213-22 https://pubmed.ncbi.nlm.nih.gov/25315360.
910. National Hospice and Palliative Care Organization. Web Page. 2019. http://www.nhpco.org (accessed Oct 2022).
911. 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 https://pubmed.ncbi.nlm.nih.gov/26238644.
912. Travaline JM, Addonizio VP, Criner GJ. Effect of bullectomy on diaphragm strength. *Am J Respir Crit Care Med* 1995; **152**(5 Pt 1): 1697-701 https://pubmed.ncbi.nlm.nih.gov/7582315.
913. Marchetti N, Criner KT, Keresztury MF, Furukawa S, Criner GJ. The acute and chronic effects of bullectomy on cardiovascular function at rest and during exercise. *J Thorac Cardiovasc Surg* 2008; **135**(1): 205-6, 6 e1 https://pubmed.ncbi.nlm.nih.gov/18179944.
914. Kanoh S, Kobayashi H, Motoyoshi K. Intrabullous blood injection for lung volume reduction. *Thorax* 2008; **63**(6): 564-5 https://pubmed.ncbi.nlm.nih.gov/18511641.
915. Kemp SV, Zoumot Z, Shah PL. Three-Year Follow-Up of a Patient with a Giant Bulla Treated by Bronchoscopic Intrabullous Autologous Blood Instillation. *Respiration* 2016; **92**(4): 283-4 https://pubmed.ncbi.nlm.nih.gov/27606975.
916. Zoumot Z, Kemp SV, Caneja C, Singh S, Shah PL. Bronchoscopic intrabullous autologous blood instillation: a novel approach for the treatment of giant bullae. *Ann Thorac Surg* 2013; **96**(4): 1488-91 https://pubmed.ncbi.nlm.nih.gov/24088475.
917. Cooper JD, Trulock EP, Triantafillou AN, et al. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg* 1995; **109**(1): 106-16; discussion 16-9 https://pubmed.ncbi.nlm.nih.gov/7815786.
918. Stolk J, Versteegh MI, Montenij LJ, et al. Densitometry for assessment of effect of lung volume reduction surgery for emphysema. *Eur Respir J* 2007; **29**(6): 1138-43 https://pubmed.ncbi.nlm.nih.gov/17331971.
919. Criner G, Cordova FC, Leyenson V, et al. Effect of lung volume reduction surgery on diaphragm strength. *Am J Respir Crit Care Med* 1998; **157**(5 Pt 1): 1578-85 https://pubmed.ncbi.nlm.nih.gov/9603141.
920. Martinez FJ, de Oca MM, Whyte RI, Stetz J, Gay SE, Celli BR. Lung-volume reduction improves dyspnea, dynamic hyperinflation, and respiratory muscle function. *Am J Respir Crit Care Med* 1997; **155**(6): 1984-90 https://pubmed.ncbi.nlm.nih.gov/9196106.
921. Fessler HE, Permutt S. Lung volume reduction surgery and airflow limitation. *Am J Respir Crit Care Med* 1998; **157**(3 Pt 1): 715-22 https://pubmed.ncbi.nlm.nih.gov/9517581.
922. Washko GR, Fan VS, Ramsey SD, et al. The effect of lung volume reduction surgery on chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med* 2008; **177**(2): 164-9 https://pubmed.ncbi.nlm.nih.gov/17962632.
923. Geddes D, Davies M, Koyama H, et al. Effect of lung-volume-reduction surgery in patients with severe emphysema. *N Engl J Med* 2000; **343**(4): 239-45 https://pubmed.ncbi.nlm.nih.gov/10911005.
924. 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): 313-24 https://pubmed.ncbi.nlm.nih.gov/30744937.
925. Lim E, Sousa I, Shah PL, Diggle P, Goldstraw P. Lung Volume Reduction Surgery: Reinterpreted With Longitudinal Data Analyses Methodology. *Ann Thorac Surg* 2020; **109**(5): 1496-501 https://pubmed.ncbi.nlm.nih.gov/31891694.
926. National Emphysema Treatment Trial Research G, Fishman A, Fessler H, et al. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med* 2001; **345**(15): 1075-83 https://pubmed.ncbi.nlm.nih.gov/11596586.
927. Greening NJ, Vaughan P, Oey I, et al. Individualised risk in patients undergoing lung volume reduction surgery: the Glenfield BFG score. *Eur Respir J* 2017; **49**(6): https://pubmed.ncbi.nlm.nih.gov/28572121.
928. Imfeld S, Bloch KE, Weder W, Russi EW. The BODE index after lung volume reduction surgery correlates with survival. *Chest* 2006; **129**(4): 873-8 https://pubmed.ncbi.nlm.nih.gov/16608932.
929. Caviezel C, Schaffter N, Schneiter D, et al. Outcome After Lung Volume Reduction Surgery in Patients With Severely Impaired Diffusion Capacity. *Ann Thorac Surg* 2018; **105**(2): 379-85 https://pubmed.ncbi.nlm.nih.gov/29223424.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

930. Caviezel C, Froehlich T, Schneiter D, et al. Identification of target zones for lung volume reduction surgery using three-dimensional computed tomography rendering. *ERJ Open Res* 2020; **6**(3): https://pubmed.ncbi.nlm.nih.gov/32963992.
931. Ramsey SD, Berry K, Etzioni R, et al. Cost effectiveness of lung-volume-reduction surgery for patients with severe emphysema. *N Engl J Med* 2003; **348**(21): 2092-102 https://pubmed.ncbi.nlm.nih.gov/12759480.
932. Ginsburg ME, Thomashow BM, Bulman WA, et al. The safety, efficacy, and durability of lung-volume reduction surgery: A 10-year experience. *J Thorac Cardiovasc Surg* 2016; **151**(3): 717-24 e1 https://pubmed.ncbi.nlm.nih.gov/26670190.
933. Abdelsattar ZM, Allen M, Blackmon S, et al. Contemporary Practice Patterns of Lung Volume Reduction Surgery in the United States. *Ann Thorac Surg* 2021; **112**(3): 952-60 https://pubmed.ncbi.nlm.nih.gov/33161015.
934. Stanifer BP, Ginsburg ME. Lung volume reduction surgery in the post-National Emphysema Treatment Trial era. *J Thorac Dis* 2018; **10**(Suppl 23): S2744-S7 https://pubmed.ncbi.nlm.nih.gov/30210827.
935. Buttery S, Lewis A, Oey I, et al. Patient experience of lung volume reduction procedures for emphysema: a qualitative service improvement project. *ERJ Open Res* 2017; **3**(3): https://pubmed.ncbi.nlm.nih.gov/28835891.
936. McNulty W, Jordan S, Hopkinson NS. Attitudes and access to lung volume reduction surgery for COPD: a survey by the British Thoracic Society. *BMJ Open Respir Res* 2014; **1**(1): e000023 https://pubmed.ncbi.nlm.nih.gov/25478175.
937. Rathinam S, Oey I, Steiner M, Spyt T, Morgan MD, Waller DA. The role of the emphysema multidisciplinary team in a successful lung volume reduction surgery programmedagger. *Eur J Cardiothorac Surg* 2014; **46**(6): 1021-6; discussion 6 https://pubmed.ncbi.nlm.nih.gov/24771753.
938. Tiong LU, Davies R, Gibson PG, et al. Lung volume reduction surgery for diffuse emphysema. *Cochrane Database Syst Rev* 2006; 10.1002/14651858.CD001001.pub2(4): CD001001 https://pubmed.ncbi.nlm.nih.gov/17054132.
939. Criner GJ, Cordova F, Sternberg AL, Martinez FJ. The National Emphysema Treatment Trial (NETT) Part II: Lessons learned about lung volume reduction surgery. *Am J Respir Crit Care Med* 2011; **184**(8): 881-93 https://pubmed.ncbi.nlm.nih.gov/21719757.
940. Herth FJ, Valipour A, Shah PL, et al. Segmental volume reduction using thermal vapour ablation in patients with severe emphysema: 6-month results of the multicentre, parallel-group, open-label, randomised controlled STEP-UP trial. *Lancet Respir Med* 2016; **4**(3): 185-93 https://pubmed.ncbi.nlm.nih.gov/26899390.
941. Criner GJ, Sue R, Wright S, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE). *Am J Respir Crit Care Med* 2018; **198**(9): 1151-64 https://pubmed.ncbi.nlm.nih.gov/29787288.
942. Kemp SV, Slebos DJ, Kirk A, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM). *Am J Respir Crit Care Med* 2017; **196**(12): 1535-43 https://pubmed.ncbi.nlm.nih.gov/28885054.
943. Valipour A, Slebos DJ, Herth F, et al. Endobronchial Valve Therapy in Patients with Homogeneous Emphysema. Results from the IMPACT Study. *Am J Respir Crit Care Med* 2016; **194**(9): 1073-82 https://pubmed.ncbi.nlm.nih.gov/27580428.
944. Criner GJ, Delage A, Voelker K, et al. Improving Lung Function in Severe Heterogenous Emphysema with the Spiration Valve System (EMPROVE). A Multicenter, Open-Label Randomized Controlled Clinical Trial. *Am J Respir Crit Care Med* 2019; **200**(11): 1354-62 https://pubmed.ncbi.nlm.nih.gov/31365298.
945. van Geffen WH, Klooster K, Hartman JE, et al. Pleural Adhesion Assessment as a Predictor for Pneumothorax after Endobronchial Valve Treatment. *Respiration* 2017; **94**(2): 224-31 https://pubmed.ncbi.nlm.nih.gov/28637047.
946. Hopkinson NS, Kemp SV, Toma TP, et al. Atelectasis and survival after bronchoscopic lung volume reduction for COPD. *Eur Respir J* 2011; **37**(6): 1346-51 https://pubmed.ncbi.nlm.nih.gov/20947683.
947. Garner J, Kemp SV, Toma TP, et al. Survival after Endobronchial Valve Placement for Emphysema: A 10-Year Follow-up Study. *Am J Respir Crit Care Med* 2016; **194**(4): 519-21 https://pubmed.ncbi.nlm.nih.gov/27525462.
948. Gompelmann D, Benjamin N, Bischoff E, et al. Survival after Endoscopic Valve Therapy in Patients with Severe Emphysema. *Respiration* 2019; **97**(2): 145-52 https://pubmed.ncbi.nlm.nih.gov/30227420.
949. Hartman JE, Welling JBA, Klooster K, Carpaij OA, Augustijn SWS, Slebos DJ. Survival in COPD patients treated with bronchoscopic lung volume reduction. *Respir Med* 2022; **196**: 106825 https://pubmed.ncbi.nlm.nih.gov/35325741.
950. Mansfield C, Sutphin J, Shriner K, Criner GJ, Celli BR. Patient Preferences for Endobronchial Valve Treatment of Severe Emphysema. *Chronic Obstr Pulm Dis* 2018; **6**(1): 51-63 https://pubmed.ncbi.nlm.nih.gov/30775424.
951. Naunheim KS, Wood DE, Mohsenifar Z, et al. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. *Ann Thorac Surg* 2006; **82**(2): 431-43 https://pubmed.ncbi.nlm.nih.gov/16888872.
952. DeCamp MM, Blackstone EH, Naunheim KS, et al. Patient and surgical factors influencing air leak after lung volume reduction surgery: lessons learned from the National Emphysema Treatment Trial. *Ann Thorac Surg* 2006; **82**(1): 197-206; discussion -7 https://pubmed.ncbi.nlm.nih.gov/16798215.
953. Shah PL, Slebos DJ, Cardoso PF, et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial. *Lancet* 2011; **378**(9795): 997-1005 https://pubmed.ncbi.nlm.nih.gov/21907863.
954. Come CE, Kramer MR, Dransfield MT, et al. A randomised trial of lung sealant versus medical therapy for advanced emphysema. *Eur Respir J* 2015; **46**(3): 651-62 https://pubmed.ncbi.nlm.nih.gov/25837041.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

955. Shah PL, Gompelmann D, Valipour A, et al. Thermal vapour ablation to reduce segmental volume in patients with severe emphysema: STEP-UP 12 month results. *Lancet Respir Med* 2016; **4**(9): e44-e5 https://pubmed.ncbi.nlm.nih.gov/27451345.
956. Deslee G, Mal H, Dutau H, et al. Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema: The REVOLENS Randomized Clinical Trial. *JAMA* 2016; **315**(2): 175-84 https://pubmed.ncbi.nlm.nih.gov/26757466.
957. Sciurba FC, Criner GJ, Strange C, et al. Effect of Endobronchial Coils vs Usual Care on Exercise Tolerance in Patients With Severe Emphysema: The RENEW Randomized Clinical Trial. *JAMA* 2016; **315**(20): 2178-89 https://pubmed.ncbi.nlm.nih.gov/27179849.
958. Shah PL, Zoumot Z, Singh S, et al. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial. *Lancet Respir Med* 2013; **1**(3): 233-40 https://pubmed.ncbi.nlm.nih.gov/24429129.
959. Slebos DJ, Cicenia J, Sciurba FC, et al. Predictors of Response to Endobronchial Coil Therapy in Patients With Advanced Emphysema. *Chest* 2019; **155**(5): 928-37 https://pubmed.ncbi.nlm.nih.gov/30797746.
960. Bavaria JE, Pochettino A, Kotloff RM, et al. Effect of volume reduction on lung transplant timing and selection for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg* 1998; **115**(1): 9-17; discussion -8 https://pubmed.ncbi.nlm.nih.gov/9451040.
961. Senbaklavaci O, Wisser W, Ozpeker C, et al. Successful lung volume reduction surgery brings patients into better condition for later lung transplantation. *Eur J Cardiothorac Surg* 2002; **22**(3): 363-7 https://pubmed.ncbi.nlm.nih.gov/12204724.
962. Slama A, Taube C, Kamler M, Aigner C. Lung volume reduction followed by lung transplantation-considerations on selection criteria and outcome. *J Thorac Dis* 2018; **10**(Suppl 27): S3366-S75 https://pubmed.ncbi.nlm.nih.gov/30450243.
963. Reece TB, Mitchell JD, Zamora MR, et al. Native lung volume reduction surgery relieves functional graft compression after single-lung transplantation for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg* 2008; **135**(4): 931-7 https://pubmed.ncbi.nlm.nih.gov/18374782.
964. Anderson MB, Kriett JM, Kapelanski DP, Perricone A, Smith CM, Jamieson SW. Volume reduction surgery in the native lung after single lung transplantation for emphysema. *J Heart Lung Transplant* 1997; **16**(7): 752-7 https://pubmed.ncbi.nlm.nih.gov/9257257.
965. Crespo MM, Johnson BA, McCurry KR, Landreneau RJ, Sciurba FC. Use of endobronchial valves for native lung hyperinflation associated with respiratory failure in a single-lung transplant recipient for emphysema. *Chest* 2007; **131**(1): 214-6 https://pubmed.ncbi.nlm.nih.gov/17218578.
966. Venuta F, De Giacomo T, Rendina EA, et al. Thoracoscopic volume reduction of the native lung after single lung transplantation for emphysema. *Am J Respir Crit Care Med* 1998; **157**(1): 292-3 https://pubmed.ncbi.nlm.nih.gov/9445313.
967. Kemp SV, Carby M, Cetti EJ, Herth FJ, Shah PL. A potential role for endobronchial valves in patients with lung transplant. *J Heart Lung Transplant* 2010; **29**(11): 1310-2 https://pubmed.ncbi.nlm.nih.gov/20708411.
968. Perch M, Riise GC, Hogarth K, et al. Endoscopic treatment of native lung hyperinflation using endobronchial valves in single-lung transplant patients: a multinational experience. *Clin Respir J* 2015; **9**(1): 104-10 https://pubmed.ncbi.nlm.nih.gov/24506317.
969. Shigemura N, Gilbert S, Bhama JK, et al. Lung transplantation after lung volume reduction surgery. *Transplantation* 2013; **96**(4): 421-5 https://pubmed.ncbi.nlm.nih.gov/23736352.
970. Slama A, Ceulemans LJ, Hedderich C, et al. Lung Volume Reduction Followed by Lung Transplantation in Emphysema-A Multicenter Matched Analysis. *Transpl Int* 2022; **35**: 10048 https://pubmed.ncbi.nlm.nih.gov/35497884.
971. Fuehner T, Clajus C, Fuge J, et al. Lung transplantation after endoscopic lung volume reduction. *Respiration* 2015; **90**(3): 243-50 https://pubmed.ncbi.nlm.nih.gov/26138023.
972. Bhatt SP, Terry NL, Nath H, et al. Association Between Expiratory Central Airway Collapse and Respiratory Outcomes Among Smokers. *JAMA* 2016; **315**(5): 498-505 https://pubmed.ncbi.nlm.nih.gov/26836732.
973. Ernst A, Majid A, Feller-Kopman D, et al. Airway stabilization with silicone stents for treating adult tracheobronchomalacia: a prospective observational study. *Chest* 2007; **132**(2): 609-16 https://pubmed.ncbi.nlm.nih.gov/17699133.
974. Wright CD, Mathisen DJ. Tracheobronchoplasty for tracheomalacia. *Ann Cardiothorac Surg* 2018; **7**(2): 261-5 https://pubmed.ncbi.nlm.nih.gov/29707504.
975. Garner JL, Shaipanich T, Hartman JE, et al. A prospective safety and feasibility study of metered cryospray for patients with chronic bronchitis in COPD. *Eur Respir J* 2020; **56**(6): https://pubmed.ncbi.nlm.nih.gov/32586881.
976. Hartman JE, Garner JL, Shah PL, Slebos DJ. New bronchoscopic treatment modalities for patients with chronic bronchitis. *Eur Respir Rev* 2021; **30**(159): https://pubmed.ncbi.nlm.nih.gov/33472961.
977. Criner GJ, Browning RF, Jr., Abu-Hijleh M, et al. Metered-Dose Liquid Nitrogen Cryospray for Chronic Bronchitis: Results From the Prospective, Sham-Controlled Trial (SPRAY-CB). *Am J Respir Crit Care Med* 2026; 10.1093/ajrccm/aamag502: https://pubmed.ncbi.nlm.nih.gov/42768446.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

978. Criner GJ, Browning RF, Jr, Abu-Hijleh M, et al. Metered-Dose Liquid Nitrogen Cryospray for Chronic Bronchitis: Results From the Prospective, Sham-Controlled Trial (SPRAY-CB). *American Journal of Respiratory and Critical Care Medicine* 2026; 10.1093/ajrccm/aamag502:
979. Valipour A, Fernandez-Bussy S, Ing AJ, et al. Bronchial Rheoplasty for Treatment of Chronic Bronchitis. Twelve-Month Results from a Multicenter Clinical Trial. *Am J Respir Crit Care Med* 2020; **202**(5): 681-9 **https://pubmed.ncbi.nlm.nih.gov/32407638**.
980. U.S. National Library of Medicine ClinicalTrials.gov. Clinical Study of the RheOx Bronchial Rheoplasty System in Treating the Symptoms of Chronic Bronchitis [accessed Oct 2026]. **https://www.clinicaltrials.gov/ct2/show/NCT04677465**.
981. Valipour A, Asadi S, Pison C, et al. Long-term safety of bilateral targeted lung denervation in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2018; **13**: 2163-72 **https://pubmed.ncbi.nlm.nih.gov/30038492**.
982. Valipour A, Shah PL, Pison C, et al. Safety and Dose Study of Targeted Lung Denervation in Moderate/Severe COPD Patients. *Respiration* 2019; **98**(4): 329-39 **https://pubmed.ncbi.nlm.nih.gov/31220851**.
983. Slebos DJ, Klooster K, Koegelenberg CF, et al. Targeted lung denervation for moderate to severe COPD: a pilot study. *Thorax* 2015; **70**(5): 411-9 **https://pubmed.ncbi.nlm.nih.gov/25739911**.
984. Slebos DJ, Shah PL, Herth FJF, et al. Safety and Adverse Events after Targeted Lung Denervation for Symptomatic Moderate to Severe Chronic Obstructive Pulmonary Disease (AIRFLOW). A Multicenter Randomized Controlled Clinical Trial. *Am J Respir Crit Care Med* 2019; **200**(12): 1477-86 **https://pubmed.ncbi.nlm.nih.gov/31404499**.
985. Valipour A, Shah PL, Herth FJ, et al. Two-Year Outcomes for the Double-Blind, Randomized, Sham-Controlled Study of Targeted Lung Denervation in Patients with Moderate to Severe COPD: AIRFLOW-2. *Int J Chron Obstruct Pulmon Dis* 2020; **15**: 2807-16 **https://pubmed.ncbi.nlm.nih.gov/33177818**.
986. Shah PL, Slebos DJ, Sue R, et al. Randomized Sham Controlled Trial of Targeted Lung Denervation in Patients with COPD (AIRFLOW-3). *Am J Respir Crit Care Med* 2025; 10.1164/rccm.202502-0404OC: **https://pubmed.ncbi.nlm.nih.gov/40920914**.
987. Chambers DC, Cherikh WS, Goldfarb SB, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth adult lung and heart-lung transplant report-2018; Focus theme: Multiorgan Transplantation. *J Heart Lung Transplant* 2018; **37**(10): 1169-83 **https://pubmed.ncbi.nlm.nih.gov/30293613**.
988. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2015; **34**(1): 1-15 **https://pubmed.ncbi.nlm.nih.gov/25085497**.
989. Arjuna A, Olson MT, Walia R. Current trends in candidate selection, contraindications, and indications for lung transplantation. *J Thorac Dis* 2021; **13**(11): 6514-27 **https://pubmed.ncbi.nlm.nih.gov/34992831**.
990. Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. *J Heart Lung Transplant* 2012; **31**(10): 1073-86 **https://pubmed.ncbi.nlm.nih.gov/22975097**.
991. Stavem K, Bjortuft O, Borgan O, Geiran O, Boe J. Lung transplantation in patients with chronic obstructive pulmonary disease in a national cohort is without obvious survival benefit. *J Heart Lung Transplant* 2006; **25**(1): 75-84 **https://pubmed.ncbi.nlm.nih.gov/16399534**.
992. Tanash HA, Riise GC, Hansson L, Nilsson PM, Piitulainen E. Survival benefit of lung transplantation in individuals with severe alpha1-anti-trypsin deficiency (PiZZ) and emphysema. *J Heart Lung Transplant* 2011; **30**(12): 1342-7 **https://pubmed.ncbi.nlm.nih.gov/21821433**.
993. Tanash HA, Riise GC, Ekstrom MP, Hansson L, Piitulainen E. Survival benefit of lung transplantation for chronic obstructive pulmonary disease in Sweden. *Ann Thorac Surg* 2014; **98**(6): 1930-5 **https://pubmed.ncbi.nlm.nih.gov/25443001**.
994. Eskander A, Waddell TK, Faughnan ME, Chowdhury N, Singer LG. BODE index and quality of life in advanced chronic obstructive pulmonary disease before and after lung transplantation. *J Heart Lung Transplant* 2011; **30**(12): 1334-41 **https://pubmed.ncbi.nlm.nih.gov/21782467**.
995. Lahzami S, Bridevaux PO, Soccal PM, et al. Survival impact of lung transplantation for COPD. *Eur Respir J* 2010; **36**(1): 74-80 **https://pubmed.ncbi.nlm.nih.gov/19996194**.
996. Thabut G, Ravaud P, Christie JD, et al. Determinants of the survival benefit of lung transplantation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; **177**(10): 1156-63 **https://pubmed.ncbi.nlm.nih.gov/18310481**.
997. ISHLT: The International Society for Heart & Lung Transplantation [Internet]. Slide Sets - Overall Lung Transplantation Statistics. Available from: **https://ishltregistries.org/registries/slides.asp** (accessed October 2025).
998. Thabut G, Christie JD, Ravaud P, et al. Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: a retrospective analysis of registry data. *Lancet* 2008; **371**(9614): 744-51 **https://pubmed.ncbi.nlm.nih.gov/18313503**.
999. Pochettino A, Kotloff RM, Rosengard BR, et al. Bilateral versus single lung transplantation for chronic obstructive pulmonary disease: intermediate-term results. *Ann Thorac Surg* 2000; **70**(6): 1813-8; discussion 8-9 **https://pubmed.ncbi.nlm.nih.gov/11156077**.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

1000. Ramos KJ, Harhay MO, Mulligan MS. Which Shall I Choose? Lung Transplantation Listing Preference for Individuals with Interstitial Lung Disease and Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2019; **16**(2): 193-5 https://pubmed.ncbi.nlm.nih.gov/30707065.
1001. Theodore J, Lewiston N. Lung transplantation comes of age. *N Engl J Med* 1990; **322**(11): 772-4 https://pubmed.ncbi.nlm.nih.gov/2308605.
1002. Nordon C, Carstens D, Fagerås M, et al. Characteristics and Outcomes of People With COPD Who Experience Exacerbations While on Inhaled Triple Therapy: Results of the SIRIUS I Cohort Study in the US (2015-2019). *Int J Chron Obstruct Pulmon Dis* 2025; **20**: 1851-64 https://pubmed.ncbi.nlm.nih.gov/40524720.
1003. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; **57**(10): 847-52 https://pubmed.ncbi.nlm.nih.gov/12324669.
1004. Halpin DM, Decramer M, Celli B, Kesten S, Liu D, Tashkin DP. Exacerbation frequency and course of COPD. *Int J Chron Obstruct Pulmon Dis* 2012; **7**: 653-61 https://pubmed.ncbi.nlm.nih.gov/23055714.
1005. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012; **67**(11): 957-63 https://pubmed.ncbi.nlm.nih.gov/22684094.
1006. Pinto-Plata VM, Livnat G, Girish M, et al. Systemic cytokines, clinical and physiological changes in patients hospitalized for exacerbation of COPD. *Chest* 2007; **131**(1): 37-43 https://pubmed.ncbi.nlm.nih.gov/17218554.
1007. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; **106**(2): 196-204 https://pubmed.ncbi.nlm.nih.gov/3492164.
1008. Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; **169**(12): 1298-303 https://pubmed.ncbi.nlm.nih.gov/14990395.
1009. Vijayasaratha K, Stockley RA. Reported and unreported exacerbations of COPD: analysis by diary cards. *Chest* 2008; **133**(1): 34-41 https://pubmed.ncbi.nlm.nih.gov/17989153.
1010. World Health Organization. WHO package of essential noncommunicable (PEN) disease interventions for primary health care. Geneva. Licence: CC BY-NC-SA 3.0 IGO, online document available here: https://www.who.int/publications/i/item/who-package-of-essential-noncommunicable-(pen)-disease-interventions-for-primary-health-care [accessed Oct 2026].
1011. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest* 2000; **117**(5 Suppl 2): 398S-401S https://pubmed.ncbi.nlm.nih.gov/10843984.
1012. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; **359**(15): 1543-54 https://pubmed.ncbi.nlm.nih.gov/18836213.
1013. Celli BR, Fabbri LM, Aaron SD, 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): 1251-8 https://pubmed.ncbi.nlm.nih.gov/34570991.
1014. Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. *Eur Respir J* 2007; **29**(6): 1224-38 https://pubmed.ncbi.nlm.nih.gov/17540785.
1015. 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): https://pubmed.ncbi.nlm.nih.gov/37228266.
1016. Cometa M, Ursitti A, Lombardo LP, et al. Can the Rome classification of chronic obstructive pulmonary disease exacerbation severity be applied in the hospital setting? *Respir Med* 2024; **222**: 107509 https://pubmed.ncbi.nlm.nih.gov/38145723.
1017. Crisafulli E, Sartori G, Huerta A, et al. Association Between Rome Classification Among Hospitalized Patients With COPD Exacerbations and Short-Term and Intermediate-Term Outcomes. *Chest* 2023; **164**(6): 1422-33 https://pubmed.ncbi.nlm.nih.gov/37516272.
1018. Zeng J, Zhou C, Yi Q, et al. Validation of the Rome Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbation: A Multicenter Cohort Study. *Int J Chron Obstruct Pulmon Dis* 2024; **19**: 193-204 https://pubmed.ncbi.nlm.nih.gov/38249828.
1019. Lee HJ, Lee JK, Park TY, Heo EY, Kim DK, Lee HW. Validation of the Rome proposal for severity of acute exacerbation of chronic obstructive pulmonary disease. *Ther Adv Respir Dis* 2023; **17**: 17534666231172917 https://pubmed.ncbi.nlm.nih.gov/37338152.
1020. Celli BR, Fabbri LM, Aaron SD, et al. Differential Diagnosis of Suspected Chronic Obstructive Pulmonary Disease Exacerbations in the Acute Care Setting: Best Practice. *Am J Respir Crit Care Med* 2023; **207**(9): 1134-44 https://pubmed.ncbi.nlm.nih.gov/36701677.
1021. Butler CC, Gillespie D, White P, et al. C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations. *N Engl J Med* 2019; **381**(2): 111-20 https://pubmed.ncbi.nlm.nih.gov/31291514.
1022. Papi A, Bellettato CM, Braccioni F, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006; **173**(10): 1114-21 https://pubmed.ncbi.nlm.nih.gov/16484677.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1023. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; **184**(6): 662-71 https://pubmed.ncbi.nlm.nih.gov/21680942.
1024. Sethi S, Sethi R, Eschberger K, et al. Airway bacterial concentrations and exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; **176**(4): 356-61 https://pubmed.ncbi.nlm.nih.gov/17478618.
1025. Crisafulli E, Manco A, Ferrer M, et al. Pneumonic versus Nonpneumonic Exacerbations of Chronic Obstructive Pulmonary Disease. *Semin Respir Crit Care Med* 2020; **41**(6): 817-29 https://pubmed.ncbi.nlm.nih.gov/32726837.
1026. Torres A, Blasi F, Dartois N, Akova M. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. *Thorax* 2015; **70**(10): 984-9 https://pubmed.ncbi.nlm.nih.gov/26219979.
1027. Restrepo MI, Mortensen EM, Pugh JA, Anzueto A. COPD is associated with increased mortality in patients with community-acquired pneumonia. *Eur Respir J* 2006; **28**(2): 346-51 https://pubmed.ncbi.nlm.nih.gov/16611653.
1028. Braeken DC, Rohde GG, Franssen FM, et al. Risk of community-acquired pneumonia in chronic obstructive pulmonary disease stratified by smoking status: a population-based cohort study in the United Kingdom. *Int J Chron Obstruct Pulmon Dis* 2017; **12**: 2425-32 https://pubmed.ncbi.nlm.nih.gov/28860737.
1029. Rello J, Rodriguez A, Torres A, et al. Implications of COPD in patients admitted to the intensive care unit by community-acquired pneumonia. *Eur Respir J* 2006; **27**(6): 1210-6 https://pubmed.ncbi.nlm.nih.gov/16510452.
1030. Beghe B, Verduri A, Roca M, Fabbri LM. Exacerbation of respiratory symptoms in COPD patients may not be exacerbations of COPD. *Eur Respir J* 2013; **41**(4): 993-5 https://pubmed.ncbi.nlm.nih.gov/23543648.
1031. Stolz D, Breidthardt T, Christ-Crain M, et al. Use of B-type natriuretic peptide in the risk stratification of acute exacerbations of COPD. *Chest* 2008; **133**(5): 1088-94 https://pubmed.ncbi.nlm.nih.gov/18339792.
1032. Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; **137**(5): 1091-7 https://pubmed.ncbi.nlm.nih.gov/20022970.
1033. Kunisaki KM, Dransfield MT, Anderson JA, et al. Exacerbations of Chronic Obstructive Pulmonary Disease and Cardiac Events. A Post Hoc Cohort Analysis from the SUMMIT Randomized Clinical Trial. *Am J Respir Crit Care Med* 2018; **198**(1): 51-7 https://pubmed.ncbi.nlm.nih.gov/29442524.
1034. Graul EL, Nordon C, Rhodes K, et al. Temporal Risk of Nonfatal Cardiovascular Events After Chronic Obstructive Pulmonary Disease Exacerbation: A Population-based Study. *Am J Respir Crit Care Med* 2024; **209**(8): 960-72 https://pubmed.ncbi.nlm.nih.gov/38127850.
1035. Couturaud F, Bertoletti L, Pastre J, et al. Prevalence of Pulmonary Embolism Among Patients With COPD Hospitalized With Acutely Worsening Respiratory Symptoms. *JAMA* 2021; **325**(1): 59-68 https://pubmed.ncbi.nlm.nih.gov/33399840.
1036. Jimenez D, Agusti A, Tabernero E, et al. Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes in Patients Hospitalized for COPD Exacerbation: A Randomized Clinical Trial. *JAMA* 2021; **326**(13): 1277-85 https://pubmed.ncbi.nlm.nih.gov/34609451.
1037. Wallstrom O, Stridsman C, Lindberg A, Nyberg F, Vanfleteren L. Exacerbation History and Risk of Myocardial Infarction and Pulmonary Embolism in COPD. *Chest* 2024; **166**(6): 1347-59 https://pubmed.ncbi.nlm.nih.gov/39094732.
1038. Celeski M, Segreti A, Polito D, et al. Traditional and Advanced Echocardiographic Evaluation in Chronic Obstructive Pulmonary Disease: The Forgotten Relation. *Am J Cardiol* 2024; **217**: 102-18 https://pubmed.ncbi.nlm.nih.gov/38412881.
1039. Freixa X, Portillo K, Paré C, et al. Echocardiographic abnormalities in patients with COPD at their first hospital admission. *Eur Respir J* 2013; **41**(4): 784-91 https://pubmed.ncbi.nlm.nih.gov/23018914.
1040. Kar TA, Qadri SM, Altaf J, et al. Echocardiographic Changes in Chronic Obstructive Pulmonary Disease Exacerbations: A Systematic Review of Pre- and Post-treatment Findings. *Cureus* 2025; **17**(8): e89985 https://pubmed.ncbi.nlm.nih.gov/40951198.
1041. Davis MD, Walsh BK, Sittig SE, Restrepo RD. AARC clinical practice guideline: blood gas analysis and hemoximetry: 2013. *Respir Care* 2013; **58**(10): 1694-703 https://pubmed.ncbi.nlm.nih.gov/23901131.
1042. Hess DR. Respiratory Care Management of COPD Exacerbations. *Respir Care* 2023; **68**(6): 821-37 https://pubmed.ncbi.nlm.nih.gov/37225653.
1043. McKeever TM, Hearson G, Housley G, et al. Using venous blood gas analysis in the assessment of COPD exacerbations: a prospective cohort study. *Thorax* 2016; **71**(3): 210-5 https://pubmed.ncbi.nlm.nih.gov/26628461.
1044. Perkhofer L, Strobel A, Gagiannis D, et al. Transcutaneous carbon dioxide monitoring as a valid complementary method in acute respiratory failure. *Eur Respir J* 2020; **56**(6): https://pubmed.ncbi.nlm.nih.gov/32616592.
1045. Lermuzeaux M, Meric H, Sauneuf B, et al. Superiority of transcutaneous CO2 over end-tidal CO2 measurement for monitoring respiratory failure in nonintubated patients: A pilot study. *J Crit Care* 2016; **31**(1): 150-6 https://pubmed.ncbi.nlm.nih.gov/26463320.
1046. Hao S, Dempsey K, Matos J, et al. Utility of Skin Tone on Pulse Oximetry in Critically Ill Patients: A Prospective Cohort Study. *Crit Care Explor* 2024; **6**(9): e1133 https://pubmed.ncbi.nlm.nih.gov/39268149.
1047. Reid CE, Considine EM, Watson GL, Telesca D, Pfister GG, Jerrett M. Associations between respiratory health and ozone and fine particulate matter during a wildfire event. *Environ Int* 2019; **129**: 291-8 https://pubmed.ncbi.nlm.nih.gov/31146163.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1048. Stowell JD, Geng G, Saikawa E, et al. Associations of wildfire smoke PM(2.5) exposure with cardiorespiratory events in Colorado 2011-2014. *Environ Int* 2019; **133**(Pt A): 105151 https://pubmed.ncbi.nlm.nih.gov/31520956.
1049. Chan CC, Chuang KJ, Chen WJ, Chang WT, Lee CT, Peng CM. Increasing cardiopulmonary emergency visits by long-range transported Asian dust storms in Taiwan. *Environ Res* 2008; **106**(3): 393-400 https://pubmed.ncbi.nlm.nih.gov/17959168.
1050. Gutierrez MP, Zuidema P, Mirsaeidi M, Campos M, Kumar N. Association between African Dust Transport and Acute Exacerbations of COPD in Miami. *J Clin Med* 2020; **9**(8): https://pubmed.ncbi.nlm.nih.gov/32756441.
1051. White AJ, Gompertz S, Stockley RA. Chronic obstructive pulmonary disease . 6: The aetiology of exacerbations of chronic obstructive pulmonary disease. *Thorax* 2003; **58**(1): 73-80 https://pubmed.ncbi.nlm.nih.gov/12511727.
1052. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; **26**(6): 1138-80 https://pubmed.ncbi.nlm.nih.gov/16319346.
1053. Li N, Ma J, Ji K, Wang L. Association of PM2.5 and PM10 with Acute Exacerbation of Chronic Obstructive Pulmonary Disease at lag0 to lag7: A Systematic Review and Meta-Analysis. *COPD* 2022; **19**(1): 243-54 https://pubmed.ncbi.nlm.nih.gov/35616887.
1054. Konstantinoudis G, Minelli C, Vicedo-Cabrera AM, Ballester J, Gasparrini A, Blangiardo M. Ambient heat exposure and COPD hospitalisations in England: a nationwide case-crossover study during 2007-2018. *Thorax* 2022; **77**(11): 1098-104 https://pubmed.ncbi.nlm.nih.gov/35459745.
1055. Liu S, Zhou Y, Liu S, et al. Association between exposure to ambient particulate matter and chronic obstructive pulmonary disease: results from a cross-sectional study in China. *Thorax* 2017; **72**(9): 788-95 https://pubmed.ncbi.nlm.nih.gov/27941160.
1056. Liang L, Cai Y, Barratt B, et al. Associations between daily air quality and hospitalisations for acute exacerbation of chronic obstructive pulmonary disease in Beijing, 2013-17: an ecological analysis. *Lancet Planet Health* 2019; **3**(6): e270-e9 https://pubmed.ncbi.nlm.nih.gov/31229002.
1057. Bafadhel M, McKenna S, Agbetile J, et al. Aspergillus fumigatus during stable state and exacerbations of COPD. *Eur Respir J* 2014; **43**(1): 64-71 https://pubmed.ncbi.nlm.nih.gov/23598955.
1058. Huerta A, Soler N, Esperatti M, et al. Importance of Aspergillus spp. isolation in Acute exacerbations of severe COPD: prevalence, factors and follow-up: the FUNGI-COPD study. *Respir Res* 2014; **15**(1): 17 https://pubmed.ncbi.nlm.nih.gov/24517318.
1059. Mir T, Uddin M, Khalil A, et al. Mortality outcomes associated with invasive aspergillosis among acute exacerbation of chronic obstructive pulmonary disease patient population. *Respir Med* 2022; **191**: 106720 https://pubmed.ncbi.nlm.nih.gov/34959147.
1060. Hammond EE, McDonald CS, Vestbo J, Denning DW. The global impact of Aspergillus infection on COPD. *BMC Pulm Med* 2020; **20**(1): 241 https://pubmed.ncbi.nlm.nih.gov/32912168.
1061. Gu Y, Ye X, Liu Y, et al. A risk-predictive model for invasive pulmonary aspergillosis in patients with acute exacerbation of chronic obstructive pulmonary disease. *Respir Res* 2021; **22**(1): 176 https://pubmed.ncbi.nlm.nih.gov/34107968.
1062. Bulpa P, Duplaquet F, Dimopoulos G, Vogelaers D, Blot S. Invasive Pulmonary Aspergillosis in Chronic Obstructive Pulmonary Disease Exacerbations. *Semin Respir Crit Care Med* 2020; **41**(6): 851-61 https://pubmed.ncbi.nlm.nih.gov/32599634.
1063. Tiew PY, Narayana JK, Quek MSL, et al. Sensitisation to recombinant Aspergillus fumigatus allergens and clinical outcomes in COPD. *Eur Respir J* 2023; **61**(1): https://pubmed.ncbi.nlm.nih.gov/35926878.
1064. Centers for Disease Control and Prevention (CDC). RSV for healthcare professionals. Available online at: https://www.cdc.gov/rsv/hcp/clinical-overview/ [accessed Oct 2026].
1065. Nam HH, Ison MG. Respiratory syncytial virus infection in adults. *BMJ* 2019; **366**: l5021 https://pubmed.ncbi.nlm.nih.gov/31506273.
1066. Juhn YJ, Wi CI, Takahashi PY, et al. Incidence of Respiratory Syncytial Virus Infection in Older Adults Before and During the COVID-19 Pandemic. *JAMA Netw Open* 2023; **6**(1): e2250634 https://pubmed.ncbi.nlm.nih.gov/36662530.
1067. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; **161**(5): 1608-13 https://pubmed.ncbi.nlm.nih.gov/10806163.
1068. Halpin DMG, Birk R, Brealey N, et al. Single-inhaler triple therapy in symptomatic COPD patients: FULFIL subgroup analyses. *ERJ Open Res* 2018; **4**(2): 00119-2017 https://pubmed.ncbi.nlm.nih.gov/29750142.
1069. Donaldson GC, Law M, Kowlessar B, et al. Impact of Prolonged Exacerbation Recovery in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015; **192**(8): 943-50 https://pubmed.ncbi.nlm.nih.gov/26151174.
1070. Hurst JR, Donaldson GC, Quint JK, Goldring JJ, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009; **179**(5): 369-74 https://pubmed.ncbi.nlm.nih.gov/19074596.
1071. Sansores RH, Paulin-Prado P, Robles-Hernandez R, et al. Clinical and microbiological characteristics and inflammatory profile during an exacerbation of COPD due to biomass exposure. A comparison with COPD due to tobacco exposure. *Respir Med* 2022; **204**: 107010 https://pubmed.ncbi.nlm.nih.gov/36272858.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

1072. Ding B, Zaha R, Makita N, et al. History of Respiratory Events Prior to a First COPD Diagnosis and Future Exacerbations: A Longitudinal Observational Cohort Database Study in Japan. *Int J Chron Obstruct Pulmon Dis* 2023; **18**: 247-58 https://pubmed.ncbi.nlm.nih.gov/36915637.
1073. Vanfleteren L, Lindberg A, Zhou C, Nyberg F, Stridsman C. Exacerbation Risk and Mortality in Global Initiative for Chronic Obstructive Lung Disease Group A and B Patients with and without Exacerbation History. *Am J Respir Crit Care Med* 2023; **208**(2): 163-75 https://pubmed.ncbi.nlm.nih.gov/37040482.
1074. Donaldson GC, Mullerova H, Locantore N, et al. Factors associated with change in exacerbation frequency in COPD. *Respir Res* 2013; **14**(1): 79 https://pubmed.ncbi.nlm.nih.gov/23899210.
1075. Lorenzana I, Galera R, Casitas R, et al. Dynamic hyperinflation is a risk factor for mortality and severe exacerbations in COPD patients. *Respir Med* 2024; **225**: 107597 https://pubmed.ncbi.nlm.nih.gov/38499274.
1076. Burgel PR, Nesme-Meyer P, Chanez P, et al. Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. *Chest* 2009; **135**(4): 975-82 https://pubmed.ncbi.nlm.nih.gov/19017866.
1077. Ferrera MC, Lopez CL, Murray S, et al. Risk Factors for Chronic Obstructive Pulmonary Disease Exacerbations among Individuals without a History of Recent Exacerbations: A COPDGene Analysis. *Ann Am Thorac Soc* 2024; **21**(3): 421-7 https://pubmed.ncbi.nlm.nih.gov/37796613.
1078. Chow R, So OW, Im JHB, et al. Predictors of Readmission, for Patients with Chronic Obstructive Pulmonary Disease (COPD) - A Systematic Review. *Int J Chron Obstruct Pulmon Dis* 2023; **18**: 2581-617 https://pubmed.ncbi.nlm.nih.gov/38022828.
1079. Waeijen-Smit K, Crutsen M, Keene S, et al. Global mortality and readmission rates following COPD exacerbation-related hospitalisation: a meta-analysis of 65 945 individual patients. *ERJ Open Res* 2024; **10**(1): https://pubmed.ncbi.nlm.nih.gov/38410700.
1080. Alqahtani JS, Njoku CM, Bereznicki B, et al. Risk factors for all-cause hospital readmission following exacerbation of COPD: a systematic review and meta-analysis. *Eur Respir Rev* 2020; **29**(156): epub 30 Jun https://pubmed.ncbi.nlm.nih.gov/32499306.
1081. Lindenauer PK, Dharmarajan K, Qin L, Lin Z, Gershon AS, Krumholz HM. Risk Trajectories of Readmission and Death in the First Year after Hospitalization for Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2018; **197**(8): 1009-17 https://pubmed.ncbi.nlm.nih.gov/29206052.
1082. Kong CW, Wilkinson TMA. Predicting and preventing hospital readmission for exacerbations of COPD. *ERJ Open Res* 2020; **6**(2): 00325-2019 https://pubmed.ncbi.nlm.nih.gov/32420313.
1083. Hartl S, Lopez-Campos JL, Pozo-Rodriguez F, et al. Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit. *Eur Respir J* 2016; **47**(1): 113-21 https://pubmed.ncbi.nlm.nih.gov/26493806.
1084. Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials. *Thorax* 2019; **74**(4): 337-45 https://pubmed.ncbi.nlm.nih.gov/30630893.
1085. Rafiq R, Aleva FE, Schrumpf JA, et al. Vitamin D supplementation in chronic obstructive pulmonary disease patients with low serum vitamin D: a randomized controlled trial. *Am J Clin Nutr* 2022; **116**(2): 491-9 https://pubmed.ncbi.nlm.nih.gov/35383823.
1086. Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012; **186**(1): 48-55 https://pubmed.ncbi.nlm.nih.gov/22447964.
1087. Burnim M, Putcha N, LaFon D, et al. Serum Immunoglobulin G Levels Are Associated with Risk for Exacerbations: An Analysis of SPIROMICS. *Am J Respir Crit Care Med* 2025; **211**(2): 215-21 https://pubmed.ncbi.nlm.nih.gov/39441116.
1088. Hoogendoorn M, Hoogenveen RT, Rutten-van Molken MP, Vestbo J, Feenstra TL. Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach. *Eur Respir J* 2011; **37**(3): 508-15 https://pubmed.ncbi.nlm.nih.gov/20595157.
1089. Piquet J, Chavaillon JM, David P, et al. High-risk patients following hospitalisation for an acute exacerbation of COPD. *Eur Respir J* 2013; **42**(4): 946-55 https://pubmed.ncbi.nlm.nih.gov/23349446.
1090. Singanayagam A, Schembri S, Chalmers JD. Predictors of mortality in hospitalized adults with acute exacerbation of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2013; **10**(2): 81-9 https://pubmed.ncbi.nlm.nih.gov/23607835.
1091. Guo Y, Zhang T, Wang Z, et al. Body mass index and mortality in chronic obstructive pulmonary disease: A dose-response meta-analysis. *Medicine (Baltimore)* 2016; **95**(28): e4225 https://pubmed.ncbi.nlm.nih.gov/27428228.
1092. Garcia-Aymerich J, Serra Pons I, Mannino DM, Maas AK, Miller DP, Davis KJ. Lung function impairment, COPD hospitalisations and subsequent mortality. *Thorax* 2011; **66**(7): 585-90 https://pubmed.ncbi.nlm.nih.gov/21515553.
1093. Daniels K, Lanes S, Tave A, et al. Risk of Death and Cardiovascular Events Following an Exacerbation of COPD: The EXACOS-CV US Study. *Int J Chron Obstruct Pulmon Dis* 2024; **19**: 225-41 https://pubmed.ncbi.nlm.nih.gov/38259591.
1094. Chen J, Yang J, Zhou M, et al. Cold spell and mortality in 31 Chinese capital cities: Definitions, vulnerability and implications. *Environ Int* 2019; **128**: 271-8 https://pubmed.ncbi.nlm.nih.gov/31071590.
1095. Howcroft M, Walters EH, Wood-Baker R, Walters JA. Action plans with brief patient education for exacerbations in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2016; **12**(12): CD005074 https://pubmed.ncbi.nlm.nih.gov/27990628.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1096. Vogelmeier CF, Rhodes K, Garbe E, et al. Elucidating the risk of cardiopulmonary consequences of an exacerbation of COPD: results of the EXACOS-CV study in Germany. *BMJ Open Respir Res* 2024; **11**(1): https://pubmed.ncbi.nlm.nih.gov/38555102.
1097. Graul EL, Nordon C, Rhodes K, et al. Factors associated with non-fatal heart failure and atrial fibrillation or flutter within the first 30 days post COPD exacerbation: a nested case-control study. *BMC Pulm Med* 2024; **24**(1): 221 https://pubmed.ncbi.nlm.nih.gov/38704538.
1098. Singh D, Han MK, Hawkins NM, et al. Implications of Cardiopulmonary Risk for the Management of COPD: A Narrative Review. *Adv Ther* 2024; **41**(6): 2151-67 https://pubmed.ncbi.nlm.nih.gov/38664329.
1099. Dransfield MT, Criner GJ, Halpin DMG, et al. Time-Dependent Risk of Cardiovascular Events Following an Exacerbation in Patients With Chronic Obstructive Pulmonary Disease: Post Hoc Analysis From the IMPACT Trial. *J Am Heart Assoc* 2022; **11**(18): e024350 https://pubmed.ncbi.nlm.nih.gov/36102236.
1100. Liu Z, Cheang I, Chen Y, et al. Risk of severe cardiovascular events and incidence rate of cardiopulmonary events among patients with COPD in China: a retrospective cohort study. *BMJ Open* 2026; **16**(4): e109712 https://pubmed.ncbi.nlm.nih.gov/42009394.
1101. Nordon C, Simons SO, Marshall J, et al. The sustained increase of cardiovascular risk following COPD exacerbations: meta-analyses of the EXACOS-CV studies. *ERJ Open Res* 2025; **11**(3): https://pubmed.ncbi.nlm.nih.gov/40524923.
1102. Hurst JR, Gale CP, Global Working Group on Cardiopulmonary R. MACE in COPD: addressing cardiopulmonary risk. *Lancet Respir Med* 2024; **12**(5): 345-8 https://pubmed.ncbi.nlm.nih.gov/38437859.
1103. Make BJ, Eriksson G, Calverley PM, et al. A score to predict short-term risk of COPD exacerbations (SCOPEX). *Int J Chron Obstruct Pulmon Dis* 2015; **10**: 201-9 https://pubmed.ncbi.nlm.nih.gov/25670896.
1104. Lapi F, Marconi E, Lombardo FP, et al. Development and validation of a prediction score to assess the risk of incurring in COPD-related exacerbations: a population-based study in primary care. *Respir Med* 2024; **227**: 107634 https://pubmed.ncbi.nlm.nih.gov/38621547.
1105. Steer J, Gibson J, Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. *Thorax* 2012; **67**(11): 970-6 https://pubmed.ncbi.nlm.nih.gov/22895999.
1106. Martinez FJ, Han MK, Flaherty K, Curtis J. Role of infection and antimicrobial therapy in acute exacerbations of chronic obstructive pulmonary disease. *Expert Rev Anti Infect Ther* 2006; **4**(1): 101-24 https://pubmed.ncbi.nlm.nih.gov/16441213.
1107. Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008; **178**(4): 332-8 https://pubmed.ncbi.nlm.nih.gov/18511702.
1108. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 2018. https://www.nice.org.uk/guidance/NG115.
1109. Celli BR, MacNee W, Force AET. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; **23**(6): 932-46 https://pubmed.ncbi.nlm.nih.gov/15219010.
1110. 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 https://pubmed.ncbi.nlm.nih.gov/27569680.
1111. Bardsley G, Pilcher J, McKinstry S, et al. Oxygen versus air-driven nebulisers for exacerbations of chronic obstructive pulmonary disease: a randomised controlled trial. *BMC Pulm Med* 2018; **18**(1): 157 https://pubmed.ncbi.nlm.nih.gov/30285695.
1112. Dhand R, Treat S, Ferris J, et al. Safety, Efficacy, and Feasibility of Nebulized Long-Acting Bronchodilators vs Short-Acting Bronchodilators in Hospitalized Patients With Acute Exacerbations of COPD: A Phase IV, Randomized, Parallel-Group Clinical Trial. *CHEST Pulm* 2024; **2**(4): 100105 https://pubmed.ncbi.nlm.nih.gov/42548489.
1113. Di Marco F, Verga M, Santus P, Morelli N, Cazzola M, Centanni S. Effect of formoterol, tiotropium, and their combination in patients with acute exacerbation of chronic obstructive pulmonary disease: a pilot study. *Respir Med* 2006; **100**(11): 1925-32 https://pubmed.ncbi.nlm.nih.gov/16626956.
1114. Bollu V, Ernst FR, Karafilidis J, Rajagopalan K, Robinson SB, Braman SS. Hospital readmissions following initiation of nebulized arformoterol tartrate or nebulized short-acting beta-agonists among inpatients treated for COPD. *Int J Chron Obstruct Pulmon Dis* 2013; **8**: 631-9 https://pubmed.ncbi.nlm.nih.gov/24353413.
1115. Barr RG, Rowe BH, Camargo CA, Jr. Methylxanthines for exacerbations of chronic obstructive pulmonary disease: meta-analysis of randomised trials. *BMJ* 2003; **327**(7416): 643 https://pubmed.ncbi.nlm.nih.gov/14500434.
1116. Duffy N, Walker P, Diamantea F, Calverley PM, Davies L. Intravenous aminophylline in patients admitted to hospital with non-acidotic exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Thorax* 2005; **60**(9): 713-7 https://pubmed.ncbi.nlm.nih.gov/15939732.
1117. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet* 1999; **354**(9177): 456-60 https://pubmed.ncbi.nlm.nih.gov/10465169.
1118. Maltais F, Ostinelli J, Bourbeau 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 https://pubmed.ncbi.nlm.nih.gov/11874817.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

1119. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med* 1999; **340**(25): 1941-7 https://pubmed.ncbi.nlm.nih.gov/10379017.
1120. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med* 1996; **154**(2 Pt 1): 407-12 https://pubmed.ncbi.nlm.nih.gov/8756814.
1121. Alia I, de la Cal MA, Esteban A, et al. Efficacy of corticosteroid therapy in patients with an acute exacerbation of chronic obstructive pulmonary disease receiving ventilatory support. *Arch Intern Med* 2011; **171**(21): 1939-46 https://pubmed.ncbi.nlm.nih.gov/22123804.
1122. Aaron SD, Vandemheen KL, Hebert P, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med* 2003; **348**(26): 2618-25 https://pubmed.ncbi.nlm.nih.gov/12826636.
1123. Leuppi JD, Schuetz P, Bingisser R, 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): 2223-31 https://pubmed.ncbi.nlm.nih.gov/23695200.
1124. Walters JA, Tan DJ, White CJ, Wood-Baker R. Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014; 10.1002/14651858.CD006897.pub3(12): CD006897 https://pubmed.ncbi.nlm.nih.gov/25491891.
1125. Sivapalan P, Ingebrigtsen TS, Rasmussen DB, et al. COPD exacerbations: the impact of long versus short courses of oral corticosteroids on mortality and pneumonia: nationwide data on 67 000 patients with COPD followed for 12 months. *BMJ Open Respir Res* 2019; **6**(1): e000407 https://pubmed.ncbi.nlm.nih.gov/31179005.
1126. de Jong YP, Uil SM, Grotjohan HP, Postma DS, Kerstjens HA, van den Berg JW. Oral or IV prednisolone in the treatment of COPD exacerbations: a randomized, controlled, double-blind study. *Chest* 2007; **132**(6): 1741-7 https://pubmed.ncbi.nlm.nih.gov/17646228.
1127. Gunen H, Hacievliyagil SS, Yetkin O, Gulbas G, Mutlu LC, In E. The role of nebulised budesonide in the treatment of exacerbations of COPD. *Eur Respir J* 2007; **29**(4): 660-7 https://pubmed.ncbi.nlm.nih.gov/17251232.
1128. Stallberg B, Selroos O, Vogelmeier C, Andersson E, Ekstrom T, Larsson K. Budesonide/formoterol as effective as prednisolone plus formoterol in acute exacerbations of COPD. A double-blind, randomised, non-inferiority, parallel-group, multicentre study. *Respir Res* 2009; **10**(1): 11 https://pubmed.ncbi.nlm.nih.gov/19228428.
1129. Ding Z, Li X, Lu Y, 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 https://pubmed.ncbi.nlm.nih.gov/27888990.
1130. Stolz D, Hirsch HH, Schilter D, et al. Intensified Therapy with Inhaled Corticosteroids and Long-Acting beta(2)-Agonists at the Onset of Upper Respiratory Tract Infection to Prevent Chronic Obstructive Pulmonary Disease Exacerbations. A Multicenter, Randomized, Double-Blind, Placebo-controlled Trial. *Am J Respir Crit Care Med* 2018; **197**(9): 1136-46 https://pubmed.ncbi.nlm.nih.gov/29266965.
1131. Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ* 2017; **357**: j1415 https://pubmed.ncbi.nlm.nih.gov/28404617.
1132. Sivapalan P, Lapperre TS, Janner J, et al. Eosinophil-guided corticosteroid therapy in patients admitted to hospital with COPD exacerbation (CORTICO-COP): a multicentre, randomised, controlled, open-label, non-inferiority trial. *Lancet Respir Med* 2019; **7**(8): 699-709 https://pubmed.ncbi.nlm.nih.gov/31122894.
1133. Ramakrishnan S, Jeffers H, Langford-Wiley B, et al. Blood eosinophil-guided oral prednisolone for COPD exacerbations in primary care in the UK (STARR2): a non-inferiority, multicentre, double-blind, placebo-controlled, randomised controlled trial. *Lancet Respir Med* 2024; **12**(1): 67-77 https://pubmed.ncbi.nlm.nih.gov/37924830.
1134. Seemungal T, Harper-Owen R, Bhowmik A, et al. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; **164**(9): 1618-23 https://pubmed.ncbi.nlm.nih.gov/11719299.
1135. 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 https://pubmed.ncbi.nlm.nih.gov/30371937.
1136. Rothberg MB, Pekow PS, Lahti M, Brody O, Skiest DJ, Lindenauer PK. Antibiotic therapy and treatment failure in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. *JAMA* 2010; **303**(20): 2035-42 https://pubmed.ncbi.nlm.nih.gov/20501925.
1137. van Velzen P, Ter Riet G, Bresser P, et al. Doxycycline for outpatient-treated acute exacerbations of COPD: a randomised double-blind placebo-controlled trial. *Lancet Respir Med* 2017; **5**(6): 492-9 https://pubmed.ncbi.nlm.nih.gov/28483402.
1138. Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. *Chest* 2008; **133**(3): 756-66 https://pubmed.ncbi.nlm.nih.gov/18321904.
1139. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006; 10.1002/14651858.CD004403.pub2(2): CD004403 https://pubmed.ncbi.nlm.nih.gov/16625602.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

1140. Wilson R, Anzueto A, Miravitlles M, et al. Moxifloxacin versus amoxicillin/clavulanic acid in outpatient acute exacerbations of COPD: MAESTRAL results. *Eur Respir J* 2012; **40**(1): 17-27 https://pubmed.ncbi.nlm.nih.gov/22135277.
1141. Miravitlles M, Kruesmann F, Haverstock D, Perroncel R, Choudhri SH, Arvis P. Sputum colour and bacteria in chronic bronchitis exacerbations: a pooled analysis. *Eur Respir J* 2012; **39**(6): 1354-60 https://pubmed.ncbi.nlm.nih.gov/22034649.
1142. Clark TW, Medina MJ, Batham S, Curran MD, Parmar S, Nicholson KG. C-reactive protein level and microbial aetiology in patients hospitalised with acute exacerbation of COPD. *Eur Respir J* 2015; **45**(1): 76-86 https://pubmed.ncbi.nlm.nih.gov/25186260.
1143. Peng C, Tian C, Zhang Y, Yang X, Feng Y, Fan H. C-reactive protein levels predict bacterial exacerbation in patients with chronic obstructive pulmonary disease. *Am J Med Sci* 2013; **345**(3): 190-4 https://pubmed.ncbi.nlm.nih.gov/23221507.
1144. Prins HJ, Duijkers R, van der Valk P, et al. CRP-guided antibiotic treatment in acute exacerbations of COPD in hospital admissions. *Eur Respir J* 2019; **53**(5): https://pubmed.ncbi.nlm.nih.gov/30880285.
1145. Miravitlles M, Moragas A, Hernandez S, Bayona C, Llor C. Is it possible to identify exacerbations of mild to moderate COPD that do not require antibiotic treatment? *Chest* 2013; **144**(5): 1571-7 https://pubmed.ncbi.nlm.nih.gov/23807094.
1146. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004; **363**(9409): 600-7 https://pubmed.ncbi.nlm.nih.gov/14987884.
1147. Schuetz P, Christ-Crain M, Thomann R, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 2009; **302**(10): 1059-66 https://pubmed.ncbi.nlm.nih.gov/19738090.
1148. Schuetz P, Muller B, Christ-Crain M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev* 2012; **2012**(9): CD007498 https://pubmed.ncbi.nlm.nih.gov/22972110.
1149. Wang JX, Zhang SM, Li XH, Zhang Y, Xu ZY, Cao B. Acute exacerbations of chronic obstructive pulmonary disease with low serum procalcitonin values do not benefit from antibiotic treatment: a prospective randomized controlled trial. *Int J Infect Dis* 2016; **48**: 40-5 https://pubmed.ncbi.nlm.nih.gov/27155210.
1150. Chen K, Pleasants KA, Pleasants RA, et al. Procalcitonin for Antibiotic Prescription in Chronic Obstructive Pulmonary Disease Exacerbations: Systematic Review, Meta-Analysis, and Clinical Perspective. *Pulm Ther* 2020; **6**(2): 201-14 https://pubmed.ncbi.nlm.nih.gov/32676981.
1151. Daubin C, Valette X, Thiolliere F, et al. Procalcitonin algorithm to guide initial antibiotic therapy in acute exacerbations of COPD admitted to the ICU: a randomized multicenter study. *Intensive Care Med* 2018; **44**(4): 428-37 https://pubmed.ncbi.nlm.nih.gov/29663044.
1152. Sheng W, Huang L, Gu X, et al. Procalcitonin-guided use of antibiotic in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease: a randomized clinical trial. *Clin Microbiol Infect* 2025; **31**(5): 785-92 https://pubmed.ncbi.nlm.nih.gov/39662822.
1153. Adams S, J. M, Luther M. Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of chronic obstructive pulmonary disease. *Chest* 2000; **117**: 1345-52
1154. Miravitlles M, Espinosa C, Fernandez-Laso E, Martos JA, Maldonado JA, Gallego M. Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. Study Group of Bacterial Infection in COPD. *Chest* 1999; **116**(1): 40-6 https://pubmed.ncbi.nlm.nih.gov/10424501.
1155. Soler N, Torres A, Ewig S, et al. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 1998; **157**(5 Pt 1): 1498-505 https://pubmed.ncbi.nlm.nih.gov/9603129.
1156. Llor C, Moragas A, Miravitlles M, Mesquita P, Cordoba G. Are short courses of antibiotic therapy as effective as standard courses for COPD exacerbations? A systematic review and meta-analysis. *Pulm Pharmacol Ther* 2022; **72**: 102111 https://pubmed.ncbi.nlm.nih.gov/35032637.
1157. Masterton RG, Burley CJ. Randomized, double-blind study comparing 5- and 7-day regimens of oral levofloxacin in patients with acute exacerbation of chronic bronchitis. *Int J Antimicrob Agents* 2001; **18**(6): 503-12 https://pubmed.ncbi.nlm.nih.gov/11738336.
1158. Black PN, Morgan-Day A, McMillan TE, Poole PJ, Young RP. Randomised, controlled trial of N-acetylcysteine for treatment of acute exacerbations of chronic obstructive pulmonary disease [ISRCTN21676344]. *BMC Pulm Med* 2004; **4**: 13 https://pubmed.ncbi.nlm.nih.gov/15581425.
1159. Zuin R, Palamidese A, Negrin R, Catozzo L, Scarda A, Balbinot M. High-dose N-acetylcysteine in patients with exacerbations of chronic obstructive pulmonary disease. *Clin Drug Investig* 2005; **25**(6): 401-8 https://pubmed.ncbi.nlm.nih.gov/17532680.
1160. Papadopoulou E, Hansel J, Lazar Z, et al. Mucolytics for acute exacerbations of chronic obstructive pulmonary disease: a meta-analysis. *Eur Respir Rev* 2023; **32**(167): https://pubmed.ncbi.nlm.nih.gov/36697209.
1161. Rizkallah J, Man SFP, Sin DD. Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis. *Chest* 2009; **135**(3): 786-93 https://pubmed.ncbi.nlm.nih.gov/18812453.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

1162. Gunen H, Gulbas G, In E, Yetkin O, Hacievliyagil SS. Venous thromboemboli and exacerbations of COPD. *Eur Respir J* 2010; **35**(6): 1243-8 https://pubmed.ncbi.nlm.nih.gov/19926740.
1163. Bertoletti L, Quenet S, Laporte S, et al. Pulmonary embolism and 3-month outcomes in 4036 patients with venous thromboembolism and chronic obstructive pulmonary disease: data from the RIETE registry. *Respir Res* 2013; **14**(1): 75 https://pubmed.ncbi.nlm.nih.gov/23865769.
1164. Kahn S, Lim W, Dunn A, et al. American College of Chest Physicians. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Pracice Guidelines. *Chest* 2012; **141**((2 Suppl)): e195S-226S
1165. Bruni A, Garofalo E, Cammarota G, et al. High Flow Through Nasal Cannula in Stable and Exacerbated Chronic Obstructive Pulmonary Disease Patients. *Rev Recent Clin Trials* 2019; **14**(4): 247-60 https://pubmed.ncbi.nlm.nih.gov/31291880.
1166. Renda T, Corrado A, Iskandar G, Pelaia G, Abdalla K, Navalesi P. High-flow nasal oxygen therapy in intensive care and anaesthesia. *Br J Anaesth* 2018; **120**(1): 18-27 https://pubmed.ncbi.nlm.nih.gov/29397127.
1167. Pisani L, Vega ML. Use of Nasal High Flow in Stable COPD: Rationale and Physiology. *COPD* 2017; **14**(3): 346-50 https://pubmed.ncbi.nlm.nih.gov/28459282.
1168. Roca O, Hernandez G, Diaz-Lobato S, et al. Current evidence for the effectiveness of heated and humidified high flow nasal cannula supportive therapy in adult patients with respiratory failure. *Crit Care* 2016; **20**(1): 109 https://pubmed.ncbi.nlm.nih.gov/27121707.
1169. Fraser JF, Spooner AJ, Dunster KR, Anstey CM, Corley A. Nasal high flow oxygen therapy in patients with COPD reduces respiratory rate and tissue carbon dioxide while increasing tidal and end-expiratory lung volumes: a randomised crossover trial. *Thorax* 2016; **71**(8): 759-61 https://pubmed.ncbi.nlm.nih.gov/27015801.
1170. Papazian L, Corley A, Hess D, et al. Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review. *Intensive Care Med* 2016; **42**(9): 1336-49 https://pubmed.ncbi.nlm.nih.gov/26969671.
1171. Li XY, Tang X, Wang R, et al. High-Flow Nasal Cannula for Chronic Obstructive Pulmonary Disease with Acute Compensated Hypercapnic Respiratory Failure: A Randomized, Controlled Trial. *Int J Chron Obstruct Pulmon Dis* 2020; **15**: 3051-61 https://pubmed.ncbi.nlm.nih.gov/33262584.
1172. Xia J, Gu S, Lei W, et al. High-flow nasal cannula versus conventional oxygen therapy in acute COPD exacerbation with mild hypercapnia: a multicenter randomized controlled trial. *Crit Care* 2022; **26**(1): 109 https://pubmed.ncbi.nlm.nih.gov/35428349.
1173. Xia J, Yang H, Zhan Q, Fan Y, Wang C. High-flow nasal cannula may prolong the length of hospital stay in patients with hypercapnic acute COPD exacerbation. *Respir Med* 2023; **220**: 107465 https://pubmed.ncbi.nlm.nih.gov/37956934.
1174. Cortegiani A, Longhini F, Carlucci A, et al. High-flow nasal therapy versus noninvasive ventilation in COPD patients with mild-to-moderate hypercapnic acute respiratory failure: study protocol for a noninferiority randomized clinical trial. *Trials* 2019; **20**(1): 450 https://pubmed.ncbi.nlm.nih.gov/31331372.
1175. Tan D, Walline JH, Ling B, et al. High-flow nasal cannula oxygen therapy versus non-invasive ventilation for chronic obstructive pulmonary disease patients after extubation: a multicenter, randomized controlled trial. *Crit Care* 2020; **24**(1): 489 https://pubmed.ncbi.nlm.nih.gov/32762701.
1176. Investigators R, the BA, Maia IS, et al. High-Flow Nasal Oxygen vs Noninvasive Ventilation in Patients With Acute Respiratory Failure: The RENOVATE Randomized Clinical Trial. *JAMA* 2025; **333**(10): 875-90 https://pubmed.ncbi.nlm.nih.gov/39657981.
1177. Pantazopoulos I, Boutlas S, Mavrovounis G, et al. Nasal high flow or noninvasive ventilation? navigating hypercapnic COPD exacerbation treatment: A randomized noninferiority clinical trial. *Respir Med* 2024; **232**: 107762 https://pubmed.ncbi.nlm.nih.gov/39111544.
1178. Haciosman O, Ergenc H, Az A, Dogan Y, Sogut O. A high-flow nasal cannula versus noninvasive ventilation in acute exacerbations of chronic obstructive pulmonary disease. *Am J Emerg Med* 2025; **87**: 38-43 https://pubmed.ncbi.nlm.nih.gov/39481328.
1179. Hernandez G, Vaquero C, Colinas L, et al. Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients: A Randomized Clinical Trial. *JAMA* 2016; **316**(15): 1565-74 https://pubmed.ncbi.nlm.nih.gov/27706464.
1180. Thille AW, Muller G, Gacouin A, et al. Effect of Postextubation High-Flow Nasal Oxygen With Noninvasive Ventilation vs High-Flow Nasal Oxygen Alone on Reintubation Among Patients at High Risk of Extubation Failure: A Randomized Clinical Trial. *JAMA* 2019; **322**(15): 1465-75 https://pubmed.ncbi.nlm.nih.gov/31577036.
1181. Oczkowski S, Ergan B, Bos L, et al. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. *Eur Respir J* 2022; **59**(4): https://pubmed.ncbi.nlm.nih.gov/34649974.
1182. Storgaard LH, Hockey HU, Laursen BS, Weinreich UM. Long-term effects of oxygen-enriched high-flow nasal cannula treatment in COPD patients with chronic hypoxemic respiratory failure. *Int J Chron Obstruct Pulmon Dis* 2018; **13**: 1195-205 https://pubmed.ncbi.nlm.nih.gov/29713153.
1183. Nagata K, Horie T, Chohnabayashi N, et al. Home High-Flow Nasal Cannula Oxygen Therapy for Stable Hypercapnic COPD: A Randomized Clinical Trial. *Am J Respir Crit Care Med* 2022; **206**(11): 1326-35 https://pubmed.ncbi.nlm.nih.gov/35771533.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1184. Nagata K, Kikuchi T, Horie T, et al. Domiciliary High-Flow Nasal Cannula Oxygen Therapy for Patients with Stable Hypercapnic Chronic Obstructive Pulmonary Disease. A Multicenter Randomized Crossover Trial. *Ann Am Thorac Soc* 2018; **15**(4): 432-9 https://pubmed.ncbi.nlm.nih.gov/29283682.
1185. 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 https://pubmed.ncbi.nlm.nih.gov/28702957.
1186. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; **333**(13): 817-22 https://pubmed.ncbi.nlm.nih.gov/7651472.
1187. Chandra D, Stamm JA, Taylor B, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008. *Am J Respir Crit Care Med* 2012; **185**(2): 152-9 https://pubmed.ncbi.nlm.nih.gov/22016446.
1188. Meyer TJ, Hill NS. Noninvasive positive pressure ventilation to treat respiratory failure. *Ann Intern Med* 1994; **120**(9): 760-70 https://pubmed.ncbi.nlm.nih.gov/8147550.
1189. Consensus Development Conference Committee. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation--a consensus conference report. *Chest* 1999; **116**(2): 521-34 https://pubmed.ncbi.nlm.nih.gov/10453883.
1190. Bott J, Carroll MP, Conway JH, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993; **341**(8860): 1555-7 https://pubmed.ncbi.nlm.nih.gov/8099639.
1191. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 1995; **151**(6): 1799-806 https://pubmed.ncbi.nlm.nih.gov/7767523.
1192. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet* 2000; **355**(9219): 1931-5 https://pubmed.ncbi.nlm.nih.gov/10859037.
1193. Sellares J, Ferrer M, Anton A, et al. Discontinuing noninvasive ventilation in severe chronic obstructive pulmonary disease exacerbations: a randomised controlled trial. *Eur Respir J* 2017; **50**(1): https://pubmed.ncbi.nlm.nih.gov/28679605.
1194. Conti G, Antonelli M, Navalesi P, et al. Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. *Intensive Care Med* 2002; **28**(12): 1701-7 https://pubmed.ncbi.nlm.nih.gov/12447511.
1195. Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002; **287**(3): 345-55 https://pubmed.ncbi.nlm.nih.gov/11790214.
1196. Wildman MJ, Sanderson C, Groves J, et al. Implications of prognostic pessimism in patients with chronic obstructive pulmonary disease (COPD) or asthma admitted to intensive care in the UK within the COPD and asthma outcome study (CAOS): multicentre observational cohort study. *BMJ* 2007; **335**(7630): 1132 https://pubmed.ncbi.nlm.nih.gov/17975254.
1197. Gunen H, Hacievliyagil SS, Kosar F, et al. Factors affecting survival of hospitalised patients with COPD. *Eur Respir J* 2005; **26**(2): 234-41 https://pubmed.ncbi.nlm.nih.gov/16055870.
1198. Whittaker H, Rubino A, Mullerova H, et al. Frequency and Severity of Exacerbations of COPD Associated with Future Risk of Exacerbations and Mortality: A UK Routine Health Care Data Study. *Int J Chron Obstruct Pulmon Dis* 2022; **17**: 427-37 https://pubmed.ncbi.nlm.nih.gov/35264849.
1199. Echevarria C, Brewin K, Horobin H, et al. Early Supported Discharge/Hospital At Home For Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Review and Meta-Analysis. *COPD* 2016; **13**(4): 523-33 https://pubmed.ncbi.nlm.nih.gov/26854816.
1200. Mannino D, Bogart M, Germain G, et al. Benefit of Prompt versus Delayed Use of Single-Inhaler Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) Following a COPD Exacerbation. *Int J Chron Obstruct Pulmon Dis* 2022; **17**: 491-504 https://pubmed.ncbi.nlm.nih.gov/35281476.
1201. Strange C, Tkacz J, Schinkel J, et al. Exacerbations and Real-World Outcomes After Single-Inhaler Triple Therapy of Budesonide/Glycopyrrolate/Formoterol Fumarate, Among Patients with COPD: Results from the EROS (US) Study. *Int J Chron Obstruct Pulmon Dis* 2023; **18**: 2245-56 https://pubmed.ncbi.nlm.nih.gov/37849918.
1202. Ismaila AS, Rothnie KJ, Wood RP, et al. Benefit of prompt initiation of single-inhaler fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI) in patients with COPD in England following an exacerbation: a retrospective cohort study. *Respir Res* 2023; **24**(1): 229 https://pubmed.ncbi.nlm.nih.gov/37749551.
1203. Bhutani M, Müllerová H, Patel D, et al. Disease burden and health-related outcomes of patients discharged from hospital following a COPD exacerbation in the United States. *Respir Med* 2025; **248**: 108337 https://pubmed.ncbi.nlm.nih.gov/40907834.
1204. Park Y, Kim WJ, Han SS, et al. Effect of Hospital-to-Home Transitional Care for COPD on Patient-Centered Outcomes. *Respir Care* 2025; **70**(1): 81-91 https://pubmed.ncbi.nlm.nih.gov/39964858.
1205. Stergiopoulos GM, Elayadi AN, Chen ES, Galiatsatos P. The effect of telemedicine employing telemonitoring instruments on readmissions of patients with heart failure and/or COPD: a systematic review. *Front Digit Health* 2024; **6**: 1441334 https://pubmed.ncbi.nlm.nih.gov/39386390.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1206. Jordan RE, Majothi S, Heneghan NR, et al. Supported self-management for patients with moderate to severe chronic obstructive pulmonary disease (COPD): an evidence synthesis and economic analysis. *Health Technol Assess* 2015; **19**(36): 1-516 https://pubmed.ncbi.nlm.nih.gov/25980984.
1207. Gavish R, Levy A, Dekel OK, Karp E, Maimon N. The Association Between Hospital Readmission and Pulmonologist Follow-up Visits in Patients With COPD. *Chest* 2015; **148**(2): 375-81 https://pubmed.ncbi.nlm.nih.gov/25611698.
1208. Roche N, Caron A, Emery C, et al. [Medico-economic evaluation of the PRADO-BPCO post-exacerbation support program]. *Rev Mal Respir* 2024; **41**(6): 409-20 https://pubmed.ncbi.nlm.nih.gov/38824115.
1209. Spece LJ, Epler EM, Duan K, et al. Reassessment of Home Oxygen Prescription after Hospitalization for Chronic Obstructive Pulmonary Disease. A Potential Target for Deimplementation. *Ann Am Thorac Soc* 2021; **18**(3): 426-32 https://pubmed.ncbi.nlm.nih.gov/33075243.
1210. Martinez-Garcia MA, de la Rosa Carrillo D, Soler-Cataluna JJ, et al. Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; **187**(8): 823-31 https://pubmed.ncbi.nlm.nih.gov/23392438.
1211. Au DH, Bryson CL, Chien JW, et al. The effects of smoking cessation on the risk of chronic obstructive pulmonary disease exacerbations. *J Gen Intern Med* 2009; **24**(4): 457-63 https://pubmed.ncbi.nlm.nih.gov/19194768.
1212. Decramer M, Nici L, Nardini S, et al. Targeting the COPD exacerbation. *Respir Med* 2008; **102 Suppl 1**: S3-15 https://pubmed.ncbi.nlm.nih.gov/18582795.
1213. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 2008; **300**(20): 2407-16 https://pubmed.ncbi.nlm.nih.gov/19033591.
1214. Noorduyn SG ea. Poster presented at: ATS Annual Meeting; May 17-21, 2024; San Diego, CA. Abstract 11212.
1215. Zhang X, Xie S, Cao X, et al. Evaluation of an air quality Alert-Based intervention in patients with stable chronic obstructive pulmonary Disease: A prospective randomized controlled trial. *Respir Med* 2026; **252**: 108668 https://pubmed.ncbi.nlm.nih.gov/41577302.
1216. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009; **33**(5): 1165-85 https://pubmed.ncbi.nlm.nih.gov/19407051.
1217. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: Role of comorbidities. *Eur Respir J* 2006; **28**(6): 1245-57 https://pubmed.ncbi.nlm.nih.gov/17138679.
1218. Iversen KK, Kjaergaard J, Akkan D, et al. The prognostic importance of lung function in patients admitted with heart failure. *Eur J Heart Fail* 2010; **12**(7): 685-91 https://pubmed.ncbi.nlm.nih.gov/20395261.
1219. Almagro P, Soriano JB, Cabrera FJ, et al. Short- and medium-term prognosis in patients hospitalized for COPD exacerbation: the CODEX index. *Chest* 2014; **145**(5): 972-80 https://pubmed.ncbi.nlm.nih.gov/24077342.
1220. Campo G, Napoli N, Serenelli C, Tebaldi M, Ferrari R. Impact of a recent hospitalization on treatment and prognosis of ST-segment elevation myocardial infarction. *Int J Cardiol* 2013; **167**(1): 296-7 https://pubmed.ncbi.nlm.nih.gov/23084113.
1221. Divo MJ, Casanova C, Marin JM, et al. COPD comorbidities network. *Eur Respir J* 2015; **46**(3): 640-50 https://pubmed.ncbi.nlm.nih.gov/26160874.
1222. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? *Lancet* 2007; **370**(9589): 797-9 https://pubmed.ncbi.nlm.nih.gov/17765529.
1223. Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; **186**(2): 155-61 https://pubmed.ncbi.nlm.nih.gov/22561964.
1224. Fabbri LM, Luppi F, Beghe B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J* 2008; **31**(1): 204-12 https://pubmed.ncbi.nlm.nih.gov/18166598.
1225. Franssen FM, Soriano JB, Roche N, et al. Lung Function Abnormalities in Smokers with Ischemic Heart Disease. *Am J Respir Crit Care Med* 2016; **194**(5): 568-76 https://pubmed.ncbi.nlm.nih.gov/27442601.
1226. Krahnke JS, Abraham WT, Adamson PB, et al. Heart failure and respiratory hospitalizations are reduced in patients with heart failure and chronic obstructive pulmonary disease with the use of an implantable pulmonary artery pressure monitoring device. *J Card Fail* 2015; **21**(3): 240-9 https://pubmed.ncbi.nlm.nih.gov/25541376.
1227. Yeoh SE, Dewan P, Serenelli M, et al. Effects of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction patients with chronic obstructive pulmonary disease in EMPHASIS-HF and RALES. *Eur J Heart Fail* 2022; **24**(3): 529-38 https://pubmed.ncbi.nlm.nih.gov/34536265.
1228. Schattner A. The clinical encounter revisited. *Am J Med* 2014; **127**(4): 268-74 https://pubmed.ncbi.nlm.nih.gov/24333201.
1229. Institute for Healthcare Improvement (IHI). website www.ihi.org [accessed Oct 2026].
1230. Manning JM. The 4M Model. *Crit Care Nurs Clin North Am* 2023; **35**(4): 367-74 https://pubmed.ncbi.nlm.nih.gov/37838412.
1231. Mate K, Fulmer T, Pelton L, et al. Evidence for the 4Ms: Interactions and Outcomes across the Care Continuum. *J Aging Health* 2021; **33**(7-8): 469-81 https://pubmed.ncbi.nlm.nih.gov/33555233.
1232. Celli BR, Fabbri LM, Yohannes AM, et al. A person-centred clinical approach to the multimorbid patient with COPD. *Eur J Intern Med* 2025; **140**: 106424 https://pubmed.ncbi.nlm.nih.gov/40803921.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1233. Yohannes AM. Palliative care provision for patients with chronic obstructive pulmonary disease. *Health Qual Life Outcomes* 2007; **5**: 17 https://pubmed.ncbi.nlm.nih.gov/17407591.
1234. Jung HW, Kim S, Jang IY, Shin DW, Lee JE, Won CW. Screening Value of Timed Up and Go Test for Frailty and Low Physical Performance in Korean Older Population: The Korean Frailty and Aging Cohort Study (KFACS). *Ann Geriatr Med Res* 2020; **24**(4): 259-66 https://pubmed.ncbi.nlm.nih.gov/33296961.
1235. Moll M, Qiao D, Regan EA, et al. Machine Learning and Prediction of All-Cause Mortality in COPD. *Chest* 2020; **158**(3): 952-64 https://pubmed.ncbi.nlm.nih.gov/32353417.
1236. Fralick M, Bartsch E, Ritchie CS, Sacks CA. Estimating the Use of Potentially Inappropriate Medications Among Older Adults in the United States. *J Am Geriatr Soc* 2020; **68**(12): 2927-30 https://pubmed.ncbi.nlm.nih.gov/32841366.
1237. Fabbri LM. Smoking, Not COPD, as the Disease. *N Engl J Med* 2016; **374**(19): 1885-6 https://pubmed.ncbi.nlm.nih.gov/27168438.
1238. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; **56**(3): M146-56 https://pubmed.ncbi.nlm.nih.gov/11253156.
1239. Azhimamatova R, Salieva RS, Zalova TB, et al. Frailty in COPD: Clinical Impact, Diagnosis, Biomarkers, and Management Strategies. *Int J Chron Obstruct Pulmon Dis* 2025; **20**: 2445-58 https://pubmed.ncbi.nlm.nih.gov/40688238.
1240. Roberts MH, Mapel DW, Ganvir N, Dodd MA. Frailty Among Older Individuals with and without COPD: A Cohort Study of Prevalence and Association with Adverse Outcomes. *Int J Chron Obstruct Pulmon Dis* 2022; **17**: 701-17 https://pubmed.ncbi.nlm.nih.gov/35411140.
1241. Xu J, Xu W, Qiu Y, Gong D, Man C, Fan Y. Association of Prefrailty and Frailty With All-Cause Mortality, Acute Exacerbation, and Hospitalization in Patients With Chronic Obstructive Pulmonary Disease: A Meta-Analysis. *J Am Med Dir Assoc* 2023; **24**(7): 937-44 e3 https://pubmed.ncbi.nlm.nih.gov/37150209.
1242. Cherian M, Masoudian P, Thavorn K, Sandoz J, Shorr R, Mulpuru S. The impact of frailty on clinical outcomes among individuals with COPD: a systematic review and meta-analysis. *BMC Pulm Med* 2025; **25**(1): 146 https://pubmed.ncbi.nlm.nih.gov/40165150.
1243. Joseph T, Gao C, Nadarajah R, et al. Chronic obstructive pulmonary disease and risk of incident cardiovascular disease, chronic kidney disease, and death: a systematic review and meta-analysis. *EClinicalMedicine* 2026; **98**: 104131 https://pubmed.ncbi.nlm.nih.gov/42602993.
1244. Cho EE, Maclagan LC, Chu A, et al. Impact of COPD on cardiovascular risk factors and outcomes in people with established cardiovascular disease. *Thorax* 2025; **80**(5): 291-9 https://pubmed.ncbi.nlm.nih.gov/40032508.
1245. Agusti A, Edwards LD, Rennard SI, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012; **7**(5): e37483 https://pubmed.ncbi.nlm.nih.gov/22624038.
1246. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2025 Report. http://www.goldcopd.org/.
1247. Zhou L, Yang H, Zhang Y, et al. Predictive value of lung function measures for cardiovascular risk: a large prospective cohort study. *Thorax* 2024; **79**(3): 250-8 https://pubmed.ncbi.nlm.nih.gov/38050152.
1248. de-Torres JP, Casanova C, Zagaceta J, et al. Cardiovascular Events in COPD: Complementary Role of Cardiac Risk and Coronary Artery Calcium Scores. *Chest* 2026; **169**(3): 631-40 https://pubmed.ncbi.nlm.nih.gov/41101639.
1249. McEvoy JW, McCarthy CP, Bruno RM, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J* 2024; **45**(38): 3912-4018 https://pubmed.ncbi.nlm.nih.gov/39210715.
1250. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021; **42**(34): 3227-337 https://pubmed.ncbi.nlm.nih.gov/34458905.
1251. Lurbe E, Agabiti-Rosei E, Cruickshank JK, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. *J Hypertens* 2016; **34**(10): 1887-920 https://pubmed.ncbi.nlm.nih.gov/27467768.
1252. Jones DW, Ferdinand KC, Taler SJ, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2025; **86**(18): 1567-678 https://pubmed.ncbi.nlm.nih.gov/40815242.
1253. Bhatt SP, Dransfield MT. Chronic obstructive pulmonary disease and cardiovascular disease. *Transl Res* 2013; **162**(4): 237-51 https://pubmed.ncbi.nlm.nih.gov/23727296.
1254. Sa-Sousa A, Rodrigues C, Jacome C, et al. Cardiovascular Risk in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review. *J Clin Med* 2024; **13**(17): https://pubmed.ncbi.nlm.nih.gov/39274386.
1255. Matamis D, Tsagourias M, Papathanasiou A, et al. Targeting occult heart failure in intensive care unit patients with acute chronic obstructive pulmonary disease exacerbation: effect on outcome and quality of life. *J Crit Care* 2014; **29**(2): 315 e7-14 https://pubmed.ncbi.nlm.nih.gov/24369757.
1256. MacDonald MI, Shafuddin E, King PT, Chang CL, Bardin PG, Hancox RJ. Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. *Lancet Respir Med* 2016; **4**(2): 138-48 https://pubmed.ncbi.nlm.nih.gov/26781000.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

1257. Axson EL, Ragutheeswaran K, Sundaram V, et al. Hospitalisation and mortality in patients with comorbid COPD and heart failure: a systematic review and meta-analysis. *Respir Res* 2020; **21**(1): 54 https://pubmed.ncbi.nlm.nih.gov/32059680.
1258. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; **42**(36): 3599-726 https://pubmed.ncbi.nlm.nih.gov/34447992.
1259. Hawkins NM, Khosla A, Virani SA, McMurray JJ, FitzGerald JM. B-type natriuretic peptides in chronic obstructive pulmonary disease: a systematic review. *BMC Pulm Med* 2017; **17**(1): 11 https://pubmed.ncbi.nlm.nih.gov/28073350.
1260. Dransfield MT, Voelker H, Bhatt SP, et al. Metoprolol for the Prevention of Acute Exacerbations of COPD. *N Engl J Med* 2019; **381**(24): 2304-14 https://pubmed.ncbi.nlm.nih.gov/31633896.
1261. Masa JF, Utrabo I, Gomez de Terreros J, et al. Noninvasive ventilation for severely acidotic patients in respiratory intermediate care units : Precision medicine in intermediate care units. *BMC Pulm Med* 2016; **16**(1): 97 https://pubmed.ncbi.nlm.nih.gov/27387544.
1262. Kibbler J, Wade C, Mussell G, Ripley DP, Bourke SC, Steer J. Systematic review and meta-analysis of prevalence of undiagnosed major cardiac comorbidities in COPD. *ERJ Open Res* 2023; **9**(6): https://pubmed.ncbi.nlm.nih.gov/38020568.
1263. Giezeman M, Sundh J, Athlin A, et al. Comorbid Heart Disease in Patients with COPD is Associated with Increased Hospitalization and Mortality - A 15-Year Follow-Up. *Int J Chron Obstruct Pulmon Dis* 2023; **18**: 11-21 https://pubmed.ncbi.nlm.nih.gov/36644219.
1264. National Heart Lung & Blood Institute. Assessing Cardiovascular Risk: Systematic Evidence Review from the Risk Assessment Work Group. 2013. https://www.nhlbi.nih.gov/health-topics/assessing-cardiovascular-risk (accessed Oct 2021).
1265. Svendsen CD, Kuiper KKJ, Ostridge K, et al. Factors associated with coronary heart disease in COPD patients and controls. *PLoS One* 2022; **17**(4): e0265682 https://pubmed.ncbi.nlm.nih.gov/35476713.
1266. MacLeod MA, Knott KD, Allinson JP, et al. Prevalence and Clinical Correlates of Radiologically Detected Coronary Artery Disease in Chronic Obstructive Pulmonary Disease: A Cross-Sectional Observational Study. *Am J Respir Crit Care Med* 2025; **211**(6): 946-56 https://pubmed.ncbi.nlm.nih.gov/39680915.
1267. Adamson PD, Anderson JA, Brook RD, et al. Cardiac Troponin I and Cardiovascular Risk in Patients With Chronic Obstructive Pulmonary Disease. *J Am Coll Cardiol* 2018; **72**(10): 1126-37 https://pubmed.ncbi.nlm.nih.gov/30165984.
1268. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2026 Report. 2026. http://www.goldcopd.org/.
1269. Bhatt SP, Nath HP, Kim YI, et al. Centrilobular emphysema and coronary artery calcification: mediation analysis in the SPIROMICS cohort. *Respir Res* 2018; **19**(1): 257 https://pubmed.ncbi.nlm.nih.gov/30563576.
1270. Blumenthal RS, Morris PB, Gaudino M, et al. 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2026; **87**(19): 2624-757 https://pubmed.ncbi.nlm.nih.gov/41824590.
1271. Liu X, Chen Z, Li S, Xu S. Association of Chronic Obstructive Pulmonary Disease With Arrhythmia Risks: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med* 2021; **8**: 732349 https://pubmed.ncbi.nlm.nih.gov/34660734.
1272. 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): 1012-6 https://pubmed.ncbi.nlm.nih.gov/12797497.
1273. Romiti GF, Corica B, Pipitone E, 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. *Eur Heart J* 2021; **42**(35): 3541-54 https://pubmed.ncbi.nlm.nih.gov/34333599.
1274. Ding N, Qiu W, Chen J, et al. Prevalence and Risk Factors of Arrhythmias in Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *Int J Chron Obstruct Pulmon Dis* 2025; **20**: 3059-72 https://pubmed.ncbi.nlm.nih.gov/40922983.
1275. Writing Committee Members, Joglar JA, Chung MK, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2024; **83**(1): 109-279 https://pubmed.ncbi.nlm.nih.gov/38043043.
1276. Singh S, Loke YK, Enright P, Furberg CD. Pro-arrhythmic and pro-ischaemic effects of inhaled anticholinergic medications. *Thorax* 2013; **68**(1): 114-6 https://pubmed.ncbi.nlm.nih.gov/22764216.
1277. Wilchesky M, Ernst P, Brophy JM, Platt RW, Suissa S. Bronchodilator use and the risk of arrhythmia in COPD: part 2: reassessment in the larger Quebec cohort. *Chest* 2012; **142**(2): 305-11 https://pubmed.ncbi.nlm.nih.gov/22871756.
1278. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004; **125**(6): 2309-21 https://pubmed.ncbi.nlm.nih.gov/15189956.
1279. Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. *N Engl J Med* 2013; **369**(16): 1491-501 https://pubmed.ncbi.nlm.nih.gov/23992515.
1280. Tashkin DP, Fabbri LM. Long-acting beta-agonists in the management of chronic obstructive pulmonary disease: current and future agents. *Respir Res* 2010; **11**(1): 149 https://pubmed.ncbi.nlm.nih.gov/21034447.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

1281. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; **361**(9356): 449-56 https://pubmed.ncbi.nlm.nih.gov/12583942.
1282. Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003; **21**(1): 74-81 https://pubmed.ncbi.nlm.nih.gov/12570112.
1283. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J* 2003; **22**(6): 912-9 https://pubmed.ncbi.nlm.nih.gov/14680078.
1284. Calverley PM, Anderson JA, Celli B, et al. Cardiovascular events in patients with COPD: TORCH study results. *Thorax* 2010; **65**(8): 719-25 https://pubmed.ncbi.nlm.nih.gov/20685748.
1285. Vestbo J, Anderson JA, Brook RD, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016; **387**(10030): 1817-26 https://pubmed.ncbi.nlm.nih.gov/27203508.
1286. Wilchesky M, Ernst P, Brophy JM, Platt RW, Suissa S. Bronchodilator use and the risk of arrhythmia in COPD: part 1: Saskatchewan cohort study. *Chest* 2012; **142**(2): 298-304 https://pubmed.ncbi.nlm.nih.gov/22871755.
1287. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014; **130**(23): e199-267 https://pubmed.ncbi.nlm.nih.gov/24682347.
1288. Ohta K, Fukuchi Y, Grouse L, et al. A prospective clinical study of theophylline safety in 3810 elderly with asthma or COPD. *Respir Med* 2004; **98**(10): 1016-24 https://pubmed.ncbi.nlm.nih.gov/15481279.
1289. Sessler CN, Cohen MD. Cardiac arrhythmias during theophylline toxicity. A prospective continuous electrocardiographic study. *Chest* 1990; **98**(3): 672-8 https://pubmed.ncbi.nlm.nih.gov/2394145.
1290. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2022; **43**(38): 3618-731 https://pubmed.ncbi.nlm.nih.gov/36017548.
1291. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2023; **61**(1): https://pubmed.ncbi.nlm.nih.gov/36028254.
1292. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation* 2011; **124**(18): 1973-81 https://pubmed.ncbi.nlm.nih.gov/21969018.
1293. Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. *Lancet Respir Med* 2016; **4**(4): 306-22 https://pubmed.ncbi.nlm.nih.gov/26975810.
1294. Thabut G, Dauriat G, Stern JB, et al. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. *Chest* 2005; **127**(5): 1531-6 https://pubmed.ncbi.nlm.nih.gov/15888824.
1295. Zeder K, Avian A, Bachmaier G, et al. Elevated pulmonary vascular resistance predicts mortality in COPD patients. *Eur Respir J* 2021; **58**(2): https://pubmed.ncbi.nlm.nih.gov/33986032.
1296. Rastoder E, Sivapalan P, Hedsund C, et al. Pulmonary pressure increases during acute exacerbation in COPD and clinical outcome. *Eur Respir J* 2025; **66**(3): https://pubmed.ncbi.nlm.nih.gov/40774812.
1297. Garcia AR, Vollmer I, Blanco I, et al. Characterization of CT Imaging-Derived Pulmonary Vascular Abnormalities Associated With Pulmonary Hypertension in Chronic Lung Disease. *Chest* 2026; 10.1016/j.chest.2026.05.027: https://pubmed.ncbi.nlm.nih.gov/42208731.
1298. Johnson SW, Wan ES, San José Estépar R, et al. Chest Computed Tomography to Improve Phenotyping in Pulmonary Hypertension Associated with Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2025; **22**(2): 175-80 https://pubmed.ncbi.nlm.nih.gov/39556097.
1299. Kovacs G, Zeder K, Humbert M, et al. European Respiratory Society clinical practice guidelines update for the treatment of pulmonary arterial hypertension. *Eur Respir J* 2026; 10.1183/13993003.01178-2026: https://pubmed.ncbi.nlm.nih.gov/42705705.
1300. Nathan SD, Argula R, Trivieri MG, et al. Inhaled treprostinil in pulmonary hypertension associated with COPD: PERFECT study results. *Eur Respir J* 2024; **63**(6): https://pubmed.ncbi.nlm.nih.gov/38811045.
1301. Houben-Wilke S, Jorres RA, Bals R, et al. Peripheral Artery Disease and Its Clinical Relevance in Patients with Chronic Obstructive Pulmonary Disease in the COPD and Systemic Consequences-Comorbidities Network Study. *Am J Respir Crit Care Med* 2017; **195**(2): 189-97 https://pubmed.ncbi.nlm.nih.gov/27532739.
1302. Conte MS, Aulivola B, Barshes NR, et al. Society for Vascular Surgery Clinical Practice Guideline on the management of intermittent claudication: Focused update. *J Vasc Surg* 2025; **82**(2): 303-26 e11 https://pubmed.ncbi.nlm.nih.gov/40316185.
1303. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**(5): E359-86 https://pubmed.ncbi.nlm.nih.gov/25220842.
1304. Tanoue LT, Tanner NT, Gould MK, Silvestri GA. Lung cancer screening. *Am J Respir Crit Care Med* 2015; **191**(1): 19-33 https://pubmed.ncbi.nlm.nih.gov/25369325.
1305. Lopez-Encuentra A, Astudillo J, Cerezal J, et al. Prognostic value of chronic obstructive pulmonary disease in 2994 cases of lung cancer. *Eur J Cardiothorac Surg* 2005; **27**(1): 8-13 https://pubmed.ncbi.nlm.nih.gov/15736303.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

1306. Mannino DM, Aguayo SM, Petty TL, Redd SC. Low lung function and incident lung cancer in the United States: data From the First National Health and Nutrition Examination Survey follow-up. *Arch Intern Med* 2003; **163**(12): 1475-80 https://pubmed.ncbi.nlm.nih.gov/12824098.
1307. de Torres JP, Marin JM, Casanova C, et al. Lung cancer in patients with chronic obstructive pulmonary disease--incidence and predicting factors. *Am J Respir Crit Care Med* 2011; **184**(8): 913-9 https://pubmed.ncbi.nlm.nih.gov/21799072.
1308. Metwally EM, Lund JL, Drummond MB, Peacock Hinton S, Poole C, Thompson CA. COPD With Lung Cancer Among Older United States Adults: Prevalence, Diagnostic Timeliness, and Association With Earlier Stage Tumors. *Chronic Obstr Pulm Dis* 2024; **11**(4): 382-5 https://pubmed.ncbi.nlm.nih.gov/38838253.
1309. Caramori G, Casolari P, Cavallesco GN, Giuffre S, Adcock I, Papi A. Mechanisms involved in lung cancer development in COPD. *Int J Biochem Cell Biol* 2011; **43**(7): 1030-44 https://pubmed.ncbi.nlm.nih.gov/20951226.
1310. Celli BR. Chronic obstructive pulmonary disease and lung cancer: common pathogenesis, shared clinical challenges. *Proc Am Thorac Soc* 2012; **9**(2): 74-9 https://pubmed.ncbi.nlm.nih.gov/22550249.
1311. Houghton AM. Mechanistic links between COPD and lung cancer. *Nat Rev Cancer* 2013; **13**(4): 233-45 https://pubmed.ncbi.nlm.nih.gov/23467302.
1312. Tammemagi MC, Lam SC, McWilliams AM, Sin DD. Incremental value of pulmonary function and sputum DNA image cytometry in lung cancer risk prediction. *Cancer Prev Res (Phila)* 2011; **4**(4): 552-61 https://pubmed.ncbi.nlm.nih.gov/21411501.
1313. de Torres JP, Bastarrika G, Wisnivesky JP, et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. *Chest* 2007; **132**(6): 1932-8 https://pubmed.ncbi.nlm.nih.gov/18079226.
1314. Wilson DO, Leader JK, Fuhrman CR, Reilly JJ, Sciurba FC, Weissfeld JL. Quantitative computed tomography analysis, airflow obstruction, and lung cancer in the pittsburgh lung screening study. *J Thorac Oncol* 2011; **6**(7): 1200-5 https://pubmed.ncbi.nlm.nih.gov/21610523.
1315. Dhariwal J, Tennant RC, Hansell DM, et al. Smoking cessation in COPD causes a transient improvement in spirometry and decreases micronodules on high-resolution CT imaging. *Chest* 2014; **145**(5): 1006-15 https://pubmed.ncbi.nlm.nih.gov/24522562.
1316. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; **365**(5): 395-409 https://pubmed.ncbi.nlm.nih.gov/21714641.
1317. International Early Lung Cancer Action Program I, Henschke CI, Yankelevitz DF, et al. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006; **355**(17): 1763-71 https://pubmed.ncbi.nlm.nih.gov/17065637.
1318. Force USPST, Krist AH, Davidson KW, et al. Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA* 2021; **325**(10): 962-70 https://pubmed.ncbi.nlm.nih.gov/33687470.
1319. Aldrich MC, Mercaldo SF, Sandler KL, Blot WJ, Grogan EL, Blume JD. Evaluation of USPSTF Lung Cancer Screening Guidelines Among African American Adult Smokers. *JAMA Oncol* 2019; **5**(9): 1318-24 https://pubmed.ncbi.nlm.nih.gov/31246249.
1320. Bandiera FC, Assari S, Livaudais-Toman J, Perez-Stable EJ. Latino and Black smokers in the Health and Retirement Study are more likely to quit: the role of light smoking. *Tob Induc Dis* 2016; **14**: 23 https://pubmed.ncbi.nlm.nih.gov/27436994.
1321. Haiman CA, Stram DO, Wilkens LR, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med* 2006; **354**(4): 333-42 https://pubmed.ncbi.nlm.nih.gov/16436765.
1322. Kaplan RC, Bangdiwala SI, Barnhart JM, et al. Smoking among U.S. Hispanic/Latino adults: the Hispanic community health study/study of Latinos. *Am J Prev Med* 2014; **46**(5): 496-506 https://pubmed.ncbi.nlm.nih.gov/24745640.
1323. Lin HH, Murray M, Cohen T, Colijn C, Ezzati M. Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: a time-based, multiple risk factor, modelling study. *Lancet* 2008; **372**(9648): 1473-83 https://pubmed.ncbi.nlm.nih.gov/18835640.
1324. Park HY, Kang D, Shin SH, et al. Chronic obstructive pulmonary disease and lung cancer incidence in never smokers: a cohort study. *Thorax* 2020; **75**(6): 506-9 https://pubmed.ncbi.nlm.nih.gov/32241883.
1325. Centers for Disease Control and Prevention. Lung Cancer Among People Who Never Smoked, November 2020, https://www.cdc.gov/lung-cancer/nonsmokers/ [accessed Oct 2026].
1326. de-Torres JP, Casanova C, Marin JM, et al. Exploring the impact of screening with low-dose CT on lung cancer mortality in mild to moderate COPD patients: a pilot study. *Respir Med* 2013; **107**(5): 702-7 https://pubmed.ncbi.nlm.nih.gov/23465176.
1327. Lam VK, Miller M, Dowling L, Singhal S, Young RP, Cabebe EC. Community low-dose CT lung cancer screening: a prospective cohort study. *Lung* 2015; **193**(1): 135-9 https://pubmed.ncbi.nlm.nih.gov/25503535.
1328. Ashraf H, Saghir Z, Dirksen A, et al. Smoking habits in the randomised Danish Lung Cancer Screening Trial with low-dose CT: final results after a 5-year screening programme. *Thorax* 2014; **69**(6): 574-9 https://pubmed.ncbi.nlm.nih.gov/24443174.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

1329. Ge F, Feng Y, Huo Z, et al. Inhaled corticosteroids and risk of lung cancer among chronic obstructive pulmonary disease patients: a comprehensive analysis of nine prospective cohorts. *Transl Lung Cancer Res* 2021; **10**(3): 1266-76 https://pubmed.ncbi.nlm.nih.gov/33889508.
1330. Raymakers AJN, Sadatsafavi M, Sin DD, FitzGerald JM, Marra CA, Lynd LD. Inhaled corticosteroids and the risk of lung cancer in COPD: a population-based cohort study. *Eur Respir J* 2019; **53**(6): https://pubmed.ncbi.nlm.nih.gov/30956205.
1331. Seijo LM, Soriano JB, Peces-Barba G. New evidence on the chemoprevention of inhaled steroids and the risk of lung cancer in COPD. *Eur Respir J* 2019; **53**(6): https://pubmed.ncbi.nlm.nih.gov/31167885.
1332. Menezes AMB, Montes de Oca M, Perez-Padilla R, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. *Chest* 2014; **145**(2): 297-304 https://pubmed.ncbi.nlm.nih.gov/24114498.
1333. Miravitlles M, Soriano JB, Ancochea J, et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. *Respir Med* 2013; **107**(7): 1053-60 https://pubmed.ncbi.nlm.nih.gov/23597591.
1334. Barrecheguren M, Pinto L, Mostafavi-Pour-Manshadi SM, et al. Identification and definition of asthma-COPD overlap: The CanCOLD study. *Respirology* 2020; **25**(8): 836-49 https://pubmed.ncbi.nlm.nih.gov/32064708.
1335. de Marco R, Pesce G, Marcon A, et al. The coexistence of asthma and chronic obstructive pulmonary disease (COPD): prevalence and risk factors in young, middle-aged and elderly people from the general population. *PLoS One* 2013; **8**(5): e62985 https://pubmed.ncbi.nlm.nih.gov/23675448.
1336. Kurashima K, Takaku Y, Ohta C, Takayanagi N, Yanagisawa T, Sugita Y. COPD assessment test and severity of airflow limitation in patients with asthma, COPD, and asthma-COPD overlap syndrome. *Int J Chron Obstruct Pulmon Dis* 2016; **11**: 479-87 https://pubmed.ncbi.nlm.nih.gov/27019598.
1337. Lange P, Colak Y, Ingebrigtsen TS, Vestbo J, Marott JL. Long-term prognosis of asthma, chronic obstructive pulmonary disease, and asthma-chronic obstructive pulmonary disease overlap in the Copenhagen City Heart study: a prospective population-based analysis. *Lancet Respir Med* 2016; **4**(6): 454-62 https://pubmed.ncbi.nlm.nih.gov/27061878.
1338. GINA Global Initiative for Asthma. Global strategy for asthma management and prevention. Available from: https://ginasthma.org/2026-gina-strategy-report/ [accessed Oct 2026]. 2026.
1339. Goto T, Camargo CA, Jr., Hasegawa K. Fractional exhaled nitric oxide levels in asthma-COPD overlap syndrome: analysis of the National Health and Nutrition Examination Survey, 2007-2012. *Int J Chron Obstruct Pulmon Dis* 2016; **11**: 2149-55 https://pubmed.ncbi.nlm.nih.gov/27660432.
1340. Reddel HK, Vestbo J, Agusti A, et al. Heterogeneity within and between physician-diagnosed asthma and/or COPD: NOVELTY cohort. *Eur Respir J* 2021; **58**(3): https://pubmed.ncbi.nlm.nih.gov/33632799.
1341. Tamura K, Shirai T, Hirai K, et al. Mucus Plugs and Small Airway Dysfunction in Asthma, COPD, and Asthma-COPD Overlap. *Allergy Asthma Immunol Res* 2022; **14**(2): 196-209 https://pubmed.ncbi.nlm.nih.gov/35255537.
1342. Bhatt SP, Rabe KF, Hanania NA, et al. Effect of Dupilumab on Health-Related Quality of Life and Respiratory Symptoms in Patients With COPD and Type 2 Inflammation: BOREAS and NOTUS. *Chest* 2025; **168**(1): 56-66 https://pubmed.ncbi.nlm.nih.gov/39894389.
1343. Amaral AF, Coton S, Kato B, et al. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. *Eur Respir J* 2015; **46**(4): 1104-12 https://pubmed.ncbi.nlm.nih.gov/26113680.
1344. Hamada Y, Fong CJ, Copas A, Hurst JR, Rangaka MX. Risk for development of active tuberculosis in patients with chronic airway disease-a systematic review of evidence. *Trans R Soc Trop Med Hyg* 2022; **116**(5): 390-8 https://pubmed.ncbi.nlm.nih.gov/34383072.
1345. Jin J, Li S, Yu W, Liu X, Sun Y. Emphysema and bronchiectasis in COPD patients with previous pulmonary tuberculosis: computed tomography features and clinical implications. *Int J Chron Obstruct Pulmon Dis* 2018; **13**: 375-84 https://pubmed.ncbi.nlm.nih.gov/29416328.
1346. Lee CH, Kim K, Hyun MK, Jang EJ, Lee NR, Yim JJ. Use of inhaled corticosteroids and the risk of tuberculosis. *Thorax* 2013; **68**(12): 1105-13 https://pubmed.ncbi.nlm.nih.gov/23749841.
1347. You Y, Ni Y, Shi G. Inhaled Corticosteroids and Mycobacterial Infection in Patients with Chronic Airway Diseases: A Systematic Review and Meta-Analysis. *Respiration* 2022; **101**(10): 970-80 https://pubmed.ncbi.nlm.nih.gov/35998604.
1348. Castellana G, Castellana M, Castellana C, et al. Inhaled Corticosteroids And Risk Of Tuberculosis In Patients With Obstructive Lung Diseases: A Systematic Review And Meta-Analysis Of Non-randomized Studies. *Int J Chron Obstruct Pulmon Dis* 2019; **14**: 2219-27 https://pubmed.ncbi.nlm.nih.gov/31576118.
1349. Huang TM, Kuo KC, Wang YH, et al. Risk of active tuberculosis among COPD patients treated with fixed combinations of long-acting beta2 agonists and inhaled corticosteroids. *BMC Infect Dis* 2020; **20**(1): 706 https://pubmed.ncbi.nlm.nih.gov/32977747.
1350. O'Brien C, Guest PJ, Hill SL, Stockley RA. Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000; **55**(8): 635-42 https://pubmed.ncbi.nlm.nih.gov/10899238.
1351. Polverino E, De Soyza A, Dimakou K, et al. The Association between Bronchiectasis and Chronic Obstructive Pulmonary Disease: Data from the European Bronchiectasis Registry (EMBARC). *Am J Respir Crit Care Med* 2024; **210**(1): 119-27 https://pubmed.ncbi.nlm.nih.gov/38271696.
1352. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008; **359**(22): 2355-65 https://pubmed.ncbi.nlm.nih.gov/19038881.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1353. Metersky ML, Dransfield MT. The Chronic Obstructive Pulmonary Disease (COPD)-Bronchiectasis Overlap Syndrome: Does My COPD Patient Have Bronchiectasis on Computed Tomography? "Frankly, My Dear, I Don't Give a Damn!". *Am J Respir Crit Care Med* 2023; **208**(12): 1265-7 https://pubmed.ncbi.nlm.nih.gov/37796579.
1354. Chalmers JD. Bronchiectasis and COPD Overlap: A Case of Mistaken Identity? *Chest* 2017; **151**(6): 1204-6 https://pubmed.ncbi.nlm.nih.gov/28599926.
1355. Ritchie AI, Singayagam A, Mitchell S, Wedzicha JA, Shah A, Bloom CI. The Effect of Inhaled Corticosteroids on Pneumonia Risk in Patients With COPD-Bronchiectasis Overlap: A UK Population-Based Case-Control Study. *Chest* 2023; **164**(4): 875-84 https://pubmed.ncbi.nlm.nih.gov/37419145.
1356. Loebinger MR, Quint JK, van der Laan R, et al. Risk Factors for Nontuberculous Mycobacterial Pulmonary Disease: A Systematic Literature Review and Meta-Analysis. *Chest* 2023; **164**(5): 1115-24 https://pubmed.ncbi.nlm.nih.gov/37429481.
1357. Choi H, McShane PJ, Aliberti S, Chalmers JD. Bronchiectasis management in adults: state of the art and future directions. *Eur Respir J* 2024; **63**(6): https://pubmed.ncbi.nlm.nih.gov/38782469.
1358. Chalmers JD, Burgel PR, Daley CL, et al. Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis. *N Engl J Med* 2025; **392**(16): 1569-81 https://pubmed.ncbi.nlm.nih.gov/40267423.
1359. Cottin V, Hirani NA, Hotchkin DL, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev* 2018; **27**(150): https://pubmed.ncbi.nlm.nih.gov/30578335.
1360. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med* 2022; **205**(9): e18-e47 https://pubmed.ncbi.nlm.nih.gov/35486072.
1361. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; **188**(6): 733-48 https://pubmed.ncbi.nlm.nih.gov/24032382.
1362. Faisal A, Alghamdi BJ, Ciavaglia CE, et al. Common Mechanisms of Dyspnea in Chronic Interstitial and Obstructive Lung Disorders. *Am J Respir Crit Care Med* 2016; **193**(3): 299-309 https://pubmed.ncbi.nlm.nih.gov/26407036.
1363. Huie TJ, Solomon JJ. Emphysema and pulmonary fibrosis: coincidence or conspiracy? *Respirology* 2013; **18**(8): 1163-4 https://pubmed.ncbi.nlm.nih.gov/24033462.
1364. Zantah M, Dotan Y, Dass C, Zhao H, Marchetti N, Criner GJ. Acute exacerbations of COPD versus IPF in patients with combined pulmonary fibrosis and emphysema. *Respir Res* 2020; **21**(1): 164 https://pubmed.ncbi.nlm.nih.gov/32605574.
1365. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur Respir J* 2005; **26**(4): 586-93 https://pubmed.ncbi.nlm.nih.gov/16204587.
1366. Cottin V, Azuma A, Raghu G, et al. Therapeutic effects of nintedanib are not influenced by emphysema in the INPULSIS trials. *Eur Respir J* 2019; **53**(4): https://pubmed.ncbi.nlm.nih.gov/30655282.
1367. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; **328**(17): 1230-5 https://pubmed.ncbi.nlm.nih.gov/8464434.
1368. Povitz M, James MT, Pendharkar SR, Raneri J, Hanly PJ, Tsai WH. Prevalence of Sleep-disordered Breathing in Obese Patients with Chronic Hypoxemia. A Cross-Sectional Study. *Ann Am Thorac Soc* 2015; **12**(6): 921-7 https://pubmed.ncbi.nlm.nih.gov/25822569.
1369. Schiza S, Schwarz EI, Bonsignore MR, McNicholas WT, Pataka A, Bouloukaki I. Co-existence of OSA and respiratory diseases and the influence of gender. *Expert Rev Respir Med* 2023; **17**(12): 1221-35 https://pubmed.ncbi.nlm.nih.gov/38198636.
1370. Sodhi A, Pisani M, Glassberg MK, Bourjeily G, D'Ambrosio C. Sex and Gender in Lung Disease and Sleep Disorders: A State-of-the-Art Review. *Chest* 2022; **162**(3): 647-58 https://pubmed.ncbi.nlm.nih.gov/35300976.
1371. Flenley DC. Sleep in chronic obstructive lung disease. *Clin Chest Med* 1985; **6**(4): 651-61 https://pubmed.ncbi.nlm.nih.gov/2935359.
1372. Chaouat A, Weitzenblum E, Krieger J, Ifoundza T, Oswald M, Kessler R. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. *Am J Respir Crit Care Med* 1995; **151**(1): 82-6 https://pubmed.ncbi.nlm.nih.gov/7812577.
1373. Shepard JW, Jr., Garrison MW, Grither DA, Evans R, Schweitzer PK. Relationship of ventricular ectopy to nocturnal oxygen desaturation in patients with chronic obstructive pulmonary disease. *Am J Med* 1985; **78**(1): 28-34 https://pubmed.ncbi.nlm.nih.gov/2578248.
1374. Bradley TD, Rutherford R, Grossman RF, et al. Role of daytime hypoxemia in the pathogenesis of right heart failure in the obstructive sleep apnea syndrome. *Am Rev Respir Dis* 1985; **131**(6): 835-9 https://pubmed.ncbi.nlm.nih.gov/4003933.
1375. Weitzenblum E, Krieger J, Apprill M, et al. Daytime pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Am Rev Respir Dis* 1988; **138**(2): 345-9 https://pubmed.ncbi.nlm.nih.gov/3143285.
1376. An X, Chen Y, Wang Y, et al. Association Between Sleep Disorders and Adverse Cardiovascular Outcomes in Patients with Chronic Obstructive Pulmonary Disease: Insights from the UK Biobank. *Int J Chron Obstruct Pulmon Dis* 2026; **21**: 607991 https://pubmed.ncbi.nlm.nih.gov/42306044.

COPYRIGHT MATERIAL DO NOT COPY OR DISTRIBUTE

1377. Li H, Yang J, Xiao Q, et al. Global prevalence of COPD-OSA overlap syndrome: A systematic review and meta-analysis. *Sleep Med* 2025; **135**: 106766 https://pubmed.ncbi.nlm.nih.gov/40884991.
1378. Sterling KL, Pepin JL, Linde-Zwirble W, et al. Impact of Positive Airway Pressure Therapy Adherence on Outcomes in Patients with Obstructive Sleep Apnea and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2022; **206**(2): 197-205 https://pubmed.ncbi.nlm.nih.gov/35436176.
1379. Le KDR, Le K, Foo F. The Impact of Glucagon-like Peptide 1 Receptor Agonists on Obstructive Sleep Apnoea: A Scoping Review. *Pharmacy (Basel)* 2024; **12**(1): https://pubmed.ncbi.nlm.nih.gov/38251405.
1380. Ellberg CC, Schwartz H, Witt A, McCowen KC, Fuentes AL, Malhotra A. The Potential Role of Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists and Glucose-Dependent Insulinotropic Polypeptide (GIP) Receptor Agonists in Obstructive Sleep Apnea and Obesity. *Curr Pulmonol Rep* 2025; **14**(1): 19 https://pubmed.ncbi.nlm.nih.gov/40727552.
1381. Kunik ME, Roundy K, Veazey C, et al. Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. *Chest* 2005; **127**(4): 1205-11 https://pubmed.ncbi.nlm.nih.gov/15821196.
1382. Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. *Arch Intern Med* 2007; **167**(1): 60-7 https://pubmed.ncbi.nlm.nih.gov/17210879.
1383. Maurer J, Rebbapragada V, Borson S, et al. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. *Chest* 2008; **134**(4 Suppl): 43S-56S https://pubmed.ncbi.nlm.nih.gov/18842932.
1384. Eisner MD, Blanc PD, Yelin EH, et al. Influence of anxiety on health outcomes in COPD. *Thorax* 2010; **65**(3): 229-34 https://pubmed.ncbi.nlm.nih.gov/20335292.
1385. Yohannes AM, Casaburi R, Dryden S, Hanania NA. The effectiveness of pulmonary rehabilitation on chronic obstructive pulmonary disease patients with concurrent presence of comorbid depression and anxiety. *Respir Med* 2022; **197**: 106850 https://pubmed.ncbi.nlm.nih.gov/35427843.
1386. Himelhoch S, Lehman A, Kreyenbuhl J, Daumit G, Brown C, Dixon L. Prevalence of chronic obstructive pulmonary disease among those with serious mental illness. *Am J Psychiatry* 2004; **161**(12): 2317-9 https://pubmed.ncbi.nlm.nih.gov/15569908.
1387. Jones DR, Macias C, Barreira PJ, Fisher WH, Hargreaves WA, Harding CM. Prevalence, severity, and co-occurrence of chronic physical health problems of persons with serious mental illness. *Psychiatr Serv* 2004; **55**(11): 1250-7 https://pubmed.ncbi.nlm.nih.gov/15534013.
1388. Ratcliffe S, Halpin DMG. COPD and Schizophrenia. *Chronic Obstr Pulm Dis* 2025; **12**(4): 328-38 https://pubmed.ncbi.nlm.nih.gov/40504939.
1389. Sampaio MS, Vieira WA, Bernardino IM, Herval AM, Flores-Mir C, Paranhos LR. Chronic obstructive pulmonary disease as a risk factor for suicide: A systematic review and meta-analysis. *Respir Med* 2019; **151**: 11-8 https://pubmed.ncbi.nlm.nih.gov/31047105.
1390. Singh G, Zhang W, Kuo YF, Sharma G. Association of Psychological Disorders With 30-Day Readmission Rates in Patients With COPD. *Chest* 2016; **149**(4): 905-15 https://pubmed.ncbi.nlm.nih.gov/26204260.
1391. Atlantis E, Fahey P, Cochrane B, Smith S. Bidirectional associations between clinically relevant depression or anxiety and COPD: a systematic review and meta-analysis. *Chest* 2013; **144**(3): 766-77 https://pubmed.ncbi.nlm.nih.gov/23429910.
1392. Divo MJ, Marin JM, Casanova C, et al. Comorbidities and mortality risk in adults younger than 50 years of age with chronic obstructive pulmonary disease. *Respir Res* 2022; **23**(1): 267 https://pubmed.ncbi.nlm.nih.gov/36167533.
1393. Ruan H, Zhang H, Wang J, Zhao H, Han W, Li J. Readmission rate for acute exacerbation of chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Respir Med* 2023; **206**: 107090 https://pubmed.ncbi.nlm.nih.gov/36528962.
1394. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care* 2003; **41**(11): 1284-92 https://pubmed.ncbi.nlm.nih.gov/14583691.
1395. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Lowe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med* 2007; **146**(5): 317-25 https://pubmed.ncbi.nlm.nih.gov/17339617.
1396. Bolton CE, Bevan-Smith EF, Blakey JD, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults. *Thorax* 2013; **68 Suppl 2**: ii1-30 https://pubmed.ncbi.nlm.nih.gov/23880483.
1397. Coventry PA, Bower P, Keyworth C, et al. The effect of complex interventions on depression and anxiety in chronic obstructive pulmonary disease: systematic review and meta-analysis. *PLoS One* 2013; **8**(4): e60532 https://pubmed.ncbi.nlm.nih.gov/23585837.
1398. Paz-Diaz H, Montes de Oca M, Lopez JM, Celli BR. Pulmonary rehabilitation improves depression, anxiety, dyspnea and health status in patients with COPD. *Am J Phys Med Rehabil* 2007; **86**(1): 30-6 https://pubmed.ncbi.nlm.nih.gov/17304686.
1399. Gordon CS, Waller JW, Cook RM, Cavalera SL, Lim WT, Osadnik CR. Effect of Pulmonary Rehabilitation on Symptoms of Anxiety and Depression in COPD: A Systematic Review and Meta-Analysis. *Chest* 2019; **156**(1): 80-91 https://pubmed.ncbi.nlm.nih.gov/31034818.
1400. van Beers M, Janssen DJA, Gosker HR, Schols A. Cognitive impairment in chronic obstructive pulmonary disease: disease burden, determinants and possible future interventions. *Expert Rev Respir Med* 2018; **12**(12): 1061-74 https://pubmed.ncbi.nlm.nih.gov/30296384.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1401. Yohannes AM, Chen W, Moga AM, Leroi I, Connolly MJ. Cognitive Impairment in Chronic Obstructive Pulmonary Disease and Chronic Heart Failure: A Systematic Review and Meta-analysis of Observational Studies. *J Am Med Dir Assoc* 2017; **18**(5): 451 e1- e11 https://pubmed.ncbi.nlm.nih.gov/28292570.
1402. Pierobon A, Ranzini L, Torlaschi V, et al. Screening for neuropsychological impairment in COPD patients undergoing rehabilitation. *PLoS One* 2018; **13**(8): e0199736 https://pubmed.ncbi.nlm.nih.gov/30067787.
1403. Cleutjens FA, Franssen FM, Spruit MA, et al. Domain-specific cognitive impairment in patients with COPD and control subjects. *Int J Chron Obstruct Pulmon Dis* 2017; **12**: 1-11 https://pubmed.ncbi.nlm.nih.gov/28031706.
1404. Cleutjens F, Spruit MA, Ponds R, et al. Cognitive impairment and clinical characteristics in patients with chronic obstructive pulmonary disease. *Chron Respir Dis* 2018; **15**(2): 91-102 https://pubmed.ncbi.nlm.nih.gov/28553720.
1405. Rusanen M, Ngandu T, Laatikainen T, Tuomilehto J, Soininen H, Kivipelto M. Chronic obstructive pulmonary disease and asthma and the risk of mild cognitive impairment and dementia: a population based CAIDE study. *Curr Alzheimer Res* 2013; **10**(5): 549-55 https://pubmed.ncbi.nlm.nih.gov/23566344.
1406. Xie F, Xie L. COPD and the risk of mild cognitive impairment and dementia: a cohort study based on the Chinese Longitudinal Health Longevity Survey. *Int J Chron Obstruct Pulmon Dis* 2019; **14**: 403-8 https://pubmed.ncbi.nlm.nih.gov/30863040.
1407. Wang J, Li X, Lei S, et al. Risk of dementia or cognitive impairment in COPD patients: A meta-analysis of cohort studies. *Front Aging Neurosci* 2022; **14**: 962562 https://pubmed.ncbi.nlm.nih.gov/36158542.
1408. Baird C, Lovell J, Johnson M, Shiell K, Ibrahim JE. The impact of cognitive impairment on self-management in chronic obstructive pulmonary disease: A systematic review. *Respir Med* 2017; **129**: 130-9 https://pubmed.ncbi.nlm.nih.gov/28732820.
1409. Martinez CH, Richardson CR, Han MK, Cigolle CT. Chronic obstructive pulmonary disease, cognitive impairment, and development of disability: the health and retirement study. *Ann Am Thorac Soc* 2014; **11**(9): 1362-70 https://pubmed.ncbi.nlm.nih.gov/25285360.
1410. von Siemens SM, Perneczky R, Vogelmeier CF, et al. The association of cognitive functioning as measured by the DemTect with functional and clinical characteristics of COPD: results from the COSYCONET cohort. *Respir Res* 2019; **20**(1): 257 https://pubmed.ncbi.nlm.nih.gov/31727165.
1411. Schure MB, Borson S, Nguyen HQ, et al. Associations of cognition with physical functioning and health-related quality of life among COPD patients. *Respir Med* 2016; **114**: 46-52 https://pubmed.ncbi.nlm.nih.gov/27109810.
1412. Chang SS, Chen S, McAvay GJ, Tinetti ME. Effect of coexisting chronic obstructive pulmonary disease and cognitive impairment on health outcomes in older adults. *J Am Geriatr Soc* 2012; **60**(10): 1839-46 https://pubmed.ncbi.nlm.nih.gov/23035917.
1413. Dodd JW, Charlton RA, van den Broek MD, Jones PW. Cognitive dysfunction in patients hospitalized with acute exacerbation of COPD. *Chest* 2013; **144**(1): 119-27 https://pubmed.ncbi.nlm.nih.gov/23349026.
1414. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**(3): 189-98 https://pubmed.ncbi.nlm.nih.gov/1202204.
1415. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; **53**(4): 695-9 https://pubmed.ncbi.nlm.nih.gov/15817019.
1416. Andrianopoulos V, Gloeckl R, Boensch M, et al. Improvements in functional and cognitive status following short-term pulmonary rehabilitation in COPD lung transplant recipients: a pilot study. *ERJ Open Res* 2019; **5**(3): https://pubmed.ncbi.nlm.nih.gov/31544112.
1417. Noh E, Jeong H, Cho IS, et al. Risk of Cardiovascular Events Associated with Chronic Obstructive Pulmonary Disease and/or Metabolic Syndrome: A Large-Scale Nationwide Population-Based Cohort Study. *Int J Chron Obstruct Pulmon Dis* 2024; **19**: 1447-56 https://pubmed.ncbi.nlm.nih.gov/38948908.
1418. Glaser S, Kruger S, Merkel M, Bramlage P, Herth FJ. Chronic obstructive pulmonary disease and diabetes mellitus: a systematic review of the literature. *Respiration* 2015; **89**(3): 253-64 https://pubmed.ncbi.nlm.nih.gov/25677307.
1419. James A. Diabetes and lung function: Linked, but how? *Respirology* 2024; **29**(5): 361-2 https://pubmed.ncbi.nlm.nih.gov/38379119.
1420. Kinney GL, Black-Shinn JL, Wan ES, et al. Pulmonary function reduction in diabetes with and without chronic obstructive pulmonary disease. *Diabetes Care* 2014; **37**(2): 389-95 https://pubmed.ncbi.nlm.nih.gov/24026562.
1421. Zaigham S, Tanash H, Nilsson PM, Muhammad IF. Triglyceride-Glucose Index is a Risk Marker of Incident COPD Events in Women. *Int J Chron Obstruct Pulmon Dis* 2022; **17**: 1393-401 https://pubmed.ncbi.nlm.nih.gov/35746923.
1422. Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. *Am J Med* 2010; **123**(11): 1001-6 https://pubmed.ncbi.nlm.nih.gov/20870201.
1423. Pradhan R, Lu S, Yin H, et al. Novel antihyperglycaemic drugs and prevention of chronic obstructive pulmonary disease exacerbations among patients with type 2 diabetes: population based cohort study. *BMJ* 2022; **379**: e071380 https://pubmed.ncbi.nlm.nih.gov/36318979.
1424. Yen FS, Wei JC, Huang YH, et al. SGLT-2 Inhibitors and the Risk of Chronic Obstructive Pulmonary Disease Exacerbations and Mortality in Chronic Obstructive Pulmonary Disease Patients. *Ann Am Thorac Soc* 2025; **22**(6): 846-54 https://pubmed.ncbi.nlm.nih.gov/39938066.
1425. Divo MJ, Cabrera C, Casanova C, et al. Comorbidity Distribution, Clinical Expression and Survival in COPD Patients with Different Body Mass Index. *Chronic Obstr Pulm Dis* 2014; **1**(2): 229-38 https://pubmed.ncbi.nlm.nih.gov/28848824.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1426. McDonald MN, Wouters EFM, Rutten E, et al. It's more than low BMI: prevalence of cachexia and associated mortality in COPD. *Respir Res* 2019; **20**(1): 100 https://pubmed.ncbi.nlm.nih.gov/31118043.
1427. Zhang J, Moll M, Hobbs BD, et al. Genetically Predicted Body Mass Index and Mortality in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2024; **210**(7): 890-9 https://pubmed.ncbi.nlm.nih.gov/38471013.
1428. Bhide P, Bapaye J, Mohan G, et al. Impact of Obesity on In-Hospital Morbidity and Mortality Among Patients Admitted for Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD). *Cureus* 2023; **15**(2): e35138 https://pubmed.ncbi.nlm.nih.gov/36949996.
1429. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *N Engl J Med* 2023; **389**(24): 2221-32 https://pubmed.ncbi.nlm.nih.gov/37952131.
1430. Huang SC, Wu JY, Kuo CY, Hsu WH, Tsai YW, Lai CC. Association Between Glucagon-Like Peptide-1 Receptor Agonists and Clinical Outcomes in Patients with Chronic Obstructive Pulmonary Disease and Obesity. *Drug Des Devel Ther* 2026; **20**: 609054 https://pubmed.ncbi.nlm.nih.gov/42292155.
1431. Martinez CH, Okajima Y, Murray S, et al. Impact of self-reported gastroesophageal reflux disease in subjects from COPDGene cohort. *Respir Res* 2014; **15**(1): 62 https://pubmed.ncbi.nlm.nih.gov/24894541.
1432. Ingebrigtsen TS, Marott JL, Vestbo J, Nordestgaard BG, Hallas J, Lange P. Gastro-esophageal reflux disease and exacerbations in chronic obstructive pulmonary disease. *Respirology* 2015; **20**(1): 101-7 https://pubmed.ncbi.nlm.nih.gov/25297724.
1433. Sasaki T, Nakayama K, Yasuda H, et al. A randomized, single-blind study of lansoprazole for the prevention of exacerbations of chronic obstructive pulmonary disease in older patients. *J Am Geriatr Soc* 2009; **57**(8): 1453-7 https://pubmed.ncbi.nlm.nih.gov/19515110.
1434. Chen JW, Vela MF, Peterson KA, Carlson DA. AGA Clinical Practice Update on the Diagnosis and Management of Extraesophageal Gastroesophageal Reflux Disease: Expert Review. *Clin Gastroenterol Hepatol* 2023; **21**(6): 1414-21 e3 https://pubmed.ncbi.nlm.nih.gov/37061897.
1435. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; **108**(3): 308-28; quiz 29 https://pubmed.ncbi.nlm.nih.gov/23419381.
1436. Viglino D, Jullian-Desayes I, Minoves M, et al. Nonalcoholic fatty liver disease in chronic obstructive pulmonary disease. *Eur Respir J* 2017; **49**(6): https://pubmed.ncbi.nlm.nih.gov/28596431.
1437. de Mattos JN, Santiago Escovar CE, Zereu M, et al. Computed tomography on lung cancer screening is useful for adjuvant comorbidity diagnosis in developing countries. *ERJ Open Res* 2022; **8**(2): https://pubmed.ncbi.nlm.nih.gov/35747230.
1438. Fernando DH, Forbes JM, Angus PW, Herath CB. Development and Progression of Non-Alcoholic Fatty Liver Disease: The Role of Advanced Glycation End Products. *Int J Mol Sci* 2019; **20**(20): https://pubmed.ncbi.nlm.nih.gov/31614491.
1439. Viglino D, Plazanet A, Bailly S, et al. Impact of Non-alcoholic Fatty Liver Disease on long-term cardiovascular events and death in Chronic Obstructive Pulmonary Disease. *Sci Rep* 2018; **8**(1): 16559 https://pubmed.ncbi.nlm.nih.gov/30410123.
1440. Fang L, Li J, Zeng H, Liu J. Effects of GLP-1 receptor agonists on the degree of liver fibrosis and CRP in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: A systematic review and meta-analysis. *Prim Care Diabetes* 2024; **18**(3): 268-76 https://pubmed.ncbi.nlm.nih.gov/38555202.
1441. Harrison SA, Bedossa P, Guy CD, et al. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. *N Engl J Med* 2024; **390**(6): 497-509 https://pubmed.ncbi.nlm.nih.gov/38324483.
1442. Celli BR, Locantore N, Tal-Singer R, et al. Emphysema and extrapulmonary tissue loss in COPD: a multi-organ loss of tissue phenotype. *Eur Respir J* 2018; **51**(2): https://pubmed.ncbi.nlm.nih.gov/29437944.
1443. Madsen H, Brixen K, Hallas J. Screening, prevention and treatment of osteoporosis in patients with chronic obstructive pulmonary disease - a population-based database study. *Clin Respir J* 2010; **4**(1): 22-9 https://pubmed.ncbi.nlm.nih.gov/20298414.
1444. Chen YW, Ramsook AH, Coxson HO, Bon J, Reid WD. Prevalence and Risk Factors for Osteoporosis in Individuals With COPD: A Systematic Review and Meta-analysis. *Chest* 2019; **156**(6): 1092-110 https://pubmed.ncbi.nlm.nih.gov/31352034.
1445. Bon J, Fuhrman CR, Weissfeld JL, et al. Radiographic emphysema predicts low bone mineral density in a tobacco-exposed cohort. *Am J Respir Crit Care Med* 2011; **183**(7): 885-90 https://pubmed.ncbi.nlm.nih.gov/20935108.
1446. Bolton CE, Cannings-John R, Edwards PH, et al. What community measurements can be used to predict bone disease in patients with COPD? *Respir Med* 2008; **102**(5): 651-7 https://pubmed.ncbi.nlm.nih.gov/18308533.
1447. Bolton CE, Ionescu AA, Shiels KM, et al. Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; **170**(12): 1286-93 https://pubmed.ncbi.nlm.nih.gov/15374843.
1448. Jaramillo JD, Wilson C, Stinson DS, et al. Reduced Bone Density and Vertebral Fractures in Smokers. Men and COPD Patients at Increased Risk. *Ann Am Thorac Soc* 2015; **12**(5): 648-56 https://pubmed.ncbi.nlm.nih.gov/25719895.
1449. Jaramillo J, Wilson C, Stinson D, et al. Erratum: reduced bone density and vertebral fractures in smokers. men and COPD patients at increased risk. *Ann Am Thorac Soc* 2015; **12**(7): 1112 https://pubmed.ncbi.nlm.nih.gov/26203620.
1450. Janson C, Lisspers K, Stallberg B, et al. Osteoporosis and fracture risk associated with inhaled corticosteroid use among Swedish COPD patients: the ARCTIC study. *Eur Respir J* 2021; **57**(2): https://pubmed.ncbi.nlm.nih.gov/32972982.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1451. Qaseem A, Hicks LA, Etxeandia-Ikobaltzeta I, et al. Pharmacologic Treatment of Primary Osteoporosis or Low Bone Mass to Prevent Fractures in Adults: A Living Clinical Guideline From the American College of Physicians. *Ann Intern Med* 2023; **176**(2): 224-38 https://pubmed.ncbi.nlm.nih.gov/36592456.
1452. Gjerde B, Bakke PS, Ueland T, Hardie JA, Eagan TM. The prevalence of undiagnosed renal failure in a cohort of COPD patients in western Norway. *Respir Med* 2012; **106**(3): 361-6 https://pubmed.ncbi.nlm.nih.gov/22129490.
1453. Incalzi RA, Corsonello A, Pedone C, et al. Chronic renal failure: a neglected comorbidity of COPD. *Chest* 2010; **137**(4): 831-7 https://pubmed.ncbi.nlm.nih.gov/19903974.
1454. Fedeli U, De Giorgi A, Gennaro N, et al. Lung and kidney: a dangerous liaison? A population-based cohort study in COPD patients in Italy. *Int J Chron Obstruct Pulmon Dis* 2017; **12**: 443-50 https://pubmed.ncbi.nlm.nih.gov/28184156.
1455. Casanova C, de Torres JP, Navarro J, et al. Microalbuminuria and hypoxemia in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; **182**(8): 1004-10 https://pubmed.ncbi.nlm.nih.gov/20558625.
1456. Polverino F, Laucho-Contreras ME, Petersen H, et al. A Pilot Study Linking Endothelial Injury in Lungs and Kidneys in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017; **195**(11): 1464-76 https://pubmed.ncbi.nlm.nih.gov/28085500.
1457. Madero M, Levin A, Ahmed SB, et al. Evaluation and Management of Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2024 Clinical Practice Guideline. *Ann Intern Med* 2025; **178**(5): 705-13 https://pubmed.ncbi.nlm.nih.gov/40063957.
1458. Yohannes AM, Ershler WB. Anemia in COPD: a systematic review of the prevalence, quality of life, and mortality. *Respir Care* 2011; **56**(5): 644-52 https://pubmed.ncbi.nlm.nih.gov/21276321.
1459. Balasubramanian A, Henderson RJ, Putcha N, et al. Haemoglobin as a biomarker for clinical outcomes in chronic obstructive pulmonary disease. *ERJ Open Res* 2021; **7**(3): https://pubmed.ncbi.nlm.nih.gov/34322549.
1460. Boutou AK, Karrar S, Hopkinson NS, Polkey MI. Anemia and survival in chronic obstructive pulmonary disease: a dichotomous rather than a continuous predictor. *Respiration* 2013; **85**(2): 126-31 https://pubmed.ncbi.nlm.nih.gov/22759351.
1461. Chambellan A, Chailleux E, Similowski T, Group AO. Prognostic value of the hematocrit in patients with severe COPD receiving long-term oxygen therapy. *Chest* 2005; **128**(3): 1201-8 https://pubmed.ncbi.nlm.nih.gov/16162707.
1462. 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 https://pubmed.ncbi.nlm.nih.gov/17251227.
1463. Martinez-Rivera C, Portillo K, Munoz-Ferrer A, et al. Anemia is a mortality predictor in hospitalized patients for COPD exacerbation. *COPD* 2012; **9**(3): 243-50 https://pubmed.ncbi.nlm.nih.gov/22360381.
1464. Xu Y, Hu T, Ding H, Chen R. Effects of anemia on the survival of patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Expert Rev Respir Med* 2020; **14**(12): 1267-77 https://pubmed.ncbi.nlm.nih.gov/32869670.
1465. Schneckenpointner R, Jorres RA, Meidenbauer N, Kollert F, Pfeifer M, Budweiser S. The clinical significance of anaemia and disturbed iron homeostasis in chronic respiratory failure. *Int J Clin Pract* 2014; **68**(1): 130-8 https://pubmed.ncbi.nlm.nih.gov/24341307.
1466. Vasquez A, Logomarsino JV. Anemia in Chronic Obstructive Pulmonary Disease and the Potential Role of Iron Deficiency. *COPD* 2016; **13**(1): 100-9 https://pubmed.ncbi.nlm.nih.gov/26418826.
1467. Andreas S, Herrmann-Lingen C, Raupach T, et al. Angiotensin II blockers in obstructive pulmonary disease: a randomised controlled trial. *Eur Respir J* 2006; **27**(5): 972-9 https://pubmed.ncbi.nlm.nih.gov/16446313.
1468. Bakris GL, Sauter ER, Hussey JL, Fisher JW, Gaber AO, Winsett R. Effects of theophylline on erythropoietin production in normal subjects and in patients with erythrocytosis after renal transplantation. *N Engl J Med* 1990; **323**(2): 86-90 https://pubmed.ncbi.nlm.nih.gov/2163024.
1469. Ferrucci L, Maggio M, Bandinelli S, et al. Low testosterone levels and the risk of anemia in older men and women. *Arch Intern Med* 2006; **166**(13): 1380-8 https://pubmed.ncbi.nlm.nih.gov/16832003.
1470. Ilan Y, Dranitzki-Elhallel M, Rubinger D, Silver J, Popovtzer MM. Erythrocytosis after renal transplantation. The response to theophylline treatment. *Transplantation* 1994; **57**(5): 661-4 https://pubmed.ncbi.nlm.nih.gov/8140628.
1471. Mrug M, Stopka T, Julian BA, Prchal JF, Prchal JT. Angiotensin II stimulates proliferation of normal early erythroid progenitors. *J Clin Invest* 1997; **100**(9): 2310-4 https://pubmed.ncbi.nlm.nih.gov/9410909.
1472. Oren R, Beeri M, Hubert A, Kramer MR, Matzner Y. Effect of theophylline on erythrocytosis in chronic obstructive pulmonary disease. *Arch Intern Med* 1997; **157**(13): 1474-8 https://pubmed.ncbi.nlm.nih.gov/9224226.
1473. Similowski T, Agusti A, MacNee W, Schonhofer B. The potential impact of anaemia of chronic disease in COPD. *Eur Respir J* 2006; **27**(2): 390-6 https://pubmed.ncbi.nlm.nih.gov/16452598.
1474. Vlahakos DV, Marathias KP, Madias NE. The role of the renin-angiotensin system in the regulation of erythropoiesis. *Am J Kidney Dis* 2010; **56**(3): 558-65 https://pubmed.ncbi.nlm.nih.gov/20400218.
1475. Calverley PM, Leggett RJ, McElderry L, Flenley DC. Cigarette smoking and secondary polycythemia in hypoxic cor pulmonale. *Am Rev Respir Dis* 1982; **125**(5): 507-10 https://pubmed.ncbi.nlm.nih.gov/7081807.
1476. Chambellan A, Coulon S, Cavailles A, Hermine O, Similowski T. [COPD and erythropoiesis: interactions and consequences]. *Rev Mal Respir* 2012; **29**(2): 213-31 https://pubmed.ncbi.nlm.nih.gov/22405115.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1477. Ferrari M, Manea L, Anton K, et al. Anemia and hemoglobin serum levels are associated with exercise capacity and quality of life in chronic obstructive pulmonary disease. *BMC Pulm Med* 2015; **15**: 58 https://pubmed.ncbi.nlm.nih.gov/25952923.
1478. Zhang J, DeMeo DL, Silverman EK, et al. Secondary polycythemia in chronic obstructive pulmonary disease: prevalence and risk factors. *BMC Pulm Med* 2021; **21**(1): 235 https://pubmed.ncbi.nlm.nih.gov/34261472.
1479. Kent BD, Mitchell PD, McNicholas WT. Hypoxemia in patients with COPD: cause, effects, and disease progression. *Int J Chron Obstruct Pulmon Dis* 2011; **6**: 199-208 https://pubmed.ncbi.nlm.nih.gov/21660297.
1480. Zeng Z, Song Y, He X, 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 https://pubmed.ncbi.nlm.nih.gov/35068930.
1481. Nakamura A, Kasamatsu N, Hashizume I, et al. Effects of hemoglobin on pulmonary arterial pressure and pulmonary vascular resistance in patients with chronic emphysema. *Respiration* 2000; **67**(5): 502-6 https://pubmed.ncbi.nlm.nih.gov/11070452.
1482. Samareh Fekri M, Torabi M, Azizi Shoul S, Mirzaee M. Prevalence and predictors associated with severe pulmonary hypertension in COPD. *Am J Emerg Med* 2018; **36**(2): 277-80 https://pubmed.ncbi.nlm.nih.gov/28797558.
1483. Guo L, Chughtai AR, Jiang H, et al. Relationship between polycythemia and in-hospital mortality in chronic obstructive pulmonary disease patients with low-risk pulmonary embolism. *J Thorac Dis* 2016; **8**(11): 3119-31 https://pubmed.ncbi.nlm.nih.gov/28066591.
1484. Xu L, Chen Y, Xie Z, et al. High hemoglobin is associated with increased in-hospital death in patients with chronic obstructive pulmonary disease and chronic kidney disease: a retrospective multicenter population-based study. *BMC Pulm Med* 2019; **19**(1): 174 https://pubmed.ncbi.nlm.nih.gov/31533673.
1485. Mazzone PJ. Preoperative evaluation of the lung cancer resection candidate. *Expert Rev Respir Med* 2010; **4**(1): 97-113 https://pubmed.ncbi.nlm.nih.gov/20387296.
1486. Schuurmans MM, Diacon AH, Bolliger CT. Functional evaluation before lung resection. *Clin Chest Med* 2002; **23**(1): 159-72 https://pubmed.ncbi.nlm.nih.gov/11901909.
1487. Smetana GW. Preoperative pulmonary evaluation. *N Engl J Med* 1999; **340**(12): 937-44 https://pubmed.ncbi.nlm.nih.gov/10089188.
1488. Brunelli A, Charloux A, Bolliger CT, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J* 2009; **34**(1): 17-41 https://pubmed.ncbi.nlm.nih.gov/19567600.
1489. Colice GL, Shafazand S, Griffin JP, Keenan R, Bolliger CT, American College of Chest P. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest* 2007; **132**(3 Suppl): 161S-77S https://pubmed.ncbi.nlm.nih.gov/17873167.
1490. Hobbins S, Chapple IL, Sapey E, Stockley RA. Is periodontitis a comorbidity of COPD or can associations be explained by shared risk factors/behaviors? *Int J Chron Obstruct Pulmon Dis* 2017; **12**: 1339-49 https://pubmed.ncbi.nlm.nih.gov/28496317.
1491. Sapey E, Yonel Z, Edgar R, et al. The clinical and inflammatory relationships between periodontitis and chronic obstructive pulmonary disease. *J Clin Periodontol* 2020; **47**(9): 1040-52 https://pubmed.ncbi.nlm.nih.gov/32567697.
1492. Shen TC, Chang PY, Lin CL, et al. Risk of Periodontal Diseases in Patients With Chronic Obstructive Pulmonary Disease: A Nationwide Population-based Cohort Study. *Medicine (Baltimore)* 2015; **94**(46): e2047 https://pubmed.ncbi.nlm.nih.gov/26579813.
1493. Takahashi T, Muro S, Tanabe N, et al. Relationship between periodontitis-related antibody and frequent exacerbations in chronic obstructive pulmonary disease. *PLoS One* 2012; **7**(7): e40570 https://pubmed.ncbi.nlm.nih.gov/22792372.
1494. Apessos I, Voulgaris A, Agrafiotis M, Andreadis D, Steiropoulos P. Effect of periodontal therapy on COPD outcomes: a systematic review. *BMC Pulm Med* 2021; **21**(1): 92 https://pubmed.ncbi.nlm.nih.gov/33736634.
1495. Calle Rubio M, Álvarez-Sala JL, Vargas Centanaro G, Navarro AMH, Hermosa JLR. Testing for Vitamin D in High-Risk COPD in Outpatient Clinics in Spain: A Cross-Sectional Analysis of the VITADEPOC Study. *J Clin Med* 2022; **11**(5): https://pubmed.ncbi.nlm.nih.gov/35268438.
1496. Lin S. A Clinician's Guide to Artificial Intelligence (AI): Why and How Primary Care Should Lead the Health Care AI Revolution. *J Am Board Fam Med* 2022; **35**(1): 175-84 https://pubmed.ncbi.nlm.nih.gov/35039425.
1497. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med* 2019; **25**(1): 44-56 https://pubmed.ncbi.nlm.nih.gov/30617339.
1498. Agusti A, Vila M, Faner R, et al. How artificial intelligence could improve the diagnosis and management of COPD: a perspective from GOLD. *Am J Respir Crit Care Med* 2026; 10.1093/ajrccm/aamag337: https://pubmed.ncbi.nlm.nih.gov/42377276.
1499. Howell MD, Corrado GS, DeSalvo KB. Three Epochs of Artificial Intelligence in Health Care. *JAMA* 2024; **331**(3): 242-4 https://pubmed.ncbi.nlm.nih.gov/38227029.
1500. Futoma J, Simons M, Panch T, Doshi-Velez F, Celi LA. The myth of generalisability in clinical research and machine learning in health care. *Lancet Digit Health* 2020; **2**(9): e489-e92 https://pubmed.ncbi.nlm.nih.gov/32864600.
1501. Diab N, Gershon AS, Sin DD, et al. Underdiagnosis and Overdiagnosis of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2018; **198**(9): 1130-9 https://pubmed.ncbi.nlm.nih.gov/29979608.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

1502. Vila M, Siso-Almirall A, Ocana A, et al. Prevalence, diagnostic accuracy, and healthcare utilization patterns in patients with COPD in primary healthcare: a population-based study. *NPJ Prim Care Respir Med* 2025; **35**(1): 17 https://pubmed.ncbi.nlm.nih.gov/40118910.
1503. Spetrini R, Pikman P, Kang V, et al. Prospective COPD Case Finding in a Lung Cancer Screening Program: A Pilot Study. *Chronic Obstr Pulm Dis* 2025; **12**(5): 411-8 https://pubmed.ncbi.nlm.nih.gov/40893032.
1504. Doe G, Banya W, Edwards G, et al. AI-Assisted Spirometry Interpretation in Primary Care: A Randomized Controlled Trial. *Nejm Ai* 2025; **2**(8):
1505. Mei S, Li X, Zhou Y, et al. Deep learning for detecting and early predicting chronic obstructive pulmonary disease from spirogram time series. *NPJ Syst Biol Appl* 2025; **11**(1): 18 https://pubmed.ncbi.nlm.nih.gov/39955293.
1506. Saad T, Pandey R, Padarya S, Singh P, Singh S, Mishra N. Application of Artificial Intelligence in the Interpretation of Pulmonary Function Tests. *Cureus* 2025; **17**(4): e82056 https://pubmed.ncbi.nlm.nih.gov/40351950.
1507. Wang Z, Liang L, Huang F, et al. The Characteristics of the Concavity of Descending Limb of Maximal Expiratory Flow-Volume Curves Generated by Spirometry. *Lung* 2025; **203**(1): 18 https://pubmed.ncbi.nlm.nih.gov/39751890.
1508. Agusti A, Alcazar B, Cosio B, et al. Time for a change: anticipating the diagnosis and treatment of COPD. *Eur Respir J* 2020; **56**(1): 2002104 https://pubmed.ncbi.nlm.nih.gov/32732302.
1509. Bush A, Greenough A, Agusti A, Bianco F, Baraldi E, Group P-T. Falling through the cracks: what happens to survivors of preterm birth? *ERJ Open Res* 2025; **11**(1): 00643-2024 https://pubmed.ncbi.nlm.nih.gov/39931667.
1510. DeBoer EM, Morgan WJ, Quiros-Alcala L, et al. Defining and Promoting Pediatric Pulmonary Health: Assessing Lung Function and Structure. *Pediatrics* 2023; **152**(Suppl 2): https://pubmed.ncbi.nlm.nih.gov/37656029.
1511. Chen W, Sin DD, FitzGerald JM, Safari A, Adibi A, Sadatsafavi M. An Individualized Prediction Model for Long-term Lung Function Trajectory and Risk of COPD in the General Population. *Chest* 2020; **157**(3): 547-57 https://pubmed.ncbi.nlm.nih.gov/31542453.
1512. Nikolaou V, Massaro S, Garn W, Fakhimi M, Stergioulas L, Price DB. Fast decliner phenotype of chronic obstructive pulmonary disease (COPD): applying machine learning for predicting lung function loss. *BMJ Open Respir Res* 2021; **8**(1): e000980 https://pubmed.ncbi.nlm.nih.gov/34716217.
1513. Das N, Topalovic M, Janssens W. Artificial intelligence in diagnosis of obstructive lung disease: current status and future potential. *Curr Opin Pulm Med* 2018; **24**(2): 117-23 https://pubmed.ncbi.nlm.nih.gov/29251699.
1514. Han TT, Le Trung K, Nguyen Anh P, Nguyen Huu P. High performance method for COPD features extraction using complex network. *Biomed Phys Eng Express* 2024; **10**(6): 065045 https://pubmed.ncbi.nlm.nih.gov/39332437.
1515. Idrisoglu A, Dallora AL, Cheddad A, Anderberg P, Jakobsson A, Sanmartin Berglund J. COPDVD: Automated classification of chronic obstructive pulmonary disease on a new collected and evaluated voice dataset. *Artif Intell Med* 2024; **156**: 102953 https://pubmed.ncbi.nlm.nih.gov/39222579.
1516. Abdo M, Watz H, Trinkmann F, et al. Oscillometry-defined Small Airway Dysfunction in Tobacco-exposed Adults with Impaired or Preserved Airflow. *Am J Respir Crit Care Med* 2025; **211**(9): 1652-61 https://pubmed.ncbi.nlm.nih.gov/40173271.
1517. Cheng Q, Juen J, Bellam S, et al. Predicting Pulmonary Function from Phone Sensors. *Telemed J E Health* 2017; **23**(11): 913-9 https://pubmed.ncbi.nlm.nih.gov/28300524.
1518. Avian C, Mahali MI, Putro NAS, Prakosa SW, Leu JS. Fx-Net and PureNet: Convolutional Neural Network architecture for discrimination of Chronic Obstructive Pulmonary Disease from smokers and healthy subjects through electronic nose signals. *Comput Biol Med* 2022; **148**: 105913 https://pubmed.ncbi.nlm.nih.gov/35940164.
1519. Phillips CO, Syed Y, Parthalain NM, Zwiggelaar R, Claypole TC, Lewis KE. Machine learning methods on exhaled volatile organic compounds for distinguishing COPD patients from healthy controls. *J Breath Res* 2012; **6**(3): 036003 https://pubmed.ncbi.nlm.nih.gov/22759349.
1520. Melekoglu E, Kocabicak U, Ucar MK, Bilgin C, Bozkurt MR, Cunkas M. A new diagnostic method for chronic obstructive pulmonary disease using the photoplethysmography signal and hybrid artificial intelligence. *PeerJ Comput Sci* 2022; **8**: e1188 https://pubmed.ncbi.nlm.nih.gov/37346306.
1521. Qu S, Feng E, Dong D, et al. Early screening of lung function by electrical impedance tomography in people with normal spirometry reveals unrecognized pathological features. *Nat Commun* 2025; **16**(1): 622 https://pubmed.ncbi.nlm.nih.gov/39805822.
1522. Sun J, Liao X, Yan Y, et al. Detection and staging of chronic obstructive pulmonary disease using a computed tomography-based weakly supervised deep learning approach. *Eur Radiol* 2022; **32**(8): 5319-29 https://pubmed.ncbi.nlm.nih.gov/35201409.
1523. Wu Q, Guo H, Li R, Han J. Deep learning and machine learning in CT-based COPD diagnosis: Systematic review and meta-analysis. *Int J Med Inform* 2025; **196**: 105812 https://pubmed.ncbi.nlm.nih.gov/39891985.
1524. Castro M, Papi A, Porsbjerg C, et al. Effect of dupilumab on exhaled nitric oxide, mucus plugs, and functional respiratory imaging in patients with type 2 asthma (VESTIGE): a randomised, double-blind, placebo-controlled, phase 4 trial. *Lancet Respir Med* 2025; **13**(3): 208-20 https://pubmed.ncbi.nlm.nih.gov/39947221.
1525. Luo Y, Hooshangnejad H, Ngwa W, Ding K. Opportunities and challenges in lung cancer care in the era of large language models and vision language models. *Transl Lung Cancer Res* 2025; **14**(5): 1830-47 https://pubmed.ncbi.nlm.nih.gov/40535072.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1526. Carrasco-Zanini J, Pietzner M, Davitte J, et al. Proteomic signatures improve risk prediction for common and rare diseases. *Nat Med* 2024; **30**(9): 2489-98 https://pubmed.ncbi.nlm.nih.gov/39039249.
1527. Olvera N, Sanchez-Valle J, Nunez-Carpintero I, et al. Lung Tissue Multilayer Network Analysis Uncovers the Molecular Heterogeneity of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2024; **210**(10): 1219-29 https://pubmed.ncbi.nlm.nih.gov/38626356.
1528. Zhu Y, Wang M, Gu XN, Wang C, Deng SM. Development and validation of the machine learning model for acute exacerbation of chronic obstructive pulmonary disease prediction based on inflammatory biomarkers. *Front Med (Lausanne)* 2025; **12**: 1616712 https://pubmed.ncbi.nlm.nih.gov/40823588.
1529. Castaldi PJ, Boueiz A, Yun J, et al. Machine Learning Characterization of COPD Subtypes: Insights From the COPDGene Study. *Chest* 2020; **157**(5): 1147-57 https://pubmed.ncbi.nlm.nih.gov/31887283.
1530. Blankemeier L, Cohen JP, Kumar A, et al. Merlin: A Vision Language Foundation Model for 3D Computed Tomography. Springer Science and Business Media LLC; 2024.
1531. Kapatais C, Karaoulani T, Papanikolaou A, et al. The role of artificial intelligence in predicting COPD exacerbations using multimodal data: a systematic review. *ERJ Open Res* 2026; **12**(3): https://pubmed.ncbi.nlm.nih.gov/42311877.
1532. Evidence-Based Medicine Working G. Evidence-based medicine. A new approach to teaching the practice of medicine. *JAMA* 1992; **268**(17): 2420-5 https://pubmed.ncbi.nlm.nih.gov/1404801.
1533. Khor YH, Poberezhets V, Buhr RG, et al. Assessment of Home-based Monitoring in Adults with Chronic Lung Disease: An Official American Thoracic Society Research Statement. *Am J Respir Crit Care Med* 2025; **211**(2): 174-93 https://pubmed.ncbi.nlm.nih.gov/39585746.
1534. Chen Z, Hao J, Sun H, Li M, Zhang Y, Qian Q. Applications of digital health technologies and artificial intelligence algorithms in COPD: systematic review. *BMC Med Inform Decis Mak* 2025; **25**(1): 77 https://pubmed.ncbi.nlm.nih.gov/39948530.
1535. Chamaon D, Sportel E, Elferink ECM, van der Palen J. Validation of an AI-Powered Smart Dry Powder Inhaler (RS01X) for Asthma and COPD in a Clinical Setting. *Int J Chron Obstruct Pulmon Dis* 2025; **20**: 811-9 https://pubmed.ncbi.nlm.nih.gov/40161395.
1536. Glyde HMG, Morgan C, Wilkinson TMA, Nabney IT, Dodd JW. Remote Patient Monitoring and Machine Learning in Acute Exacerbations of Chronic Obstructive Pulmonary Disease: Dual Systematic Literature Review and Narrative Synthesis. *J Med Internet Res* 2024; **26**: e52143 https://pubmed.ncbi.nlm.nih.gov/39250789.
1537. Spielmanns M, Gloeckl R, Jarosch I, et al. Using a smartphone application maintains physical activity following pulmonary rehabilitation in patients with COPD: a randomised controlled trial. *Thorax* 2023; **78**(5): 442-50 https://pubmed.ncbi.nlm.nih.gov/35450945.
1538. Rubio O, Vila M, Escobar M, Agusti A, en representacion del grupo J. How could artificial intelligence improve patient experience in the ambulatory setting? Reflections from the JANUS group. *Med Clin (Barc)* 2025; **164**(4): 190-5 https://pubmed.ncbi.nlm.nih.gov/39581803.
1539. Ayers JW, Poliak A, Dredze M, et al. Comparing Physician and Artificial Intelligence Chatbot Responses to Patient Questions Posted to a Public Social Media Forum. *JAMA Intern Med* 2023; **183**(6): 589-96 https://pubmed.ncbi.nlm.nih.gov/37115527.
1540. Smith LA, Oakden-Rayner L, Bird A, et al. Machine learning and deep learning predictive models for long-term prognosis in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Digit Health* 2023; **5**(12): e872-e81 https://pubmed.ncbi.nlm.nih.gov/38000872.
1541. Singh D, Hurst JR, Martinez FJ, et al. Predictive modeling of COPD exacerbation rates using baseline risk factors. *Ther Adv Respir Dis* 2022; **16**: 17534666221107314 https://pubmed.ncbi.nlm.nih.gov/35815359.
1542. Janjua S, Pike KC, Carr R, Coles A, Fortescue R, Batavia M. Interventions to improve adherence to pharmacological therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev* 2021; **9**(9): CD013381 https://pubmed.ncbi.nlm.nih.gov/34496032.
1543. Schrijver J, Lenferink A, Brusse-Keizer M, et al. Self-management interventions for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2022; **1**(1): CD002990 https://pubmed.ncbi.nlm.nih.gov/35001366.
1544. Kermelly SB, Bourbeau J. eHealth in Self-Managing at a Distance Patients with COPD. *Life (Basel)* 2022; **12**(6): https://pubmed.ncbi.nlm.nih.gov/35743804.
1545. van der Meer RM, Wagena EJ, Ostelo RW, Jacobs JE, van Schayck CP. Smoking cessation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2003; **2003**(2): CD002999 https://pubmed.ncbi.nlm.nih.gov/12804448.
1546. Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev* 2016; **3**(3): CD008286 https://pubmed.ncbi.nlm.nih.gov/27009521.
1547. Okuyemi KS, Nollen NL, Ahluwalia JS. Interventions to facilitate smoking cessation. *Am Fam Physician* 2006; **74**(2): 262-71 https://pubmed.ncbi.nlm.nih.gov/16883923.
1548. Fiore MC, Bailey WC, Cohen SJ. Smoking Cessation: information for specialists. Rockville, MD; 1996.
1549. Lee PN, Fariss MW. A systematic review of possible serious adverse health effects of nicotine replacement therapy. *Arch Toxicol* 2017; **91**(4): 1565-94 https://pubmed.ncbi.nlm.nih.gov/27699443.
1550. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 2013; **382**(9905): 1629-37 https://pubmed.ncbi.nlm.nih.gov/24029165.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1551. Hajek P, Phillips-Waller A, Przulj D, et al. E-cigarettes compared with nicotine replacement therapy within the UK Stop Smoking Services: the TEC RCT. *Health Technol Assess* 2019; **23**(43): 1-82 https://pubmed.ncbi.nlm.nih.gov/31434605.
1552. 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): https://pubmed.ncbi.nlm.nih.gov/35321930.
1553. Morphett K, Fraser D, Borland R, et al. A Pragmatic Randomized Comparative Trial of e-Cigarettes and Other Nicotine Products for Quitting or Long-Term Substitution in Smokers. *Nicotine Tob Res* 2022; **24**(7): 1079-88 https://pubmed.ncbi.nlm.nih.gov/34929031.
1554. Walker N, Parag V, Verbiest M, Laking G, Laugesen M, Bullen C. Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial. *Lancet Respir Med* 2020; **8**(1): 54-64 https://pubmed.ncbi.nlm.nih.gov/31515173.
1555. Malvi A, Khatib MN, Ganesan S, et al. Assessing the impact of electronic nicotine delivery systems on chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Respir Med* 2025; **241**: 108059 https://pubmed.ncbi.nlm.nih.gov/40157397.
1556. Shabil M, Malvi A, Khatib MN, et al. Association of electronic cigarette use and risk of COPD: a systematic review and meta-analysis. *NPJ Prim Care Respir Med* 2025; **35**(1): 31 https://pubmed.ncbi.nlm.nih.gov/40624045.
1557. Jiang Y, Wang Y, Yang M. Association between current e-cigarette use and chronic obstructive pulmonary disease: a meta-analysis focusing on exclusive e-cigarette users. *Front Public Health* 2026; **14**: 1802572 https://pubmed.ncbi.nlm.nih.gov/42100525.
1558. He T, Oks M, Esposito M, Steinberg H, Makaryus M. "Tree-in-Bloom": Severe Acute Lung Injury Induced by Vaping Cannabis Oil. *Ann Am Thorac Soc* 2017; **14**(3): 468-70 https://pubmed.ncbi.nlm.nih.gov/28248584.
1559. Henry TS, Kanne JP, Kligerman SJ. Imaging of Vaping-Associated Lung Disease. *N Engl J Med* 2019; **381**(15): 1486-7 https://pubmed.ncbi.nlm.nih.gov/31491070.
1560. Layden JE, Ghinai I, Pray I, et al. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin - Final Report. *N Engl J Med* 2020; **382**(10): 903-16 https://pubmed.ncbi.nlm.nih.gov/31491072.
1561. Centers for Disease Control and Prevention; U.S. Department of Health & Human Services. Outbreak of Lung Injury Associated with E-Cigarette Use, or Vaping https://archive.cdc.gov/#/details?url=https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html [accessed Oct 2026].
1562. Allbright K, Villandre J, Crotty Alexander LE, et al. The paradox of the safer cigarette: understanding the pulmonary effects of electronic cigarettes. *Eur Respir J* 2024; **63**(6): https://pubmed.ncbi.nlm.nih.gov/38609098.
1563. Blount BC, Karwowski MP, Shields PG, et al. Vitamin E Acetate in Bronchoalveolar-Lavage Fluid Associated with EVALI. *N Engl J Med* 2020; **382**(8): 697-705 https://pubmed.ncbi.nlm.nih.gov/31860793.
1564. Garcia-Arcos I, Geraghty P, Baumlin N, et al. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. *Thorax* 2016; **71**(12): 1119-29 https://pubmed.ncbi.nlm.nih.gov/27558745.
1565. Higham A, Bostock D, Booth G, Dungwa JV, Singh D. The effect of electronic cigarette and tobacco smoke exposure on COPD bronchial epithelial cell inflammatory responses. *Int J Chron Obstruct Pulmon Dis* 2018; **13**: 989-1000 https://pubmed.ncbi.nlm.nih.gov/29615835.
1566. Higham A, Rattray NJ, Dewhurst JA, et al. Electronic cigarette exposure triggers neutrophil inflammatory responses. *Respir Res* 2016; **17**(1): 56 https://pubmed.ncbi.nlm.nih.gov/27184092.
1567. Lerner CA, Sundar IK, Yao H, et al. Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung. *PLoS One* 2015; **10**(2): e0116732 https://pubmed.ncbi.nlm.nih.gov/25658421.
1568. Reidel B, Radicioni G, Clapp PW, et al. E-Cigarette Use Causes a Unique Innate Immune Response in the Lung, Involving Increased Neutrophilic Activation and Altered Mucin Secretion. *Am J Respir Crit Care Med* 2018; **197**(4): 492-501 https://pubmed.ncbi.nlm.nih.gov/29053025.
1569. Gotts JE, Jordt SE, McConnell R, Tarran R. What are the respiratory effects of e-cigarettes? *BMJ* 2019; **366**: l5275 https://pubmed.ncbi.nlm.nih.gov/31570493.
1570. Xie W, Kathuria H, Galiatsatos P, et al. Association of Electronic Cigarette Use With Incident Respiratory Conditions Among US Adults From 2013 to 2018. *JAMA Netw Open* 2020; **3**(11): e2020816 https://pubmed.ncbi.nlm.nih.gov/33180127.
1571. Bowler RP, Hansel NN, Jacobson S, et al. Electronic Cigarette Use in US Adults at Risk for or with COPD: Analysis from Two Observational Cohorts. *J Gen Intern Med* 2017; **32**(12): 1315-22 https://pubmed.ncbi.nlm.nih.gov/28884423.
1572. Li J, Hui X, Fu J, Ahmed MM, Yao L, Yang K. Electronic cigarettes versus nicotine-replacement therapy for smoking cessation: A systematic review and meta-analysis of randomized controlled trials. *Tob Induc Dis* 2022; **20**: 90 https://pubmed.ncbi.nlm.nih.gov/36339933.
1573. Glantz SA, Nguyen N, Oliveira da Silva AL. Population-Based Disease Odds for E-Cigarettes and Dual Use versus Cigarettes. *NEJM Evid* 2024; **3**(3): EVIDoa2300229 https://pubmed.ncbi.nlm.nih.gov/38411454.
1574. Jimenez Ruiz CA, Ramos Pinedo A, Cicero Guerrero A, Mayayo Ulibarri M, Cristobal Fernandez M, Lopez Gonzalez G. Characteristics of COPD smokers and effectiveness and safety of smoking cessation medications. *Nicotine Tob Res* 2012; **14**(9): 1035-9 https://pubmed.ncbi.nlm.nih.gov/22345320.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

1575. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; **320**(7245): 1297-303 https://pubmed.ncbi.nlm.nih.gov/10807619.
1576. Anthonisen NR, Connett JE, Kiley JP, 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): 1497-505 https://pubmed.ncbi.nlm.nih.gov/7966841.
1577. Pauwels RA, Lofdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *N Engl J Med* 1999; **340**(25): 1948-53 https://pubmed.ncbi.nlm.nih.gov/10379018.
1578. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999; **353**(9167): 1819-23 https://pubmed.ncbi.nlm.nih.gov/10359405.
1579. Celli BR, Anderson JA, Cowans NJ, et al. Pharmacotherapy and Lung Function Decline in Patients with Chronic Obstructive Pulmonary Disease. A Systematic Review. *Am J Respir Crit Care Med* 2021; **203**(6): 689-98 https://pubmed.ncbi.nlm.nih.gov/32966751.
1580. Birch H, Pascoe A, McCormick A, et al. Diversity and inclusivity in clinical trial populations for maintenance inhaler therapy in people with COPD: a systematic review. *ERJ Open Res* 2026; **12**(1): https://pubmed.ncbi.nlm.nih.gov/41601582.
1581. Umer M, Jagra AS, Al Seidi J, et al. Underrepresentation of Women in COPD Pharmacologic Trials Relative to Disease Burden: A Systematic Review and Meta-Analysis. *Int J Chron Obstruct Pulmon Dis* 2026; **21**: 585685 https://pubmed.ncbi.nlm.nih.gov/41773232.
1582. O'Donnell DE, Fluge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004; **23**(6): 832-40 https://pubmed.ncbi.nlm.nih.gov/15218994.
1583. O'Donnell DE, Sciurba F, Celli B, et al. Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. *Chest* 2006; **130**(3): 647-56 https://pubmed.ncbi.nlm.nih.gov/16963658.
1584. Berger R, Smith D. Effect of inhaled metaproterenol on exercise performance in patients with stable "fixed" airway obstruction. *Am Rev Respir Dis* 1988; **138**(3): 624-9 https://pubmed.ncbi.nlm.nih.gov/3202416.
1585. Hay JG, Stone P, Carter J, et al. Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease. *Eur Respir J* 1992; **5**(6): 659-64 https://pubmed.ncbi.nlm.nih.gov/1628722.
1586. Chrystyn H, Mulley BA, Peake MD. Dose response relation to oral theophylline in severe chronic obstructive airways disease. *BMJ* 1988; **297**(6662): 1506-10 https://pubmed.ncbi.nlm.nih.gov/3147048.
1587. Gross NJ, Petty TL, Friedman M, Skorodin MS, Silvers GW, Donohue JF. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease. A three-center study. *Am Rev Respir Dis* 1989; **139**(5): 1188-91 https://pubmed.ncbi.nlm.nih.gov/2523681.
1588. Higgins BG, Powell RM, Cooper S, Tattersfield AE. Effect of salbutamol and ipratropium bromide on airway calibre and bronchial reactivity in asthma and chronic bronchitis. *Eur Respir J* 1991; **4**(4): 415-20 https://pubmed.ncbi.nlm.nih.gov/1830277.
1589. Vathenen AS, Britton JR, Ebden P, Cookson JB, Wharrad HJ, Tattersfield AE. High-dose inhaled albuterol in severe chronic airflow limitation. *Am Rev Respir Dis* 1988; **138**(4): 850-5 https://pubmed.ncbi.nlm.nih.gov/2462383.
1590. Donohue JF, Anzueto A, Brooks J, Mehta R, Kalberg C, Crater G. A randomized, double-blind dose-ranging study of the novel LAMA GSK573719 in patients with COPD. *Respir Med* 2012; **106**(7): 970-9 https://pubmed.ncbi.nlm.nih.gov/22498110.
1591. Donohue JF, Kalberg C, Shah P, et al. Dose response of umeclidinium administered once or twice daily in patients with COPD: a pooled analysis of two randomized, double-blind, placebo-controlled studies. *J Clin Pharmacol* 2014; **54**(11): 1214-20 https://pubmed.ncbi.nlm.nih.gov/24895108.
1592. Chowdhury BA, Seymour SM, Michele TM, Durmowicz AG, Liu D, Rosebraugh CJ. The risks and benefits of indacaterol--the FDA's review. *N Engl J Med* 2011; **365**(24): 2247-9 https://pubmed.ncbi.nlm.nih.gov/22168640.
1593. O'Driscoll BR, Kay EA, Taylor RJ, Weatherby H, Chetty MC, Bernstein A. A long-term prospective assessment of home nebulizer treatment. *Respir Med* 1992; **86**(4): 317-25 https://pubmed.ncbi.nlm.nih.gov/1448587.
1594. Jenkins SC, Heaton RW, Fulton TJ, Moxham J. Comparison of domiciliary nebulized salbutamol and salbutamol from a metered-dose inhaler in stable chronic airflow limitation. *Chest* 1987; **91**(6): 804-7 https://pubmed.ncbi.nlm.nih.gov/3556051.
1595. Sestini P, Renzoni E, Robinson S, Poole P, Ram FS. Short-acting beta 2 agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002; 10.1002/14651858.CD001495(4): CD001495 https://pubmed.ncbi.nlm.nih.gov/12519559.
1596. Cazzola M, Rogliani P, Ruggeri P, et al. Chronic treatment with indacaterol and airway response to salbutamol in stable COPD. *Respir Med* 2013; **107**(6): 848-53 https://pubmed.ncbi.nlm.nih.gov/23490225.
1597. Kew KM, Mavergames C, Walters JA. Long-acting beta2-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013; **2013**(10): CD010177 https://pubmed.ncbi.nlm.nih.gov/24127118.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1598. Han J, Dai L, Zhong N. Indacaterol on dyspnea in chronic obstructive pulmonary disease: a systematic review and meta-analysis of randomized placebo-controlled trials. *BMC Pulm Med* 2013; **13**: 26 https://pubmed.ncbi.nlm.nih.gov/23617268.
1599. Geake JB, Dabscheck EJ, Wood-Baker R, Cates CJ. Indacaterol, a once-daily beta2-agonist, versus twice-daily beta(2)-agonists or placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015; **1**(1): CD010139 https://pubmed.ncbi.nlm.nih.gov/25575340.
1600. Koch A, Pizzichini E, Hamilton A, et al. Lung function efficacy and symptomatic benefit of olodaterol once daily delivered via Respimat(R) versus placebo and formoterol twice daily in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. *Int J Chron Obstruct Pulmon Dis* 2014; **9**: 697-714 https://pubmed.ncbi.nlm.nih.gov/25045258.
1601. Kempsford R, Norris V, Siederer S. Vilanterol trifenatate, a novel inhaled long-acting beta2 adrenoceptor agonist, is well tolerated in healthy subjects and demonstrates prolonged bronchodilation in subjects with asthma and COPD. *Pulm Pharmacol Ther* 2013; **26**(2): 256-64 https://pubmed.ncbi.nlm.nih.gov/23232038.
1602. Lipworth BJ, McDevitt DG, Struthers AD. Hypokalemic and ECG sequelae of combined beta-agonist/diuretic therapy. Protection by conventional doses of spironolactone but not triamterene. *Chest* 1990; **98**(4): 811-5 https://pubmed.ncbi.nlm.nih.gov/2209135.
1603. Uren NG, Davies SW, Jordan SL, Lipkin DP. Inhaled bronchodilators increase maximum oxygen consumption in chronic left ventricular failure. *Eur Heart J* 1993; **14**(6): 744-50 https://pubmed.ncbi.nlm.nih.gov/8325299.
1604. Khoukaz G, Gross NJ. Effects of salmeterol on arterial blood gases in patients with stable chronic obstructive pulmonary disease. Comparison with albuterol and ipratropium. *Am J Respir Crit Care Med* 1999; **160**(3): 1028-30 https://pubmed.ncbi.nlm.nih.gov/10471636.
1605. McGarvey L, Niewoehner D, Magder S, et al. One-Year Safety of Olodaterol Once Daily via Respimat(R) in Patients with GOLD 2-4 Chronic Obstructive Pulmonary Disease: Results of a Pre-Specified Pooled Analysis. *COPD* 2015; **12**(5): 484-93 https://pubmed.ncbi.nlm.nih.gov/25692310.
1606. Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. *Thorax* 2010; **65**(6): 473-9 https://pubmed.ncbi.nlm.nih.gov/20522841.
1607. Melani AS. Long-acting muscarinic antagonists. *Expert Rev Clin Pharmacol* 2015; **8**(4): 479-501 https://pubmed.ncbi.nlm.nih.gov/26109098.
1608. Barnes P. Bronchodilators: basic pharmacology. In: Calverley PMA, Pride NB, eds. Chronic Obstructive Pulmonary Disease. London: Chapman and Hall; 1995: 391-417.
1609. Appleton S, Jones T, Poole P, et al. Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006; **2006**(3): CD006101 https://pubmed.ncbi.nlm.nih.gov/16856113.
1610. Jones PW, Singh D, Bateman ED, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. *Eur Respir J* 2012; **40**(4): 830-6 https://pubmed.ncbi.nlm.nih.gov/22441743.
1611. Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014; **2014**(7): CD009285 https://pubmed.ncbi.nlm.nih.gov/25046211.
1612. Calzetta L, Ritondo BL, Zappa MC, et al. The impact of long-acting muscarinic antagonists on mucus hypersecretion and cough in chronic obstructive pulmonary disease: a systematic review. *Eur Respir Rev* 2022; **31**(164): https://pubmed.ncbi.nlm.nih.gov/35508331.
1613. Kesten S, Casaburi R, Kukafka D, Cooper CB. Improvement in self-reported exercise participation with the combination of tiotropium and rehabilitative exercise training in COPD patients. *Int J Chron Obstruct Pulmon Dis* 2008; **3**(1): 127-36 https://pubmed.ncbi.nlm.nih.gov/18488436.
1614. Casaburi R, Kukafka D, Cooper CB, Witek TJ, Jr., Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest* 2005; **127**(3): 809-17 https://pubmed.ncbi.nlm.nih.gov/15764761.
1615. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med* 2011; **364**(12): 1093-103 https://pubmed.ncbi.nlm.nih.gov/21428765.
1616. Decramer ML, Chapman KR, Dahl R, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. *Lancet Respir Med* 2013; **1**(7): 524-33 https://pubmed.ncbi.nlm.nih.gov/24461613.
1617. Tashkin DP. Long-acting anticholinergic use in chronic obstructive pulmonary disease: efficacy and safety. *Curr Opin Pulm Med* 2010; **16**(2): 97-105 https://pubmed.ncbi.nlm.nih.gov/20019615.
1618. Disse B, Speck GA, Rominger KL, Witek TJ, Jr., Hammer R. Tiotropium (Spiriva): mechanistical considerations and clinical profile in obstructive lung disease. *Life Sci* 1999; **64**(6-7): 457-64 https://pubmed.ncbi.nlm.nih.gov/10069510.
1619. Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. *Chest* 2006; **130**(6): 1695-703 https://pubmed.ncbi.nlm.nih.gov/17166984.
1620. Anthonisen NR, Connett JE, Enright PL, Manfreda J, Lung Health Study Research G. Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med* 2002; **166**(3): 333-9 https://pubmed.ncbi.nlm.nih.gov/12153966.
1621. Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium--the FDA's conclusions. *N Engl J Med* 2010; **363**(12): 1097-9 https://pubmed.ncbi.nlm.nih.gov/20843240.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

1622. Verhamme KM, Afonso A, Romio S, Stricker BC, Brusselle GG, Sturkenboom MC. Use of tiotropium Respimat Soft Mist Inhaler versus HandiHaler and mortality in patients with COPD. *Eur Respir J* 2013; **42**(3): 606-15 https://pubmed.ncbi.nlm.nih.gov/23520322.
1623. Packe GE, Cayton RM, Mashhoudi N. Nebulised ipratropium bromide and salbutamol causing closed-angle glaucoma. *Lancet* 1984; **2**(8404): 691 https://pubmed.ncbi.nlm.nih.gov/6147708.
1624. Mulpeter KM, Walsh JB, O'Connor M, O'Connell F, Burke C. Ocular hazards of nebulized bronchodilators. *Postgrad Med J* 1992; **68**(796): 132-3 https://pubmed.ncbi.nlm.nih.gov/1533281.
1625. Hall SK. Acute angle-closure glaucoma as a complication of combined beta-agonist and ipratropium bromide therapy in the emergency department. *Ann Emerg Med* 1994; **23**(4): 884-7 https://pubmed.ncbi.nlm.nih.gov/8161065.
1626. Aubier M. Pharmacotherapy of respiratory muscles. *Clin Chest Med* 1988; **9**(2): 311-24 https://pubmed.ncbi.nlm.nih.gov/3292130.
1627. McKay SE, Howie CA, Thomson AH, Whiting B, Addis GJ. Value of theophylline treatment in patients handicapped by chronic obstructive lung disease. *Thorax* 1993; **48**(3): 227-32 https://pubmed.ncbi.nlm.nih.gov/8497820.
1628. Moxham J. Aminophylline and the respiratory muscles: an alternative view. *Clin Chest Med* 1988; **9**(2): 325-36 https://pubmed.ncbi.nlm.nih.gov/3292131.
1629. Ram FS, Jones PW, Castro AA, et al. Oral theophylline for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002; **2002**(4): CD003902 https://pubmed.ncbi.nlm.nih.gov/12519617.
1630. Zhou Y, Dai C, Wu F, et al. Low-dose theophylline in mild to moderate Chronic Obstructive Pulmonary Disease: A randomized clinical trial in China. *Pulmonology* 2026; **32**(1): 2652159 https://pubmed.ncbi.nlm.nih.gov/41944062.
1631. ZuWallack RL, Mahler DA, Reilly D, et al. Salmeterol plus theophylline combination therapy in the treatment of COPD. *Chest* 2001; **119**(6): 1661-70 https://pubmed.ncbi.nlm.nih.gov/11399688.
1632. Zacarias EC, Castro AA, Cendon S. Effect of theophylline associated with short-acting or long-acting inhaled beta2-agonists in patients with stable chronic obstructive pulmonary disease: a systematic review. *J Bras Pneumol* 2007; **33**(2): 152-60 https://pubmed.ncbi.nlm.nih.gov/17724534.
1633. Cosio BG, Shafiek H, Iglesias A, et al. Oral Low-dose Theophylline on Top of Inhaled Fluticasone-Salmeterol Does Not Reduce Exacerbations in Patients With Severe COPD: A Pilot Clinical Trial. *Chest* 2016; **150**(1): 123-30 https://pubmed.ncbi.nlm.nih.gov/27107490.
1634. Zhou Y, Wang X, Zeng X, et al. Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for 1 year. *Respirology* 2006; **11**(5): 603-10 https://pubmed.ncbi.nlm.nih.gov/16916334.
1635. Devereux G, Cotton S, Fielding S, et al. Effect of Theophylline as Adjunct to Inhaled Corticosteroids on Exacerbations in Patients With COPD: A Randomized Clinical Trial. *JAMA* 2018; **320**(15): 1548-59 https://pubmed.ncbi.nlm.nih.gov/30326124.
1636. Jenkins CR, Wen FQ, Martin A, et al. The effect of low-dose corticosteroids and theophylline on the risk of acute exacerbations of COPD: the TASCS randomised controlled trial. *Eur Respir J* 2021; **57**(6): https://pubmed.ncbi.nlm.nih.gov/33334939.
1637. Cazzola M, Molimard M. The scientific rationale for combining long-acting beta2-agonists and muscarinic antagonists in COPD. *Pulm Pharmacol Ther* 2010; **23**(4): 257-67 https://pubmed.ncbi.nlm.nih.gov/20381630.
1638. Ray R, Tombs L, Naya I, Compton C, Lipson DA, Boucot I. Efficacy and safety of the dual bronchodilator combination umeclidinium/vilanterol in COPD by age and airflow limitation severity: A pooled post hoc analysis of seven clinical trials. *Pulm Pharmacol Ther* 2019; **57**: 101802 https://pubmed.ncbi.nlm.nih.gov/31096036.
1639. Gross N, Tashkin D, Miller R, Oren J, Coleman W, Linberg S. Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease. Dey Combination Solution Study Group. *Respiration* 1998; **65**(5): 354-62 https://pubmed.ncbi.nlm.nih.gov/9782217.
1640. Tashkin DP, Pearle J, Iezzoni D, Varghese ST. Formoterol and tiotropium compared with tiotropium alone for treatment of COPD. *COPD* 2009; **6**(1): 17-25 https://pubmed.ncbi.nlm.nih.gov/19229704.
1641. Farne HA, Cates CJ. Long-acting beta2-agonist in addition to tiotropium versus either tiotropium or long-acting beta2-agonist alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015; **2015**(10): CD008989 https://pubmed.ncbi.nlm.nih.gov/26490945.
1642. Halpin DMG, Rothnie KJ, Banks V, et al. Comparative Adherence and Persistence of Single- and Multiple-Inhaler Triple Therapies Among Patients with Chronic Obstructive Pulmonary Disease in an English Real-World Primary Care Setting. *Int J Chron Obstruct Pulmon Dis* 2022; **17**: 2417-29 https://pubmed.ncbi.nlm.nih.gov/36185170.
1643. Beeh KM, Claussen J, Shah D, et al. Cost-Effectiveness of Single-Inhaler Versus Multiple-Inhaler Triple Therapy in COPD: A German Healthcare Perspective. *Int J Chron Obstruct Pulmon Dis* 2025; **20**: 2011-22 https://pubmed.ncbi.nlm.nih.gov/40551758.
1644. van der Molen T, Cazzola M. Beyond lung function in COPD management: effectiveness of LABA/LAMA combination therapy on patient-centred outcomes. *Prim Care Respir J* 2012; **21**(1): 101-8 https://pubmed.ncbi.nlm.nih.gov/22222945.
1645. Mahler DA, Decramer M, D'Urzo A, et al. Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: the BLAZE study. *Eur Respir J* 2014; **43**(6): 1599-609 https://pubmed.ncbi.nlm.nih.gov/24176997.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

1646. Singh D, Ferguson GT, Bolitschek J, et al. Tiotropium + olodaterol shows clinically meaningful improvements in quality of life. *Respir Med* 2015; **109**(10): 1312-9 https://pubmed.ncbi.nlm.nih.gov/26320402.
1647. Bateman ED, Chapman KR, Singh D, et al. Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). *Respir Res* 2015; **16**(1): 92 https://pubmed.ncbi.nlm.nih.gov/26233481.
1648. Martinez FJ, Fabbri LM, Ferguson GT, et al. Baseline Symptom Score Impact on Benefits of Glycopyrrolate/Formoterol Metered Dose Inhaler in COPD. *Chest* 2017; **152**(6): 1169-78 https://pubmed.ncbi.nlm.nih.gov/28720336.
1649. Vogelmeier CF, Kerwin EM, Bjermer LH, et al. Impact of baseline COPD symptom severity on the benefit from dual versus mono-bronchodilators: an analysis of the EMAX randomised controlled trial. *Ther Adv Respir Dis* 2020; **14**: 1753466620968500 https://pubmed.ncbi.nlm.nih.gov/33167780.
1650. Mahler DA, Kerwin E, Ayers T, et al. FLIGHT1 and FLIGHT2: Efficacy and Safety of QVA149 (Indacaterol/Glycopyrrolate) versus Its Monocomponents and Placebo in Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015; **192**(9): 1068-79 https://pubmed.ncbi.nlm.nih.gov/26177074.
1651. Bai C, Ichinose M, Lee SH, et al. Lung function and long-term safety of tiotropium/olodaterol in East Asian patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2017; **12**: 3329-39 https://pubmed.ncbi.nlm.nih.gov/29200840.
1652. Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med* 2013; **1**(3): 199-209 https://pubmed.ncbi.nlm.nih.gov/24429126.
1653. Calverley PMA, Anzueto AR, Carter K, et al. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. *Lancet Respir Med* 2018; **6**(5): 337-44 https://pubmed.ncbi.nlm.nih.gov/29605624.
1654. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. *N Engl J Med* 2016; **374**(23): 2222-34 https://pubmed.ncbi.nlm.nih.gov/27181606.
1655. Suissa S, Dell'Aniello S, Ernst P. Comparative Effectiveness and Safety of LABA-LAMA vs LABA-ICS Treatment of COPD in Real-World Clinical Practice. *Chest* 2019; **155**(6): 1158-65 https://pubmed.ncbi.nlm.nih.gov/30922950.
1656. Barnes PJ. New anti-inflammatory targets for chronic obstructive pulmonary disease. *Nat Rev Drug Discov* 2013; **12**(7): 543-59 https://pubmed.ncbi.nlm.nih.gov/23977698.
1657. Boardman C, Chachi L, Gavrila A, et al. Mechanisms of glucocorticoid action and insensitivity in airways disease. *Pulm Pharmacol Ther* 2014; **29**(2): 129-43 https://pubmed.ncbi.nlm.nih.gov/25218650.
1658. Sonnex K, Alleemudder H, Knaggs R. Impact of smoking status on the efficacy of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review. *BMJ Open* 2020; **10**(4): e037509 https://pubmed.ncbi.nlm.nih.gov/32300001.
1659. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; **2012**(7): CD002991 https://pubmed.ncbi.nlm.nih.gov/22786484.
1660. Calverley PMA, Anderson JA, Brook RD, et al. Fluticasone Furoate, Vilanterol, and Lung Function Decline in Patients with Moderate Chronic Obstructive Pulmonary Disease and Heightened Cardiovascular Risk. *Am J Respir Crit Care Med* 2018; **197**(1): 47-55 https://pubmed.ncbi.nlm.nih.gov/28737971.
1661. Suissa S, Dell'Aniello S, Gonzalez AV, Ernst P. Inhaled corticosteroid use and the incidence of lung cancer in COPD. *Eur Respir J* 2020; **55**(2): 1901720 https://pubmed.ncbi.nlm.nih.gov/31744837.
1662. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; **2012**(9): CD006829 https://pubmed.ncbi.nlm.nih.gov/22972099.
1663. Nannini LJ, Poole P, Milan SJ, Kesterton A. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013; **2013**(8): CD006826 https://pubmed.ncbi.nlm.nih.gov/23990350.
1664. Beech AS, Lea S, Kolsum U, et al. Bacteria and sputum inflammatory cell counts; a COPD cohort analysis. *Respir Res* 2020; **21**(1): 289 https://pubmed.ncbi.nlm.nih.gov/33131502.
1665. Martinez-Garcia MA, Faner R, Oscullo G, et al. Inhaled Steroids, Circulating Eosinophils, Chronic Airway Infection, and Pneumonia Risk in Chronic Obstructive Pulmonary Disease. A Network Analysis. *Am J Respir Crit Care Med* 2020; **201**(9): 1078-85 https://pubmed.ncbi.nlm.nih.gov/31922913.
1666. Roche N, Chapman KR, Vogelmeier CF, et al. Blood Eosinophils and Response to Maintenance Chronic Obstructive Pulmonary Disease Treatment. Data from the FLAME Trial. *Am J Respir Crit Care Med* 2017; **195**(9): 1189-97 https://pubmed.ncbi.nlm.nih.gov/28278391.
1667. Watz H, Tetzlaff K, Wouters EF, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med* 2016; **4**(5): 390-8 https://pubmed.ncbi.nlm.nih.gov/27066739.
1668. Leitao Filho FS, Takiguchi H, Akata K, et al. Effects of Inhaled Corticosteroid/Long-Acting beta(2)-Agonist Combination on the Airway Microbiome of Patients with Chronic Obstructive Pulmonary Disease: A Randomized Controlled Clinical Trial (DISARM). *Am J Respir Crit Care Med* 2021; **204**(10): 1143-52 https://pubmed.ncbi.nlm.nih.gov/34464242.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1669. Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med* 2013; **1**(3): 210-23 https://pubmed.ncbi.nlm.nih.gov/24429127.
1670. Crim C, Dransfield MT, Bourbeau J, et al. Pneumonia risk with inhaled fluticasone furoate and vilanterol compared with vilanterol alone in patients with COPD. *Ann Am Thorac Soc* 2015; **12**(1): 27-34 https://pubmed.ncbi.nlm.nih.gov/25490706.
1671. Crim C, Calverley PMA, Anderson JA, et al. Pneumonia risk with inhaled fluticasone furoate and vilanterol in COPD patients with moderate airflow limitation: The SUMMIT trial. *Respir Med* 2017; **131**: 27-34 https://pubmed.ncbi.nlm.nih.gov/28947039.
1672. Pavord ID, Lettis S, Anzueto A, Barnes N. Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis. *Lancet Respir Med* 2016; **4**(9): 731-41 https://pubmed.ncbi.nlm.nih.gov/27460163.
1673. Johnell O, Pauwels R, Lofdahl CG, et al. Bone mineral density in patients with chronic obstructive pulmonary disease treated with budesonide Turbuhaler. *Eur Respir J* 2002; **19**(6): 1058-63 https://pubmed.ncbi.nlm.nih.gov/12108857.
1674. Ferguson GT, Calverley PMA, Anderson JA, et al. Prevalence and progression of osteoporosis in patients with COPD: results from the TOwards a Revolution in COPD Health study. *Chest* 2009; **136**(6): 1456-65 https://pubmed.ncbi.nlm.nih.gov/19581353.
1675. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. *Thorax* 2011; **66**(8): 699-708 https://pubmed.ncbi.nlm.nih.gov/21602540.
1676. Wang JJ, Rochtchina E, Tan AG, Cumming RG, Leeder SR, Mitchell P. Use of inhaled and oral corticosteroids and the long-term risk of cataract. *Ophthalmology* 2009; **116**(4): 652-7 https://pubmed.ncbi.nlm.nih.gov/19243828.
1677. Andrejak C, Nielsen R, Thomsen VO, Duhaut P, Sorensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. *Thorax* 2013; **68**(3): 256-62 https://pubmed.ncbi.nlm.nih.gov/22781123.
1678. Dong YH, Chang CH, Wu FL, et al. Use of inhaled corticosteroids in patients with COPD and the risk of TB and influenza: A systematic review and meta-analysis of randomized controlled trials. a systematic review and meta-analysis of randomized controlled trials. *Chest* 2014; **145**(6): 1286-97 https://pubmed.ncbi.nlm.nih.gov/24504044.
1679. Price D, Yawn B, Brusselle G, Rossi A. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. *Prim Care Respir J* 2013; **22**(1): 92-100 https://pubmed.ncbi.nlm.nih.gov/23135217.
1680. Brusselle G, Price D, Gruffydd-Jones K, et al. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. *Int J Chron Obstruct Pulmon Dis* 2015; **10**: 2207-17 https://pubmed.ncbi.nlm.nih.gov/26527869.
1681. Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009; **180**(8): 741-50 https://pubmed.ncbi.nlm.nih.gov/19644045.
1682. Singh D, Brooks J, Hagan G, Cahn A, O'Connor BJ. Superiority of "triple" therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. *Thorax* 2008; **63**(7): 592-8 https://pubmed.ncbi.nlm.nih.gov/18245142.
1683. Jung KS, Park HY, Park SY, et al. Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: a randomized controlled study. *Respir Med* 2012; **106**(3): 382-9 https://pubmed.ncbi.nlm.nih.gov/21975275.
1684. Hanania NA, Crater GD, Morris AN, Emmett AH, O'Dell DM, Niewoehner DE. Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. *Respir Med* 2012; **106**(1): 91-101 https://pubmed.ncbi.nlm.nih.gov/22040533.
1685. Frith PA, Thompson PJ, Ratnavadivel R, et al. Glycopyrronium once-daily significantly improves lung function and health status when combined with salmeterol/fluticasone in patients with COPD: the GLISTEN study, a randomised controlled trial. *Thorax* 2015; **70**(6): 519-27 https://pubmed.ncbi.nlm.nih.gov/25841237.
1686. Lipson DA, Barnacle H, Birk R, et al. FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017; **196**(4): 438-46 https://pubmed.ncbi.nlm.nih.gov/28375647.
1687. Siler TM, Kerwin E, Singletary K, Brooks J, Church A. Efficacy and Safety of Umeclidinium Added to Fluticasone Propionate/Salmeterol in Patients with COPD: Results of Two Randomized, Double-Blind Studies. *COPD* 2016; **13**(1): 1-10 https://pubmed.ncbi.nlm.nih.gov/26451734.
1688. Singh D, Papi A, Corradi M, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting beta2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016; **388**(10048): 963-73 https://pubmed.ncbi.nlm.nih.gov/27598678.
1689. Bardsley S, Criner GJ, Halpin DMG, et al. Single-inhaler triple therapy fluticasone furoate/umeclidinium/vilanterol versus dual therapy in current and former smokers with COPD: IMPACT trial post hoc analysis. *Respir Med* 2022; **205**: 107040 https://pubmed.ncbi.nlm.nih.gov/36470149.
1690. Vestbo J, Fabbri L, Papi A, et al. Inhaled corticosteroid containing combinations and mortality in COPD. *Eur Respir J* 2018; **52**(6): 1801230 https://pubmed.ncbi.nlm.nih.gov/30209195.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1691. Lipson DA, Crim C, Criner GJ, et al. Reduction in All-Cause Mortality with Fluticasone Furoate/Umeclidinium/Vilanterol in Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2020; **201**(12): 1508-16 https://pubmed.ncbi.nlm.nih.gov/32162970.
1692. Manson SC, Brown RE, Cerulli A, Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. *Respir Med* 2009; **103**(7): 975-94 https://pubmed.ncbi.nlm.nih.gov/19372037.
1693. 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 https://pubmed.ncbi.nlm.nih.gov/25178099.
1694. Renkema TE, Schouten JP, Koeter GH, Postma DS. Effects of long-term treatment with corticosteroids in COPD. *Chest* 1996; **109**(5): 1156-62 https://pubmed.ncbi.nlm.nih.gov/8625660.
1695. Rice KL, Rubins JB, Lebahn F, et al. Withdrawal of chronic systemic corticosteroids in patients with COPD: a randomized trial. *Am J Respir Crit Care Med* 2000; **162**(1): 174-8 https://pubmed.ncbi.nlm.nih.gov/10903238.
1696. Rabe KF. Update on roflumilast, a phosphodiesterase 4 inhibitor for the treatment of chronic obstructive pulmonary disease. *Br J Pharmacol* 2011; **163**(1): 53-67 https://pubmed.ncbi.nlm.nih.gov/21232047.
1697. Calverley PM, Rabe KF, Goehring UM, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 2009; **374**(9691): 685-94 https://pubmed.ncbi.nlm.nih.gov/19716960.
1698. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. *Lancet* 2009; **374**(9691): 695-703 https://pubmed.ncbi.nlm.nih.gov/19716961.
1699. Chong J, Leung B, Poole P. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013; **11**(11): CD002309 https://pubmed.ncbi.nlm.nih.gov/24190161.
1700. Francis RS, May JR, Spicer CC. Chemotherapy of bronchitis. Influence of penicillin and tetracycline administered daily, or intermittently for exacerbations. A report to the Research Committee of the British Tuberculosis Association by its Bronchitis Subcommittee. *Br Med J* 1961; **2**(5258): 979-85 https://pubmed.ncbi.nlm.nih.gov/13894512.
1701. Francis RS, Spicer CC. Chemotherapy in chronic bronchitis. Influence of daily penicillin and tetracycline on exacerbations and their cost. *Br Med J* 1960; **1**(5169): 297-303 https://pubmed.ncbi.nlm.nih.gov/13824401.
1702. Johnston RN, McNeill RS, Smith DH, et al. Five-year winter chemoprophylaxis for chronic bronchitis. *Br Med J* 1969; **4**(5678): 265-9 https://pubmed.ncbi.nlm.nih.gov/4899454.
1703. Herath SC, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev* 2013; 10.1002/14651858.CD009764.pub2(11): CD009764 https://pubmed.ncbi.nlm.nih.gov/24288145.
1704. Ni W, Shao X, Cai X, et al. Prophylactic use of macrolide antibiotics for the prevention of chronic obstructive pulmonary disease exacerbation: a meta-analysis. *PLoS One* 2015; **10**(3): e0121257 https://pubmed.ncbi.nlm.nih.gov/25812085.
1705. Seemungal TA, Wilkinson TM, Hurst JR, Perera WR, Sapsford RJ, Wedzicha JA. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med* 2008; **178**(11): 1139-47 https://pubmed.ncbi.nlm.nih.gov/18723437.
1706. Uzun S, Djamin RS, Kluytmans JA, et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2014; **2**(5): 361-8 https://pubmed.ncbi.nlm.nih.gov/24746000.
1707. Sethi S, Jones PW, Theron MS, et al. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Respir Res* 2010; **11**(1): 10 https://pubmed.ncbi.nlm.nih.gov/20109213.
1708. Allinson JP, Vlies BH, Brill SE, et al. A Double-Blind, Randomized, Placebo-controlled Trial of Long-Term Doxycycline Therapy on Exacerbation Rate in Patients with Stable Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2023; **208**(5): 549-58 https://pubmed.ncbi.nlm.nih.gov/37450935.
1709. Cazzola M, Calzetta L, Page C, et al. Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis. *Eur Respir Rev* 2015; **24**(137): 451-61 https://pubmed.ncbi.nlm.nih.gov/26324807.
1710. Poole P, Chong J, Cates CJ. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015; 10.1002/14651858.CD001287.pub5(7): CD001287 https://pubmed.ncbi.nlm.nih.gov/26222376.
1711. Dal Negro RW, Wedzicha JA, Iversen M, et al. Effect of erdosteine on the rate and duration of COPD exacerbations: the RESTORE study. *Eur Respir J* 2017; **50**(4): PA675 https://pubmed.ncbi.nlm.nih.gov/29025888.
1712. Rogliani P, Matera MG, Page C, Puxeddu E, Cazzola M, Calzetta L. Efficacy and safety profile of mucolytic/antioxidant agents in chronic obstructive pulmonary disease: a comparative analysis across erdosteine, carbocysteine, and N-acetylcysteine. *Respir Res* 2019; **20**(1): 104 https://pubmed.ncbi.nlm.nih.gov/31133026.
1713. Zhou Y, Wu F, Shi Z, et al. Effect of high-dose N-acetylcysteine on exacerbations and lung function in patients with mild-to-moderate COPD: a double-blind, parallel group, multicentre randomised clinical trial. *Nat Commun* 2024; **15**(1): 8468 https://pubmed.ncbi.nlm.nih.gov/39349461.
1714. 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 https://pubmed.ncbi.nlm.nih.gov/31107966.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1715. Anzueto A, Barjaktarevic IZ, Siler TM, et al. Ensifentrine, a Novel Phosphodiesterase 3 and 4 Inhibitor for the Treatment of Chronic Obstructive Pulmonary Disease: Randomized, Double-Blind, Placebo-controlled, Multicenter Phase III Trials (the ENHANCE Trials). *Am J Respir Crit Care Med* 2023; **208**(4): 406-16 https://pubmed.ncbi.nlm.nih.gov/37364283.
1716. Singh D, Lea S, Mathioudakis AG. Inhaled Phosphodiesterase Inhibitors for the Treatment of Chronic Obstructive Pulmonary Disease. *Drugs* 2021; **81**(16): 1821-30 https://pubmed.ncbi.nlm.nih.gov/34731461.
1717. Criner GJ, Celli BR, Brightling CE, et al. Benralizumab for the Prevention of COPD Exacerbations. *N Engl J Med* 2019; **381**(11): 1023-34 https://pubmed.ncbi.nlm.nih.gov/31112385.
1718. Papi A, Greening NJ, Bhatt SP, et al. Safety and efficacy of astegolimab for COPD with frequent exacerbations regardless of baseline blood eosinophil counts (ALIENTO and ARNASA): randomised, double-blind, placebo-controlled, phase 2b and 3 trials. *Lancet* 2026; **407**(10543): 2027-39 https://pubmed.ncbi.nlm.nih.gov/42150581.
1719. Sciurba FC, Watz H, Bourdin A, et al. Tozorakimab to Prevent COPD Exacerbations. *N Engl J Med* 2026; 10.1056/NEJMoa2606998: https://pubmed.ncbi.nlm.nih.gov/42708515.
1720. 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): 477-86 https://pubmed.ncbi.nlm.nih.gov/25972156.
1721. 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): 829-34 https://pubmed.ncbi.nlm.nih.gov/29461616.
1722. Rennard SI, Fogarty C, Kelsen S, et al. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; **175**(9): 926-34 https://pubmed.ncbi.nlm.nih.gov/17290043.
1723. Fraser A, Poole P. Immunostimulants versus placebo for preventing exacerbations in adults with chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2022; **11**(11): CD013343 https://pubmed.ncbi.nlm.nih.gov/36373977.
1724. Devereux G, Cotton S, Nath M, et al. Bisoprolol in Patients With Chronic Obstructive Pulmonary Disease at High Risk of Exacerbation: The BICS Randomized Clinical Trial. *JAMA* 2024; **332**(6): 462-70 https://pubmed.ncbi.nlm.nih.gov/38762800.
1725. Jenkins CR, Martin A, Chang CL, et al. Bisoprolol to prevent adverse cardiac events (PACE) in COPD: a multicentre, double-blind, randomised, controlled, phase 3 trial. *Lancet Respir Med* 2026; **14**(3): 203-14 https://pubmed.ncbi.nlm.nih.gov/41579873.
1726. Criner GJ, Connett JE, Aaron SD, et al. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med* 2014; **370**(23): 2201-10 https://pubmed.ncbi.nlm.nih.gov/24836125.
1727. Ingebrigtsen TS, Marott JL, Nordestgaard BG, Lange P, Hallas J, Vestbo J. Statin use and exacerbations in individuals with chronic obstructive pulmonary disease. *Thorax* 2015; **70**(1): 33-40 https://pubmed.ncbi.nlm.nih.gov/25349333.
1728. Lehouck A, Mathieu C, Carremans C, et al. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2012; **156**(2): 105-14 https://pubmed.ncbi.nlm.nih.gov/22250141.
1729. World Health Organization. Adherence to long-term therapies : evidence for action (2003) [edited by Eduardo Sabaté]. Online document available at https://www.paho.org/sites/default/files/WHO-Adherence-Long-Term-Therapies-Eng-2003.pdf [accessed Oct 2026].
1730. Chen R, Gao Y, Wang H, Shang H, Xuan J. Association Between Adherence to Maintenance Medication in Patients with COPD and Acute Exacerbation Occurrence and Cost in China: A Retrospective Cohort Database Study. *Int J Chron Obstruct Pulmon Dis* 2020; **15**: 963-71 https://pubmed.ncbi.nlm.nih.gov/32440108.
1731. Chrystyn H, Small M, Milligan G, Higgins V, Gil EG, Estruch J. Impact of patients' satisfaction with their inhalers on treatment compliance and health status in COPD. *Respir Med* 2014; **108**(2): 358-65 https://pubmed.ncbi.nlm.nih.gov/24209768.
1732. Ierodiakonou D, Sifaki-Pistolla D, Kampouraki M, et al. Adherence to inhalers and comorbidities in COPD patients. A cross-sectional primary care study from Greece. *BMC Pulm Med* 2020; **20**(1): 253 https://pubmed.ncbi.nlm.nih.gov/32977779.
1733. Ingebrigtsen TS, Marott JL, Nordestgaard BG, et al. Low use and adherence to maintenance medication in chronic obstructive pulmonary disease in the general population. *J Gen Intern Med* 2015; **30**(1): 51-9 https://pubmed.ncbi.nlm.nih.gov/25245885.
1734. Moreira ATA, Pinto CR, Lemos ACM, Assuncao-Costa L, Souza GS, Martins Netto E. Evidence of the association between adherence to treatment and mortality among patients with COPD monitored at a public disease management program in Brazil. *J Bras Pneumol* 2021; **48**(1): e20210120 https://pubmed.ncbi.nlm.nih.gov/34909924.
1735. van Boven JF, Chavannes NH, van der Molen T, Rutten-van Molken MP, Postma MJ, Vegter S. Clinical and economic impact of non-adherence in COPD: a systematic review. *Respir Med* 2014; **108**(1): 103-13 https://pubmed.ncbi.nlm.nih.gov/24070566.
1736. van Boven JF, Tommelein E, Boussery K, et al. Improving inhaler adherence in patients with chronic obstructive pulmonary disease: a cost-effectiveness analysis. *Respir Res* 2014; **15**(1): 66 https://pubmed.ncbi.nlm.nih.gov/24929799.
1737. Vestbo J, Anderson JA, Calverley PM, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. *Thorax* 2009; **64**(11): 939-43 https://pubmed.ncbi.nlm.nih.gov/19703830.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1738. Wisniewski D, Porzezinska M, Gruchala-Niedoszytko M, Niedoszytko M, Slominski JM, Jassem E. Factors influencing adherence to treatment in COPD patients and its relationship with disease exacerbations. *Pneumonol Alergol Pol* 2014; **82**(2): 96-104 https://pubmed.ncbi.nlm.nih.gov/24615193.
1739. Kim JA, Lim MK, Kim K, Park J, Rhee CK. Adherence to Inhaled Medications and its Effect on Healthcare Utilization and Costs Among High-Grade Chronic Obstructive Pulmonary Disease Patients. *Clin Drug Investig* 2018; **38**(4): 333-40 https://pubmed.ncbi.nlm.nih.gov/29209982.
1740. Moradkhani B, Mollazadeh S, Niloofar P, Bashiri A, Oghazian MB. Association between medication adherence and health-related quality of life in patients with chronic obstructive pulmonary disease. *J Pharm Health Care Sci* 2021; **7**(1): 40 https://pubmed.ncbi.nlm.nih.gov/34775992.
1741. Bhattarai B, Walpola R, Mey A, Anoopkumar-Dukie S, Khan S. Barriers and Strategies for Improving Medication Adherence Among People Living With COPD: A Systematic Review. *Respir Care* 2020; **65**(11): 1738-50 https://pubmed.ncbi.nlm.nih.gov/32576706.
1742. Unni EJ, Gupta S, Sternbach N. Using the Medication Adherence Reasons Scale (MAR-Scale) in asthma and chronic obstructive pulmonary disease to determine the extent and identify the reasons for non-adherence. *Respir Med* 2021; **179**: 106337 https://pubmed.ncbi.nlm.nih.gov/33639405.
1743. Jarab AS, Mukattash TL. Exploring variables associated with medication non-adherence in patients with COPD. *Int J Clin Pharm* 2019; **41**(5): 1202-9 https://pubmed.ncbi.nlm.nih.gov/31468254.
1744. Montes de Oca M, Menezes A, Wehrmeister FC, et al. Adherence to inhaled therapies of COPD patients from seven Latin American countries: The LASSYC study. *PLoS One* 2017; **12**(11): e0186777 https://pubmed.ncbi.nlm.nih.gov/29140978.
1745. Ngo CQ, Phan DM, Vu GV, et al. Inhaler Technique and Adherence to Inhaled Medications among Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease in Vietnam. *Int J Environ Res Public Health* 2019; **16**(2): https://pubmed.ncbi.nlm.nih.gov/30634631.
1746. Shrestha R, Pant A, Shakya Shrestha S, Shrestha B, Gurung RB, Karmacharya BM. A Cross-Sectional Study of Medication Adherence Pattern and Factors Affecting the Adherence in Chronic Obstructive Pulmonary Disease. *Kathmandu Univ Med J (KUMJ)* 2015; **13**(49): 64-70 https://pubmed.ncbi.nlm.nih.gov/26620752.
1747. Rand CS. I took the medicine like you told me, doctor: Self-report of adherence with medical regimens. In: Stone A, ed. The science of self-report: implications for research and practice. Mahway, NJ: Lawrence Erlbaum Associates; 2000: 257-76.
1748. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care* 2004; **42**(3): 200-9 https://pubmed.ncbi.nlm.nih.gov/15076819.
1749. Bourbeau J, Bartlett SJ. Patient adherence in COPD. *Thorax* 2008; **63**(9): 831-8 https://pubmed.ncbi.nlm.nih.gov/18728206.
1750. Swiatoniowska N, Chabowski M, Polanski J, Mazur G, Jankowska-Polanska B. Adherence to Therapy in Chronic Obstructive Pulmonary Disease: A Systematic Review. *Adv Exp Med Biol* 2020; **1271**: 37-47 https://pubmed.ncbi.nlm.nih.gov/32016912.
1751. Le TT, Bjarnadottir M, Qato DM, Magder L, Zafari Z, Simoni-Wastila L. Prediction of treatment nonadherence among older adults with chronic obstructive pulmonary disease using Medicare real-world data. *J Manag Care Spec Pharm* 2022; **28**(6): 631-44 https://pubmed.ncbi.nlm.nih.gov/35621722.
1752. Tottenborg SS, Lange P, Johnsen SP, Nielsen H, Ingebrigtsen TS, Thomsen RW. Socioeconomic inequalities in adherence to inhaled maintenance medications and clinical prognosis of COPD. *Respir Med* 2016; **119**: 160-7 https://pubmed.ncbi.nlm.nih.gov/27692139.
1753. Tabyshova A, Sooronbaev T, Akylbekov A, et al. Medication availability and economic barriers to adherence in asthma and COPD patients in low-resource settings. *NPJ Prim Care Respir Med* 2022; **32**(1): 20 https://pubmed.ncbi.nlm.nih.gov/35637220.
1754. Bosnic-Anticevich S, Chrystyn H, Costello RW, et al. The use of multiple respiratory inhalers requiring different inhalation techniques has an adverse effect on COPD outcomes. *Int J Chron Obstruct Pulmon Dis* 2017; **12**: 59-71 https://pubmed.ncbi.nlm.nih.gov/28053517.
1755. Ammous O, Kampo R, Wollsching-Strobel M, et al. Adherence-enhancing interventions for pharmacological and oxygen therapy in patients with COPD: a systematic review and component network meta-analyses. *Eur Respir Rev* 2024; **33**(173): https://pubmed.ncbi.nlm.nih.gov/39231596.
1756. Gallefoss F, Bakke PS. Impact of patient education and self-management on morbidity in asthmatics and patients with chronic obstructive pulmonary disease. *Respir Med* 2000; **94**(3): 279-87 https://pubmed.ncbi.nlm.nih.gov/10783940.
1757. Chapman KR, Stockley RA, Dawkins C, Wilkes MM, Navickis RJ. Augmentation therapy for alpha1 antitrypsin deficiency: a meta-analysis. *COPD* 2009; **6**(3): 177-84 https://pubmed.ncbi.nlm.nih.gov/19811373.
1758. The Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. The Alpha-1-Antitrypsin Deficiency Registry Study Group. *Am J Respir Crit Care Med* 1998; **158**(1): 49-59 https://pubmed.ncbi.nlm.nih.gov/9655706.
1759. Dirksen A, Dijkman JH, Madsen F, et al. A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. *Am J Respir Crit Care Med* 1999; **160**(5 Pt 1): 1468-72 https://pubmed.ncbi.nlm.nih.gov/10556107.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1760. Dirksen A, Piitulainen E, Parr DG, et al. Exploring the role of CT densitometry: a randomised study of augmentation therapy in alpha1-antitrypsin deficiency. *Eur Respir J* 2009; **33**(6): 1345-53 https://pubmed.ncbi.nlm.nih.gov/19196813.
1761. McElvaney NG, Burdon J, Holmes M, et al. Long-term efficacy and safety of alpha1 proteinase inhibitor treatment for emphysema caused by severe alpha1 antitrypsin deficiency: an open-label extension trial (RAPID-OLE). *Lancet Respir Med* 2017; **5**(1): 51-60 https://pubmed.ncbi.nlm.nih.gov/27916480.
1762. Stockley RA, Edgar RG, Pillai A, Turner AM. Individualized lung function trends in alpha-1-antitrypsin deficiency: a need for patience in order to provide patient centered management? *Int J Chron Obstruct Pulmon Dis* 2016; **11**: 1745-56 https://pubmed.ncbi.nlm.nih.gov/27536086.
1763. Stoller JK, Aboussouan LS. A review of alpha1-antitrypsin deficiency. *Am J Respir Crit Care Med* 2012; **185**(3): 246-59 https://pubmed.ncbi.nlm.nih.gov/21960536.
1764. Sandhaus RA, Turino G, Brantly ML, et al. The Diagnosis and Management of Alpha-1 Antitrypsin Deficiency in the Adult. *Chronic Obstr Pulm Dis* 2016; **3**(3): 668-82 https://pubmed.ncbi.nlm.nih.gov/28848891.
1765. Fraughen DD, Ghosh AJ, Hobbs BD, et al. Augmentation Therapy for Severe Alpha-1 Antitrypsin Deficiency Improves Survival and Is Decoupled from Spirometric Decline-A Multinational Registry Analysis. *Am J Respir Crit Care Med* 2023; **208**(9): 964-74 https://pubmed.ncbi.nlm.nih.gov/37624745.
1766. Schildmann EK, Remi C, Bausewein C. Levodropropizine in the management of cough associated with cancer or nonmalignant chronic disease--a systematic review. *J Pain Palliat Care Pharmacother* 2011; **25**(3): 209-18 https://pubmed.ncbi.nlm.nih.gov/21806417.
1767. Barbera JA, Roger N, Roca J, Rovira I, Higenbottam TW, Rodriguez-Roisin R. Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease. *Lancet* 1996; **347**(8999): 436-40 https://pubmed.ncbi.nlm.nih.gov/8618485.
1768. Blanco I, Santos S, Gea J, et al. Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial. *Eur Respir J* 2013; **42**(4): 982-92 https://pubmed.ncbi.nlm.nih.gov/23429918.
1769. Goudie AR, Lipworth BJ, Hopkinson PJ, Wei L, Struthers AD. Tadalafil in patients with chronic obstructive pulmonary disease: a randomised, double-blind, parallel-group, placebo-controlled trial. *Lancet Respir Med* 2014; **2**(4): 293-300 https://pubmed.ncbi.nlm.nih.gov/24717626.
1770. Mullen JB, Wright JL, Wiggs BR, Pare PD, Hogg JC. Structure of central airways in current smokers and ex-smokers with and without mucus hypersecretion: relationship to lung function. *Thorax* 1987; **42**(11): 843-8 https://pubmed.ncbi.nlm.nih.gov/3424265.
1771. Burgel PR, Nadel JA. Roles of epidermal growth factor receptor activation in epithelial cell repair and mucin production in airway epithelium. *Thorax* 2004; **59**(11): 992-6 https://pubmed.ncbi.nlm.nih.gov/15516478.
1772. Alghamdi SM, Alsulayyim AS, Alasmari AM, et al. Oscillatory positive expiratory pressure therapy in COPD (O-COPD): a randomised controlled trial. *Thorax* 2023; **78**(2): 136-43 https://pubmed.ncbi.nlm.nih.gov/35948418.
1773. Coppolo DP, Schloss J, Suggett JA, Mitchell JP. Non-Pharmaceutical Techniques for Obstructive Airway Clearance Focusing on the Role of Oscillating Positive Expiratory Pressure (OPEP): A Narrative Review. *Pulm Ther* 2022; **8**(1): 1-41 https://pubmed.ncbi.nlm.nih.gov/34860355.
1774. Kellett F, Redfern J, Niven RM. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable bronchiectasis. *Respir Med* 2005; **99**(1): 27-31 https://pubmed.ncbi.nlm.nih.gov/15672845.
1775. Kellett F, Robert NM. Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. *Respir Med* 2011; **105**(12): 1831-5 https://pubmed.ncbi.nlm.nih.gov/22018993.
1776. Clarke SW, Lopez-Vidriero MT, Pavia D, Thomson ML. The effect of sodium 2-mercapto-ethane sulphonate and hypertonic saline aerosols on bronchial clearance in chronic bronchitis. *Br J Clin Pharmacol* 1979; **7**(1): 39-44 https://pubmed.ncbi.nlm.nih.gov/104724.
1777. Valderramas SR, Atallah AN. Effectiveness and safety of hypertonic saline inhalation combined with exercise training in patients with chronic obstructive pulmonary disease: a randomized trial. *Respir Care* 2009; **54**(3): 327-33 https://pubmed.ncbi.nlm.nih.gov/19245725.
1778. Zhang Y, Song A, Liu J, Dai J, Lin J. Therapeutic effect of nebulized hypertonic saline for muco-obstructive lung diseases: a systematic review and meta-analysis with trial sequential analysis. *J Investig Med* 2021; **69**(3): 742-8 https://pubmed.ncbi.nlm.nih.gov/33272932.
1779. Calzetta L, Rogliani P, Matera MG, Cazzola M. A Systematic Review With Meta-Analysis of Dual Bronchodilation With LAMA/LABA for the Treatment of Stable COPD. *Chest* 2016; **149**(5): 1181-96 https://pubmed.ncbi.nlm.nih.gov/26923629.
1780. McGarvey L, Morice AH, Smith JA, et al. Effect of aclidinium bromide on cough and sputum symptoms in moderate-to-severe COPD in three phase III trials. *BMJ Open Respir Res* 2016; **3**(1): e000148 https://pubmed.ncbi.nlm.nih.gov/28074135.
1781. Hasani A, Toms N, Agnew JE, Sarno M, Harrison AJ, Dilworth P. The effect of inhaled tiotropium bromide on lung mucociliary clearance in patients with COPD. *Chest* 2004; **125**(5): 1726-34 https://pubmed.ncbi.nlm.nih.gov/15136383.
1782. Powrie DJ, Wilkinson TM, Donaldson GC, et al. Effect of tiotropium on sputum and serum inflammatory markers and exacerbations in COPD. *Eur Respir J* 2007; **30**(3): 472-8 https://pubmed.ncbi.nlm.nih.gov/17504798.

COPYRIGHT MATERIAL. DO NOT COPY OR DISTRIBUTE

1783. O'Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. rhDNase Study Group. *Chest* 1998; **113**(5): 1329-34 https://pubmed.ncbi.nlm.nih.gov/9596315.
1784. Wilkinson M, Sugumar K, Milan SJ, Hart A, Crockett A, Crossingham I. Mucolytics for bronchiectasis. *Cochrane Database Syst Rev* 2014; **2014**(5): CD001289 https://pubmed.ncbi.nlm.nih.gov/24789119.
1785. Ehre C, Rushton ZL, Wang B, et al. An Improved Inhaled Mucolytic to Treat Airway Muco-obstructive Diseases. *Am J Respir Crit Care Med* 2019; **199**(2): 171-80 https://pubmed.ncbi.nlm.nih.gov/30212240.
1786. Rowe SM, Jones I, Dransfield MT, et al. Efficacy and Safety of the CFTR Potentiator Icenticaftor (QBW251) in COPD: Results from a Phase 2 Randomized Trial. *Int J Chron Obstruct Pulmon Dis* 2020; **15**: 2399-409 https://pubmed.ncbi.nlm.nih.gov/33116455.
1787. Slebos DJ, Breen D, Coad J, et al. Safety and Histological Effect of Liquid Nitrogen Metered Spray Cryotherapy in the Lung. *Am J Respir Crit Care Med* 2017; **196**(10): 1351-2 https://pubmed.ncbi.nlm.nih.gov/28358989.
1788. Fan VS, Gaziano JM, Lew R, et al. A comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalizations: a randomized, controlled trial. *Ann Intern Med* 2012; **156**(10): 673-83 https://pubmed.ncbi.nlm.nih.gov/22586006.
1789. Peytremann-Bridevaux I, Taffe P, Burnand B, Bridevaux PO, Puhan MA. Mortality of patients with COPD participating in chronic disease management programmes: a happy end? *Thorax* 2014; **69**(9): 865-6 https://pubmed.ncbi.nlm.nih.gov/24718640.
1790. Kessler R, Casan-Clara P, Koehler D, et al. COMET: a multicomponent home-based disease-management programme versus routine care in severe COPD. *Eur Respir J* 2018; **51**(1): 1701612 https://pubmed.ncbi.nlm.nih.gov/29326333.
1791. Rose L, Istanboulian L, Carriere L, et al. Program of Integrated Care for Patients with Chronic Obstructive Pulmonary Disease and Multiple Comorbidities (PIC COPD(+)): a randomised controlled trial. *Eur Respir J* 2018; **51**(1): https://pubmed.ncbi.nlm.nih.gov/29326330.
1792. Benzo R, Vickers K, Novotny PJ, et al. Health Coaching and Chronic Obstructive Pulmonary Disease Rehospitalization. A Randomized Study. *Am J Respir Crit Care Med* 2016; **194**(6): 672-80 https://pubmed.ncbi.nlm.nih.gov/26953637.
1793. Benzo R, McEvoy C. Effect of Health Coaching Delivered by a Respiratory Therapist or Nurse on Self-Management Abilities in Severe COPD: Analysis of a Large Randomized Study. *Respir Care* 2019; **64**(9): 1065-72 https://pubmed.ncbi.nlm.nih.gov/30914491.
1794. Bourbeau J, Lavoie KL, Sedeno M. Comprehensive Self-Management Strategies. *Semin Respir Crit Care Med* 2015; **36**(4): 630-8 https://pubmed.ncbi.nlm.nih.gov/26238647.
1795. Griffiths B, Alajmi R, Clifton IJ, Birch RJ, Peckham D, Price OJ. Physical inactivity in chronic airways disease: an important candidate in the treatable traits paradigm. *Eur Respir Rev* 2026; **35**(179): https://pubmed.ncbi.nlm.nih.gov/41741005.
1796. Harding S, Richardson A, Glynn A, Middleton L, Hodgson L. The Associations Between Socioeconomic Deprivation, Social Isolation and Sedentary Time in COPD: A UK Biobank Study. *Copd* 2026; **23**(1): 2713066 https://pubmed.ncbi.nlm.nih.gov/42695939.
1797. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. *Thorax* 2006; **61**(9): 772-8 https://pubmed.ncbi.nlm.nih.gov/16738033.
1798. Yohannes AM, Baldwin RC, Connolly M. Mortality predictors in disabling chronic obstructive pulmonary disease in old age. *Age Ageing* 2002; **31**(2): 137-40 https://pubmed.ncbi.nlm.nih.gov/11937477.
1799. Mantoani LC, Rubio N, McKinstry B, MacNee W, Rabinovich RA. Interventions to modify physical activity in patients with COPD: a systematic review. *Eur Respir J* 2016; **48**(1): 69-81 https://pubmed.ncbi.nlm.nih.gov/27103381.
1800. Hipólito N, Pimenta S, Encantado J, Cruz J. Physical activity in COPD: a scoping review of methods and behaviour change techniques. *ERJ Open Res* 2026; **12**(4): https://pubmed.ncbi.nlm.nih.gov/42577517.
1801. Diciolla NS, Yuste-Sánchez MJ, Torres-Lacomba M, Paixão C, Marques A. Physical activity coaching in people with chronic obstructive pulmonary disease: a systematic literature review with meta-analysis. *Ann Behav Med* 2025; **59**(1): https://pubmed.ncbi.nlm.nih.gov/40673868.
1802. Shah AJ, Althobiani MA, Saigal A, Ogbonnaya CE, Hurst JR, Mandal S. Wearable technology interventions in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *NPJ Digit Med* 2023; **6**(1): 222 https://pubmed.ncbi.nlm.nih.gov/38012218.
1803. Blondeel A, Hermans F, Breuls S, et al. A Long-Term Physical Activity Coaching Program for Patients with COPD: A Randomized Controlled Trial. *Am J Respir Crit Care Med* 2025; 10.1164/rccm.202501-0170OC: https://pubmed.ncbi.nlm.nih.gov/40700740.
1804. Moy ML, Martinez CH, Kadri R, et al. Long-Term Effects of an Internet-Mediated Pedometer-Based Walking Program for Chronic Obstructive Pulmonary Disease: Randomized Controlled Trial. *J Med Internet Res* 2016; **18**(8): e215 https://pubmed.ncbi.nlm.nih.gov/27502583.
1805. Nguyen HQ, Moy ML, Liu IA, et al. Effect of Physical Activity Coaching on Acute Care and Survival Among Patients With Chronic Obstructive Pulmonary Disease: A Pragmatic Randomized Clinical Trial. *JAMA Netw Open* 2019; **2**(8): e199657 https://pubmed.ncbi.nlm.nih.gov/31418811.
1806. Wan ES, Kantorowski A, Polak M, et al. Long-term effects of web-based pedometer-mediated intervention on COPD exacerbations. *Respir Med* 2020; **162**: 105878 https://pubmed.ncbi.nlm.nih.gov/32056676.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1807. Lahham A, McDonald CF, Holland AE. Exercise training alone or with the addition of activity counseling improves physical activity levels in COPD: a systematic review and meta-analysis of randomized controlled trials. *Int J Chron Obstruct Pulmon Dis* 2016; **11**: 3121-36 https://pubmed.ncbi.nlm.nih.gov/27994451.
1808. Ortega F, Toral J, Cejudo P, et al. Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; **166**(5): 669-74 https://pubmed.ncbi.nlm.nih.gov/12204863.
1809. Ward TJ, Plumptre CD, Fraser-Pye AV, et al. Understanding the effectiveness of different exercise training programme designs on V̇O(2peak) in COPD: a component network meta-analysis. *Thorax* 2023; **78**(10): 1035-8 https://pubmed.ncbi.nlm.nih.gov/37263780.
1810. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011; **43**(7): 1334-59 https://pubmed.ncbi.nlm.nih.gov/21694556.
1811. Horowitz MB, Littenberg B, Mahler DA. Dyspnea ratings for prescribing exercise intensity in patients with COPD. *Chest* 1996; **109**(5): 1169-75 https://pubmed.ncbi.nlm.nih.gov/8625662.
1812. Alexiou C, Ward L, Hume E, Armstrong M, Wilkinson M, Vogiatzis I. Effect of interval compared to continuous exercise training on physiological responses in patients with chronic respiratory diseases: A systematic review and meta-analysis. *Chron Respir Dis* 2021; **18**: 14799731211041506 https://pubmed.ncbi.nlm.nih.gov/34666528.
1813. Velloso M, do Nascimento NH, Gazzotti MR, Jardim JR. Evaluation of effects of shoulder girdle training on strength and performance of activities of daily living in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2013; **8**: 187-92 https://pubmed.ncbi.nlm.nih.gov/23589685.
1814. Cunha BLM, Costa LSP, Porfírio PV, de Sousa Dantas D, de Melo Marinho PE. Effects of whole-body vibration exercise on functional capacity, muscle strength, and quality of life in individuals with severe chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Physiother Theory Pract* 2025; **41**(4): 861-71 https://pubmed.ncbi.nlm.nih.gov/38953511.
1815. Alves IGN, da Silva ESCM, Martinez BP, de Queiroz RS, Gomes-Neto M. Effects of neuromuscular electrical stimulation on exercise capacity, muscle strength and quality of life in COPD patients: A Systematic Review with Meta-Analysis. *Clin Rehabil* 2022; **36**(4): 449-71 https://pubmed.ncbi.nlm.nih.gov/35014892.
1816. Gao Q, Li P, Han X, et al. Comparative efficacy of mind-body exercises for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis. *Clin Rehabil* 2026; **40**(10): 1340-52 https://pubmed.ncbi.nlm.nih.gov/42053497.
1817. Ramirez-Venegas A, Ward J, Lentine T, Mahler DA. Salmeterol reduces dyspnea and improves lung function in patients with COPD. *Chest* 1997; **112**(2): 336-40 https://pubmed.ncbi.nlm.nih.gov/9266866.
1818. Troosters T, Maltais F, Leidy N, et al. Effect of Bronchodilation, Exercise Training, and Behavior Modification on Symptoms and Physical Activity in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2018; **198**(8): 1021-32 https://pubmed.ncbi.nlm.nih.gov/29664681.
1819. 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 https://pubmed.ncbi.nlm.nih.gov/17443585.
1820. Oltra G, Ricciardelli M, Virgilio S, et al. High-flow nasal cannula during pulmonary rehabilitation for people with chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Physiother Res Int* 2024; **29**(2): e2088 https://pubmed.ncbi.nlm.nih.gov/38581398.
1821. Beaumont M, Forget P, Couturaud F, Reychler G. Effects of inspiratory muscle training in COPD patients: A systematic review and meta-analysis. *Clin Respir J* 2018; **12**(7): 2178-88 https://pubmed.ncbi.nlm.nih.gov/29665262.
1822. Ammous O, Feki W, Lotfi T, et al. Inspiratory muscle training, with or without concomitant pulmonary rehabilitation, for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev* 2023; **1**(1): Cd013778 https://pubmed.ncbi.nlm.nih.gov/36606682.
1823. Yang Y, Wei L, Wang S, et al. The effects of pursed lip breathing combined with diaphragmatic breathing on pulmonary function and exercise capacity in patients with COPD: a systematic review and meta-analysis. *Physiother Theory Pract* 2022; **38**(7): 847-57 https://pubmed.ncbi.nlm.nih.gov/32808571.
1824. Song F, Ding K, Qi W, et al. Effects of Baduanjin Exercise on lung function and 6 min walk in COPD patients: a systematic review and meta-analysis. *Sci Rep* 2024; **14**(1): 17788 https://pubmed.ncbi.nlm.nih.gov/39090183.
1825. Spruit MA, Singh SJ, Garvey C, et al. An Official American Thoracic Society/European Respiratory Society Statement: Key Concepts and Advances in Pulmonary Rehabilitation. *American Journal of Respiratory and Critical Care Medicine* 2013; **188**(8): e13-e64
1826. Dai S, Kwok CS. The impact of pulmonary rehabilitation on sleep quality in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. *PLoS One* 2025; **20**(6): e0318424 https://pubmed.ncbi.nlm.nih.gov/40465766.
1827. Moecke DP, Zhu K, Gill J, et al. Safety and Efficacy of Inpatient Pulmonary Rehabilitation for Patients Hospitalized with an Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Systematic Review and Meta-analyses. *Ann Am Thorac Soc* 2023; **20**(2): 307-19 https://pubmed.ncbi.nlm.nih.gov/36191273.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1828. Sahin H, Naz I, Varol Y, Aksel N, Tuksavul F, Ozsoz A. Is a pulmonary rehabilitation program effective in COPD patients with chronic hypercapnic failure? *Expert Rev Respir Med* 2016; **10**(5): 593-8 https://pubmed.ncbi.nlm.nih.gov/26954769.
1829. Cheung CC, Ng GL, Li TS, et al. The Combined Efficacy of Adjunctive Psychological Interventions and Pulmonary Rehabilitation in People With Chronic Obstructive Pulmonary Disease - A Systematic Review and Meta-Analysis. *Chronic Obstr Pulm Dis* 2026; **13**(5): 416-32 https://pubmed.ncbi.nlm.nih.gov/42622334.
1830. Alkandari S, Nuhmani S, AlSubaiei M, Abualait T. The efficacy of pulmonary rehabilitation on cognitive functions in patients with chronic obstructive pulmonary disease: systematic review. *Front Med (Lausanne)* 2026; **13**: 1753968 https://pubmed.ncbi.nlm.nih.gov/41924729.
1831. Stefan MS, Pekow PS, Priya A, et al. Association between Initiation of Pulmonary Rehabilitation and Rehospitalizations in Patients Hospitalized with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2021; **204**(9): 1015-23 https://pubmed.ncbi.nlm.nih.gov/34283694.
1832. Chen TA, Mao ST, Chen TT, Yeh YK, Chen KY, Tseng CH. Optimal Pulmonary Rehabilitation Program and Timing of Program Initiation for Patients With Chronic Obstructive Pulmonary Disease: A Systematic Review and Network Meta-Analysis. *J Cardiopulm Rehabil Prev* 2025; **45**(5): 318-26 https://pubmed.ncbi.nlm.nih.gov/40455963.
1833. Rutkowski S, Rutkowska A, Kiper P, et al. Virtual Reality Rehabilitation in Patients with Chronic Obstructive Pulmonary Disease: A Randomized Controlled Trial. *Int J Chron Obstruct Pulmon Dis* 2020; **15**: 117-24 https://pubmed.ncbi.nlm.nih.gov/32021150.
1834. Coultas DB, Jackson BE, Russo R, et al. Home-based Physical Activity Coaching, Physical Activity, and Health Care Utilization in Chronic Obstructive Pulmonary Disease. Chronic Obstructive Pulmonary Disease Self-Management Activation Research Trial Secondary Outcomes. *Ann Am Thorac Soc* 2018; **15**(4): 470-8 https://pubmed.ncbi.nlm.nih.gov/29283670.
1835. Stone PW, Hickman K, Steiner MC, Roberts CM, Quint JK, Singh SJ. Predictors of pulmonary rehabilitation completion in the UK. *ERJ Open Res* 2021; **7**(1): https://pubmed.ncbi.nlm.nih.gov/33585658.
1836. Machado A, Burtin C, Spruit MA. Alternative Modes of Delivery in Pulmonary Rehabilitation: A Critical Appraisal of the Literature. *J Cardiopulm Rehabil Prev* 2024; **44**(6): 399-408 https://pubmed.ncbi.nlm.nih.gov/39485893.
1837. Holland AE, Mahal A, Hill CJ, et al. Home-based rehabilitation for COPD using minimal resources: a randomised, controlled equivalence trial. *Thorax* 2017; **72**(1): 57-65 https://pubmed.ncbi.nlm.nih.gov/27672116.
1838. Maltais F, Bourbeau J, Shapiro S, et al. Effects of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2008; **149**(12): 869-78 https://pubmed.ncbi.nlm.nih.gov/19075206.
1839. Bourne S, DeVos R, North M, et al. Online versus face-to-face pulmonary rehabilitation for patients with chronic obstructive pulmonary disease: randomised controlled trial. *BMJ Open* 2017; **7**(7): e014580 https://pubmed.ncbi.nlm.nih.gov/28716786.
1840. Horton EJ, Mitchell KE, Johnson-Warrington V, et al. Comparison of a structured home-based rehabilitation programme with conventional supervised pulmonary rehabilitation: a randomised non-inferiority trial. *Thorax* 2018; **73**(1): 29-36 https://pubmed.ncbi.nlm.nih.gov/28756402.
1841. Nolan CM, Kaliaraju D, Jones SE, et al. Home versus outpatient pulmonary rehabilitation in COPD: a propensity-matched cohort study. *Thorax* 2019; **74**(10): 996-8 https://pubmed.ncbi.nlm.nih.gov/31278173.
1842. Wuyts M, Coosemans I, Everaerts S, et al. Hybrid compared to conventional pulmonary rehabilitation: an equivalence analysis. *ERJ Open Res* 2024; **10**(4): https://pubmed.ncbi.nlm.nih.gov/39104952.
1843. Guell MR, Cejudo P, Ortega F, et al. Benefits of Long-Term Pulmonary Rehabilitation Maintenance Program in Patients with Severe Chronic Obstructive Pulmonary Disease. Three-Year Follow-up. *Am J Respir Crit Care Med* 2017; **195**(5): 622-9 https://pubmed.ncbi.nlm.nih.gov/27611807.
1844. Cox NS, McDonald CF, Mahal A, et al. Telerehabilitation for chronic respiratory disease: a randomised controlled equivalence trial. *Thorax* 2022; **77**(7): 643-51 https://pubmed.ncbi.nlm.nih.gov/34650004.
1845. Houchen-Wolloff L, Steiner MC. Pulmonary rehabilitation at a time of social distancing: prime time for tele-rehabilitation? *Thorax* 2020; **75**(6): 446-7 https://pubmed.ncbi.nlm.nih.gov/32398319.
1846. Holland AE, Malaguti C, Hoffman M, et al. Home-based or remote exercise testing in chronic respiratory disease, during the COVID-19 pandemic and beyond: A rapid review. *Chron Respir Dis* 2020; **17**: 1479973120952418 https://pubmed.ncbi.nlm.nih.gov/32840385.
1847. Bhatt SP, Casaburi R, Mosher CL, Rochester CL, Garvey C. Telehealth Pulmonary Rehabilitation: A Call for Minimum Standards. *Am J Respir Crit Care Med* 2024; **210**(2): 145-6 https://pubmed.ncbi.nlm.nih.gov/38536108.
1848. Collins PF, Elia M, Kurukulaaratchy RJ, Stratton RJ. The influence of deprivation on malnutrition risk in outpatients with chronic obstructive pulmonary disease (COPD). *Clin Nutr* 2018; **37**(1): 144-8 https://pubmed.ncbi.nlm.nih.gov/27866758.
1849. Collins PF, Stratton RJ, Kurukulaaratchy RJ, Elia M. Influence of deprivation on health care use, health care costs, and mortality in COPD. *Int J Chron Obstruct Pulmon Dis* 2018; **13**: 1289-96 https://pubmed.ncbi.nlm.nih.gov/29719384.
1850. Gunay E, Kaymaz D, Selcuk NT, Ergun P, Sengul F, Demir N. Effect of nutritional status in individuals with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation. *Respirology* 2013; **18**(8): 1217-22 https://pubmed.ncbi.nlm.nih.gov/23714353.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

1851. Hoong JM, Ferguson M, Hukins C, Collins PF. Economic and operational burden associated with malnutrition in chronic obstructive pulmonary disease. *Clin Nutr* 2017; **36**(4): 1105-9 https://pubmed.ncbi.nlm.nih.gov/27496063.
1852. Nguyen HT, Collins PF, Pavey TG, Nguyen NV, Pham TD, Gallegos DL. Nutritional status, dietary intake, and health-related quality of life in outpatients with COPD. *Int J Chron Obstruct Pulmon Dis* 2019; **14**: 215-26 https://pubmed.ncbi.nlm.nih.gov/30666102.
1853. Collins PF, Elia M, Stratton RJ. Nutritional support and functional capacity in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Respirology* 2013; **18**(4): 616-29 https://pubmed.ncbi.nlm.nih.gov/23432923.
1854. King DA, Cordova F, Scharf SM. Nutritional aspects of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008; **5**(4): 519-23 https://pubmed.ncbi.nlm.nih.gov/18453365.
1855. Creutzberg EC, Wouters EF, Vanderhoven-Augustin IM, Dentener MA, Schols AM. Disturbances in leptin metabolism are related to energy imbalance during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; **162**(4 Pt 1): 1239-45 https://pubmed.ncbi.nlm.nih.gov/11029324.
1856. Schols A. Nutrition as a metabolic modulator in COPD. *Chest* 2013; **144**(4): 1340-5 https://pubmed.ncbi.nlm.nih.gov/24081345.
1857. Wilson DO, Rogers RM, Wright EC, Anthonisen NR. Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. *Am Rev Respir Dis* 1989; **139**(6): 1435-8 https://pubmed.ncbi.nlm.nih.gov/2658702.
1858. Kim V, Kretschman DM, Sternberg AL, DeCamp MM, Jr., Criner GJ, National Emphysema Treatment Trial Research G. Weight gain after lung reduction surgery is related to improved lung function and ventilatory efficiency. *Am J Respir Crit Care Med* 2012; **186**(11): 1109-16 https://pubmed.ncbi.nlm.nih.gov/22878279.
1859. Casaburi R. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 2001; **33**(7 Suppl): S662-70 https://pubmed.ncbi.nlm.nih.gov/11462075.
1860. Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. *Eur Respir J* 1994; **7**(10): 1793-7 https://pubmed.ncbi.nlm.nih.gov/7828687.
1861. Franssen FM, Wouters EF, Schols AM. The contribution of starvation, deconditioning and ageing to the observed alterations in peripheral skeletal muscle in chronic organ diseases. *Clin Nutr* 2002; **21**(1): 1-14 https://pubmed.ncbi.nlm.nih.gov/11884007.
1862. Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. *Am J Respir Crit Care Med* 1995; **152**(4 Pt 1): 1268-74 https://pubmed.ncbi.nlm.nih.gov/7551381.
1863. Steiner MC, Barton RL, Singh SJ, Morgan MD. Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomised controlled trial. *Thorax* 2003; **58**(9): 745-51 https://pubmed.ncbi.nlm.nih.gov/12947128.
1864. Vermeeren MA, Wouters EF, Geraerts-Keeris AJ, Schols AM. Nutritional support in patients with chronic obstructive pulmonary disease during hospitalization for an acute exacerbation; a randomized controlled feasibility trial. *Clin Nutr* 2004; **23**(5): 1184-92 https://pubmed.ncbi.nlm.nih.gov/15380912.
1865. van Wetering CR, Hoogendoorn M, Broekhuizen R, et al. Efficacy and costs of nutritional rehabilitation in muscle-wasted patients with chronic obstructive pulmonary disease in a community-based setting: a prespecified subgroup analysis of the INTERCOM trial. *J Am Med Dir Assoc* 2010; **11**(3): 179-87 https://pubmed.ncbi.nlm.nih.gov/20188315.
1866. Deutz NE, Ziegler TR, Matheson EM, et al. Reduced mortality risk in malnourished hospitalized older adult patients with COPD treated with a specialized oral nutritional supplement: Sub-group analysis of the NOURISH study. *Clin Nutr* 2021; **40**(3): 1388-95 https://pubmed.ncbi.nlm.nih.gov/32921503.
1867. Kruis AL, Boland MR, Assendelft WJ, et al. Effectiveness of integrated disease management for primary care chronic obstructive pulmonary disease patients: results of cluster randomised trial. *BMJ* 2014; **349**: g5392 https://pubmed.ncbi.nlm.nih.gov/25209620.
1868. Licskai C, Hussey A, Rowley V, et al. Quantifying sustained health system benefits of primary care-based integrated disease management for COPD: a 6-year interrupted time series study. *Thorax* 2024; **79**(8): 725-34 https://pubmed.ncbi.nlm.nih.gov/38889973.
1869. Gregersen TL, Green A, Frausing E, Ringbaek T, Brondum E, Suppli Ulrik C. Do telemedical interventions improve quality of life in patients with COPD? A systematic review. *Int J Chron Obstruct Pulmon Dis* 2016; **11**: 809-22 https://pubmed.ncbi.nlm.nih.gov/27143872.
1870. Cartwright M, Hirani SP, Rixon L, et al. Effect of telehealth on quality of life and psychological outcomes over 12 months (Whole Systems Demonstrator telehealth questionnaire study): nested study of patient reported outcomes in a pragmatic, cluster randomised controlled trial. *BMJ* 2013; **346**: f653 https://pubmed.ncbi.nlm.nih.gov/23444424.

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

©2026, 2027 Global Initiative for Chronic Obstructive Lung Disease, Inc.

Visit the GOLD website at **www.goldcopd.org**