# Global Initiative for Chronic Obstructive Lung Disease




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

## 2021 REPORT

# GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE

## GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (2021 REPORT)



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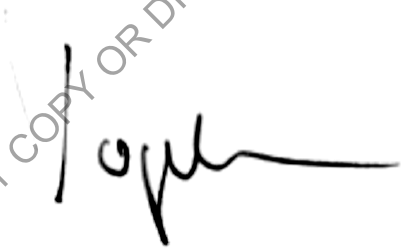
# PREFACE

The GOLD report is revised annually and has been used worldwide by healthcare professionals as a “strategy document” and tool to implement effective management programs based on local healthcare systems.

The major change in the 2021 revision is the addition of Chapter 7 in which we summarize the relevant key points regarding COVID-19 in the context of COPD including recommendations for remote follow-up during pandemic restrictions. In recognition of the enormous role of COPD in LMIC countries we added references to the WHO minimum set of interventions for the diagnosis of COPD and the management of exacerbations.

GOLD has been fortunate to have a network of international distinguished health professionals from multiple disciplines. Many of these experts have initiated investigations of 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.





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# GLOBAL STRATEGY FOR DIAGNOSIS, MANAGEMENT AND PREVENTION OF COPD 2021 UPDATE[†]

## 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 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[‡] 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.

Updates of the 2011-revised report were released in January 2013, 2014, 2015, and 2016. The 2017 GOLD Report, the 4th major revision of GOLD, incorporates an update of recent information that has been reviewed by the science committee from 2015 to 2016 and a comprehensive reassessment and revision of prior recommendations for the diagnosis, assessment and treatment of COPD. Updates of the 2017-revised report were made in 2018, 2019 and 2020.

***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



[†] The Global Strategy for Diagnosis, Management and Prevention of COPD (updated 2021), the Pocket Guide (updated 2021) and the complete list of references examined by the Committee is available on the GOLD website: www.goldcopd.org.

[‡] GOLD Science Committee Members (2020-2021): C. Vogelmeier, Chair, A. Agusti, A. Anzueto, P. Barnes, J. Bourbeau, G. Criner, P. Frith, D. Halpin, M. Han, F. Martinez, M. Montes de Oca, A. Papi, I. Pavord, N. Roche, D. Sin, D. Singh, R. Stockley, M. Victorina Lopez Varela, J. Wedzicha.

Committee. Only high-quality systematic reviews and meta-analyses that provide strong evidence for changing clinical 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 2021 report is a revision of the GOLD 2020 report. 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 2019 to July 2020. In total, 244 new references have been added to the GOLD 2021 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 patients with COPD that can aid the clinician. One of the strengths of GOLD reports is the treatment objectives. These have stood the test of time, but 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 $FEV_1$ 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 limitation. 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, $FEV_1$ is an unreliable marker of the severity of breathlessness, exercise limitation, and health status impairment.

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 to the construction of a new approach to management – one that matches assessment to treatment objectives. 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] 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.[2]

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.[3] 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.[4]



## 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

| EVIDENCE CATEGORY | SOURCES OF EVIDENCE | DEFINITION |
|---|---|---|
| A | Randomized controlled trials (RCTs)<br><br>Rich body of high quality evidence without any significant limitation or bias | 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.<br><br>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<br><br>Limited Body of Evidence | Evidence is from RCTs that include only a limited number of patients, post hoc or subgroup analyses of RCTs or meta analyses of RCTs.<br><br>Also pertains when few RCTs exist, or important limitations are evident (methodologic 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<br><br>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.<br><br>Panel consensus is based on clinical experience or knowledge that does not meet the above stated criteria. |

TABLE A.



## REFERENCES


1. Halpin DMG, Celli BR, Criner GJ, et al. The GOLD Summit on chronic obstructive pulmonary disease in low- and middle-income countries. *Int J Tuberc Lung Dis* 2019; **23**(11): 1131-41.
2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; **3**(11): e442.
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# CHAPTER 1: DEFINITION AND OVERVIEW

**OVERALL KEY POINTS:**

- *Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.*

- *The most common respiratory symptoms include dyspnea, cough and/or sputum production. These symptoms may be under-reported by patients.*

- *The main risk factor for COPD is tobacco smoking but other environmental exposures such as biomass fuel exposure and air pollution may contribute. Besides exposures, host factors predispose individuals to develop COPD. These include genetic abnormalities, abnormal lung development and accelerated aging.*

- *COPD may be punctuated by periods of acute worsening of respiratory symptoms, called exacerbations.*

- *In most patients, COPD is associated with significant concomitant chronic diseases, which increase its morbidity and mortality.*



## DEFINITION

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development. Significant comorbidities may have an impact on morbidity and mortality.

There may be significant lung pathology (e.g., emphysema) in the absence of airflow limitation that needs further evaluation (**Figure 1.1**). The chronic airflow limitation that is characteristic of COPD is caused by a mixture of small airways disease and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. These changes do not always occur together, but evolve at different rates over time. Chronic inflammation causes structural changes, narrowing of 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 limitation and mucociliary dysfunction is a characteristic feature of the disease. Airflow limitation is usually measured by spirometry as this is the most widely available and reproducible test of lung function. Many previous definitions of COPD have emphasized the terms “emphysema” and “chronic bronchitis”, which are not included in the definition used in this or earlier GOLD reports. Emphysema, or destruction of the gas-exchanging surfaces of the lung (alveoli), is a pathological term that is often (but incorrectly) used clinically and describes only one of several structural abnormalities present in patients with COPD. Chronic bronchitis, or the presence of cough and sputum production for at least 3 months in each of two consecutive years, remains a clinically and epidemiologically useful term, but is present in only a minority of subjects when this definition is used. However, when alternative definitions are used to define chronic bronchitis, or older populations with greater levels of smoke or occupational inhalant exposure are queried, the prevalence of chronic bronchitis is greater.[1,2] It is important to recognize that chronic respiratory symptoms may precede the development of airflow limitation and may be associated with the development of acute respiratory

events.[3] Chronic respiratory symptoms also exist in individuals with normal spirometry[3,4] and a significant number of smokers without airflow limitation have structural evidence of lung disease manifested by the varying presence of emphysema, airway wall thickening and gas trapping.[3,4]

# BURDEN OF COPD

COPD is a leading cause of morbidity and mortality worldwide that induces an economic and social burden that is both substantial and increasing.[5,6] COPD prevalence, morbidity and mortality vary across countries and across different groups within countries. COPD is the result of a complex interplay of long-term cumulative exposure to noxious gases and particles, combined with a variety of host factors including genetics, airway hyper-responsiveness and poor lung growth during childhood.[7-9] Often, the prevalence of COPD is directly related to the prevalence of tobacco smoking, although in many countries outdoor, occupational and indoor air pollution (resulting from the burning of wood and other biomass fuels) are major COPD risk factors.[10,11] The prevalence and burden of COPD are projected to increase over the coming decades due to continued exposure to COPD risk factors and aging of the world's population; as longevity increases more people will express the long-term effects of exposure to COPD risk factors.[12] Information on the burden of COPD can be found on international websites, for example the:

- World Health Organization (WHO)[13]
- World Bank/WHO Global Burden of Disease Study[14]



## Prevalence

Existing COPD prevalence data vary widely due to differences in survey methods, diagnostic criteria, and analytical approaches.[12] Importantly, all of the studies defined COPD by spirometry alone and not by the combination of symptoms and spirometry. 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.[15] This is likely to be a reflection of the widespread under-recognition and under-diagnosis of COPD.[16]

Despite the complexities, data are emerging that enable more accurate estimates of COPD prevalence. A systematic review and meta-analysis, including studies carried out in 28 countries between 1990 and 2004,[15] provided 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. The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO)[17] examined the prevalence of post-bronchodilator airflow limitation among persons > 40 years in one major city from each of five Latin American countries – Brazil, Chile, Mexico, Uruguay, and Venezuela. In each country, the prevalence of COPD increased steeply with age, with the highest prevalence among those > 60 years. Prevalence in the total population ranged from a low of 7.8% in Mexico City, Mexico, to a high of 19.7% in Montevideo, Uruguay. In all five cities, the prevalence was appreciably higher in men than in women,[17] which contrasts with findings from European cities such as Salzburg, Austria.[18]

The Burden of Obstructive Lung Diseases (BOLD) program has also used a standardized methodology comprising questionnaires and pre- and post-bronchodilator spirometry to assess the prevalence and risk factors for COPD in people aged 40 and over around the world. Surveys have been completed in 29 countries and studies are on-going in a further nine.[19] BOLD reported worse lung function than earlier studies, with a prevalence of COPD grade 2 or higher of 10.1% (SE 4.8) overall, 11.8% (SE 7.9) for men, and 8.5% (SE 5.8) for women[20] and a substantial prevalence of COPD of 3-11% among never-smokers.[20] BOLD also examined the prevalence of COPD in north and sub-Saharan Africa and Saudi Arabia and found similar results.[21-24]

Based on BOLD and other large scale epidemiological studies, it is estimated that the number of COPD cases was 384

million in 2010, with a global prevalence of 11.7% (95% confidence interval (CI) 8.4%–15.0%).[25] Globally, there are around three million deaths annually.[26] With the increasing prevalence of smoking in developing countries, and aging populations in high-income countries, the prevalence of COPD is expected to rise over the next 40 years and by 2060 there may be over 5.4 million deaths annually from COPD and related conditions.[27,28]

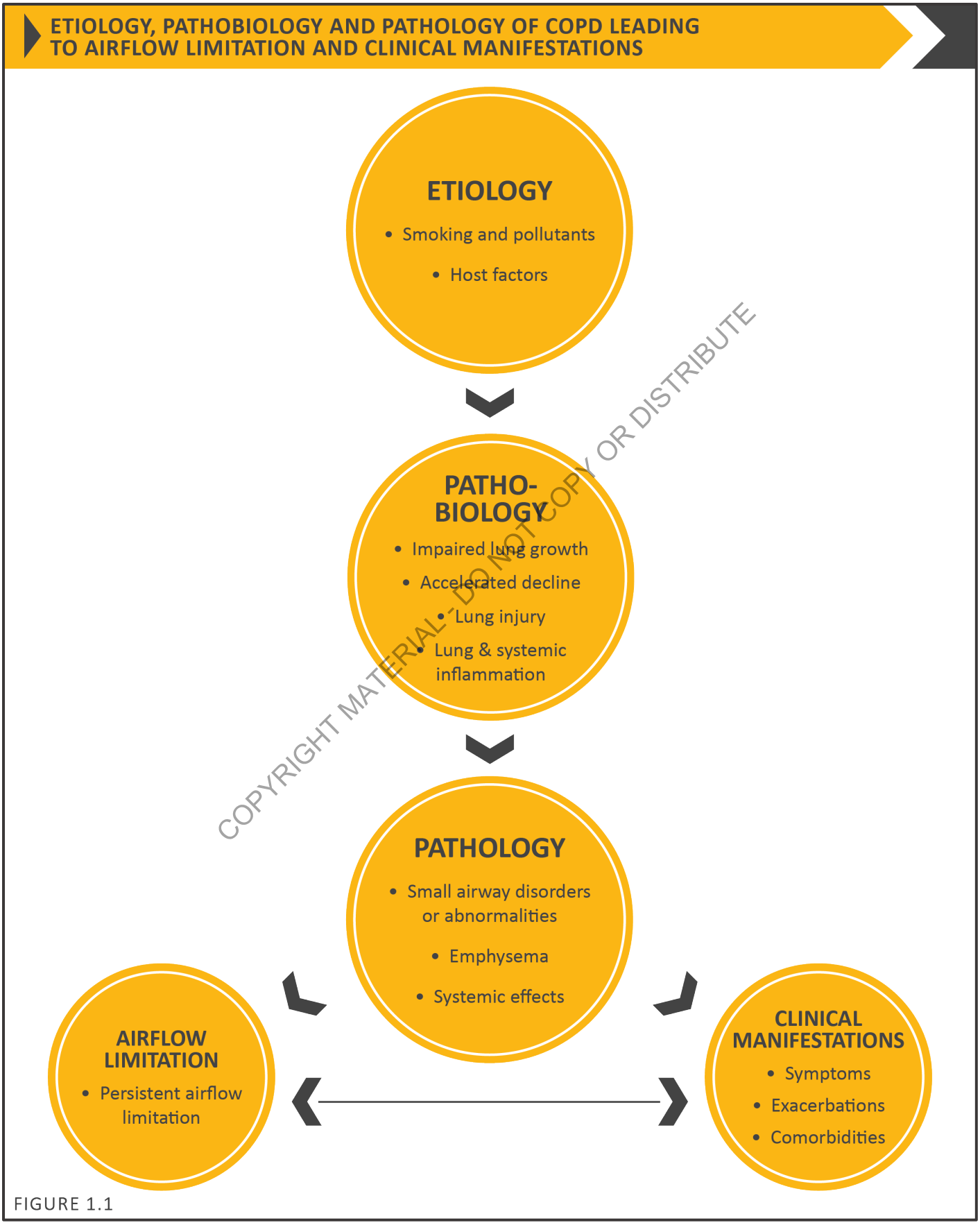





FIGURE 1.1

## Morbidity

Morbidity measures traditionally include physician visits, emergency department visits, and hospitalizations. Although COPD databases for these outcome parameters are less readily available and usually less reliable than mortality databases, to date studies on the available data indicate that morbidity due to COPD increases with age,[15-17] and in patients with COPD the development of comorbidities may be seen at an earlier age.[29] Morbidity from COPD may be affected by other concomitant chronic conditions (e.g., cardiovascular disease,[30] musculoskeletal impairment, diabetes mellitus) that are related to smoking, aging and COPD. These chronic conditions may significantly impair patient's health status, in addition to interfering with COPD management and are major drivers of hospitalizations and costs for patients with COPD.[31]

## Mortality

The World Health Organization (WHO) publishes mortality statistics for selected causes of death annually for all WHO regions; additional information is available from the WHO Evidence for Health Policy Department.[32] 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.[33,34] Furthermore, the accuracy of COPD diagnosis codes recorded in administrative health databases is also uncertain.[35,36] In some jurisdictions, reliance on administrative health data, particularly those that only record hospitalizations, may underestimate the burden of COPD.[37] 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.[38] 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.[39] 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.



## 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.[40] In the United States the estimated direct costs of COPD are $32 billion and the indirect costs $20.4 billion.[41] COPD exacerbations account for the greatest proportion of the total COPD burden on the healthcare system. 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 developing countries, direct medical costs may be less important than the impact of COPD on workplace and home productivity. 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.[42] Since human capital is often the most important national asset for developing countries, the indirect costs of COPD may represent a serious threat to the 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 authors of the Global Burden of Disease (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 Year (DALY).[43] The DALYs 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 COPD is an increasing contributor to disability and mortality around the world. In 2005 COPD was the eighth leading cause of DALYs lost across the world but by 2013 COPD was ranked as the fifth leading cause of DALYs lost.[44] In the United States, COPD is the second leading cause of reduced DALYs, trailing only ischemic heart disease.[45]

# FACTORS THAT INFLUENCE DISEASE DEVELOPMENT AND PROGRESSION

Although cigarette smoking is the most well studied COPD risk factor, it is not the only risk factor and there is consistent evidence from epidemiologic studies that non-smokers may also develop chronic airflow limitation.[20] Much of the evidence concerning risk factors for COPD comes from cross-sectional epidemiological studies that identify associations rather than causal relationships. Nevertheless, compared to smokers with COPD, never smokers with chronic airflow limitation have fewer symptoms, milder disease and lower burden of systemic inflammation.[46] Interestingly, never smokers with chronic airflow limitation do not appear to have an increased risk of lung cancer, or cardiovascular comorbidities, compared to those without chronic airflow limitation. However, there is evidence that they have an increased risk of pneumonia and mortality from respiratory failure.[46]

Although several longitudinal studies of COPD have followed groups and populations for up to 20 years,[7] to date no studies have monitored the progression of the disease through its entire course, or included the pre and perinatal periods that may be important in shaping an individual's future COPD risk. Thus, the current understanding of risk factors for COPD is in many respects still incomplete.

COPD results from a complex interaction between genes and the environment. Cigarette smoking is the leading environmental risk factor for COPD, yet even for heavy smokers, fewer than 50% develop COPD during their lifetime.[47] Although genetics may play a role in modifying the risk of COPD in smokers, there may also be other risk factors involved. For example, sex may influence whether a person takes up smoking or experiences certain occupational or environmental exposures; socioeconomic status may be linked to a child's birth weight (as it impacts on lung growth and development, and in turn on susceptibility to developing the disease); and longer life expectancy will allow greater lifetime exposure to risk factors. Understanding the relationships and interactions between risk factors requires further investigation.



## Genetic factors

The genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin (AATD),[48] 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.[49]

A significant familial risk of airflow limitation has been observed in people who smoke and are siblings of patients with severe COPD,[50] suggesting that genetics together with environmental factors could influence this susceptibility. Single genes, such as the gene encoding matrix metalloproteinase 12 (*MMP-12*) and glutathione *S*-transferase have been related to a decline in lung function[51] or risk of COPD.[52] Several genome-wide association studies have linked genetic

loci with COPD (or $FEV_1$ or $FEV_1$/FVC as the phenotype) including markers near the alpha-nicotinic acetylcholine receptor, hedgehog interacting protein (HHIP), and several others. Nevertheless, it remains uncertain whether these genes are directly responsible for COPD or are merely markers of causal genes.[53-57]

## Age and sex

Age is often listed as a risk factor for COPD. It is unclear if healthy aging as such leads to COPD or if age reflects the sum of cumulative exposures throughout life.[58] Aging of the airways and parenchyma mimic some of the structural changes associated with COPD.[58] Gender related differences in immune pathways and pattern of airway damage may be seen and might be clinically important. 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 reported that the prevalence of COPD is now almost equal in men and women, probably reflecting the changing patterns of tobacco smoking.[59] Although controversial, some studies have even suggested that women are more susceptible to the effects of tobacco smoke than men,[60-62] leading to more severe disease for the equivalent quantity of cigarettes consumed. 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.[63,64]

## Lung growth and development

Processes occurring during gestation, birth, and exposures during childhood and adolescence affect lung growth.[65,66] Reduced maximal attained lung function (as measured by spirometry) may identify individuals who are at increased risk for the development of COPD.[4,8] Any factor that affects lung growth during gestation and childhood has the potential for increasing an individual's risk of developing COPD. For example, a large study and meta-analysis confirmed a positive association between birthweight and $FEV_1$ in adulthood,[67] and several studies have found an effect of early childhood lung infections. Factors in early life termed "childhood disadvantage factors" seem to be as important as heavy smoking in predicting lung function in adult life.[67] One study evaluated three different longitudinal cohorts and found that approximately 50% of patients developed COPD due to accelerated decline in $FEV_1$ over time, while the other 50% developed COPD due to abnormal lung growth and development (with normal decline in lung function over time; **Figure 1.2**).[7] The Medical Research Council National Survey of Health and Development documented a synergistic interaction between smoking and infant respiratory infection as well as early life home overcrowding with lung function at age 43.[68]



## Exposure to particles

Across the world, cigarette smoking is the most commonly encountered risk factor for COPD. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in $FEV_1$, and a greater COPD mortality rate than non-smokers.[69] 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), may also contribute to respiratory symptoms and COPD[74] by increasing the lung's total burden of inhaled particles and gases. Smoking during pregnancy may pose a risk for the fetus, by affecting lung growth and development *in utero*, and possibly the priming of the immune system.[75]

Occupational exposures, including organic and inorganic dusts, chemical agents and fumes, are an under-appreciated risk factor for COPD.[10,76] 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 and never-asthmatics.[77] A cross-sectional observational study demonstrated that self-reported exposure to workplace dust and fumes is not only associated with increased airflow limitation and respiratory symptoms, but also with more emphysema and gas trapping, assessed by computed tomography scan, in both men and women.[78] 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.[79] 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.[80] 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.

Wood, animal dung, crop residues, and coal, typically burned in open fires or poorly functioning stoves, may lead to very high levels of indoor air pollution.[81] There is growing evidence that indoor biomass exposure to modern and traditional fuels used during cooking may predispose women to develop COPD in many developing countries.[82-85] 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.[86,87] There is a lack of research about biomass related COPD,[88] although there is limited evidence from an observational study that switching to cleaner cooking fuels or reducing exposure may reduce COPD risk in non-smokers.[89]

High levels of urban air pollution are harmful to individuals with existing heart or lung disease. The role of outdoor air pollution as a risk factor for COPD is unclear, but its role appears to be relatively small in adults compared to the role of cigarette smoking.[10] Cross-sectional analyses have shown an association between ambient levels of particulate matter (PM2.5/10) and COPD prevalence.[90,91] However, there is evidence that air pollution has a significant impact on lung maturation and development. For instance, the Children's Health Study found that children from communities with the highest levels of outdoor nitrogen dioxide ($NO_2$) and particulate matter < 2.5 µm in aerodynamic diameter (PM2.5) were nearly 5 times more likely to have reduced lung function (defined as $FEV_1$ < 80% of predicted) compared to children from communities with the lowest levels of $NO_2$ and PM2.5.[92] Importantly, reduction in ambient $NO_2$ and PM2.5 levels significantly mitigated the risk of experiencing impaired lung growth.[93] However, the relative effects of short-term, high-peak exposures and long-term, low-level exposures are yet to be resolved.



## Socioeconomic status

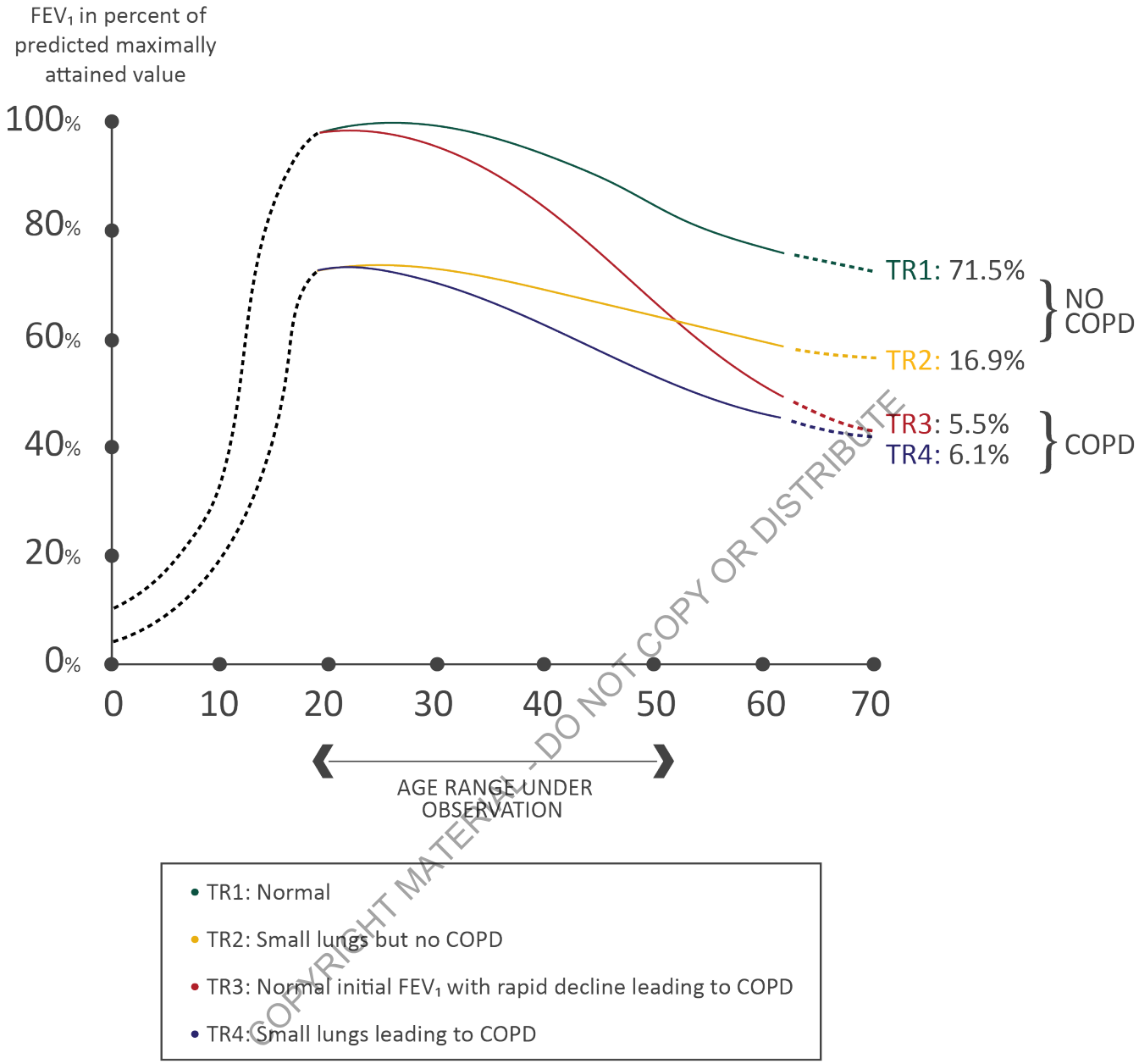
Poverty is consistently associated with airflow obstruction[94] and lower socioeconomic status is associated with an increased risk of developing COPD.[95,96] It is not clear, however, whether this pattern reflects exposures to indoor and outdoor air pollutants, crowding, poor nutrition, infections, or other factors related to low socioeconomic status.

## Asthma and airway hyper-reactivity

Asthma may be a risk factor for the development of chronic airflow limitation and COPD. In a report from a longitudinal cohort of the Tucson Epidemiological Study of Airway Obstructive Disease, adults with asthma were found to have a 12-fold higher risk of acquiring COPD over time compared to those without asthma, after adjusting for smoking.[97] Another longitudinal study of people with asthma found that around 20% of subjects developed irreversible airflow limitation and reduced transfer coefficient.[98] A third longitudinal study observed that self-reported asthma was associated with excess loss of $FEV_1$ in the general population.[99] 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.[100] 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%).[101] The pathology of chronic airflow limitation 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.[97,102,103] However, separating asthma from COPD in adults may be clinically difficult at times.

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[104,105] as well as an indicator of risk of excess decline in lung function in patients with mild COPD.[106]

## $FEV_1$ PROGRESSION OVER TIME






**Note:** This is a simplified diagram of $FEV_1$ progression over time. In reality, there is tremendous heterogeneity in the rate of decline in $FEV_1$ owing to the complex interactions of genes with environmental exposures and risk factors over an individual's lifetime [adapted from Lange et al. NEJM 2015;373:111-22].

FIGURE 1.2

## Chronic bronchitis

In the seminal study by Fletcher and colleagues, chronic bronchitis was not associated with an accelerated decline in lung function.[96,107] However, subsequent studies have observed an association between mucus hypersecretion and increased $FEV_1$ decline,[108] and in younger adults who smoke, the presence of chronic bronchitis has been associated with an increased likelihood of developing COPD.[109] Chronic bronchitis has also been associated with an increased risk in the total number as well as severity of exacerbations.[110]

### Infections

A history of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood.[101] Susceptibility to infections plays a role in exacerbations of COPD but the effect on disease development is less clear. In a large observational study *Pseudomonas aeruginosa* colonization independently predicted an increased risk of hospitalization for exacerbation and all-cause mortality.[111] There is evidence that 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)[112]; tuberculosis has also been identified as a risk factor for COPD.[113] In addition, tuberculosis is both a differential diagnosis for COPD and a potential comorbidity.[114,115]

## PATHOLOGY, PATHOGENESIS AND PATHOPHYSIOLOGY

Inhalation of cigarette smoke or other noxious particles, such as smoke from biomass fuels, causes lung inflammation. Lung inflammation is a normal response that appears to be modified in patients who develop COPD. This chronic inflammatory response may induce parenchymal tissue destruction (resulting in emphysema), and disruption of normal repair and defense mechanisms (resulting in small airway fibrosis). These pathological changes lead to gas trapping and progressive airflow limitation. A brief overview follows that describes and summarizes the pathologic changes in COPD, their cellular and molecular mechanisms, and how these underlie the physiological abnormalities and symptoms characteristic of this disease.



### Pathology

Pathological changes characteristic of COPD are found in the airways, lung parenchyma, and pulmonary vasculature.[116] The pathological changes observed in COPD include chronic inflammation, with increased numbers of specific inflammatory cell types in different parts of the lung, and structural changes resulting from repeated injury and repair. In general, the inflammatory and structural changes in the airways increase with disease severity and persist on smoking cessation. Most pathology data come from studies in smokers and the same balance of airway and parenchymal disease cannot necessarily be assumed when other factors are operative. Systemic inflammation may be present and could play a role in the multiple comorbid conditions found in patients with COPD.[117]

### Pathogenesis

The inflammation observed in the respiratory tract of COPD patients appears to be a modification of the normal inflammatory response of the respiratory tract to chronic irritants such as cigarette smoke. The mechanisms for this amplified inflammation are not yet understood but may, at least in part, be genetically determined. Although some patients develop COPD without smoking, the nature of the inflammatory response in these patients is as yet unknown. Oxidative stress and an excess of proteinases in the lung are likely to further modify lung inflammation. Together, these mechanisms may lead to the characteristic pathological changes in COPD. Lung inflammation persists after smoking cessation through unknown mechanisms, although autoantigens and perturbations in the lung microbiome may play a role.[118,119] Similar mechanisms may occur for concomitant chronic diseases.

***Oxidative stress.*** Oxidative stress may be an important amplifying mechanism in COPD.[117,120] 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. There may also be a reduction in endogenous antioxidants in COPD patients as a result of reduction in levels of the transcription factor *Nrf2* that regulates many antioxidant genes.[114,121]

***Protease-antiprotease imbalance.*** There is compelling evidence for an imbalance in the lungs of COPD patients between proteases that break down connective tissue components and antiproteases that counterbalance this

action.[122] Increased levels of several proteases, derived from inflammatory cells and epithelial cells, have been observed in COPD patients. There is increasing evidence that these proteases may interact with each other. Protease-mediated destruction of elastin, a major connective tissue component in lung parenchyma, is believed to be an important feature of emphysema but may be more difficult to establish in airway changes.[123]

***Inflammatory cells.*** COPD is characterized by increased numbers of macrophages in peripheral airways, lung parenchyma and pulmonary vessels, together with increased activated neutrophils and increased lymphocytes that include Tc1, Th1, Th17 and ILC3 cells. In some patients, there may also be increases in eosinophils, Th2 or ILC2 cells. All of these inflammatory cells, together with epithelial cells and other structural cells release multiple inflammatory mediators.[117] A study suggests that local IgA deficiency is associated with bacterial translocation, small airway inflammation and airway remodeling.[124]

***Inflammatory mediators.*** The wide variety of inflammatory mediators that have been shown to be increased in COPD patients attract inflammatory cells from the circulation (chemotactic factors), amplify the inflammatory process (proinflammatory cytokines), and induce structural changes (growth factors).[125]

***Peribronchiolar and interstitial fibrosis.*** Peribronchiolar fibrosis and interstitial opacities have been reported in patients with COPD or those who are asymptomatic smokers.[118,126-128] An excessive production of growth factors may be found in smokers or those with preceding airway inflammation who have COPD.[129] 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.[130] This may be a contributing factor to the development of small airways limitation and eventually the obliteration that may precede the development of emphysema.[131]

***Differences in inflammation between COPD and asthma.*** 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.[132] Some patients with COPD have an inflammatory pattern with increased eosinophils.[133]

## Pathophysiology

There is now a good understanding of how the underlying disease process in COPD leads to the characteristic physiological abnormalities and symptoms. For example, inflammation and narrowing of peripheral airways leads to decreased $FEV_1$.[134] Parenchymal destruction due to emphysema also contributes to airflow limitation and leads to decreased gas transfer. There is also emerging evidence to suggest that in addition to airway narrowing, there is a loss of small airways, which may contribute to airflow limitation.[135]

***Airflow limitation and gas trapping.*** The extent of inflammation, fibrosis, and luminal exudates in the small airways correlates with the reduction in the $FEV_1$ and $FEV_1$/FVC ratio, and probably with the accelerated decline in $FEV_1$ that is characteristic of COPD.[134] This peripheral airway limitation progressively traps gas during expiration, resulting in hyperinflation. Static hyperinflation reduces inspiratory capacity and is commonly associated with dynamic hyperinflation during exercise leading to increased dyspnea and limitation of exercise capacity. These factors contribute to impairment of the intrinsic contractile properties of respiratory muscles. It is thought that hyperinflation develops early in the disease and is the main mechanism for exertional dyspnea.[136,137] Bronchodilators acting on peripheral airways reduce gas trapping, thereby reducing lung volumes and improving symptoms and exercise capacity.[138]

***Gas exchange abnormalities.*** Gas exchange abnormalities result in hypoxemia and hypercapnia, and have several mechanisms in COPD. In general, gas transfer for oxygen and carbon dioxide worsens as the disease progresses. Reduced ventilation may also be due to reduced ventilatory drive or increased dead space ventilation.[137] This may lead to carbon dioxide retention when it is combined with reduced ventilation, due to increased effort to breathe because

of severe limitation and hyperinflation coupled with ventilatory muscle impairment. The abnormalities in alveolar ventilation and a reduced pulmonary vascular bed further worsen the $V_A/Q$ (ventilation perfusion ratio) abnormalities.[139]

***Mucus hypersecretion.*** Mucus hypersecretion, resulting in a chronic productive cough, is a feature of chronic bronchitis and is not necessarily associated with airflow limitation. Conversely, not all patients with COPD have symptomatic mucus hypersecretion. When present, mucus hypersecretion is due to an increased number of goblet cells and enlarged submucosal glands, both because of chronic airway irritation by cigarette smoke and other noxious agents. Several mediators and proteases stimulate mucus hypersecretion and many of them exert their effects through the activation of epidermal growth factor receptor (*EGFR*).[140]

***Pulmonary hypertension.*** Pulmonary hypertension may develop late in the course of COPD and is due mainly to hypoxic vasoconstriction of the small pulmonary arteries, eventually resulting in structural changes that include intimal hyperplasia and later smooth muscle hypertrophy/hyperplasia.[141] Even in mild COPD, or in smokers susceptible to emphysema,[142,143] there are significant abnormalities in pulmonary microvascular blood flow, that worsen with disease progression.[144]

An inflammatory response in vessels, similar to that seen in the airways, is also observed in COPD, along with evidence of endothelial cell dysfunction. The loss of the pulmonary capillary bed in emphysema may further contribute to increased pressure in the pulmonary circulation. Progressive pulmonary hypertension may lead to right ventricular hypertrophy and eventually to right-side cardiac failure. Interestingly, the diameter of pulmonary artery as measured on computed tomography (CT) scans has been shown to relate to the risk of exacerbation, independent of previous history of exacerbations.[145] This suggests that perturbations in pulmonary vasculature are major, but under-recognized, drivers of symptoms and exacerbations in COPD.



***Exacerbations.*** Exacerbations of respiratory symptoms triggered by respiratory infections with bacteria or viruses (which may coexist), environmental pollutants, or unknown factors often occur in patients with COPD; a characteristic response with increased inflammation occurs during episodes of bacterial or viral infection. During exacerbations there is increased hyperinflation and gas trapping, with reduced expiratory flow, thus accounting for increased dyspnea.[146] There is also worsening of $V_A/Q$ abnormalities that can result in hypoxemia.[147] During exacerbations there is evidence of increased airway inflammation. Other conditions (pneumonia, thromboembolism, and acute cardiac failure) may mimic or aggravate an exacerbation of COPD.

***Systemic features.*** Most patients with COPD have concomitant chronic diseases linked to the same risk factors i.e., smoking, aging, and inactivity, which may have a major impact on health status and survival.[148] Airflow limitation and particularly hyperinflation affect cardiac function and gas exchange.[146] 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.

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# CHAPTER 2: DIAGNOSIS AND INITIAL ASSESSMENT

## OVERALL KEY POINTS:

- *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.*

- *Spirometry is required to make the diagnosis; the presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation.*

- *The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on the patient's health status, and the risk of future events (such as exacerbations, hospital admissions, or death), in order to guide therapy.*

- *Concomitant chronic diseases 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 as they can influence mortality and hospitalizations independently.*



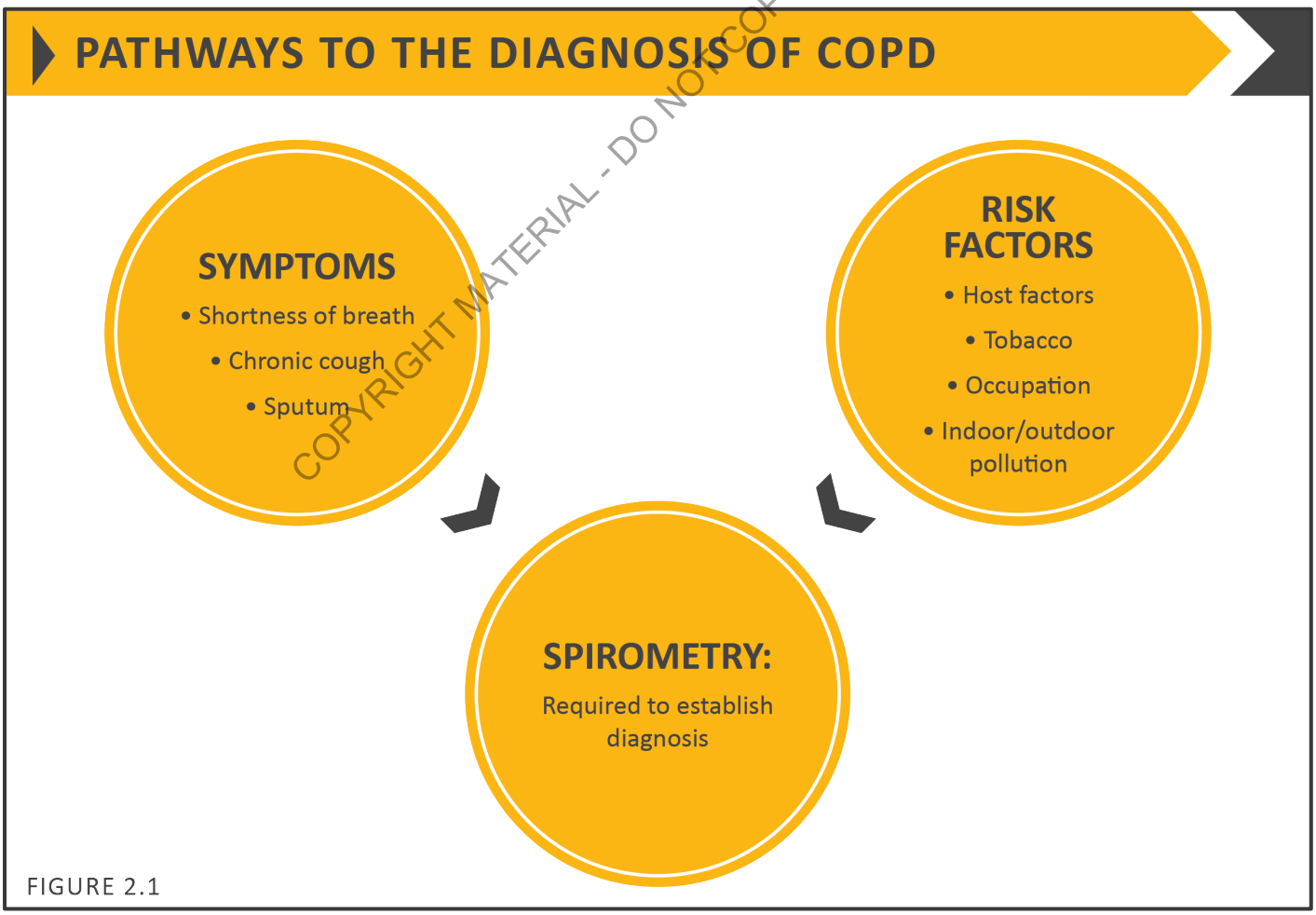


FIGURE 2.1

# DIAGNOSIS

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** and **Table 2.1**). Spirometry is required to make the diagnosis in this clinical context[1]; the presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and thus of COPD in patients with appropriate symptoms and significant exposures to noxious stimuli. The WHO has defined a minimum set of interventions for the diagnosis of COPD in primary care.[2]

## KEY INDICATORS FOR CONSIDERING A DIAGNOSIS OF COPD

*Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is required to establish a diagnosis of COPD.*

| | |
|---|---|
| **Dyspnea that is:** | Progressive over time.<br>Characteristically worse with exercise.<br>Persistent. |
| **Chronic Cough:** | May be intermittent and may be unproductive.<br>Recurrent wheeze. |
| **Chronic Sputum Production:** | Any pattern of chronic sputum production may indicate COPD. |
| **Recurrent Lower Respiratory Tract Infections** | |
| **History of Risk Factors:** | Host factors (such as genetic factors, congenital/developmental abnormalities etc.).<br>Tobacco smoke (including popular local preparations).<br>Smoke from home cooking and heating fuels.<br>Occupational dusts, vapors, fumes, gases and other chemicals. |
| **Family History of COPD and/or Childhood Factors:** | For example low birthweight, childhood respiratory infections etc. |

TABLE 2.1



# SYMPTOMS

Chronic and progressive 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[3] and may precede the development of airflow limitation by many years. Individuals, particularly those with COPD risk factors, presenting with these symptoms should be examined to search for the underlying cause(s). These patient symptoms should be used to help develop appropriate interventions. Significant airflow limitation may also be present without chronic dyspnea and/or cough and sputum production and *vice versa*.[4] Although COPD is defined on the basis of airflow limitation, 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.

***Dyspnea.*** Dyspnea, a cardinal symptom of COPD, is a major cause of the disability and anxiety that is associated with the disease.[5] Typical COPD patients describe their dyspnea as a sense of increased effort to breathe, chest heaviness,

air hunger, or gasping.[6] However, the terms used to describe dyspnea may vary both individually and culturally.[6]

***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 may be present every day, often throughout the day. Chronic cough in COPD may be productive or unproductive.[7] In some cases, significant airflow limitation may develop without the presence of a cough. Other causes of chronic cough are listed in **Table 2.2**.

***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,[8] but this is a somewhat arbitrary definition that does not reflect the entire range of sputum production that occurs in COPD. 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.[9] Patients producing large volumes of sputum may have underlying bronchiectasis. The presence of purulent sputum reflects an increase in inflammatory mediators,[10,11] and its development may identify the onset of a bacterial exacerbation, though the association is relatively weak.[11,12]



## OTHER CAUSES OF CHRONIC COUGH

| INTRATHORACIC |
| --- |
| • Asthma |
| • Lung Cancer |
| • Tuberculosis |
| • Bronchiectasis |
| • Left Heart Failure |
| • Interstitial Lung Disease |
| • Cystic Fibrosis |
| • Idiopathic Cough |
| **EXTRATHORACIC** |
| • Chronic Allergic Rhinitis |
| • Post Nasal Drip Syndrome (PNDS) |
| • Upper Airway Cough Syndrome (UACS) |
| • Gastroesophageal Reflux |
| • Medication (e.g. ACE Inhibitors) |

TABLE 2.2

***Wheezing and chest tightness.*** Wheezing and chest tightness are symptoms that may vary between days, and over the course of a single day. Audible wheeze may arise at the laryngeal level and need not be accompanied by abnormalities heard on auscultation. 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.

***Additional features in severe disease.*** Fatigue, weight loss, muscle loss, and anorexia are common problems in patients with severe and very severe COPD.[13-15] They have prognostic importance[16,17] and can also be a sign of other diseases, such as tuberculosis or lung cancer, and therefore should always be investigated. Syncope during cough occurs due to rapid increases in intrathoracic pressure during prolonged attacks of coughing. Coughing spells may also cause rib fractures, which are sometimes asymptomatic. Ankle swelling may be the only indicator of 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[18] and are associated with poorer health status, increased risk of exacerbations, and emergency hospital admission.[19]

# 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 occupational or environmental exposures.
- *Past medical history*, including asthma, allergy, sinusitis, or nasal polyps; respiratory infections in childhood; other chronic respiratory and non-respiratory diseases.
- *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, 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, well-being and sexual activity.
- *Social and family support available to the patient.*
- *Possibilities for reducing risk factors, especially smoking cessation.*



## Physical examination

Although an important part of patient care, a physical examination is rarely diagnostic in COPD. Physical signs of airflow limitation are usually not present until significant impairment of lung function has occurred,[20,21] and detection based on physical examination has relatively low sensitivity and specificity. A number of physical signs may be present in COPD, but absence does not exclude the diagnosis.

## Spirometry

Spirometry is the most reproducible and objective measurement of airflow limitation. It is a noninvasive and readily available test. Despite its good sensitivity, peak expiratory flow measurement alone cannot be reliably used as the only diagnostic test because of its weak specificity.[22,23] Good quality spirometric measurement is possible in any healthcare setting and all healthcare workers who care for COPD patients should have access to spirometry. Some of the factors needed to achieve accurate test results are summarized in **Table 2.3**.[24,25]

Spirometry should measure the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC) and the volume of air exhaled during the first second of this maneuver (forced expiratory volume in one second, $FEV_1$), and the ratio of these two measurements ($FEV_1$/FVC) should be calculated. The ratio between $FEV_1$ and slow vital capacity (VC), $FEV_1$/VC, is sometimes measured instead of the $FEV_1$/FVC ratio. This will often lead to lower values of the ratio, especially in pronounced airflow limitation. Spirometry measurements are evaluated by comparison with reference values[25] based on age, height, sex, and race.

A normal spirometry tracing is shown in **Figure 2.2A**. A spirometry tracing typical of a patient with obstructive disease is shown in **Figure 2.2B**. Patients with COPD typically show a decrease in both $FEV_1$ and FVC.

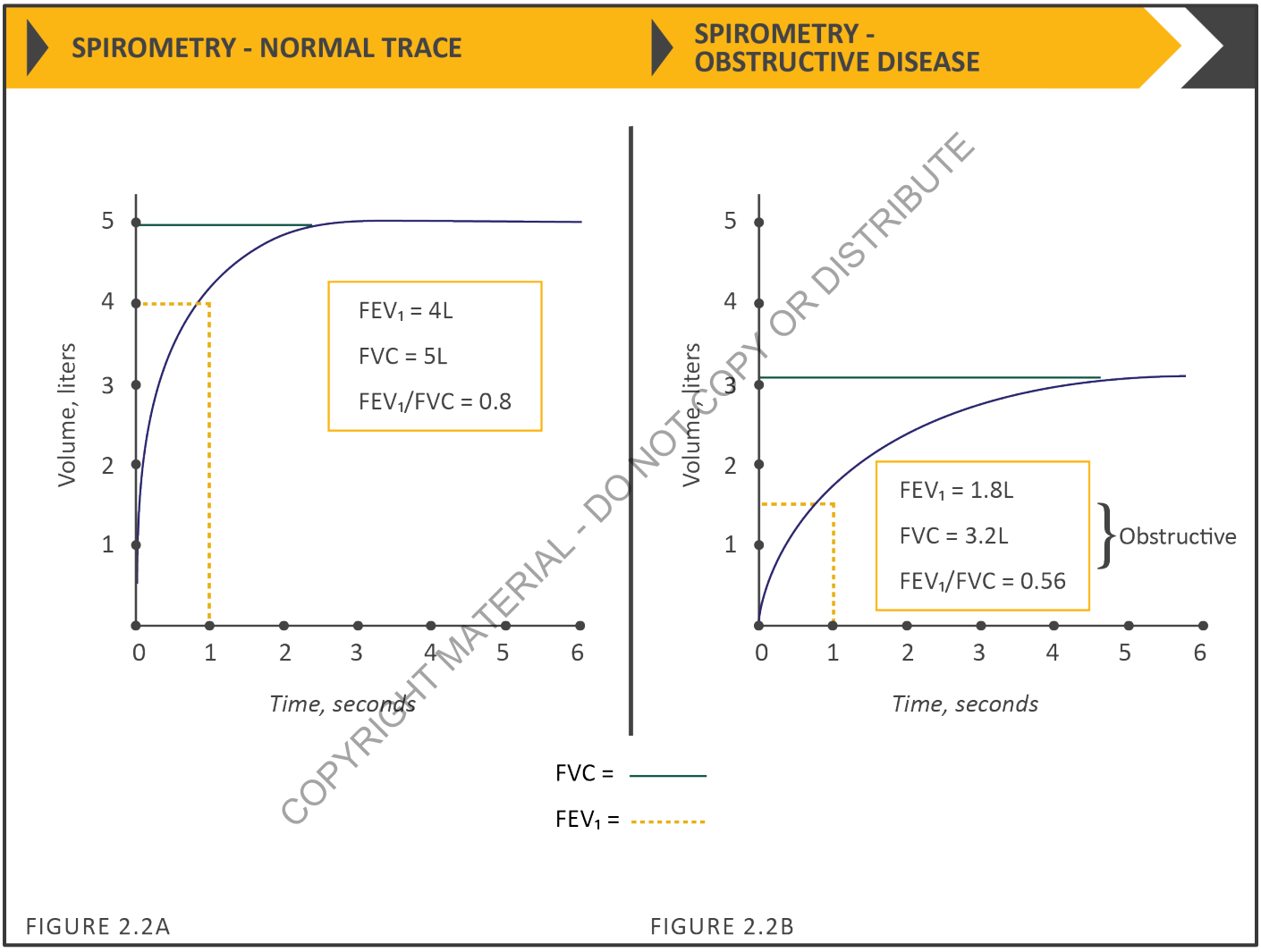




FIGURE 2.2A

FIGURE 2.2B

## CONSIDERATIONS IN PERFORMING SPIROMETRY

### PREPARATION

- Spirometers need calibration on a regular basis.
- 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.

### BRONCHODILATION

- Possible dosage protocols are 400 mcg short-acting beta$_2$-agonist, 160 mcg short-acting anticholinergic, or the two combined.[a] $FEV_1$ 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.

### PERFORMANCE

- Spirometry should be performed using techniques that meet published standards.[b]
- The expiratory volume/time traces should be smooth and free from irregularities. The pause between inspiration and expiration should be < 1 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 $FEV_1$ should be the largest value obtained from any of three technically satisfactory curves and the FVC and $FEV_1$ values in these three curves should vary by no more than 5% or 150 ml, whichever is greater.
- The $FEV_1$/FVC ratio should be taken from the technically acceptable curve with the largest sum of FVC and $FEV_1$.

### EVALUATION

- Spirometry measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex, and race.
- The presence of a postbronchodilator $FEV_1$/FVC < 0.70 confirms the presence of airflow limitation.

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

TABLE 2.3



The spirometric criterion for airflow limitation remains a post-bronchodilator fixed ratio of $FEV_1$/FVC < 0.70. This criterion is simple and independent of reference values, and has been used in numerous clinical trials that form the evidence base from which most of our treatment recommendations are drawn. It should be noted that the use of the fixed $FEV_1$/FVC ratio to define airflow limitation may result in more frequent diagnosis of COPD in the elderly,[26,27] and less frequent diagnosis in adults < 45 years,[27] especially in mild disease, compared to using a cut-off based on the lower limit of normal (LLN) values for $FEV_1$/FVC.

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 $FEV_1$, 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.[28]

Normal spirometry may be defined by a new approach from the Global Lung Initiative (GLI).[29,30] Using GLI equations, *z* scores were calculated for $FEV_1$, FVC, and $FEV_1$/FVC. The diagnostic algorithm was initially based on a single threshold, namely a *z* score of -1.64 (defining the LLN at the fifth percentile of the normal distribution). 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.

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 parameter for establishing the clinical diagnosis of COPD; the additional parameters being symptoms and other 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 $FEV_1$/FVC ratio should be confirmed by repeat spirometry on a separate occasion if the value is between 0.6 and 0.8, as in some cases the ratio may change as a result of biological variation when measured at a later interval.[31,32] If the initial post-bronchodilator $FEV_1$/FVC ratio is less than 0.6 it is very unlikely to rise above 0.7 spontaneously.[31]

While post-bronchodilator spirometry is required for the diagnosis and assessment of COPD, assessing the degree of reversibility of airflow limitation (e.g., measuring $FEV_1$ before and after bronchodilator or corticosteroids) to inform therapeutic decisions is no longer recommended.[33] The degree of reversibility has not been shown to augment the diagnosis of COPD, differentiate the diagnosis from asthma, or to predict the response to long-term treatment with bronchodilators or corticosteroids.[34]

The role of screening spirometry in the general population is controversial.[35,36] In asymptomatic individuals without any significant exposures to tobacco or other noxious stimuli, screening spirometry is probably not indicated; whereas in those with symptoms or risk factors (e.g., > 20 pack-years of smoking or recurrent chest infections), the diagnostic yield for COPD is relatively high and spirometry should be considered as a method for early case finding.[37,38] Both $FEV_1$ 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 screening spirometry should be employed as a global health assessment tool.[39,40] A risk score based on routine data from electronic health records in primary care may facilitate case-finding and be cost-effective.[41,42] However, there are no data to indicate that screening spirometry is effective in directing management decisions or in improving COPD outcomes in patients who are identified before the development of significant symptoms.[43] 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.[44,45] Thus, GOLD advocates active case finding[37,46,47] 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.[48]

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.[49] For instance, compared with individuals living in North America or Europe, people living in Southeast Asia had $FEV_1$ 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 $FEV_1$ 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.[49] Unless relevant predicted values are used the severity of airflow limitation will be overestimated.

# ASSESSMENT

The goals of COPD assessment are to determine the level of airflow limitation, its impact on the patient's health status and the risk of future events (such as exacerbations, hospital admissions or death), in order to, eventually, guide therapy.

To achieve these goals, COPD assessment must consider the following aspects of the disease separately:

- The presence and severity of the spirometric abnormality
- Current nature and magnitude of the patient's symptoms
- History of moderate and severe exacerbations and future risk
- Presence of comorbidities

## Classification of severity of airflow limitation

The classification of airflow limitation severity in COPD is shown in **Table 2.4**. Specific spirometric cut-points are used for purposes of simplicity. Spirometry should be performed after the administration of an adequate dose of at least one short-acting inhaled bronchodilator in order to minimize variability.

It should be noted that there is only a weak correlation between $FEV_1$, symptoms and impairment of a patient's health status.[50,51] For this reason, formal symptomatic assessment is required.



**CLASSIFICATION OF AIRFLOW LIMITATION SEVERITY IN COPD (BASED ON POST-BRONCHODILATOR $FEV_1$)**

| In patients with FEV1/FVC < 0.70: | | |
|---|---|---|
| **GOLD 1:** | Mild | $FEV_1 \geq 80\%$ predicted |
| **GOLD 2:** | Moderate | $50\% \leq FEV_1 < 80\%$ predicted |
| **GOLD 3:** | Severe | $30\% \leq FEV_1 < 50\%$ predicted |
| **GOLD 4:** | Very Severe | $FEV_1 < 30\%$ predicted |

TABLE 2.4

## Assessment of symptoms

Here we present the two measures of symptoms that are most widely used.

In the past, COPD was viewed as a disease largely characterized by breathlessness. A simple measure of breathlessness such as the Modified British Medical Research Council (mMRC) Questionnaire[52] (**Table 2.5**) was considered adequate for assessment of symptoms, as the mMRC relates well to other measures of health status[53] and predicts future mortality risk.[54,55]

## MODIFIED MRC DYSPNEA SCALE[a]

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

| | | |
|---|---|---|
| **mMRC Grade 0.** | I only get breathless with strenuous exercise. | ☐ |
| **mMRC Grade 1.** | I get short of breath when hurrying on the level or walking up a slight hill. | ☐ |
| **mMRC Grade 2.** | 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. | ☐ |
| **mMRC Grade 3.** | I stop for breath after walking about 100 meters or after a few minutes on the level. | ☐ |
| **mMRC Grade 4.** | I am too breathless to leave the house or I am breathless when dressing or undressing. | ☐ |

[a] Fletcher CM. BMJ 1960; 2: 1662.

TABLE 2.5



However, it is now recognized that COPD impacts patients beyond just dyspnea.[56] For this reason, a comprehensive assessment of symptoms is recommended rather than just a measure of breathlessness. The most comprehensive disease-specific health status questionnaires such as the Chronic Respiratory Questionnaire (CRQ)[57] and St. George's Respiratory Questionnaire (SGRQ)[58] are too complex to use in routine practice, but shorter comprehensive measures e.g., COPD Assessment Test (CAT™) and The COPD Control Questionnaire (The CCQ©) have been developed and are suitable.

***COPD Assessment Test (CAT™).*** The COPD Assessment Test™* is an 8-item uni-dimensional measure of health status impairment in COPD (**Figure 2.3**).[59] It was developed to be applicable worldwide and validated translations are available in a wide range of languages. The score ranges from 0-40, correlates very closely with the SGRQ, and has been extensively documented in numerous publications.[60]

## Choice of thresholds

The CAT™ and the CCQ© provide measures of the symptomatic impact of COPD but do not categorize patients into symptom severity groups for the purpose of treatment. The SGRQ is the most widely documented comprehensive measure; scores < 25 are uncommon in diagnosed COPD patients[61] and scores ≥ 25 are very uncommon in healthy persons.[62,63] 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.[64]

An equivalent mMRC score cannot be calculated because a simple breathlessness cut-point cannot equate to a

* 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.

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.[65] 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.[65]

There are other scales available such as the COPD Control Questionnaire (CCQ) and the Chronic Respiratory Disease Questionnaire (CRQ) that will not be discussed in detail.

## Assessment of exacerbation risk

COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy.[66-69] These events are classified as mild (treated with short acting bronchodilators (SABDs) only), moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) or severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure. A number of large studies that classified patients using the GOLD spirometric grading systems have been conducted.[70-72] These studies demonstrate that exacerbation rates vary greatly between patients[72] and during follow-up.[73] The best predictor of having frequent exacerbations (defined as two or more exacerbations per year) is a history of earlier treated events.[72]



### CAT™ ASSESSMENT

*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** |
| 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 |

**SCORE**

**TOTAL SCORE:**

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

FIGURE 2.3

In addition, deteriorating airflow limitation is associated with an increasing prevalence of exacerbations, hospitalization[74] and risk of death.[61,75] Hospitalization for a COPD exacerbation is associated with poor prognosis and increased risk of death.[76] There is also a significant relationship between spirometric severity and the risk of exacerbation and death. At the population level, approximately 20% of GOLD 2 (moderate airflow limitation) patients may experience frequent exacerbations requiring treatment with antibiotics and/or systemic corticosteroids.[72] The risk of exacerbations is significantly higher for patients with GOLD 3 (severe) and GOLD 4 (very severe). However, $FEV_1$ by itself lacks sufficient precision (i.e., wide variation) to be used clinically as a predictor of exacerbation or mortality in patients with COPD.[75]

The association between blood eosinophil count and risk of exacerbations is outlined in **Chapter 3**.

## Assessment of concomitant chronic diseases (comorbidities)

Patients with COPD often have important concomitant chronic illnesses at the time of diagnosis and COPD represents an important component of multimorbidity development particularly in the elderly in response to common risk factors (e.g., aging, smoking, alcohol, diet and inactivity).[76-79] COPD itself also has significant extrapulmonary (systemic) effects including weight loss, nutritional abnormalities and skeletal muscle dysfunction. Skeletal muscle dysfunction is characterized by both sarcopenia (loss of muscle cells) and abnormal function of the remaining cells.[80] Its causes are likely multifactorial (e.g., inactivity, poor diet, inflammation and hypoxia) and it can contribute to exercise intolerance and poor health status in patients with COPD. Importantly, skeletal muscle dysfunction is a rectifiable source of exercise intolerance.[81]

Common comorbidities include cardiovascular disease,[82] skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety and lung cancer. The existence of COPD may actually increase the risk for other diseases; this is particularly striking for COPD and lung cancer.[83,84] Whether this association is due to common risk factors (e.g., smoking), involvement of susceptibility genes, or impaired clearance of carcinogens is not clear.

Comorbidities can occur in patients with mild, moderate or severe airflow limitation,[61] influence mortality and hospitalizations independently,[85] and deserve specific treatment. Therefore, comorbidities should be looked for routinely, and treated appropriately, in any patient with COPD. Recommendations for the diagnosis, assessment of severity, and management of individual comorbidities in patients with COPD are the same as for all other patients. A more detailed description of the management of COPD and comorbidities is provided in **Chapter 6**.



## Combined COPD assessment

An understanding of the impact of COPD on an individual patient combines the symptomatic assessment with the patient's spirometric classification and/or risk of exacerbations. The "ABCD" assessment tool of the 2011 GOLD update was a major step forward from the simple spirometric grading system of the earlier versions of GOLD because it incorporated patient-reported outcomes and highlighted the importance of exacerbation prevention in the management of COPD. However, there were some important limitations. Firstly, the ABCD assessment tool performed no better than the spirometric grades for mortality prediction or other important health outcomes in COPD.[75,86,87] Moreover, group "D" outcomes were modified by two parameters: lung function and/or exacerbation history, which caused confusion.[51] To address these and other concerns (while at the same time maintaining consistency and simplicity for the practicing clinician), a refinement of the ABCD assessment tool is proposed that separates spirometric grades from the "ABCD" groups. For some therapeutic recommendations, ABCD groups will be derived exclusively from patient symptoms and their history of exacerbation. Spirometry, in conjunction with patient symptoms and history of moderate and severe exacerbations, remains vital for the diagnosis, prognostication and consideration of other important therapeutic approaches. This new approach to assessment is illustrated in **Figure 2.4**.

In the revised assessment scheme, patients should undergo spirometry to determine the severity of airflow limitation

(i.e., spirometric grade). They should also undergo assessment of either dyspnea using mMRC or symptoms using CAT™. Finally, their history of moderate and severe exacerbations (including prior hospitalizations) should be recorded.

The number provides information regarding severity of airflow limitation (spirometric grade 1 to 4) while the letter (groups A to D) provides information regarding symptom burden and risk of exacerbation which can be used to guide therapy. $FEV_1$ is a very important parameter at the population-level in the prediction of important clinical outcomes such as mortality and hospitalizations or prompting consideration for non-pharmacological therapies such as lung volume reduction or lung transplantation. However, it is important to note that at the individual patient level, $FEV_1$ loses precision and thus cannot be used alone to determine all therapeutic options. Furthermore, in some circumstances, such as during hospitalization or urgent presentation to the clinic or emergency room, the ability to assess patients based on symptoms and exacerbation history, independent of the spirometric value, allows clinicians to initiate a treatment plan based on the revised ABCD scheme alone. This assessment approach acknowledges the limitations of $FEV_1$ in making treatment decisions for individualized patient care and highlights the importance of patient symptoms and exacerbation risks in guiding therapies in COPD. The separation of airflow limitation from clinical parameters makes it clearer what is being evaluated and ranked. This will facilitate more precise treatment recommendations based on parameters that are driving the patient's symptoms at any given time.



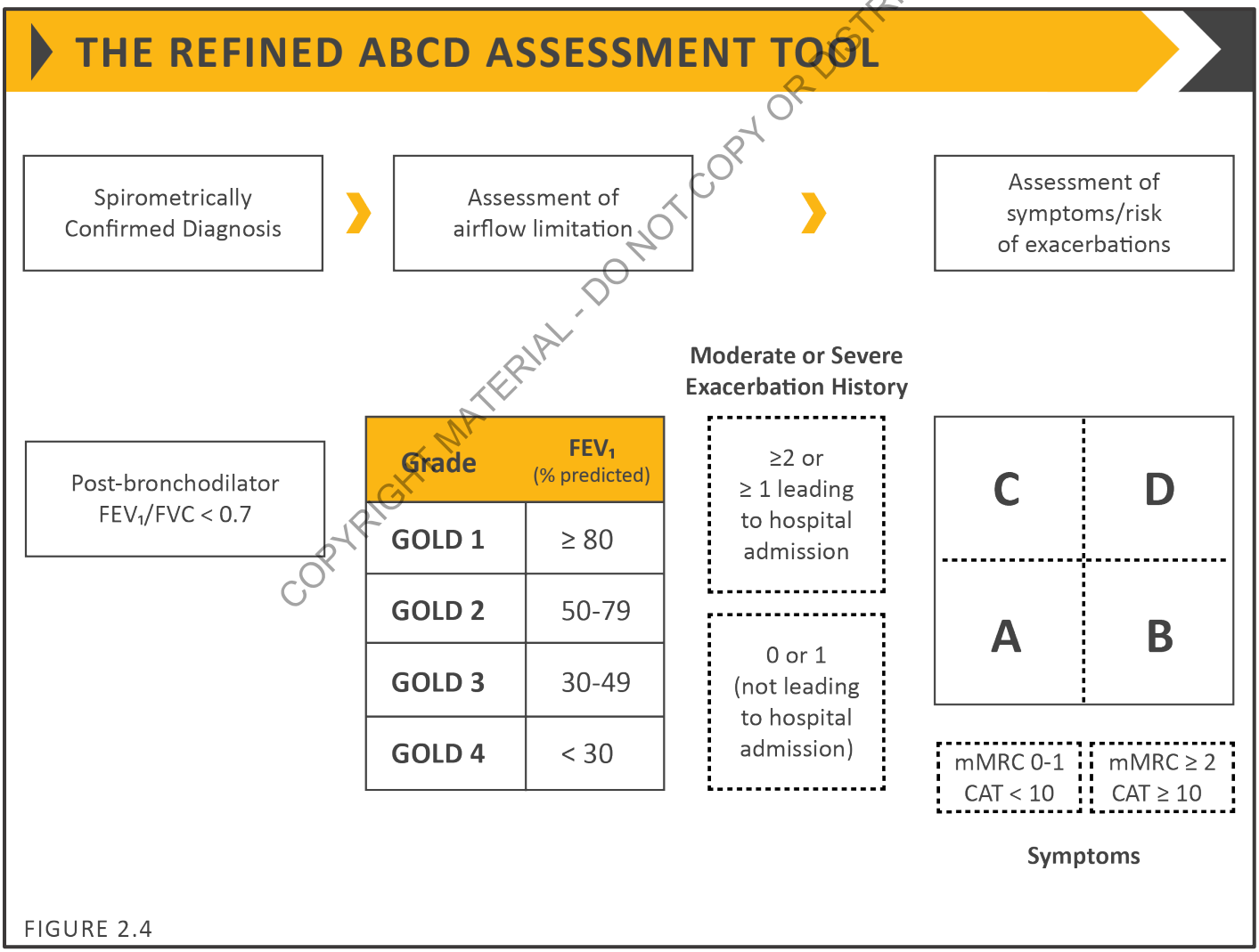


FIGURE 2.4

**Example**: Consider two patients – both patients with $FEV_1$ < 30% of predicted, CAT™ scores of 18 and one with no exacerbations in the past year and the other with three moderate exacerbations in the past year. Both would have been labelled GOLD D in the prior classification scheme. However, with the new proposed scheme, the subject with three moderate exacerbations in the past year would be labelled GOLD grade 4, group D.

Individual decisions on pharmacotherapeutic approaches would use the recommendations in **Chapter 4** based on the ABCD assessment to treat the patient's major problem at this time i.e., persistent exacerbations. The other patient, who has had no exacerbations, would be classified as GOLD grade 4, group B. In such patients – besides pharmacotherapy and rehabilitation – lung volume reduction, lung transplant or bullectomy may be important considerations for therapy given their symptom burden and level of spirometric limitation.

**Note:** In cases where there is a marked discordance between the level of airflow limitation and the perceived symptoms, a more detailed evaluation should be carried out to better understand lung mechanics (e.g., full lung function tests), lung structure (e.g., computed tomography) and/or comorbidities (e.g., ischemic heart disease) that might impact patient symptoms. In some cases, patients may endorse minimal symptoms despite demonstrating severe airflow limitation. Adapting to the limitations induced by COPD, these patients may reduce their level of physical activity in a way that may result in an underestimation of the symptom load. In these cases, exercise tests like the 6-minute walking distance may reveal that the patients are severely constrained and do need more intense treatment than the initial evaluation would have suggested.

The role of spirometry for the diagnosis, assessment and follow-up of COPD is summarized in **Table 2.6**.



## ROLE OF SPIROMETRY

- **Diagnosis**
- **Assessment of severity of airflow obstruction (for prognosis)**
- **Follow-up assessment**
  - » Therapeutic decisions.
    - – Pharmacological in selected circumstances (e.g., discrepancy between spirometry and level of symptoms).
    - – Consider alternative diagnoses when symptoms are disproportionate to degree of airflow obstruction.
    - – Non-pharmacological (e.g., interventional procedures).
  - » Identification of rapid decline.

TABLE 2.6

## Alpha-1 antitrypsin deficiency (AATD)

***Alpha-1 antitrypsin deficiency (AATD) screening.*** The World Health Organization recommends that all patients with a diagnosis of COPD should be screened once especially in areas with high AATD prevalence.[88,89] 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).[90] 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**).

## Additional investigations

The following additional investigations may be considered as part of the diagnosis and assessment of COPD.

***Imaging.*** 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 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) of the chest is not routinely recommended except for detection of bronchiectasis and COPD patients that meet the criteria for lung cancer risk assessment. The presence of emphysema in particular may increase the risk for development of lung cancer. However, CT scanning may be helpful in the differential diagnosis where concomitant diseases are present. In addition, if a surgical procedure such as lung volume reduction,[91] or increasingly non-surgical based lung volume reduction[92] is contemplated, a chest CT scan is necessary since the distribution of emphysema is one of the most important determinants of surgical suitability. A CT scan is also required for patients being evaluated for lung transplantation.

***Lung volumes and diffusing capacity.*** COPD patients exhibit gas trapping (a rise in residual volume) from the early stages of the disease, and as airflow limitation worsens, static hyperinflation (an increase in total lung capacity) occurs. 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. Measurement of diffusing capacity (DLCO) provides information on the functional impact of emphysema in COPD and is often helpful in patients with breathlessness that may seem out of proportion to the degree of airflow limitation.

***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. Pulse oximetry 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 or capillary blood gases should be assessed.[93,94]

***Exercise testing and assessment of physical activity.*** Objectively measured exercise impairment, assessed by a reduction in self-paced walking distance[95,96] or during incremental exercise testing in a laboratory,[97] is a powerful indicator of health status impairment and predictor of prognosis; exercise capacity may fall in the year before death.[98] Walking tests can be useful for assessing disability and risk of mortality[99] and are used to assess the effectiveness of pulmonary rehabilitation. Both the paced shuttle walk test[100] and the unpaced 6-minute walk test can be used.[101,102] 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.[103] Laboratory testing using cycle or treadmill ergometry can assist in identifying co-existing or alternative conditions e.g., cardiac diagnoses.

Monitoring of physical activity may be more relevant regarding prognosis than evaluating exercise capacity.[104] This can be conducted using accelerometers or multi-sensor instruments.

***Composite scores.*** Several variables identify patients at increased risk for mortality including $FEV_1$, exercise tolerance assessed by walking distance or peak oxygen consumption, weight loss, and reduction in arterial oxygen tension. A relatively simple approach to identifying disease severity using a combination of most of the above variables has been proposed. 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.[105,106] Simpler alternatives that do not include an exercise test have been suggested but all these approaches need validation across a wide range of disease severities and clinical settings to confirm that they are suitable for routine clinical use.[107,108]

***Differential diagnoses.*** In some patients with chronic asthma, a clear distinction from COPD is difficult using current imaging and physiological testing techniques, since the two conditions share common traits and clinical expressions. Most other potential differential diagnoses are easier to distinguish from COPD (**Table 2.7**).

***Biomarkers.*** There is rapidly increasing interest in the use of biomarkers in COPD. Biomarkers are 'characteristics 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[109] which was further confirmed in the SUMMIT study.[110] Some studies (see **Chapter 5** – Exacerbations) have indicated the use of C-reactive protein (CRP) and procalcitonin[111] in reducing antibiotic usage during exacerbations, although the observed sputum color remains highly sensitive and specific for a high bacterial load during such episodes.

At present the assessment of eosinophils provides the best guidance to the use of corticosteroids[109] especially in the prevention of some exacerbations (see **Chapter 3** – Inhaled Corticosteroids).

Continued cautious and realistic interpretation of the role of biomarkers in the management of identified clinical traits is required.

***Other considerations.*** It is clear that some patients *without evidence of airflow limitation* have evidence of structural lung disease on chest imaging (emphysema, gas trapping, airway wall thickening) that is consistent with what is found in patients with COPD. Such patients may report exacerbations of respiratory symptoms or even require treatment with respiratory medications on a chronic basis. Whether these patients have acute or chronic bronchitis, a persistent form of asthma or an earlier presentation of what will become COPD as it is currently defined, is unclear at present and will require further study.

## DIFFERENTIAL DIAGNOSIS OF COPD

| DIAGNOSIS | SUGGESTIVE FEATURES |
|---|---|
| **COPD** | Onset in mid-life.<br>Symptoms slowly progressive.<br>History of tobacco smoking or exposure to other types of smoke. |
| **Asthma** | Onset early in life (often childhood).<br>Symptoms vary widely from day to day.<br>Symptoms worse at night/early morning.<br>Allergy, rhinitis, and/or eczema also present.<br>Family history of asthma.<br>Obesity coexistence. |
| **Congestive Heart Failure** | Chest X-ray shows dilated heart, pulmonary edema.<br>Pulmonary function tests indicate volume restriction, not airflow limitation. |
| **Bronchiectasis** | Large volumes of purulent sputum.<br>Commonly associated with bacterial infection.<br>Chest X-ray/CT shows bronchial dilation, bronchial wall thickening. |
| **Tuberculosis** | Onset all ages.<br>Chest X-ray shows lung infiltrate.<br>Microbiological confirmation.<br>High local prevalence of tuberculosis. |
| **Obliterative Bronchiolitis** | Onset at younger age, nonsmokers.<br>May have history of rheumatoid arthritis or acute fume exposure.<br>Seen after lung or bone marrow transplantation.<br>CT on expiration shows hypodense areas. |
| **Diffuse Panbronchiolitis** | Predominantly seen in patients of Asian descent.<br>Most patients are male and nonsmokers.<br>Almost all have chronic sinusitis.<br>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 the developing world where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even in elderly patients.*

TABLE 2.7

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# CHAPTER 3: EVIDENCE SUPPORTING PREVENTION AND MAINTENANCE THERAPY

**OVERALL KEY POINTS:**

- *Smoking cessation is key. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates. Legislative smoking bans and counseling, delivered by healthcare professionals, improve quit rates.*
- *The effectiveness and safety of e-cigarettes as a smoking cessation aid is uncertain at present.*
- *Pharmacological therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Recent data suggest beneficial effects on 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.*
- *Influenza vaccination decreases the incidence of lower respiratory tract infections.*
- *Pneumococcal vaccination decreases lower respiratory tract infections.*
- *CDC recommends the Tdap vaccination (dTaP/dTPa) in COPD patients to protect against pertussis, tetanus and diphtheria, in those who were not vaccinated in adolescence.*
- *Pulmonary rehabilitation improves symptoms, quality of life, and physical and emotional participation in everyday activities.*
- *In patients with severe resting chronic hypoxemia, 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.*



This chapter summarizes the evidence about the effectiveness and safety of maintenance and prevention strategies in COPD. The way in which the evidence is translated into clinical practice is provided in **Chapter 4**.

## SMOKING CESSATION

Smoking cessation has the greatest capacity to influence the natural history of COPD. If effective resources and time are dedicated to smoking cessation, long-term quit success rates of up to 25% can be achieved.[1] Besides individual

approaches to smoking cessation, legislative smoking bans are effective in increasing quit rates and reducing harm from second-hand smoke exposure.[2]

## Pharmacotherapies for smoking cessation

***Nicotine replacement products.*** Nicotine replacement therapy (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge) reliably increases long-term smoking abstinence rates[3-5] and is significantly more effective than placebo. Medical contraindications to nicotine replacement therapy include recent myocardial infarction or stroke.[6,7] The contraindication to nicotine replacement therapy after acute coronary syndrome remains unclear and the evidence suggests that this treatment should be started > 2 weeks after a cardiovascular event.[8] 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. Acidic beverages, particularly coffee, juices, and soft drinks, interfere with the absorption of nicotine.

Electronic cigarettes (e-cigarettes, vaping) have been evaluated with regard to smoking cessation, although efficacy remains controversial.[9,10] E-cigarettes provide a vaporized and doseable nicotine inhalation and have increased in usage as an alternative to cigarettes for those wishing to quit but also as a rising trend for younger previous never smokers. E-cigarettes have been available for over 15 years and may contain not only the 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 of which 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.[11-14] 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). As of February 18, 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).[14] Patients were reported to have had clinical improvement with systemic glucocorticoid therapy and the majority received prolonged courses.[13] Laboratory data have shown that vitamin E acetate, an additive in some THC-containing e-cigarettes, was strongly linked to the EVALI outbreak.[15] Following the identification of vitamin E acetate as a primary cause of EVALI there has been a decline in new cases since September 2019.



Neutrophilic inflammation of the airways, airways irritability, ciliary paresis and increased mucus hypersecretion are seen in animal models and *in vitro* human airway studies similar to changes induced by cigarette smoke and recognised features of COPD. These data are summarized in a review by Gotts and colleagues,[16] although it is likely to be many years before the long-term risks of vaping, including risks of cancer, are clarified, particularly in patients with COPD or whether this is an independent risk factor for developing COPD. [11-14]

***Pharmacological products.*** Varenicline,[17] bupropion,[18] and nortriptyline[19] have been shown to increase long-term quit rates,[19] but should always be used as a component of a supportive intervention program rather than a sole intervention for smoking cessation. The effectiveness of the antihypertensive drug clonidine is limited by side effects.[19] Recommendations for treating tobacco use and dependence are summarized in **Chapter 4**.

A five-step program for intervention (**Table 3.1**)[3,5,20] provides a helpful strategic framework to guide healthcare providers interested in helping their patients stop smoking.[3,5,21] Because tobacco dependence is a chronic disease,[3,5] 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.[22] Even brief (3-minute) periods of counseling urging a smoker to quit improve smoking cessation rates.[22] There is a relationship between counseling intensity and cessation success.[23] Ways to intensify treatment include increasing the length of the treatment session, the number of treatment sessions, and the number of weeks over which the treatment is delivered. Sustained quit rates of 10.9% at 6 months have been achieved when clinician tutorials and feedback are linked to counseling sessions.[24] Financial incentive models for smoking cessation have also been reported to be effective in facilitating smoking cessation. In general, incentive programs were more effective than usual care in increasing smoking cessation rates at 6 months.[25] The combination of pharmacotherapy and behavioral support increases smoking cessation rates.[26]

### BRIEF STRATEGIES TO HELP THE PATIENT WILLING TO QUIT

| | |
|---|---|
| • **ASK:** | Systematically identify all tobacco users at every visit.<br>*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.<br>*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.<br>*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.<br>*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.<br>*Schedule follow-up contact, either in person or via telephone.* |

TABLE 3.1



## VACCINATIONS

### Influenza vaccine

Influenza vaccination can reduce serious illness (such as lower respiratory tract infections requiring hospitalization)[27] and death in COPD patients.[28-31] 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.[28] Vaccines containing either killed or live inactivated viruses are recommended[32] as they are more effective in elderly patients with COPD.[33] Findings from a population-based study suggested that COPD patients, particularly the elderly, had decreased risk of ischemic heart disease when they were vaccinated with influenza vaccine over many years.[34] Occurrence of adverse reactions is generally mild and transient.

### Pneumococcal vaccine

Pneumococcal vaccinations, PCV13 and PPSV23, are recommended for all patients ≥ 65 years of age (**Table 3.2**). The PPSV23 is also recommended for younger COPD patients with significant comorbid conditions including chronic heart

or lung disease.[35] Specific data on the effects of PPSV and PCV in COPD patients are limited and contradictory.[36] 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.[37] PPSV23 has been shown to reduce the incidence of community-acquired pneumonia in COPD patients < 65 years, with an $FEV_1$ < 40% predicted, or comorbidities (especially cardiac comorbidities).[38] 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.[39] 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.[40]

### Other vaccines

In adults with COPD the US Centers for Disease Control (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. [41,42]



#### VACCINATION FOR STABLE COPD

- Influenza vaccination reduces serious illness and death in COPD patients **(Evidence B)**.
- The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been shown to reduce the incidence of community-acquired pneumonia in COPD patients aged < 65 years with an $FEV_1$ < 40% predicted and in those with comorbidities **(Evidence B)**.
- In the general population of adults ≥ 65 years the 13-valent conjugated pneumococcal vaccine (PCV13) has demonstrated significant efficacy in reducing bacteremia & serious invasive pneumococcal disease **(Evidence B)**.
- The CDC recommends the Tdap (dTaP/dTPa) vaccination for adults with COPD who were not vaccinated in adolescence to protect against pertussis (whooping cough).

TABLE 3.2

## PHARMACOLOGICAL THERAPY FOR STABLE COPD

### Overview of the medications

Pharmacological therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and health status. To date, there is no conclusive clinical trial evidence that any existing medications for COPD modify the long-term decline in lung function.[43-47] *Post-hoc* evidence of such an effect with long-acting bronchodilators and/or inhaled corticosteroids[48,49] requires confirmation in specifically designed trials.

The classes of medications commonly used to treat COPD are shown in **Table 3.3**. The choice within each class depends on the availability and cost of medication and favorable clinical response balanced against side effects. Each treatment regimen needs to be individualized as the relationship between severity of symptoms, airflow limitation, 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.[50]

## Bronchodilators

Bronchodilators are medications that increase $FEV_1$ and/or change other spirometric variables. 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,[51,52] 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 $FEV_1$ measured at rest.[53,54]

Bronchodilator dose-response ($FEV_1$ change) curves are relatively flat with all classes of bronchodilators.[55-61] 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[62] but is not necessarily helpful in stable disease.[63] Bronchodilator medications in COPD are most often given on a regular basis to prevent or reduce symptoms. Toxicity is also dose-related (**Table 3.3**). Use of short acting bronchodilators on a regular basis is not generally recommended.

***Beta$_2$-agonists.*** The principal action of beta$_2$-agonists is to relax airway smooth muscle by stimulating beta$_2$-adrenergic receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. There are short-acting (SABA) and long-acting (LABA) beta$_2$-agonists. The effect of SABAs usually wears off within 4 to 6 hours.[57,58] Regular and as-needed use of SABAs improve $FEV_1$ and symptoms.[64] For single-dose, as-needed use in COPD, there appears to be no advantage in routinely using levalbuterol over conventional bronchodilators.[65] LABAs show duration of action of 12 or more hours and do not preclude additional benefit from as-needed SABA therapy.[66]

Formoterol and salmeterol are twice-daily LABAs that significantly improve $FEV_1$ and lung volumes, dyspnea, health status, exacerbation rate and number of hospitalizations,[67] but have no effect on mortality or rate of decline of lung function. Indacaterol is a once daily LABA that improves breathlessness,[68,69] health status[69] and exacerbation rate.[69] Some patients experience cough following the inhalation of indacaterol. Oladaterol and vilanterol are additional once daily LABAs that improve lung function and symptoms.[70,71]

***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,[72] and oxygen consumption can be increased under resting conditions in patients with chronic heart failure,[73] 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[74] 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.[67,75,76]

# COMMONLY USED MAINTENANCE MEDICATIONS IN COPD*

| Generic Drug Name | Inhaler Type | DELIVERY OPTIONS *Nebulizer* | *Oral* | *Injection* | Duration Of Action |
|---|---|---|---|---|---|
| **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<br>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 |
| Glycopyrrolate | | √ | | | 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 | | |

TABLE 3.3

**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.*

## Antimuscarinic drugs

Antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle.[77] Short-acting antimuscarinics (SAMAs), namely ipratropium and oxitropium, also block the inhibitory neuronal receptor M2, which potentially can cause vagally induced bronchoconstriction.[78] Long-acting muscarinic antagonists (LAMAs), such as tiotropium, aclidinium, glycopyrronium bromide (also known as glycopyrrolate) and umeclidinium have prolonged binding to M3 muscarinic receptors, with faster dissociation from M2 muscarinic receptors, thus prolonging the duration of bronchodilator effect.[77]

A systematic review of randomized controlled trials 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.[79] Among LAMAs, some are administered once a day (tiotropium and umeclidinium), others twice a day (aclidinium), and some are approved for once daily dosing in some countries and twice daily dosing in others (glycopyrronium).[77,80] LAMA treatments (tiotropium) improve symptoms and health status.[77,81] They also improve the effectiveness of pulmonary rehabilitation[82,83] and reduce exacerbations and related hospitalizations.[81] Clinical trials have shown a greater effect on exacerbation rates for LAMA treatment (tiotropium) versus LABA treatment.[84,85] In a long-term clinical trial of 5,993 patients with COPD, tiotropium added to other standard therapies had no effect on the rate of lung function decline.[47] However, a study conducted in patients with early stage COPD defined by low symptom burden and mild to moderate airflow obstruction treated with tiotropium showed an increase in $FEV_1$, reduction in moderate but not severe exacerbations, and attenuation of the post-bronchodilator, but not pre-bronchodilator decline in $FEV_1$.[86]

***Adverse effects.*** Inhaled anticholinergic drugs are poorly absorbed which limits the troublesome systemic effects observed with atropine.[77,87] 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.[78,88] Although occasional urinary symptoms have been reported, there are no data to prove a true causal relationship.[89] 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.[90,91] In a large, long-term clinical trial in COPD patients, tiotropium added to other standard therapies had no effect on cardiovascular risk.[47] Although there were some initial concerns regarding the safety of tiotropium delivery via the Respimat®[92] 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.[93] 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.[94-96]



## 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.[97-99] 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,[97] 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.[100] Addition of theophylline to salmeterol produces a greater improvement in $FEV_1$ and breathlessness than salmeterol alone.[101,102]

There is limited and contradictory evidence regarding the effect of low-dose theophylline on exacerbation rates.[103,104] 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.[105]

***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.[98,100] Methylxanthines are non-specific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include the development of palpitations caused by 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.

## BRONCHODILATORS IN STABLE COPD

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**.
- Regular and as-needed use of SABA or SAMA improves $FEV_1$ and symptoms **(Evidence A)**.
- Combinations of SABA and SAMA are superior compared to either medication alone in improving $FEV_1$ and symptoms **(Evidence A)**.
- 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)**.
- Combination treatment with a LABA and LAMA increases $FEV_1$ and reduces symptoms compared to monotherapy **(Evidence A)**.
- Combination treatment with a LABA/LAMA reduces exacerbations compared to monotherapy **(Evidence B)**.
- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance **(Evidence B)**.
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**.

TABLE 3.4



## 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.[106,107] Combinations of SABAs and SAMAs are superior compared to either medication alone in improving $FEV_1$ and symptoms. [108] Treatment with formoterol and tiotropium in *separate inhalers* has a bigger impact on $FEV_1$ than either component alone.[109] There are numerous combinations of a LABA and LAMA in a *single inhaler* available (**Table 3.3**). These combinations improve lung function compared to placebo[106]; 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.[110] 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.[111-114] 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.[115] 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.[116] 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[117] (**Table 3.4**). These findings have been shown in people across different ethnic groups (Asian as well as European).[118]

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.[119] 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.[120] Another study in patients with a history of exacerbations confirmed that a combination LABA/LAMA decreased exacerbations to a greater extent than an LABA/ICS combination.[121] 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 an LABA/LAMA combination at higher blood eosinophil concentrations (see **Chapter 2**).[122] 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.[123]

## 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 (**Table 3.5**).

## Inhaled corticosteroids (ICS)

***Preliminary 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.[124,125] 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 inhaled corticosteroids (ICS) in patients with COPD are unclear and require further investigation.[109] 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. [122,126]

***Efficacy of ICS (alone).*** Most studies have found that regular treatment with ICS alone does not modify the long-term decline of $FEV_1$ nor mortality in patients with COPD.[127] Studies and meta-analyses assessing the effect of regular treatment with ICS alone on mortality in patients with COPD have not provided conclusive evidence of benefit.[127] 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.[128] 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.[129] However, in moderate COPD, fluticasone furoate alone or in combination with vilanterol was associated with slower decline in $FEV_1$ compared with placebo or vilanterol alone by on average 9 ml/year.[130] A number of studies have investigated whether there is a relationship between ICS treatment and risk of lung cancer with conflicting results.[131]

***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.[132,133] Clinical trials powered on all-cause mortality as the primary outcome failed to demonstrate a statistically significant effect of combination therapy on survival.[128,129]

## ANTI-INFLAMMATORY THERAPY IN STABLE COPD

### INHALED CORTICOSTEROIDS

- 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)**.
- Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)**.
- 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 suggest a beneficial effect versus fixed-dose LABA/LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations.

### 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:
  - » A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations **(Evidence A)**.
  - » A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations **(Evidence A)**.

### ANTIBIOTICS

- Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)**.
- 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)**.

### OTHER ANTI-INFLAMMATORY AGENTS

- 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.

TABLE 3.5

Most studies that found a beneficial effect of LABA/ICS fixed dose combination (FDC) over LABA alone on exacerbation rate, recruited patients with a history of at least one exacerbation in the previous year.[132] 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.[134]

***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.[122,135-139] 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. Data modelling indicates that ICS containing regimens have little or no effect at a blood eosinophil count < 100 cells/µL,[135] therefore this threshold can be used to identify patients with a low likelihood of treatment benefit with ICS. 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. These thresholds of < 100 cells/µL and > 300 cells/µL should be regarded as estimates, rather than precise cut-off values, that can predict different probabilities of treatment benefit. All in all, therefore, 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.

Sources of evidence include: 1) *Post-hoc* analyses comparing LABA/ICS versus LABA[135,136,138]; 2) Pre-specified analyses comparing triple therapy versus LABA/LAMA or LAMA[122,137,139] and, 3) other analyses comparing LABA/ICS versus LABA/LAMA[140] or studying ICS withdrawal.[141-143]

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).[121,122,137] 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. The mechanism for an increased ICS effect in COPD patients with higher blood eosinophil counts remains unclear.

The repeatability of blood eosinophil counts in a large primary care population appears reasonable,[144] although greater variability is observed at higher thresholds.[145] Better reproducibility is observed at the lower thresholds (e.g., 100 cells/µL).[146]

Cohort studies have produced differing results with regard to the ability of blood eosinophils to predict future exacerbation outcomes, with either no relationship[147] or a positive relationship reported.[148,149] 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.

Factors to consider when initiating ICS treatment in combination with one or two long-acting bronchodilators are shown in **Figure 3.1**.[150]

***Adverse effects.*** There is high quality evidence from randomized controlled trials (RCTs) that ICS use is associated with higher prevalence of oral candidiasis, hoarse voice, skin bruising and pneumonia.[127] This excess risk has been

confirmed in ICS studies using fluticasone furoate, even at low doses.[151] 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 limitation.[152,153] Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of developing pneumonia.[154] In studies of patients with moderate COPD, ICS by itself or in combination with a LABA did not increase the risk of pneumonia.[129,153]

## FACTORS TO CONSIDER WHEN INITIATING ICS TREATMENT

Factors to consider when initiating ICS treatment in combination with one or two long-acting bronchodilators (note the scenario is different when considering ICS withdrawal):

| · STRONG SUPPORT · | · CONSIDER USE · | · AGAINST USE · |
|---|---|---|
| • History of hospitalization(s) for exacerbations of COPD# | • 1 moderate exacerbation of COPD per year# | • Repeated pneumonia events |
| • ≥ 2 moderate exacerbations of COPD per year# | • Blood eosinophils 100-300 cells/µL | • Blood eosinophils <100 cells/µL |
| • Blood eosinophils >300 cells/µL | | • History of mycobacterial infection |
| • History of, or concomitant, asthma | | |

#despite appropriate long-acting bronchodilator maintenance therapy (see Table 3.4 and Figure 4.3 for recommendations);

*note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.



FIGURE 3.1



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.[45,151,155-157] Results of observational studies suggest that ICS treatment could also be associated with increased risk of diabetes/poor control of diabetes,[158] cataracts,[159] and mycobacterial infection[160] including tuberculosis.[161,162] In the absence of RCT data on these issues, it is not possible to draw firm conclusions.[163] An increased risk of tuberculosis has been found in both observational studies and a meta-analysis of RCTs.[124,125]

***Withdrawal of ICS.*** Results from withdrawal studies provide equivocal results regarding consequences of withdrawal on lung function, symptoms and exacerbations.[164-168] Some studies, but not all, 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 $FEV_1$ (approximately 40 mL) with ICS withdrawal,[168] which could be associated with increased baseline circulating eosinophil level.[141] A study examining ICS withdrawal on a background of dual bronchodilator therapy demonstrated that both $FEV_1$ 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.[143] 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[169] and has been shown to improve lung function, patient reported outcomes and reduce exacerbations when compared to LAMA alone, LABA/LAMA and LABA/ICS.[122,137,139,170-177]

A *post-hoc* pooled analysis of three triple therapy clinical trials in COPD patients with severe airflow limitation 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.[178] Two large one-year randomized controlled trials reviewed below (named IMPACT and ETHOS) provide new evidence on mortality reduction with fixed-dose inhaled triple combinations compared to dual bronchodilation.[179,180] Both trials compared a fixed triple (LABA/LAMA/ICS) combination (at two ICS dosages in ETHOS) to two dual therapy options (LABA/LAMA and LABA/ICS). They were enriched for symptomatic patients with a history of frequent and/or severe exacerbations. The majority of patients were receiving open triple or LABA/ICS based therapy before study randomization. While mortality was not a primary endpoint for either study, it was a pre-specified outcome; vital status was rigorously collected so that missing data was minimal. Both studies performed intention to treat analyses. In IMPACT (n=10,355), mortality in the triple therapy arm was significantly lower compared to the dual bronchodilation arm,[179] with similar findings observed in ETHOS (n=8,509) with the higher dose ICS (but not the lower dose).[180] For both studies, there were no differences versus LABA/ICS.

Together these results suggest a beneficial effect of fixed-dose triple inhaled therapy versus fixed-dose LABA/LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations who were previously receiving maintenance therapy with triple therapy, LABA/ICS or single or dual long-acting bronchodilators. Further analyses or studies may help determining whether other specific patient subgroups demonstrate a greater survival benefit.



## Oral glucocorticoids

Oral glucocorticoids have numerous side effects, including steroid myopathy[181] which can contribute to muscle weakness, decreased functionality, and respiratory failure in subjects 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 improve lung function and breathlessness.[182] Conversely, prospective studies on the long-term effects of oral glucocorticoids in stable COPD are limited.[183,184] 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) inhibitors

***Efficacy.*** The principal action of PDE4 inhibitors is to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP.[185] 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.[186] The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators,[187] and in patients who are not controlled on fixed-dose LABA/ICS combinations.[188] The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation.[189,190] There has been no study directly comparing roflumilast with an inhaled corticosteroid.

***Adverse effects.*** PDE4 inhibitors have more adverse effects than inhaled medications for COPD.[191] 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[192,193] 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.[194] Later studies have shown that regular use of some antibiotics may reduce exacerbation rate.[195,196]

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.[197-199] Azithromycin use was associated with an increased incidence of bacterial resistance, prolongation of QTc interval, and impaired hearing tests.[199] A *post-hoc* analysis suggests lesser benefit in active smokers.[190] 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 exacerbation rate overall.[200]

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

In COPD patients not receiving inhaled corticosteroids, regular treatment with mucolytics such as carbocysteine and N-acetylcysteine (NAC) may reduce exacerbations and modestly improve health status.[201-204] 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 one to identify precisely the potential target population for antioxidant agents in COPD.[205]

## Other drugs with potential to reduce exacerbations

Two RCTs in COPD patients performed before 2005 that investigated the use of an immunoregulator reported a decrease in the severity and frequency of exacerbations.[206,207] Additional studies are needed to examine the long-term effects of this therapy in patients receiving currently recommended COPD maintenance therapy.

More recently four large phase 3 studies have investigated the efficacy of the anti-IL-5 monoclonal antibody mepolizumab[208] and the anti-IL-5 receptor-$\alpha$ antibody benralizumab[209] in patients with severe COPD, recurrent exacerbations and peripheral blood evidence of eosinophilic inflammation despite high intensity inhaled therapy. The studies showed a 15-20% 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 $FEV_1$ 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.

Nedocromil and leukotriene modifiers have not been tested adequately in COPD patients and the available evidence does not support their use.[210,211]

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.[212]

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 placebo group and hospitalization for exacerbation was more common among the patients treated with metoprolol.[213] There is no evidence that beta-blockers should be used in patients with COPD who do not have a cardiovascular indication for their use.

Simvastatin did not prevent exacerbations in patients with COPD who had no metabolic or cardiovascular indication for statin treatment.[214] An association between statin use and improved outcomes (including decreased exacerbations and mortality) has been reported in observational studies of patients with COPD who received them for cardiovascular and metabolic indications.[215]

There is no evidence that supplementation with vitamin D has a positive impact on exacerbations in unselected patients.[216] In a meta-analysis vitamin D supplementation reduced exacerbation rates in patients with low baseline vitamin D levels.[217]

## Issues related to inhaled delivery

When a treatment is given by the inhaled route the importance of education and training in inhaler device technique cannot be over-emphasized. Inhalation devices include nebulizers, metered-dose inhalers (MDIs) used without spacers, soft-mist inhalers and breath-actuated devices i.e., breath-actuated MDIs (BAIs) and single-dose and multi-dose dry powder inhalers (DPIs).[218] In multi-dose DPIs, the powder is contained in a reservoir or in individual blisters.[218] All classes of inhaled drugs are not available in all types of device. 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).[218] Randomized controlled trials have not identified superiority of one device/formulation.[218] 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. On average more than two thirds of patients make at least one error in using an inhalational device.[219-222] A rigorous, prospective observational study of COPD patients discharged from the hospital confirmed appropriate adherence to the use of a DPI in only 23% of patients.[223]



Observational studies have identified a significant relationship between poor inhaler use and symptom control in patients with COPD.[220] Determinants of poor inhaler technique in asthma and COPD patients include: older age, use of multiple devices, and lack of previous education on inhaler technique.[224] In such populations, education improves inhalation technique in some but not all patients,[224] especially when the “teach-back” approach (patients being asked to show how the device has to be used) is implemented.[225] It is important to check 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. Those who do not reach mastery may require a change in inhalational delivery device. Pharmacist-led interventions[226] and lay health coaching[227] can improve inhalation technique and adherence in COPD patients.

## THE INHALED ROUTE

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

TABLE 3.6

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 (**Table 3.6**).[223] Specific instructions are available for each type of device.[218] Observational studies in patients with COPD 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.[228-234] Strategies for inhaler choice based on patients' characteristics have been proposed by experts and consensus-based taskforces (**Table 3.6**), but none have yet been prospectively tested.[218,234,235] There is no evidence for superiority of nebulized therapy over hand-held devices in patients who are able to use these devices properly.



### Other pharmacological treatments

Other pharmacological treatments for COPD are summarized in **Table 3.7**.

## OTHER PHARMACOLOGICAL TREATMENTS

**ALPHA-1 ANTITRYPSIN AUGMENTATION THERAPY**

- Intravenous augmentation therapy may slow down the progression of emphysema **(Evidence B)**.

**ANTITUSSIVES**

- There is no conclusive evidence of a beneficial role of antitussives in patients with COPD **(Evidence C)**.

**VASODILATORS**

- Vasodilators do not improve outcomes and may worsen oxygenation **(Evidence B)**.

TABLE 3.7

***Alpha-1 antitrypsin augmentation therapy.*** The logical approach to minimize the development and progression of lung disease in 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, formal clinical trials to assess efficacy with conventional spirometric outcome have never been undertaken. However, a wealth of observational studies suggest a reduction in spirometric progression in treated versus non-treated patients[236] and that this reduction is most effective for patients with $FEV_1$ 35-49% predicted.[237] Never or ex-smokers with an $FEV_1$ of 35-60% predicted have been suggested as those

most suitable for AATD augmentation therapy (**Evidence B**).

Studies using sensitive parameters of emphysema progression determined by CT scans have provided evidence for an effect on preserving lung tissue compared to placebo.[238-240] 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.[241] 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.[241]

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.[242] Intravenous augmentation therapy has been recommended for individuals with alpha-1 antitrypsin deficiency (AATD) and an $FEV_1$ ≤ 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 $FEV_1$ > 65%. Individual discussion is recommended with consideration of the cost of therapy and lack of evidence for much benefit.[243] The main limitation for this therapy is very high cost and lack of availability in many countries.

***Antitussives.*** The role of antitussives in patients with COPD is inconclusive.[244]

***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.[245] Studies have shown that sildenafil does not improve the results of rehabilitation in patients with COPD and moderately increases pulmonary artery pressure.[246] Tadalafil does not appear improve exercise capacity or health status in COPD patients with mild pulmonary hypertension.[247]



# 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.”[248]

Pulmonary rehabilitation should be considered part of integrated patient management, and usually includes a range of healthcare professionals to ensure optimum coverage of the many aspects involved.[249] Patients should undergo careful assessment prior to enrollment, including identification of the patient’s goals, specific healthcare needs, smoking status, nutritional health, self-management capacity, health literacy, psychological health status and social circumstances, comorbid conditions as well as exercise capabilities and limitations.[250,251] 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.[251] 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.[251] 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.[252] The importance of long-term behavior change to improve physical functionality, and reduce the psychological impact of COPD, should be emphasized to the patient.

The benefits to COPD patients from pulmonary rehabilitation are considerable (**Table 3.8**), and rehabilitation has been shown to be the most effective therapeutic strategy to improve shortness of breath, health status and exercise tolerance.[253] Pulmonary rehabilitation is appropriate for most patients 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.[254]

**PULMONARY REHABILITATION, SELF-MANAGEMENT AND INTEGRATIVE CARE IN COPD**

**PULMONARY REHABILITATION**

- 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 alone has not been shown to be effective **(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)**.

TABLE 3.8



Exercise-induced oxygen desaturation can be a problem among COPD patients without chronic hypoxemia. 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,[255] but most evidence was limited by low study quality. A large RCT,[256] 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.[257] 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.[258] However, a greater improvement in 6-minute walking distance (6MWD) test was observed with HFNT. 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.

Limited data exist regarding the effectiveness of pulmonary rehabilitation after an acute exacerbation of COPD, but systematic reviews have shown that among those patients who have had a recent exacerbation (≤ 2 weeks from prior hospitalization), pulmonary rehabilitation can reduce readmissions and mortality.[259] However, initiating pulmonary rehabilitation before the patient's discharge may compromise survival through unknown mechanisms.[260] Pulmonary rehabilitation also ranks as one of the most cost-effective treatment strategies.[249]

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.[261] 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.[262] A major barrier to full participation is access, which is particularly limited by geography, culture, finances, transport and other logistics.[248,263,264]

Pulmonary rehabilitation can be conducted at a range of sites.[248] Community-based and home-based programs have been shown to be as effective as hospital-based programs in randomized controlled trials,[265,266] as long as the frequency and intensity are equivalent.[267] There is also evidence that standardized home-based pulmonary rehabilitation programs improve dyspnea in COPD patients.[268] 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 patients with COPD who are unable to attend pulmonary rehabilitation.[269] 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.[251,270] Pulmonary rehabilitation may help reduce anxiety and depression symptoms.[271]



## Education, self-management and integrative care

***Education.*** 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 takes into account specific issues relating to the individual patients, and that aims to enhance long-term functionality and appropriate health behaviors are likely to benefit patients more. These are addressed under self-management.

***Self-management.*** A recent 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."[272] 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.[272]

Systematic reviews have provided evidence that self-management interventions improve outcomes in COPD. Cochrane reviews on COPD self-management have reported that self-management interventions that include written negotiated action plans for worsening symptoms lead to a lower probability of both respiratory-related hospitalization and all cause hospitalizations. A Cochrane review on COPD self-management interventions that includes action plans for exacerbations demonstrated lower probability of respiratory-related hospital admissions and improvements in health related quality of life.[273] There have been concerns that health benefits from such self-management programs in COPD could be counterbalanced by increased mortality.[274,275] The Cochrane review and another meta-analysis, however, reported no impact of self-management interventions on overall mortality.[273,276] The Cochrane review did find a small, but statistically significant, higher respiratory related mortality rate in the self-management intervention group as compared to usual care. However, the authors also indicate 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[277] and the PIC-COPD,[278] 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.

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.[279]

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 patients 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.[280] 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.[281]

***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 small trials concluded that an integrated care program improved a number of clinical outcomes, although not mortality.[282] In contrast, a large multicenter study in primary care within an existing well-organized system of care did not confirm this.[283] Besides, delivering integrated interventions by telemedicine did not show a significant effect.[284,285] 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.

# 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.[286] 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 patients with COPD are less likely to receive such services compared to patients with lung cancer.[287,288] 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.[286] 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.[289] 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.[288]

## Therapy relevant to all patients with COPD

Even when receiving optimal medical therapy many patients with COPD continue to experience distressing breathlessness, impaired exercise capacity, fatigue, and suffer panic, anxiety and depression.[264] 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.*** Opiates,[290-292] neuromuscular electrical stimulation (NMES),[292,293] chest wall vibration (CWV)[292] and fans blowing air onto the face[292,294,295] can relieve breathlessness. Immediate-release morphine extended exercise endurance time in over half of patients with advanced COPD, although further research is required to determine what patient characteristics predict response.[296] Oxygen may offer some benefit even if the patient is not hypoxemic ($Sp0_2$ > 92%).[297] Pulmonary rehabilitation is effective and in severe cases non-invasive ventilation 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.[298] Refractory dyspnea may be more effectively managed with a multidisciplinary integrated palliative and respiratory care service.[299]

There is no evidence for a beneficial effect of benzodiazepines[300] and there is not enough data to recommend distractive auditory stimuli (music), relaxation, counseling and support, with or without breathing relaxation training, or psychotherapy.[301]

***Nutritional support.*** Low BMI and particularly low fat free mass is associated with worse outcomes in people with COPD.[302] In malnourished patients with COPD, nutritional supplementation promotes significant weight gain and leads to significant improvements in respiratory muscle strength and overall health-related quality of life.[303] 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.[304] A 12-month nutritional intervention in muscle wasted patients had no effect on physical capacity but physical activity was significantly higher.[305]

***Panic, anxiety & depression.*** The causes of depression and anxiety symptoms in people with COPD are multifactorial and include behavioral, social and biological factors.[306] Pulmonary rehabilitation may help reduce

anxiety symptoms. The efficacy of antidepressants in patients 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.[307]

***Fatigue.*** Fatigue in people with COPD can be improved by self-management education, pulmonary rehabilitation, nutritional support and mind-body interventions.[308]

## 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.[309] Although mortality rates following hospitalization for an acute exacerbation of COPD are declining,[310] reported rates still vary from 23%[311] to 80%.[312] Progressive respiratory failure, cardiovascular diseases, malignancies and other diseases are the primary cause of death in patients with COPD hospitalized for an exacerbation.[312] In qualitative studies, as well as describing the high symptom burden, patients 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.[313] 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.[314] At an individual level, prediction of 6-month survival in patients with COPD is unreliable and therefore early discussion of these issues is important together with phased introduction of supportive care.[315] 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 death will result from worsening dyspnea and suffocation.[316] 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.[317,318]



### PALLIATIVE CARE, END OF LIFE AND HOSPICE CARE IN COPD

- Opiates, neuromuscular electrical stimulation (NMES), oxygen and fans blowing air on to the face can relieve breathlessness **(Evidence C)**.
- In malnourished patients, nutritional supplementation 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)**.

TABLE 3.9

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[319] 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).[287,288] 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.[286] Key points for palliative, end-of-life and hospice care in COPD are summarized in **Table 3.9**.

# OTHER TREATMENTS

## 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.[320] 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.[321] 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 (**Table 3.10**).[321,322] There are contradictory studies although the majority do not demonstrate changes.[323]

Although air travel is safe for most patients with chronic respiratory failure who are on long-term oxygen therapy,[324] 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.[325] Those with a resting oxygen saturation > 95% and 6-minute walk oxygen saturation > 84% may travel without further assessment,[326] although it is important to emphasize that resting oxygenation at sea level does not exclude the development of severe hypoxemia when travelling by air.[324] 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.[327]



## Ventilatory Support

***During exacerbations of COPD.*** Noninvasive ventilation (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[328-331](see also **Chapter 5**).

***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.[332]

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.[333] A multicenter (13 sites) prospective RCT of COPD patients (n=116) 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 noninvasive ventilation (NIV) plus oxygen compared to home oxygen alone on time to readmission or death.[333] Patients with BMI >35 kg/m$^2$, obstructive sleep apnea syndrome, or other causes of respiratory failure were excluded. Of 2,021 patients screened, only 124 (6%) were eligible. Results showed that adding home NIV to oxygen therapy significantly prolonged the time to readmission or death within 12 months.[333] 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.[331]

Two previous retrospective studies[334,335] and two of three RCTs[333,336-339] 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. 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.[340] NPPV when indicated should be instituted and monitored under the direction of personnel familiar with the process and the devices utilized.[341,342] 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.[332]

### OXYGEN THERAPY AND VENTILATORY SUPPORT IN STABLE COPD

#### OXYGEN THERAPY

- The long-term administration of oxygen increases survival in patients with severe chronic resting arterial hypoxemia **(Evidence A)**.
- In patients with stable COPD and moderate resting or exercise-induced arterial desaturation, prescription of long-term oxygen does not lengthen time to death or first hospitalization or provide sustained benefit in health status, lung function and 6-minute walk distance **(Evidence A)**.
- Resting oxygenation at sea level does not exclude the development of severe hypoxemia when traveling by air **(Evidence C)**.

#### VENTILATORY SUPPORT

- NPPV may improve hospitalization-free survival in selected patients after recent hospitalization, particularly in those with pronounced daytime persistent hypercapnia ($PaCO_2 \geq 52$ mmHg) **(Evidence B)**.

TABLE 3.10



# INTERVENTIONAL THERAPY

## Surgical Interventions

***Lung volume reduction surgery (LVRS).*** LVRS is a surgical procedure in which parts of the lungs are resected to reduce hyperinflation,[343] making respiratory muscles more effective pressure generators by improving their mechanical efficiency.[344,345] LVRS increases the elastic recoil pressure of the lung and thus improves expiratory flow rates and reduces exacerbations.[346,347] In an RCT that included severe emphysema patients, with an upper-lobe emphysema and low post-rehabilitation exercise capacity, LVRS resulted in improved survival when compared to medical treatment.[348] 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. LVRS has been demonstrated to result in higher mortality than medical management in severe emphysema patients with an $FEV_1 \leq 20\%$ predicted and either homogeneous emphysema high resolution computed tomography or a DLCO of ≤ 20% of predicted.[349] A prospective economic analysis indicated that LVRS is costly relative to healthcare programs that do not include surgery.[350]

***Bullectomy.*** Bullectomy is an older surgical procedure for bullous emphysema. Removal of a large bulla that does not contribute to gas exchange and is, or has been, responsible for complications decompresses the adjacent lung parenchyma. In selected patients with relatively preserved underlying lung, bullectomy is associated with decreased dyspnea, improved lung function and exercise tolerance.[351] Pulmonary hypertension, hypercapnia and severe emphysema are not absolute contraindications for bullectomy.

***Lung transplantation.*** In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve health status and functional capacity but not prolong survival.[351-353] Over 70% of lung transplants

conducted in COPD patients are double lung transplants; the remainder are single lung transplants.[354] Bilateral lung transplantation has been reported to provide longer survival than single lung transplantation in COPD patients, especially those < 60 years of age.[355] The median survival for lung transplantation in all COPD patients has increased to 5.5 years; it is 7 years in those receiving a bilateral lung transplant and 5 years in those receiving a single lung transplant.[354]

Lung transplantation is limited by the shortage of donor organs and cost. The complications most commonly seen in COPD patients after lung transplantation are acute rejection, bronchiolitis obliterans, opportunistic infections and lymphoproliferative disease.[356]

## 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.[357] These include a variety of different bronchoscopic procedures.[357] 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.

Prospective studies have shown that the use of bronchial stents is not effective.[358] 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.[359]

A large prospective multicenter RCT of endobronchial valve placement showed statistically significant improvements in $FEV_1$ and 6-minute walk distance compared to control therapy at 6 months post intervention.[360] However, the magnitude of the observed improvements was not clinically meaningful. Subsequently, efficacy of the same endobronchial valve has been studied in patients with heterogeneous,[361] or heterogeneous and homogenous emphysema[362] with mixed outcomes. Non-significant increases in median $FEV_1$ at three months post valve implantation in one study was attributed to valve placement in some patients with interlobar collateral ventilation.[361] Another study showed significant increases in $FEV_1$ and 6-minute walk distance in subjects selected for the absence of interlobar collateral ventilation compared to the control group at 6 months.[362] Adverse effects in the endobronchial valve treatment group in both studies included pneumothorax, valve removal or valve replacement.[362] Greater benefit was shown in patents with heterogeneous compared to those with homogenous emphysema.[362] An RCT of endobronchial valve placement compared with usual care conducted only in homogenous emphysematous patients without interlobar collateral ventilation reported improvements in $FEV_1$, 6-minute walk distance and health status at 6 months with targeted lobe reduction in 97% of subjects as measured by volumetric CT (mean reduction 1,195 ml).[363] A large multicenter, prospective, RCT of endobronchial valve treatment in patients with heterogeneous emphysema distribution and little to no collateral ventilation, demonstrated significant clinically meaningful benefits over current standard care in lung function, dyspnea, exercise capacity, and quality of life out to at least 12-months post-procedure.[364] Pneumothorax was seen in 26.6% of subjects treated with the endobronchial valve usually within the first 72 hours of the procedure (76%).[363-365] Another large multicenter prospective RCT using a different type of endobronchial valve in patients selected for targeted lobe treatment based on fissure integrity assessed by high resolution chest CT showed a significant between-group increase in mean $FEV_1$ from baseline (0.101L) and a 25.7% between-group difference in $FEV_1$ responder rates (improvement ≥15%). These results persisted at 12 months. The endobronchial valve treated group also had significant reductions in hyperinflation and dyspnea. Improved health status and quality of life was also observed. Consistent with prior studies, pneumothorax occurred in 25.5% of endobronchial valve treated patients; the majority occurred in the first three days following the procedure during the period of average hospitalization. Early-onset pneumothorax in the endobronchial valve treatment group likely results from lung conformation 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.[366] The occurrence of pneumothorax highlights the

need for physicians performing this procedure to have expertise in the management of procedural complications.[366] After the post-procedural period however, patients treated with the endobronchial valve 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 endobronchial valve placement compared to LVRS show comparable benefits with endobronchial valve treatment but with fewer complications.[364] Endobronchial valve therapy is now clinically available and approved for treatment in many countries in the treatment of patients who have intact fissures or lack of collateral ventilation.[364,367,368]

Other bronchoscopic lung volume reduction techniques do not depend upon the presence of intact fissures or absence of collateral ventilation. In a prospective RCT, targeted thermal vapour ablation of more diseased segments 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.[369,370] This therapy has limited clinical availability.

Two 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. Both studies reported an increase in 6-minute walk distance with coil treatment compared to control and smaller improvements in $FEV_1$, and quality of life measured by St George's Respiratory Questionnaire.[371,372] Major complications included pneumonia, pneumothorax, hemoptysis and COPD exacerbations occurring more frequently in the coil group.[372] 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.[372]

Key points for interventional therapy in stable COPD are summarized in **Table 3.11**.



## INTERVENTIONAL THERAPY IN STABLE COPD

### 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)**.

### 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)**.

TABLE 3.11

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# CHAPTER 4: MANAGEMENT OF STABLE COPD

**OVERALL KEY POINTS:**

- *The management strategy of stable COPD should be predominantly based on the assessment of symptoms and future risk of exacerbations.*
- *All individuals who smoke should be strongly encouraged and supported to quit.*
- *The main treatment goals are reduction of symptoms and future risk of exacerbations.*
- *Management strategies include pharmacologic and non-pharmacologic interventions.*

## INTRODUCTION



COPD patients should have an assessment of the severity of their airflow obstruction, symptoms, history of exacerbations, exposure to risk factors and comorbidities (**Figure 4.1**) to guide management. The assessment is summarized in **Chapter 2**.

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 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.

It is crucial for people with COPD to understand the nature of the disease, risk factors for its progression, and the role that they and their healthcare workers must play in order to achieve optimal management and health outcomes.

Following the assessment, initial management should address reducing exposure to risk factors including smoking cessation. Vaccination should be offered, and patients should receive general advice on healthy living, including diet, and that physical exercise is safe and encouraged for people with COPD. Initial pharmacotherapy should be based on the patient's GOLD group (**Figure 4.2**). Patients should be offered guidance on self-management of breathlessness, energy conservation and stress management, and they should be given a written action plan. Comorbidities should also be managed (**Figure 4.1**).

Patients should be reviewed after a suitable interval 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. Physical activity should be encouraged and referral for pulmonary rehabilitation considered. The need for oxygen therapy, ventilatory support, lung volume reduction and palliative approaches should be reviewed. The action plan should be updated. Spirometry should be repeated at least annually.

We no longer refer to asthma & COPD overlap (ACO), instead we emphasize that asthma and COPD are different disorders, although they may share some common 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, but pharmacological and non-pharmacological approaches may also be needed for their COPD.

Pharmacological and non-pharmacological therapy should be adjusted as necessary (see below) and further reviews undertaken (**Figure 4.1**).

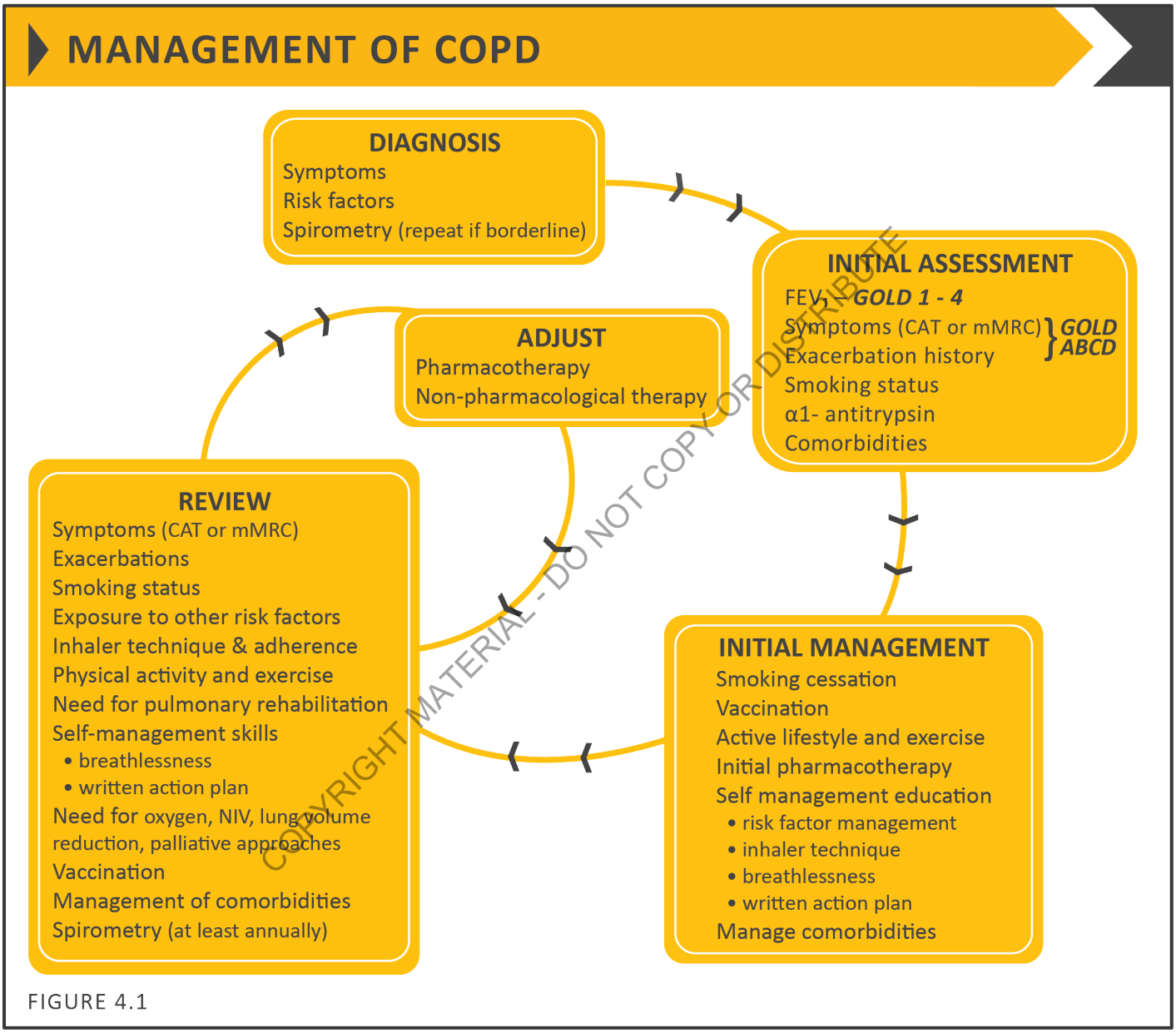
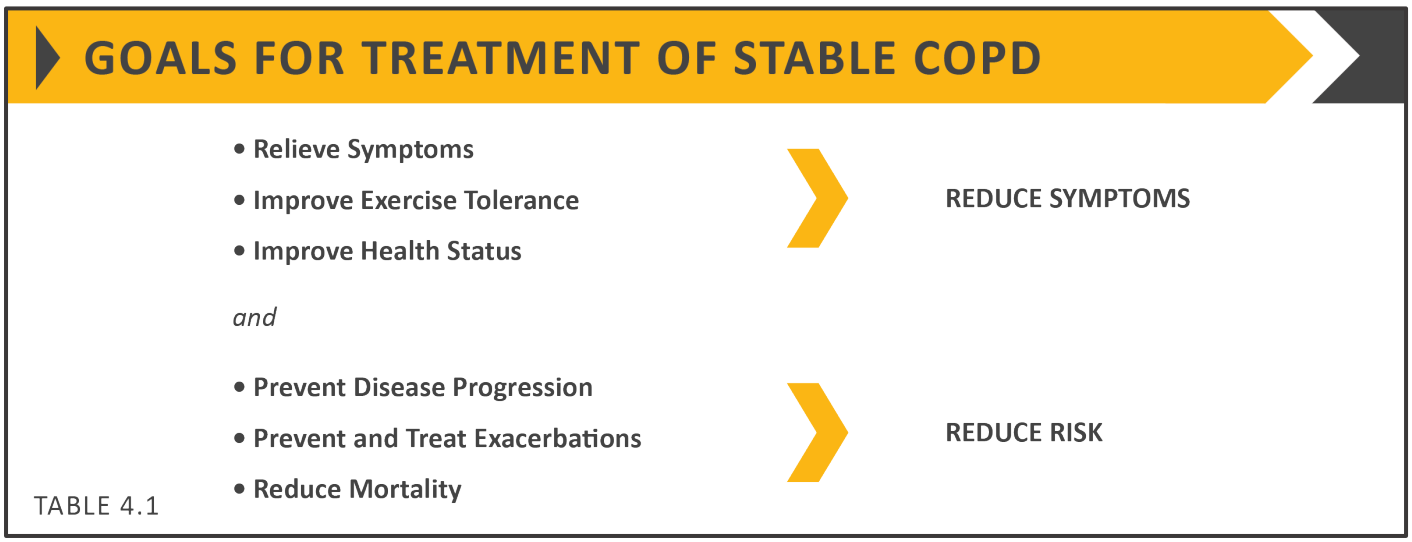



FIGURE 4.1

The aim of management is to reduce both current symptoms and future risks of exacerbations (**Table 4.1**).




## IDENTIFY AND REDUCE EXPOSURE TO RISK FACTORS

Identification and reduction of exposure to risk factors is important in the treatment and prevention of COPD. Cigarette smoking is the most commonly encountered and easily identifiable risk factor for COPD, and smoking cessation should be continually encouraged for all individuals who smoke. Reduction of total personal exposure to occupational dusts, fumes, and gases, and to indoor and outdoor air pollutants, should also be addressed.



### Tobacco smoke

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 to patients and should encourage patients to quit at every available opportunity.

Smokers should be provided with counseling when attempting to quit. When possible, the patient should be referred to a comprehensive smoking cessation program that incorporates behavior change techniques that enhance patient motivation and confidence, patient education, and pharmacological and non-pharmacological interventions. Recommendations for treating tobacco use and dependence are summarized in **Table 4.2**.[1]

### Indoor and outdoor air pollution

Reducing exposure to indoor 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.[2,3] Measures to reduce risk factor exposure are summarized in **Table 4.3**.

### 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 if possible.

## TREATING TOBACCO USE AND DEPENDENCE: A CLINICAL PRACTICE GUIDELINE — MAJOR FINDINGS & RECOMMENDATIONS

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

TABLE 4.2



## IDENTIFY & REDUCE RISK FACTOR EXPOSURE

- Smoking cessation interventions should be actively pursued in all COPD patients **(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)**.

TABLE 4.3

# TREATMENT OF STABLE COPD: PHARMACOLOGICAL TREATMENT

Pharmacological therapies can reduce symptoms, and the risk and severity of exacerbations, as well as improve the health status and exercise tolerance of patients with COPD.

The classes of medications commonly used to treat COPD are shown in **Table 3.3** and a detailed description of the effects of these medications is given in **Chapter 3**. The choice within each class depends on the availability of medication and the patient's responses and preferences.

Most of the drugs are inhaled so proper inhaler technique is highly relevant. Key points for the inhalation of drugs are given in **Table 4.4**. Key points for bronchodilator use are given in **Table 4.5**. Key points for the use of anti-inflammatory agents are summarized in **Table 4.6**. Key points for the use of pharmacological treatments are summarized in **Table 4.7**.



## KEY POINTS FOR INHALATION OF DRUGS

- The choice of inhaler device has to be individually tailored and will depend on access, cost, prescriber, and most importantly, patient's ability and preference.
- It is essential to provide instructions and to demonstrate the proper inhalation technique when prescribing a device, to ensure that inhaler technique is adequate and re-check at each visit that patients continue to use their inhaler correctly.
- Inhaler technique (and adherence to therapy) should be assessed before concluding that the current therapy requires modification.

TABLE 4.4

## KEY POINTS FOR THE USE OF BRONCHODILATORS

- 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.
- Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator treatment should be escalated to two **(Evidence A)**.
- Inhaled bronchodilators are recommended over oral bronchodilators **(Evidence A)**.
- Theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable **(Evidence B)**.

TABLE 4.5

## KEY POINTS FOR THE USE OF ANTI-INFLAMMATORY AGENTS

- Long-term monotherapy with ICS is not recommended **(Evidence A)**.
- Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators **(Evidence A)**.
- Long-term therapy with oral corticosteroids is not recommended **(Evidence A)**.
- In patients with severe to very severe airflow limitation, chronic bronchitis and exacerbations the addition of a PDE4 inhibitor to a treatment with long acting bronchodilators with/without ICS can be considered **(Evidence B)**.
- Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, macrolides, in particular azithromycin, can be considered **(Evidence B)**.
- Statin therapy is not recommended for prevention of exacerbations **(Evidence A)**.
- Antioxidant mucolytics are recommended only in selected patients **(Evidence A)**.

TABLE 4.6



## KEY POINTS FOR THE USE OF OTHER PHARMACOLOGICAL TREATMENTS

- Patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy **(Evidence B)**.
- Antitussives cannot be recommended **(Evidence C)**.
- Drugs approved for primary pulmonary hypertension are not recommended for patients with a pulmonary hypertension secondary to COPD **(Evidence B)**.
- Low-dose long acting oral and parenteral opioids may be considered for treating dyspnea in COPD patients with severe disease **(Evidence B)**.

TABLE 4.7

## Algorithms for the assessment, initiation and follow-up management of pharmacological treatment

A model for the **INITIATION** of pharmacological management of COPD according to the individualized assessment of symptoms and exacerbation risk following the ABCD assessment scheme is shown in **Figure 4.2**. There is no high-quality evidence such as randomized controlled trials to support initial pharmacological treatment strategies in newly diagnosed COPD patients. However, a real-world observational study has demonstrated that initial COPD treatment with an LABA/ICS is more effective than treatment with a LAMA in patients with previous exacerbations and high blood eosinophils > 300 cells/µL.[4] **Figure 4.2** is an attempt to provide clinical guidance using the best available evidence.

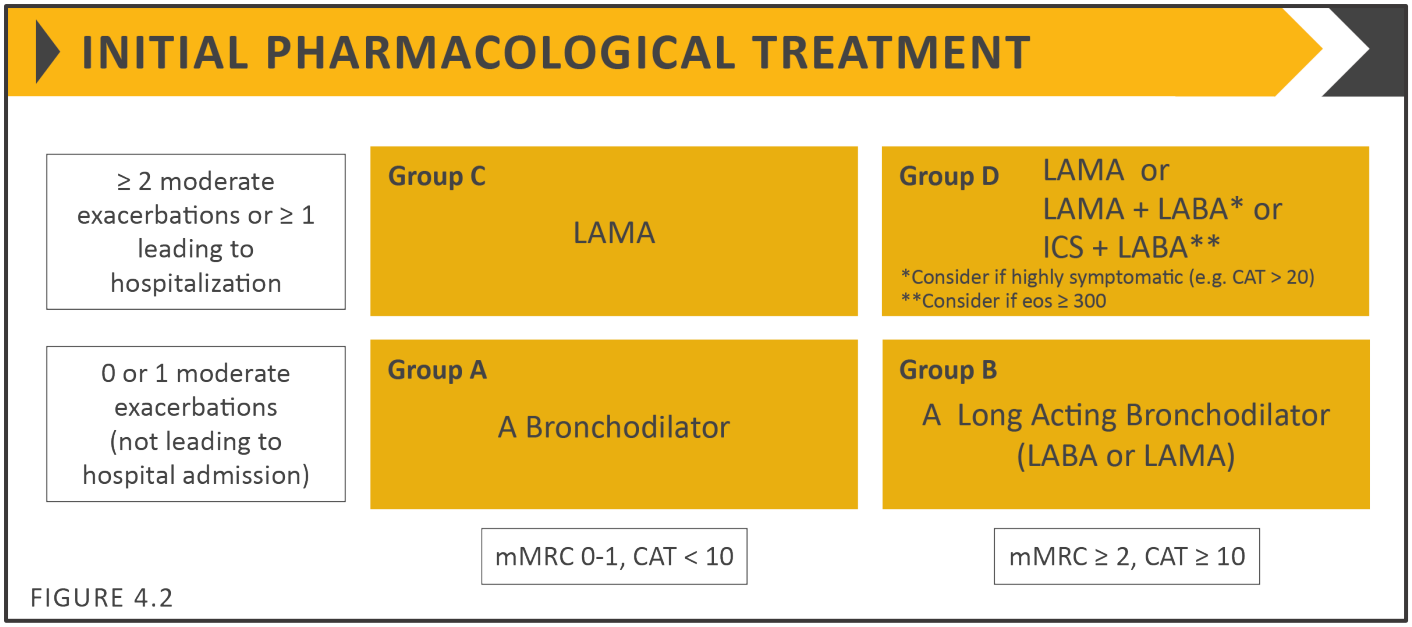



FIGURE 4.2

**Definition of abbreviations:** eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.



Following implementation of therapy, patients should be reassessed for attainment of treatment goals and identification of any barriers for successful treatment (**Figure 4.3**). Following review of the patient response to treatment initiation, adjustments in pharmacological treatment may be needed.

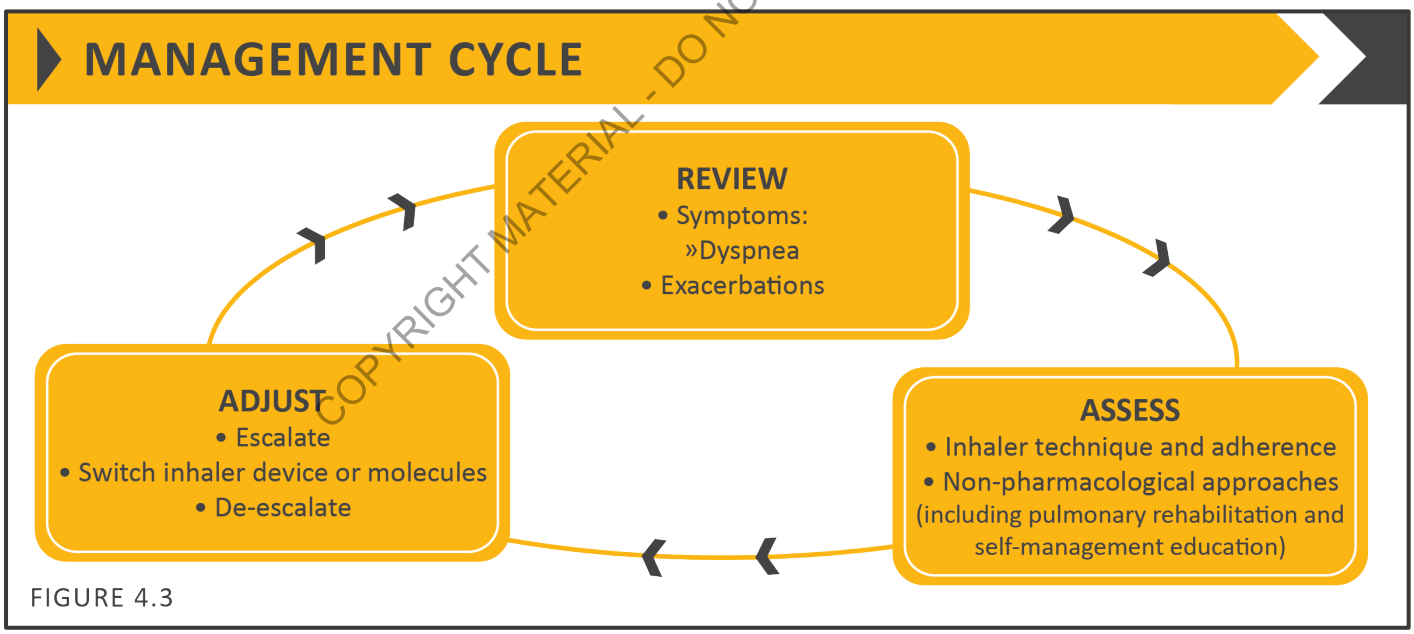



FIGURE 4.3

A separate algorithm is provided for **FOLLOW-UP** treatment, where the management is still based on symptoms and exacerbations, but the recommendations do not depend on the patient's GOLD group at diagnosis (**Figure 4.4**). These follow-up recommendations are designed to facilitate management of patients taking maintenance treatment(s), whether early after initial treatment or after years of follow-up. These recommendations incorporate the evidence from clinical trials and the use of peripheral blood eosinophil counts as a biomarker to guide the use of ICS therapy for exacerbation prevention (see more detailed information regarding blood eosinophil counts as a predictor of ICS effects in **Chapter 3**).

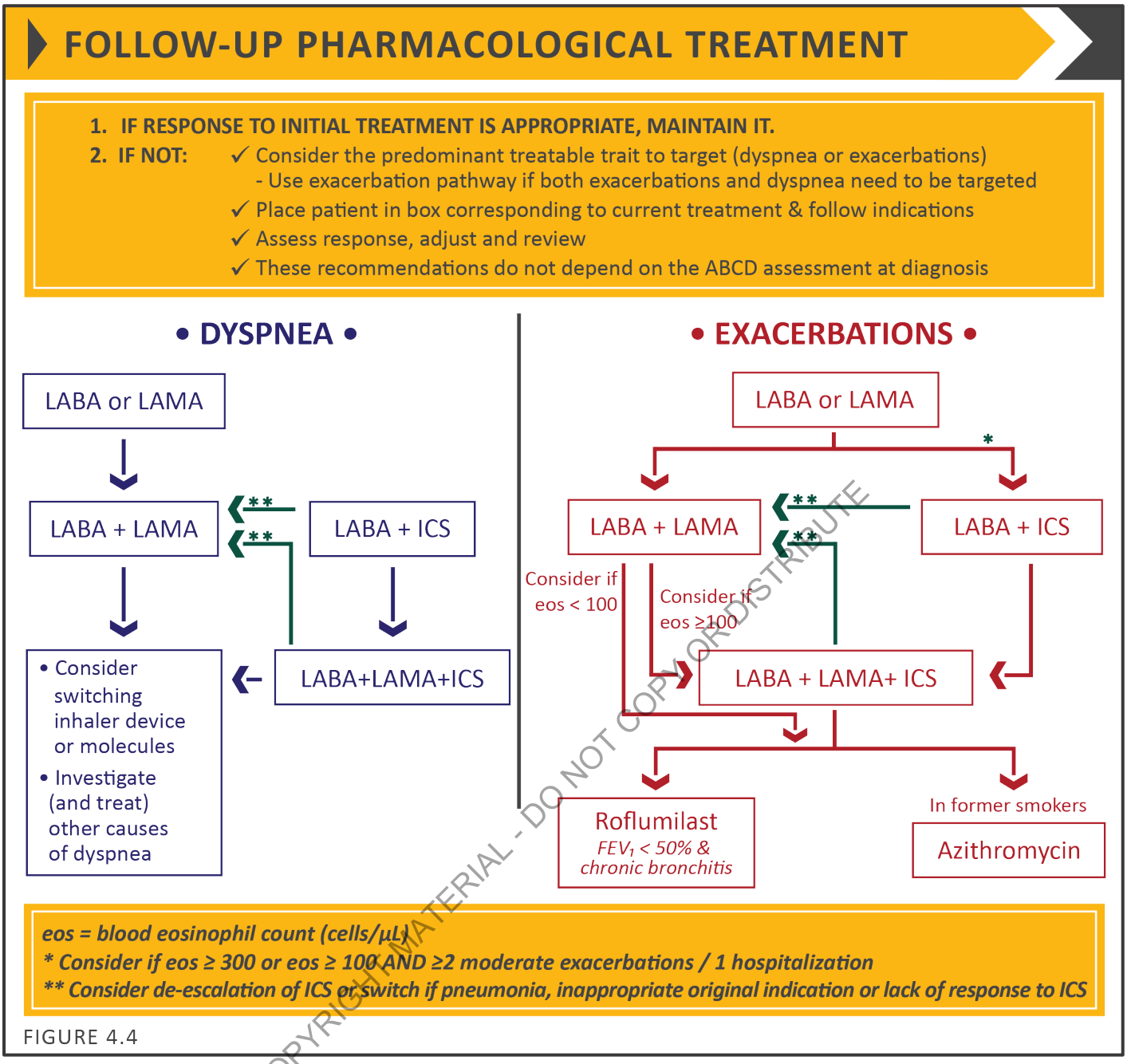



FIGURE 4.4



**Figure 4.4** suggests escalation and de-escalation strategies based on available efficacy as well as safety data. The response to treatment escalation should always be reviewed, and de-escalation should be considered if there is a lack of clinical benefit and/or side effects occur. De-escalation may also be considered in COPD patients receiving treatment who return with resolution of some symptoms that subsequently may require less therapy. Patients, in whom treatment modification is considered, in particular de-escalation, should be undertaken 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.

### *Initial pharmacological management*

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

#### *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.

► This should be continued if benefit is documented.

### Group B

► Initial therapy should consist of a long acting bronchodilator. Long-acting inhaled bronchodilators are superior to short-acting bronchodilators taken as needed i.e., *pro re nata* (prn) and are therefore recommended.[5,6]

► There is no evidence to recommend one class of long-acting bronchodilators over another 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.

► For patients with severe breathlessness initial therapy with two bronchodilators may be considered.[7]

► Group B patients are likely to have comorbidities that may add to their symptomatology and impact their prognosis, and these possibilities should be investigated.[8,9]

### Group C

► Initial therapy should consist of a single long acting bronchodilator. In two head-to-head comparisons[10,11] the tested LAMA was superior to the LABA regarding exacerbation prevention (for details see **Chapter 3**) therefore we recommend starting therapy with a LAMA in this group.

### Group D

► In general, therapy can be started with a LAMA as it has effects on both breathlessness and exacerbations (see **Chapter 3**).

► For patients with more severe symptoms (order of magnitude of CAT™ ≥ 20), especially driven by greater dyspnea and / or exercise limitation, LABA/LAMA may be chosen as initial treatment based on studies with patient reported outcomes as the primary endpoint where LABA/LAMA combinations showed superior results compared to the single substances (see **Chapter 3**). An advantage of LABA/LAMA over LAMA for exacerbation prevention has not been consistently demonstrated, so the decision to use LABA/LAMA as initial treatment should be guided by the level of symptoms.

► In some patients, initial therapy with LABA/ICS may be the first choice; this treatment has the greatest likelihood of reducing exacerbations in patients with blood eosinophil counts ≥ 300 cells/µL. LABA/ICS may also be first choice in COPD patients with a history of asthma.

► ICS may cause side effects such as pneumonia,[10,12] so should be used as initial therapy only after the possible clinical benefits versus risks have been considered.

### *Follow-up pharmacological management*

The follow-up pharmacological treatment algorithm (**Figure 4.4**) 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 treat primarily dyspnea/exercise limitation or prevent exacerbations further should be evaluated. If a change in treatment is considered necessary then select the corresponding algorithm for dyspnea (**Figure 4.4** left column) or exacerbations (**Figure 4.4** 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 the current treatment.

Follow up pharmacological management should be guided by the principles of first ***review*** and ***assess***, then ***adjust*** if needed:

► Review
- Review symptoms (dyspnea) and exacerbation risk.

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

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

### ***Dyspnea***

► For patients with persistent breathlessness or exercise limitation on ***long acting bronchodilator*** monotherapy,[13] the use of two bronchodilators is recommended.

- If the addition of a second long acting bronchodilator does not improve symptoms, we suggest the treatment could be stepped down again to monotherapy. Switching inhaler device or molecules can also be considered.

► For patients with persistent breathlessness or exercise limitation on ***LABA/ICS*** treatment, LAMA can be added to escalate to triple therapy.

- Alternatively, switching from LABA/ICS to LABA/LAMA should be considered if the original indication for ICS was inappropriate (e.g., an ICS was used to treat symptoms in the absence of a history of exacerbations), or there has been a lack of response to ICS treatment, or if ICS side effects warrant discontinuation.

► 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.



### ***Exacerbations***

► For patients with persistent exacerbations on ***long acting bronchodilator*** monotherapy, escalation to either LABA/LAMA or LABA/ICS is recommended. LABA/ICS may be preferred for patients with a history or findings suggestive of asthma. Blood eosinophil counts may identify patients with a greater likelihood of a beneficial response to ICS. For patients with one exacerbation per year, a peripheral blood level ≥ 300 eosinophils/µL identifies patients more likely to respond to LABA/ICS treatment.[14,15] For patients with ≥ 2 moderate exacerbations per year or at least one severe exacerbation requiring hospitalization in the prior year, LABA/ICS treatment can be considered at blood eosinophil counts ≥ 100 cells/µL, as ICS effects are more pronounced in patients with greater exacerbation frequency and/or severity.[16]

► In patients who develop further exacerbations on **LABA/LAMA** therapy we suggest two alternative pathways. Blood eosinophil counts < 100 cells/µL can be used to predict a low likelihood of a beneficial ICS response:
- 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.

- Add roflumilast or azithromycin (see below) if blood eosinophils < 100 cells/µL.

► In patients who develop further exacerbations on **LABA/ICS** therapy, we recommend escalation to triple therapy by adding a LAMA.[16,17] Alternatively, treatment can be switched to LABA/LAMA if there has been a lack of response to

ICS treatment, or if ICS side effects warrant discontinuation.

- If patients treated with **LABA/LAMA/ICS** who still have exacerbations the following options may be considered:
  - **Add roflumilast.** This may be considered in patients with an $FEV_1$ < 50% predicted and chronic bronchitis,[18] particularly if they have experienced at least one hospitalization for an exacerbation in the previous year.[19,20]
  - **Add a macrolide.** The best available evidence exists for the use of azithromycin, especially in those who are not current smokers.[21,22] Consideration to the development of resistant organisms should be factored into decision-making.
  - **Stopping ICS.** This can be considered if there are adverse effects (such as pneumonia) or a reported lack of efficacy. However, a blood eosinophil count ≥ 300 cells /µL identifies patients with the greatest likelihood of experiencing more exacerbations after ICS withdrawal and who subsequently should be followed closely for relapse of exacerbations.[23,24]

## TREATMENT OF STABLE COPD: NON-PHARMACOLOGICAL TREATMENT



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, prescribe vaccinations, empower adherence to prescribed medication, ensure proper inhaler technique, promote physical activity and refer patients (GOLD B - GOLD D) to pulmonary rehabilitation.

Some relevant non-pharmacological measures based on the GOLD group **AT DIAGNOSIS** are summarized in **Table 4.8**.

**NON-PHARMACOLOGIC MANAGEMENT OF COPD***

| PATIENT GROUP | ESSENTIAL | RECOMMENDED | DEPENDING ON LOCAL GUIDELINES |
|---|---|---|---|
| A | Smoking Cessation (can include pharmacologic treatment) | Physical Activity | Flu Vaccination<br>Pneumococcal Vaccination<br>Pertussis Vaccination |
| B, C and D | Smoking Cessation (can include pharmacologic treatment)<br>Pulmonary Rehabilitation | Physical Activity | Flu Vaccination<br>Pneumococcal Vaccination<br>Pertussis Vaccination |

*Can include pharmacologic treatment.

TABLE 4.8

Recommendations for **FOLLOW UP** non-pharmacological treatments are based on patient's treatable traits e.g., symptoms and exacerbations (**Table 4.9**).

## Education and 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.[25] 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,[26,27] but it can play a role in improving skills, ability to cope with illness, and health status.[28]



### FOLLOW-UP OF NON-PHARMACOLOGICAL TREATMENT

**1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT AND OFFER:**

- Flu 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 •

- Self-management education (written action plan) with integrated self-management regarding:
  - Breathlessness and energy conservation techniques, and stress management strategies
- Pulmonary rehabilitation (PR) program and/or maintenance exercise program post PR

#### • EXACERBATIONS •

- 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

**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

TABLE 4.9

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 well-being, 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.[29] 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.

## 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.[30] This leads to a downward spiral of inactivity which predisposes patients to reduced quality of life, increased rates of hospitalization and mortality.[31-33] As such, there has been tremendous interest in implementing behavior-targeted interventions with the aim of improving physical activity[34] and these should be encouraged.[31] 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. The use of an internet-mediated intervention may benefit patients with COPD with low baseline self-efficacy to increase physical activity.[35] 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. A randomized clinical trial that evaluated the long-term effectiveness of a community-based physical activity coaching intervention in patients with COPD exacerbation history showed no benefits in acute care use or survival.[36] 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.[37]



## Pulmonary rehabilitation programs

Patients with high symptom burden and risk of exacerbations (Groups B, C and D), 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.[28,38,39]

There are key time points when it may be appropriate to consider referral: (a) at diagnosis; (b) at discharge following hospitalization for an exacerbation; and (c) when symptoms are found to be progressively deteriorating. These could relate to each patient at different time points of the disease trajectory.

Because benefits diminish over time if activity and other positively adaptive behaviors are not continued, patients should be offered a maintenance program, or at least supported sufficiently to increase and maintain physical activity in daily living. If deterioration is noted in physical or functional health status a year or more after improvement from an initial pulmonary rehabilitation program, it may be feasible to refer the patient for additional rehabilitation.

The components of pulmonary rehabilitation may vary but evidence-based best practice for program delivery includes:

structured and supervised exercise training, smoking cessation; nutrition counseling; and self-management education. Further details and recommendations on the components of pulmonary rehabilitation, the program organization (duration and structure) and evaluation are presented in **Chapter 3**.[28]

The World Health Organization (WHO) "Rehabilitation 2030: a call for action"[40] makes the case for accessible and affordable rehabilitation as an essential component of health services, stating that this is crucial to achieve Sustainable Development Goal 3: 'good health and wellbeing'. Although there is clear potential for pulmonary rehabilitation to improve health, wellbeing and economic productivity, research is necessary to develop culturally appropriate pulmonary rehabilitation in low- and middle-income countries; programs are likely to be different across cultures and countries.[41] The COVID-19 pandemic has led to the need to modify the operation of pulmonary rehabilitation programs under alternative conditions to enable physical distancing. Home-based pulmonary rehabilitation programs with remote supervision may facilitate earlier access post-discharge and may be cost-effective.[42-44]

## 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.[45] A combination of constant load or interval training with strength training provides better outcomes than either method alone.[46]

Where possible, endurance exercise training to 60-80% of the symptom-limited maximum work or heart rate is preferred,[47] or to a Borg-rated dyspnea or fatigue score of 4 to 6 (moderate to severe).[48] 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.[49,50]

Exercise training can be enhanced by optimizing bronchodilators,[51] since both LAMA and LABA have shown reduced resting and dynamic hyperinflation. These changes contribute to better training effects.[52,53] Adding strength training to aerobic training is effective in improving strength, but does not improve health status or exercise tolerance.[54] Upper extremities exercise training improves arm strength and endurance, and results in improved functional capacity for upper extremity activities.[55] Exercise capacity may also be improved by whole-body vibration training.[56]

Inspiratory muscle training increases strength of inspiratory muscles,[57] 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.[58,59,60]



***Assessment and follow-up.*** 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.[61] 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)*[62] and the *Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Questionnaire*[63] have been used to improve identification and treatment of anxious and depressed patients.

## End-of-life and palliative care

The goal of palliative care is to relieve the suffering of patients and their families by the comprehensive assessment and treatment of physical, psychosocial, and spiritual symptoms experienced by patients.

Patients with a chronic life-limiting illness like COPD should be informed that, should they become critically ill, they or their family members may be in a position where they would need to decide whether a course of intensive care is likely to achieve their personal goals of care, and they are willing to accept the burdens of such treatment.

Clinicians should develop and implement methods to help patients and their families to make informed choices that are consistent with patients' values. Simple, structured approaches to facilitate these conversations may help to improve the occurrence and quality of communication from the patients' perspective.[64]

## Nutritional support

For malnourished patients with COPD nutritional supplementation is recommended. This is based on systematic review findings of positive effects on body weight, fat mass and fat-free mass when nutritional supplementation is provided alone to COPD patients (especially if malnourished) and when used as an adjunct to exercise training. Optimal supplementation, including amount and duration, are not clearly established.[65]

## Vaccination

Influenza vaccination is recommended for all patients with COPD.[66]

Pneumococcal vaccinations, PCV13 and PPSV23, are recommended for all patients > 65 years of age. The PPSV23 is also recommended for younger COPD patients with significant comorbid conditions including chronic heart or lung disease.[67]

## Oxygen therapy

Long-term oxygen therapy is indicated for stable patients who have:

- $PaO_2$ at or below 7.3 kPa (55 mmHg) or $SaO_2$ at or below 88%, with or without hypercapnia confirmed twice over a three-week period; or
- $PaO_2$ between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), 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 long-term oxygen therapy (LTOT) the patient should be re-evaluated after 60 to 90 days with repeat arterial blood gas (ABG) or oxygen saturation while inspiring the same level of oxygen or room air to determine if oxygen is therapeutic and still indicated, respectively. An appropriate algorithm for the prescription of oxygen to COPD patients is shown in **Figure 4.5**.

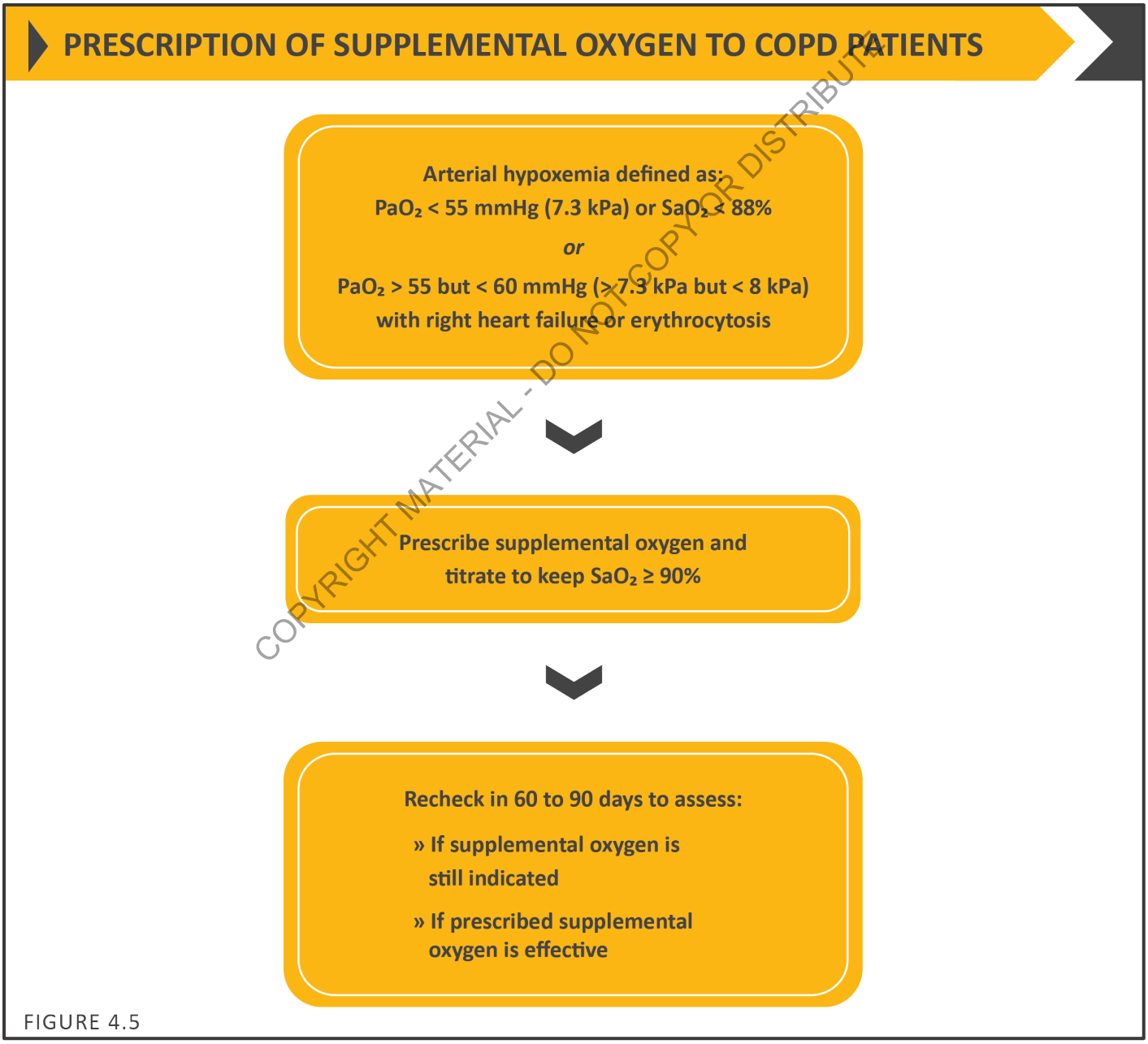



FIGURE 4.5

## Ventilatory support

NIV is occasionally used in patients with stable very severe COPD. NIV may be considered of some use in a selected group of patients, particularly in those with pronounced daytime hypercapnia and recent hospitalization, although systematic review is unable to support or refute this.[68] However, in patients with both COPD and obstructive sleep apnea there are clear indications for continuous positive airway pressure (CPAP).[69]

## Interventional bronchoscopy and surgery

- In selected patients with heterogeneous or homogenous emphysema and significant hyperinflation refractory to optimized medical care, surgical or bronchoscopic modes of lung volume reduction (e.g., endobronchial one-way valves, lung coils or thermal ablation) may be considered.[70] 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.

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. Vapor ablation therapy is the only lung reduction therapy that has been reported to be successfully performed at the segmental rather than lobar level.[71]

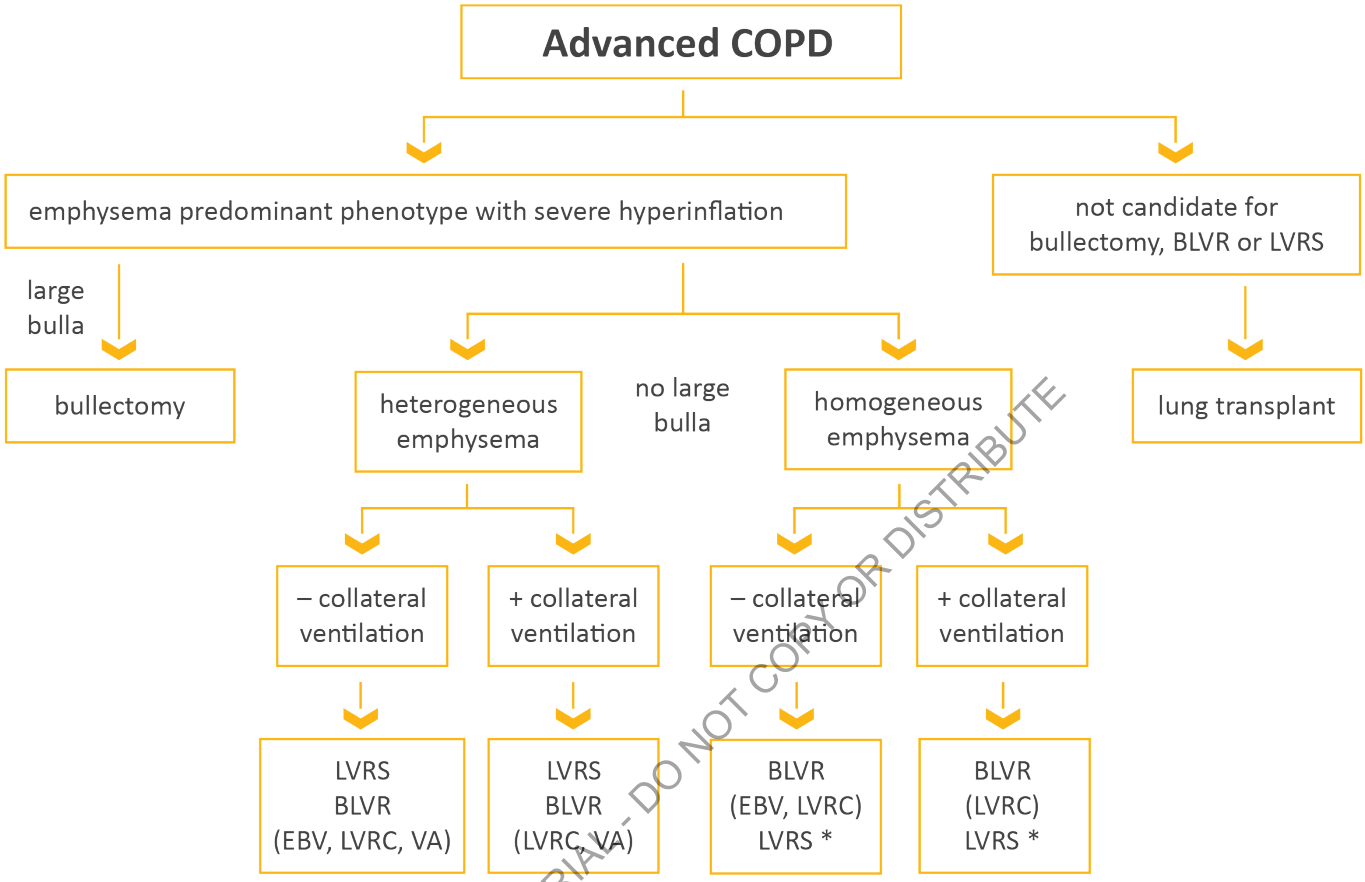
In patients with fissure integrity or lack of interlobar collateral ventilation based on physiologic assessment, endobronchial valve, lung coil treatment, vapor ablation therapy or LVRS could all be useful. In patients with lack of fissure integrity or interlobar collateral ventilation, vapor ablation, lung coil therapy or LVRS may be performed but endobronchial valve therapy is not useful. Patients with heterogeneous upper lobe predominant emphysema may be candidates for either LVRS or bronchoscopic lung reduction approaches. The presence of interlobar collateral ventilation would exclude the use of endobronchial valve therapy but lung coil or vapor ablation therapies could be considered along with LVRS. Patients with homogenous emphysema are not routinely considered candidates for LVRS at most centers, however, bronchoscopic lung reduction can be successful using endobronchial valve, vapor ablation or coil therapies. Again the presence of interlobar collateral ventilation is important in selecting endobronchial valve as the intervention of choice. An algorithm depicting an overview of various interventions is shown in **Figure 4.6**.



Criteria for referral for lung transplantation include COPD with progressive disease, not a candidate for endoscopic or surgical lung volume reduction, BODE index of 5 to 6, $Pco_2$ > 50 mmHg or 6.6 kPa and/or $PaO_2$ < 60 mmHg or 8.0 kPa, and $FEV_1$ < 25% predicted.[72] Recommended criteria for listing include one of the following: BODE index > 7, $FEV_1$ < 15-20% predicted, three or more severe exacerbations during the preceding year, one severe exacerbation with acute hypercapnic respiratory failure, or moderate to severe pulmonary hypertension.[72,73] Key points for the use of non-pharmacological treatments are given in **Table 4.10**.

## INTERVENTIONAL BRONCHOSCOPIC AND SURGICAL TREATMENTS FOR COPD

Overview of various therapies used to treat patients with COPD and emphysema worldwide. Note that all therapies are not approved for clinical care in all countries. Additionally, the effects of BLVR on survival or other long term outcomes or comparison to LVRS are unknown.




Definition of Abbreviations: BLVR, Bronchoscopic Lung Volume Reduction, EBV, endobronchial Valve, LVRS, Lung volume reduction surgery, LVRC, Lung volume reduction coil, VA, Vapor ablation

*at some but not all centers

FIGURE 4.6

## KEY POINTS FOR THE USE OF NON-PHARMACOLOGICAL TREATMENTS

### EDUCATION, SELF-MANAGEMENT AND PULMONARY REHABILITATION

- Education is needed to change patient's knowledge but there is no evidence that used alone it will change patient behavior .
- Education self-management with the support of a case manager with or without the use of a written action plan is recommended for the prevention of exacerbation complications such as hospital admissions **(Evidence B)**.
- Rehabilitation is indicated in all patients with relevant symptoms and/or a high risk for exacerbation **(Evidence A)**.
- Physical activity is a strong predictor of mortality **(Evidence A)**. Patients should be encouraged to increase the level of physical activity although we still don't know how to best insure the likelihood of success.

### VACCINATION

- Influenza vaccination is recommended for all patients with COPD **(Evidence A)**.
- Pneumococcal vaccination: the PCV13 and PPSV23 are recommended for all patients> 65 years of age, and in younger patients with significant comorbid conditions including chronic heart or lung disease **(Evidence B)**.

### NUTRITION

- Nutritional supplementation should be considered in malnourished patients with COPD **(Evidence B)**.

### END OF LIFE AND PALLIATIVE CARE

- 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)**.

### TREATMENT OF HYPOXEMIA

- In patients with severe resting hypoxemia long-term oxygen therapy is indicated **(Evidence A)**.
- In patients with stable COPD and resting or exercise-induced moderate desaturation, long term oxygen treatment should not be routinely prescribed. However, individual patient factors may be considered when evaluating the patient's needs for supplemental oxygen **(Evidence A)**.
- Resting oxygenation at sea level does not exclude the development of severe hypoxemia when travelling by air **(Evidence C)**.

### TREATMENT OF HYPERCAPNIA

- In patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure, long term noninvasive ventilation may be considered **(Evidence B)**.

### INTERVENTION BRONCHOSCOPY AND SURGERY

- Lung volume reduction surgery should be considered in selected patients with upper-lobe emphysema **(Evidence A)**.
- In selected patients with a large bulla surgical bullectomy may be considered **(Evidence C)**.
- In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, quality of life and lung function at 6-12 months following treatment. Endobronchial valves **(Evidence A)**; Lung coils **(Evidence B)**; Vapor ablation **(Evidence B)**.
- In patients with very severe COPD (progressive disease, BODE score of 7 to 10, and not candidate 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 mm Hg); (2) pulmonary hypertension and/or cor pulmonale, despite oxyqen therapy; or (3) $FEV_1$ < 20% and either DLCO < 20% or homogenous distribution of emphysema **(Evidence C)**.

TABLE 4.10

# 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 limitation should be monitored to determine when to modify management and to identify any complications and/or comorbidities that may develop. Based on current literature, comprehensive self-management or routine monitoring has not shown long-term benefits in terms of health status over usual care alone for COPD patients in general practice.[74]

## Monitoring disease progression and development of complications and/or comorbidities

***Measurements.*** Decline in $FEV_1$ can be tracked by spirometry performed at least once a year to identify patients who are declining quickly, although other lung function parameters reflecting hyperinflation and gas transfer may also be informative.

Functional capacity as measured by a timed walking test (6-minute walking distance or shuttle-walking test) provides additional information regarding prognosis.[75,76] 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.

***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. Questionnaires such as the COPD Assessment Test (CAT™)[77] can be used; trends and changes are more valuable than single measurements.

***Exacerbations.*** The frequency, severity, type and likely causes of all exacerbations[78] 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.

***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.

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



## Pharmacotherapy and other medical treatment

In order to adjust therapy appropriately as the disease progresses, each follow-up visit should include a discussion of the current therapeutic regimen. Monitoring should focus on:

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

Treatment modifications should be recommended (**Figure 4.2**).

## Comorbidities

Those symptoms that may indicate the worsening or development of another comorbid condition such as obstructive sleep apnea, congestive heart failure, ischemic heart disease, etc. should be recorded and an approach to their evaluation and treatment enacted. Therefore, monitoring is recommended for conditions including heart failure, ischemic heart disease, arrhythmias, osteoporosis, depression/anxiety, and lung cancer (see also **Chapter 6**).

## Surgery in the COPD patient

***General.*** Postoperative pulmonary complications are as important and common as postoperative cardiac complications and, consequently, are a key component of the increased risk posed by surgery in COPD patients.[79] 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 limitation, which all potentially result in acute respiratory failure and aggravation of COPD.[80-82]

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.[82] 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%.[83] 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.[84,85] 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.[84,85]

The risk of postoperative complications from lung resection appears to be increased in patients with decreased predicted postoperative pulmonary function ($FEV_1$ 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.



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# CHAPTER 5: MANAGEMENT OF EXACERBATIONS

**OVERALL KEY POINTS:**

- *An exacerbation of COPD is defined as an acute worsening of respiratory symptoms that results in additional therapy.*
- *As the symptoms are not specific to COPD relevant differential diagnoses should be considered.*
- *Exacerbations of COPD can be precipitated by several factors. The most common causes are respiratory tract infections.*
- *The goal for treatment of COPD exacerbations is 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 acute exacerbation.*
- *Maintenance therapy with long-acting bronchodilators should be initiated as soon as possible before hospital discharge.*
- *Systemic corticosteroids can improve lung function (FEV$_1$), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not be more than 5-7 days.*
- *Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be 5-7 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.*
- *Following an exacerbation, appropriate measures for exacerbation prevention should be initiated (see **Chapter 3** and **Chapter 4**).*



## INTRODUCTION

An exacerbation of chronic obstructive pulmonary disease (COPD) is defined as an acute worsening of respiratory symptoms that results in additional therapy. [1,2] 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. COPD exacerbations are complex events 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.[3] As other comorbidities that may worsen respiratory symptoms are common in COPD patients, clinical assessment to rule out differential diagnoses should be considered before diagnosis of a COPD exacerbation (**Table 5.1**).

## DIFFERENTIAL DIAGNOSIS OF COPD EXACERBATION

**WHEN THERE IS CLINICAL SUSPICION OF THE FOLLOWING ACUTE CONDITIONS, CONSIDER THE FOLLOWING INVESTIGATIONS:**

**PNEUMONIA**
- Chest radiograph
- Assessment of C-reactive protein (CRP) and/or procalcitonin

**PNEUMOTHORAX**
- Chest radiograph or ultrasound

**PLEURAL EFFUSION**
- Chest radiograph or ultrasound

**PULMONARY EMBOLISM**
- D-dimer and/or Doppler sonogram of lower extremities
- Chest tomography – pulmonary embolism protocol

**PULMONARY EDEMA DUE TO CARDIAC RELATED CONDITIONS**
- Electrocardiogram and cardiac ultrasound
- Cardiac enzymes

**CARDIAC ARRHYTHMIAS – ATRIAL FIBRILLATION/FLUTTER**
- Electrocardiogram

TABLE 5.1



Exacerbations are classified as:

- Mild (treated with short acting bronchodilators only, SABDs)
- Moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) or
- Severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure.

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.[4,5] 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.[6]

Exacerbations are mainly triggered by respiratory viral infections although bacterial infections and environmental factors such as pollution and ambient temperature may also initiate and/or amplify these events.[7] Short-term exposure to fine particulate matter (PM2.5) is associated with increased hospitalizations for acute exacerbations and increased mortality of COPD.[8-10] The most common virus isolated is human rhinovirus (the cause of the common cold) and can be detected for up to a week after an exacerbation onset.[7,11] When associated with viral infections, exacerbations are often more severe, last longer and precipitate more hospitalizations, as seen during winter.

Exacerbations can be associated with increased sputum production and, if purulent, there are studies that

demonstrated increased bacteria in the sputum[3,11,12] There is reasonable evidence to support the concept that eosinophils are increased in the airways, lung, and blood in a significant proportion of patients with COPD. Furthermore, eosinophil numbers increase together with neutrophils and other inflammatory cells during exacerbations in a proportion of subjects with COPD exacerbations.[13-15] The presence of sputum eosinophilia has been related to susceptibility to viral infection.[12] It has been suggested that exacerbations associated with an increase in sputum or blood eosinophils may be more responsive to systemic steroids[16] although more prospective trials are needed to test this hypothesis.[16]

During a COPD exacerbation, symptoms usually last between 7 to 10 days, but some events may last longer. At 8 weeks, 20% of patients have not recovered to their pre-exacerbation state.[17] It is well established that COPD exacerbations contribute to disease progression.[18] Disease progression is even more likely if recovery from exacerbations is slow.[19] Exacerbations can also cluster in time and once a COPD patient experiences an exacerbation, they will show increased susceptibility to another event[20,21] (see **Chapter 2**).

Some COPD patients are particularly susceptible to frequent exacerbations (defined as two or more exacerbations per year), and these patients have been shown to have worse health status and morbidity than patients with less frequent exacerbations.[2] Patients at high risk of frequent exacerbations can be recognized across all disease severity groups. 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,[22] suggesting that a perception of breathing difficulty may contribute to precipitating the respiratory symptoms of an exacerbation 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.[20] 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 $FEV_1$.[23]



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),[24] a greater percentage of emphysema or airway wall thickness[25] measured by chest CT imaging and the presence of chronic bronchitis.[26,27]

Vitamin D has an immune-modulating role and has been implicated in the pathophysiology of exacerbations. As with all chronic diseases vitamin D levels are lower in COPD than in health. Studies have shown that supplementation in subjects with severe deficiency results in a 50% reduction in episodes and hospital admission.[28] 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.[29] 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. [15,23,24]

The indications for assessing the need for hospitalization during a COPD exacerbation are shown in **Table 5.2**. When patients with a COPD exacerbation come to the emergency department, 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 the respiratory or intensive care unit of the hospital. Otherwise, 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 **Table 5.3**.

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.[30]

***No respiratory failure:*** Respiratory rate: 20-30 breaths per minute; no use of accessory respiratory muscles; no changes in mental status; hypoxemia improved with supplemental oxygen given via Venturi mask 28-35% inspired oxygen ($FiO_2$); no increase in $PaCO_2$.

***Acute respiratory failure – non-life-threatening:*** Respiratory rate: > 30 breaths per minute; using accessory respiratory muscles; no change in mental status; hypoxemia improved with supplemental oxygen via Venturi mask 24-35% $FiO_2$; hypercarbia i.e., $PaCO_2$ increased compared with baseline or elevated 50-60 mmHg.

***Acute respiratory failure – life-threatening:*** Respiratory rate: > 30 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).



## POTENTIAL INDICATIONS FOR HOSPITALIZATION ASSESSMENT*

- Severe symptoms such as sudden worsening of resting dyspnea, high respiratory rate, decreased oxygen saturation, confusion, drowsiness.
- Acute respiratory failure.
- Onset of new physical signs (e.g., cyanosis, peripheral edema).
- Failure of an exacerbation to respond to initial medical management.
- Presence of serious comorbidities (e.g., heart failure, newly occurring arrhythmias, etc.).
- Insufficient home support.

*Local resources need to be considered.

TABLE 5.2

Long-term prognosis following hospitalization for COPD exacerbation is poor, with a five-year mortality rate of about 50%.[31] 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.[32-34] 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.[35] Mortality risk may be heightened during spells of cold weather.[36]

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.[37]

Key points for the management of all exacerbations are given in **Table 5.4.**

## MANAGEMENT OF SEVERE BUT NOT LIFE-THREATENING EXACERBATIONS*

- 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-active 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.

TABLE 5.3



## KEY POINTS FOR THE MANAGEMENT OF EXACERBATIONS

- Short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation **(Evidence C)**.
- Systemic corticosteroids can improve lung function ($FEV_1$), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not be more than 5-7 days **(Evidence A)**.
- Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be 5-7 days **(Evidence B)**.
- Methylxanthines are not recommended due to increased side effect profiles **(Evidence B)**.
- 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 **(Evidence A)**.

TABLE 5.4

## 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.[38,39] A systematic review of the route of delivery of short-acting bronchodilators found no significant differences in $FEV_1$ between using metered dose inhalers (MDI) (with or without a spacer device) or nebulizers to deliver the agent,[40,41] 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 inhaled corticosteroids 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.[42,43] 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.[44]

***Glucocorticoids.*** Data from studies indicate that systemic glucocorticoids in COPD exacerbations shorten recovery time and improve lung function ($FEV_1$). They also improve oxygenation,[45-48] the risk of early relapse, treatment failure,[49] and the length of hospitalization.[45,47,50] A dose of 40 mg prednisone per day for 5 days is recommended.[51] One observational study suggests that longer courses of oral corticosteroids for COPD exacerbations are associated with an increased risk of pneumonia and mortality.[52] Therapy with oral prednisolone is equally effective to intravenous administration.[53] Nebulized budesonide alone may be a suitable alternative for treatment of exacerbations in some patients,[46,54,55] and provides similar benefits to intravenous methylprednisolone, although the choice between these options may depend on local cost issues.[56] Intensified combination therapy with LABA/ICS for 10 days at URTI onset could be associated with a reduction of exacerbations, particularly in patients with severe disease.[57] Even short bursts of corticosteroids are associated with subsequent increased risk of pneumonia, sepsis and death[58] 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[13,16,20,59] and more trials of steroid-sparing treatment regimens are required.



***Antibiotics.*** Although the infectious agents in COPD exacerbations can be viral or bacterial,[7,60] the use of antibiotics in exacerbations remains controversial.[61-63] 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.[62,63] 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.[63]

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%.[64] The review provides evidence to treat moderately or severely ill patients with COPD exacerbations and increased cough and sputum purulence with antibiotics.[64,65] These data are supported by more RCTs in patients with diagnoses of moderate COPD.[66] In an RCT, the addition of doxycycline to oral corticosteroid an outpatient setting did not prolong time to next exacerbation.[67] 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.[68,69] A randomized trial found a marked reduction in antibiotic prescriptions without impaired outcomes in UK primary care outpatients with AECOPD in whom antibiotics prescriptions were guided by point-of-care CRP testing.[70] Another trial in patients hospitalized for acute 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.[71]

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.[72] 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.[73-75] 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.[76] 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.[77] 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).[3,7] The recommended length of antibiotic therapy is 5-7 days.[78]

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, or tetracycline. In patients with frequent exacerbations, severe airflow limitation,[79,80] and/or exacerbations requiring mechanical ventilation,[81] 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. At all times, healthcare providers should strongly enforce the need for smoking cessation. Given that patients hospitalized with COPD exacerbations are at increased risk of deep vein thrombosis and pulmonary proca,[82,83] prophylactic measures for thromboembolism should be instituted.[84,85]

## 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%.[86] Once oxygen is started, blood gases should be checked frequently to ensure satisfactory oxygenation without carbon dioxide retention and/or worsening acidosis. A study demonstrated that venous blood gas to assess bicarbonate levels and pH is accurate when compared with arterial blood gas assessment.[87] 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 limitation was not reported.[87] Venturi masks offer more accurate and controlled delivery of oxygen than do nasal prongs.[39]

***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.[88] 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.[89,90] These physiologic benefits positively improve oxygenation and clinical outcomes in patients with acute hypoxemic respiratory failure.[89-92] 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.[89,93-95] 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.[96] There is a need for well-designed, prospective, randomized and controlled multicenter trials to study the effects of HFNT in patients 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) (**Table 5.5**). 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.[38]



**INDICATIONS FOR RESPIRATORY OR MEDICAL INTENSIVE CARE UNIT ADMISSION***

- Severe dyspnea that responds inadequately to initial emergency therapy.
- Changes in mental status (confusion, lethargy, coma).
- Persistent or worsening hypoxemia ($PaO_2$ < 5.3 kPa or 40mmHg) and/or severe/worsening respiratory acidosis (pH < 7.25) despite supplemental oxygen and noninvasive ventilation.
- Need for invasive mechanical ventilation.
- Hemodynamic instability - need for vasopressors.

*Local resources need to be considered.

TABLE 5.5

***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%.[97-101] 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.[98,102-104] 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.[105] The indications for NIV[101] are summarized in **Table 5.6**.

## INDICATIONS FOR NONINVASIVE MECHANICAL VENTILATION (NIV)

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.

TABLE 5.6

## INDICATIONS FOR INVASIVE MECHANICAL VENTILATION

- 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.

TABLE 5.7



***Invasive mechanical ventilation.*** The indications for initiating invasive mechanical ventilation during an exacerbation are shown in **Table 5.7**, and include failure of an initial trial of NIV.[106] 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.[106] 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.[99] 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.[99] 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.[107] 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.[108] A large study of COPD patients with acute respiratory failure reported in-hospital mortality of 17-49%.[109] Further deaths were reported over the next 12 months, particularly among those patients who had poor lung function before invasive ventilation ($FEV_1$ < 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.[110]

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.[111] 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.[112] Mortality relates to patient age, the presence of acidotic respiratory failure, the need for ventilatory support and comorbidities including anxiety and depression.[113]

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 (**Table 5.8**).[114] While these measures all seem sensible there is insufficient data that they influence either readmission rates or short-term mortality[111,113,115,116] and there is little evidence of cost-effectiveness.[113] One RCT showed that telemonitoring did not change hospitalization or exacerbation rates in patients with COPD.[117] 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.[118]

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.[116] However, other data suggest that early rehabilitation post hospital discharge (i.e., < 4 weeks) may be associated with improved survival.[119]

Early follow-up (within one month) following discharge should be undertaken when possible and has been related to less exacerbation-related readmissions.[120] 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.[121] 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.[122]

CT assessment to determine the presence of bronchiectasis and emphysema should be done in patients with recurrent exacerbations/ and or hospitalizations.[123,124] A further detailed assessment of the presence and management of comorbidities should also be undertaken (**Table 5.8**).[86]

## Prevention of exacerbations

After an acute exacerbation, appropriate measures for prevention of further exacerbations should be initiated (**Table 5.4** and **Table 5.9**). For the following treatment modalities significant effects on exacerbation risk/frequency could be shown in clinical trials. For details and references refer to **Chapter 3** and **Chapter 4**.

## DISCHARGE CRITERIA AND RECOMMENDATIONS FOR FOLLOW-UP

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

### 1 – 4 WEEKS FOLLOW-UP

- Evaluate ability to cope in his/her usual environment.
- Review and understanding treatment regimen.
- Reassessment of inhaler techniques.
- Reassess need for long-term oxygen.
- Document the capacity to do physical activity and activities of daily living.
- 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 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: $FEV_1$.
- Document symptoms: CAT or mMRC.
- Determine status of comorbidities.

TABLE 5.8

## INTERVENTIONS THAT REDUCE THE FREQUENCY OF COPD EXACERBATIONS

| INTERVENTION CLASS | INTERVENTION |
|---|---|
| Bronchodilators | LABAs<br>LAMAs<br>LABA + LAMA |
| Corticosteroid-containing regimens | LABA + ICS<br>LABA + LAMA + ICS |
| Anti-inflammatory (non-steroid) | Roflumilast |
| Anti-infectives | Vaccines<br>Long Term Macrolides |
| Mucoregulators | N-acetylcysteine<br>Carbocysteine<br>Erdosteine |
| Various others | Smoking Cessation<br>Rehabilitation<br>Lung Volume Reduction<br>Vitamin D |

TABLE 5.9



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# CHAPTER 6: COPD AND COMORBIDITIES

**OVERALL 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 patients with COPD and is a major cause of death.*
- *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.[1-8] 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.[9] This 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[10] 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 outcome of other disorders. For example, patients hospitalized with congestive heart failure or undergoing cardiac procedures such as coronary artery bypass grafting have greater morbidity and mortality when COPD is present compared to when it is absent.[11-13]

Below is a brief guide to the management of some common comorbidities occurring in patients 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)

### Heart failure

► The prevalence of systolic or diastolic heart failure in COPD patients ranges from 20 to 70%,[14] and its annual incidence 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.[15,16]

► Treatment with $ß_1$-blockers improves survival in heart failure and is recommended in patients with heart failure who also have COPD. Selective $ß_1$-blockers should be used, and only used, to treat patients with COPD for approved cardiovascular indications; not solely for the purpose of preventing exacerbations of COPD.[17]

► 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.[18]

### Ischaemic heart disease (IHD)

► Ischaemic heart disease should be considered in all COPD patients depending on their risk factor profile. The cardiovascular risk may be assessed by the global risk calculator, which can be found on the US National Heart Blood Lung Institute website[19] 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.[20] Hospitalization for an acute COPD exacerbation has been associated with 90-day mortality of acute myocardial infarction, ischemic stroke, and intracranial hemorrhage.[21] Patients who demonstrate abnormal cardiac troponins in isolation are at increased risk of adverse outcomes including short-term (30-day) and long-term mortality.[22,23]

► 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*. Atrial fibrillation is frequent and associated with a lower $FEV_1$.[24]

► 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.[25]

► The presence of atrial fibrillation does not alter the treatment of COPD. Bronchodilators have been previously described as potentially pro-arrhythmic agents[26,27]; however, available evidence suggests an overall acceptable safety profile for long-acting $beta_2$-agonists,[28] anticholinergic drugs (and inhaled corticosteroids).[29-36] Nevertheless, caution is advised when using short-acting $beta_2$-agonists[28,37] and theophylline, which may precipitate atrial fibrillation and make control of the ventricular response rate difficult.[38-40]

## Peripheral vascular disease

► Peripheral artery disease (PAD) is an atherosclerotic process that refers to the occlusion of the arteries in the lower limbs; PAD is commonly associated with atherosclerotic heart disease and may have significant implications for functional activity as well as quality of life in patients with COPD.[41]

► In a large cohort of patients 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%).[41]

► COPD patients with PAD reported a worse functional capacity and worse health status compared to those without PAD. Clinicians should consider PAD in patients 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.[9,42] Diastolic dysfunction as a result of optimally treated hypertension may be associated with exercise intolerance and mimic symptoms associated with an acute exacerbation thereby provoking hospitalization in COPD.[14] These data stress the importance of optimal blood pressure control in COPD patients with underlying hypertension.[43,44]

► 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 patients with COPD and increased cardiovascular risk beta-blockers either reduce the benefits of treatment with LABA or increase cardiovascular risk.[45]

► 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.[46] Unfortunately, the great majority of lung cancers are diagnosed at an advanced stage, resulting in poor overall survival.[47] 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.[42,48-50] 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.[51-53] Whether the spirometric severity of airflow obstruction is directly or inversely associated with a greater risk for lung cancer development remains controversial.[50,54] 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 subjects with the combination of emphysema diagnosed by CT and airflow obstruction determined by spirometry.[55,56]

The best preventive measure for lung cancer (as it is for COPD) is smoking prevention and in smokers, smoking cessation.[57] Several studies involving the use of low-dose chest computed tomography (LDCT) screening have shown improved survival in older subjects (aged between 55 and 74 years), current smokers or those who quit within the previous 15 years, with a smoking history of at least 30 pack-years).[58-60] Those studies were decisive for the recommendation by the United States Preventive Services Task Force (USPSTF) in favor of annual lung cancer screening

with low radiation dose CT.[61] This recommendation is supported by several major medical societies but 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.[62,63]

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.[64] On the other hand, one Danish study showed that being part of a lung cancer screening programme significantly promotes smoking abstinence[65] 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.[57] Smoking cessation interventions as part of CT scan screening programs could be of use (**Table 6.1**).

**COMMON RISK FACTORS FOR DEVELOPMENT OF LUNG CANCER**

- Age > 55
- Smoking history > 30 pack years
- Presence of emphysema by CT scan
- Presence of airflow limitation $FEV_1/FVC < 0.7$
- BMI < 25 kg/m$^2$
- Family history of lung cancer

TABLE 6.1



## Osteoporosis

► Osteoporosis is a major comorbidity[2,9] which is often under-diagnosed[66] and associated with poor health status and prognosis.

► Osteoporosis is often associated with emphysema,[67] decreased body mass index[68] and low fat-free mass.[69] 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.[70,71]

► Osteoporosis should be treated according to usual guidelines.

► COPD should be treated as usual despite the presence of osteoporosis. An association between inhaled corticosteroids 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

## Anxiety and depression

► Anxiety and depression are important comorbidities in COPD[72-75] and both are associated with a poor prognosis,[74,76] younger age, female sex, smoking, lower $FEV_1$, cough, higher SGRQ score, and a history of cardiovascular disease.[72,75,77]

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

► COPD should be treated as usual. The potential impact of pulmonary rehabilitation should be stressed as studies have found that physical exercise has a beneficial effect on depression in general.[78,79]

► COPD is very common in patients with other psychiatric illnesses, often under-diagnosed and treated.[80,81]

► A systematic review has shown that COPD patients are 1.9 times more likely to commit suicide than people without COPD.[82]

## 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.[3]

► The prevalence of metabolic syndrome has been estimated to be more than 30%.[83]

► 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.[84-86] 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,[87] but their value in preventing these events remains controversial most effective treatment for this condition in COPD has yet to be established.[88,89]



## Bronchiectasis

► With increasing use of computed tomography in the assessment of patients with COPD, the presence of previously unrecognized bronchiectasis is being identified.[90]

► Whether this diagnosis based on radiological criteria has the same impact as a clinical diagnosis of bronchiectasis remains unknown at present, although it is associated with longer exacerbations[91] and increased mortality.[92]

► Bronchiectasis should be treated according to usual guidelines.

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

## Obstructive sleep apnea

► COPD has an estimated prevalence in U.S. adults of 13.9%[93,94] 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.[95]

► The term “overlap syndrome” has been used to describe the association of both conditions in a single patient.[96] Patients with overlap syndrome have a worse prognosis compared with COPD or OSA. 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.[97]

► The apneic events in patients with combined OSA and COPD have more profound hypoxemia and more cardiac arrhythmias.[98] Additionally, patients with combined COPD and OSA are more likely to develop daytime pulmonary hypertension[99,100] than patients with just OSA or COPD alone.

## Cognitive impairment

► Cognitive impairment (CI) is common in patients with COPD.[101] An average prevalence of 32% has been suggested.[102] The prevalence and severity varies by the type of assessment.[103] Extensive neuropsychological testing suggests that up to 56% of patients may suffer CI.[104,105] Longitudinal studies suggest greater risk of developing CI in COPD diagnosed in midlife,[101,106] and associate COPD with the development of dementia.[107]

► CI has been reported in patients suffering from the entire range of spirometric severity.[105]

► CI has been associated with impairment in basic activities of daily living,[108,109] and variably associated with impaired health status.[110,111]

► The coexistence of CI and COPD has been associated with an increased risk of hospitalization[112] and increased length of stay during acute exacerbation hospitalization.[113]

► The impact of CI on self-management skills in COPD patients remains unclear,[108] although inhaler incompetency has been linked to CI.[108]

## 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 the majority of 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 patients with COPD as the only significant disease.[114]

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

## Other considerations

► Consider checking for anemia and vitamin D deficiency in COPD patients.



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# CHAPTER 7: COVID-19 AND COPD

**OVERALL KEY POINTS:**

- *Patients 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 as there is no evidence that COPD medications should be changed during this COVID-19 pandemic.*
- *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 imposes additional stressors to their condition. The COVID-19 pandemic has 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 have also faced shortages of medication.[1]

The dramatic spread of the SARS-CoV-2 virus has been accompanied by an enormous number of publications on the virus and its consequences. The statements made in this Chapter utilize the published GOLD approach to data review and should be seen as ***provisional*** based on the best assessment of the current evidence.

## RISK OF INFECTION WITH SARS-CoV-2

It appears that 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).[2] 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,[3,4] and may be modulated by ICS use.[3,5]

It is not known definitively yet 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 population survey with random sampling found no increased risk of infection.[6] Similarly, 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,[7,8] although at least one has.[9]

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[10,11]; 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%),[12] although many patients had multiple comorbidities, and a further study of a primary care cohort of 8.28 million patients showed having COPD was an independent risk factor for hospital admission (HR 1.55; 95%CI 1.46-1.64).[9]

COPD has also been reported to independently increase the risk of severe disease or death in some series[12-15] but not all.[9,16,17] 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.[18,19] There is evidence of a fall in hospitalization rates for COPD during the pandemic.[20,21] 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.

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.[22]

In summary, on current evidence, patients 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

Patients 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 7.1**). False-negative RT-PCR tests have been reported in patients with CT findings of COVID-19 who eventually tested positive with serial sampling.[23] If patients 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.[24] The U.S. Centers for Disease Control and Prevention (CDC) encourages 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.[25] Repeat testing should be performed in patients with suspected recurrence or relapse of COVID-19.

The lung microbiome is different in COPD patients versus healthy subjects.[26] 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[27] nor on its potential effects in patients 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.[28,29] 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.[28,29] 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.

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.[30-33] However, PEF does not correlate well with the results of spirometry[34-36] has low specificity[37] 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,[38,39] and instructing them in their use and observing them in their homes using video conferencing technology.

## Bronchoscopy

In some patients with COPD, diagnostic and therapeutic bronchoscopy may be required during the COVID-19 pandemic. Elective bronchoscopy should be delayed until patients have a negative PCR test.[40,41] 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[40] and staff should wear PPE.



## Radiology

Chest radiography is insensitive in mild or early COVID-19 infection[42] and is not routinely indicated as a screening test for COVID-19 in asymptomatic individuals. Chest radiography is indicated in patients with COPD with moderate to severe symptoms of COVID-19 and for those with evidence of worsening respiratory status (**Figure 7.1**).[43] COVID-19 pneumonia changes are mostly bilateral.[44] 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.[45]

Computed tomography (CT) screening may show evidence of pneumonia in asymptomatic individuals infected with SARS-CoV-2[46] and false-negative RT-PCR tests have been reported in patients with CT findings of COVID-19 who eventually tested positive.[23] Recommendations have been made on the use of CT as part of diagnostic testing and severity assessment in COVID-19[43] and there are no special considerations for patients with COPD. The initial features of COVID-19 on CT and their progression over time have been reviewed.[47] 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.[48] 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.[49]

The availability of CT may be limited by infection control requirements[50] 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,[51-56] if pulmonary embolism is suspected chest CT angiography should be performed.

## KEY POINTS FOR THE MANAGEMENT OF STABLE COPD DURING COVID-19 PANDEMIC

### PROTECTIVE STRATEGIES

- Follow basic infection control measures
- Wear a face covering
- Consider shielding/sheltering-in-place

### INVESTIGATIONS

- Only essential spirometry

### PHARMACOTHERAPY

- Ensure adequate supplies of medications
- Continue unchanged including ICS

### NON-PHARMACOLOGICAL THERAPY

- Ensure annual influenza vaccination
- Maintain physical activity

TABLE 7.1



# PROTECTIVE STRATEGIES FOR PATIENTS WITH COPD

Patients with COPD should follow basic infection control measures to help prevent SARS-CoV-2 infection including social distancing and washing hands. Wearing a mask or face covering can reduce the risk of *spreading* infection (source control).[57] 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.[58] 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 during the COVID-19 pandemic.[59]

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 [60]; however, wearing a surgical mask does not appear to affect ventilation even in patients with severe airflow limitation.[61] In some countries where wearing face masks is compulsory in certain settings exemptions can be made for patients who are breathless and cannot tolerate wearing a mask. Whenever possible patients should wear masks. In most cases, a looser face covering, or even a face shield may be tolerable and effective.[62,63]

The normal rules for patients on LTOT should be followed if air travel is planned,[64] although patients should avoid travel unless essential. Supplementary oxygen should be delivered by nasal cannula[65] with a surgical mask be worn and distancing maintained.

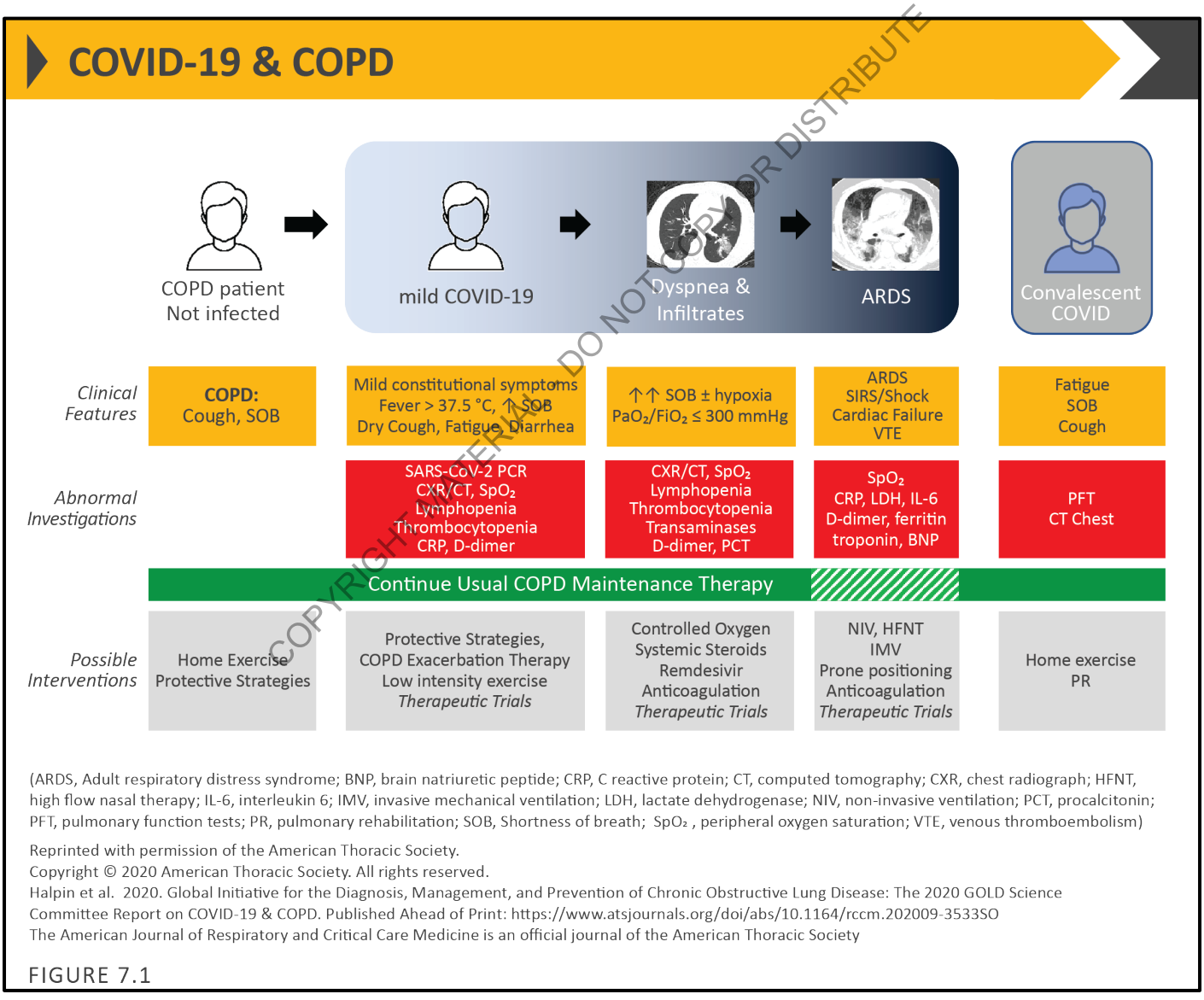
Shielding, or sheltering-in-place, is a way to protect people who are extremely vulnerable from coming into contact with coronavirus. It is an alternative to full-scale physical distancing measures or lockdowns. It has been introduced in some countries for patients with severe COPD. In the UK COPD patients were advised to shield if they had an $FEV_1$ < 50%, mMRC ≥ 3, a history of hospitalization for an exacerbation, or required LTOT or NIV. Modelling suggests shielding is an effective strategy to protect individuals and control the impact of SARS-CoV-2.[66] If patients 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.[67]

## 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.[12]




(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)



FIGURE 7.1



In COVID-19 symptoms may be mild at first, but rapid deterioration in lung function may occur (**Figure 7.1**). 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 patients with COPD reporting exacerbations and suspected of having COVID-19 infection were

infrequently tested for its presence.[68] A high index of suspicion for COVID-19 needs to be maintained in patients with COPD who present with symptoms of an exacerbations, especially if accompanied by fever, impaired taste or smell or GI complaints.

Persistent symptoms in patients 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.[69] Some patients continue to experience cough, fatigue and breathlessness for weeks and a smaller proportion for months.[69-71] Delayed recovery was more common in people with multiple chronic medical conditions but was not specifically linked to having COPD.[69]

# 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.[72-74] In contrast, other laboratory data show that corticosteroids and long acting bronchodilators can reduce the replication of coronaviruses including SARS-CoV-2.[75] 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).[76] 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[77] but the results are likely to be confounded by the indication for ICS.[78] 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 patients with COPD and clinical outcomes/risk of SARS-CoV-2 infection; thus, unless evidence emerges, these patients should continue these medications required for COPD.

## Use of nebulizers

Aerosol therapy increases the droplet generation and risk of disease transmission. Although most of the aerosol emitted comes from the device[79,80] 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[81] and transmission to health care workers exposed to a hospitalized patient with COVID-19 receiving nebulized therapy has been reported.[82] 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 minimised 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.[83]

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.[84]

## NON-PHARMACOLOGICAL TREATMENT FOR COPD DURING THE COVID-19 PANDEMIC

During the COVID-19 pandemic patients with COPD should continue with their non-pharmacological therapy (**Chapter 4**).[85] Patients should receive their annual influenza vaccination, although the logistics of providing these whilst maintaining social distancing will be challenging.[86] There is no reason to modify palliative care approaches because of COVID-19.

Many pulmonary rehabilitation programmes have been suspended during the pandemic to reduce risks of spreading SARS-CoV-2. Whilst case rates are high, centre-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[87] may be useful to support home rehabilitation during the pandemic. As programmes are restarted general principles of infection control should be applied and local guidance followed.[88]

## REVIEW OF COPD PATIENTS DURING THE COVID-19 PANDEMIC

To minimize the spread of SARS-CoV-2 many health systems have reduced face-to-face visits and introduced remote consultations using online, phone and video-links. Routine review of patients with COPD can be undertaken remotely[89] 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 7**).



## 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 the anti-viral drug remdesivir[90] and systemic steroids for hospitalized patients with severe COVID-19.[91] Sub-group analysis on COPD patients have not been presented in these trials.

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 7.1**). Importantly, there are no known drug interactions between remdesivir and inhaled COPD treatments. 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

### 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
- Avoid nebulization when possible

### COPD NON-PHARMACOLOGICAL THERAPY

- Maintain physical activity as able

### PROTECTIVE STRATEGIES

- Follow basic infection control measures
- Maintain physical distancing
- Wear a face covering

### COVID-19 THERAPY

- Use systemic steroids and remdesivir as recommended for patients with COVID-19
- 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

TABLE 7.2



# EXACERBATIONS OF COPD

The prevention and treatment of exacerbations are important goals in COPD management (**Chapter 4**). COVID-19 infection has introduced unique obstacles to the prevention and management of exacerbations.[19] 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.[19] Conversely, as countries went into lockdown and industrial activities shut down, pollutant emissions reduced substantially and environmental air quality improved.[92] This could have contributed to the reported reductions in hospital admissions for COPD during the COVID-19 pandemic.[20,21]

Coronaviruses are among the respiratory viruses that trigger COPD exacerbations.[93] 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 5**). 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.[94,95] These features are very different from typical COPD exacerbations.[96] 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.[53,97] COPD patients who develop COVID-19 reported more severe fatigue, dyspnea, and diarrhea than those without COPD.[48]

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.[98] There is no reason to suspect that this is different in COPD patients with COVID-19 (**Figure 7.1**).

## Systemic corticosteroids

Caution has been raised about the widespread use of systemic corticosteroids in patients with COVID-19.[99,100] 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.[101-104] 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.[105]



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.[91] A small observational study has also reported that methylprednisolone use was associated with improved survival in COVID-19 patients with ARDS.[106] 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.[107]

Systemic steroids should be used in COPD exacerbations according to the usual indications (**Chapter 5**) 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 7.1**).

## 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 5**).

Bacterial co-infections have been reported infrequently in COVID-19.[108] 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.[109] Diagnosing co-infection in COVID-19 patients may be difficult, particularly in critically ill subjects, 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.[97,110] Current WHO guideline 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.[105] In the absence of specific studies, these general considerations would also apply to COPD patients infected with SARS-CoV-2.

Antibiotics should be used in COPD exacerbations according to the usual indications (**Chapter 5**) whether or not there is evidence of SARS-COV-2 infection, particularly as patients with COPD who develop COVID-19 are reported to more frequently develop bacterial or fungal coinfections.[48]

# PULMONARY AND EXTRA-PULMONARY COMPLICATIONS

ARDS may be part of COVID-19 and could be considered the major pulmonary complication of COVID-19[111] with viral infection in areas of ongoing active injury contributing to persistent and temporally heterogeneous lung damage.[112] Some early reports suggested that ARDS in this setting may differ from the typical ARDS.[113,114] Subsequent studies, however, suggested that classical ARDS also presented with a large variation in lung severity[115] and there is considerable overlap between classical ARDS and COVID-19 patients.[116,117] Whether the long-term consequences of this form of ARDS differ from fibrotic lesions described previously is unclear.[118,119]

Although the respiratory tract is the main target of COVID-19, extra-pulmonary involvement is frequent and contributes to morbidity, disability, and mortality.[95,120] Renal, cardiac, nervous, cutaneous, hepatic and gastrointestinal manifestations occur.[121] 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,[122] suggesting secondary rather than primary involvement of these organs.



## Anticoagulation

COVID-19 has been associated with a hypercoagulable state[51] 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.[123] Patients with COPD are already at increased risk of VTE[124,125] and those hospitalized with COVID-19 should receive pharmacologic thromboprophylaxis (**Figure 7.1**). 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.[126] 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 is around 19%.[127] Ventilatory support has been used in up to 20% of patients that develop severe hypoxemia due to COVID-19[128] and approximately 5% of patients require ICU care and advanced respiratory support.[129] Patients requiring ventilatory support have a high risk of mortality[14,130] and COPD has been reported to increase the risk respiratory failure and ICU admissions in some, but not all studies.[9,13]

There is wide variation (2.3% to 33%) in the reported rates of use of invasive mechanical ventilation (IMV) in hospitalized patients with moderate to severe hypoxemic respiratory failure due to COVID-19.[131] This may, in part, reflect differences in use of non-invasive ventilation (NIV) and high flow nasal therapy (HFNT),[131] possibly as a result

of advocation of early intubation during the pandemic's initial phases because of concerns about viral dissemination.[132,133] Data supporting those concerns are lacking.[134]

Although early reports showed mixed outcomes,[135] several studies have now shown showed HFNT significantly reduces rates of intubation and IMV, although with variable effects on mortality.[136,137] 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.[138-140] Prone positioning has also been suggested for awake non intubated hypoxemic patients.[141]

NIV is the normal standard of care for COPD patients with acute respiratory failure (**Chapter 5**). 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.[142] 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.[143,144] A $PaO_2/FiO_2$ < 150 mmHg may be a useful indicator for NIV failure and increased risk of mortality.[145]

Evidence on the effects of extracorporeal membrane oxygenation (ECMO) in COVID-19 is scant and retrospective.[131,146-150] Indications in COVID-19 are similar to indications for other causes of ARDS[151,152] and ECMO should be considered only after other strategies fail to achieve goals of oxygenation or ventilation.[147,148,150]

Aerosol generation can occur when any form of additional pressures or flows are applied to the upper or lower respiratory tract.[153] Data regarding aerosol dispersion with the use of NIV is limited and contradictory [80,153-155]; however, staff should use appropriate personal protective equipment (PPE)[140,156] 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.[157]



## REHABILITATION

COPD patients with COVID-19 are particularly at risk for poor nutritional status and skeletal muscle loss.[158] Hospital treatment should therefore include dietary support and early mobilization. Mechanical ventilation, sedation, and prolonged bed rest, may lead to post-traumatic stress disorder[159] and respiratory, cognitive, and mental health impairments as well as physical deconditioning.[160,161] Older people and patients with COPD, are more susceptible to these consequences.[162,163]

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.[164]

## FOLLOW-UP OF COPD PATIENTS WHO DEVELOPED COVID-19

Approximately 30% of patients with SARS or MERS had persistent lung abnormalities and abnormal radiology consistent with fibrotic lung disease after their acute illness.[165,166] There are not yet long-term studies on the follow-up of COVID-19 patients, nor recommendations for monitoring these patients,[143,167] thus the follow-up of patients with COPD who developed COVID-19 is still based on expert opinion and consensus. The intensity of the monitoring obviously depends on the severity of the COVID-19 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.

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 1 year. Complications occurring during/after the COVID-19 episode should also be monitored.

COPD patients are at higher risk of developing severe COVID-19[143,168] and multimorbid survivors frequently have required prolonged ICU stays.[143] Until we have evidence from prospective studies, COPD survivors of severe COVID-19 should be considered at high risk of developing a "critical illness"[169] or "chronic critical illness",[170] a severe heterogeneous condition linked not only to the acute infectious episode but also to the underlying conditions before they became severely ill.[161]

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.[171]

# REMOTE COPD PATIENT FOLLOW-UP DURING COVID-19 PANDEMIC RESTRICTIONS

## Introduction

During the COVID-19 pandemic, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recognizes that there is 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.[172]

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 □ ICS/LABA/LAMA

□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 change in dyspnea, cough, sputum volume and color (from least to most purulent: mucous; 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. for example 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 to cover 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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