Global Initiative for Chronic Obstructive Lung Disease

2024 REPORT

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 (2024 REPORT)

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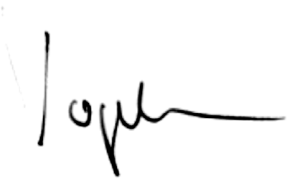
GOLD 2024 REPORT HIGHLIGHTS

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 2024 revision of the GOLD report several important changes have been made as follows:

i. **Chapter 3** and **Chapter 4** have been consolidated into one chapter to reduce repetitive information
ii. Some tables have been consolidated to remove repetition; all table and figure numbers have been changed to consecutive figure numbers only.
iii. PubMed links (where available) have now been included in the reference list and all references can now be found at the end of the GOLD report (rather than at the end of each chapter).
iv. Information about **PRISm** (preserved ratio but impaired spirometry) has been expanded (Page 13)
v. A new section on **Hyperinflation** has been added (Page 17)
vi. In the **Spirometry** section further clarification about pre-bronchodilator spirometry has been added (Page 26)
vii. A new section on **Screening for COPD in Targeted Populations** (Page 29) has been added with information on **Leveraging Lung Cancer Imaging for COPD screening** (Page 29), including spirometry screening in targeted populations, and **Leveraging Incidental Lung Imaging Abnormalities for COPD Screening** (Page 30)
viii. In the **Initial Assessment** section, the paragraphs on **Blood Eosinophil Count** have been updated (Page 34)
ix. **Interstitial Lung Abnormalities** are now covered (Page 38)
x. The section on **Smoking Cessation** has been revised (Page 43)
xi. **Vaccination Recommendations** for people with COPD have been updated in line with current guidance from the US Centers for Disease Control (CDC) (Page 46)
xii. **Managing Inhaled Therapy** has been expanded (Page 53) and includes information on a patient's **Ability to use the Delivery System Correctly** (Page 54) and **Choice of Inhaler Device** (Page 54)
xiii. A new section on **Pharmacotherapies for Smoking Cessation** has been added (Page 68)

GOLD has been fortunate to have a network of international 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 general 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 2024 UPDATE[1]

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[2] 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 2024 GOLD Report is an update of the 2023-revised report. The 2023 GOLD Report was the 5th major revision of GOLD, and incorporated a reassessment and revision of recommendations for the diagnosis, assessment and treatment of COPD. 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, U.S. 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 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

[1] The Global Strategy for Diagnosis, Management and Prevention of COPD (updated 2024), the Pocket Guide (updated 2024) and the complete list of references examined by the Committee is available on the GOLD website: www.goldcopd.org.

[2] GOLD Science Committee Members (2023-2024): C. Vogelmeier, Chair, A. Agusti, A. Anzueto, P. Barnes, 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, R. Stockley, M. Victorina Lopez Varela, 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 Committees 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

The GOLD 2024 report is an update GOLD 2023 report which was a major revision. 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 2022 to July 2023. In total, 148 new references have been added to the GOLD 2024 report.

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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. These have stood the test of time, and 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.

A second strength of the original strategy was the simple, intuitive system for classifying COPD severity. This was based on FEV1 and was called a staging system because it was believed, at the time, that the majority of patients followed a path of disease progression in which the severity of COPD tracked the severity of airflow obstruction. Much is now known about the characteristics of patients in the different GOLD stages – for example, their risk of exacerbations, hospitalization, and death. However, at an individual patient level, FEV1 is an unreliable marker of the severity of breathlessness, exercise limitation, health status impairment, and risk of exacerbation.

At the time of the original report, improvement in both symptoms and health status was a GOLD treatment objective, but symptoms assessment did not have a direct relation to the choice of management, and health status measurement was a complex process largely confined to clinical studies. Now, there are simple and reliable questionnaires designed for use in routine daily clinical practice. These are available in many languages. These developments have 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.

BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD) is now one of the top three causes of death worldwide and 90% of these deaths occur in low- and middle-income countries (LMICs).[1,2] More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally. 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.[3]

In 1998, with the cooperation of the National Heart, Lung, and Blood Institute, National Institutes of Health and the World Health Organization the Global Initiative for Chronic Obstructive Lung Disease (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.[4] 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.[5]

LEVELS OF EVIDENCE

Levels of evidence have been assigned to evidence-based recommendations where appropriate (**Table A**). 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

Table A

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.

CHAPTER 1: DEFINITION AND OVERVIEW

KEY POINTS:

Definition

- Chronic Obstructive Pulmonary Disease (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.
- The most relevant (albeit rare) genetic risk factor for COPD identified to date are mutations in the SERPINA1 gene that lead to α-1 antitrypsin deficiency. A number of other genetic variants have also been associated with reduced lung function and risk of COPD, but their individual effect size is small.

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.
- Some individuals can have respiratory symptoms and/or 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' (Preserved Ratio Impaired Spirometry) 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.

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 as well. 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.

WHAT IS COPD?

Definition

Chronic Obstructive Pulmonary Disease (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.[6]

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.[7]

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[8,9] and host factors (including abnormal lung development and accelerated lung aging) can also contribute.[7]

The most relevant (albeit epidemiologically rare) genetic risk factor for COPD identified to date are mutations in the SERPINA1 gene, leading to α1-antitrypsin deficiency, but other genetic variants, with a low individual effect size, are associated with reduced lung function and risk of COPD too.[10]

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'* (Preserved Ratio Impaired Spirometry) 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.[11,12] 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 as well. 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 treatment 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.[13]

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.[14,15] COPD prevalence, morbidity and mortality vary across countries.[16,17] The prevalence of COPD is often directly related to the prevalence of tobacco smoking, but in many countries outdoor, occupational and household air pollution (resulting from the burning of wood and other biomass fuels) are important COPD risk factors.[18,19]

The prevalence and burden of COPD are projected to increase over the coming decades due to a combination of continued exposure to COPD risk factors and aging of the world's population.[3] Information on the burden of COPD can be found on international websites, such as the World Health Organization (WHO)[20] and the World Bank/WHO Global Burden of Disease (GBD) Study.[21,22]

Prevalence

Existing COPD prevalence data vary widely due to differences in survey methods, diagnostic criteria, and analytical approaches.[3] Of note, all of these epidemiologic studies defined COPD by spirometry alone. The lowest estimates of prevalence are those based on self-reporting of a doctor's 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.[23] This is likely to be a reflection of the widespread under-recognition and under-diagnosis of COPD.[24]

Data are emerging that enable more accurate estimates of COPD prevalence. 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.[25-27] The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO)[28] examined the prevalence of post-bronchodilator airflow obstruction among persons ≥ 40 years in one major city from each of five Latin American countries – Brazil, Chile, Mexico, Uruguay, and Venezuela. The prevalence of COPD increased steeply with age, with the highest prevalence among those > 60 years. Prevalence in the total population ranged from 7.8% in Mexico City to 19.7% in Montevideo, Uruguay. The prevalence was appreciably higher in men than in women,[28] which contrasts with findings from European cities such as Salzburg, Austria.[29] Analyses of the GBD database suggests an overall increase in COPD prevalence in females while it has decreased in males and in some countries in the European Union between 2001 and 2019.[30] The Burden of Obstructive Lung Diseases (BOLD) program used standardized methodology comprising questionnaires and pre- and post-bronchodilator spirometry to assess prevalence and risks for COPD globally in people aged ≥ 40 years.[29,31,32] BOLD reported an overall prevalence of COPD of 11.8% (standard error (SE) 7.9) for men and 8.5% (SE 5.8) for women[33] and a substantial prevalence of COPD of 3%-11% among never-smokers.[33] BOLD examined the prevalence of COPD in north and sub-Saharan Africa and Saudi Arabia and found similar results.[34-37] Based on BOLD and other large scale epidemiological studies, it is estimated that **the global prevalence of COPD is 10.3%** (95% confidence interval (CI) 8.2%,12.8%).[25,38] With the increasing prevalence of smoking in LMICs, and aging populations in high-income countries, the prevalence of COPD is expected to rise.[39]

Morbidity

Morbidity measures traditionally include physician visits, emergency department visits, and hospitalizations. To date studies indicate that morbidity due to COPD increases with age,[23,24,28] and in patients with COPD the development of comorbidities are seen at an earlier age.[40,41] Morbidity in COPD may also be influenced by concomitant chronic

conditions (e.g., cardiovascular disease, musculoskeletal impairment, diabetes mellitus)[42] that are related to smoking, aging and/or COPD.[43]

Mortality

The World Health Organization (WHO) publishes mortality statistics for selected causes of death annually for all WHO regions.[44] However, data must be interpreted with caution because of the inconsistent use of COPD terminology. In the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (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.[45,46] Furthermore, the accuracy of COPD diagnosis codes recorded in administrative health databases is also uncertain.[47,48] In some jurisdictions, reliance on administrative health data, particularly those that only record hospitalizations, may underestimate the burden of COPD.[49] 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.[50] However, it is clear that COPD is one of the most important causes of death in most countries. For instance, in 2011, COPD was the third leading cause of death in the United States.[51] This increase in COPD-related mortality has mainly been driven by the expanding epidemic of smoking; reduced mortality from other common causes of death (e.g., ischemic heart disease, infectious diseases); the aging of the world's population, particularly in high-income countries; and scarcity of effective disease modifying therapies. Data from the GBD Study 2017 estimated a COPD-attributable death rate was 42/100,000 (4.72% of all-cause deaths)[3,52]

With these caveats in mind, it can be estimated that **globally there are around three million deaths annually due to COPD.**[53] 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.[54,55]

Economic burden

COPD is associated with significant economic burden. In the European Union, the total direct costs 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.[56] In the United States 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.[57,58] Dynamic modeling also predicts that women are expected to incur higher direct costs than men and lose more quality-adjusted life years.[58] COPD exacerbations account for the greatest proportion of the total COPD burden on the healthcare system.[59] 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 LMICs both direct and indirect medical costs may be substantial. Recent work from the WHO and other organizations suggest that inhaled medicines for COPD are poorly available and largely unaffordable in LMICs.[60] 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.[61] 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 Disability-Adjusted Life Years (DALY).[62] The DALY for a specific condition are the sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of disability. The GBD Study found that from 1990 to 2019, COPD was the primary driver of increased DALY worldwide, especially in LMICs.[21,63] The global health burden caused by COPD increasing by 25.7% from 59.2 million DALY in 1990 to 74.4 DALY in 2019 with largest increases in South East Asia, India, Sub-Saharan Africa and South America.[64] In 2005 COPD was the eighth leading cause of DALY lost across the world but by 2013 COPD was ranked as the fifth leading cause of DALY lost.[52,65] In the United States, COPD is the second leading cause of reduced DALY, trailing only ischemic heart disease.[66] Data from GBD 2017 estimated that the DALY rate was 1068.02/100,000 for COPD.[52]

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.[7] 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. The term GETomics has been recently proposed to illustrate the complex and dynamic series of interactions between Genetics and Environment over Time.[7] 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).[7]

Environmental risk factors

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.[67] Yet fewer than 50% of heavy smokers develop COPD[68] 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.[9]

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);[69] and longer life expectancy will allow greater lifetime exposure to risk factors.

Other types of tobacco (e.g., pipe, cigar, water pipe)[70-72] and marijuana[73] are also risk factors for COPD. Passive exposure to cigarette smoke, also known as environmental tobacco smoke (ETS) and second-hand smoking, may also contribute to respiratory symptoms and COPD,[74] especially after long-term exposure.[75] 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.[76] 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.[7]

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,[19] it became apparent that non-smoking risk factors were 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.[9] 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.[9]

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.[77] Household air pollution exposure is associated with an increased risk of developing COPD in LMICs[78] although the extent to which household air pollution versus other poverty-related exposures explain the association is unclear.[79-82] Almost three billion people worldwide use biomass and coal as their main source of energy for cooking, heating, and other household needs, so the population at risk worldwide is very large.[83,84] There is limited research about household air pollution related COPD or the interventions that could reduce the risk of developing it.[85]

Many of the environmental exposures in LMICs are currently unregulated and, in combination with poverty and poor nutrition, amplify the risk of airway and lung parenchymal damage. Advocacy efforts to minimize exposure to risk factors must continue, based on robust evidence from epidemiological, translational, clinical and implementation research.[9] There are no randomized controlled trials (RCTs) that have addressed the appropriate pharmacotherapy of non-smoking COPD. There is therefore an urgent need to conduct robust RCTs to better understand the most effective treatment that can be offered to non-smoking COPD. Phenotypic differences between smoking and non-smoking COPD have been reported in only a few studies. In brief, compared to COPD in smokers, non-smoking COPD is more common in females, in younger age groups, exhibits similar (or milder) respiratory symptoms and quality of life, a lesser rate of decline in lung function over time, lower neutrophils and a trend towards higher eosinophil numbers in the airway sputum, similar spirometric indices, greater small airways obstruction (respiratory oscillometry and radiology), less emphysema and a similar defect in macrophage phagocytosis of pathogenic bacteria.[86-88] Potential molecular mechanisms for non-smoking COPD include inflammation, oxidative stress, airway remodeling and lung aging.[9] However, there are still several knowledge gaps that exist. Research is urgently needed to fill these gaps, as COPD related to biomass exposure, tobacco smoking or various other causes (see below) might exhibit different clinical features and trajectories, and benefit from different approaches to both pharmacological and non-pharmacological treatments.[9]

Occupational exposures

Occupational exposures, including organic and inorganic dusts, chemical agents and fumes, are an under-appreciated environmental risk factor for COPD.[18,89] Individuals with exposure to inhalation of high doses of pesticides have a higher incidence of respiratory symptoms, airways obstruction and COPD.[90,91] 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.[92] 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.[93] An analysis of the large U.S. 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.[94] These estimates are consistent with a statement published by the American Thoracic Society that concluded that occupational exposures account for 10-20% of either symptoms or functional impairment consistent with COPD.[95] 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 (PM), ozone, oxides of nitrogen or sulfur, heavy metals, and other greenhouse gases, is a major worldwide cause of COPD, responsible for approximately 50% of the attributable risk for COPD in low and middle income countries (LMICs).[96] In never smokers, air pollution is the leading known risk factor for COPD.[97] 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,[98] accelerates lung function decline in adults and increases the risk for COPD, especially among those with additional risk factors for COPD.[99] Poor air quality from air pollution also increases the risk of COPD exacerbations, hospitalizations and mortality.[100,101] Thus, reduction in both indoor and outdoor air pollution is a key goal in the prevention and management of COPD.

Genetic factors

A significant familial risk of airflow obstruction has been observed in people who smoke and are siblings of patients with severe COPD,[102] 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 (AATD),[103] a major circulating inhibitor of serine proteases. Although AATD deficiency 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 COPD patients (range 0.08-0.24%), and a prevalence ranging from 1 in 408 in Northern Europe to 1 in 1,274 in Eastern Europe.[104]

There has been a long-standing controversy concerning the risk of heterozygotes (MZ and SZ) for the development of COPD. This has largely reflected acquisition bias but is of critical importance due to the large numbers of such individuals worldwide[105] who may potentially benefit from augmentation therapy. Recent careful sibling studies[106,107] 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 of it[108] and is not an indication for augmentation therapy (discussed in more detail in **Chapter 3**).

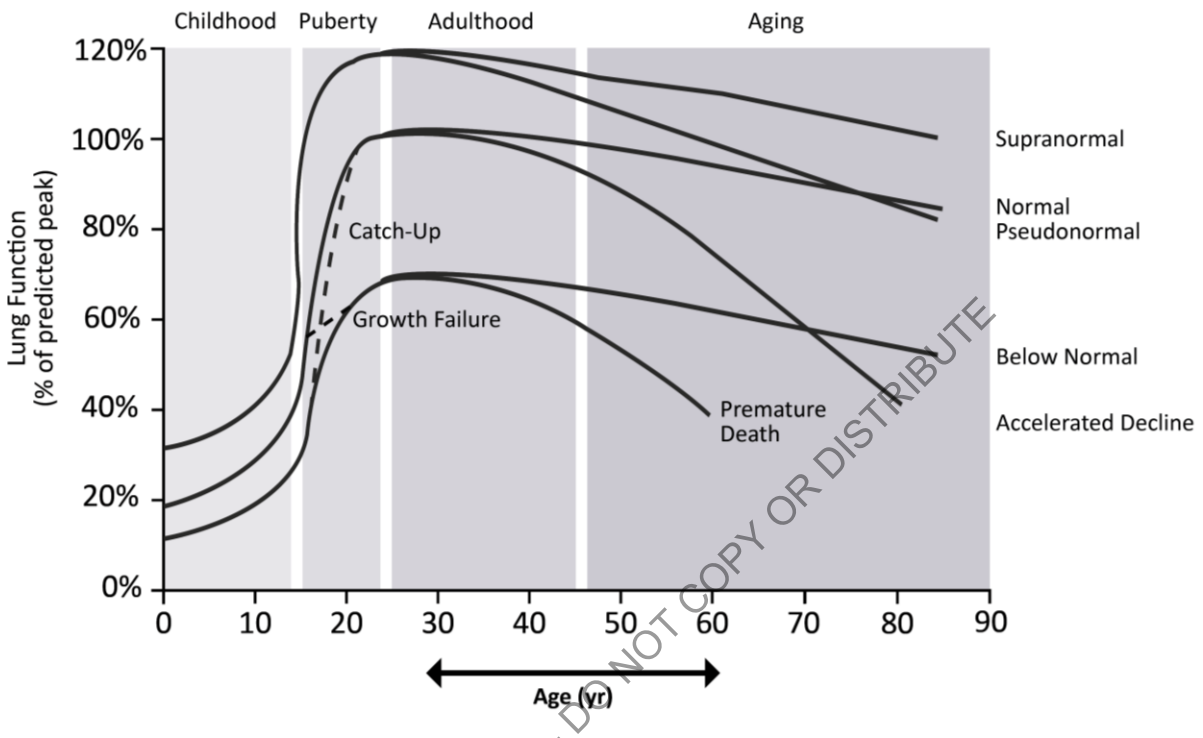
To date, hundreds of genetic variants associated with reduced lung function and risk of COPD have been identified, including genes encoding matrix metalloproteinase 12 (MMP-12), glutathione S-transferase, the alpha-nicotinic acetylcholine receptor, and the hedgehog interacting protein (HHIP).[109,110] Yet, their individual effect size is small[10] and it remains uncertain whether these genes are directly responsible for COPD or are merely markers of other causal genes.[111-115]

Trajectories of lung function: development and aging

At birth, the lung is not fully developed. It grows and matures until about 20-25 years of age (earlier in females), when lung function reaches its peak (**Figure 1.1**).[67] This is followed by a not very well defined but relatively short plateau and a final phase of mild lung function decline due to physiological lung aging. This constitutes the normal lung function trajectories labeled TR1 in **Figure 1.1**.[116] 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).[117]

FEV1 Trajectories (TR) Over the Life Course

Figure 1.1



Modified from: Agusti A, Hogg JC. Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. N Engl J Med. 2019;381:1248-56.

Spirometrically measured reduced maximal attained lung function can identify individuals who are at increased risk for the development of COPD.[16,118] A large study and meta-analysis confirmed a positive association between birthweight and FEV1 in adulthood.[119] Factors in early life termed "childhood disadvantage factors" are key determinants of lung function in adult life.[119-126] 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),[127] while the other 50% developed COPD due to abnormal lung growth and development (with normal lung function decline over time; **Figure 1.1**).[116]

Age is often listed as a risk factor for COPD because there is a physiologic decline in lung function with age. Yet, it is unclear if healthy aging as such leads to COPD or if age reflects the sum of cumulative exposures throughout life.[128] However, aging of the airways and parenchyma mimic some of the structural changes associated with COPD[128] and there is evidence of accelerated aging in patients with COPD.[121] 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 COPD patients followed over 10 years.[129] Further, persistently shorter telomeres over this observation time increase the risk for all-cause mortality.[129] Age-related epigenetic changes in DNA in immune cells are also associated with increased risk of exacerbations and mortality in COPD patients.[130,131] In the Tasmanian Longitudinal Health Study, the mixed (low FVC and low FEV1/FVC ratio) and the obstructive-only (low FEV1/FVC ratio) spirometric patterns showed the highest prevalence of COPD at age 53 (37% and 22% respectively).[125]

The term *dysanapsis* refers to an anthropometric mismatch of airway tree calibre relative to lung volume.[132,133] It was first proposed by Green and colleagues almost fifty years ago from maximal expiratory airflow variation among healthy adults.[120] There are still major gaps in our understanding of the origins and clinical implications of dysanapsis, but recent research using computed tomography (CT) has shown that: (1) it is common in the general population;[120,124,134](2) it is associated with FEV1/FVC from early adulthood;[135] (3) in explanted lungs from adult healthy donors, central airway dysanapsis (detectable by CT) extended to peripheral airways (non-visible on CT);[135] (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.[124] 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;[136-138] 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[120,122,124] and factors affecting airway tree homeostasis later in life have been implicated.[121,123] Of note, investigating the aetiology 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[117,139] opens novel opportunities for prevention, and earlier diagnosis and treatment of the disease[13] but, at the same time, has generated several nosological terms that require proper definition to avoid confusion and facilitate future research:[140]

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. Further, a biological “early” related to the initial mechanisms that eventually lead to COPD should be differentiated from a clinical “early”, which reflects the initial perception of symptoms, functional limitation and/or structural abnormalities noted. Thus, we propose to use the term “early COPD” only to discuss the “biological” first steps of the disease in an experimental setting.

Mild COPD

Some studies have used “mild” airflow obstruction as a surrogate for “early” disease.[141] This assumption is incorrect because not all patients started their journey from a normal peak lung function in early adulthood, so some of them may never suffer “mild” disease in terms of “severity” of airflow obstruction.[117] Further, “mild” disease can occur at any age and may progress or not over time.[139] Accordingly, we propose that “mild” should not be used to identify “early” COPD and used only to describe the severity of airflow obstruction measured spirometrically.

Young COPD

The term “young COPD” is seemingly straightforward because it directly relates to the chronological age of the patient. Given that lung function peaks at around 20-25 years,[67] we propose to operationally consider “young COPD” in

patients aged 20–50 years.[142] Of note, this can include patients who had never achieved normal peak lung function in early adulthood and/or those with shorter *plateau* and/or early lung function decline.[143,144] Young COPD may be associated with significant structural and functional lung abnormalities (i.e., young COPD is not necessarily synonymous with "mild" COPD) that can have a substantial impact on health and, importantly, is frequently not diagnosed and thus not treated. A family history of respiratory diseases and/or early-life events (including hospitalizations before the age of 5 years) is reported by a significant proportion of young patients with COPD, further supporting the possibility of early-life origins of COPD.[140,144]

Pre-COPD

This term has been recently proposed to identify individuals (importantly, of any age) who have respiratory symptoms and/or other detectable structural and/or functional abnormalities, in the absence of airflow obstruction on forced spirometry. These patients may (or not) develop persistent airflow obstruction (i.e., COPD) over time.[145] A recent publication highlights the need for RCTs, both in patients with 'Pre-COPD', and in young people with COPD.[146]

PRISm

The term PRISm (preserved ratio impaired spirometry) describes individuals with preserved ratio (FEV1/FVC ≥ 0.7 after bronchodilation) but impaired spirometry (FEV1 < 80% of reference, after bronchodilation).[12,147] The prevalence of PRISm in population-based studies ranges from 7.1% to 11%[148-151] and from 10.4% to 11.3% in a selected population of current and former smokers such as the COPDGene cohort.[152] The prevalence of PRISm is particularly high in current and former smokers, and it is associated with both high and low body mass index (BMI) values, female gender, obesity and multimorbidity.[148-151] PRISm is associated with increased risk of: cardiopulmonary disease; all-cause and cardiovascular mortality; hospitalization; and an increased risk of developing airways obstruction.[148,149,151,153-155]

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 FET in the second assessment.[149,151,152] 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.[156]

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 of the Tucson Epidemiological Study of Airway Obstructive Disease, adults diagnosed of asthma were found to have a 12-fold higher risk of acquiring COPD over time compared to those without asthma, after adjusting for smoking.[157] Another longitudinal study of people with asthma found that around 20% developed irreversible airflow obstruction and reduced diffusing lung capacity.[158] A third longitudinal study observed that self-reported asthma was associated with excess loss of FEV1 in the general population.[159] A study examining the pattern of lung-growth decline in children with asthma found that 11% met lung function impairment consistent with the spirometric classification of COPD in early adulthood.[160] In the European Community Respiratory Health Survey, airway hyper-responsiveness was second only to cigarette smoking as the leading risk factor for COPD, responsible for 15% of the population attributable risk (smoking had a population attributable risk of 39%).[161] 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.[157,162,163] 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 1.1**), these infants and adolescents may have been mislabeled as 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[164,165] as well as an indicator of risk of excess decline in lung function in patients with mild COPD.[166]

Chronic bronchitis

Chronic bronchitis (CB) is a common, but variable condition in patients with COPD. CB is defined by the presence of cough with expectorated sputum on a regular basis over a defined period. Variability in the prevalence of CB depends upon the definition used which differs in the regularity or duration of CB symptoms.[167] The classic description defines CB 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 CB ranges from 27-35% in large observational studies in patients with COPD.[168-170] Other factors associated with increased prevalence of CB in COPD includes male sex, younger age, greater pack-years of smoking, more severe airflow obstruction, rural location and increased occupational exposures.[167-173] Although the primary risk for CB is smoking, 4-22% of CB is found in never smokers suggesting other factors are involved.[174,175] Inhalational exposures to dusts, biomass fuels, chemical fumes or domestic heating and cooking fuels may be important.[172,173,176] Gastroesophageal reflux is also associated with an increased incidence of CB.[177,178]

Normal airway mucus is a gel comprised of 97% water and 3% solids (mucins, non-mucin proteins, cellular debris, salts and lipids) that traps inhaled toxins which are subsequentially expectorated via the processes of ciliary beating and cough.[179] Mucins are large glycoproteins, two of the secreted mucin polymers, MUC5AC and MUC5B, line the human airways.[180,181] In healthy normal individuals, MUC5AC is produced by proximal airway surface goblet cells while MUC5B is produced by surface secretory cells found throughout the airways and submucosal glands.[180-184] In COPD, MUC5B levels markedly increase due to submucosal gland hyperplasia and airway occlusion can occur.[185-187] Viruses, acrolein and many cytokines (IL-4, IL-13, IL-17, IL-23 and IL-25) can also increase MUC5AC production.[188-193]

Lung health depends upon effective mucus clearance. In disease states, thick and viscoid mucus can lead to airway inflammation and infection. Cough and dyspnea are the principal symptoms of impaired mucous clearance.[194,195] 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.[196,197] Radiographic manifestations of mucous plugging may be present and persist in patients with COPD despite a lack of CB symptoms and is associated with greater airflow obstruction, lower oxygen saturation and worsened quality of life[198,199] and all-cause mortality.[200] A high index of suspicion for mucus hypersecretion should be maintained in all patients with COPD due to the protean clinical problems that accompanies its presence.[201] How patients who have mucus hypersecretion evident on CT but do not manifest symptoms differ phenotypically and vice versa is not fully understood.

The relationship between chronic mucus production and lung function, exacerbations and mortality has been the subject of multiple investigations. In young adults without a history of asthma and normal lung function, the presence of chronic cough with sputum identified a subgroup at high risk of developing COPD independently of smoking habits.[202] In adults less than 50 years of age, CB without airflow obstruction represents an early marker for susceptibility to the long-term risk of COPD and all-cause mortality.[203] In smokers between 36 to 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.[204] Importantly, the longer chronic mucus hypersecretion is present, the greater the concurrent decrease in FEV1. While both MUC5AC and MUC5B have

been associated with CB symptoms, among current smokers, it is sputum MUC5AC that has been associated more specifically with increased exacerbation frequency, increased symptoms and greater lung function decline.[205,206] Large epidemiologic studies have shown after adjustment for height, age and smoking history, men with cough or phlegm and women with cough show accelerated loss of lung function.[207] Other studies have suggested an association between chronic sputum production and lower lung function, or greater FEV1 decline in patients with COPD.[207-211]

The association of 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;[212-214] other studies state sputum production has an independent role in predicting both overall and COPD-specific mortality.[171,215-217] In the Copenhagen city heart study, chronic mucus hypersecretion was associated with pulmonary infection that was implicated in 54% of the deaths.[218] Moreover, chronic mucus hypersecretion was associated with excessive FEV1 decline and increased COPD hospitalizations.[210] In patients with advanced emphysema, chronic bronchitis has been associated with increased hospitalizations and mortality.[219] In patients with non-obstructive chronic bronchitis, increased all-cause and respiratory disease related mortality has been reported.[220,221]

Infections

A history of severe childhood respiratory infections has been associated with reduced lung function and increased respiratory symptoms in adulthood.[161] 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.[222] Chronic bronchial infection, particularly with *Pseudomonas aeruginosa*, has been associated with accelerated FEV1 decline.[223] Tuberculosis (TB) is a risk factor for COPD (23 studies; pooled odds ratio 2.59 (95% CI 2.12,3.15); pooled prevalence of COPD in patients with prior pulmonary TB was 21% (95% CI: 16–25%)).[224,225] Tuberculosis is both a differential diagnosis for COPD and a potential comorbidity.[226,227] Finally, HIV patients are at increased risk of COPD compared to HIV negative controls (11 studies; pooled odds ratio for 1.14 (95% CI 1.05,1.25))[228,229] probably due to methylation disruptions in airway epithelium.[230] IgG subclass deficiency has also been observed in hospitalized patients with COPD and this was associated with a significantly increased risk of mortality.[231]

Sex

Sex related differences in immune pathways and 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.[232] Although controversial, some studies have suggested that women may be more susceptible to the harmful effects of smoking than men,[26,233-235] leading to more severe disease for the equivalent quantity of cigarettes consumed.[236] This notion has been validated in animal studies and human pathology specimens, which have demonstrated a greater burden of small airway disease in females compared with males with COPD despite a similar history of tobacco smoke exposure.[237,238] A systematic review and meta-analysis of the global prevalence of COPD reported sex-based prevalence differences across WHO Global Burden of Disease sub-regions. In females the highest prevalence of COPD was observed in North America (8.07% vs 7.30%) and in urban settings (13.03% vs 8.34%). Using the World Bank's income categories prevalence was highest in upper-middle income countries for males (9.00%) and in high-income countries for females.

Race and ethnicity

An ATS workshop report[239] 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.[239]

Socioeconomic status

Poverty is consistently associated with airflow obstruction[240] and lower socioeconomic status is associated with an increased risk of developing COPD.[241,242] 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.

PATHOBIOLOGY

In patients with COPD pathological changes can be found in the airways, lung parenchyma, and pulmonary vasculature.[243] These include inflammatory and structural changes which increase with the severity of airflow obstruction and can persist on smoking cessation (**Figure 1.1**).

Inflammatory changes

The inflammation observed in the lungs of COPD patients 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[244] which attract inflammatory cells from the circulation (chemotactic factors), amplify the inflammatory process (via proinflammatory cytokines), and induce structural changes (via growth factors).[245] Lung inflammation can persist after smoking cessation through as yet unclear mechanisms, although autoantigens and perturbations in the lung microbiome may play a role.[246,247] Systemic inflammation may also be present and could play a role in the comorbid conditions frequently found in patients with COPD.[244] 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.[248] albeit some patients with COPD have an inflammatory pattern with increased eosinophils and ILC2 cells, similar to that of asthma.[249]

Oxidative stress can also contribute to COPD.[244,250] Biomarkers of oxidative stress (e.g., hydrogen peroxide, 8-isoprostane) are increased in the exhaled breath condensate, sputum, and systemic circulation of COPD patients. 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.[226,251]

Structural changes

There is compelling evidence for an imbalance in the lungs of COPD patients between proteases derived from inflammatory and epithelial cells that break down connective tissue components and antiproteases that counterbalance this action.[252] 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.[253]

Peribronchiolar fibrosis and interstitial opacities have been reported in patients with COPD and in asymptomatic smokers.[246,254-256] An excessive production of growth factors may be found in smokers and patients with COPD.[257] 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.[258] This may be a contributing factor to the development of small airways obstruction.[259]

The lung vasculature can also be altered in patients with COPD, even those with mild disease.[260]

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.[261] The reduced number of small airways identified in patients with COPD[261] may be due to an enhanced loss of airways and/or to deficient lung development (see dysanapsis above; **Figure 1.1**).[139] Collectively, all 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.[262]

Hyperinflation

Hyperinflation occurs when gas volume in the lungs is increased compared to normal values at the end of spontaneous expiration.[263,264] Hyperinflation is clinically relevant in patients with COPD and contributes to dyspnea,[265-268]impaired exercise tolerance,[269-271] increased number of hospitalizations,[272] development of respiratory failure[273] and increased mortality.[270,272,274] In patients with COPD, hyperinflation arises due to loss of elastic recoil and expiratory flow obstruction.[275] 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.[263] 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.[263,264]

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.[276,277] 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.[263,269]

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.[278,279] 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.[280] Hyperinflation can also be detected on chest imaging but standardization is lacking.[263]

Hyperinflation can be addressed with bronchodilators,[281,282] supplemental oxygen,[283,284] heliox,[285] pulmonary rehabilitation,[286] pursed lip breathing,[287] inspiratory muscle training[288] or in selected cases of emphysema causing severe hyperinflation, lung reduction surgery[289] or bronchoscopic lung reduction techniques.[290,291]

Pulmonary gas exchange abnormalities

Structural abnormalities in the airways, alveoli and pulmonary circulation in patients with COPD alter the normal ventilation-perfusion (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.[292] Rarely, reduced ventilation may also be due to reduced ventilatory drive (e.g., sedatives and hypnotic drugs), causing hypercapnic respiratory failure and acidosis.[293] Parenchymal destruction due to emphysema also leads to decreased lung diffusing capacity (DLco). In general, pulmonary gas exchange worsens as the disease progresses.

Pulmonary hypertension

In smokers with normal spirometry and in COPD patients with mild airflow obstruction there may be abnormalities in the pulmonary circulation that include intimal hyperplasia and smooth muscle hypertrophy/hyperplasia.[294-297] Moreover, an inflammatory response in 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.[298,299] 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.[300] Interestingly, the diameter of pulmonary artery as measured on computed tomography (CT) scans has been shown to relate to the risk of suffering exacerbations, independent of previous history of exacerbations.[301]

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,[302] and worsening of VA/Q abnormalities that can result in arterial hypoxemia with or without hypercapnia.[303] Other conditions, such as pneumonia, pulmonary, and/or heart failure, among others, may mimic or aggravate an exacerbation of COPD, and need to be considered in the clinical management of these episodes.[304] See **Chapter 4** for an extended discussion on exacerbations.

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.[305] Airflow obstruction and particularly hyperinflation affect cardiac function.[302] 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.[127] Accordingly, most efforts have been devoted to the study of the pathogenetic mechanisms of only one major cause of COPD (cigarette smoking), failing to expand the horizon about the heterogeneity of processes that we know can contribute to its final clinical presentation.[7] 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*.[306] **Figure 1.2** combines two recent taxonomic proposals developed independently.[6,307] 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.

Proposed Taxonomy (Etiotypes) for COPD

Figure 1.2

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)

CHAPTER 2: DIAGNOSIS AND ASSESSMENT

KEY POINTS:

- 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 for the disease, but **spirometry** showing the presence of a post-bronchodilator FEV1/FVC < 0.7 is **mandatory** to establish the diagnosis of COPD.
- The goals of the initial COPD assessment are to determine the severity of airflow obstruction, the impact of disease on the patient's health status, and the risk of future events (such as exacerbations, hospital admissions, or death), to guide therapy.
- Additional clinical assessment, including the measurement of lung volumes, diffusion capacity, exercise testing and/or lung imaging may be considered in COPD patients with persistent symptoms after initial treatment.
- Concomitant chronic diseases (multimorbidity) occur frequently in COPD patients, 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.

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.[45]

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[308] 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*.[309] 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.)

Dyspnea

Dyspnea is a cardinal symptom of COPD and a major cause of the disability and anxiety associated with the disease.[310] Dyspnea comprises a sensory and an affective component.[311] Typically COPD patients describe their dyspnea as a sense of increased effort to breathe, chest heaviness, air hunger, or gasping.[312] However, the terms used to describe dyspnea may vary both individually and culturally.[312]

Dyspnea is highly prevalent across all stages of airflow obstruction.[313] 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.[314]

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.[315,316]

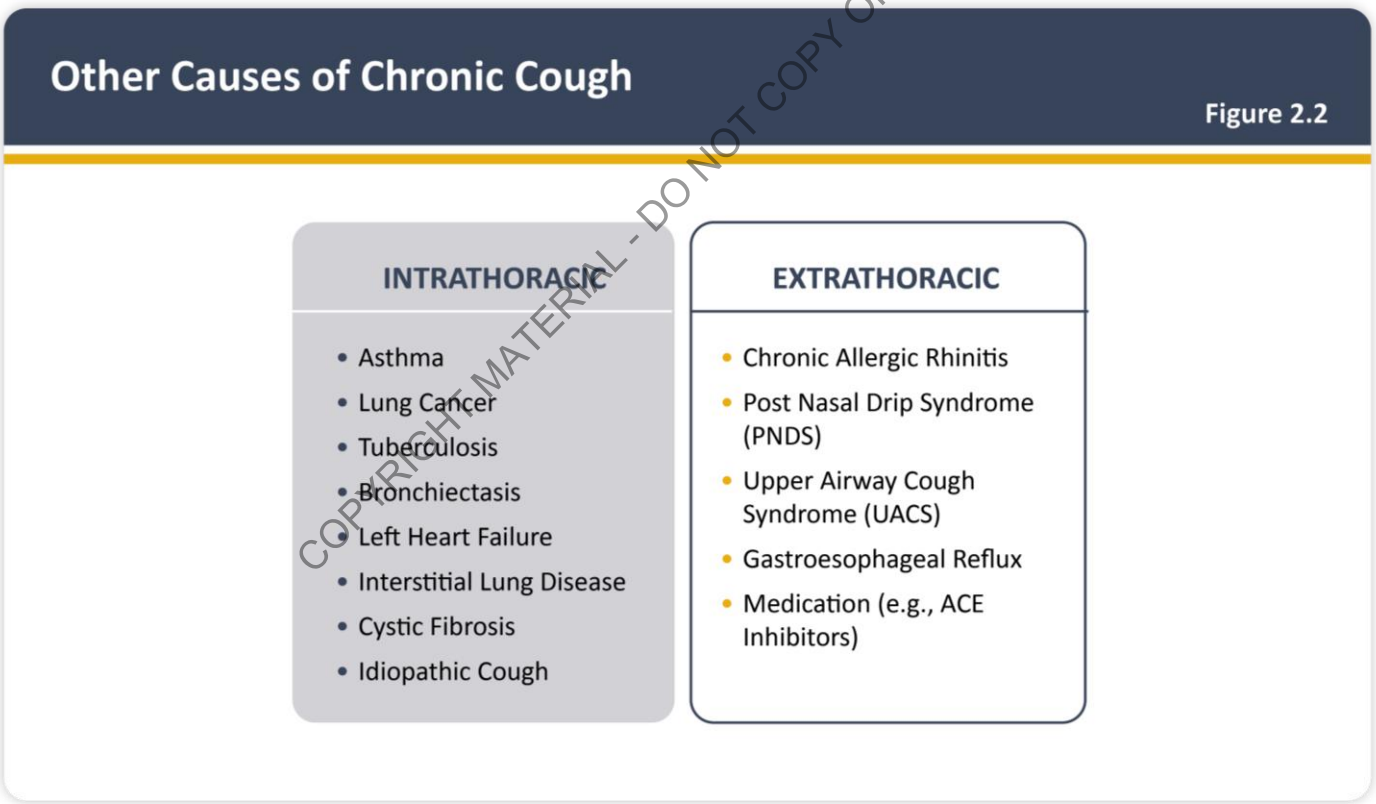
Dyspnea measured by the 5-level modified Medical Research Council scale is integrated in the GOLD clinical classification scheme (see below) because patients with high dyspnea scores incur higher healthcare resource utilization and costs.[317] Dyspnea in daily life can be measured by a number of detailed questionnaires that are more discriminant and sensitive to change.[318,319]

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.[320] 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 severe COPD 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

COPD patients 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,[321] 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.[204] Patients producing large volumes of sputum may have underlying bronchiectasis.[322,323] The presence of purulent sputum reflects an increase in inflammatory mediators,[324,325] and its development may identify the onset of a bacterial exacerbation, though the association is relatively weak.[325,326]



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 wheezes 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.[327] People with COPD describe their fatigue as a feeling of "general tiredness" or as a feeling of being "drained of energy".[328,329] 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 severe and very severe COPD.[330-332] They have prognostic importance[333,334] 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 presence of *cor pulmonale*. Symptoms of depression and/or anxiety merit specific enquiry when obtaining the medical history because they are common in COPD,[335] are associated with poorer health status, increased risk of exacerbations, and emergency hospital admission, and are treatable.[336]

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.[337] Most other potential differential diagnoses are easier to distinguish from COPD (**Figure 2.3**).

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.*

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).

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,[338,339] 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**.[340,341] Despite its good sensitivity, peak expiratory flow measurement alone cannot be reliably used as the only diagnostic test because of its weak specificity.[342,343]

Considerations in Performing Spirometry

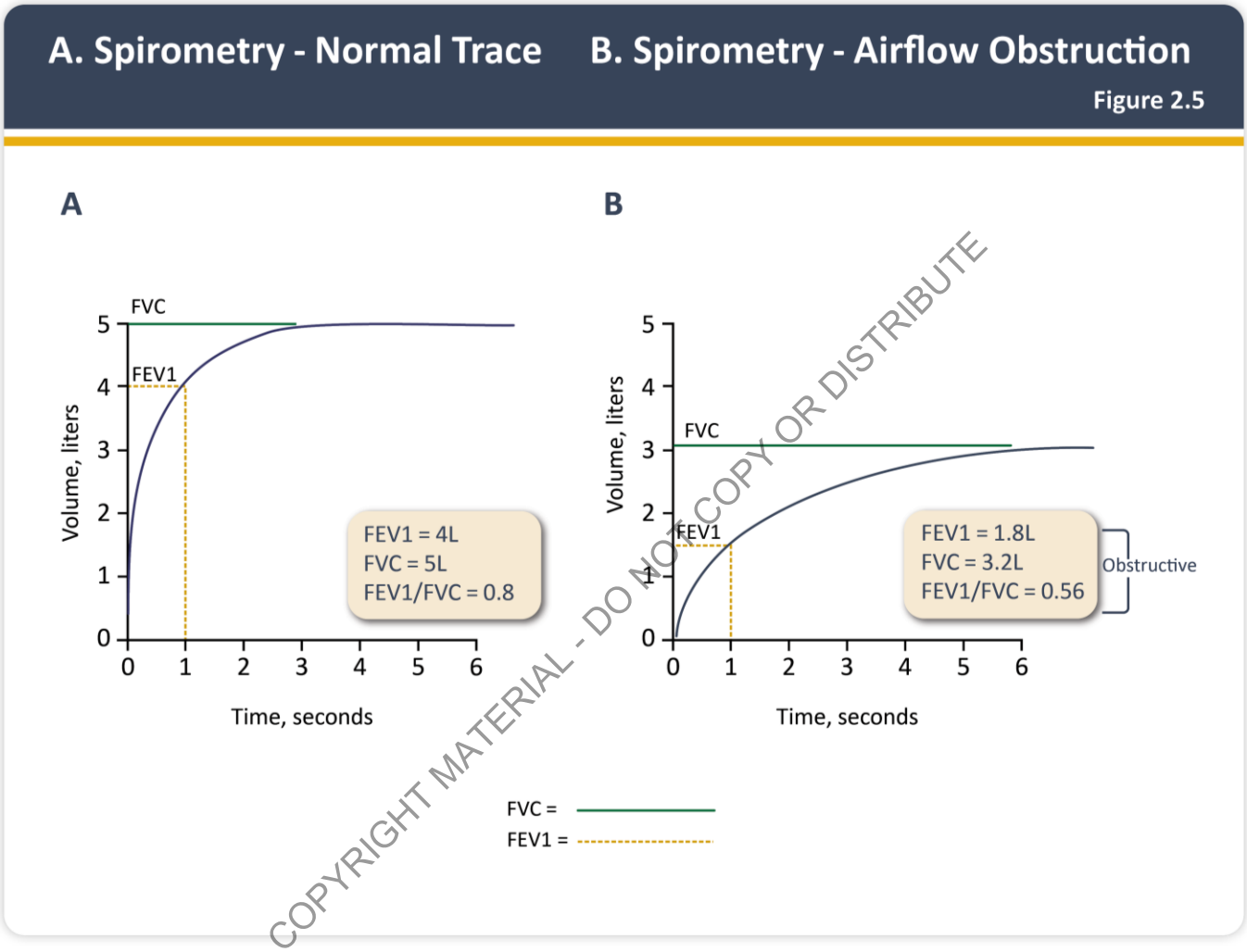
Figure 2.4

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 taken from the technically acceptable curve with the largest sum of FVC and FEV1
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; [b]Pellegrino *et al.* Eur Respir J 2005; 26(5): 948.

As shown in **Figure 2.5**, forced spirometry measures: (1) the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC); (2) the volume of air exhaled during the first second of this maneuver (forced expiratory volume in one second, FEV1); and (3) the ratio of these two measurements (FEV1/FVC). Spirometry measurements are evaluated by comparison with reference values[341,344] based on age, height and sex.

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).



In line with other National and International guidelines, GOLD has recommended 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.[345] However, it is now recognised that the bronchodilator response has little value in differentiating asthma from COPD,[346] that pre-bronchodilator values are reproducible[347] and obstruction only found on post-bronchodilator measurements is uncommon.[348] Obtaining post-bronchodilator values is more time consuming and this may deter clinicians from performing spirometry. GOLD states that pre-bronchodilator spirometry can be used as an initial test to investigate whether symptomatic patients have airflow obstruction. 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 FEV1/FVC < 0.7. 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 < 0.7 that increases to ≥ 0.7 post-bronchodilator have been shown to have an increased risk of future development of COPD, and should be followed closely.[349]

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. It should be noted that the use of a fixed FEV1/FVC ratio (< 0.7) to define airflow obstruction may result in over-diagnosis of COPD in the elderly,[350,351] and under-diagnosis in approximately 1% of young adults,[351-353] especially in mild disease, compared to using a cut-off based on the lower limit of normal (LLN) values for FEV1/FVC. 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 may help when deciding how to best manage this small number of patients.

The LLN values are based on the normal distribution and classify the bottom 5% of the healthy population as abnormal. From a scientific or clinical perspective, it is difficult to determine which of these criteria will result in optimal COPD diagnostic accuracy. However, LLN values are highly dependent on the choice of valid reference equations using post-bronchodilator FEV1, and 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. Using the fixed ratio is not inferior to LLN regarding prognosis.[354]

It is important to emphasize that airflow obstruction that is not fully reversible is not specific for 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.

Normal spirometry may be defined by a new approach from the Global Lung Initiative (GLI).[355,356] Using GLI equations, *z* scores (the number of standard deviations by which the value of a raw score (i.e., an observed value or data point) is above or below the mean value of what is being measured) were calculated for FEV1, FVC, and FEV1/FVC. The results were compared to fixed ratio data. The findings suggest that among adults with GLI-defined normal spirometry, the use of a fixed ratio may misclassify individuals as having respiratory impairment. It is important that these findings are reproduced in other cohorts.

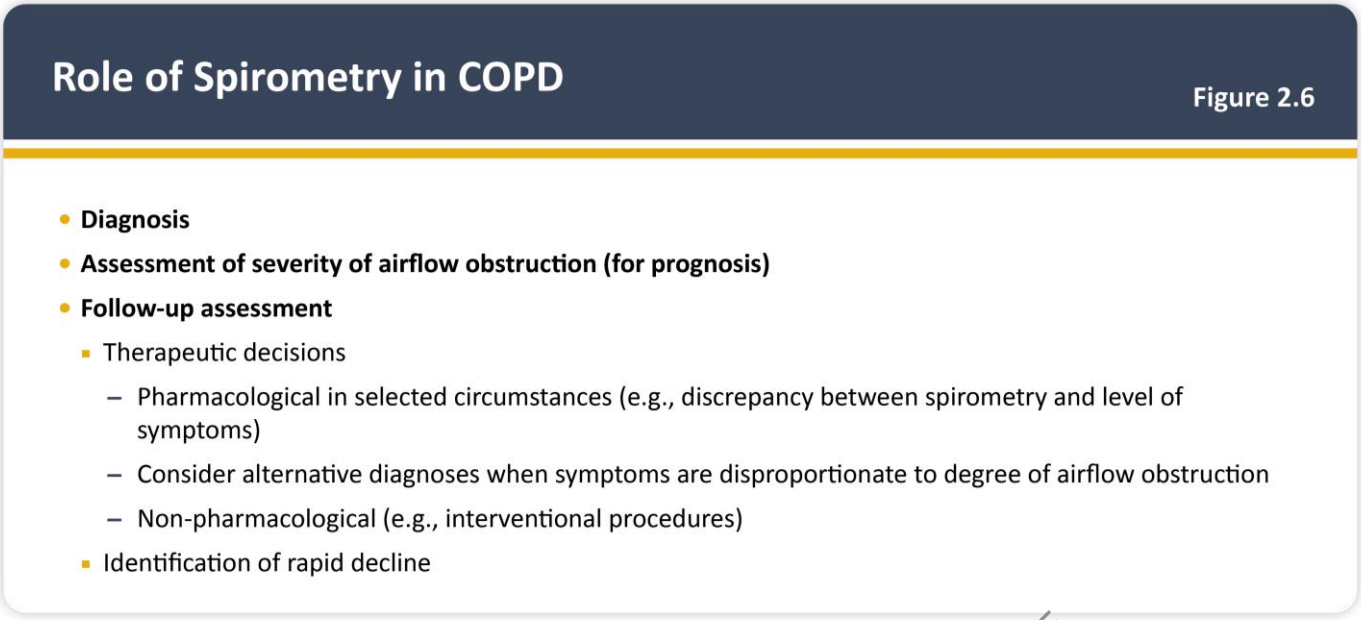
Importantly, the risk of misdiagnosis and over-treatment of individual patients using the fixed ratio as a diagnostic criterion is limited, as spirometry is only one biologic measurement to establish the clinical diagnosis of COPD in the appropriate clinical context (symptoms and risk factors). Diagnostic simplicity and consistency are crucial for the busy clinician. Thus, GOLD favors the use of the fixed ratio over LLN.

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 0.60 and 0.80, as in some cases the ratio may change as a result of biological variation when measured at a later interval.[357,358] If the initial post-bronchodilator FEV1/FVC ratio is less than 0.60 it is very unlikely to rise spontaneously above 0.7.[357]

While post-bronchodilator spirometry is required for the diagnosis and assessment of COPD, assessing 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.[359] 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.[360] Accordingly, it is not necessary to stop inhaled medication before obtaining spirometry measurements during follow-up of patients. **Figure 2.6** shows the role of spirometry in patients with COPD.

Role of Spirometry in COPD

Figure 2.6



Interpretation of the severity of lung function impairment is dependent on having appropriate reference values. The Prospective Urban and Rural Epidemiological (PURE) study analyzed pre-bronchodilator spirometry data from 153,996 healthy people with less than 5 pack-year smoking histories in 17 countries and observed wide variation in lung function.[46] Compared with individuals living in North America or Europe, people living in Southeast Asia had FEV1 values that were on average 31% lower, adjusted for age, height and sex. Similarly, those living in sub-Saharan Africa, East Asia, Middle East and South America had FEV1 values that were on average 21%, 13%, 11%, and 6% lower than individuals living in North America or Europe, respectively, independent of age, height, sex, and smoking status.[46] Unless relevant predicted values are used the severity of airflow obstruction will be overestimated. Even in high income countries, lung reference values change over time and require periodic revision.[361]

SCREENING AND CASE-FINDING

The role of screening spirometry for the diagnosis of COPD in the general population is controversial.[362,363] In asymptomatic individuals without any significant exposures to tobacco or other risk factors, screening spirometry is probably not indicated; whereas in those with symptoms or risk factors (e.g., > 20 pack-years of smoking, recurrent chest infections, early life events), the diagnostic yield for COPD is relatively high and spirometry should be considered as a method for early case finding.[364-366]

Both FEV1 and FVC predict all-cause mortality independent of tobacco smoking, and abnormal lung function identifies a subgroup of smokers at increased risk for lung cancer. This has been the basis of an argument that spirometry should be employed as a global health assessment tool.[367-369] A risk score based on routine data from electronic health records in primary care may facilitate case-finding and be cost-effective.[370,371] However, data to support that population-based screening spirometry is effective in directing management decisions or in improving COPD outcomes in patients who are identified before the development of significant symptoms is weak.[363] This may reflect the design and application of current case finding instruments that have not been utilized to identify patients with undiagnosed COPD who are most likely to benefit from existing therapies.[372,373] Novel approaches to screening have been developed that incorporate exposures, symptoms and health care utilization and simple peak flow measurement; one of these has been developed for low- and middle-income countries and has shown discriminatory properties.[374,375] GOLD advocates active case finding[364,376,377] i.e., performing spirometry in patients with symptoms and/or risk factors, but not screening spirometry. Systematic active case-finding in a primary care setting via mail-out of a screening

questionnaire was also found to be an effective way to identify undiagnosed COPD patients.[378] The potential use of 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.[41]

COPD case-finding tools have been created based on existing epidemiologic literature or expert opinion[373,379,380] or with a multimodality approach.[374,375] Increasingly, it appears that the combination of questionnaires with simple physiological measurements enhances the operating characteristics and performance of these approaches.[379,381,382] In a variety of settings case-finding has been able to identify previously undiagnosed COPD.[378,381,383,384] In general, these tools identify a high proportion of patients with mild or minimally symptomatic disease, exhibiting modest sensitivity and specificity,[385] or higher specificity but low sensitivity.[386] COPD screening/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 but with limited data suggesting a significant impact on patient outcomes.[378,387-389] In the Veterans Affairs system, the use of a clinical decision support system algorithm that incorporates case-finding for COPD and AATD, improved COPD over- and under-diagnosis and screening rates of AATD in a primary care setting.[390] It remains vital to critically assess how the introduction of case finding approaches can optimally improve clinician behavior, enhance health care utilization, and improve patient outcomes while ensuring that patients identified with these techniques have access to affordable and clinically and cost-effective interventions.[2,391,392] 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 elevated symptoms, risk of exacerbations or hospitalization.[393]

Screening for COPD in targeted populations

The United States Preventative Service Task Force (USPSTF) recommended against screening for COPD in asymptomatic adults.[394] This recommendation was based upon a systematic review of data from asymptomatic or mildly symptomatic COPD patients enrolled in pharmacological or non-pharmacological clinical trials. This recommendation is not applicable to populations at increased risk for COPD (e.g., those undergoing annual low dose chest computed tomography (LDCT) for lung cancer detection, particularly when airways or parenchymal abnormalities are found incidentally) or with radiologically identified structural abnormalities found on chest imaging done for clinical respiratory complaints (e.g., emphysema, airway wall thickening, bronchiectasis, etc.).

Leveraging lung cancer imaging for COPD screening

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. Clinical trials have shown annual LDCT significantly improves survival.[395,396] 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.[395,397-399] Thoroughly assessing symptoms and performing spirometry in individuals undergoing LDCT for lung cancer screening therefore represents a unique opportunity to simultaneously screen patients for both the presence of unrecognized symptoms of COPD and airflow obstruction.

Studies that have evaluated patients 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%.[398,400,401] Male sex, younger age, lower smoking duration and being asymptomatic were associated with detection of airflow obstruction without a prior diagnosis of COPD.[401] Those without a prior diagnosis of COPD were less symptomatic, however, the prevalence of symptoms was still high and 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.[368,402-407]

In a lung cancer screening cohort, over half of those with visually detected emphysema had airflow obstruction.[408]

Quantitative analysis of density can also be used to detect COPD with varying sensitivity and specificity depending on the threshold chosen. In the National Lung Cancer Screening Trial (NLST), among individuals > 65 years, a threshold of 1% quantitative emphysema was associated with a sensitivity of around 65% for women and 75% for men and a specificity of over 70% and 65% respectively.[409] 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.[410]

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.[368,395,396,403-407]

Leveraging incidental lung imaging abnormalities for COPD screening

Besides cigarette smoking other factors can increase the risk of COPD (e.g., developmental, genetic, 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 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.[368,403-407]

Emphysema is a hallmark of COPD and easily detected on chest imaging, either through visual inspection via a radiologist or through quantitative lung density.[408-410] Lung imaging may also identify other abnormalities that may indicate the presence of COPD including air trapping, airway wall thickening and mucus plugging.[401,402,411-413] These abnormalities may not only indicate the presence of airflow obstruction but indicate patients that might have a more rapid decline in lung function and worse quality of life.[414-417]

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.

There is currently a missed opportunity to perform spirometry in people at high risk of having COPD during lung cancer screening programs or when incidental lung abnormalities are found on imaging that may indicate the presence of COPD. The use of spirometry in targeted patients undergoing lung cancer screening or when incidental imaging abnormalities are found consistent with parenchymal or airway manifestations of airways disorders is recommended by GOLD.[418]

INITIAL ASSESSMENT

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

- 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 (% reference). The specific spirometric cut points are proposed for purposes of simplicity (**Figure 2.7**).

GOLD Grades and Severity of Airflow Obstruction in COPD (based on post-bronchodilator FEV1) Figure 2.7

In COPD patients (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

Symptoms

Because there is only a weak correlation between the severity of airflow obstruction (**Figure 2.7**) and the symptoms experienced by the patient or the impairment of their health status,[419,420] formal assessment of symptoms using validated questionnaires is required.

Dyspnea questionnaire: the modified Medical Research Council (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.[421] (**Figure 2.8**) Of note, the mMRC score relates well to other multidimensional health status measures[422] and predicts future mortality risk.[423,424]

Modified MRC Dyspnea Scale

Figure 2.8

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: ATS (1982) Am Rev Respir Dis. Nov;126(5):952-6.

Multidimensional questionnaires

It is now recognized that COPD impacts patients beyond dyspnea.[425] For this reason, multidimensional questionnaires are recommended. The most comprehensive disease-specific health status questionnaires such as the Chronic Respiratory Questionnaire (CRQ)[426] and St. George's Respiratory Questionnaire (SGRQ)[427] are important research tools but they are too complex to use in routine practice. Shorter comprehensive measures, such as the COPD Assessment Test (CAT™) and the Clinical COPD Questionnaire (CCQ©) have been developed and are suitable for use in the clinic. Below we discuss the CAT™ and the SGRQ.

The CAT™* is an 8-item questionnaire that assesses health status in patients with COPD (**Figure 2.9**).[428] 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.[429]

* 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.

CAT™ Assessment

Figure 2.9

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: ☐

The SGRQ is the most widely documented comprehensive measure; scores < 25 are uncommon in diagnosed COPD patients[168] and scores ≥ 25 are very uncommon in healthy persons.[430,431] 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 CAT™ is 10.[432] 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.[433] 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.[433]

Exacerbation risk

Exacerbations of COPD (ECOPD) are episodes of acute respiratory symptom worsening often associated with increased local and systemic inflammation (see **Chapter 4**).[434-437] ECOPD are key events in the natural history of the disease because they impact significantly on 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 most of the healthcare costs of COPD.[438] ECOPD rates vary greatly between patients[439] and during follow-up.[440] The best predictor of having

frequent exacerbations (defined as two or more exacerbations per year) is the previous history of exacerbations.[439] Worsening of airflow obstruction is associated with an increasing prevalence of exacerbations, hospitalization[377,441] and risk of death.[168,442]

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 and blood eosinophil counts are recommended by GOLD to guide the use of ICS as part of pharmacological management (see **Chapter 3**, **Figure 3.7** & **Figure 3.9**).[443-448]

There is evidence that on average blood eosinophil counts are higher in COPD patients, although there is marked overlap with controls.[449,450] Higher blood eosinophil counts in COPD patients are associated with increased lung eosinophil numbers and the presence of higher levels of markers of type-2 inflammation in the airways, although the concordance between blood and lung/airways T2 biomarkers is not strict.[451,452] These differences in airway inflammation may explain the differential response to ICS treatment according to blood eosinophil counts.[453]

The repeatability of blood eosinophil counts in a large primary care population appears reasonable,[454] although greater variability is observed at higher thresholds.[455] Better reproducibility is observed at the lower thresholds (e.g., 100 cells/µL).[456] Blood eosinophil counts can help clinicians estimate the likelihood of a beneficial preventive response to the addition of ICS to regular bronchodilator treatment, and thus can be used as a biomarker in conjunction with clinical assessment when making decisions regarding ICS use.

Cohort studies have produced differing results with regard to the ability of blood eosinophils to predict future exacerbation outcomes, with either no relationship[457] or a positive relationship reported.[458,459] 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 COPD patients. Greater FEV1 decline was observed in mild to moderate COPD patients with higher blood eosinophil counts in a population where ICS use was low,[460] 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.[461]

Multimorbidity

People with COPD often suffer other concomitant chronic diseases (multimorbidity). This can occur in patients with mild, moderate or severe airflow obstruction.[168] Multimorbidity influences mortality and hospitalizations independently of the severity of airflow obstruction,[462] 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 cardiovascular disease,[42] metabolic syndrome, osteoporosis, depression and anxiety, likely in relation to shared risk factors (e.g., aging, smoking, alcohol, diet and inactivity).[438,463-465] Besides, COPD itself may increase the risk for other comorbid diseases (e.g., COPD (particularly emphysema) and lung cancer).[466,467] 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.[468] 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

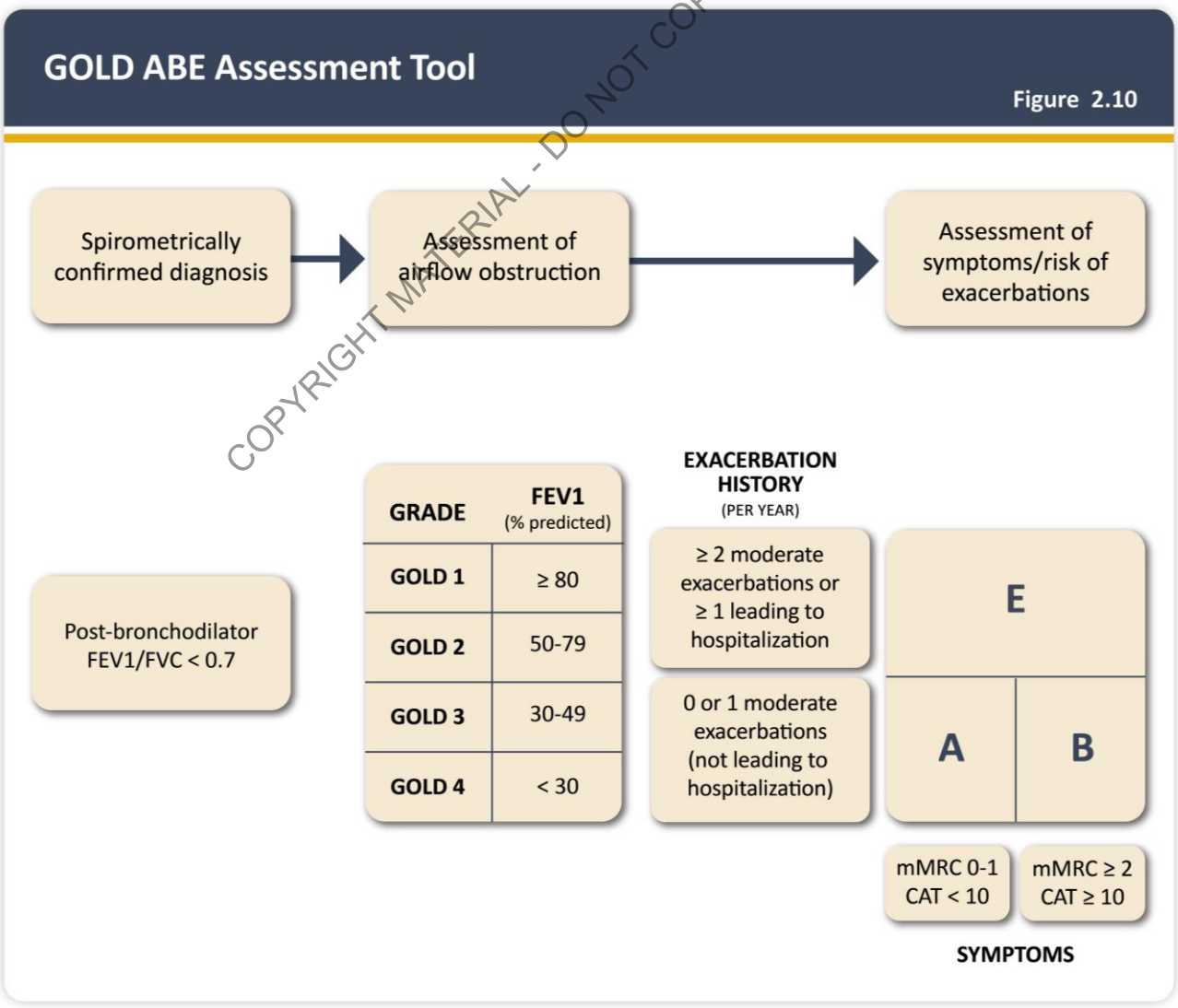
dysfunction is a modifiable source of exercise intolerance by rehabilitation.[469] A more detailed description of the management of COPD and comorbidities is provided in **Chapter 5**.

Combined initial COPD assessment

In 2011, GOLD proposed to move from the simple spirometric grading system for disease severity assessment and treatment to a combined assessment strategy based on the level of symptoms (mMRC or CAT™), 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.[420,442,470,471]

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 2.10** presents this proposal. 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 would have to be validated by appropriate clinical research.



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., computed tomography) and/or comorbidities (e.g., ischemic heart disease) that might impact patient symptoms.

Physiological tests

Lung volumes

COPD patients exhibit gas trapping (a rise in residual volume) from the early stages of the disease, and as airflow obstruction worsens, static hyperinflation (an increase in total lung capacity) occurs, particularly during exercise (dynamic hyperinflation). These changes can be documented by body plethysmography, or less accurately by helium dilution lung volume measurement. These measurements help characterize the severity of COPD but are not essential to patient management.

Carbon monoxide diffusing capacity of the lungs (DLco)

The single breath DLco measurement [472] evaluates the gas transfer properties of the respiratory system. DLco is well-standardized and with valid predicted values of practical utility.[344,473-475] 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.[476] 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,[477-479] and increased risk of death, independently of the severity of airflow obstruction and other clinical variables.[480-483] Additionally, in COPD patients, low DLco values help preclude surgical lung resection in patients with lung cancer[484] while in smokers without airflow obstruction, values < 80% predicted (as a marker of emphysema) signal an increased risk for developing COPD over time.[485]

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.[486,487] 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 arterial 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.[488] 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 and assessment of physical activity

In some cases, patients may complain of minimal symptoms despite severe airflow obstruction. This may be due to reduced dyspnea perception[489] and/or life-style adaptations (sedentarism) to reduce dyspnea generation. In these cases, exercise tests such as the 6-minute walking distance 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, objectively measured exercise impairment, assessed by a reduction in self-paced walking distance[490,491] or during incremental exercise testing in a laboratory,[492] is a powerful indicator of health status impairment and

predictor of prognosis.[493] 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[494] and are used to assess the effectiveness of pulmonary rehabilitation. Both the paced shuttle walk test[495] and the self-paced 6-minute walk test can be used.[496,497] As the course length has a substantial impact on the distance walked, existing reference equations established for a 30 meter course cannot be applied to predict the distance achieved on shorter courses.[498]

Monitoring of physical activity may be more relevant regarding prognosis than evaluating only exercise capacity.[499] This can be conducted using accelerometers or multi-sensor instruments.

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 rapid tapering of the vascular markings.

Computed tomography (CT)

In recent years computed tomography (CT) has become increasingly available, both as a research tool and in clinical practice, providing additional insights into the structural and pathophysiologic abnormalities present in COPD. This has led to enhanced understanding of disease phenotypes, severity, and outcomes.

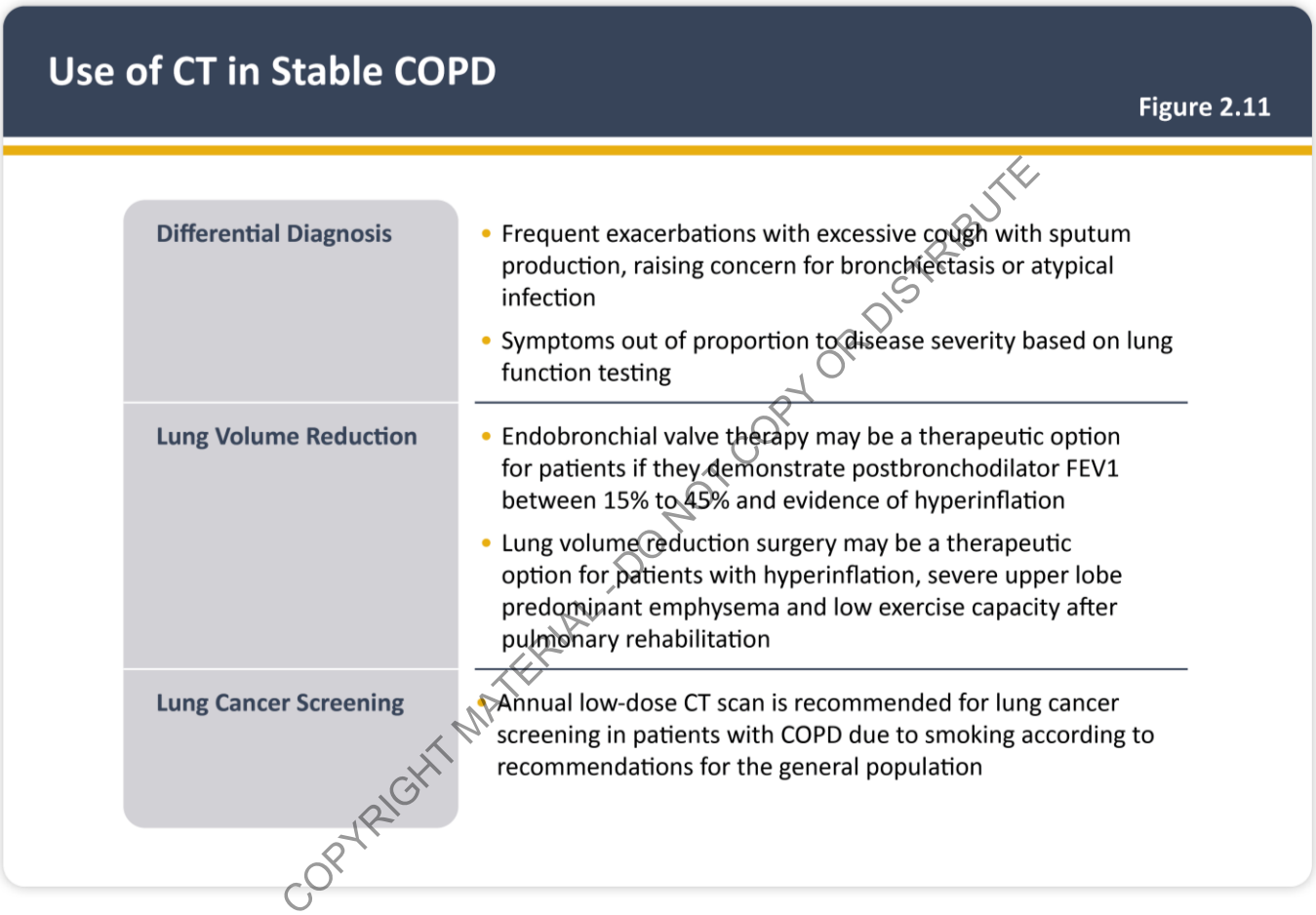
From a clinical perspective, emphysema distribution and severity can be readily discerned and can assist with decision making for lung volume reduction surgery (LVRS) or endobronchial valve placement. While historically this has been performed based on expert radiologist visual analysis, particularly for LVRS, increasingly quantitative analysis for emphysema extent, location and fissure integrity is also being performed to assist with endobronchial valve therapy decision making. The presence of emphysema is also associated with more rapid progression of FEV1 decline and mortality and increased likelihood of development of lung cancer.[483] Further, about 30% of COPD patients have bronchiectasis visible on CT, which is now the radiological examination of choice when this is suspected. Bronchiectasis is associated with increased exacerbation frequency and mortality,[500] although it is not yet known whether treatment according to bronchiectasis guidelines influences these clinical outcomes.

Historically chest CT has not been considered a requirement for COPD diagnosis, but increasingly more COPD patients do undergo 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. First, this is due to the recent lowering of the age for lung cancer screening to 50 years old. Second, the advent of endobronchial valve therapy for emphysema has also expanded the pool of patients where CT evaluation may be helpful, in particular patients with post-bronchodilator FEV1 between 15%-45% and evidence of marked hyperinflation on plethysmography.[501] In such instances, quantification of emphysema on chest CT by lobe and ensuring fissure integrity of the target lobe is required as part of the evaluation process.

More detailed computer assisted CT analysis enables quantification of airway abnormality as well, although these methods are less well standardized than the methods used for emphysema quantification. Hence, historically airway measures have been used more in the research setting. While segmental and subsegmental measures of wall thickness can be made directly, measurements of small airways (< 2 mm diameter) must be inferred by comparing inspiratory and expiratory to identify areas of non-emphysematous gas trapping. Validated algorithms are becoming increasingly available, even in the clinical setting, that can identify small airway abnormality through this method.[502,503] Small

airway abnormality may also be present even among individuals without detectable spirometric obstruction and identify individuals at increased risk for lung function decline.[504] It should also be noted that CT imaging of the chest can also provide a wealth of information about COPD comorbidities including coronary artery calcium, pulmonary artery enlargement, bone density and muscle mass. Such CT extracted features have been shown to be independently associated with all-cause mortality.[505] As technology advances, such information is likely to become increasingly available to clinicians to enhance patient management.

In summary, for COPD patients with persistent exacerbations, symptoms out of proportion to disease severity on lung function testing, FEV1 less than 45% predicted with significant hyperinflation and gas trapping, or for those who meet criteria for lung cancer screening, chest CT imaging should be considered (**Figure 2.11**).



Interstitial lung abnormalities (ILA)

Findings suggestive of parenchymal lung fibrosis or inflammation are common on chest CT imaging of both smokers and nonsmokers, and have been termed interstitial lung abnormalities (ILA) when discovered incidentally in patients without known interstitial lung disease (ILD).[506] 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.[506] 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 less than 80% predicted or DLCO less than 70% predicted.[255,507] Individuals with suspected ILD had increased respiratory symptoms and mortality.[507] 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.[508,509] 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 (AATD)

The World Health Organization recommends that all patients with a diagnosis of COPD should be screened once for AATD, especially in areas with high AATD prevalence.[510,511] Although the classical patient 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).[512] A low concentration (< 20% normal) is highly suggestive of homozygous deficiency. Family members should be screened 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 (Body mass index, Obstruction, Dyspnea, and Exercise) method gives a composite score that is a better predictor of subsequent survival than any single component.[513,514] 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.[515,516]

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.[517]

At present blood eosinophil counts (≥ 300 cells/µL) provide guidance to identify COPD patients at higher risk of exacerbations and more likely to benefit from preventive treatment with inhaled corticosteroids (see **Chapter 3**).[517]

Treatable traits

To address the heterogeneity and complexity of COPD in clinical practice, a strategy based on so-called 'Treatable Traits' (TTs) has been proposed.[518] TTs 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 COPD patients at risk of exacerbations (a TT) in whom treatment with inhaled corticosteroid is most effective).[519] TTs can co-exist in the same patient[337] and change with time (spontaneously or because of treatment). GOLD highlights the role of two key TTs (persistent dyspnea and exacerbations) in the follow up algorithm of pharmacological treatment (**Figure 3.9**) 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.[337]

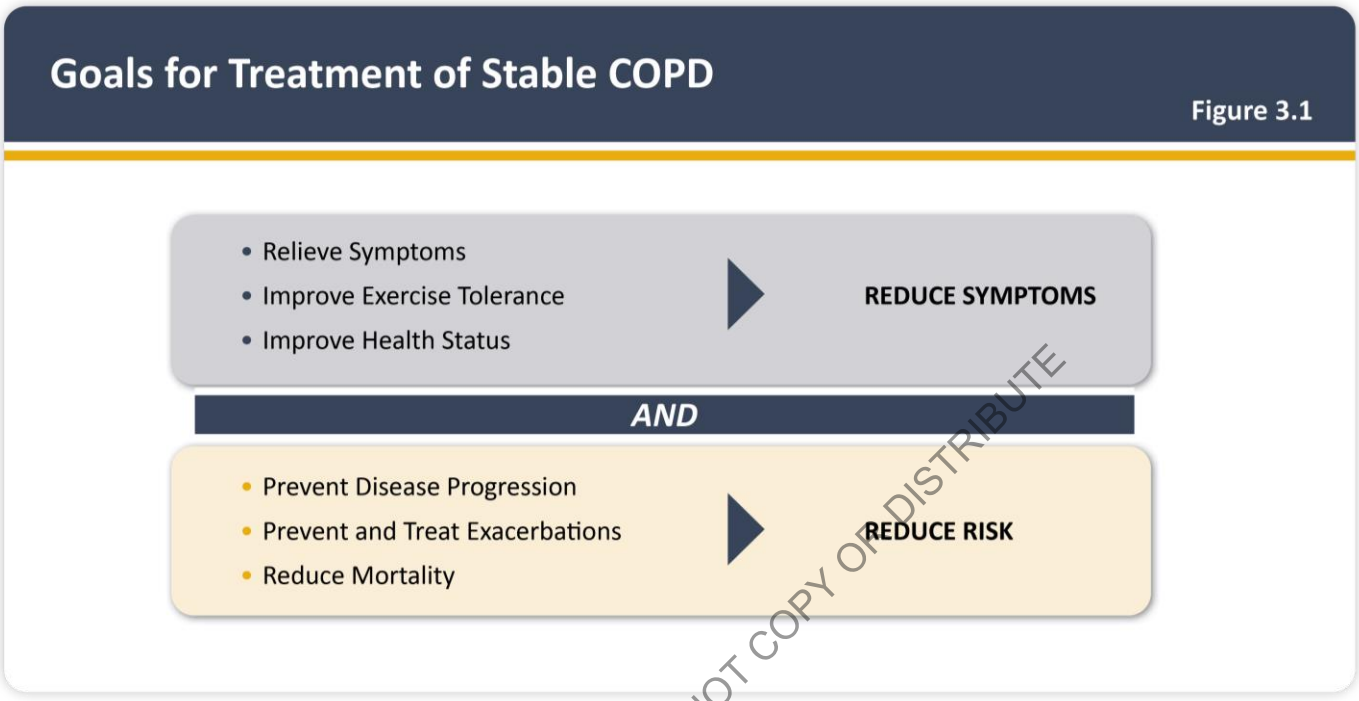
CHAPTER 3: PREVENTION & MANAGEMENT OF COPD

KEY POINTS:

- 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.
- The main treatment goals are to reduce symptoms and future risk of exacerbations. The management strategy of stable COPD should be predominantly based on the assessment of symptoms and the history of exacerbations.
- Pharmacotherapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Data suggest beneficial effects on rates of lung function decline and mortality.
- Each pharmacological treatment regimen should be individualized and guided by the severity of symptoms, risk of exacerbations, side-effects, comorbidities, drug availability and cost, and the patient's response, preference, and ability to use various drug delivery devices.
- Inhaler technique needs to be assessed regularly.
- COVID-19 vaccines are highly effective against SARS-CoV-2 infection and people with COPD should have the COVID-19 vaccination in line with national recommendations.
- Influenza vaccination and pneumococcal vaccination decrease the incidence of lower respiratory tract infections.
- The CDC recommends: the Tdap vaccination (dTaP/dTPa; pertussis, tetanus and diptheria) for COPD patients who were not vaccinated in adolescence; routine use of shingles vaccine in all COPD patients; the new respiratory syncytial virus (RSV) vaccine for individuals over 60 years and/or with chronic heart or lung disease.
- Pulmonary rehabilitation with its core components, including exercise training combined with disease-specific education, improves exercise capacity, symptoms, and quality of life across all grades of COPD severity.
- 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 oxygen therapy improves survival.
- In patients with stable COPD and resting or exercise-induced moderate desaturation, long-term oxygen treatment should not be prescribed routinely. However, individual patient factors must be considered when evaluating the patient's need for supplemental oxygen.
- In patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure, long-term non-invasive ventilation may decrease mortality and prevent re-hospitalization.
- 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.

INTRODUCTION

The aim of COPD management is to reduce symptoms and future risk (**Figure 3.1**). COPD patients 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.



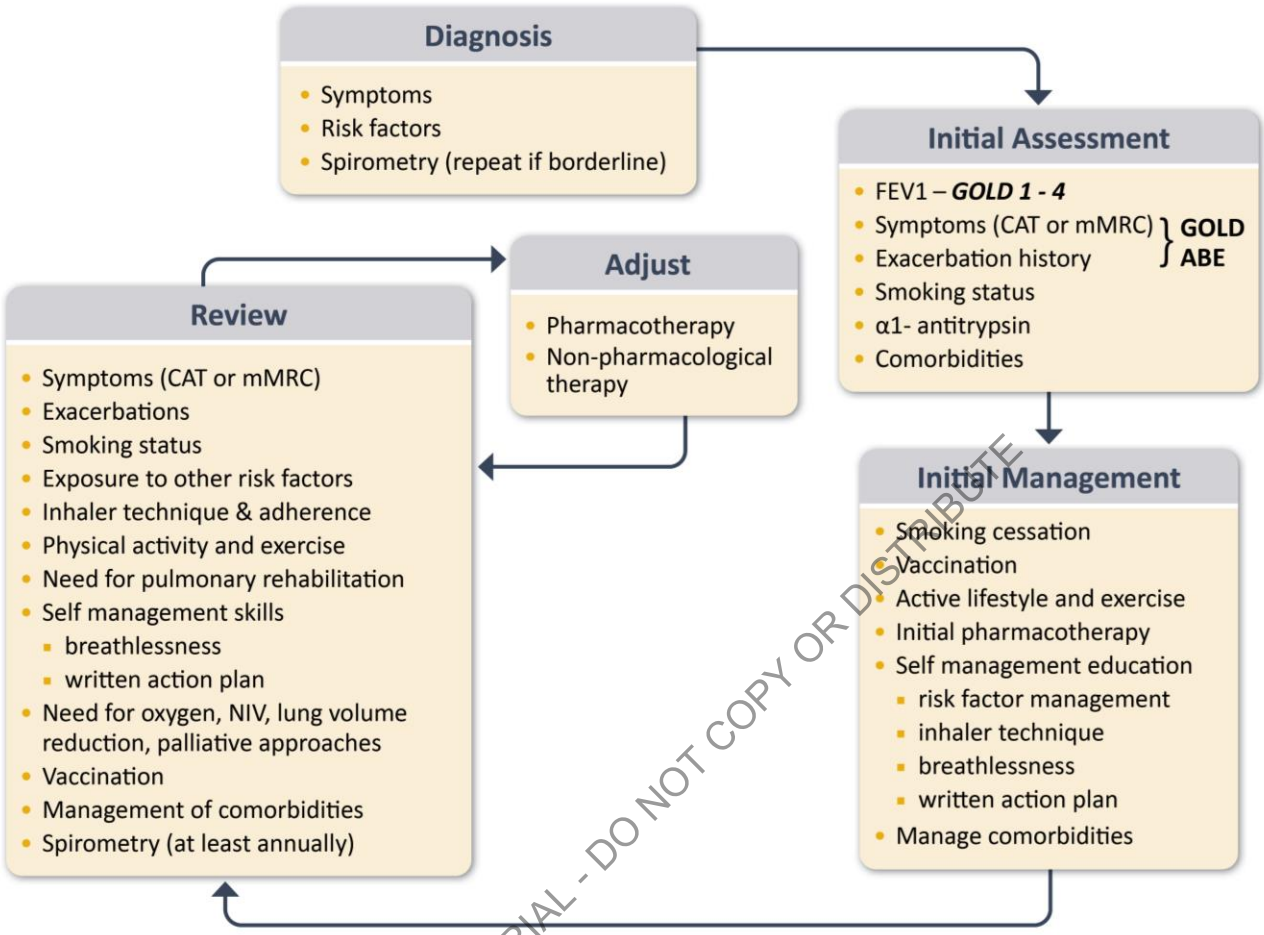
Pharmacological and non-pharmacological therapy should be adjusted as necessary (see below) and further reviews undertaken (**Figure 3.2**). This chapter contains recommendations on how to manage patients with COPD in clinical practice and summarizes the evidence about the effectiveness and safety of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

IDENTIFY AND REDUCE EXPOSURE TO RISK FACTORS

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 COPD patient. 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**).

Management of COPD

Figure 3.2



Identify & Reduce Risk Factor Exposure

Figure 3.3

- Smoking cessation interventions should be actively pursued in all people with COPD **(Evidence A)**
- Efficient ventilation, non-polluting cooking stoves and similar interventions should be recommended **(Evidence B)**
- Clinicians should advise patients to avoid continued exposures to potential irritants, if possible **(Evidence D)**

Smoking cessation

Smoking cessation is a key intervention for all COPD patients 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 this behavior has a negative impact on prognosis and progression of the disease.[520] Smoking cessation has the greatest capacity to influence the natural history of COPD, it also improves daily symptoms,[521] and decreases the frequency of exacerbations.[522]

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.[523-525] In addition, it has been reported that depression is more common in smokers with COPD[526] and this could contribute to failed attempts to quit.[526,527] 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.[527]

Brief Strategies to Help the Patient Willing to Quit

Figure 3.4

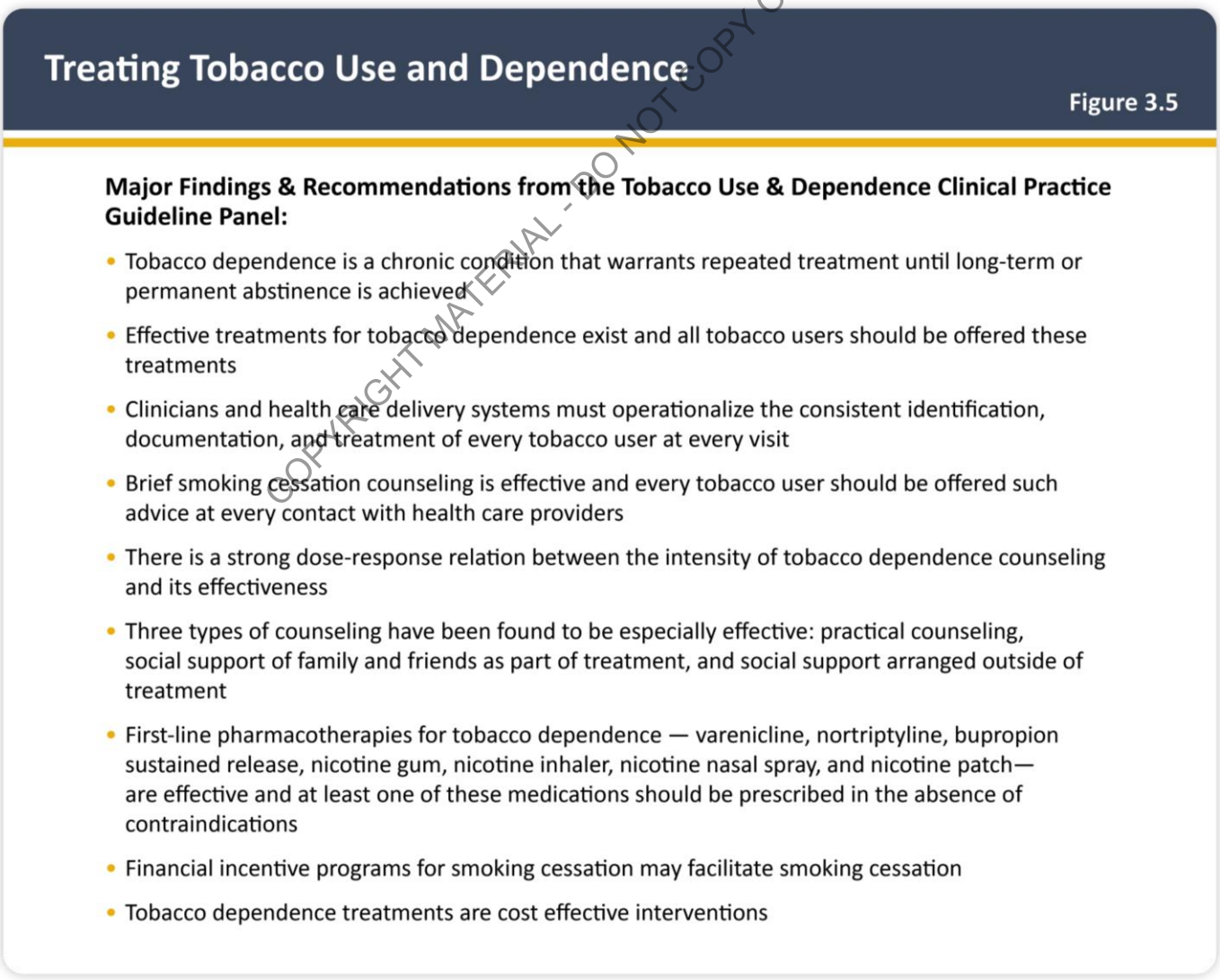
ASK	Systematically identify all tobacco users at every visit *Implement an office-wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco-use status is queried and documented*
ADVISE	Strongly urge all tobacco users to quit *In a clear, strong, and personalized manner, urge every tobacco user to quit*
ASSESS	Determine willingness and rationale of patient's desire to make a quit attempt. *Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days)*
ASSIST	Aid the patient in quitting *Help the patient with a quit plan; provide practical counseling; provide intra-treatment social support; help the patient obtain extra-treatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials*
ARRANGE	Schedule follow-up contact *Schedule follow-up contact, either in person or via telephone*

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.[527-529] 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.[530,531]

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.[532]

Advice and counseling interventions

A five-step program for intervention (**Figure 3.4**)[533-535] provides a helpful strategic framework to guide healthcare providers interested in helping their patients stop smoking.[533,535,536] When possible, the patient should be referred to a comprehensive smoking cessation program that incorporates behavior change techniques enhancing 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**.[533] Because tobacco dependence is a chronic disease,[533,535] 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.



Counseling delivered by physicians and other health professionals significantly increases quit rates over self-initiated strategies.[537] Even brief (3-minute) periods of counseling urging a smoker to quit improve smoking cessation rates.[537]

In patients with COPD a network meta-analysis showed a trend for smoking cessation counseling alone to be superior than usual care.[538] 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.[528] However, controversy remains as to whether more intensive individual counseling is more effective when combined with pharmacotherapy.[538]

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.[8,9]

Occupational exposures

There are no studies that demonstrate whether interventions that reduce occupational exposures 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.

Vaccinations

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

Influenza vaccine

Influenza vaccination can reduce serious illness (such as lower respiratory tract infections requiring hospitalization)[539] and death in people with COPD.[540-543] Only a few studies have evaluated exacerbations and they have shown significant reduction in the total number of exacerbations per vaccinated subject compared with those who received placebo.[540] Vaccines containing either killed or live inactivated viruses are recommended[544] as they are more effective in elderly people with COPD.[545] 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.[546] Occurrence of adverse reactions is generally mild and transient.

Pneumococcal vaccines

Pneumococcal vaccinations, pneumococcal conjugated vaccine (PCV20 or PCV15) and pneumococcal polysaccharide vaccine (PPSV23), are approved for adults aged ≥ 65 years. They are also approved for adults aged 19-64 years if they have an underlying medical condition such as chronic lung disease (including COPD, emphysema, and asthma), cigarette smoking, solid organ transplant etc. 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 PCV15 followed by PPSV23 OR one dose PCV20.[547] Adults who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥ 1 year after their last PPSV23 dose (**Figure 3.6**).

Vaccination for Stable COPD

Figure 3.6

- Influenza vaccination is recommended for people with COPD **(Evidence B)**
- The WHO and CDC recommends SARS-CoV-2 (COVID-19) vaccination for people with COPD **(Evidence B)**
- The CDC recommends one dose of 20-valent pneumococcal conjugate vaccine (PCV20); or one dose of 15-valent pneumococcal conjugate vaccine (PCV15) followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) for people with COPD **(Evidence B)**
- Pneumococcal vaccination has been shown to reduce the incidence of community-acquired pneumonia and exacerbations for people with COPD **(Evidence B)**
- The CDC recommends the new respiratory syncytial virus (RSV) vaccine for individuals over 60 years and/or with chronic heart or lung disease **(Evidence A)**
- The CDC recommends Tdap (dTaP/dTPa) vaccination to protect against pertussis (whooping cough) for people with COPD that were not vaccinated in adolescence **(Evidence B)**, and Zoster vaccine to protect against shingles for people with COPD over 50 years **(Evidence B)**

Specific data on the effects of PPSV and PCV in people with COPD are limited.[548] A systematic review of injectable vaccines in COPD patients identified twelve randomized studies for inclusion and observed injectable polyvalent pneumococcal vaccination provides significant protection against community-acquired pneumonia, although no evidence indicates that vaccination reduced the risk of confirmed pneumococcal pneumonia, which was a relatively rare event. Vaccination reduced the likelihood of a COPD exacerbation, and moderate-quality evidence suggests the benefits of pneumococcal vaccination in COPD patients. Evidence was insufficient for comparison of different pneumococcal vaccine types.[549] PPSV23 has been shown to reduce the incidence of community-acquired pneumonia in COPD patients < 65 years, with an FEV1 < 40% predicted, or comorbidities (especially cardiac comorbidities).[550] The PCV13 has been shown to exhibit at least the same or greater immunogenicity than the PPSV23 up to two years after vaccination in COPD patients.[551] 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.[552]

A study compared the effectiveness of PPSV23 and PCV13 in COPD patients over a 5-year follow-up cohort study. 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 COPD exacerbations.[553]

PCV15, PCV20, or PPSV23 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.[554]

Respiratory syncytial virus (RSV) vaccine

The US Centers for Disease Control (CDC) Advisory Committee on Immunization Practices' (ACIP) and the European Commission recommend use of the new respiratory syncytial virus (RSV) bivalent prefusion F protein-based vaccine[555] and prefusion F protein vaccine[556] for individuals 60 years and older. Adults at the highest risk for severe RSV illness include adults with chronic heart or lung disease, immune compromise, and those living in nursing homes or long-term care facilities. The CDC estimates that every year, RSV causes approximately 60,000–160,000 hospitalizations and 6,000–10,000 deaths among older adults.[557,558]

Other vaccines

In adults with COPD the CDC recommends the Tdap vaccination (also called dTaP/dTPa) to protect against pertussis (whooping cough), tetanus and diphtheria, in those who were not vaccinated in adolescence and also the routine use of shingles vaccine.[559,560] People with COPD should have the COVID-19 vaccinations in line with national recommendations.[561]

PHARMACOLOGICAL TREATMENT OF STABLE COPD

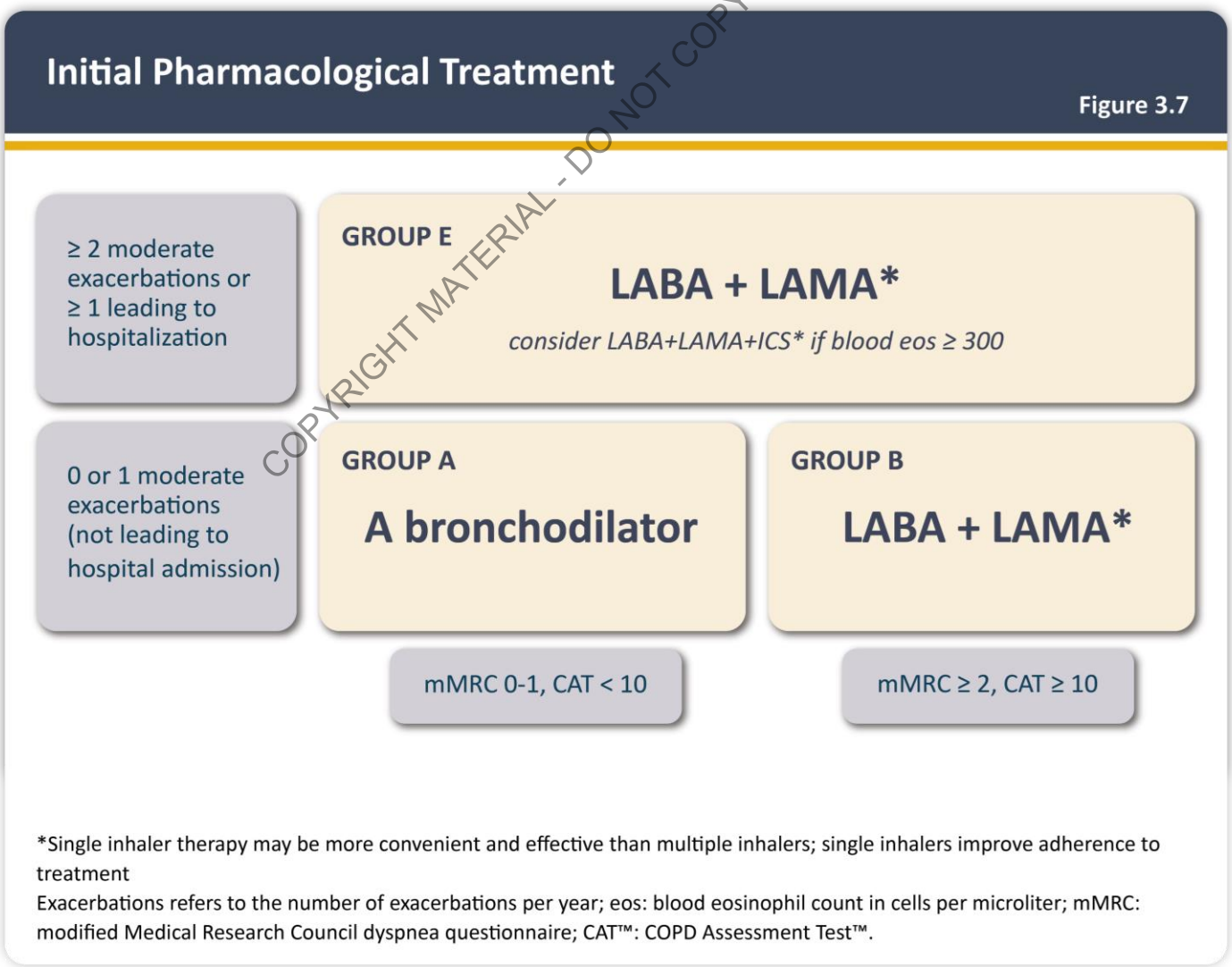
We propose a tailored approach to initiate treatment based on the level of symptoms and risk for exacerbations. Treatment can be escalated/de-escalated based on the presence of the predominant symptoms (treatable traits) of breathlessness and exercise limitation, and the continued occurrence of exacerbations whilst on maintenance therapy. The basis for these recommendations, which propose an organized approach to treatment, was partly derived from evidence generated from randomized controlled trials. However, as these recommendations are intended to support clinician decision-making, they also incorporate expert advice based on clinical experience.

Initial pharmacotherapy should be based on the patient's GOLD group (**Figure 3.7**). Patients should be offered guidance and follow up on self-management of breathlessness, and stress management, and they should be given a written action plan (**Figure 3.13**). Comorbidities should also be managed as per specific guidelines, irrespective of the presence of COPD (**Figure 3.2**).

Patients should be reviewed after a suitable interval (shorter in more severe patients and longer in less severe patients) and their current level of symptoms (using either the CAT 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 checked at each clinical visit. 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 also 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 (ACO), 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.



*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; CAT™: COPD Assessment Test™.

Algorithms for the initiation and follow-up of pharmacological treatment

Further information on the evidence that underpins these recommendations is given later in **Chapter 3** in the section entitled **"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 3.7**. It is an attempt to provide clinical guidance. There is no high-quality evidence such as randomized controlled trials to support initial pharmacological treatment strategies in newly diagnosed COPD patients.

Group A

► All Group A patients should be offered bronchodilator treatment based on its effect on breathlessness. This can be either a short- or a long-acting bronchodilator. If available and affordable a long-acting bronchodilator is the preferred choice except in patients with very occasional breathlessness.

► 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 CAT™ ≥ 10 LABA+LAMA is superior to a LAMA with regard to several endpoints.[562] 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.

► Group B patients 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.[563,564]

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 COPD exacerbations.[565] Therefore, provided there are no issues regarding availability, cost and side-effects LABA+LAMA is the preferred choice for initial therapy in group E patients.

► 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.[448,566]

► Consider LABA+LAMA+ICS in group E if eos ≥ 300 cells/µL (practical recommendation). As detailed later in this chapter, the effect of ICS on exacerbation prevention is correlated to blood eosinophil count. 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.

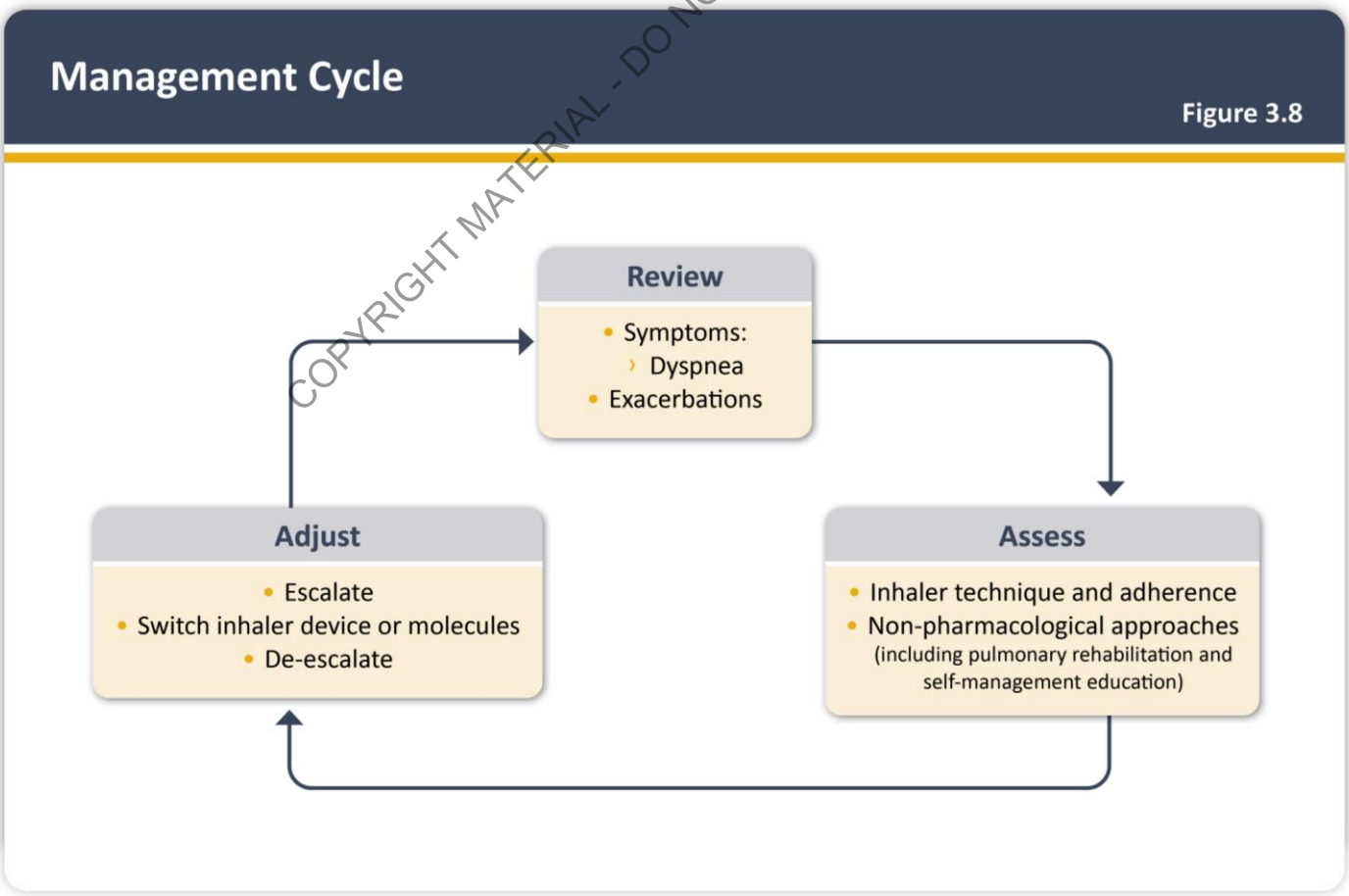
Following implementation of therapy, patients should be reassessed for attainment of treatment goals and identification of any barriers for successful treatment (**Figure 3.8**). Following review of the patient's response to treatment initiation, adjustments may be needed.

This is guided by the principles of first ***review*** and ***assess***, then ***adjust*** if necessary (**Figure 3.8**):

► **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 earlier 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.



Follow-up pharmacological management

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**). 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 later in **Chapter 3**).

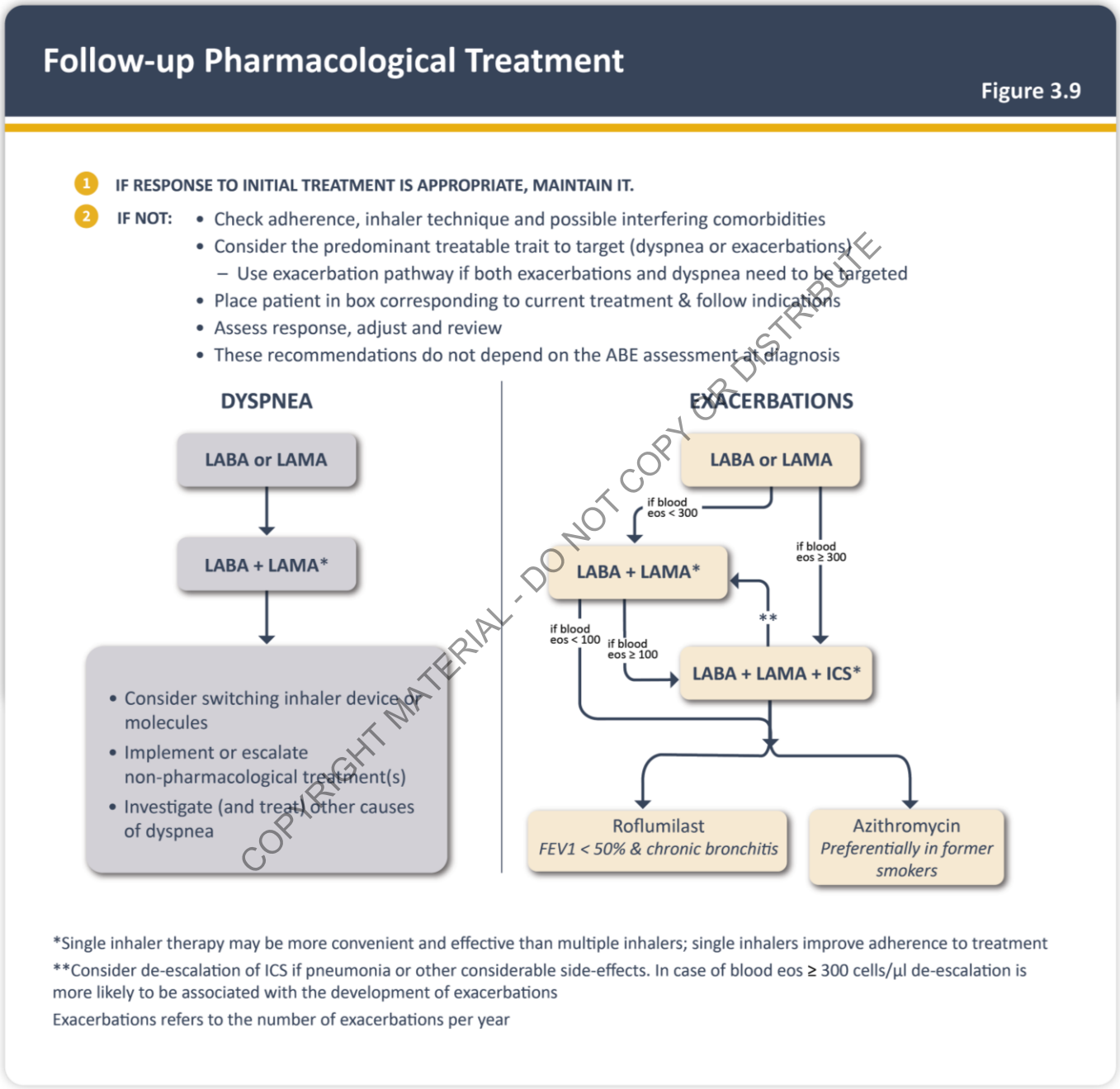


Figure 3.9 presents suggested escalation and de-escalation strategies based on available efficacy and safety data. The response to treatment escalation should always be reviewed. Patients, in whom treatment modification is considered, in particular de-escalation, should be under close medical supervision. We are fully aware that treatment escalation has not been systematically tested; trials of de-escalation are also limited and only include ICS.

The 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. The need to target primarily dyspnea/activity limitation or to prevent further exacerbations should be evaluated in each patient. 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); the exacerbation algorithm should also be used for patients who require a change in treatment for both dyspnea and exacerbations. 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,[567] the use of two long acting bronchodilators is recommended.

- If the addition of a second long acting bronchodilator does not improve symptoms, we suggest considering switching inhaler device or molecules.

► 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 with persistent exacerbations on ***bronchodilator*** monotherapy, escalation to LABA+LAMA is recommended.

► In patients who develop further exacerbations on **LABA+LAMA** therapy we suggest escalation to **LABA+LAMA+ICS.** 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.[448]

► If patients treated with **LABA+LAMA+ICS** (or those with eos < 100 cells/µL) still have exacerbations the following options may be considered:

- **Add roflumilast.** This may be considered in patients with an FEV1 < 50% predicted and chronic bronchitis,[568] particularly if they have experienced at least one hospitalization for an exacerbation in the previous year.[569,570]
- **Add a macrolide.** The best available evidence exists for the use of azithromycin, especially in those who are not current smokers.[571,572] Consideration to the development of resistant organisms should be factored into decision-making.
- **Withdrawing ICS** can be considered if pneumonia or other considerable side-effects develop. If blood eosinophils are ≥ 300 cells/µL de-escalation is more likely to be associated with the development of exacerbations.[573,574] Carefully consider the dose of ICS used to reduce the potential of ICS related side effects that are more frequent at higher doses.

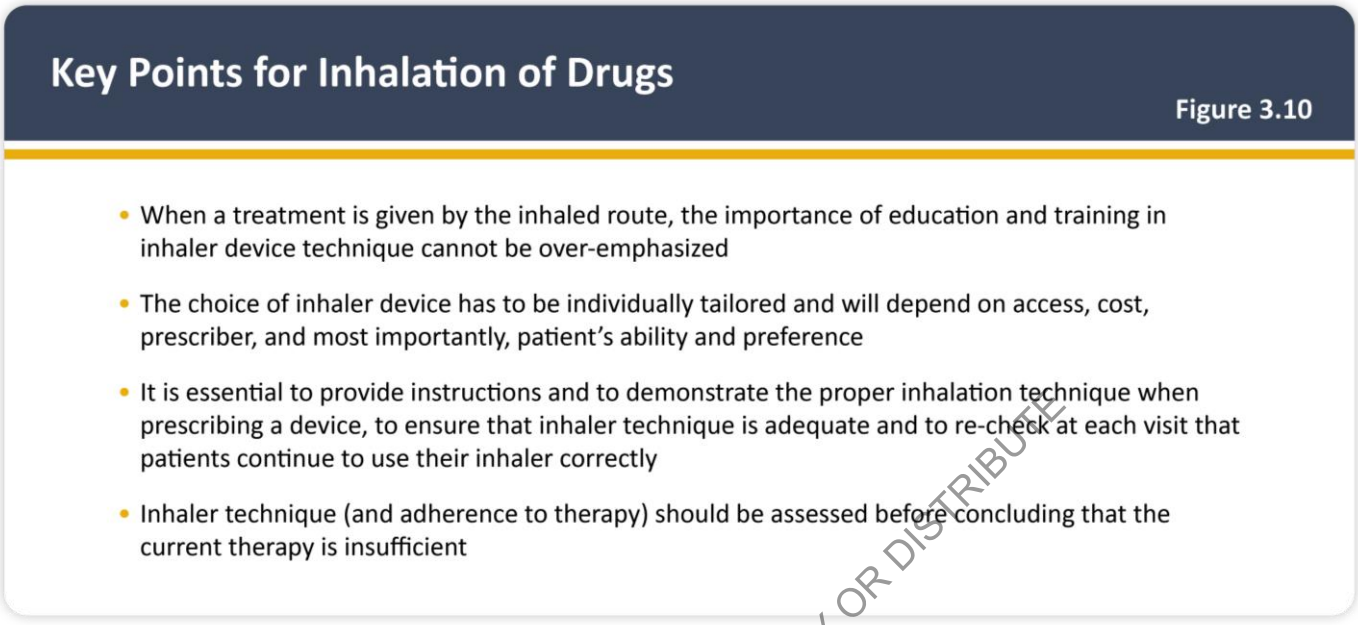
Patients under treatment with LABA+ICS

► 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. 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.
- **Major symptoms:** switching to LABA+LAMA should be considered.

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 3.10**).



There are currently at least 33 different inhaled therapies containing different bronchodilators (both short- and long-acting) and inhaled corticosteroids (ICS) alone or in combinations (**Figure 3.18**). In addition, at least 22 different inhaler devices are available,[575] including nebulizers, metered-dose inhalers (MDIs) used with or without valved holding chamber (VHC)/spacers, breath-actuated MDIs (BAIs), soft mist inhalers (SMIs) and dry powder inhalers (DPIs)[576] In multi-dose DPIs, the powder is contained in a reservoir or in individual blisters.[576] More information about inhalation devices is available on the Asthma + Lung UK website.[577]

Devices differ in their size and portability. They also differ in the number of steps required to prepare them,[578] in the force needed to load or actuate them,[579] in the time taken to deliver the drug, and in the need for cleaning and maintenance, as well as in the inspiratory manoeuvre required to use them effectively.[576] Increased steps reduces the ease of use and likelihood that patients use the inhaler correctly.[580] 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.[581] 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).[581] 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[582] and can provide objective data on adherence and technique.[583,584]

Particles > 5 microns (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).[576] 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.[576,585] MDIs 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[586,587] or switch to an MDI+/-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.[588]

Randomized controlled trials 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.[576] 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.[589]

Ability to use delivery system correctly

Specific instructions are available for each type of device.[576,577] On average more than two thirds of patients make at least one error in using an inhalational device.[590-593] 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.[594-600] 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.[601]

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.[591,602] Poor inhaler technique and errors using devices are more common with advancing age,[603] but this is likely to be mainly due to cofounders such as cognitive impairment or reduced manual dexterity.[604,605] 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.[579] 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.[579] Tremor may result in shaking of the device and loss of the dose.[606]

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 incorrect use of pMDIs is more common in older patients if they use a VHC.[607] Currently available VHCs range in volume from < 50 to 750 mL[608] but VHC with volumes from 150 to 250 mL have been shown to be as effective as those with larger volumes[609] 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.[576]

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.[580] Using the "teach-back" approach (patients being asked to show how the device has to be used) appears to be particularly effective.[610] Pharmacist-, physician-, physiotherapist- and nurse-led interventions[611] as well as lay health coaching[612] can improve inhalation technique and adherence in COPD patients. As in asthma, digital inhalers could contribute to improved adherence and inhaler technique in patients with COPD.[613]

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. **Figure 3.11** summarises the main principles that should be considered to guide the individualized selection of the appropriate device for a given patient.

Basic Principles for Appropriate Inhalation Device Choice

Figure 3.11

- Availability of the drug in the device
- Patients' beliefs, satisfaction with current and previous devices and preferences need to be assessed and considered
- The number of different device types should be minimized for each patient. Ideally, only one device type should be used
- Device type should not be switched in the absence of clinical justification nor without proper information, education and medical follow-up
- Shared decision-making is the most appropriate strategy for inhalation device choice
- Patient's cognition, dexterity and strength must be taken into account
- Patient's ability to perform the correct specific inhalation maneuver for the device must be assessed:
  - Dry powder inhalers are appropriate only if the patient can make a forceful and deep inhalation. Check visually that the patient can inhale forcefully through the device - if there is doubt assess objectively or choose alternative device
  - Metered-dose inhalers and, to a lesser extent, soft mist inhalers require coordination between device triggering and inhalation and patients need to be able to perform a slow and deep inhalation. Check visually that the patient can inhale slowly and deeply from the device - if there is doubt consider adding a spacer/VHC or choose an alternative device
  - For patients unable to use an MDI (with or without spacer/VHC), SMI or DPI a nebulizer should be considered
- Other factors to consider include size, portability, cost
- Smart inhalers may be useful if there are issues with adherence/persistence or inhalation technique (for devices that can check it)
- Physicians should prescribe only devices they (and the other members of the caring team) know how to use

Appropriate education must be provided by health care professionals, including physical, video- or be-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 STABLE COPD

Non-pharmacological treatment is complementary to pharmacological 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. Physicians should emphasize the importance of a smoke free environment, empower adherence to prescribed medication, ensure proper inhaler technique, promote physical activity, prescribe vaccinations, and refer patients to pulmonary rehabilitation.

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

Some relevant non-pharmacological measures based on the patient's GOLD A,B,E group **AT DIAGNOSIS** are summarized in **Figure 3.12**.

Non-Pharmacological Management of COPD*

Figure 3.12

Patient Group	Essential	Recommended	Depending on Local Guidelines
A	Smoking cessation (can include pharmacological treatment)	Physical activity	Influenza vaccination COVID-19 vaccinations Pneumococcal vaccination Pertussis vaccination Shingles vaccination RSV vaccination
B and E	Smoking cessation (can include pharmacological treatment) Pulmonary rehabilitation	Physical activity	Influenza vaccination COVID-19 vaccinations Pneumococcal vaccination Pertussis vaccination Shingles vaccination RSV vaccination

*Can include pharmacological treatment

Recommendations for **FOLLOW UP** non-pharmacological treatments are based on a patient's treatable traits e.g., symptoms and exacerbations (**Figure 3.13**).

Follow-up of Non-Pharmacological Treatment

Figure 3.13

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.

Rehabilitation, Education & Self-Management

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."[614]

Patients with high symptom burden and risk of exacerbations (Groups B and E), 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 and comorbidities.[614-616] This includes patients who are older, female, more deprived, or have a comorbidity of diabetes, asthma, or painful condition and currently appear less likely to be referred for pulmonary rehabilitation.[617]

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.[615] Optimum benefits are achieved from programs lasting 6 to 8 weeks. Available evidence indicates that there are no additional benefits from extending pulmonary rehabilitation to 12 weeks.[618] Supervised exercise training at least twice weekly is recommended, and this can include any regimen from endurance training, interval training, resistance/strength training; upper and lower limbs ideally should 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.[618] When the intervention includes ongoing feedback (telephone calls, biofeedback provided via pedometer and progressive goal setting) but the program is not supervised, it is no more effective in improving physical activity than a walking program with no feedback.[619] The importance of long-term behavior change to improve physical functionality, and reduce the psychological impact of COPD, should be emphasized to the patient.

Assessment and follow-up of pulmonary rehabilitation

Baseline and outcome assessments of each participant in 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.

Assessments should include:

- Detailed history and physical examination
- Measurement of post-bronchodilator spirometry
- Assessment of exercise capacity
- Measurement of health status and impact of breathlessness
- Assessment of inspiratory and expiratory muscle strength and lower limb strength in patients who suffer from muscle wasting
- Discussion about individual patient goals and expectations

The first two assessments are important for establishing entry suitability and baseline status but are not used in outcome assessment.

Exercise tolerance can be assessed by cycle ergometry or treadmill exercise with the measurement of a number of physiological variables, including maximum oxygen consumption, maximum heart rate, and maximum work performed. Standardized self-paced, timed walking tests (e.g., 6-minute walking distance) are useful in clinical practice as they require minimal facilities and are relevant to routine functioning. Shuttle walking tests provide more complete information than an entirely self-paced test, and are simpler to perform than a treadmill test.[620] Walking tests do require at least one practice session before data can be interpreted.

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.

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 CAT™, CRQ or SGRQ. The *Hospital Anxiety and Depression Scale (HADS)*[621] and the *Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Questionnaire*[622] have been used to improve identification and treatment of anxious and depressed patients.

Education, self-management and integrative care

Patient "education" often takes the form of providers giving information and advice, and assumes that knowledge will lead to behavior change. Although enhancing patient knowledge is an important step towards behavior change, didactic group sessions are insufficient for promoting self-management skills. Topics such as smoking cessation, correct use of inhaler devices, early recognition of exacerbation, decision-making and taking action, and when to seek help, surgical interventions, considering advance directives, and others will be better dealt with using self-management interventions. Personalized education and training that considers specific issues relating to the individual patients, and that aims to enhance long-term functionality and appropriate health behaviors, is likely to benefit patients more. These are addressed under self-management.

Education

Patients may have individual and/or group education sessions. During group sessions, patients engage in active, participatory-based learning of program content. During one-on-one interactions, a motivational communication style should be used, as this approach empowers patients to take greater responsibility for their health and wellbeing, where physicians and other healthcare professionals only serve as guides in the behavior change process.

Topics considered appropriate for an education program include: smoking cessation; basic information about COPD; general approach to therapy and specific aspects of medical treatment (respiratory medications and inhalation devices); strategies to help minimize dyspnea; advice about when to seek help; decision-making during exacerbations; and advance directives and end-of-life issues. The intensity and content of these educational messages will vary depending on the severity of the patient's disease, although the specific contributions of education to the improvements seen after pulmonary rehabilitation remain unclear.[623] Implicit in this description is the provision of "self-management support/coaching", which refers to the strategies, techniques and skills used by healthcare providers to arm patients with the knowledge, confidence and skills required to self-manage their disease effectively. However, the individual patient's evaluation and risk assessment with respect to exacerbations, patient's needs, preferences, and personal goals should inform the personalized design of the self-management education plan.

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.[624] 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,[625,626] but it can play a role in improving skills, ability to cope with illness, and health status.[614]

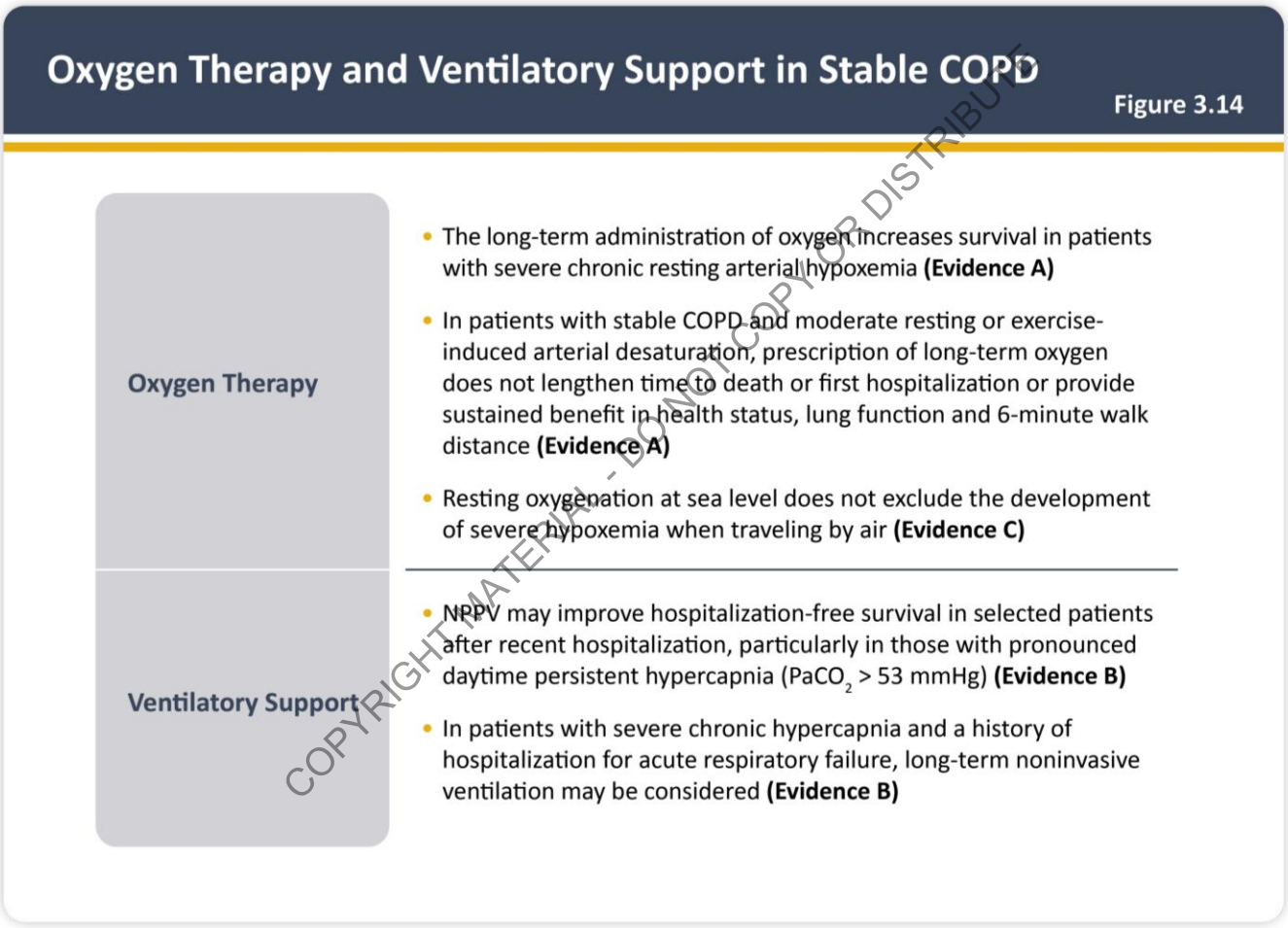
Integrative care

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.

Oxygen therapy and ventilatory support

Oxygen therapy

The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival in patients with severe resting hypoxemia.[627] Long-term oxygen therapy does not lengthen time to death or first hospitalization or provide sustained benefit for any of the measured outcomes in patients with stable COPD and resting or exercise-induced moderate arterial oxygen desaturation.[628] Breathlessness may be relieved in COPD patients 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 3.14**).[628-630] There are contradictory studies although the majority do not demonstrate changes.[631]

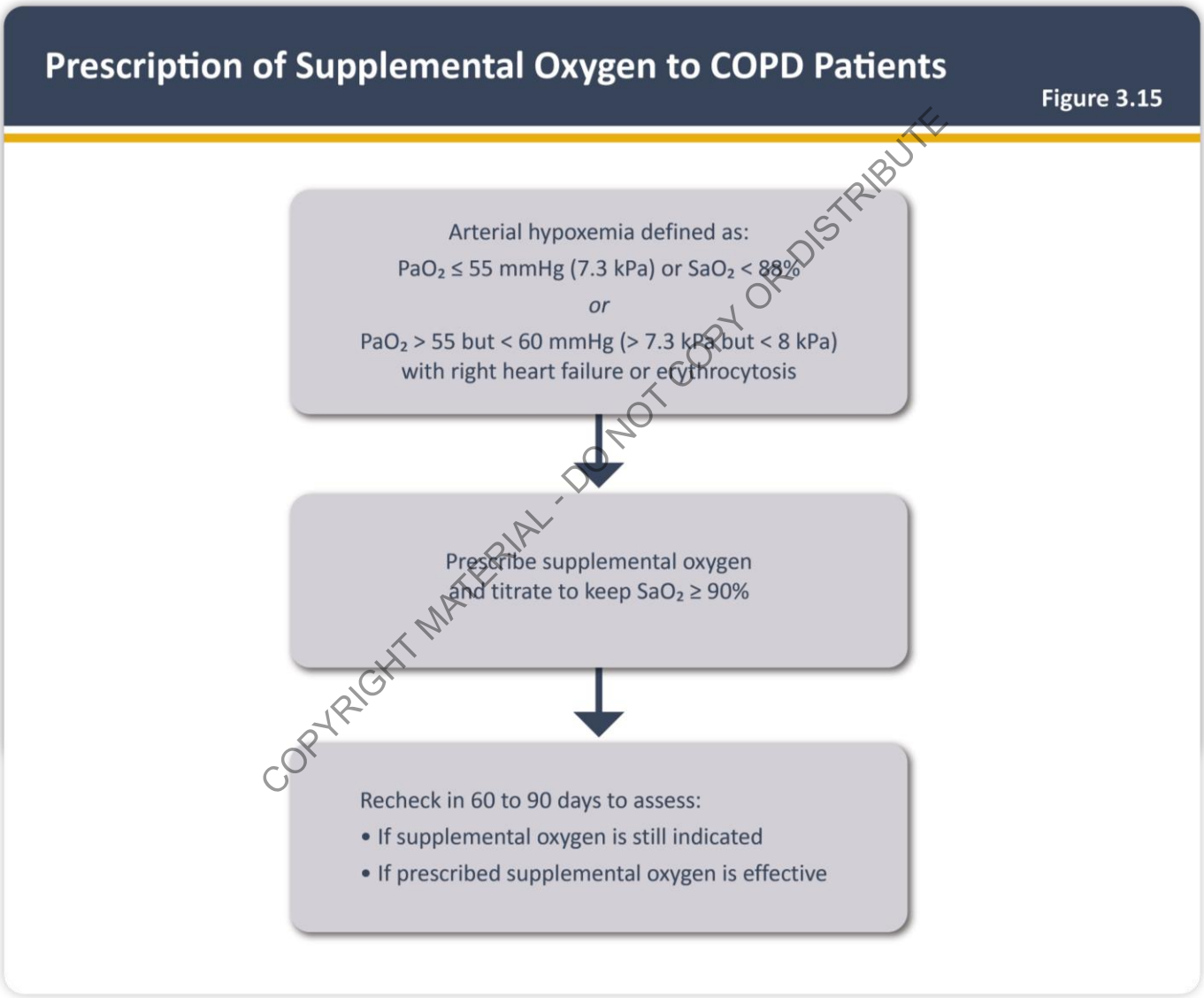


Although air travel is safe for most patients with chronic respiratory failure who are on long-term oxygen therapy,[632] patients should ideally maintain an in-flight PaO_2 of at least 6.7 kPa (50 mmHg). Studies indicate that this can be achieved in those with moderate to severe hypoxemia at sea level by supplementary oxygen at 3 liters/min by nasal cannula or 31% by Venturi facemask.[633] Those with a resting oxygen saturation > 95% and 6-minute walk oxygen saturation > 84% may travel without further assessment,[634] although it is important to emphasize that resting oxygenation at sea level does not exclude the development of severe hypoxemia when travelling by air.[632] 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 may profoundly aggravate hypoxemia.[635]

Long-term oxygen therapy (LTOT) is indicated for stable patients 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%).

Once placed on LTOT the patient should be re-evaluated after 60 to 90 days with repeat arterial blood gas (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 COPD patients is shown in **Figure 3.15**.



Ventilatory support

Noninvasive ventilation (NIV) is occasionally used in patients with stable very severe COPD.[636] NIV may be considered of some use in a selected group of patients, particularly in those with pronounced daytime hypercapnia and recent hospitalization, although a systematic review was unable to support or refute this.[637] In contrast, in patients with both COPD and obstructive sleep apnea there are clear indications for continuous positive airway pressure (CPAP).[638,639]

During exacerbations of COPD

NIV in the form of noninvasive positive pressure ventilation (NPPV) is the standard of care for decreasing morbidity and mortality in patients hospitalized with an exacerbation of COPD and acute respiratory failure[640-643] (see also **Chapter 4**).

Stable patient

In patients with both COPD and obstructive sleep apnea there are clear benefits associated with the use of continuous positive airway pressure (CPAP) to improve both survival and the risk of hospital admissions.[638,639]

Whether to use NPPV chronically at home to treat patients with acute on chronic respiratory failure following hospitalization remains undetermined and outcome may be affected by persistent hypercapnia.[644] A multicenter prospective RCT of COPD patients with persistent hypercapnia ($PaCO_2$ > 53 mmHg) after 2-4 weeks of hospital discharge because an acute episode of exacerbation, compared the effects of home NIV plus oxygen compared to home oxygen alone on time to readmission or death.[644] Results showed that adding home NIV to oxygen therapy significantly prolonged the time to readmission or death within 12 months.[644] 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.[643]

Two previous retrospective studies[645,646] and two of three RCTs[644,647-650] reported reductions in re-hospitalization and improved survival with using NPPV post-hospitalization. Two studies reported decreases in mortality and hospitalization rates while another showed no benefit of NPPV for survival.[648] Several factors may account for discrepancies: differences in patient selection, underpowered studies, NPPV settings incapable of achieving adequate ventilation, and poor adherence with NPPV therapy.[651] NPPV when indicated should be instituted and monitored under the direction of personnel familiar with the process and the devices utilized.[652,653]

MONITORING AND FOLLOW-UP

Routine follow-up of COPD patients 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 COPD Assessment Test (CAT™)[428] can be used; trends and changes are more valuable than single measurements.

Exacerbations

The frequency, severity, type and likely causes of all exacerbations[654] 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 COPD patients that should be mandatory in each clinical visit. The following aspects need careful and personalized attention:

- Dosages of prescribed medications
- Adherence to the regimen
- Inhaler technique
- Effectiveness of the current regime
- Side effects

Treatment modifications should be recommended (**Figure 3.7**).

Smoking status

At each visit, the current smoking status and smoke exposure should be determined followed by appropriate action.

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 (6-minute walking distance or shuttle-walking test) provides additional information regarding prognosis.[655,656] 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 etc. should be recorded. If present, an appropriate diagnostic work-up should follow (see also **Chapter 5**).

Telehealth and remote monitoring

The COVID-19 pandemic has dramatically changed how outpatient care is delivered in health care 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. However, incorporation of virtual care into ambulatory care should be based on evidence.

From a recent Cochrane review[657] on telehealth for remote monitoring and consultations for patients with COPD, different models have been reviewed based on RCTs:

- 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 5 RCTs that transferred data and allowed review by health professionals in real time (synchronous).[657] 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.

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.[658] 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.[659,660] 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.[658] 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.[661] 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.[660] Key points for palliative, end-of-life and hospice care in COPD are summarized in **Figure 3.16**.

Palliative Care, End of Life and Hospice Care in COPD

Figure 3.16

- 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)**

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.[662] 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, high-flow nasal therapy (HFNT) and non-invasive ventilation (NIV) for palliation of dyspnea are debated.[663]

Opiates,[664-666] neuromuscular electrical stimulation (NMES),[666,667] chest wall vibration (CWV)[666] and fans blowing air onto the face[666,668,669] can relieve breathlessness. Morphine may improve health status in COPD patients.[317] Immediate-release morphine extended exercise endurance time in over half of the patients with advanced COPD in one study.[317] 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 breathlessness scale scores of 3 or 4.[670] Further research is required to determine what patient characteristics predict response to opioid therapy.[671] The optimal formulation and administration route remain under discussion.[666,672]

Oxygen may offer some benefit even if the patient is not hypoxemic ($Sp0_2$ > 92%) (**Figure 3.14**).[673] 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.[674] Refractory dyspnea may be more effectively managed with a multidisciplinary integrated palliative and respiratory care service.[675]

There is no evidence for a beneficial effect of benzodiazepines[676] and there is not enough data to recommend distractive auditory stimuli (music), relaxation, counseling and support, with or without breathing relaxation training, or psychotherapy.[677]

Nutritional support

Low BMI and particularly low fat-free mass is associated with worse outcomes in people with COPD.[678] 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.[679] 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 6-minute walk test, respiratory muscle strength and health status.[680] A 12-month nutritional intervention in muscle wasted patients had no effect on physical capacity but physical activity was significantly higher.[681]

Panic, anxiety & depression

The causes of depression and anxiety symptoms in people with COPD are multifactorial and include behavioral, social and biological factors.[682] 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.[683]

Fatigue

Fatigue in people with COPD can be improved by self-management education, pulmonary rehabilitation, nutritional support and mind-body interventions.[684]

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.[685] Although mortality rates following hospitalization for an acute exacerbation of COPD are declining,[686] reported rates still vary from 23%[687] to 80%.[688] Progressive respiratory failure, cardiovascular diseases, malignancies and other diseases are the primary cause of death in people with COPD hospitalized for an exacerbation.[688] 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.[689] 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.[690] 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.[691] 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.[692] 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.[693,694]

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 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[695] 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).[659,660] 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.[658]

Therapeutic interventions that reduce COPD mortality

COPD is the third leading cause of death worldwide, causing 3.23 million deaths in 2019. As we move towards targeting subgroups of COPD patients 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 COPD exacerbations, GOLD groups B and D, and those with lower FEV1 (particularly GOLD 3 and 4).[696] 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 3.17** presents a summary of pharmacological and non-pharmacological therapies with evidence of efficacy in reducing the mortality of COPD patients.

Pharmacological therapy

Previous studies such as the TORCH clinical trial[697] and the SUMMIT trial[698] failed to provide evidence for the efficacy of a LABA+ICS combination compared to placebo in reducing mortality (primary outcome) in COPD patients. 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.

Recently, evidence has emerged from two large randomized clinical trials, IMPACT[448] and ETHOS,[566] that fixed-dose inhaled triple combinations (LABA+LAMA+ICS), reduce all-cause mortality compared to dual inhaled long-acting bronchodilation therapy. These trials were enriched for symptomatic patients (CAT ≥ 10) with a history of frequent (≥ 2 moderate exacerbations) and/or severe exacerbations (≥ 1 exacerbation requiring a hospital admission) (**Figure 3.17**).

Evidence Supporting a Reduction in Mortality with Pharmacotherapy and Non-pharmacotherapy in COPD Patients — Figure 3.17

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 ≤ 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

*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 anti-muscarinic; LTOT: long-term oxygen therapy; NPPV: noninvasive positive pressure ventilation; LVRS: lung volume reduction surgery; UC: usual treatment control group.

Non-pharmacological therapy

Smoking cessation. From the Lung Health Study, a randomized clinical trial (RCT) that included asymptomatic or mildly symptomatic COPD patients 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.[699]

Pulmonary rehabilitation (PR). A systematic review of RCTs reported a reduction in mortality for patients who had PR initiated during hospitalization or 4 weeks after discharge compared to those who did not have PR.[700-703] 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 PR within 90 days of discharge, while rare, was associated with a statistically significant reduced mortality.[704]

Long term oxygen therapy (LTOT). 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 (NOTT)(≥ 19 hours of continuous oxygen compared to ≤ 13 hours)[705] and the Medical Research Council (MRC)(≥ 15 hours compared to no oxygen),[706] two RCTs in COPD patients 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.[707]

Non-invasive positive pressure ventilation (NPPV). Recent meta-analyses[643,708] have shown positive results of long-term NPPV in patients with stable COPD. Although RCT results have being inconsistent on survival, larger trials with mortality as the primary outcome, enrolling patients with marked hypercapnia and applying higher IPAP levels demonstrated a reduction of mortality.[648,709]

Lung transplantation and lung volume reduction surgery (LVRS). Because of the absence of randomized trials, observational data has 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 2/5 of transplanted COPD patients.[710]

LVRS has been shown to prolong survival compared to medical therapy in a very select group of patients with severe COPD, predominantly upper lobe emphysema, and low exercise capacity.[289] Among patients with non-upper-lobe emphysema and high exercise capacity, mortality was higher in the surgery group than in the medical-therapy group.

In summary, available data suggest that several pharmacological and non-pharmacological treatments may reduce mortality. Further analyses or studies may help to determine whether specific patient subgroups demonstrate a greater survival benefit.

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[533,535,537,711,712] 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.[537,713,714] 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.[715] 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.[716-720] 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.

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.[721-724] The U.S. Centers for Disease Control (CDC), the U.S. Food and Drug Administration (FDA), state and other clinical and public health partners investigated an outbreak of e-cigarette, or vaping, product use-associated lung injury (EVALI). By February 2020, a total of 2,807 cases of lung illness and 68 deaths had been associated with using e-cigarette products (devices, liquids, refill pods, and/or cartridges).[724] Patients were reported to have had clinical improvement with systemic glucocorticoid therapy and the majority received prolonged courses.[723] Laboratory data showed that vitamin E acetate, an additive in some THC-containing e-cigarettes, was strongly linked to the EVALI outbreak.[725] 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 recognised features of COPD.[726-730] These data are summarized in a review by Gotts and colleagues,[731] although it 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.[721-724] 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.[732] 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.[733]

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.[734] 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.

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.[527] Prolonged abstinence rates in the pharmacotherapy groups ranged from 14% to 27%, and in the placebo group from 5% to 9%.[527]

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%).[735] Varenicline and bupropion showed similar efficacy, however, the group receiving varenicline compared with bupropion smoked more cigarettes per day.[735]

Pharmacotherapy to treat 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.[736-740] However, a systematic review combining data from 9 studies demonstrated a reduction in the rate of FEV1 decline of 5.0 mL/year in active treatment arms compared with placebo arms.[741] The difference between long-acting bronchodilator containing treatment arms and placebo arms was 4.9 mL/year. The difference between inhaled corticosteroid 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 3.18**. The choice within each class depends on the availability and cost of medication, and the clinical response balanced against side effects. 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.[742]

Bronchodilators

Bronchodilators are medications that increase FEV1 and/or change other spirometric variables (**Figure 3.19**). 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,[282,743] 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.[744,745]

Bronchodilator dose-response (FEV1 change) curves are relatively flat with all classes of bronchodilators.[746-752] 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[753] but is not necessarily helpful in stable disease.[754] Bronchodilator medications in COPD are most often given on a regular basis to prevent or reduce symptoms. Toxicity is also dose-related (**Figure 3.18**). Use of short acting bronchodilators on a regular basis is not generally recommended.

Commonly Used Maintenance Medications in COPD*

Figure 3.18

Generic Drug Name	Inhaler Type	DELIVERY OPTIONS			Duration of Action
		Nebulizer	Oral	Injection	
BETA$_2$-Agonists					
Short-acting (SABA)					
Fenoterol	MDI	✓	pill, syrup		4-6 hours
Levalbuterol	MDI	✓			6-8 hours
Salbutamol (albuterol)	MDI & DPI	✓	pill, syrup, extended release tablet	✓	4-6 hours 12 hours (ext. release)
Terbutaline	DPI		pill	✓	4-6 hours
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				MDI 12 hours
Glycopyrronium bromide	DPI		solution	✓	12-24 hours
Tiotropium	DPI, SMI, MDI				24 hours
Umeclidinium	DPI				24 hours
Glycopyrronium		✓			12 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	✓			6-8 hours
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	✓	Variable, up to 24 hours
Theophylline (SR)			pill	✓	Variable, up to 24 hours
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				12 hours
Budesonide/formoterol/glycopyrrolate	MDI				12 hours
Phosphodiesterase-4 Inhibitors					
Roflumilast			pill		24 hours
Mucolytic Agents					
Erdosteine			pill		12 hours
Carbocysteine†			pill		
N-acetylcysteine†			pill		

*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.

Bronchodilators in Stable COPD

Figure 3.19

- 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
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**

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.[748,749] Regular and as-needed use of SABAs improve FEV1 and symptoms.[755] LABAs show duration of action of 12 or more hours and do not preclude additional benefit from as-needed SABA therapy.[756]

Formoterol and salmeterol are twice-daily LABAs that significantly improve FEV1 and lung volumes, dyspnea, health status, exacerbation rate and number of hospitalizations,[757] but have no effect on mortality or rate of decline of lung function. Indacaterol is a once daily LABA that improves breathlessness,[758,759] health status[759] and exacerbation rate.[759] Some patients experience cough following the inhalation of indacaterol. Oladaterol and vilanterol are additional once daily LABAs that improve lung function and symptoms.[760,761]

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,[762] and oxygen consumption can be increased under resting conditions in patients with chronic heart failure,[763] these metabolic effects decrease over time (i.e., show tachyphylaxis). Mild falls in partial pressure of oxygen (PaO_2) can occur after administration of both SABAs and LABAs[764] 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.[757,765,766]

Antimuscarinic drugs

Antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle.[767] Short-acting antimuscarinics (SAMAs), namely ipratropium and oxitropium, also block the inhibitory neuronal receptor M2, which potentially can cause vagally induced bronchoconstriction.[768] Long-acting muscarinic antagonists (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.[767]

A systematic review of RCTs concluded that ipratropium, a short acting muscarinic antagonist, alone provided small benefits over short-acting beta$_2$-agonist in terms of lung function, health status and requirement for oral steroids.[769] 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).[767,770] LAMA treatments improve symptoms, including cough and sputum and health status.[767,771,772] They also improve the effectiveness of pulmonary rehabilitation[773,774] and reduce exacerbations and related hospitalizations.[771] Clinical trials have shown a greater effect on exacerbation rates for LAMA treatment (tiotropium) versus LABA treatment.[775,776]

Adverse effects

Inhaled anticholinergic drugs are poorly absorbed which limits the troublesome systemic effects observed with atropine.[767,777] 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.[768,778] Although occasional urinary symptoms have been reported, there are no data to prove a true causal relationship.[779] Some patients using ipratropium report a bitter, metallic taste. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported.[780,781] In a large, long-term clinical trial in COPD patients, tiotropium added to other standard therapies had no effect on cardiovascular risk.[740] Although there were some initial concerns regarding the safety of tiotropium delivery via the Respimat®[782] inhaler, 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.[783] 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.[784-786]

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.[787-789] 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,[787] 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.[790] Addition of theophylline to salmeterol produces a greater improvement in FEV1 and breathlessness than salmeterol alone.[791,792] Earlier studies reported contradictory evidence regarding the effect of low-dose theophylline on exacerbation rates.[793,794] A study that investigated the effectiveness of adding low-dose theophylline to ICS in COPD patients at increased risk of exacerbation showed no difference compared with placebo in the number of COPD exacerbations over a one-year period.[795] A large placebo-controlled trial showed no effect of oral theophylline alone or in combination with prednisolone 5 mg daily on exacerbations of severe COPD.[796]

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.[788,790] 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.[797,798] Combinations of SABAs and SAMAs are superior compared to either medication alone in improving FEV1 and symptoms.[799] Treatment with formoterol and tiotropium in *separate inhalers* has a bigger impact on FEV1 than either component alone.[800] There are numerous combinations of a LABA and LAMA in a *single inhaler* available (**Figure 3.18**). These combinations improve lung function compared to placebo;[797] 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.[801] Single inhalers improve adherence to treatment.[802] In studies where patient reported outcomes (PROs) are the primary endpoint or in pooled analyses, combination bronchodilators have a greater impact on PROs compared to monotherapies.[803-806] 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.[807] 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.[562] The LABA+LAMA combination demonstrated favorable improvements compared with the monotherapies for the majority of outcomes irrespective of baseline HRQoL.[808] 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 COPD patients[809] (**Figure 3.19**). These findings have been shown in people across different ethnic groups (Asian as well as European).[810]

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.[811] 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.[812] 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.[813] 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.[448] 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.[814]

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 end-point used for efficacy assessment of drugs with anti-inflammatory effects (**Figure 3.20**).

Anti-Inflammatory Therapy in Stable COPD

Figure 3.20

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)**
PDE4 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)**
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 and Antioxidant Agents	• Regular treatment with mucolytics such as erdosteine, carbocysteine and NAC reduces the risk of exacerbations in select populations **(Evidence B)** • Antioxidant mucolytics are recommended only in selected patients **(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

Inhaled corticosteroids (ICS)

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.[815,816] 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.[813] 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. [448,817]

Efficacy of ICS (alone)

Most studies have found that regular treatment with ICS alone does not modify the long-term decline of FEV1 nor mortality in people with COPD.[818] 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.[818] 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.[697] However, an increase in mortality was not observed in COPD patients treated with fluticasone furoate in the Survival in Chronic Obstructive Pulmonary Disease with Heightened Cardiovascular Risk (SUMMIT) trial.[819] In moderate COPD, 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.[820] A number of studies have investigated whether there is a relationship between ICS treatment and risk of lung cancer with conflicting results.[821]

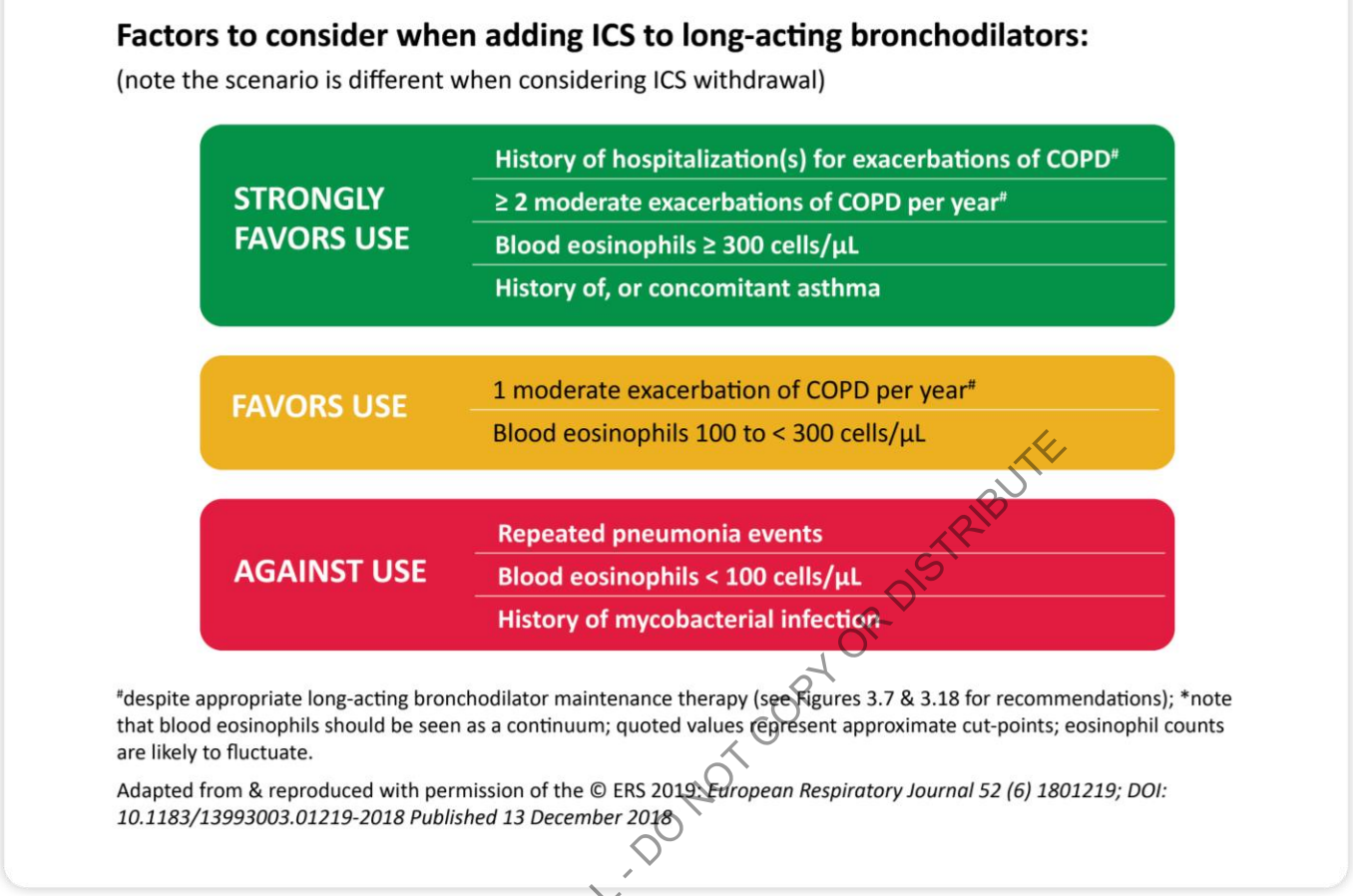
ICS in combination with long-acting bronchodilator therapy

In patients with moderate to very severe COPD and exacerbations, an ICS combined with a LABA is more effective than either component alone in improving lung function, health status and reducing exacerbations.[822,823] Clinical trials powered on all-cause mortality as the primary outcome failed to demonstrate a statistically significant effect of combination therapy on survival.[697,819]

Most studies that found a beneficial effect of a LABA+ICS fixed dose combination (FDC) over a LABA alone on exacerbation rate, recruited patients with a history of at least one exacerbation in the previous year.[822] A pragmatic RCT conducted in a primary healthcare setting in the United Kingdom compared a LABA+ICS combination with usual care. Findings showed an 8.4% reduction in moderate-to-severe exacerbations (primary outcome) and a significant improvement in CAT™ score, with no difference in the rate of healthcare contacts or pneumonias. However, basing recommendations on these results is difficult because of the heterogeneity of treatments reported in the usual care group, the higher rate of treatment changes in the group receiving the LABA+ICS combination of interest, and the medical practice patterns unique to the UK region where the study was conducted.[824]

Factors to Consider when Initiating ICS Treatment

Figure 3.21



#despite appropriate long-acting bronchodilator maintenance therapy (see Figures 3.7 & 3.18 for recommendations); *note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

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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.[443-448] 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.[453] Data modeling indicates that ICS containing regimens have little or no effect at a blood eosinophil count < 100 cells/µL,[443] 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,[825-827] notably haemophilus, and increased bacterial infections and pneumonia.[828] Lower blood eosinophil counts therefore may identify individuals with microbiome profiles associated with increased risk of clinical worsenings 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[443,444,446]; 2) Pre-specified analyses comparing triple therapy versus LABA+LAMA or LAMA[445,447,448]; and 3) other analyses comparing LABA+ICS versus LABA+LAMA[829] or studying ICS withdrawal.[573,574,830]

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).[445,448,813] 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 one or two long-acting bronchodilators are shown in **Figure 3.21**.[519]

Adverse effects

There is high quality evidence from RCTs that ICS use modifies the airway microbiome[831] and is associated with higher prevalence of oral candidiasis, hoarse voice, skin bruising and pneumonia.[818] This excess risk has been confirmed in ICS studies using fluticasone furoate, even at low doses.[832] Patients at higher risk of pneumonia include those who currently smoke, are aged ≥ 55 years, have a history of prior exacerbations or pneumonia, a body mass index (BMI) < 25 kg/m^2, a poor MRC dyspnea grade and/or severe airflow obstruction.[833,834] Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of developing pneumonia.[835] In studies of patients with moderate COPD, ICS by itself or in combination with a LABA did not increase the risk of pneumonia.[819,834]

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.[738,832,836-838] Results of observational studies suggest that ICS treatment could also be associated with increased risk of diabetes/poor control of diabetes,[839] cataracts,[840] and mycobacterial infection.[841] An increased risk of tuberculosis has been found in both observational studies and a meta-analysis of RCTs.[842-844] In the absence of RCT data on these issues, it is not possible to draw firm conclusions.[845] ICS and lung cancer incidence is discussed in **Chapter 5**.

Withdrawal of ICS

Results from withdrawal studies provide equivocal results regarding consequences of withdrawal on lung function, symptoms and exacerbations.[846-850] Some studies have shown an increase in exacerbations and/or symptoms following ICS withdrawal, while others have not. There has been evidence for a modest decrease in FEV1 (approximately 40 mL) with ICS withdrawal,[850] which could be associated with increased baseline circulating eosinophil numbers.[830] A study examining ICS withdrawal on a background of dual bronchodilator therapy demonstrated that both FEV1 loss and an increase in exacerbation frequency associated with ICS withdrawal was greatest among patients with a blood eosinophil count ≥ 300 cells/µL at baseline.[573] Differences between studies may relate to differences in methodology, including the use of background long-acting bronchodilator medication(s) which may minimize any effect of ICS withdrawal.

Triple therapy (LABA+LAMA+ICS)

The step up in inhaled treatment to LABA plus LAMA plus ICS (triple therapy) can occur by various approaches[851] and has been shown to improve lung function, patient reported outcomes and reduce exacerbations when compared to LAMA alone, LABA+LAMA and LABA+ICS.[445,447,448,852-859] 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.[860]

A *post-hoc* pooled analysis of three triple therapy clinical trials in COPD patients with 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.[861] Two large one-year randomized controlled trials (named IMPACT and ETHOS) were reviewed earlier 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.[566,862]

Oral glucocorticoids

Oral glucocorticoids have numerous side effects, including steroid myopathy[863] which can contribute to muscle weakness, decreased functionality, and respiratory failure in people with very severe COPD. 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.[864] Conversely, prospective studies on the long-term effects of oral glucocorticoids in stable COPD are limited.[865,866] 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.

Phosphodiesterase-4 (PDE4) inhibitor

The principal action of PDE4 inhibitors is to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP.[867] 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 COPD, and a history of exacerbations.[868] The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators,[869] and in patients who are not controlled on fixed-dose LABA+ICS combinations.[568] The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation.[570,572] There has been no study directly comparing roflumilast with an inhaled corticosteroid.

Adverse effects

Roflumilast has more adverse effects than inhaled medications for COPD.[870] 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.

Antibiotics

In older studies prophylactic, *continuous* use of antibiotics had no effect on the frequency of exacerbations in COPD[871,872] 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.[873] Later studies have shown that regular use of some antibiotics may reduce exacerbation rate.[874,875]

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.[571,876,877] Azithromycin use was associated with an increased incidence of bacterial resistance, prolongation of QTc interval, and impaired hearing tests.[571] A *post-hoc* analysis suggests lesser benefit in active smokers.[572] 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.[878] Long-term doxycycline did not reduce exacerbations, although there may be responder subgroups.[879]

Mucolytic (mucokinetics, mucoregulators) and antioxidant agents (N-acetylcysteine, carbocysteine, erdosteine)

In COPD patients not receiving ICS, regular treatment with mucolytics such as carbocysteine and N-acetylcysteine

(NAC) may reduce exacerbations and modestly improve health status.[880-883] 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.[884]

Other drugs with potential to reduce exacerbations

Four large phase 3 studies have investigated the efficacy of the anti-IL-5 monoclonal antibody mepolizumab[885] and the anti-IL-5 receptor-α antibody benralizumab[886] in patients with severe COPD, recurrent exacerbations and peripheral blood evidence of eosinophilic inflammation despite high intensity inhaled therapy. The studies showed a 15% to 20% reduction in the rate of severe exacerbations but the effect was not always statistically significant, and it was variable between studies and doses. There was no effect on FEV1 or quality of life scores and no consistent relationship between the response to treatment and the peripheral blood eosinophil count. A *post-hoc* analysis of the mepolizumab trial showed greater benefit and more clear evidence of a blood eosinophil related treatment effect against oral corticosteroid treated exacerbations raising the possibility that this treatment might find a role in a highly selected subgroup of patients with eosinophilic COPD and frequent requirement for oral corticosteroids. Further studies are required to investigate this possibility.

A RCT showed that treatment with the humanized anti-IL-4 receptor alpha monoclonal antibody dupilumab reduced exacerbations and improved FEV1 as well as symptoms and health-related quality of life in patients with COPD, chronic bronchitis, a baseline blood eosinophil count ≥ 300 cells/µL, and a relevant exacerbation history. These findings are potentially important and clinical practice changing but require confirmation in further studies.[887]

Nedocromil and leukotriene modifiers have not been tested adequately in COPD patients and the available evidence does not support their use. [888,889]

There was no evidence of benefit, and some evidence of harm, including malignancy and pneumonia, following treatment with an anti-TNF-alpha antibody (infliximab) in moderate to severe COPD.[890]

A recent Cochrane meta-analysis did not show sufficient evidence to support the use of immunostimulants.[891]

An RCT of the selective β1 receptor blocker metoprolol in patients with moderate or severe COPD, 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.[892] There is no evidence that beta-blockers should be used in people with COPD who do not have a cardiovascular indication for their use.

Simvastatin did not prevent exacerbations in people with COPD who had no metabolic or cardiovascular indication for statin treatment.[893] 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.[894]

There is no evidence that supplementation with vitamin D has a positive impact on exacerbations in unselected patients.[895] In a meta-analysis vitamin D supplementation reduced exacerbation rates in patients with low baseline vitamin D levels,[896] but a more recent study has shown no effect.[897]

Adherence to inhaled COPD medications

Adherence is defined as the process by which a person takes their medication as prescribed by a healthcare provider.[898] 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.[899-909]

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[910] 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.[910] Most studies included were conducted in high-income countries and many used pharmacy claims data to assess adherence.[910] Self-reported non-adherence to COPD medication varies between 28% and 74% (mean 50.9%) in high income countries[901,910,911] and between 46% and 93% (mean 61.7%) in low- and middle-income countries (LMICs).[912-915] 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.[916,917]

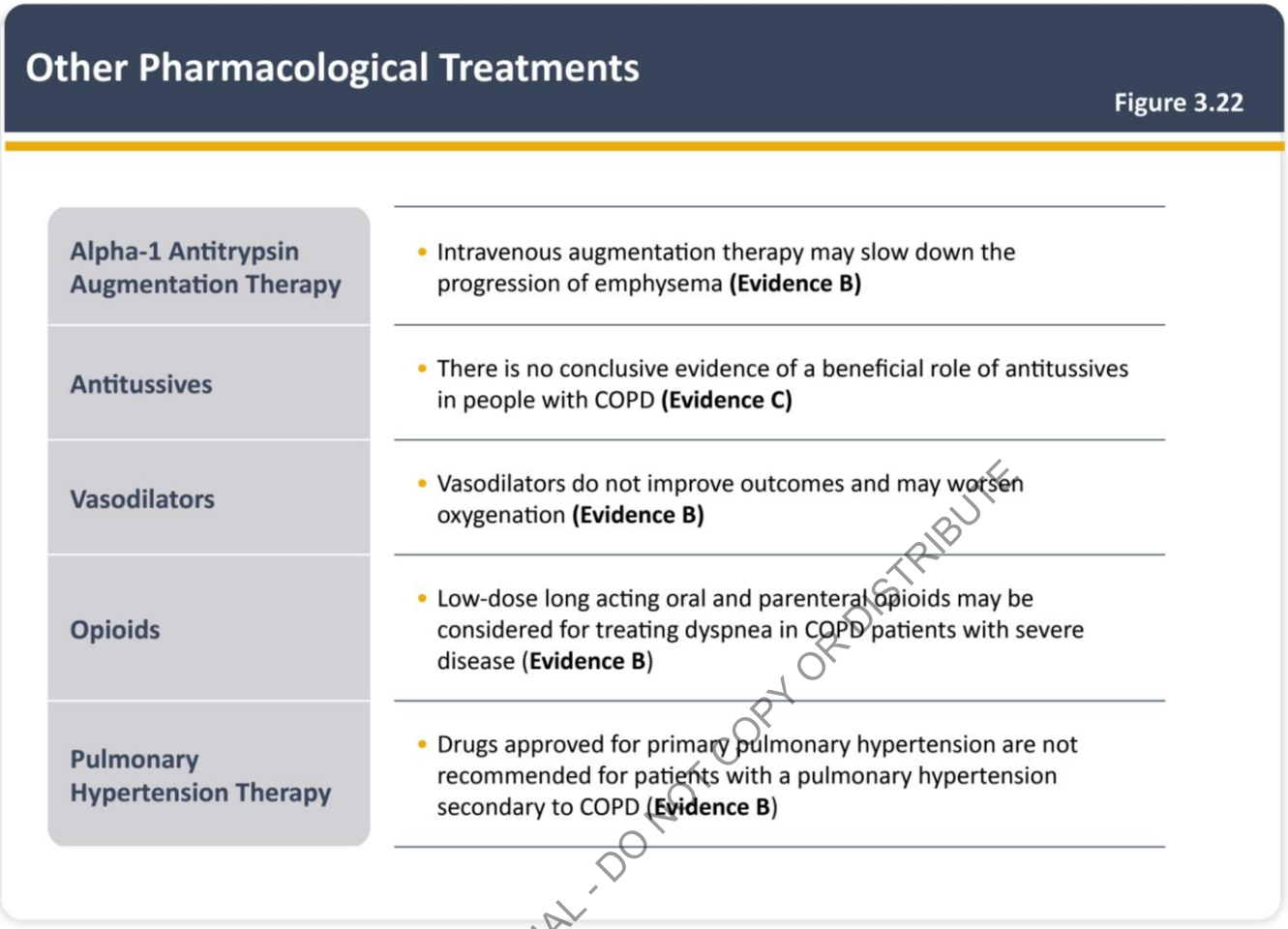
Adherence is a complex concept, influenced by multiple factors including social/environmental, person-related and treatment-related factors.[918] Several studies have explored the variables associated with medication adherence in people with COPD.[910,912] Factors such as the presence of co-morbidities, 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.[909,910,912,913,919,920] In addition, socioeconomic factors, including unemployment, low-income status, immigration status, living alone and poor medication availability[60] have been shown to negatively influence inhaled medication adherence and to be related to the non-use of medication.[919,921,922]

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. [589,923]

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.[611,910] 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.[657] Involving a person in establishing an individually tailored treatment plan has been shown to improve adherence.[924] 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 3.22**.



Alpha-1 antitrypsin augmentation therapy

The logical approach to minimize the development and progression of lung disease in alpha-1 antitrypsin deficiency (AATD) patients 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[925] and that this reduction is most effective for patients with FEV1 35% to 49% predicted.[926] 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 focussed 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 mild COPD in heterozygotes for the Z gene[106,107] 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.[927-929] 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.[930] 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.[930]

The indication for AAT augmentation is emphysema although there are no fixed criteria for diagnosis or confirmation. The evidence for augmentation therapy efficacy varies according to the outcome studied.[931] Intravenous augmentation therapy has been recommended for individuals with AATD and an FEV1 ≤ 65% predicted based on previous observational studies. However, the last study powered on CT scan as an outcome has recommended that all patients with evidence of progressive lung disease should be considered for those with lung disease related to AATD, and an FEV1 > 65%. Individual discussion is recommended with consideration of the cost of therapy and lack of evidence for much benefit.[932] The main limitation for this therapy is the very high cost and lack of availability in many countries.

Antitussives

The role of antitussives in people with COPD is inconclusive.[933]

Vasodilators

Vasodilators have not been properly assessed in COPD patients with 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.[934] Studies have shown that sildenafil does not improve the results of rehabilitation in people with COPD and moderately increases pulmonary artery pressure.[935] Tadalafil does not appear improve exercise capacity or health status in COPD patients with mild pulmonary hypertension.[936]

Management of mucus hypersecretion

Treatment goals for patient with chronic bronchitis (CB) 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.[937] Smoking cessation may decrease airway injury by limiting immune mechanisms that cause persistent inflammation and abnormal epithelial cell gene expression.[938]

Mucus clearance treatments that promote mechanical movement through the airway such as oscillating positive expiratory pressure (OPEP) therapy may improve mucus mobilization, symptoms and quality of life in people with COPD who produce sputum daily or most days.[939,940] 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 [941-945]

Long-acting muscarinic antagonists, predominantly tiotropium and aclidinium, can improve sputum production and decrease cough in patients with moderate to severe COPD.[946-949] Triple therapy with dual long acting bronchodilators combined with inhaled steroids 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.[881] 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.[881] Recombinant human DNase has similarly shown lack of benefit in mucopurulent patients with COPD.[950,951] New classes of mucolytics agents are being developed.[952] In a small double-blind placebo-controlled study, patients randomized to receive a CFTR potentiator icenticaftor had improvements in FEV1 and sputum bacterial colonization compared to placebo.[953] 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.[954-957]

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."[624] 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.[624]

Systematic reviews have provided evidence that self-management interventions improve outcomes in COPD. A 2022 Cochrane review reported that interventions for people with COPD are associated with improvements in HRQoL, a lower probability of respiratory-related hospital admissions, and no excess respiratory-related and all-cause mortality risks.[958] 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.[959,960] However, a previous Cochrane review and another meta-analysis reported no impact of self-management interventions on overall mortality, and while the Cochrane review did find a small, but statistically significant, higher respiratory-related mortality rate in the self-management invention group as compared to usual care, the authors of the review stated the results should be interpreted with caution as misclassification in cause of death is common, the overall effect was dominated by two studies, and no effect on all-cause mortality was seen in the overall analysis. Furthermore, two independent, well designed studies, the COMET[961] and the PIC-COPD,[962] 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, once again strengthens the view that self-management interventions are unlikely to cause harm.[958]

An RCT has shown that implementation of a comprehensive 3-month program to improve long-term self-management of *patients recently discharged from hospital* with COPD exacerbation resulted in nearly two-fold higher rates of COPD-related hospitalizations and emergency visits over 6 months. These data suggest that self-management strategies in recently hospitalized patients may lead to increased health care service utilization compared with usual care.[963]

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.[964] 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.[965]

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. A meta-analysis of 52 studies shows that integrated disease management probably results in improvement in disease-specific quality of life, exercise capacity, hospital admissions, and hospital days, although not mortality.[966] In contrast, a large multicenter study in primary care within an existing well-organized system of care did not confirm this.[967] Besides, delivering integrated interventions by telemedicine did not show a significant effect.[968,969] The pragmatic conclusion is that well organized care is important, but there may be no advantage in structuring it tightly into a formalized program. Furthermore, integrated care needs to be individualized to the stage of the person's illness and health literacy.

Physical activity

Pulmonary rehabilitation, including community and home-based, is an approach with clear evidence of benefits. However, the challenge is promoting physical activity and maintaining it. There is evidence that physical activity is decreased in COPD patients.[970] This leads to a downward spiral of inactivity which predisposes patients to reduced quality of life, increased rates of hospitalization and mortality.[971-973] As such, there has been tremendous interest in implementing behavior-targeted interventions with the aim of improving physical activity[974] and these should be encouraged.[971] Technology-based interventions have the potential to provide convenient and accessible means to enhance exercise self-efficacy, and to educate and motivate people in their efforts to make healthy lifestyle changes.[975] The use of an internet-mediated intervention may benefit people with COPD with low baseline self-efficacy to increase physical activity.[976] However, most published studies to date provide little guidance, being inconsistent in the techniques, and lacking 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. 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.[977] 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.[978] Non-pharmacological interventions such as pursed lip breathing and diaphragmatic breathing have also been shown to improve pulmonary function and increased exercise capacity in patients with COPD.[979]

Exercise training

A meta-analysis of RCTs found that exercise training alone, or with the addition of activity counseling, significantly improved physical activity levels in COPD patients.[980] A combination of constant load or interval training with strength training provides better outcomes than either method alone.[981]

Where possible, endurance exercise training to 60-80% of the symptom-limited maximum work or heart rate is preferred,[982] or to a Borg-rated dyspnea or fatigue score of 4 to 6 (moderate to severe).[983] Endurance training can be accomplished through either continuous or interval exercise programs. The latter 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 other comorbidities.[984,985]

In some cultures, other alternatives such as Tai Chi practice, emphasizing the use of 'mind' or concentration for control of breathing and circular body movement, has been shown to improve exercise capacity in comparison to usual care in COPD patients.[986] However from this meta-analysis, the effects of Tai Chi in reducing dyspnea level and improving quality of life remain inconclusive. Future studies addressing these topics and the most beneficial protocols for Tai Chi practice are warranted.

Exercise training can be enhanced by optimizing bronchodilators,[774] since both LAMA and LABA have shown reduced resting and dynamic hyperinflation. These changes contribute to better training effects.[282,987] Adding strength training to aerobic training is effective in improving strength, but does not improve health status or exercise tolerance.[988] Upper extremities exercise training improves arm strength and endurance, and results in improved functional capacity for upper extremity activities.[989] Exercise capacity may also be improved by whole-body vibration training.[990]

Inspiratory muscle training increases strength of inspiratory muscles,[991] but this not consistently translate to better performance, reduced dyspnea or improved health related quality of life when added to a comprehensive pulmonary rehabilitation program.[992-994]

Pulmonary rehabilitation

The benefits to COPD patients from pulmonary rehabilitation are considerable (**Figure 3.23**), and rehabilitation has been shown to be the most effective therapeutic strategy to improve shortness of breath, health status and exercise tolerance.[995] 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.[996,997]

Exercise-induced oxygen desaturation can be seen in a significant minority of COPD patients and has been associated with impaired quality of life, exacerbation risk, and mortality.[998] A large RCT did not suggest clinical improvement with long term oxygen therapy for patients without resting hypoxemia but exertional desaturation.[999] During pulmonary rehabilitation 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,[1000] but most evidence was limited by low study quality. A large RCT,[631] with blinding of participants, trainers and assessors, demonstrated that COPD patients 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 severe COPD on long-term oxygen therapy (LTOT) 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 (HFNT). HFNT may reduce respiratory muscle load and respiratory rate, while increasing expiratory time.[1001] In an RCT, the delivery of HFNT during training sessions, as compared with usual oxygen, was not associated with a greater improvement in endurance time, the primary outcome, or in health status.[1002] However, a greater improvement in 6-minute walking distance (6MWD) test was observed with HFNT. A similar small trial suggested an improved walking distance.[1003] The proportion of patients reaching the minimal clinically important difference (MCID) in endurance time and 6MWD was also significantly higher with HFNT. Finally, there was no significant difference between the two therapies in patients' satisfaction. Further studies are needed to evaluate the efficacy of this treatment.

Pulmonary Rehabilitation, Self-Management and Integrative Care in COPD

Figure 3.23

Pulmonary Rehabilitation	• Rehabilitation is indicated in all patients with relevant symptoms and/or a high risk for exacerbation **(Evidence A)** • Pulmonary rehabilitation improves dyspnea, health status and exercise tolerance in stable patients **(Evidence A)** • Pulmonary rehabilitation reduces hospitalization among patients who have had a recent exacerbation (≤ 4 weeks from prior hospitalization) **(Evidence B)** • Pulmonary rehabilitation leads to a reduction in symptoms of anxiety and depression **(Evidence A)**
Education and Self-Management	• Education is needed to change patient's knowledge but there is no evidence that used alone it will change patient behavior **(Evidence C)** • Self-management intervention with communication with a health care professional improves health status and decreases hospitalizations and emergency department visits **(Evidence B)**
Integrated Care Programs	• Integrative care and telehealth have no demonstrated benefit at this time **(Evidence B)**
Physical Activity	• Physical activity is a strong predictor of mortality **(Evidence A)**. People with COPD should be encouraged to increase their level of physical activity although we still do not know how to best ensure the likelihood of success

There are data from large RCTs regarding the effectiveness of pulmonary rehabilitation after hospitalization for an acute exacerbation of COPD. 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.[701] 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[704] and fewer rehospitalizations at one year.[1004] One study has reported that initiating pulmonary rehabilitation before the patient's discharge may compromise survival through unknown mechanisms.[1005] Pulmonary rehabilitation ranks as one of the most cost-effective treatment strategies.[615]

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. Virtual reality pulmonary rehabilitation could be an alternative combined or not with traditional exercise training; this may be of particular interest in countries where the length of pulmonary rehabilitation programs is limited to less than 4 weeks.[1006] Another challenge is encouraging sustained long-term physical activity. Although the

approach may need to be personalized, behavioral lifestyle physical activity intervention has shown promising results i.e., the potential to decrease sedentarity and increase physical activity in patients with moderate to severe COPD.[1007] A major barrier to full participation is access, which is particularly limited by geography, culture, finances, transport and other logistics.[614,656,662,1008]

Pulmonary rehabilitation can be conducted at a range of sites.[614] Community-based and home-based programs have been shown to be as effective as hospital-based programs in randomized controlled trials,[1009,1010] as long as the frequency and intensity are equivalent.[1011] 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[1009] or a walking program[1010] could be considered as alternative to traditional hospital rehabilitation training programs. There is also evidence that standardized home-based pulmonary rehabilitation programs improve dyspnea in COPD patients.[1012] 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.[1013] Another challenge is that the benefits of rehabilitation tend to wane over time. There is insufficient evidence, with conflicting research findings in the 11 available RCTs, to recommend continuation of lower intensity or lower frequency exercise programs with the aim of maintaining benefit long-term. However, if such programs are available they should target health behavior taking into account the patient's own preferences, needs and personal goals.[618,1014] Pulmonary rehabilitation may help reduce anxiety and depression symptoms.[1015]

Tele-rehabilitation

In- or out-patient pulmonary rehabilitation (PR) in COPD is effective in improving several clinically relevant outcomes.[995,1016] There is clear evidence that core components of PR including exercise training combined with disease-specific education and self-management interventions[614,995] can benefit almost every COPD patient.[1017-1019]

However, there are many challenges encountered in the delivery of PR, which include systemic barriers integral to some health care systems leading to a scarcity of in-person PR programs and facilities. In many regions, the programs that do exist tend to be located in urban areas. Hence attending PR is challenging for many COPD patients. Even for those patients residing in urban areas, availability of frequent transportation that is required for out-patient PR may still be a challenge.

Tele-rehabilitation has been proposed as an alternative to the traditional approaches. This has become even more relevant in the COVID-19 pandemic era where in-person PR has not been feasible, and models of delivery had to be adapted. However, it is important to distinguish between evidence-based tele-rehabilitation models and pandemic-adapted models. Most of the available evidence regarding tele-rehabilitation has been analyzed in a recent Cochrane review.[1020]

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 PR 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[1021] and accurately prescribing exercise capacity.[1022]

Promoting physical activity is also central to the recommendations that should be given to every COPD patient regardless of disease severity. Promoting physical activity using smartphone apps is gaining popularity although at present data on effectiveness are lacking.[1023]

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; 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 PR). 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 PR is accessible to all, we must understand the barriers that might be unique to tele-rehabilitation.

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.[334,1024-1028] Malnutrition has been reported in 30-60% of patients hospitalized with COPD;[1029] up to 50% of people with COPD weigh less than 90% of ideal body weight.[1030] 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.[1031,1032] The severity of airflow obstruction correlates with the presence of malnutrition[1033] since ventilator inefficiency increases daily energy requirements.[1034] 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.[1035-1037]

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 body weight, quality of life, respiratory muscle strength and 6-minute walk distance.[679,1029] However, nutritional support has not been consistently shown to improve lung function.[679,1038-1040] Multimodality treatment that incorporates rehabilitation with nutritional support and protein supplementation may improve fat free mass, BMI and exercise performance.[1041] Among malnourished, hospitalized people with COPD, a protein enriched supplementation decreased mortality and improved handgrip strength, body weight and nutritional biomarkers 90 days post hospital discharge.[1042]

INTERVENTIONAL & SURGICAL THERAPIES 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 mucous production, and improve quality of life (**Figure 3.24**).

Overview of Current and Proposed Surgical and Bronchoscopic Interventions for People with COPD Figure 3.24

Symptoms	Chronic Mucus Production	Exacerbations	Dyspnea
Disorders	• Chronic bronchitis	• Acute and chronic bronchitis • Bulla • Emphysema • Tracheobronchomalcia	• Bulla • Emphysema • Tracheobronchomalcia
Surgical and Bronchoscopic Interventions	• Nitrogen cryospray • Rheoplasty	• Targeted lung denervation	• Giant bullectomy • Large airway stenting • EBV • Coil • Thermal vapor ablation • Lung sealants • LVRS • Lung transplantation

Lung structural related therapies for COPD 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 III 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.

Lung surgical treatments for patients with emphysema

Bullectomy

Giant bullectomy is a rare, but effective procedure for surgical resection of bulla that occupies > 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.[1043-1045] Blood or thrombin instillation may be effective in those unfit for resection.[1046-1048]

Lung volume reduction surgery (LVRS)

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,[1049] and increase lung elastic recoil pressure and density.[1050] The structural changes that result from LVRS can significantly improve expiratory flow and chest wall, respiratory muscle and cardiac mechanics.[1051,1052] that results in improvements in FEV1, walking distance and quality of life.[1053-1056] LVRS can be performed unilaterally or bilaterally. In the National Emphysema Treatment Trial (NETT), a RCT that included severe emphysema patients, bilateral LVRS improved survival in patients with upper-lobe emphysema and low post-rehabilitation exercise capacity.[289] 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.[1057]

LVRS has been demonstrated to result in higher mortality than medical management in severe emphysema patients with FEV1 ≤ 20% predicted and either homogeneous emphysema on high resolution computed tomography or a DLco ≤ 20% of predicted.[1058] In addition to a lower DLco, a lower FEV1 and BMI have also been reported to increase mortality.[1059] Postoperative BODE (body mass index, degree of airflow obstruction, level of dyspnea and exercise capacity) is a predictor of survival following LVRS.[1060] 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.[1061] Identification of target zones using three-dimensional computed tomographic imaging is beneficial in selecting resectable target zones.[1062] A prospective economic analysis in NETT indicated that LVRS is costly relative to healthcare programs that do not include surgery.[1063]

Post NETT, experienced centers have reported substantial physiological and functional improvements with LVRS with reduced morbidity and mortality.[1064,1065] However, the numbers of patients undergoing LVRS remain low worldwide.[1065,1066] 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.[1067] 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.[1068] To achieve successful outcomes, a multidisciplinary team is key to select potential LVRS patients and coordinate postoperative care.[1069]

Lung transplantation

Over 1,000 patients with COPD undergo lung transplantation on an annual basis, about 30.6% of all patients that undergo transplantation.[1070] Since implementation of the lung allocation severity (LAS) scoring system, the numbers of patients undergoing lung transplantation for COPD is 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%.[1071] They should be considered for listing for lung transplantation when the BODE index is > 7, FEV1 is < 15% to 20%, and 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.[1071] 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.[1072]

Lung transplantation in patients with COPD has been predominately associated with an improvement in quality of life, not an increase in survival except for COPD patients with severe AATD or those severely impaired with high BODE scores.[1043,1073-1079] The median survival post lung transplantation for COPD is 5.9 years.[1070] Over 70% of lung transplants conducted in COPD patients are double lung transplants; the remainder are single lung transplants.[1080] Bilateral lung transplantation leads to longer survival in patients with COPD especially in those < 60 years of age.[1081,1082]

Two unique native lung complications have been proposed to account for the superiority of double lung transplantation in patients with COPD, native lung hyperinflation and lung cancer occurrence in the native lung.[1083,1084] Lung cancer has been reported to occur in the native lung following single lung transplantation with an incidence of 5.2-6.1%.[1083,1085] Native lung hyperinflation following single lung transplantation for COPD has been reported to occur 15-30% of the time.[1086,1087] Positive pressure ventilation in a patient with COPD with an overly compliant native lung coupled with reduced compliance in an edematous allograft may result in native lung hyperinflation. However, some studies have shown no impact of single lung transplant on post-transplant morbidity, and even improved survival following single lung transplantation in patients with COPD.[1086,1088,1089]

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.[1090] The complications most seen in COPD patients after lung transplantation are acute rejection, bronchiolitis obliterans, opportunistic infections and lymphoproliferative disease.[1091]

Bronchoscopic interventions in COPD

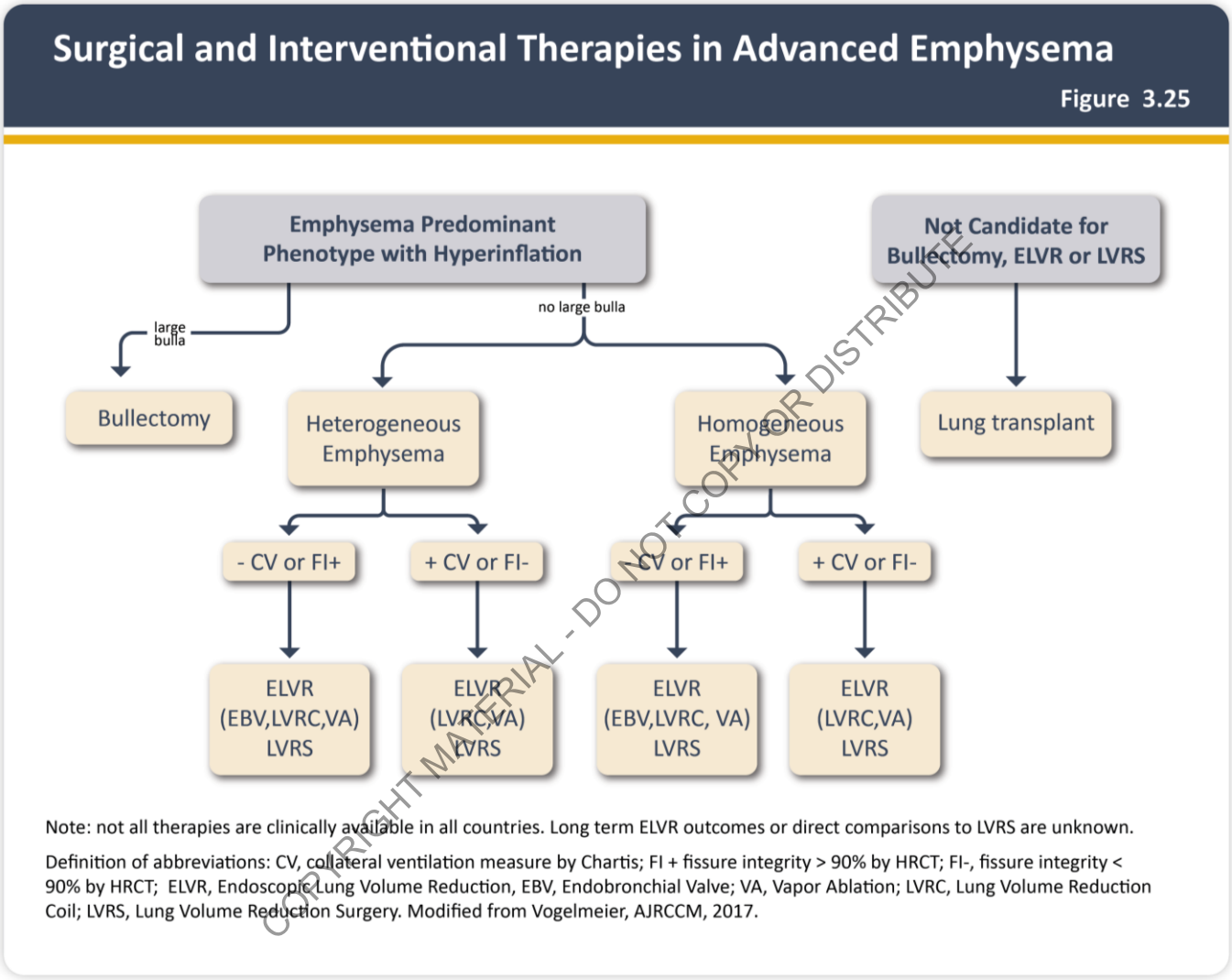
- In selected patients with heterogeneous or homogenous emphysema and significant hyperinflation refractory to optimized medical care, surgical or bronchoscopic modes of lung volume reduction (e.g., endobronchial one-way valves, lung coils or thermal ablation) may be considered.[1092] Some of these therapies (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 very severe COPD and without 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.[1093] These include a variety of different bronchoscopic procedures to perform lung volume reduction (i.e., endoscopic lung volume reduction, ELVR) including airway bypass stents, endobronchial one-way valves (EBV) , self-activating coils, sealants and thermal ablative techniques.[1093] 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 (endobronchial valve, coil placement or thermal ablation) or surgical resection (lung volume reduction surgery, LVRS) to treat hyperinflation in an emphysematous patient 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.[1094] **Figure 3.25** provides an overview of the various interventional and surgical options for patients with emphysema.



Endobronchial one-way valves (EBV)

EBV are the most well studied therapy of all the ELVR techniques. RCTs showed significant increases in FEV1 and 6-minute walk distance 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.[291,501] Adverse effects in the endobronchial valve treatment group in both studies included pneumothorax, valve removal or valve replacement.[501] Pneumothorax was seen in 26.6% of subjects treated with the endobronchial valve usually within the first 72 hours of the procedure (76%).[291,1095,1096] But benefits have also been shown in patients with heterogeneous compared to those with homogenous emphysema in one study.[501]

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.[290] Pleural adhesions may also be a contributing factor to the development of a pneumothorax.[1097] The occurrence of pneumothorax highlights the need for physicians performing this procedure to have expertise in the management of procedural complications.[290]

After the post-procedural period however, patients treated with EBV compared to usual care tend to have a lower number of exacerbations and episodes of respiratory failure. A comparison of treatment benefits and complications associated with EBV compared to LVRS show comparable benefits with endobronchial valve treatment but with fewer complications.[291] Additionally, ELVR has similar beneficial effects whether it is performed in the upper or lower lobes.[290,291]

Improved survival has been associated with post procedural atelectasis of the treated lobe post EBV.[1098-1100] Improved survival has also been reported in patients with severe hyperinflation undergoing EBV compared to a matched population not undergoing ELVR.[1101]

When preferences for medical treatment for patients with severe emphysema are elicited, the majority chose treatments with EBV over LVRS or continued medial therapy.[1102] 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.[291,1103,1104]

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, 6 MWD or quality of life.[1105]

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.[1106]

Vapor ablation

In a prospective RCT, targeted thermal vapour 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.[1094,1107] 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 6-minute walk distance, lung function and health status in patients with advanced homogenous and heterogeneous emphysema. Studies reported an increase in 6-minute walk distance with coil treatment compared to control and smaller improvements in FEV1, and quality of life measured by St George's Respiratory Questionnaire.[1108-1110] 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.[1111]

Major complications included pneumonia, pneumothorax, hemoptysis and COPD exacerbations occurring more frequently in the coil group.[1109] 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.[1109]

Sequential performance of LVRS or ELVR prior to or following 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 hyperinflated patients with advanced emphysema, 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.[1112-1114] 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.[1115-1120] The incidence of postoperative bleeding requiring re-exploration and renal dysfunction requiring dialysis or the use of extracorporeal membrane oxygenation (ECMO) may be higher in patients undergoing lung transplantation following LVRS.[1121,1122] Previous ELVR has been reported to have no impact on morbidity or survival post subsequent lung transplantation but may affect microbial colonization.[1122,1123]

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 (EDAC)

EDAC or tracheobronchomalacia (TBM) 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.[1124] Airway stenting and tracheoplasty may be beneficial in select patients.[1125,1126]

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 mucous hypersecretion by eliminating airway goblet cell hyperplasia and submucosal glands.

Nitrogen cryospray

Liquid nitrogen metered cryospray is delivered to the central airways and ablates the epithelium to a depth of 0.1 to 0.5 mm.[954] After treatment, rapid regeneration of normal epithelium occurs without scarring and may potentially treat chronic bronchitis.[1127]

Another novel treatment for chronic bronchitis is rheoplasty.[1128] Rheoplasty 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. Ongoing phase III randomized clinical trials are evaluating the efficacy of these therapies.[1129,1130]

Lung denervation

Targeted lung denervation is another therapy currently undergoing phase III clinical trial study to determine its impact of frequent moderate or severe exacerbations in patients with COPD already on maximal inhaled respiratory

treatment.[1131,1132] The therapy intends to disrupt the parasympathetic nerve transmission to and from the lungs. 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.[956,957,1132,1133]

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

Interventional Therapy in Stable COPD

Table 3.26

Lung Volume Reduction Surgery	• Lung volume reduction surgery improves survival in severe emphysema patients with an upper-lobe emphysema and low post-rehabilitation exercise capacity **(Evidence A)**
Bullectomy	• In selected patients, bullectomy is associated with decreased dyspnea, improved lung function and exercise tolerance **(Evidence C)**
Transplantation	• In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity **(Evidence C)** • In patients with very severe COPD (progressive disease, BODE score of 7 to 10, and not candidates for lung volume reduction) lung transplantation may be considered for referral with at least one of the following: (1) history of hospitalization for exacerbation associated with acute hypercapnia (Pco_2 > 50 mmHg); (2) pulmonary hypertension and/or cor pulmonale, despite oxygen therapy; or (3) FEV1 < 20% and either DLco < 20% or homogenous distribution of emphysema **(Evidence C)**
Bronchoscopic Interventions	• In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, health status and lung function at 6-12 months following treatment. Endobronchial valves **(Evidence A)**; Lung coils **(Evidence B)**; Vapor ablation **(Evidence B)**
Bronchoscopic Interventions Under Study	• Phase III trials are currently being conducted to determine the efficacy of treatments for patients with refractory exacerbations and chronic bronchitis using cryospray, rheoplasty and targeted lung denervation technology

Surgery in the COPD patient

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 COPD patients.[1134] 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.[1135-1137]

Increased risk of postoperative pulmonary complications in COPD patients 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.[1137] 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%.[1105] These data suggest that intubation and/or simple airway manipulation may increase the risk of exacerbation in select COPD patients.

To prevent postoperative pulmonary complications, stable COPD patients clinically symptomatic and/or with limited exercise capacity should be treated medically intensively before surgery, with all the measures already well established for stable COPD 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.

Lung resection

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.[1138,1139] COPD patients 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.[1138,1139]

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.

CHAPTER 4: MANAGEMENT OF EXACERBATIONS

KEY POINTS:

- An exacerbation of COPD is defined as an event characterized by dyspnea and/or cough and sputum that worsen over < 14 days. Exacerbations of COPD are often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insults to the lungs.
- As the symptoms are not specific to COPD relevant differential diagnoses should be considered, particularly pneumonia, congestive heart failure and pulmonary embolism.
- The goals for treatment of COPD exacerbations are to minimize the negative impact of the current exacerbation and to prevent subsequent events.
- Short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an exacerbation.
- Maintenance therapy with long-acting bronchodilators should be initiated as soon as possible. In patients with frequent exacerbations and elevated blood eosinophil levels addition of inhaled corticosteroids to the double bronchodilator regimen should be considered.
- In patients with severe exacerbations, systemic corticosteroids can improve lung function (FEV1), oxygenation and shorten recovery time including hospitalization duration. Duration of therapy should not normally be more than 5 days.
- Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be 5 days.
- Methylxanthines are not recommended due to increased side effect profiles.
- Non-invasive mechanical ventilation should be the first mode of ventilation used in COPD patients with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduces work of breathing and the need for intubation, decreases hospitalization duration and improves survival.
- Exacerbation recovery time varies, taking up to 4-6 weeks to recover, with some patients failing to return to the pre-exacerbation functional state. Following an exacerbation, appropriate measures for exacerbation prevention should be initiated (see **Chapter 3**).

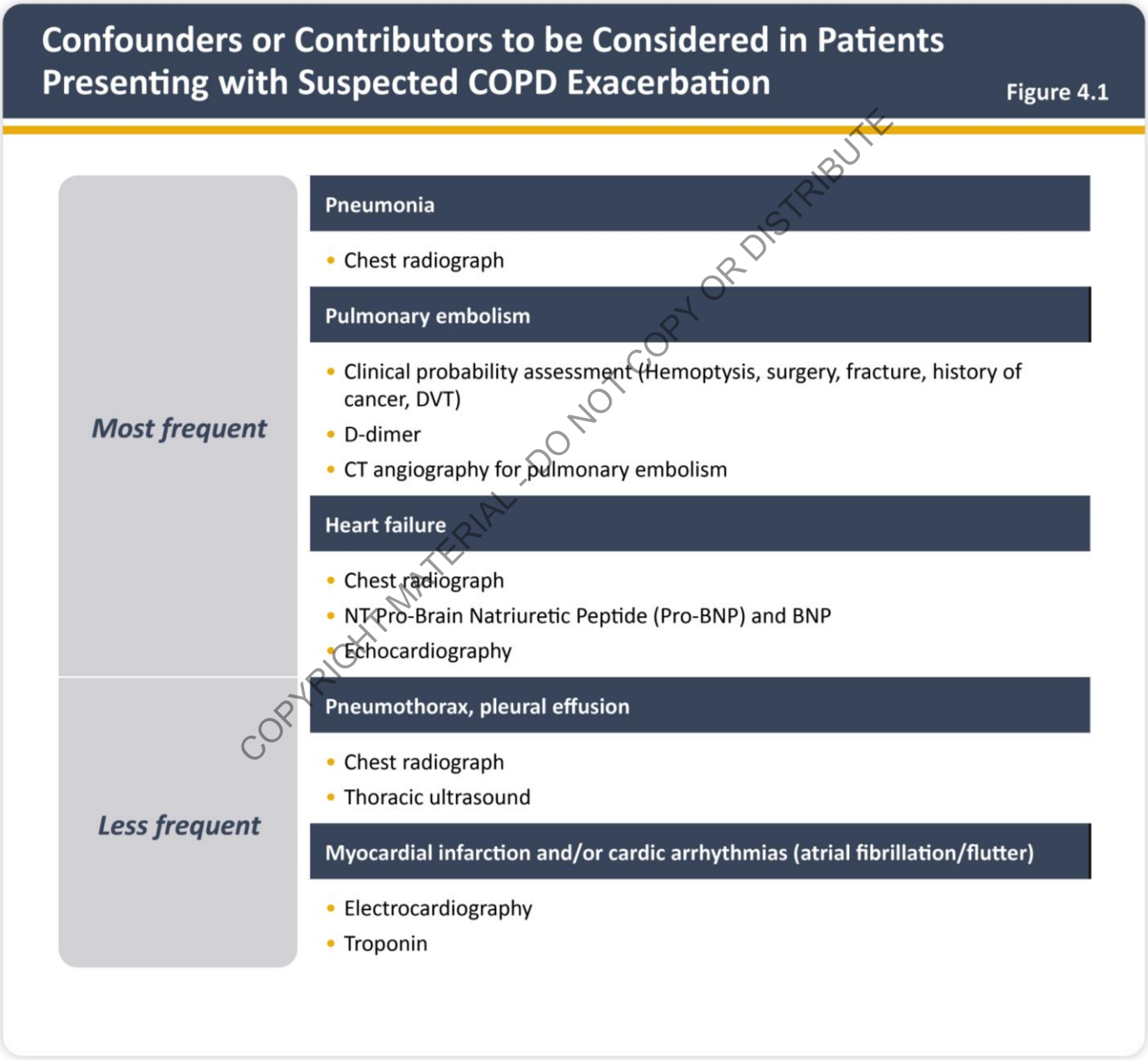
DEFINITION

An exacerbation of chronic obstructive pulmonary disease (ECOPD) is defined as an event characterized by increased dyspnea and/or cough and sputum that worsens in < 14 days 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.[304]

Considerations

Exacerbations of COPD are important events in the management of COPD because they negatively impact health

status, rates of hospitalization and readmission, and disease progression.[435,436] COPD exacerbations are usually associated with increased airway inflammation, increased mucus production and marked gas trapping. These changes contribute to increased dyspnea that is the key symptom of an exacerbation. Other symptoms include increased sputum purulence and volume, together with increased cough and wheeze.[1140,1141] Patients with COPD are at increased risk of other acute events, particularly decompensated heart failure,[1142,1143] pneumonia,[1144,1145] pulmonary embolism[1146,1147] that may also mimic or aggravate an ECOPD. Thus, while worsening of dyspnea, particularly if associated with cough and, purulent sputum, and no other symptoms or signs in a patient with COPD may be diagnosed as an ECOPD, other patients may have worsening of respiratory symptoms, particularly dyspnea without the classic characteristics of ECOPD, that should prompt careful consideration and/or search of those potential confounders, or contributors. In some patients one or more of these diagnoses may contribute to the clinical presentations and should be addressed appropriately (**Figure 4.1**).



Currently, exacerbations are classified after the event has occurred as:

- Mild (treated with short acting bronchodilators only, SABDs)
- Moderate (treated with SABDs and oral corticosteroids ± antibiotics) or

- Severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure.

The current grading of the severity of an ECOPD, based on *post facto* use of healthcare resources, is a major limitation of the current definition. Because of global variability in the available resources to treat patients and local customs affecting the criteria for hospital visits and admissions, there is substantial variability in reported ECOPD outcomes.[1148] **Figure 4.2** shows a proposed clinical approach based on the current best available evidence.[304]

Diagnosis and Assessment

Figure 4.2

1.	Complete a thorough clinical assessment for evidence of COPD and potential respiratory and non-respiratory concomitant diseases, including consideration of alternative causes for the patient's symptoms and signs: primarily pneumonia, heart failure, 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.	Evaluate severity by using appropriate additional investigations such as pulse oximetry, laboratory assessment, CRP, arterial blood gases.
4.	Establish the cause of the event (viral, bacterial, environmental, other).

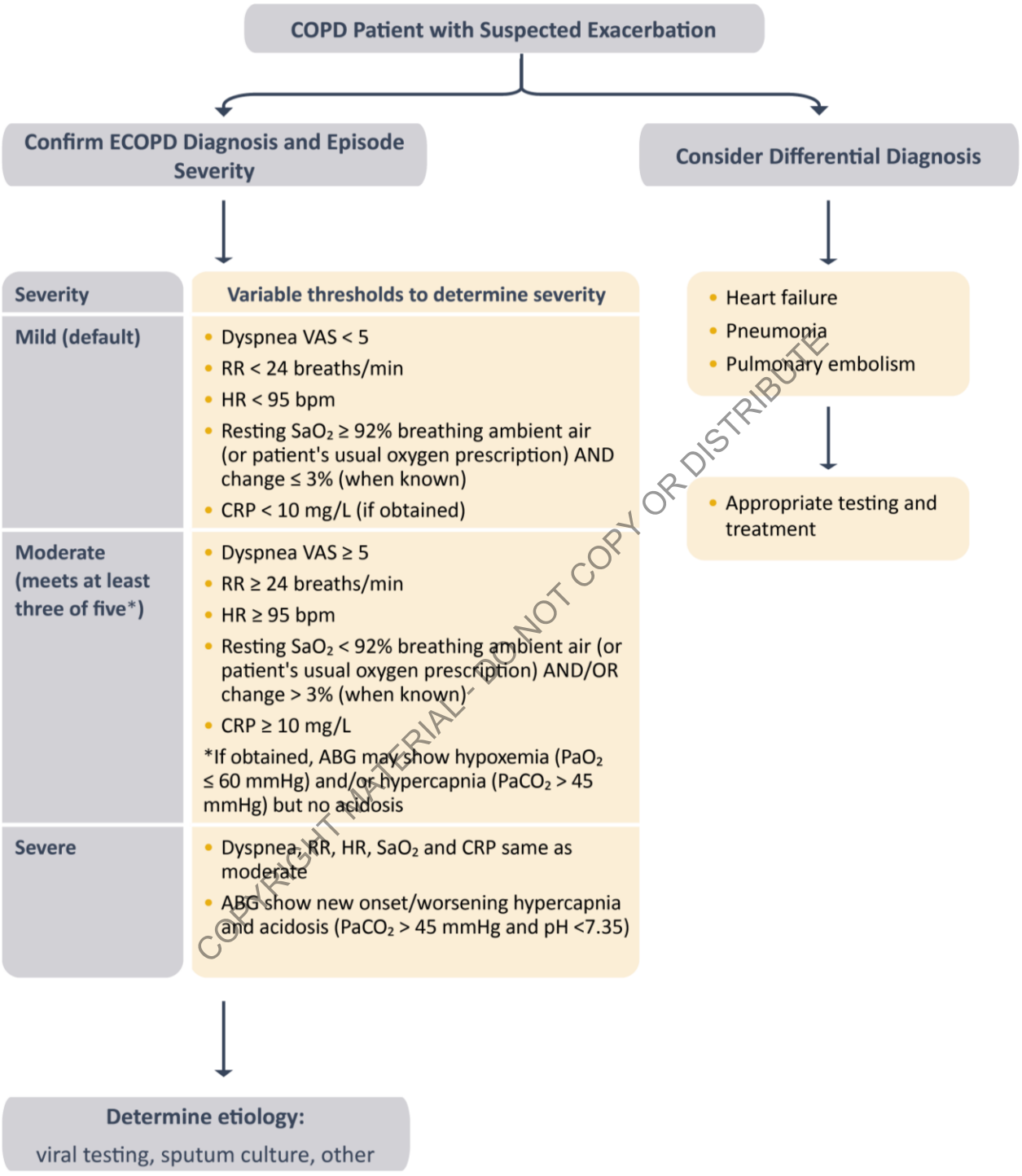
Abbreviations: COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; VAS = visual analog scale.

It has been proposed that these easy to obtain clinical variables can help define the severity of exacerbations on point of contact (The ROME Proposal).[304] Using The ROME Proposal for exacerbations, hospitalized patients with acute exacerbations can be further subclassified into mild, moderate and severe events with differences in mortality.[1149,1150] Based on a thorough review of the available literature and using a Delphi approach to agree on the variable thresholds, the severity classification is summarized in **Figure 4.3**.

In the primary care setting, where laboratories may not be available, severity can be determined with the easily obtainable dyspnea intensity (using a VAS 0 to 10 dyspnea scale with zero being not short of breath at all and 10 the worst shortness of breath you have ever experienced), respiratory rate, heart rate and oxygen saturation level. Where available, blood C-reactive protein (CRP) level is recommended. To determine the need for ventilator support (usually in the emergency room or hospital setting) arterial blood gases or equivalent should be measured. To move from a mild to a moderate level, 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 proposed thresholds of the variables now included. It is proposed that prospective research can help determine a more specific marker of lung injury than the more generic CRP, as has been true for other organs acute events.

Classification of the Severity of COPD Exacerbations

Figure 4.3



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.

It is now recognized that many exacerbations are not reported to healthcare professionals for therapy and yet these events, although often shorter in duration, also have a significant impact on health status.[1151,1152] Thus COPD patients need to receive education about the importance of understanding exacerbation symptoms and when to seek professional healthcare. The WHO has defined a minimum set of interventions for the management of exacerbations.[742]

Exacerbations are mainly triggered by respiratory viral infections although bacterial infections and environmental factors such as ambient air pollution and excess heat may also initiate and/or amplify these events.[1153,1154] Short-term exposure to fine (PM2.5) and coarse (PM10) particulate matter is associated with increased hospitalizations, ER visits, and outpatient visits,[1154] as well as increased mortality of COPD exacerbations.[1153,1155,1156] Another study also showed that short-term exposure to ambient nitrogen dioxide and PM2.5 was associated with exacerbations in mild to moderate COPD patients.[101] 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.[1157,1158] When associated with viral infections, exacerbations are often more severe, last longer and precipitate more hospitalizations, as seen during winter. Filamentous fungi, particularly *Aspergillus* species, may be identified in sputum samples of patients during moderate or severe exacerbations[1159-1161] although their clinical relevance remains unclear. Invasive pulmonary aspergillosis is rare (1.3%-3.9%)[1162] and more frequent in patients with more severe baseline airflow obstruction, recent use of broad spectrum antibiotics or parenteral steroids, and hypoalbuminemia.[1163] Aspergillus sensitization is also a marker of increased risk of exacerbations.[1164] The diagnostic approach to invasive aspergillosis in this setting remains challenging.[1165]

Exacerbations can be associated with increased sputum production and, if purulent, they are most likely due to bacterial infection[1141,1157,1166] There is reasonable evidence to support the concept that eosinophils are increased in the airways, lung, and blood in a significant proportion of people with COPD.[1167-1169] The presence of sputum eosinophilia has been related to susceptibility to viral infection.[1166] It has been suggested that exacerbations associated with an increase in sputum or blood eosinophils may be more responsive to systemic steroids[1170] although more prospective trials are needed to test this hypothesis.[1170]

During a COPD exacerbation, increased symptoms are usually present for 7 to 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.[1171] COPD exacerbations contribute to disease progression,[1172] which is more likely if recovery from exacerbations is slow.[1173] Exacerbations can also cluster in time and once they occur there is increased likelihood of another event[439,1174] (see **Chapter 2**).

Some patients are susceptible to frequent exacerbations (defined as two or more exacerbations per year), and these patients have worse health status and morbidity than patients with less frequent exacerbations.[436] The exact reason for an individual's increased susceptibility to exacerbation symptoms remains largely unknown. However, the perception of breathlessness is greater in frequent exacerbators than infrequent exacerbators,[489] suggesting that a perception of breathing difficulty may contribute to precipitating the respiratory symptoms rather than solely physiological, or causative factors. The strongest predictor of a patient's future exacerbation frequency remains the number of exacerbations they have had in the prior year.[439] It is recognized that these patients form a moderately stable phenotype, although some studies have shown that a significant proportion of patients change their exacerbation frequency especially with worsening FEV1.[1175]

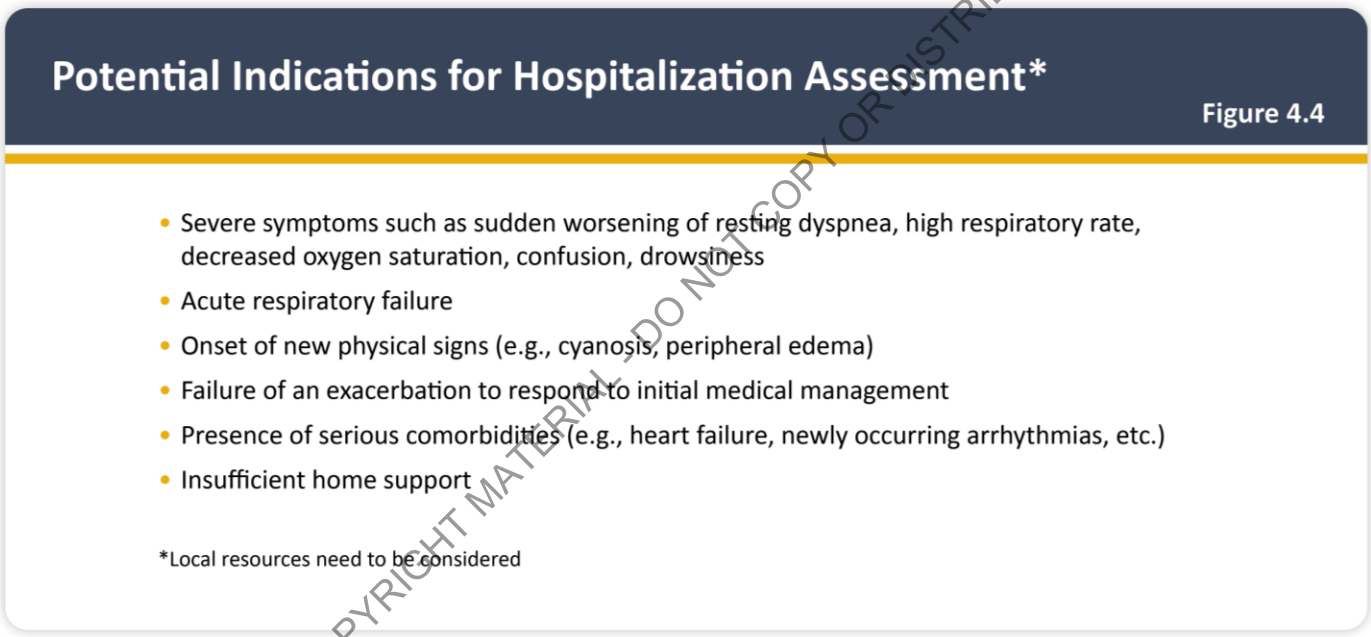
Other factors that have been associated with an increased risk of acute exacerbations and/or severity of exacerbations include an increase in the ratio of the pulmonary artery to aorta cross sectional dimension (i.e., ratio > 1),[301] a greater percentage of emphysema or airway wall thickness[1176] measured by chest CT imaging and the presence of chronic bronchitis.[169,1177]

Vitamin D has an immune-modulating role and has been implicated in the pathophysiology of exacerbations. As with many chronic diseases vitamin D levels are lower in COPD than in health. Some, but not all studies have shown that supplementation in people with severe deficiency results in a 50% reduction in episodes and hospital admission.[896,1178] 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.

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.[1179] 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.[439,740,1180]



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 emergency department, if hypoxemic they should be provided with supplemental oxygen and undergo assessment to determine whether the exacerbation is life-threatening and if increased work of breathing or impaired gas exchange requires consideration for non-invasive ventilation. 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 emergency department 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 4.5**.

The clinical presentation of COPD exacerbation is heterogeneous, thus we recommend that in **hospitalized patients** the severity of the exacerbation should be based on the patient's clinical signs and recommend the following classification:[1181]

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

Acute respiratory failure – non-life-threatening: Respiratory rate: > 24 breaths per minute; using accessory respiratory muscles; no change in mental status; hypoxemia improved with supplemental oxygen via Venturi mask > 35% FiO_2; hypercarbia i.e., $PaCO_2$ increased compared with baseline or elevated 50-60 mmHg.

Acute respiratory failure – life-threatening: Respiratory rate: > 24 breaths per minute; using accessory respiratory muscles; acute changes in mental status; hypoxemia not improved with supplemental oxygen via Venturi mask or requiring FiO_2 > 40%; hypercarbia i.e., $PaCO_2$ increased compared with baseline or elevated > 60 mmHg or the presence of acidosis (pH ≤ 7.25).

Management of Severe but not Life-threatening Exacerbations*

Figure 4.5

Assess severity of symptoms, blood gases, chest radiograph

Administer supplemental oxygen therapy, obtain serial arterial blood gas, venous blood gas and pulse oximetry measurements

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) when signs of bacterial infection are present

Consider noninvasive mechanical ventilation (NIV)

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.)

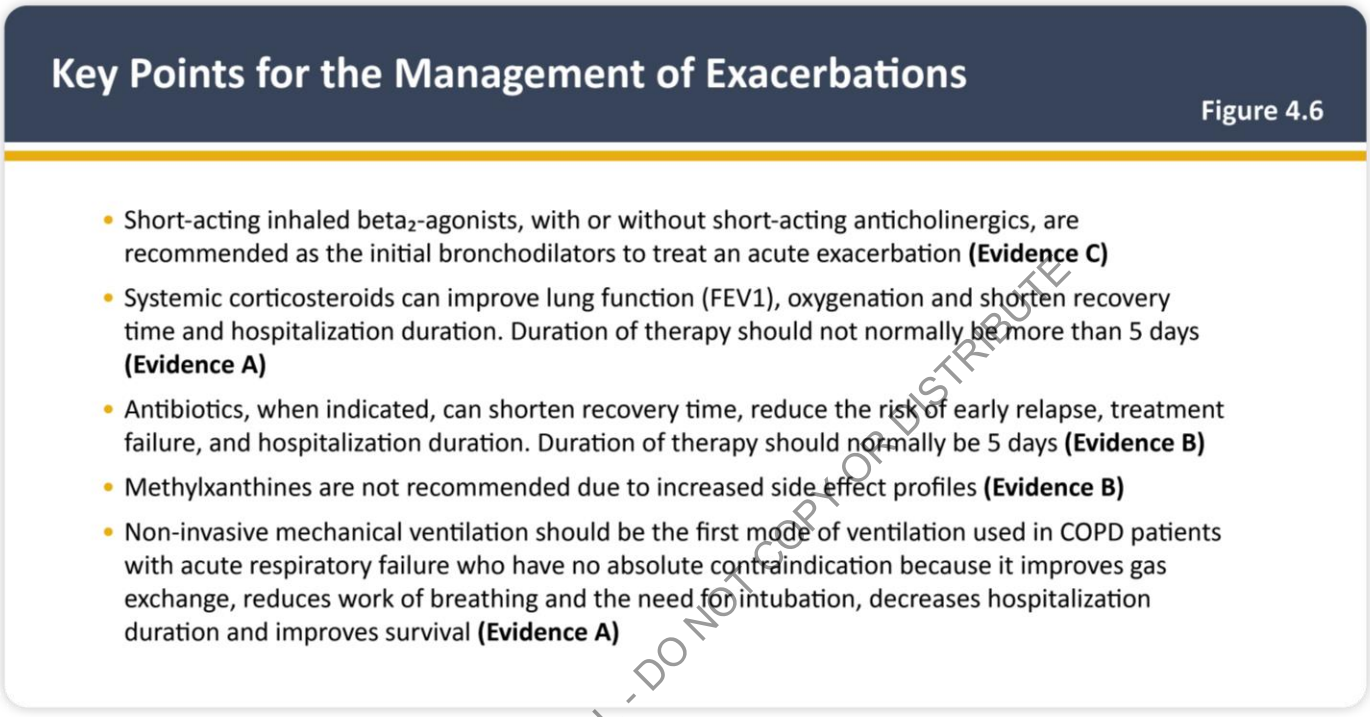
*Local resources need to be considered

Long-term prognosis following hospitalization for COPD exacerbation is poor, with a five-year mortality rate of about 50%.[1182] Factors independently associated with poor outcome include older age, lower BMI, comorbidities (e.g., cardiovascular disease or lung cancer), previous hospitalizations for COPD exacerbations, clinical severity of the index exacerbation and need for long-term oxygen therapy at discharge.[1183-1185] 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 for a higher mortality following

an acute COPD exacerbation.[1186] Mortality risk may be heightened during spells of cold weather.[1187]

An updated 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.[1188]

Key points for the management of all exacerbations are given in **Figure 4.6.**



Pharmacological treatment

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

Bronchodilators

Although there is no high-quality evidence from RCTs, it is recommended that short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are the initial bronchodilators for acute treatment of a COPD exacerbation.[1135,1189] A systematic review of the route of delivery of short-acting bronchodilators found no significant differences in FEV1 between using metered dose inhalers (MDI) (with or without a spacer device) or nebulizers to deliver the agent,[527,1190] although the latter may be an easier delivery method for sicker patients. It is recommended that patients do not receive continuous nebulization but use the MDI inhaler 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 no clinical studies that have evaluated the use of inhaled long-acting bronchodilators (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. Intravenous methylxanthines (theophylline or aminophylline) are not recommended to use in these patients due to significant side effects.[1191,1192] If a nebulizer is chosen to deliver the bronchodilator agent, air-driven bronchodilator nebulization is preferable to oxygen-driven in acute exacerbations of COPD in order to avoid the potential risk of increasing the $PaCO_2$ associated with oxygen-driven bronchodilator administration.[1193]

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,[1194-1197] the risk of early relapse, treatment failure,[1198] and the length of hospitalization.[1194,1196,1199] A dose of 40 mg prednisone-equivalent per day for 5 days is recommended.[1200] One observational study suggests that longer courses of oral corticosteroids for COPD exacerbations are associated with an increased risk of pneumonia and mortality.[1201] Therapy with oral prednisolone is equally effective to intravenous administration.[1202] Nebulized budesonide alone may be a suitable alternative for treatment of exacerbations in some patients,[1195,1203,1204] and provides similar benefits to intravenous methylprednisolone, although the choice between these options may depend on local cost issues.[1205,1206] Even short bursts of corticosteroids are associated with subsequent increased risk of pneumonia, sepsis and death[1207] and use should be confined to patients with significant exacerbations. Recent studies suggest that glucocorticoids may be less efficacious to treat acute COPD exacerbations in patients with lower levels of blood eosinophils[439,1167,1170,1208] and more trials of steroid-sparing treatment regimens are required.

Antibiotics

Although the infectious agents in COPD exacerbations can be viral or bacterial,[1158,1209] the use of antibiotics in exacerbations remains controversial.[326,1210,1211] The uncertainties originate from studies that did not differentiate between bronchitis (acute or chronic) and COPD exacerbations, studies without placebo-control, and/or studies without chest X-rays that do not exclude that patients may have had underlying pneumonia. There is evidence supporting the use of antibiotics in exacerbations when patients have clinical signs of a bacterial infection e.g., increased sputum purulence.[326,1211] Indeed the use of observed sputum color can safely modulate antibiotic therapy with no adverse effects if sputum is white or clear in color. On the other hand observed sputum purulence has 94.4% sensitivity and 52% specificity for high bacterial load, indicative of a causative relationship.[326]

A systematic review of placebo-controlled studies has shown that antibiotics reduce the risk of short-term mortality by 77%, treatment failure by 53% and sputum purulence by 44%.[1212] The review provides evidence to treat moderately or severely ill patients with COPD exacerbations and increased cough and sputum purulence with antibiotics.[1212,1213] These data are supported by more RCTs in patients with diagnoses of moderate COPD.[1214] In an RCT, the addition of doxycycline to oral corticosteroid an outpatient setting did not prolong time to next exacerbation.[1215] In the outpatient setting, sputum cultures are not feasible as they take at least two days and frequently do not give reliable results for technical reasons. Several biomarkers of airway infection are being studied in exacerbations of COPD that have a better diagnostic profile. Earlier studies of C-reactive protein (CRP) have reported contradictory findings.[1216,1217] A randomized trial found a marked reduction in antibiotic prescriptions without impaired outcomes in UK primary care outpatients with ECOPD in whom antibiotics prescriptions were guided by point-of-care CRP testing.[1218] Another trial in patients hospitalized for exacerbations of COPD in The Netherlands found similar results (reduced antibiotic use with no increase in treatment failure). These findings need confirmation in other settings before a recommendation to generalize this approach. However, data has indicated that antibiotic usage can be safely reduced from 77.4% to 47.7% when CRP is low.[1219]

Procalcitonin is an acute phase reactant that increases in response to inflammation and infection and has been studied to determine the use of antibiotics in COPD exacerbations.[1220] The efficacy of this biomarker is controversial. Several studies, mainly done in the outpatient setting, suggested that procalcitonin-guided antibiotic treatment reduces antibiotic exposure and side effects with the same clinical efficacy.[1221-1223] 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.[1224] 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.[1225] Based on these conflicting results we cannot recommend at this time the use of procalcitonin-based protocols to make the decision on using antibiotics in patient with COPD

exacerbations; however, confirmatory trials with rigorous methodology are required.

In summary, antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or noninvasive).[1141,1158] A metanalysis demonstrated that ≤ 5 days of antibiotic treatment had the same clinical and bacteriological efficacy to longer conventional treatment in outpatients with COPD exacerbations. Furthermore, shorter exposure to antibiotics may decrease the risk developing antimicrobial resistance and complications associated with this therapy. The recommended length of antibiotic therapy is 5-7 days.[1226] We recommend a duration of ≤ 5 days of antibiotic treatment for outpatient treatment of COPD exacerbations.[1225,1227]

The choice of the antibiotic should be based on the local bacterial resistance pattern. Usually, initial empirical treatment is an aminopenicillin with clavulanic acid, macrolide, tetracycline or, in selected patients, quinolone. In patients with frequent exacerbations, severe airflow obstruction,[1228,1229] and/or exacerbations requiring mechanical ventilation,[1230] 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 patient's ability to eat and the pharmacokinetics of the antibiotic, although it is preferable that antibiotics be given orally. Improvements in dyspnea and sputum purulence suggest clinical success.

Adjunct therapies

Depending on the clinical condition of the patient, an appropriate fluid balance, use of diuretics when clinically indicated, anticoagulants, treatment of comorbidities and nutritional aspects should be considered. Among COPD patients hospitalized with a suspected exacerbation, up to 5.9% were found to have pulmonary embolism.[1146] Hospitalized patients with COPD are at an increased risk of deep vein thrombosis and pulmonary embolism[1231,1232] and prophylactic measures for thromboembolism should be instituted.[1233,1234] At all times, healthcare providers should strongly enforce the need for smoking cessation.

Respiratory support

Oxygen therapy

This is a key component of hospital treatment of an exacerbation. Supplemental oxygen should be titrated to improve the patient's hypoxemia with a target saturation of 88-92%.[1235] Once oxygen is started, blood gases should be checked frequently, or as clinically indicated, to ensure satisfactory oxygenation without carbon dioxide retention and/or worsening acidosis. Pulse oximetry is not as accurate as arterial blood gas[488] and in particular, may overestimate blood oxygen content among individuals with darker skin tones.[1236] A study demonstrated that venous blood gas to assess bicarbonate levels and pH is accurate when compared with arterial blood gas assessment.[1237] Additional data are needed to clarify the utility of venous blood gas sampling to make clinical decisions in scenarios of acute respiratory failure; most patients included had a pH > 7.30 on presentation, PCO_2 levels were dissimilar when measured by venous compared to arterial blood samples and the severity of airflow obstruction was not reported.[1237] Venturi masks offer more accurate and controlled delivery of oxygen than do nasal prongs.[1135]

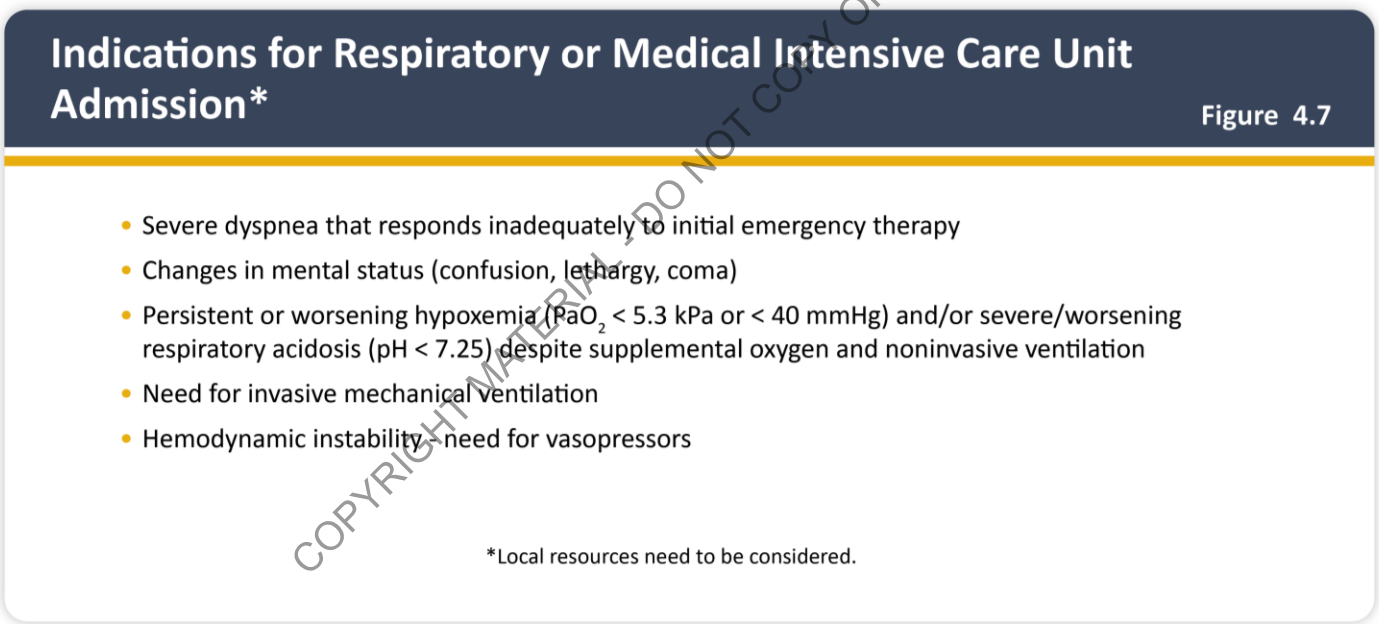
High-flow nasal therapy

High-flow nasal therapy (HFNT) delivers heated and humidified air-oxygen blends via special devices (e.g., Vapotherm®, Comfort Flo®, or Optiflow®) at rates up to 8 L/min in infants and up to 60 L/min in adults.[1238] HFNT has been associated with decreased respiratory rate and effort, decreased work of breathing, improved gas exchange, improved lung volume and dynamic compliance, transpulmonary pressures and homogeneity.[1239,1240] These physiologic benefits positively improve oxygenation and clinical outcomes in patients with acute hypoxemic respiratory failure.[1239-1242] HFNT has been reported to improve oxygenation and ventilation, decrease hypercarbia and

improve health-related quality of life in patients with acute hypercapnia during an acute exacerbation, and also in select patients with stable hypercapnic COPD.[1239,1243-1245] However, the small sample sizes, heterogeneity of the patient populations and short duration of follow-up are current limitations in the interpretation of the value of HFNT for the COPD patient population at large.[1246] A meta-analysis, based on poor quality studies, showed no clear benefit.[1247] HFNT has been reported to improve oxygenation and ventilation, decrease hypercarbia, prolong the time to next moderate exacerbation and improve health-related quality of life scores in patients with acute hypercapnia during an exacerbation or in select patients with stable hypercapnic COPD receiving long term oxygen therapy.[1248] HFNT did not prevent intubation in a RCT conducted in patients hospitalized with an acute exacerbation.[1249] It should be noted that European Respiratory Society (ERS) Clinical Practice Guidelines recommend trialling NIV prior to use of HFNT in patients with COPD and hypercapnic ARF.[1250] There is a need for well-designed, prospective, randomized and controlled multicenter trials to study the effects of HFNT in people with COPD experiencing episodes of either acute or chronic hypercapnic respiratory failure.

Ventilatory support

Some patients need immediate admission to the respiratory care or intensive care unit (ICU) (**Figure 4.7**). Admission of patients with severe exacerbations to intermediate or special 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 (oro-tracheal tube or tracheostomy) ventilation. Respiratory stimulants are not recommended for acute respiratory failure.[1189]



Indications for Noninvasive Mechanical Ventilation (NIV)

Figure 4.8

At least one of the following:

- Respiratory acidosis ($PaCO_2 \geq 6.0$ kPa or 45 mmHg and arterial pH ≤ 7.35)
- Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces
- Persistent hypoxemia despite supplemental oxygen therapy

Indications for Invasive Mechanical Ventilation

Figure 4.9

- Unable to tolerate NIV or NIV failure
- Status post-respiratory or cardiac arrest
- Diminished consciousness, psychomotor agitation inadequately controlled by sedation
- Massive aspiration or persistent vomiting
- Persistent inability to remove respiratory secretions
- Severe hemodynamic instability without response to fluids and vasoactive drugs
- Severe ventricular or supraventricular arrhythmias
- Life-threatening hypoxemia in patients unable to tolerate NIV

Noninvasive mechanical ventilation

The use of noninvasive mechanical ventilation (NIV) is preferred over invasive ventilation (intubation and positive pressure ventilation) as 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%.[641,1251-1254] NIV has been shown to improve oxygenation and acute respiratory acidosis i.e., NIV increases pH and decreases $PaCO_2$. NIV also decreases respiratory rate, work of breathing and the severity of breathlessness but also decreases complications such as ventilator associated pneumonia, and length of hospital stay. More importantly, mortality and intubation rates are reduced by this intervention.[1252,1255-1257] 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.[1258] The indications for NIV[1254] are summarized in **Figure 4.8**.

Invasive mechanical ventilation

The indications for initiating invasive mechanical ventilation during an exacerbation are shown in **Figure 4.9**, and include failure of an initial trial of NIV.[1259] 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.[1259] In patients who fail non-invasive ventilation as initial therapy and receive invasive ventilation as

subsequent rescue therapy, morbidity, hospital length of stay and mortality are greater.[641] 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.[641] 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, and the risk of tracheostomy and consequential prolonged ventilation.

Acute mortality among COPD patients with respiratory failure is lower than mortality among patients ventilated for non-COPD causes.[1260] Despite this, there is evidence that patients who might otherwise survive are frequently denied admission to intensive care for intubation because of unwarranted prognostic pessimism.[1261] A large study of COPD patients with acute respiratory failure reported in-hospital mortality of 17-49%.[1262] Further deaths were reported over the next 12 months, particularly among those patients who had poor lung function before invasive ventilation (FEV1 < 30% predicted), had a non-respiratory comorbidity, 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.

Hospital discharge and follow-up

The cause, severity, impact, treatment and time course of exacerbations varies from patient to patient and facilities in the community, and healthcare systems, differ from country to country. Accordingly, there are no standards that can be applied to the timing and nature of discharge. However, it is recognized that recurrent exacerbations leading to short-term readmission and increased all-cause mortality are associated with the initial hospitalization for an acute episode of deterioration.[1263]

When features related to re-hospitalization and mortality have been studied, defects in perceived optimal management have been identified including spirometric assessment and arterial blood gas analysis.[1264] A systematic review has shown that comorbidities, previous exacerbations and hospitalization, and increased length of stay were significant risk factors for 30- and 90-day all-cause readmission after an index hospitalization with an exacerbation of COPD.[1265] Mortality relates to patient age, the presence of acidotic respiratory failure, the need for ventilatory support and comorbidities including anxiety and depression.[1266]

The introduction of care bundles at hospital discharge to include education, optimization of medication, supervision and correction of inhaler technique, assessment and optimal management of comorbidities, early rehabilitation, telemonitoring and continued patient contact have all been investigated to address these issues (**Figure 4.10**).[1267] While these measures all seem sensible there is insufficient data that they influence either readmission rates or short-term mortality[1264,1266,1268,1269] and there is little evidence of cost-effectiveness.[1266] One RCT showed that telemonitoring did not change hospitalization or exacerbation rates in people with COPD.[1270] Nevertheless, it remains good clinical practice to cover these issues before discharge and their effectiveness on health status and readmission rates may be increased if they are delivered with an approach that includes motivational interview-based health coaching.[964]

Discharge Criteria and Recommendations for Follow-up

Figure 4.10

1. Full review of all clinical and laboratory data
2. Check maintenance therapy and understanding
3. Reassess inhaler technique
4. Ensure understanding of withdrawal of acute medications (steroids and/or antibiotics)
5. Assess need for continuing any oxygen therapy
6. Provide management plan for comorbidities and follow-up
7. Ensure follow-up arrangements: early follow-up < 4 weeks, and late follow-up < 12 weeks as indicated
8. All clinical or investigational abnormalities have been identified

1 – 4 Weeks Follow-up

- Evaluate ability to cope in his/her usual environment
- Review understanding of treatment regimen
- Reassessment of inhaler techniques
- Reassess need for long-term oxygen
- Document the capacity to do physical activity and consider patient eligibility to be enrolled in pulmonary rehabilitation
- Document symptoms: CAT or mMRC
- Determine status of comorbidities

12 – 16 Weeks Follow-up

- Evaluate ability to cope in his/her usual environment
- Review understanding of treatment regimen
- Reassessment of inhaler techniques
- Reassess need for long-term oxygen
- Document the capacity to do physical activity and activities of daily living
- Measure spirometry: FEV1
- Document symptoms: CAT or mMRC
- Determine status of comorbidities

The only possible exception is early rehabilitation as there is some evidence that this factor is associated with increased mortality, although the reasons remain unknown.[1269] However, other data suggest that early rehabilitation post hospital discharge (i.e., < 4 weeks) may be associated with improved survival.[702]

Early follow-up (within one month) following discharge should be undertaken when possible and has been related to less exacerbation-related readmissions.[1271] There are many patient issues that prevent early follow-up; those not attending early follow-up have increased 90-day mortality. This may reflect both patient compliance, limited access to medical care, poor social support, and/or the presence of more severe disease. Nevertheless, early follow-up permits a careful review of discharge therapy and an opportunity to make any needed changes in therapy.

Additional follow-up at three months is recommended to ensure return to a stable clinical state and 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.[1272] In addition, arterial oxygen saturation and blood gas assessment will determine the need for long-term oxygen therapy more accurately at prolonged follow-up compared to shortly after discharge.[1273]

CT assessment to determine the presence of bronchiectasis and emphysema should be done in patients with recurrent exacerbations and/or hospitalizations.[483,1274] A further detailed assessment of the presence and management of comorbidities should also be undertaken (**Figure 4.10**).[1274]

Prevention of exacerbations

After an acute exacerbation, appropriate measures for prevention of further exacerbations should be initiated (**Figure 4.6** and **Figure 4.11**). For the following treatment modalities significant effects on exacerbation risk/frequency could be shown in clinical trials. For details refer to **Chapter 3**.

Based on findings from observational studies in various countries[1275-1278] there was a major decrease in hospital admissions for COPD exacerbations during the COVID-19 epidemic. It was hypothesized that this phenomenon may be a consequence of shielding measures (e.g., wearing masks, avoiding social contact, regular hand washing etc). An alternative explanation is that patients may not have been seeking medical assistance during an exacerbation due to concern about becoming infected with the SARS-CoV-2 virus. If this was the case, then a corresponding increase in COPD related mortality would be expected. However, two major studies from the US and the UK[1275,1279] did not report increased COPD associated mortality during the pandemic. Accordingly, shielding measures could be considered during the winter months (on top of established pharmacological and non-pharmacological measures) in patients at risk of exacerbation.

Interventions that Reduce the Frequency of COPD Exacerbations

Figure 4.11

Intervention Class	Intervention
Bronchodilators	LABAs LAMAs LABA + LAMA
Corticosteroid-containing regimens	LABA + ICS LABA + LAMA + ICS
Anti-inflammatory (non-steroid)	Roflumilast
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)

CHAPTER 5: COPD AND COMORBIDITIES

KEY POINTS:

- COPD often coexists with other diseases (comorbidities) that may have a significant impact on disease course.
- In general, the presence of comorbidities should not alter COPD treatment and comorbidities should be treated per usual standards regardless of the presence of COPD.
- Cardiovascular diseases are common and important comorbidities in COPD.
- Lung cancer is frequently seen in people with COPD and is a major cause of death.
    - Annual low-dose CT scan (LDCT) is recommended for lung cancer screening in people with COPD due to smoking according to recommendations for the general population
    - Annual LDCT is not recommended for lung cancer screening in people with COPD not due to smoking due to insufficient data to establish benefit over harm
- Osteoporosis and depression/anxiety are frequent, important comorbidities in COPD, are often under-diagnosed, and are associated with poor health status and prognosis.
- Gastroesophageal reflux (GERD) is associated with an increased risk of exacerbations and poorer health status.
- When COPD is part of a multimorbidity care plan, attention should be directed to ensure simplicity of treatment and to minimize polypharmacy.

INTRODUCTION

COPD often coexists with other diseases (comorbidities) that may have a significant impact on prognosis.[305,462,463,1280-1284] Some of these arise independently of COPD whereas others may be causally related, either with shared risk factors or by one disease increasing the risk or compounding the severity of the other. It is possible that features of COPD, are shared with other diseases and as such this mechanism represents a link between COPD and some of its comorbidities.[1285,1286] The risk of comorbid disease can be increased by the sequelae of COPD e.g., reduced physical activity or continued smoking. Whether or not COPD and comorbid diseases are related, management of the COPD patient must include identification and treatment of its comorbidities. Importantly, comorbidities with symptoms also associated with COPD may be overlooked e.g., heart failure and lung cancer (breathlessness) or depression (fatigue and reduced physical activity).

Comorbidities are common at any severity of COPD[168] and the differential diagnosis can often be difficult. For example, in a patient with both COPD and heart failure, an exacerbation of COPD may be accompanied by worsening of heart failure or *vice versa*. Although COPD is negatively impacted by multiple comorbid diseases, COPD itself is one of the most important comorbid conditions that adversely affects the outcomes of other disorders. For example, patients with congestive heart failure 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.[1287,1288]

Below is a brief guide to the management of some common comorbidities occurring in people with COPD with stable disease. The recommendations may be insufficient for the management of all COPD patients and are not a substitute for the use of guidelines for the management of each individual comorbid condition.

Cardiovascular diseases (CVD)

► A large primary care population study in COPD patients with no history of cardiovascular disease found a 25% increase in the adjusted risk of major adverse cardiac events including acute myocardial infarction, stroke, or cardiovascular death.[1289]

Heart failure

► The prevalence of systolic or diastolic heart failure in COPD patients ranges from 20% to 70%,[1290] and its annual incidence is between 3-4%. Incident heart failure is a significant and independent predictor of all-cause mortality.

► Unrecognized heart failure may mimic or accompany acute COPD; 40% of COPD patients that are mechanically ventilated because of hypercapnic respiratory failure have evidence of left ventricular dysfunction.[1291,1292]

► Treatment with β_1-blockers improves survival in heart failure and is recommended in patients with heart failure who also have COPD. Selective β_1-blockers should be used, and only used, to treat people with COPD for approved cardiovascular indications; not solely for the purpose of preventing exacerbations of COPD.[892]

► Acute heart failure should be treated according to usual heart failure guidelines since there is no evidence to support an alternative management strategy. Noninvasive ventilation added to conventional therapy improves outcomes for patients with either hypercapnic respiratory failure due to an exacerbation of COPD as well as heart failure with acute pulmonary edema.[1293]

Ischaemic heart disease (IHD)

► Ischaemic heart disease should be considered in all COPD patients depending on their risk factor profile. Cardiovascular risk may be assessed by the global risk calculator, which can be found on the US National Heart Blood Lung Institute website[1294] and treatment initiated based on the current recommendations.

► During, and for at least 90 days after, acute COPD exacerbations there is an increased risk of cardiovascular events (death, myocardial infarction, stroke, unstable angina, and transient ischemic attack) in patients at high risk of concomitant IHD.[1295] Hospitalization for an acute COPD exacerbation has been associated with 90-day mortality of acute myocardial infarction, ischemic stroke, and intracranial hemorrhage.[1296] Patients who demonstrate abnormal cardiac troponins in isolation are at increased risk of adverse outcomes including short-term (30-day) and long-term mortality.[1297,1298]

► The treatment of ischaemic heart disease should be according to guidelines irrespective of the presence of COPD and *vice versa*.

Arrhythmias

► Cardiac arrhythmias are common in COPD and *vice versa*.[1299] Atrial fibrillation is frequent and associated with a lower FEV1.[1300]

► In COPD patients presenting with severe worsening dyspnea, associated atrial fibrillation is frequently documented, and it may be either a trigger or a consequence of an acute exacerbation episode.[1301]

► The presence of atrial fibrillation does not alter the treatment of COPD. Bronchodilators have been previously described as potentially pro-arrhythmic agents;[1302,1303] however, available evidence suggests an overall acceptable safety profile for long-acting beta$_2$-agonists,[1304] anticholinergic drugs (and ICS).[740,783,819,1305-1309] Nevertheless, caution is advised when using short-acting beta$_2$-agonists[1304,1310] and theophylline, which may precipitate atrial fibrillation and make control of the ventricular response rate difficult.[1311-1313]

Peripheral vascular disease

► Peripheral artery disease (PAD) is commonly associated with atherosclerotic heart disease and may have significant implications for functional activity as well as quality of life in people with COPD.[1314]

► In a large cohort of people with COPD of all degrees of severity, 8.8% were diagnosed with PAD that was higher than the prevalence in non-COPD controls (1.8%).[1314]

► COPD patients with PAD reported a worse functional capacity and worse health status compared to those without PAD. Clinicians should consider PAD in people with COPD to those at risk for vascular events and to fully understand their functional impairments.

Hypertension

► Hypertension is likely to be the most frequently occurring comorbidity in COPD and may have implications for prognosis.[1285,1286] Diastolic dysfunction as a result of sub-optimally treated hypertension may be associated with exercise intolerance and mimic symptoms associated with an acute exacerbation thereby provoking hospitalization in COPD.[1290] These data stress the importance of optimal blood pressure control in COPD patients with underlying hypertension.[1315,1316]

► Hypertension should be treated according to usual guidelines. There is no evidence that hypertension should be treated differently in the presence of COPD. The role of treatment with selective beta-blockers is less prominent in recent hypertension guidelines and there is no evidence that in people with COPD and increased cardiovascular risk cardio-selective beta-blockers either reduce the benefits of treatment with LABA or increase cardiovascular risk.[1317]

► COPD should be treated as usual as there is no direct evidence that COPD should be treated differently in the presence of hypertension.

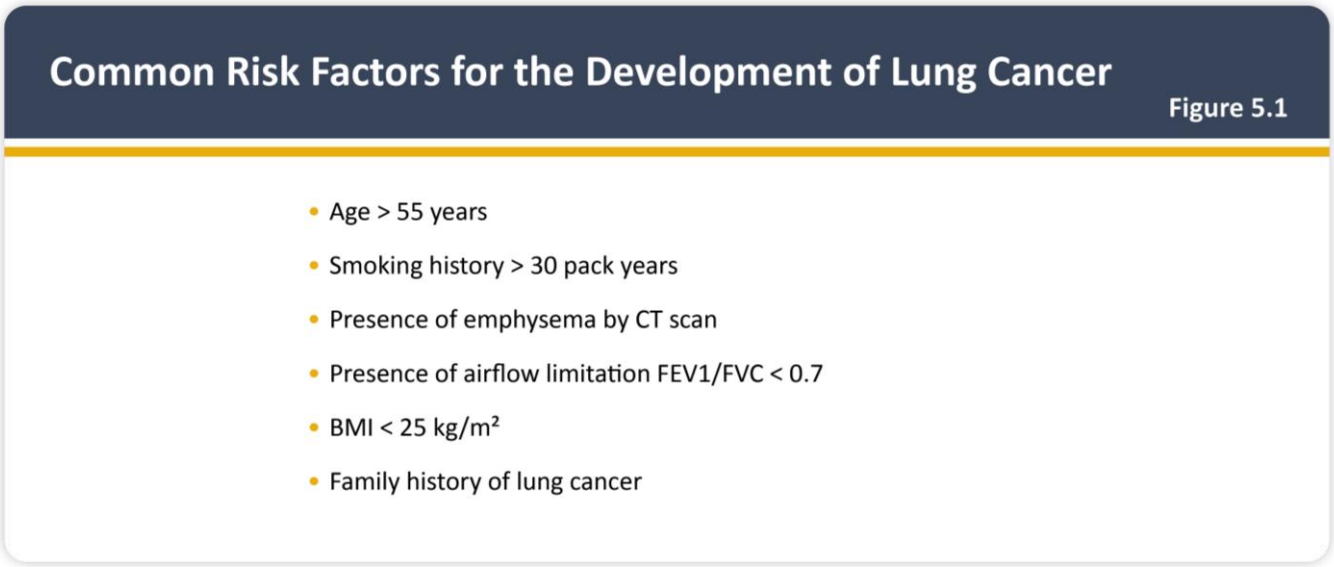
Lung cancer

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 together and it causes an estimated 1.6 million deaths worldwide each year.[1318] Unfortunately, the great majority of lung cancers are diagnosed at an advanced stage, resulting in poor overall survival.[1319] Therefore, primary, and secondary prevention and early detection are important to improve survival. There is evidence for an association between COPD and lung cancer that has been systematically confirmed in several epidemiological and observational cohort studies.[1286,1320-1322] These two diseases appear to share more than tobacco exposure as their common origin. 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.[1323-1325] Whether the spirometric severity of airflow obstruction is directly or inversely associated with a greater risk for lung cancer development remains controversial.[367,1322] The association between lung cancer and 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.[1326,1327] The best preventive measure for lung cancer (as it is for COPD) is smoking prevention and in smokers, smoking cessation.[1328]

Several studies involving the use of low-dose chest computed tomography (LDCT) screening have shown improved survival.[395,396,1329] The United States Preventive Services Task Force (USPSTF) updated its recommendation for lung cancer screening in 2021.[1330] Their recommendation was based on a systematic review that examined the accuracy of screening for lung cancer considering the benefits and harms associated with lung cancer screening. USPSTF also commissioned collaborative modeling studies from the National Cancer Institute (NCI) Cancer Intervention and surveillance modeling Network (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 UPSTF now recommends annual screening for lung cancer with LDCT in adults aged 50-80 years who have a 20-pack year smoking history and currently smoke or quit smoking within the past 15 years. They recommend stopping screening once a 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 modeling 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.[1330-1334] In patients with smoking related COPD, annual screening for lung cancer with LDCT should be conducted in those 50-80 years of age with a 20-pack year smoking history who currently smoke, or who have quit smoking within the past 15 years. COPD has also been reported to be an independent risk factor for lung cancer incidence in never smokers.[1335,1336] Risk factors include biomass fuel exposure, second-hand smoke, radon, air pollution, a family history of lung cancer, and asbestos exposure. 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 because the possible harms of screening seem to outweigh the possible benefit of finding early lung cancer.[1337]

Although this recommendation is supported by several major medical societies several important questions 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.[399,1338]

The implementation of a screening program, where available, could be useful, but has to be implemented in the appropriate environment to avoid over diagnosis, greater morbidity and mortality with needless diagnostic procedures for benign abnormalities, anxiety and incomplete follow-up, as has been suggested by studies in primary care.[1339] On the other hand, one Danish study showed that being part of a lung cancer screening programme significantly promotes smoking abstinence[1340] 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.[1328] Smoking cessation interventions as part of CT scan screening programs could be of use (**Figure 5.1**).



Inhaled corticosteroids (ICS) and lung cancer incidence

ICS are recommended in selected people with COPD and their potential impact on development of lung cancer has been the subject of conflicting reports. Several retrospective analyses of large databases or observational cohorts[1341] have suggested a reduction in lung cancer risk with the use of ICS but confounding factors have not been consistently controlled for in all studies.[1342-1347] A more pronounced protective effect of ICS was reported in former compared to current smokers,[1345] those with a concurrent diagnosis of asthma[1347] or, those prescribed a higher dose of ICS.[1346] A systematic review that included two observational studies and 4 RCTs, reported a protective effect of ICS on lung cancer risk in the observational studies that used a higher dose of ICS, but no benefit in the RCTs.[1348] An analysis designed to avoid immortal time bias [839] and an observational study (> 65,000 patients) reported no effect of ICS use on lung cancer incidence.[1349] In contrast, one database study reported an increased risk of lung cancer in patients prescribed ICS compared to those not prescribed ICS.[1350] Reports from large prospective RCTs focused on lung function decline, exacerbation reduction or mortality, conducted in patients with moderate to severe COPD where cause of death was analyzed using clinical end-point committees reported no difference in cancer deaths in patients randomized to ICS versus non-ICS use.[448,566,697,740,819,1308]

The conflicting results between observational and RCTs are probably due to differences in the patient populations, characterization of lung cancer risk, follow-up time (shorter in interventional trials), impact of immortal time bias, and the rigorousness used to detect lung cancer. Based on the available data ICS do not appear to increase or decrease the risk of lung cancer pending studies adequately planned to clarify these important questions.

Bronchiectasis

► With increasing use of computed tomography in the assessment of people with COPD, the presence of previously unrecognized bronchiectasis is being identified.[1351] The prevalence of bronchiectasis in COPD patients has been analyzed in several studies with conflicting results ranging from 20% to 69% (mean prevalence was 54.3%).[323]

► Whether this diagnosis based on radiological criteria has the same impact as a clinical diagnosis of bronchiectasis remains unknown at present. Two systematic reviews and meta-analyses have compared the characteristics of COPD patients with and without bronchiectasis. The results indicated that people with COPD and comorbid bronchiectasis are more often male with a longer smoking history, greater daily sputum production, more frequent exacerbations, poorer lung function, higher level of inflammatory biomarkers, more chronic colonization by potentially pathogenic microorganisms, higher rate of *Pseudomonas aeruginosa* isolation and increased mortality.[322,323]

► Bronchiectasis should be treated according to usual guidelines.

► Regarding COPD treatment, some patients may need more aggressive and prolonged antibiotic therapy. ICS may not be indicated in patients with bacterial colonization or recurrent lower respiratory tract infections.

Obstructive sleep apnea & insomnia

► COPD has an estimated prevalence in U.S. adults of 13.9%[1352,1353] and obstructive sleep apnea (OSA), a sleep disorder hallmarked by repeated episodes of upper airway closure, affects 9% to 26% of the U.S. adult population.[1354]

► Patients with both COPD and OSA have a worse prognosis compared with either condition alone.[1355] During sleep, patients with both COPD and OSA suffer more frequent episodes of oxygen desaturation and have more total sleep time with hypoxemia and hypercapnia than OSA patients without COPD.[1356]

► The apneic events in patients with combined OSA and COPD have more profound hypoxemia and more cardiac arrhythmias.[1357] Additionally, patients with combined COPD and OSA are more likely to develop daytime pulmonary hypertension[1358,1359] than patients with just OSA or COPD alone.

► The use of positive pressure ventilation in patients with COPD and OSA has been reported to reduce all- cause hospitalizations, emergency room visits, moderate and severe exacerbations and associated healthcare costs.[639,1360]

► Insomnia in COPD is associated with higher rates of outpatients' visits and hospitalizations.[1361]

Periodontitis & dental hygiene

The association between COPD and periodontitis has been noted mainly in the dental literature although whether this reflects common causative factors such as age, smoking and socioeconomic circumstances remains speculative. Although both conditions have a common (neutrophilic) relationship whether this reflects cause or effect is difficult to elucidate.[1362] In a more complete study the data supported shared pathophysiology between periodontitis and COPD with similar aberrant neutrophil function, especially when associated with alpha-1-antitrypsin deficiency.[1363]

The risk of developing periodontitis increases with the number of emergency room visits for COPD.[1364] High antibody levels to common periodontal pathogens is associated with less exacerbations of COPD.[1365] In a recent systematic review low to moderate evidence suggests that periodontal treatment is associated with slower lung function decline, reduced frequency of exacerbations and less use of healthcare resources in patients with COPD and chronic periodontitis.[1366] 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.

Metabolic syndrome and diabetes

► Studies have shown that metabolic syndrome and manifest diabetes are more frequent in COPD and the latter is likely to affect prognosis.[462]

► Insulin resistance has been associated with increased risk of COPD in women but not in men.[1367]

► The prevalence of metabolic syndrome has been estimated to be more than 30%.[1368]

► Diabetes should be treated according to usual guidelines for diabetes. COPD should be treated as usual.

Gastroesophageal reflux (GERD)

► GERD is an independent risk factor for exacerbations and is associated with worse health status.[439,1369,1370] The mechanisms responsible for increased risk of exacerbations are not yet fully established.

► Proton pump inhibitors are often used for treatment of GERD. One small, single-blind study suggested these agents decrease the risk of exacerbation,[1371] but their value in preventing these events remains controversial most effective treatment for this condition in COPD has yet to be established.[1372,1373]

Osteoporosis

► Osteoporosis is an important and common comorbidity[463,1285] which is often under-diagnosed[1374] and associated with poor health status and prognosis.

► Osteoporosis is often associated with emphysema,[1375] decreased body mass index[1376] and low fat-free mass.[1377] Low bone mineral density and fractures are commonly in COPD patients even after adjustment for steroid use, age,

pack-years of smoking, current smoking, and exacerbations.[1378,1379]

► Osteoporosis should be treated according to usual guidelines.

► COPD should be treated as usual despite the presence of osteoporosis. An association between ICS and fractures has been found in pharmaco- epidemiological studies; however, these studies have not fully taken severity of COPD or exacerbations and their treatment into account.

► Systemic corticosteroids significantly increase the risk of osteoporosis and repeated courses for COPD exacerbations should be avoided if possible

Anemia

Anemia is frequent in people with COPD, with a reported prevalence of 7.5% to 34%.[1380] People with COPD and anemia are generally older, have more frequent cardiometabolic comorbidities, greater dyspnea, worse quality of life and airflow obstruction, reduced exercise capacity, an increased risk of severe exacerbations and higher mortality.[1380-1386]

Anemia due to chronic disease is the most common type seen in COPD, followed by iron deficiency anemia,[1387,1388] and is 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, angiotensin-converting-enzyme inhibitors, angiotensin II receptor inhibitors, renal dysfunction, and androgens.[1389-1397]

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 its correction 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

Secondary polycythemia has long been recognized as a common comorbidity in COPD with a reported prevalence of 6% to 10.2% in COPD outpatients (when defined as hemoglobin ≥ 17g/dL in males and ≥ 15g/dL in females).[1382,1384,1398] Interestingly, in the COPDGene cohorts 9.2% of men and 3.5% of women had secondary polycythemia.[1399] Although the prevalence of polycythemia in COPD has decreased following the introduction of long-term oxygen therapy (LTOT),[1400] one study reported a prevalence of 8.4% in patients with severe COPD receiving LTOT.[1383]

Data from a large cohort (COPDGene cohort) of individuals with moderate to very severe COPD, indicate that male sex, current smoking, living at high altitude (e.g., Denver, Colorado, USA), impaired DLco, and severe hypoxemia were associated with increased risk for secondary polycythemia, whereas, LTOT use was associated with a decreased risk of polycythemia.[1399] The coexistence of obstructive sleep apnea has also been associated with increased risk of polycythemia in patients with COPD.[1401] Smoking causes an increase in carboxyhemoglobin, thereby increasing red blood cell mass and risk of secondary polycythemia in people with COPD.[1402,1403]

Secondary polycythemia in COPD may be associated with pulmonary hypertension,[1404,1405] venous thromboembolism,[1405] and mortality.[1406,1407] 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 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.

Anxiety and depression

► Anxiety and depression are important and underdiagnosed comorbidities in COPD[335,1408-1410] and both are associated with a poor prognosis,[1409,1411] younger age, female sex, smoking, lower FEV1, cough, higher SGRQ score, and a history of cardiovascular disease.[42,335,1410]

► There is no evidence that anxiety and depression should be treated differently in the presence of COPD.

► 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.[1412,1413]

► COPD is very common in patients with other psychiatric illnesses, often under-diagnosed and treated.[1414,1415]

► A systematic review has shown that COPD patients are 1.9 times more likely to commit suicide than people without COPD.[1416]

► Following a diagnosis of COPD patients are more likely to develop depression and the risk is greater in patients with worse breathlessness.[1417]

Cognitive impairment

► Cognitive impairment (CI) is common in people with COPD.[1418] An average prevalence of 32% has been suggested.[1419] The prevalence and severity varies by the type of assessment.[1420] Extensive neuropsychological testing suggests that up to 56% of patients may suffer CI.[1421,1422] Longitudinal studies suggest greater risk of developing CI in COPD diagnosed in midlife,[1418,1423] and associate COPD with the development of dementia.[1424]

► CI has been reported in patients across the entire range of spirometric severity.[1422]

► CI has been associated with impairment in basic activities of daily living,[1425,1426] and variably associated with impaired health status.[1427,1428]

► The coexistence of CI and COPD has been associated with an increased risk of hospitalization[1429] and increased length of stay during acute exacerbation hospitalization.[1430]

► The impact of CI on self-management skills in COPD patients remains unclear,[1425] although inhaler incompetency has been linked to CI.[1425]

Frailty

► Frailty can be defined as the presence of five components: weakness, slowness, exhaustion, low physical activity, and unintentional weight loss.[1431]

► 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.[1432]

► In a meta-analysis it was reported that frailty and prefrailty were associated with all-cause mortality, acute exacerbation, and hospitalization in patients with COPD.[1433]

► The European Respiratory Society 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.[1434]

COPD as part of multimorbidity

► An increasing number of people in any aging population will suffer from multi-morbidity, defined as the presence of two or more chronic conditions, and COPD is present in most multi-morbid patients.

► Multi-morbid 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.

► There is no evidence that COPD should be treated differently when part of multi-morbidity; however, it should be kept in mind that most evidence comes from trials in people with COPD as the only significant disease.[464]

► Treatments should be kept simple in the light of the unbearable polypharmacy that these patients are often exposed to.

Other considerations

► Consider checking for vitamin D deficiency in COPD patients.

CHAPTER 6: COVID-19 AND COPD

KEY POINTS:

- People with COPD presenting with new or worsening respiratory symptoms, fever, and/or any other symptoms that could be COVID-19 related, even if these are mild, should be tested for possible infection with SARS-CoV-2.
- Patients should keep taking their oral and inhaled respiratory medications for COPD as directed.
- During periods of high prevalence of COVID-19 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.
- Physical distancing and shielding, or sheltering-in-place, should not lead to social isolation and inactivity. Patients should stay in contact with their friends and families by telecommunication and continue to keep active. They should also ensure they have enough medication.
- Patients should be encouraged to use reputable resources for medical information regarding COVID-19 and its management.
- Guidance for remote (phone/virtual/online) COPD patient follow-up and a printable checklist are provided.

INTRODUCTION

For COPD patients the worry of developing COVID-19 as well as the effects of the pandemic on the basic functions of society and/or social services pertaining to their health imposed additional stressors to their condition. The COVID-19 pandemic made routine management and diagnosis of COPD more difficult as a result of reductions in face-to-face consultations, difficulties in performing spirometry and limitation in traditional pulmonary rehabilitation and home care programmes. Patients also faced shortages of medication.[1435] Some health services are still working to catch up.

The dramatic spread of the SARS-CoV-2 virus was accompanied by an enormous number of publications on the virus and its consequences. Over time knowledge has grown, but the emergence of SARS-CoV-2 variants and the introduction of vaccines limits the interpretation of studies performed at earlier stages of the pandemic. The statements made in this chapter utilize the published GOLD approach to data review and are based on the best assessment of the current evidence.

RISK OF INFECTION WITH SARS-CoV-2

The spike protein of the virus binds to ACE2 (angiotensin-converting enzyme 2) during viral attachment to host cells and that viral entry is also facilitated by transmembrane protease serine 2 (TMPRSS2).[1436] Differences in the expression of ACE2 and TMPRSS2 may modulate the individual susceptibility to and clinical course of SARS-CoV-2 infection. ACE2 mRNA expression is increased in COPD,[1437-1439] and further increased in COPD patients with a higher

BMI and more frequent exacerbations.[1440,1441] It may be modulated by ICS use.[1437,1442-1444]

It is still not known definitively whether having COPD affects the risk of becoming infected with SARS-CoV-2. Very few population studies using random sampling have assessed risk factors for testing positive for SARS-CoV-2, most have looked at samples of patients referred for testing or presenting with symptoms and very few contain information on comorbidities. A comprehensive review compared the prevalence of COPD among COVID-19 populations to the country-specific populations in 16 countries worldwide with high quality data and found no significant differences in ten countries, a higher prevalence of COPD in 4 and a lower prevalence in two countries.[1445] Most studies of people in the community tested for SARS-CoV-2 have not shown chronic respiratory disease as an independent risk factor for testing positive,[1446,1447] although at least one has.[1448]

Many studies reporting the comorbidities of patients admitted to hospital with COVID-19 have suggested a lower prevalence of COPD than would be expected from population prevalence;[1449-1451] these findings are limited by small sample sizes and incomplete data on comorbidities. A large study with comprehensive data on comorbidities showed a high prevalence of COPD among those admitted (19%),[1452] although many patients had multiple comorbidities, and a further study of a primary care cohort of 8.28 million patients also showed having COPD was an independent risk factor for hospital admission (HR 1.55; 95%CI 1.46-1.64).[1448] A systematic review, including only high quality studies from around the world, found that after accounting for confounding variables COPD patients were at slightly higher risk of hospitalization (adjusted odds ratio (aOR) 1.45; 95% CI 1.30,1.61).[1445]

COPD has also been reported to independently increase the risk of severe disease or death in some series[1275,1451-1458] but not all.[1448,1459-1461] Globally, looking at high quality studies and after accounting for confounding variables, COPD patients were found to be at slightly higher risk of ICU admission (aOR 1.28; 95% CI 1.08,1.51), and mortality (aOR 1.41; 95% CI 1.37,1.65).[1445] In patients with COPD, decreased lung function, higher CAT score, underweight, depression and prior COPD treated in inpatient or secondary care have been shown to be factors predicting severe COVID-19.[1462]

Many factors have been proposed to account for the increased risk for poor outcomes including prior poor adherence to therapy, difficulties performing self-management, limited access to care during the pandemic and a reduced pulmonary reserve.[1463,1464] There is evidence of a fall in hospitalization rates for COPD during the pandemic.[1275-1277,1465] The reasons for this remain unclear, but patients experiencing symptoms of an exacerbation should be evaluated in the usual way during the pandemic and hospitalized if necessary.

In multivariate analyses pre-existing COPD does not appear to increase the risk of patients developing long term symptoms post acute COVID.[1466,1467]

There are currently no peer-reviewed studies that have evaluated the effect of smoking on the risk of infection with SARS-CoV-2, but studies suggest that smoking is associated with increased severity of disease and risk of death in hospitalized COVID-19 patients.[1468,1469]

In summary, on current evidence, people with COPD do not seem to be at greatly increased risk of infection with SARS-CoV-2, but this may reflect the effect of protective strategies. They are at an increased risk of hospitalization for COVID-19 and may be at increased risk of developing severe disease and death.

INVESTIGATIONS

Testing for SARS-CoV-2 infection

People with COPD presenting with respiratory symptoms, fever or other symptoms suggesting SARS-CoV-2 infection, even if mild, should be tested for possible infection (**Figure 6.2**). False-negative RT-PCR tests have been reported in patients with CT findings of COVID-19 who eventually tested positive with serial sampling.[1470] If people with COPD have been exposed to someone with known COVID-19 infection they should contact their health care provider to define the need for specific testing. Antibody testing may be used to support clinical assessment of patients who present late.

Detection of SARS-CoV-2 does not exclude the potential for co-infection with other respiratory pathogens.[1471] The U.S. Centers for Disease Control and Prevention (CDC) encouraged testing for other causes of respiratory illness, in addition to testing for SARS-CoV-2 depending on patient age, season, or clinical setting.

Some patients experience re-activation of long-lasting virus carriage or become re-infected, and this might be influenced by comorbidities or drugs that hamper the immune response.[1472] Repeat testing should be performed in patients with suspected recurrence or relapse of COVID-19.

The lung microbiome is different in people with COPD compared to those without.[1473] The lung microbiome can modify the immune response to viral infections but, to date there is no direct evidence from human or animal studies on the role of lung microbiome in modifying COVID-19 disease[1474] nor on its potential effects in people with COPD.

Spirometry & pulmonary function testing

Performing spirometry and pulmonary function testing may lead to SARS-CoV-2 transmission as a result of coughing and droplet formation during the tests.[1475,1476] During periods of high prevalence of COVID-19 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.[1475,1476] Whenever possible, patients should have a RT-PCR test for SARS-CoV-2 performed and the results available prior to performing the test. Patients with a positive RT-PCR test should normally have the test delayed until negative. As the prevalence of COVID-19 changes over time operating procedures should be reassessed and resumption of routine spirometry may be possible.[1477-1479]

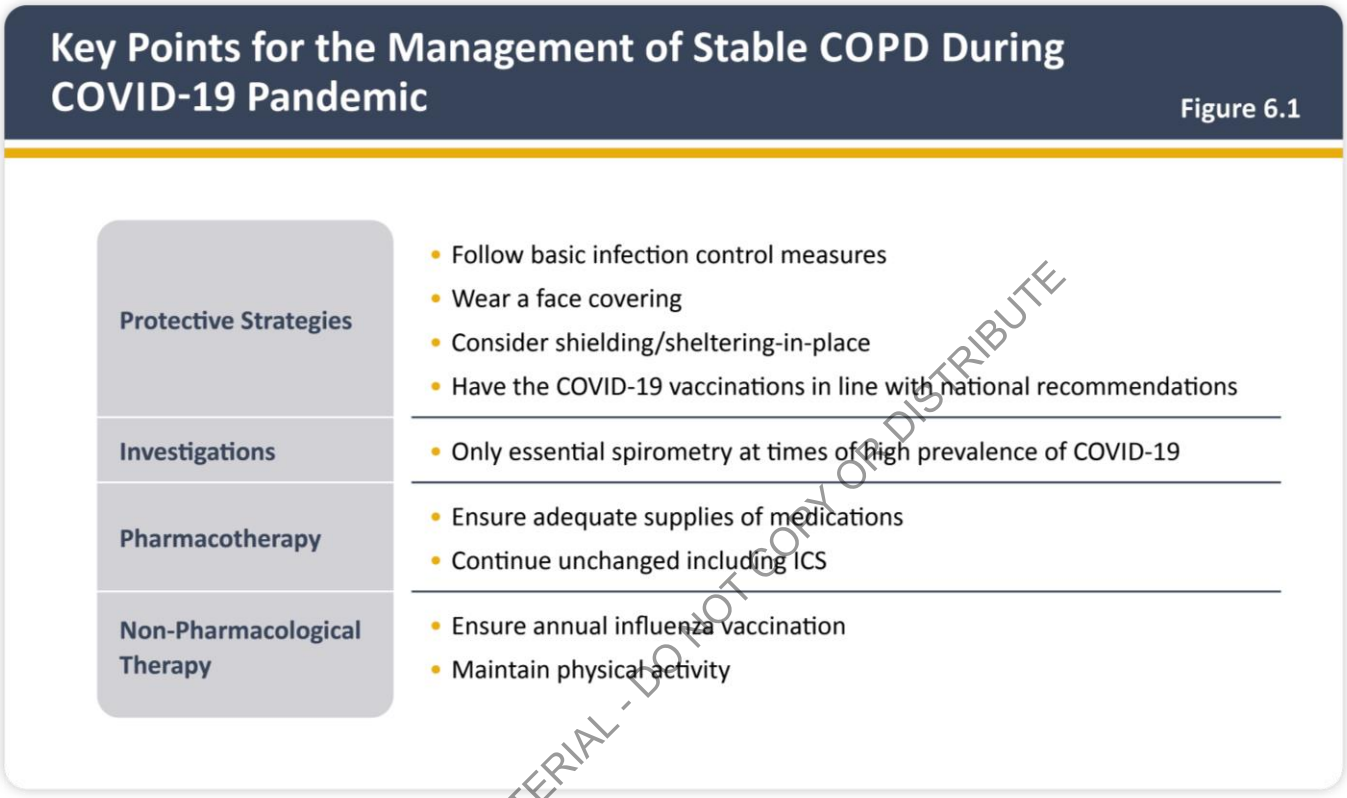
When routine spirometry is not available, home measurement of peak expiratory flow (PEF) combined with validated patient questionnaires could be used to support or refute a possible diagnosis of COPD.[375,1480-1482] However, PEF does not correlate well with the results of spirometry[1483-1485] has low specificity[343] and cannot differentiate obstructive and restrictive lung function abnormalities. When making a diagnosis of COPD, airflow obstruction could also be confirmed by giving patients a personal electronic portable spirometers,[1486,1487] and instructing them in their use and observing them in their homes using video conferencing technology.

Bronchoscopy

In some people with COPD, diagnostic and therapeutic bronchoscopy may be required. Elective bronchoscopy should be delayed until patients have a negative PCR test.[1488,1489] In urgent cases where COVID-19 infection status is unknown, all cases should be managed as if positive. A disposable bronchoscope should be used if available[1488] and staff should wear PPE.

Radiology

Chest radiography is insensitive in mild or early COVID-19 infection[1490] and is not routinely indicated as a screening test for COVID-19 in asymptomatic individuals. Chest radiography is indicated in people with COPD with moderate to severe symptoms of COVID-19 and for those with evidence of worsening respiratory status (**Figure 6.1**).[1491] COVID-19 pneumonia changes are mostly bilateral.[1492] Chest radiography can be useful for excluding or confirming alternative diagnoses (e.g., lobar pneumonia, pneumothorax, or pleural effusion). Point-of-care lung ultrasound can also be used to detect the pulmonary manifestations of COVID-19.[1493]



Computed tomography (CT) screening may show evidence of pneumonia in asymptomatic individuals infected with SARS-CoV-2[1494] and false-negative RT-PCR tests have been reported in patients with CT findings of COVID-19 who eventually tested positive.[1470] Recommendations have been made on the use of CT as part of diagnostic testing and severity assessment in COVID-19[1491] and there are no special considerations for people with COPD. The initial features of COVID-19 on CT and their progression over time have been reviewed.[1495] COPD patients with COVID-19 have an increased prevalence of ground-glass opacities, local patchy shadowing, and interstitial abnormalities on CT compared with patients without COPD.[1496] A small case series of patients with emphysema and COVID-19 found that many had bilateral ground glass opacities with areas of consolidation; however, the pattern was variable and patients had more pronounced disease in the lung bases.[1497]

The availability of CT may be limited by infection control requirements[1498] and where access to CT is limited, chest radiography may be preferred for patients with COVID-19 unless features of respiratory worsening warrant the use of CT. An increased occurrence of deep venous thrombosis and pulmonary thromboembolism has been reported in patients with COVID-19,[1499-1504] if pulmonary embolism is suspected chest CT angiography should be performed.

PROTECTIVE STRATEGIES FOR PATIENTS WITH COPD

During periods of high prevalence of COVID-19 in the community people with COPD should follow basic infection control measures to help prevent SARS-CoV-2 infection including social distancing and washing hands which are associated with reductions in the incidence COVID-19 (**Figure 6.1**).[1505] Wearing a mask or face covering can reduce the risk of *spreading* infection (source control).[1506] The efficacy of masks and respirators in *protecting* patients against infection are unknown but both surgical masks and N95 respirators were effective in preventing influenza-like illness and laboratory-confirmed influenza among healthcare workers.[1507] The American College of Chest Physicians, American Lung Association, ATS and COPD Foundation have issued a joint statement on the importance of patients with chronic lung disease wearing facial coverings at times of high COVID-19 prevalence during the pandemic.[1508]

Wearing a tight-fitting N95 mask introduces an additional inspiratory resistance. Respiratory rate, peripheral oxygen saturation and exhaled CO_2 levels were adversely affected in COPD patients wearing a N95 mask for 10 minutes at rest followed by 6 minutes of walking;[1509] however, wearing a surgical mask does not appear to affect ventilation even in patients with severe airflow obstruction[1510] and overall the negative effects of using cloth or surgical face masks during physical activity appear negligible.[1511] In some countries where wearing face masks was compulsory in certain settings exemptions could be made for patients who are breathless and cannot tolerate wearing a mask; however, whenever required people with COPD should try to wear masks. In most cases, a looser face covering, or even a face shield may be tolerable and effective.[1512]

The normal rules for patients on LTOT should be followed if air travel is planned,[1513] although patients should avoid travel unless essential. Supplementary oxygen should be delivered by nasal cannula[1514] with a surgical mask be worn and distancing maintained if appropriate.

Shielding, or sheltering-in-place, is a way to protect people who are extremely vulnerable from coming into contact with coronavirus. It is an alternative to full-scale physical distancing measures or lockdowns. It was introduced in some countries for patients with severe COPD. In the UK COPD patients were advised to shield if they had an FEV1 < 50%, mMRC ≥ 3, a history of hospitalization for an exacerbation, or required LTOT or NIV. Modeling suggests shielding was an effective strategy to protect individuals and control the impact of SARS-CoV-2.[1515] If people with COPD are asked to shield it is important that they are given advice about keeping active and exercising as much as possible whilst shielded. Plans should be made to ensure supplies of food, medications, oxygen, supportive health services and other basic necessities can be maintained.

There are likely to be particular challenges in using shielding in low- and middle-income countries including the fact that many families will not be able to designate a separate room for high-risk individuals and may rely on the income or domestic support that these individuals provide.[1516]

Vaccination

COVID-19 vaccines are highly effective against SARS-CoV-2 infection requiring hospitalization, ICU admission, or an emergency department or urgent care clinic visit, including those with chronic respiratory disease.[561] People with COPD should have COVID-19 vaccination in line with national recommendations.

DIFFERENTIATING COVID-19 INFECTION FROM DAILY SYMPTOMS OF COPD

Differentiating the symptoms of COVID-19 infection from the usual symptoms of COPD can be challenging. Cough and breathlessness are found in over 60% of patients with COVID-19 but are usually also accompanied by fever (> 60% of patients) as well as fatigue, confusion, diarrhea, nausea, vomiting, muscle aches and pains, anosmia, dysgeusia and headaches.[1452]

In COVID-19 symptoms may be mild at first, but rapid deterioration in lung function may occur (**Figure 6.2**). The prodrome of milder symptoms is especially problematic in patients with underlying COPD who may already have diminished lung reserve. Lack of recognition of the prodromal symptoms may delay early diagnosis and preliminary data suggest that people with COPD reporting exacerbations and suspected of having COVID-19 infection were infrequently tested for its presence.[1517] A high index of suspicion for COVID-19 needs to be maintained in people with COPD who present with symptoms of an exacerbations, especially if accompanied by fever, impaired taste or smell or GI complaints.

Persistent symptoms in people with COPD may cause diagnostic difficulty. A study found that only 65% of people had returned to their previous level of health 14-21 days after testing positive for SARS-CoV-2.[1518] Some patients continue to experience cough, fatigue and breathlessness for weeks and a smaller proportion for months.[1518-1520] Delayed recovery was more common in people with multiple chronic medical conditions but was not specifically linked to having COPD.[1518]

MAINTENANCE PHARMACOLOGICAL TREATMENT FOR COPD DURING THE COVID-19 PANDEMIC

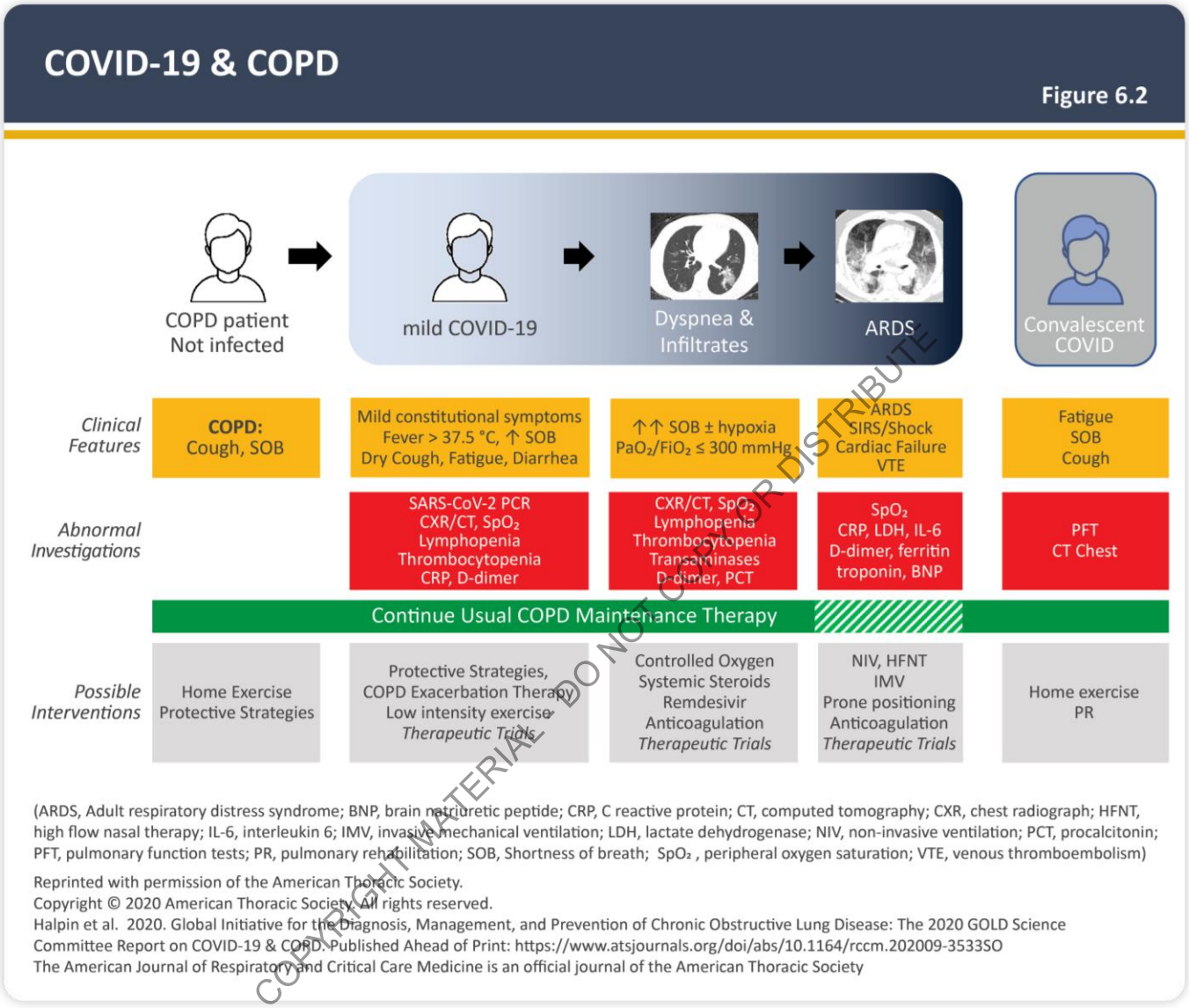
The use of inhaled and systemic corticosteroids has been controversial in the prevention and treatment of COPD during the COVID-19 pandemic. ICS have an overall protective effect against exacerbations in COPD patients with a history of exacerbations (**Chapter 3**). However, there is an increased risk of pneumonia associated with ICS use, raising concerns that immunosuppression with ICS could increase susceptibility to infections in some individuals.

Laboratory experiments show that corticosteroids reduce the production of anti-viral interferons (type I and III), increasing the replication of rhinovirus and influenza virus.[1521-1523] In contrast, other laboratory data show that corticosteroids and long acting bronchodilators can reduce the replication of coronaviruses including SARS-CoV-2.[1524] These laboratory experiments suggesting a potential protective effect of ICS against COVID-19 have not been validated by clinical studies.

A systematic literature review identified no clinical studies in COPD patients concerning the relationship between ICS use and clinical outcomes with coronavirus infections including COVID-19, SARS and Middle East Respiratory Syndrome (MERS).[1525] A more recent study has shown ICS use in COPD was not protective and raised the possibility that it increased the risk of developing COVID-19[1526] but the results are likely to be confounded by the indication for ICS.[1527] A systematic review of more recent studies found no evidence that ICS use was associated with worse outcomes;[1445] however the conclusions were again limited by similar confounding, lack of reporting of and adjustment for comorbidities, and studies with small sample sizes. In people who do not have COPD, ICS use appears to reduce the risk of admission to hospital or death and reduce the duration of symptoms.[1528] There are no conclusive data to support alteration of maintenance COPD pharmacological treatment either to reduce the risk of developing COVID-

19, or conversely because of concerns that pharmacological treatment may increase the risk of developing COVID-19.

Similarly, there is no data on the use of long-acting bronchodilators, LAMA or LABA, roflumilast, macrolides in people with COPD and clinical outcomes/risk of SARS-CoV-2 infection; thus, unless evidence emerges, these patients should continue these medications required for COPD.



(ARDS, Adult respiratory distress syndrome; BNP, brain natriuretic peptide; CRP, C reactive protein; CT, computed tomography; CXR, chest radiograph; HFNT, high flow nasal therapy; IL-6, interleukin 6; IMV, invasive mechanical ventilation; LDH, lactate dehydrogenase; NIV, non-invasive ventilation; PCT, procalcitonin; PFT, pulmonary function tests; PR, pulmonary rehabilitation; SOB, Shortness of breath; SpO_2 , peripheral oxygen saturation; VTE, venous thromboembolism)

Halpin et al. 2020. Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: The 2020 GOLD Science Committee Report on COVID-19 & COPD. Published Ahead of Print: https://www.atsjournals.org/doi/abs/10.1164/rccm.202009-3533SO
The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society

Use of nebulizers

Aerosol therapy increases the droplet generation and risk of disease transmission. Although most of the aerosol emitted comes from the device[1529,1530] there is a risk that patients may exhale contaminated aerosol and droplets produced by coughing when using a nebulizer may be dispersed more widely by the driving gas. SARS-CoV-2 has been shown to be viable in aerosols for up to 3 hours[1531] and transmission to health care workers exposed to a hospitalized patient with COVID-19 receiving nebulized therapy has been reported.[1532] If possible, pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) and soft mist inhalers (SMI) should be used for drug delivery instead of nebulizers. The risks of nebulized therapy spreading infection to other people in patient's homes may can be minimized by avoiding use in the presence of other people, and ensuring that the nebulizer is used near open windows or in areas of increased air circulation.[1533]

Nebulizers may be needed in critically ill patients with COVID-19 receiving ventilatory support. In this case, it is vital

to keep the circuit intact and prevent the transmission of the virus. Using a mesh nebulizer in ventilated patients allows adding medication without requiring the circuit to be broken for aerosol drug delivery.[1534]

PULMONARY REHABILITATION

Many pulmonary rehabilitation programmes were suspended during the pandemic to reduce risks of spreading SARS-CoV-2. When case rates are high, center-based rehabilitation is not appropriate. Patients should be encouraged to keep active at home and can be supported by home-based rehabilitation programmes which, although likely to be less effective than traditional pulmonary rehabilitation with supervision (**Chapter 3**), are likely to be better than not offering rehabilitation. Technology-based solutions, such as web-based or smartphone applications[975,1535] may be useful to support home rehabilitation. General principles of infection control should be applied and local guidance followed.[1536]

REVIEW OF COPD PATIENTS

To minimize the spread of SARS-CoV-2 many health systems reduced face-to-face visits and introduced remote consultations using online, phone and video-links. Routine review of people with COPD can be undertaken remotely[1537] and we have produced a tool to support these interactions that includes instructions on how to prepare for the remote visit, set the visit agenda with the patient, and provides a standardized checklist for follow-up (see section on follow-up at the end of **Chapter 6**).

TREATMENT OF COVID-19 IN PATIENTS WITH COPD

Randomized clinical trials of treatments targeting COVID-19 have focused on anti-viral agents and anti-inflammatory treatments. Some have produced positive results, including systemic steroids for hospitalized patients with severe COVID-19.[1538] The WHO has produced a COVID-19 therapeutics living guideline[1539] which currently recommends antivirals, corticosteroids, IL-6 receptor blockers and baricitinib for the treatment of COVID-19. The European Respiratory Society has also produced a living guideline on the management of hospitalized adults with COVID-19.[1540] Sub-group analysis of the effectiveness of these therapies in COPD patients have not been presented.

In the absence of subgroup data, we recommend that COPD patients suffering with COVID-19 should be treated with the same standard of care treatments as other COVID-19 patients (**Figure 6.3**). Furthermore, we advocate that COPD patients should be included in randomized controlled trials of COVID-19 treatments and that subgroup analysis of their outcomes are presented.

Key Points for the Management of Patients with COPD and Suspected or Proven COVID-19

Figure 6.3

SARS-CoV-2 Testing	• Swab/saliva PCR if new or worsening respiratory symptoms, fever, and/or any other symptoms that could be COVID related
Other Investigations	• Avoid spirometry unless essential • Consider CT for COVID pneumonia and to exclude other diagnoses e.g. PE • Avoid bronchoscopy unless essential • Assess for co-infection
COPD Pharmacotherapy	• Ensure adequate supplies of medication • Continue maintenance therapy unchanged including ICS • Use antibiotics and oral steroids in line with recommendations for exacerbations • If indicated, nebulization therapy can be used with appropriate personal protective equipment worn by providers
COPD Non-Pharmacological Therapy	• Maintain physical activity as able
Protective Strategies	• Have the COVID-19 vaccinations in line with national recommendations • Follow basic infection control measures • Maintain physical distancing • Wear a face covering
COVID-19 Therapy	• Use antivirals, corticosteroids, and immunomodulator therapy • Use HFNT or NIV for respiratory failure if possible • Use invasive mechanical ventilation if HFNT or NIV fails • Post COVID-19 rehabilitation • Ensure appropriate post COVID-19 follow-up

EXACERBATIONS OF COPD

The prevention and treatment of exacerbations are important goals in COPD management (**Chapter 3**). COVID-19 infection has introduced unique obstacles to the prevention and management of exacerbations.[1464] These include limited access to therapies due to their use for COVID-19 patients without COPD, disruptions in global supply chains and the inability of patients to afford medications due to economic hardships associated with the pandemic.[1464] Conversely, as countries went into lockdown and industrial activities shut down, pollutant emissions reduced substantially and environmental air quality improved.[1541] This could have contributed to the reported reductions in hospital admissions for COPD during the COVID-19 pandemic.[1276,1465,1542]

Coronaviruses are among the respiratory viruses that trigger COPD exacerbations.[1543] To date MERS-CoV, SARS-CoV,

and SARS-CoV-2 infection have not been reported in COPD exacerbations. Nonetheless, any COPD patients with SARS-CoV-2 infection presenting with respiratory symptoms requiring changes in their maintenance medications would fulfil the definition of an exacerbation (**Chapter 4**). Distinguishing the symptoms of a typical exacerbation from COVID-19 infection can be extremely difficult as many of the symptoms overlap. If COVID-19 infection is suspected, then RT-PCR testing should be conducted. If COVID-19 infection is confirmed, then treatment for COVID-19 infection should be conducted regardless of the presence of COPD.

SARS-CoV-2 infection causes a distinct pattern of pathophysiological changes including vascular injury, pneumonitis associated with hypoxemia, coagulopathy, high levels of systemic inflammation ("cytokine storm") and multi-organ involvement.[1544,1545] These features are very different from typical COPD exacerbations.[1546] However, SARS-CoV-2 infection may resemble an exacerbation of COPD. Fever, anorexia, myalgias, and gastrointestinal symptoms are more frequently reported in COVID-19 than in exacerbations of COPD, whereas sputum production is less uncommon. Pronounced lymphopenia is a common finding of SARS-CoV-2 infection.[1501,1547] COPD patients who develop COVID-19 reported more severe fatigue, dyspnea, and diarrhea than those without COPD.[1496]

In patients with COVID-19 lymphopenia, thrombocytopenia, elevated D-dimer, C-reactive peptide (CRP), procalcitonin, creatinine kinase, transaminases, creatinine, and lactate dehydrogenase (LDH) are independently associated with higher risk of poor outcomes.[1548] There is no reason to suspect that this is different in COPD patients with COVID-19 (**Figure 6.2**).

Systemic corticosteroids

Caution has been raised about the widespread use of systemic corticosteroids in patients with COVID-19.[1549,1550] Observational studies in patients with SARS and MERS reported no association between systemic corticosteroids (often at high dose) and improved survival, but suggested that corticosteroids induced side effects, including osteonecrosis, and reduced viral clearance.[1551-1554] The WHO initially recommended against the routine use of corticosteroids in COVID-19 infection at the beginning of the pandemic except in two clinical settings: adult respiratory distress syndrome (ARDS) and COPD exacerbations, where a specific indication for systemic corticosteroids was recognized.[1555]

A large randomized trial in hospitalized patients with COVID-19 has shown that dexamethasone treatment at 6 mg/day for up to 10 days reduced mortality in patients receiving either invasive mechanical ventilation or oxygen alone.[1538] A small observational study has also reported that methylprednisolone use was associated with improved survival in COVID-19 patients with ARDS.[1556] Further studies have also reported the benefits of systemic glucocorticoids on reduction of mortality at 28 days in patients with COVID-19 pneumonia, especially those that are not on invasive mechanical ventilation or on pressor support.[1557]

Systemic steroids should be used in COPD exacerbations according to the usual indications (**Chapter 4**) whether or not there is evidence of SARS-CoV-2 infection as there is no evidence that this approach modifies the susceptibility to SARS-CoV-2 infection or worsens outcomes (**Figure 6.2**).

Antibiotics

Antibiotic treatment for a COPD exacerbation is indicated if patients have at least two of the three cardinal symptoms including increased sputum purulence, or if the patient requires mechanical ventilation (**Chapter 4**).

Bacterial co-infections have been reported infrequently in COVID-19.[1558] However, the risk of co-infections increases with the severity of COVID-19. Bacterial co-infections have been detected by multiplex PCR testing in up to 46% of samples collected in a small cohort of COVID-19 patients admitted to an ICU.[1559] Diagnosing co-infection in COVID-19 patients may be difficult, particularly in critically ill patients, as the clinical presentation, biomarkers and imaging data

may be unhelpful. In practice, most hospitalized patients, particularly the severe ones, have been prescribed empirical antibiotic therapy.[1547] Current WHO guidelines recommend broad-spectrum antibiotics in severe COVID-19 patients, guided by local/national guidelines, and in milder COVID-19 infections when there is clinical suspicion of a bacterial infection.[1555] In the absence of specific studies, these general considerations would also apply to people with COPD infected with SARS-CoV-2.

Antibiotics should be used in COPD exacerbations according to the usual indications (**Chapter 4**) whether or not there is evidence of SARS-COV-2 infection, particularly as people with COPD who develop COVID-19 are reported to more frequently develop bacterial or fungal coinfections.[1496]

PULMONARY AND EXTRA-PULMONARY COMPLICATIONS

ARDS may be part of COVID-19 and could be considered the major pulmonary complication of COVID-19[1560] with viral infection in areas of ongoing active injury contributing to persistent and temporally heterogeneous lung damage.[1561] Some early reports suggested that ARDS in this setting may differ from the typical ARDS.[1562,1563] Subsequent studies, however, suggested that classical ARDS also presented with a large variation in lung severity[1564] and there is considerable overlap between classical ARDS and COVID-19 patients.[1565,1566] Whether the long-term consequences of this form of ARDS differ from fibrotic lesions described previously is unclear.[1567,1568]

Although the respiratory tract is the main target of COVID-19, extra-pulmonary involvement is frequent and contributes to morbidity, disability, and mortality.[1545,1569] Renal, cardiac, nervous, cutaneous, hepatic and gastrointestinal manifestations occur.[1570] It remains unclear, however, if these manifestations are directly caused by infection of SARS-CoV-2, or to secondary phenomena including inappropriate or overwhelming immune responses, angiopathy, treatment or ischemic damage due to the impairment of the respiratory functions. Concomitant respiratory comorbidities, such COPD, may aggravate these processes. Compared to lung viral load, lower levels of SARS-CoV-2 have been reported in the kidneys, liver, heart, and brain,[1571] suggesting secondary rather than primary involvement of these organs.

Anticoagulation

COVID-19 has been associated with a hypercoagulable state[1499] and venous thromboembolism (VTE) rates in both ICU and ward patients are 2- to 4-fold higher than expected despite thromboprophylaxis with low molecular weight heparin (LMWH) or unfractionated heparin.[1572] People with COPD are already at increased risk of VTE[1573,1574] and those hospitalized with COVID-19 should receive pharmacologic thromboprophylaxis (**Figure 6.2**). In response to the high rates despite prophylactics many institutional protocols have adopted intermediate-intensity (i.e., twice daily LMWH rather than once daily) or even a therapeutic-intensity dose strategy for thromboprophylaxis.[1575] Generally, LMWH is favored over unfractionated heparin to reduce staff exposure but clinicians should follow local guidelines on dosing and drug.

VENTILATORY SUPPORT FOR COPD PATIENTS WITH COVID-19 PNEUMONIA

The prevalence of hypoxic respiratory failure in patients with COVID-19 was around 19%.[1576] Ventilatory support has been used in up to 20% of patients that develop severe hypoxemia due to COVID-19[1577] and approximately 5% of patients require ICU care and advanced respiratory support.[1578] Since the introduction of vaccination the rates of ICU admission have fallen.[1579] However, some patients still require ventilatory support and these individuals still have a

high risk of mortality.[1454,1580,1581] COPD has been reported to increase the risk respiratory failure and ICU admissions in some, but not all studies.[1448,1453]

There was wide variation (2.3% to 33%) in the early reported rates of use of invasive mechanical ventilation (IMV) in hospitalized patients with moderate to severe hypoxemic respiratory failure due to COVID-19.[1582] This may, in part, have reflected differences in use of non-invasive ventilation (NIV) and high flow nasal therapy (HFNT),[1582] possibly as a result of advocation of early intubation during the pandemic's initial phases because of concerns about viral dissemination.[1583,1584] Data supporting those concerns are lacking.[1585]

Although early reports showed mixed outcomes,[1586] several studies have now shown showed HFNT significantly reduces rates of intubation and IMV, although with variable effects on mortality.[1587,1588] HFTN should be considered in preference to NIV for acute hypoxemic respiratory failure despite conventional oxygen therapy as it may have a lower failure rate.[1589-1591] Prone positioning has also been suggested for awake non intubated hypoxemic patients.[1592]

NIV is the normal standard of care for COPD patients with acute respiratory failure (**Chapter 4**). NIV may be beneficial for the treatment of hypercapnic respiratory in COPD patients with COVID-19 pneumonia, but it also has the potential to worsen lung injury as a result of high transpulmonary pressures and tidal volumes.[1593] Patients on HFNT or NIV should be monitored closely for worsening and early intubation and IMV with adoption of a protective lung strategy, similar to that used in other forms of ARDS, considered.[1594,1595] A PaO_2/FiO_2 < 150 mmHg may be a useful indicator for NIV failure and increased risk of mortality.[1596]

At the start of the COVID-19 pandemic, there was a reasonable rationale for using extracorporeal membrane oxygenation ECMO in patients with very severe COVID-19-related ARDS, and results from large cohorts suggest outcomes during the first wave of the pandemic were similar to those in non-COVID-19 cohorts.[1582,1597-1603] As the pandemic continued, mortality of patients supported with ECMO has increased, possibly because of differences in patients referred for ECMO as a result of more widespread use of NIV and corticosteroids prior to intubation, changes in mechanical ventilation strategies and possible pathophysiological changes due to emerging viral variants.[1604] Indications in COVID-19 remain similar to indications for other causes of ARDS[1605,1606] and ECMO should be considered only after other strategies fail to achieve goals of oxygenation or ventilation.[1600,1601,1603]

Aerosol generation can occur when any form of additional pressures or flows are applied to the upper or lower respiratory tract.[1607] Data regarding aerosol dispersion with the use of NIV is limited and contradictory;[1530,1607-1609] however, staff should use appropriate personal protective equipment (PPE)[1591,1610] and viral filters fitted to exhalation ports of invasive or noninvasive ventilation devices. Isolation hoods have also been suggested by some to be used to further decrease staff exposure.[1611]

REHABILITATION

COPD patients with COVID-19 are particularly at risk for poor nutritional status and skeletal muscle loss.[334] Hospital treatment should therefore include dietary support and early mobilization. Mechanical ventilation, sedation, and prolonged bed rest, may lead to post-traumatic stress disorder[1612] and respiratory, cognitive, and mental health impairments as well as physical deconditioning.[1613,1614] Older people and people with COPD, are more susceptible to these consequences.[1615,1616]

Rehabilitation should be provided to all COPD patients with COVID-19, particularly to those that have been more severely affected or required ICU admission. A multinational task force has recommended early rehabilitation during

the hospital admission and the screening for traits treatable with rehabilitation in all patients at discharge, and at 6-8 weeks after discharge for patients with severe COVID-19.[1617]

FOLLOW-UP OF COPD PATIENTS WHO DEVELOPED COVID-19

Several organizations have developed guidelines to address the evaluation and management of patients recovering from COVID-19[1519,1617-1620] but none of these have specific recommendations for patients with underlying COPD. Assessment protocols generally include a comprehensive physical, cognitive, and psychological assessment and there is no reason why these should not also apply to patients with COPD; however. high quality data on the outcomes of these evaluation and management strategies are still lacking.

The intensity of the monitoring of people with COPD who developed COVID-19 should be determined by the severity of the initial episode.

Patients who developed mild COVID-19 should be followed with the usual protocols used for COPD patients (**Chapter 3**). Patients who developed moderate COVID-19, including hospitalization and pneumonia but no respiratory failure, should be monitored more frequently and accurately than the usual COPD patients with particular attention to the need for oxygen therapy.

One year after COVID-19 one third of patients have residual CT abnormalities,[1621] with ground-glass opacities and fibrotic-like changes seen in 20% of patients, but no specific data are available on patients with COPD. The frequency of CT abnormalities was higher in severe/critical cases than in mild/moderate cases (38% vs. 21%). Gradual improvement is seen on CT over time but fibrotic changes showed little improvement between 4-7 months and one year after COVID-19. If chest X-ray abnormalities have not resolved at hospital discharge, a chest X-ray, possibly a CT scan should be considered at 6 months to one year. Complications occurring during/after the COVID-19 episode should also be monitored.

COPD patients are at higher risk of developing severe COVID-19[1594,1622] and multimorbid survivors frequently have required prolonged ICU stays.[1594] Until we have evidence from prospective studies, COPD survivors of severe COVID-19 should be considered at high risk of developing a “critical illness”[1623] or “chronic critical illness”,[1624] a severe heterogeneous condition linked not only to the acute infectious episode but also to the underlying conditions before they became severely ill.[1614]

There are informative candidate models for the comprehensive management of complex care delivery that are already published and undergoing study in the primary care setting, and these may be adapted for application after COVID-19.[1625]

REMOTE COPD PATIENT FOLLOW-UP

Introduction

During the COVID-19 pandemic, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recognized that there was a need for developing new approaches to interact with COPD patients. Remote consultations are superb tools to minimize the risk of transmitting coronavirus and will be necessary for some time. The systems put in place to facilitate remote consultations should also help increase the efficiency and capacity of the health care system into the future.[1626]

In this short document, GOLD provides guidance to support the remote interaction with COPD patients who are usually seen in primary or secondary care. The tool includes instructions on how i) to prepare for the remote visit; ii) to set up the visit agenda with the patient; and iii) provides a standardized checklist for follow-up of COPD patients whether in-person, by phone or in a virtual/online setting.

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.

Triage and prioritizing process

The process of triage should help decide: a.) whether to offer an in-person as opposed to a remote (telephone or virtual/online) consultation, and b.) 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 the COPD patient 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 health care 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 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.

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 **CAT: /40**

Maintenance Medication and adherence:

□ SABA □ LABA+LAMA

□ LABA □ LABA+ICS

□ LAMA □ LABA+LAMA+ICS

□Other:

Non pharmacological Rx:

O2: CPAP: BIPAP :

2. COVID-19 – If patient is feeling unwell, check other symptoms: □ Fever____ □ Sore throat □ Anosmia □ Others_____

Contact with someone COVID-19 positive? □ no □ yes Tested for COVID-19? □ 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/ER	Where	Date	Length	Reason (Dx)

Comments:

5. COPD Self-management (healthy behaviors) – Integrated (patient has used it in his 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 need:

6. MAIN ISSUES

1.	*2.*	*3.*

7. SUMMARY, INTERVENTIONS & PLAN

(healthcare professional name & signature)

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 – COVID-19**
    a. Assess whether the patient has any symptoms of COVID-19 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 COVID-19 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 [1]. 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 ER visits**
    a. Write down recent admissions and ER 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) [2]. 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).

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