Global Initiative for Chronic Obstructive Lung Disease

2025 POCKET GUIDE

POCKET GUIDE TO COPD DIAGNOSIS, MANAGEMENT, AND PREVENTION

A Guide for Health Care Professionals

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2025 EDITION

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

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is now one of the top three causes of death worldwide and 90% of these deaths occur in low- and middle-income countries (LMICs).[1,2] More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally. COPD represents an important public health challenge that is both preventable and treatable. COPD is a major cause of chronic morbidity and mortality throughout the world; many people suffer from this disease for years and die prematurely from it or its complications. Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population.[3]

This Pocket Guide has been developed from the Global Strategy for the Diagnosis, Management, and Prevention of COPD (**GOLD 2025 Report**), which aims 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. Discussions of COPD and COPD management, evidence levels, and specific citations from the scientific literature are included in that source document.

WHAT IS COPD?

KEY POINTS:

Definition

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

Causes and Risk Factors

- COPD results from gene(G)-environment(E) interactions occurring over the lifetime(T) of the individual (GETomics) that can damage the lungs and/or alter their normal development/aging processes.
- The main environmental exposures leading to COPD are tobacco smoking and the inhalation of toxic particles and gases from household and outdoor air pollution, but other environmental and host factors (including abnormal lung development and accelerated lung aging) can also contribute.
- The most relevant (albeit rare) genetic risk factor for COPD identified to date are mutations in the SERPINA1 gene that lead to α-1 antitrypsin deficiency. A number of other genetic variants have also been associated with reduced lung function and risk of COPD, but their individual effect size is small.

Diagnostic Criteria

- In the appropriate clinical context (see 'Definition' & 'Causes and Risk Factors' above), the presence of non-fully reversible airflow obstruction (i.e., FEV1/FVC < 0.7 post-bronchodilation) measured by spirometry confirms the diagnosis of COPD.
- Some individuals can have respiratory symptoms and/or structural lung lesions (e.g., emphysema) and/or physiological abnormalities (including low FEV1, gas trapping, hyperinflation, reduced lung diffusing capacity and/or rapid FEV1 decline) without airflow obstruction (FEV1/FVC ≥ 0.7 post-bronchodilation). These subjects are labeled 'Pre-COPD'. The term 'PRISm' (Preserved Ratio Impaired Spirometry) has been proposed to identify those with normal ratio but abnormal spirometry. Subjects with Pre-COPD or PRISm are at risk of developing airflow obstruction over time, but not all of them do.

Clinical Presentation

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

New Opportunities

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

DIAGNOSIS AND ASSESSMENT

KEY POINTS:

- A diagnosis of COPD should be **considered** in any patient who has dyspnea, chronic cough or sputum production, a history of recurrent lower respiratory tract infections and/or a history of exposure to risk factors for the disease, but **spirometry** showing the presence of a post-bronchodilator FEV1/FVC < 0.7 is **mandatory** to establish the diagnosis of COPD.
- The goals of the initial COPD assessment are to determine the severity of airflow obstruction, the impact of disease on the patient's health status, and the risk of future events (such as exacerbations, hospital admissions, or death), to guide therapy.
- Additional clinical assessment, including the measurement of lung volumes, diffusion capacity, exercise testing and/or lung imaging may be considered in COPD patients with persistent symptoms after initial treatment.
- Concomitant chronic diseases (multimorbidity) occur frequently in COPD patients, including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety, and lung cancer. These comorbidities should be actively sought, and treated appropriately when present, because they influence health status, hospitalizations and mortality independently of the severity of airflow obstruction due to COPD.

DIAGNOSIS

A diagnosis of COPD should be **considered** in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease (**Figure 2.1**) but **spirometry** that demonstrates the presence of a post-bronchodilator FEV1/FVC < 0.7 is **mandatory** to establish the diagnosis of COPD.[4].

CLINICAL PRESENTATION

Symptoms

Chronic dyspnea is the most characteristic symptom of COPD. Cough with sputum production is present in up to 30% of patients. These symptoms may vary from day-to-day[5] and may precede the development of airflow obstruction by many years. Individuals, particularly those with COPD risk factors, presenting with these symptoms should be examined to search for the underlying cause(s). Airflow obstruction may also be present without chronic dyspnea and/or cough and sputum production and *vice versa*.[6] Although COPD is defined on the basis of airflow obstruction, in practice the decision to seek medical help is usually determined by the impact of symptoms on a patient's functional status. A person may seek medical attention either because of chronic respiratory symptoms or because of an acute, transient episode of exacerbated respiratory symptoms.

Clinical Indicators for Considering a Diagnosis of COPD

Figure 2.1

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

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

Dyspnea

Dyspnea is a cardinal symptom of COPD and a major cause of the disability and anxiety associated with the disease.[7] Dyspnea comprises a sensory and an affective component.[8] Typically COPD patients describe their dyspnea as a sense of increased effort to breathe, chest heaviness, air hunger, or gasping.[9] However, the terms used to describe dyspnea may vary both individually and culturally.[9]

Dyspnea is highly prevalent across all stages of airflow obstruction.[10] It occurs particularly during exertion or physical activity. Moderate-to-severe dyspnea has been reported by > 40% of patients diagnosed with COPD in primary care.[11]

Dyspnea is complex and multiple mechanisms can be involved in its pathogenesis, including impaired respiratory mechanics as a consequence of airflow obstruction and lung hyperinflation, gas exchange abnormalities, peripheral muscle dysfunction related to deconditioning (and systemic inflammation in some patients), psychological distress, dysfunctional breathing, cardiovascular or other comorbid diseases.[12,13]

Dyspnea measured by the 5-level modified Medical Research Council scale is integrated in the GOLD clinical classification scheme (see below) because patients with high dyspnea scores incur higher healthcare resource utilization and costs.[14] Dyspnea in daily life can be measured by a number of detailed questionnaires that are more discriminant and sensitive to change.[15,16]

Chronic cough

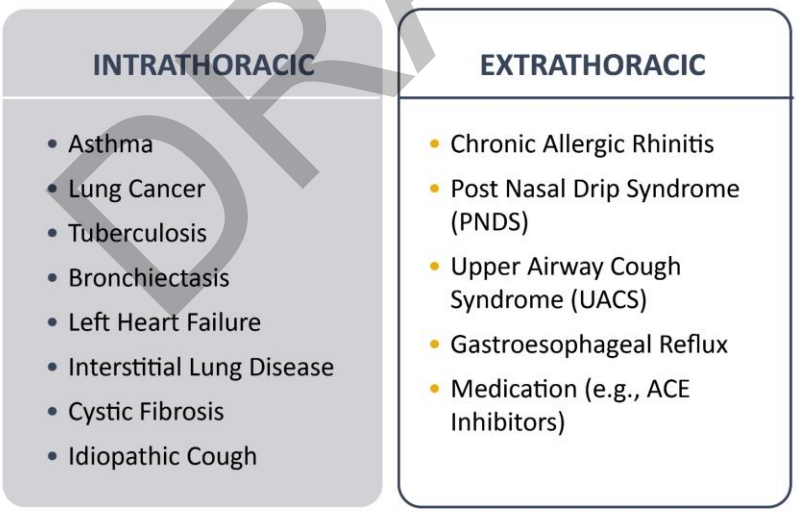
Chronic cough is often the first symptom of COPD and is frequently discounted by the patient as an expected consequence of smoking and/or environmental exposures. Initially, the cough may be intermittent, but subsequently it may be present every day, often throughout the day. Chronic cough in COPD may be productive or non-productive.[17] In some cases, significant airflow obstruction may develop without the presence of a cough. Other causes of chronic cough are listed in **Figure 2.2**. Syncope during cough in patients with severe COPD can occur due to rapid increases in intrathoracic pressure during prolonged attacks of coughing. Coughing spells may also cause rib fractures, which are sometimes asymptomatic.

Sputum production

COPD patients commonly raise small quantities of tenacious sputum with coughing. Regular production of sputum for three or more months in two consecutive years (in the absence of any other conditions that may explain it) is the classical definition of chronic bronchitis,[18] but this is a somewhat arbitrary definition that does not reflect the entire range of sputum production that occurs in COPD (see detailed discussion in **Chapter 1** of the **GOLD 2025 Report**). 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.[19] Patients producing large volumes of sputum may have underlying bronchiectasis.[20,21] The presence of purulent sputum reflects an increase in inflammatory mediators,[22,23] and its development may identify the onset of a bacterial exacerbation, though the association is relatively weak.[23,24]

Other Causes of Chronic Cough

Figure 2.2



Wheezing and chest tightness

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

Fatigue

Fatigue is the subjective feeling of tiredness or exhaustion and is one of the most common and distressing symptoms experienced by people with COPD.[25] People with COPD describe their fatigue as a feeling of "general tiredness" or as a feeling of being "drained of energy".[26,27] Fatigue impacts a patient's ability to perform activities of daily living and their quality of life.

Additional clinical features in severe disease

Weight loss, muscle mass loss, and anorexia are common problems in patients with severe and very severe COPD.[28-30] They have prognostic importance[31,32] and can also be a sign of other diseases, such as tuberculosis or lung cancer, and therefore should always be investigated. Ankle swelling may indicate the presence of *cor pulmonale*. Symptoms of depression and/or anxiety merit specific enquiry when obtaining the medical history because they are common in COPD,[33] are associated with poorer health status, increased risk of exacerbations, and emergency hospital admission, and are treatable.[34]

MEDICAL HISTORY

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

- *Patient's exposure to risk factors*, such as smoking and environmental exposures (household/outdoor).
- *Past medical history*, including early life events (prematurity, low birthweight, maternal smoking during pregnancy, passive smoking exposure during infancy), asthma, allergy, sinusitis, or nasal polyps; respiratory infections in childhood; HIV; tuberculosis.
- *Family history of COPD or other chronic respiratory disease.*
- *Pattern of symptom development*: COPD typically develops in adult life and most patients are conscious of increased breathlessness, more frequent or prolonged "winter colds," and some social restriction for a number of years before seeking medical help.
- *History of exacerbations or previous hospitalizations for respiratory disorder.* Patients may be aware of periodic worsening of symptoms even if these episodes have not been identified as exacerbations of COPD.
- *Presence of comorbidities*, such as heart disease, osteoporosis, musculoskeletal disorders, anxiety and depression, and malignancies that may also contribute to restriction of activity.
- *Impact of disease on patient's life*, including limitation of activity, missed work and economic impact, effect on family routines, feelings of depression or anxiety, wellbeing, and sexual activity.
- *Social and family support available to the patient.*
- *Possibilities for reducing risk factors, especially smoking cessation.*

SPIROMETRY

Forced spirometry is the most reproducible and objective measurement of airflow obstruction. It is a noninvasive, reproducible, cheap, and readily available test. Good quality spirometric measurement is possible in any healthcare setting and all healthcare workers who care for people with COPD should have access to spirometry. Some of the factors needed to achieve accurate test results are summarized in the **Figure 2.4** below.[35,36] Despite its good sensitivity, peak expiratory flow measurement alone cannot be reliably used as the only diagnostic test because of its weak specificity.[37,38]

Considerations in Performing Spirometry

Figure 2.4

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

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

In line with other National and International guidelines, GOLD has recommended using post-bronchodilator values when considering a diagnosis of COPD. See the **GOLD 2025 Report** for further information on pre- or post-bronchodilator spirometry.

INITIAL ASSESSMENT

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

- Severity of airflow obstruction
- Nature and magnitude of current symptoms
- Previous history of moderate and severe exacerbations

- Blood eosinophil count
- Presence and type of other diseases (multimorbidity)

Severity of airflow obstruction

In the presence of FEV1/FVC ratio < 0.7 the assessment of **airflow obstruction severity** in COPD (note that this may be different from severity of the *disease*) is based on the post-bronchodilator value of FEV1 (% GLI-Global; see **Spirometry** section of the **GOLD 2025 Report**). The specific spirometric cut points are proposed for purposes of simplicity (**Figure 2.8**).

Symptoms

Because there is only a weak correlation between the severity of airflow obstruction (**Figure 2.8**) and the symptoms experienced by the patient or the impairment of their health status,[39,40] formal assessment of symptoms using validated questionnaires is required.

Dyspnea questionnaire: the modified Medical Research Council (mMRC) dyspnea scale

The mMRC scale was the first questionnaire developed to measure breathlessness, which is a key symptom in many patients with COPD, although often unrecognized.[41] (**Figure 2.9**) Of note, the mMRC score relates well to other multidimensional health status measures[42] and predicts future mortality risk.[43,44]

GOLD Grades and Severity of Airflow Obstruction in COPD (based on post-bronchodilator FEV1) Figure 2.8

In COPD patients (FEV1/FVC < 0.7):

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

Multidimensional questionnaires

It is now recognized that COPD impacts patients beyond dyspnea.[45] For this reason, multidimensional questionnaires are recommended. The most comprehensive disease-specific health status questionnaires such as the Chronic Respiratory Questionnaire (CRQ)[46] and St. George's Respiratory Questionnaire (SGRQ)[47] are important research tools but they are too complex to use in routine practice. Shorter comprehensive measures, such as the COPD Assessment Test (CAT™) and the Clinical COPD Questionnaire (CCQ©) have been developed and are suitable for use in the clinic. Below we discuss the CAT™ and the SGRQ.

Modified MRC Dyspnea Scale

Figure 2.9

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

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

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

The CAT™[†‡] is an 8-item questionnaire that assesses health status in patients with COPD (**Figure 2.10**).[48] It was developed to be applicable worldwide and validated translations are available in a wide range of languages. The score ranges from 0 to 40, correlates very closely with the SGRQ, and has been extensively documented in numerous publications.[49]

The SGRQ is the most widely documented comprehensive measure; scores < 25 are uncommon in diagnosed COPD patients[50] and scores ≥ 25 are very uncommon in healthy persons.[51,52] 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.[53] An equivalent mMRC score cannot be calculated because a simple breathlessness cut-point cannot equate to a comprehensive symptom score cut-point. The great majority of patients with an SGRQ of ≥ 25 will have an mMRC of ≥ 1; however, patients with mMRC < 1 may also have a number of other COPD symptoms.[54] 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.[54]

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

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

CAT™ Assessment

Figure 2.10

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

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

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

TOTAL SCORE:

Exacerbation risk

Exacerbations of COPD (ECOPD) are episodes of acute respiratory symptom worsening often associated with increased local and systemic inflammation (see **GOLD 2025 Report Chapter 4**).[55-58] ECOPD are key events in the natural history of the disease because they impact significantly on the health status of the patient (often for a prolonged period of time), enhance the rate of lung function decline, worsen the prognosis of the patient and are associated with most of the healthcare costs of COPD.[59] ECOPD rates vary greatly between patients[60] and during follow-up.[61] The best predictor of having frequent exacerbations (defined as two or more exacerbations per year) is the previous history of exacerbations.[60] Worsening of airflow obstruction is associated with an increasing prevalence of exacerbations, hospitalization[62,63] and risk of death.[50,64]

Blood eosinophil count

A number of studies have shown that blood eosinophil counts predict the magnitude of the effect of ICS (added on top of regular maintenance bronchodilator treatment) in preventing future exacerbations and blood eosinophil counts are recommended by GOLD to guide the use of ICS as part of pharmacological management (see **Figure 3.7** & **Figure 3.9**).[65-70]

There is evidence that on average blood eosinophil counts are higher in COPD patients, although there is marked overlap with controls.[71,72] Higher blood eosinophil counts in COPD patients are associated with increased lung

eosinophil numbers and the presence of higher levels of markers of type-2 inflammation in the airways, although the concordance between blood and lung/airways T2 biomarkers is not strict.[73,74] These differences in airway inflammation may explain the differential response to ICS treatment according to blood eosinophil counts.[75]

The repeatability of blood eosinophil counts in a large primary care population appears reasonable,[76] although greater variability is observed at higher thresholds.[77] Better reproducibility is observed at the lower thresholds (e.g., 100 cells/µL).[78] Blood eosinophil counts can help clinicians estimate the likelihood of a beneficial preventive response to the addition of ICS to regular bronchodilator treatment, and thus can be used as a biomarker in conjunction with clinical assessment when making decisions regarding ICS use.

Cohort studies have produced differing results with regard to the ability of blood eosinophils to predict future exacerbation outcomes, with either no relationship[79] or a positive relationship reported.[80,81] Differences between studies are likely to be related to different previous exacerbation histories and ICS use. There is insufficient evidence to recommend that blood eosinophils should be used to predict future exacerbation risk on an individual basis in COPD patients. Greater FEV1 decline was observed in mild to moderate COPD patients with higher blood eosinophil counts in a population where ICS use was low,[82] highlighting the possible usefulness of blood eosinophil counts as a prognostic biomarker for lung function decline when not confounded by ICS use. In younger individuals without COPD, higher blood eosinophil counts are associated with increased risk of subsequent development of COPD.[83]

Multimorbidity

People with COPD often suffer other concomitant chronic diseases (multimorbidity). This can occur in patients with mild, moderate or severe airflow obstruction.[50] Multimorbidity influences mortality and hospitalizations independently of the severity of airflow obstruction,[84] and deserves specific treatment. Therefore, comorbid conditions should be looked for routinely, and treated appropriately if present, in any patient with COPD. Recommendations for the diagnosis, assessment of severity, and management of individual comorbid diseases are the same as for patients without COPD.

Frequent multimorbid diseases in COPD include cardiovascular disease,[85] metabolic syndrome, osteoporosis, depression and anxiety, likely in relation to shared risk factors (e.g., aging, smoking, alcohol, diet and inactivity).[59,86-88] Besides, COPD itself may increase the risk for other comorbid diseases (e.g., COPD (particularly emphysema) and lung cancer).[89,90] Whether the association between COPD and lung cancer is due to common risk factors (e.g., smoking), involvement of shared susceptibility genes and/or impaired clearance of carcinogens is unclear. COPD can also have significant extrapulmonary (systemic) effects including weight loss, nutritional abnormalities, and skeletal muscle dysfunction. The latter is characterized by both sarcopenia (loss of muscle cells) and abnormal function of the remaining cells.[91] Its causes are likely multifactorial (e.g., inactivity, poor diet, inflammation and/or hypoxia) and it can contribute to exercise intolerance and poor health status in patients with COPD. Importantly, skeletal muscle dysfunction is a modifiable source of exercise intolerance by rehabilitation.[92] A more detailed description of the management of COPD and comorbidities is provided in **Chapter 5** of the **GOLD 2025 Report**.

Cardiovascular risk in COPD

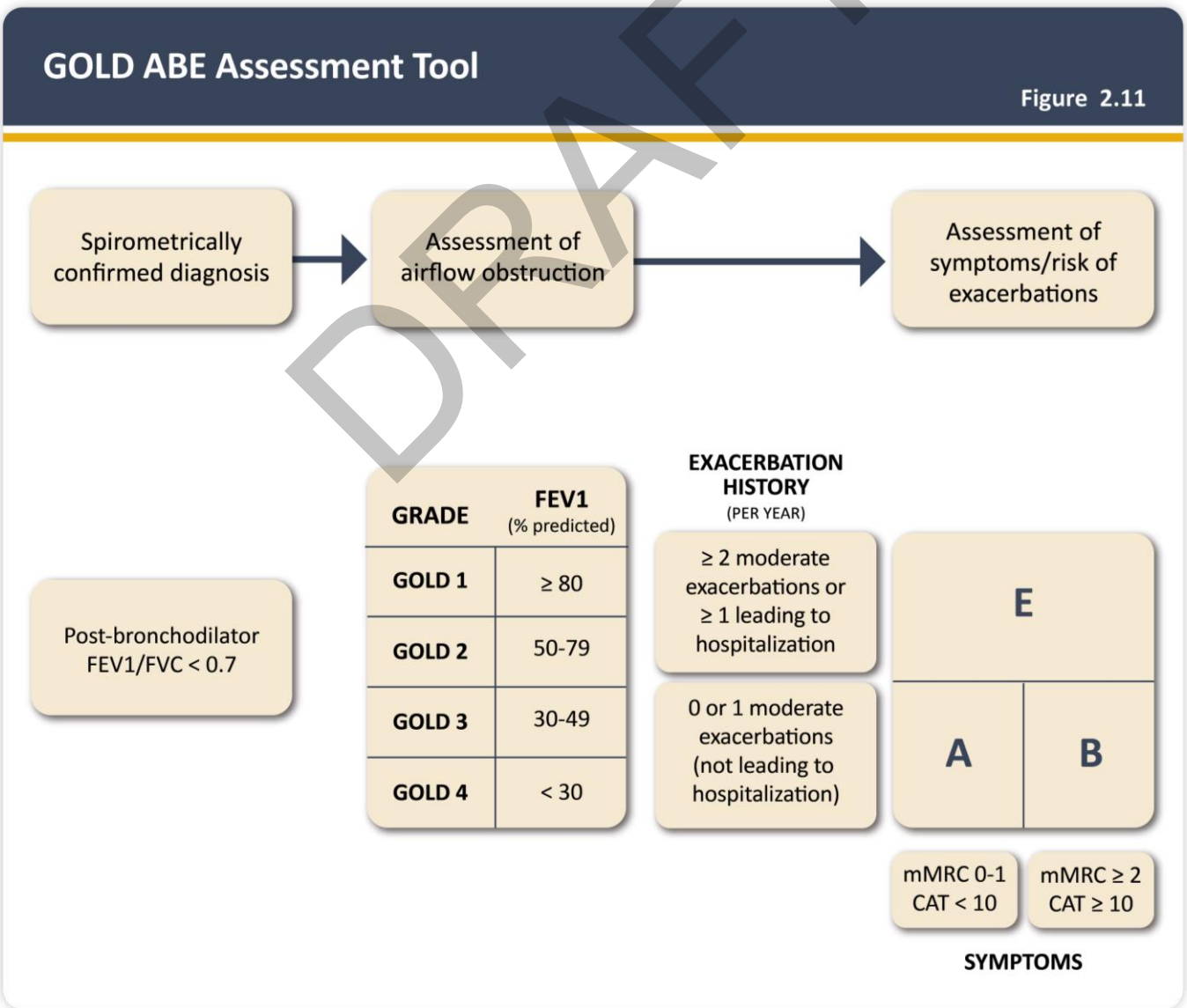
Patients with COPD often suffer cardiovascular diseases and *vice versa*, although these may be ignored by the attending physician who focuses on her/his disease of interest (lung or heart).[93,94] This has important clinical implications because the appropriate treatment of lung and heart diseases may be associated with better outcomes for the patient. It is important, however, to differentiate between clinically stable patients and patients suffering acute episodes of increased symptoms, so-called exacerbations of COPD (ECOPD). Please see the **GOLD 2025 Report** for further information.

Combined initial COPD assessment

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

The severity of airflow obstruction was subsequently removed from this combined assessment scheme considering its lower precision at the individual level (versus that at a population level) to predict outcomes and drive treatment decisions, while complexifying the use of the classification by clinicians.[40,64,95,96]

In the 2023 GOLD report, GOLD proposed a further evolution of the ABCD combined assessment tool that recognized the clinical relevance of exacerbations, independently of the level of symptoms of the patient. **Figure 2.11** presents this proposal. The A and B groups remained unchanged, but the C and D groups were merged into a single group termed "E" to highlight the clinical relevance of exacerbations. It was acknowledged that this proposal would have to be validated by appropriate clinical research.



PREVENTION AND MANAGEMENT OF COPD

KEY POINTS:

- All individuals who smoke should be strongly encouraged and supported to quit. Nicotine replacement and pharmacotherapy reliably increase long-term smoking abstinence rates. Legislative smoking bans and counseling, delivered by healthcare professionals, improve quit rates. There is no evidence to support the effectiveness and safety of e-cigarettes as a smoking cessation aid at present.

- The main treatment goals are to reduce symptoms and future risk of exacerbations. The management strategy of stable COPD should be predominantly based on the assessment of symptoms and the history of exacerbations.

- Pharmacotherapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Data suggest beneficial effects on rates of lung function decline and mortality.

- Each pharmacological treatment regimen should be individualized and guided by the severity of symptoms, risk of exacerbations, side-effects, comorbidities, drug availability and cost, and the patient's response, preference, and ability to use various drug delivery devices.

- Inhaler technique needs to be assessed regularly.

- COVID-19 vaccines are highly effective against SARS-CoV-2 infection and people with COPD should have the COVID-19 vaccination in line with national recommendations.

- Influenza vaccination and pneumococcal vaccination decrease the incidence of lower respiratory tract infections.

- The CDC recommends: the Tdap vaccination (dTaP/dTPa; pertussis, tetanus and diptheria) for COPD patients who were not vaccinated in adolescence; routine use of shingles vaccine in all COPD patients; the new respiratory syncytial virus (RSV) vaccine for individuals over 60 years and/or with chronic heart or lung disease.

- Pulmonary rehabilitation with its core components, including exercise training combined with disease-specific education, improves exercise capacity, symptoms, and quality of life across all grades of COPD severity.

- In patients with severe resting chronic hypoxemia ($PaO_2 \leq 55$ mmHg or < 60 mmHg if there is *cor pulmonale* or secondary polycythemia), long-term oxygen therapy improves survival.

- In patients with stable COPD and resting or exercise-induced moderate desaturation, long-term oxygen treatment should not be prescribed routinely. However, individual patient factors must be considered when evaluating the patient's need for supplemental oxygen.

- In patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure, long-term non-invasive ventilation may decrease mortality and prevent re-hospitalization.

- In select patients with advanced emphysema refractory to optimized medical care, surgical or bronchoscopic interventional treatments may be beneficial.

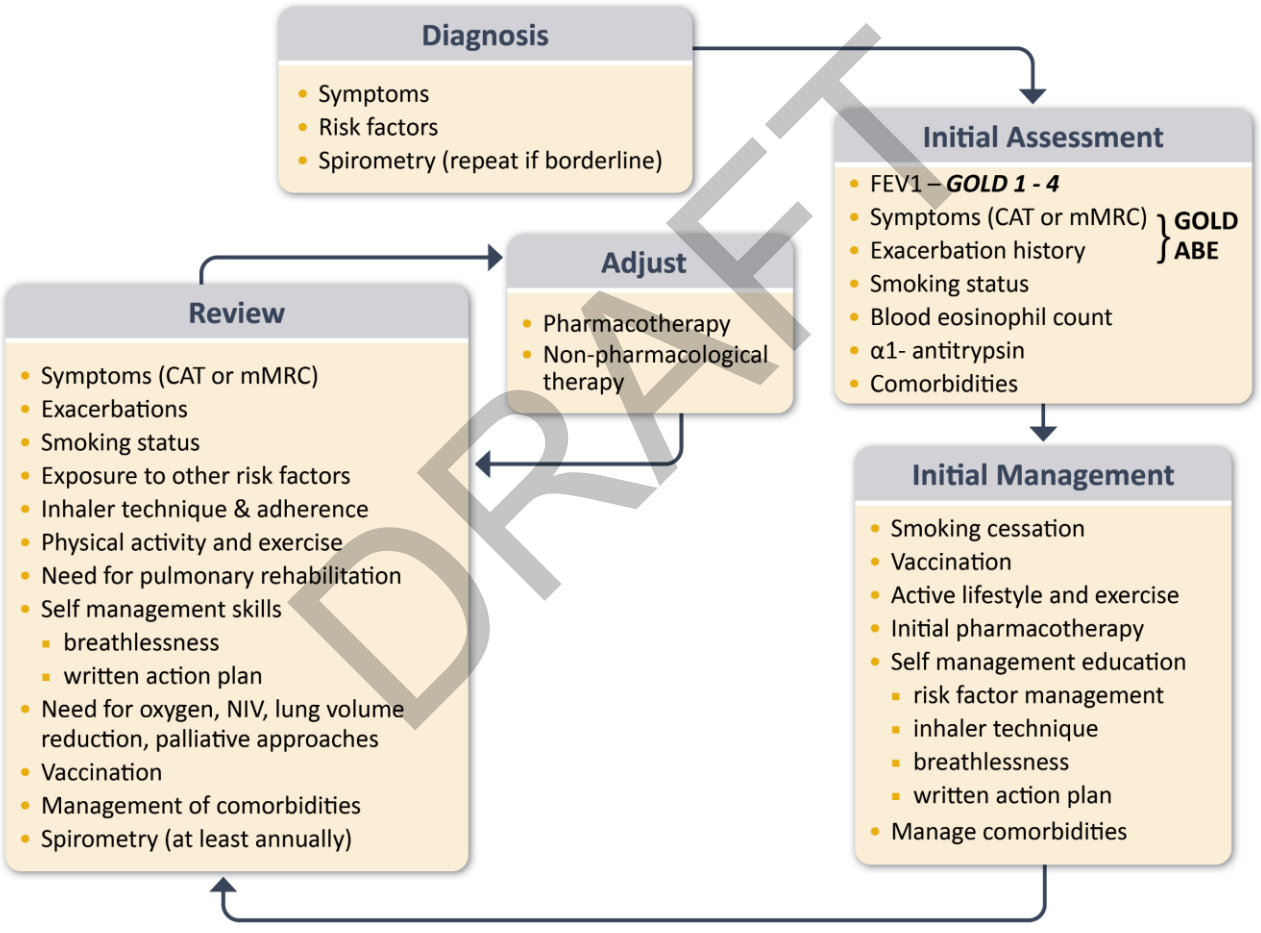
- Palliative approaches are effective in controlling symptoms in advanced COPD.

INTRODUCTION

The aim of COPD management is to reduce symptoms and future risk. COPD patients should have an assessment of the severity of their airflow obstruction, symptoms, history of exacerbations, exposure to risk factors and comorbidities to guide management.

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

Management of COPD Figure 3.2



IDENTIFY AND REDUCE EXPOSURE TO RISK FACTORS

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

Identify & Reduce Risk Factor Exposure

Figure 3.3

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

Smoking cessation

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

A significant proportion of people with COPD continue to smoke despite knowing they have the disease (approximately 40% of those with COPD are current smokers), and this behavior has a negative impact on prognosis and progression of the disease.[97] Smoking cessation has the greatest capacity to influence the natural history of COPD, it also improves daily symptoms,[98] and decreases the frequency of exacerbations.[99]

For smokers with COPD, the quitting may be more challenging than for smokers without COPD due to greater nicotine dependence, lower self-efficacy and lower self-esteem.[100-102] In addition, it has been reported that depression is more common in smokers with COPD[103] and this could contribute to failed attempts to quit.[103,104] Despite these adverse conditions, if effective time and resources are dedicated to smoking cessation, long-term quit rates of 14% to 27% have been reported.[104]

Vaccinations

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

Vaccination for Stable COPD

Figure 3.6

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

- Yearly influenza vaccination **(Evidence B)**
- SARS-CoV-2 (COVID-19) vaccination based on WHO and CDC updated recommendations **(Evidence B)**
- Either one dose of 21-valent pneumococcal conjugate vaccine (PCV21) or one dose PCV20, as recommended by the CDC **(Evidence B)**. Pneumococcal vaccination has been shown to reduce the incidence of community-acquired pneumonia and exacerbations for people with COPD **(Evidence B)**
- Respiratory syncytial virus (RSV) vaccination for individuals aged ≥ 60 years and/or with chronic heart or lung disease, as recommended by the CDC **(Evidence A)**
- Tdap (dTaP/dTPa) vaccination to protect against pertussis (whooping cough) for people with COPD that were not vaccinated in adolescence, as recommended by the CDC **(Evidence B)**
- Zoster vaccine to protect against shingles for people with COPD aged > 50 years, as recommended by the CDC **(Evidence B)**

PHARMACOLOGICAL TREATMENT OF STABLE COPD

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

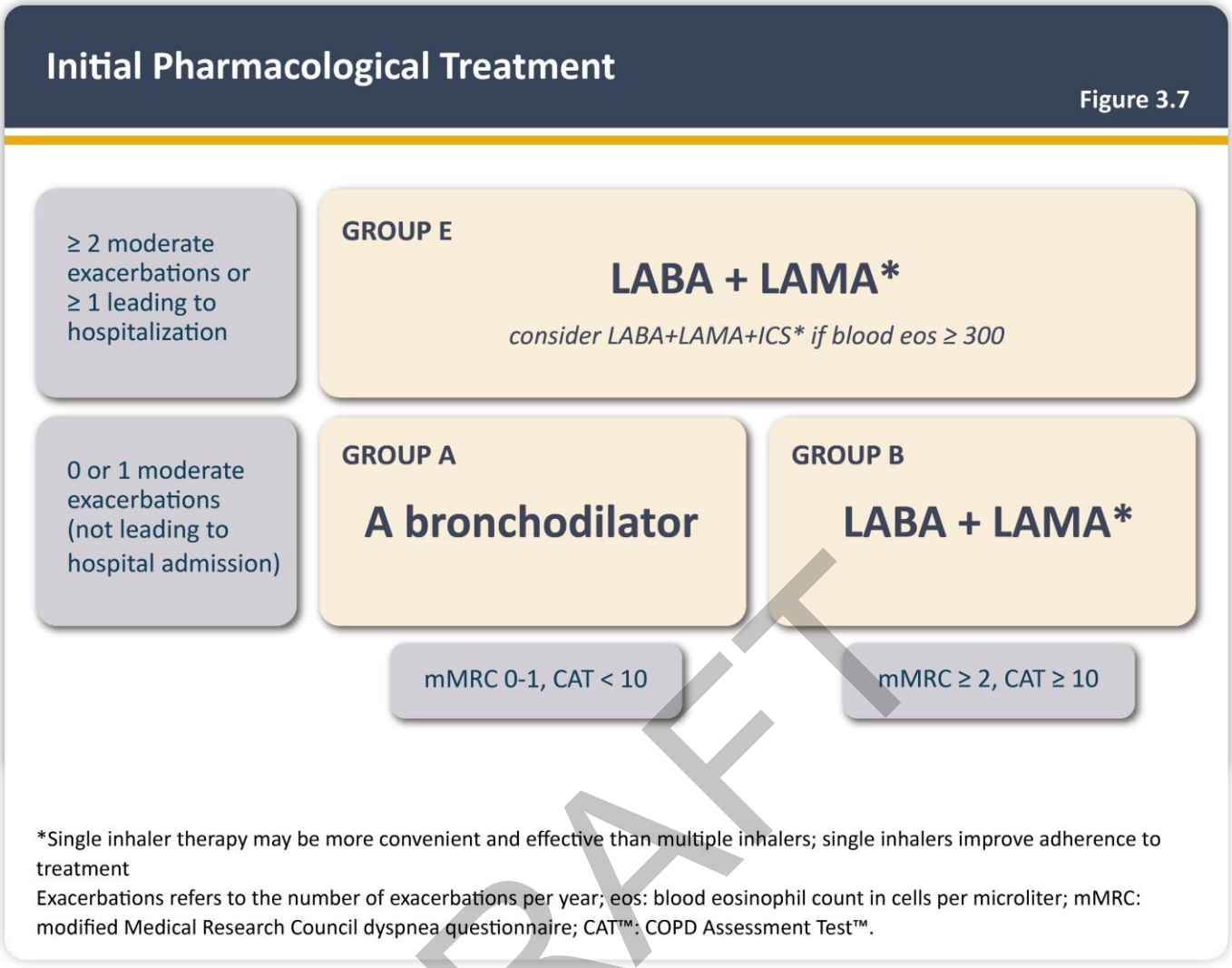
Initial pharmacotherapy should be based on the patient's GOLD group (see **Figure 3.7**). Patients should be offered guidance and follow up on self-management of breathlessness, and stress management, and they should be given a written action plan. Comorbidities should also be managed as per specific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

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

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

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

suspected, pharmacotherapy should primarily follow asthma guidelines.



Algorithms for the initiation and follow-up of pharmacological treatment

Further information on the evidence that underpins these recommendations is given later in **Chapter 3** of the **GOLD 2025 Report** in the section entitled **"Overview of the evidence: Pharmacotherapy"**.

Initial pharmacological management

A proposal for the **INITIATION** of pharmacological management of COPD according to the individualized assessment of symptoms and exacerbation risk following the ABE scheme, and also accounting for blood eosinophil count, is shown in **Figure 3.7**. It is an attempt to provide clinical guidance. There is no high-quality evidence such as randomized controlled trials to support initial pharmacological treatment strategies in newly diagnosed COPD patients.

Group A

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

► This should be continued if benefit is documented.

Group B

► Treatment should be initiated with a LABA+LAMA combination. It has been shown in a RCT that in patients with ≤ 1 moderate exacerbation in the year before the study and a CAT™ ≥ 10 LABA+LAMA is superior to a LAMA with regard to several endpoints.[105] Therefore, providing there are no issues regarding availability, cost and side-effects LABA+LAMA is the recommended initial pharmacological choice.

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

► Group B patients are likely to have comorbidities that may add to their symptomatology and impact their prognosis, and these possibilities should be investigated and treated, if present, by following national and international guidelines.[106,107]

Group E

► A Cochrane systematic review and network meta-analysis comparing dual combination therapy versus mono long-acting bronchodilators showed that the LABA+LAMA combination was the highest ranked treatment group to reduce COPD exacerbations.[108] Therefore, provided there are no issues regarding availability, cost and side-effects LABA+LAMA is the preferred choice for initial therapy in group E patients.

► Use of LABA+ICS in COPD is not encouraged. If there is an indication for an ICS, then LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice.[70,109]

► Consider LABA+LAMA+ICS in group E if eos ≥ 300 cells/µL (practical recommendation). As detailed later in this chapter, the effect of ICS on exacerbation prevention is correlated to blood eosinophil count. There are no direct data in the literature concerning initiation of triple therapy in newly diagnosed patients. However, we think available studies performed mostly in treated patients provide a rationale for considering this treatment option as initial therapy for patients with a high eosinophil count (≥ 300 cells/µL).

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

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

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

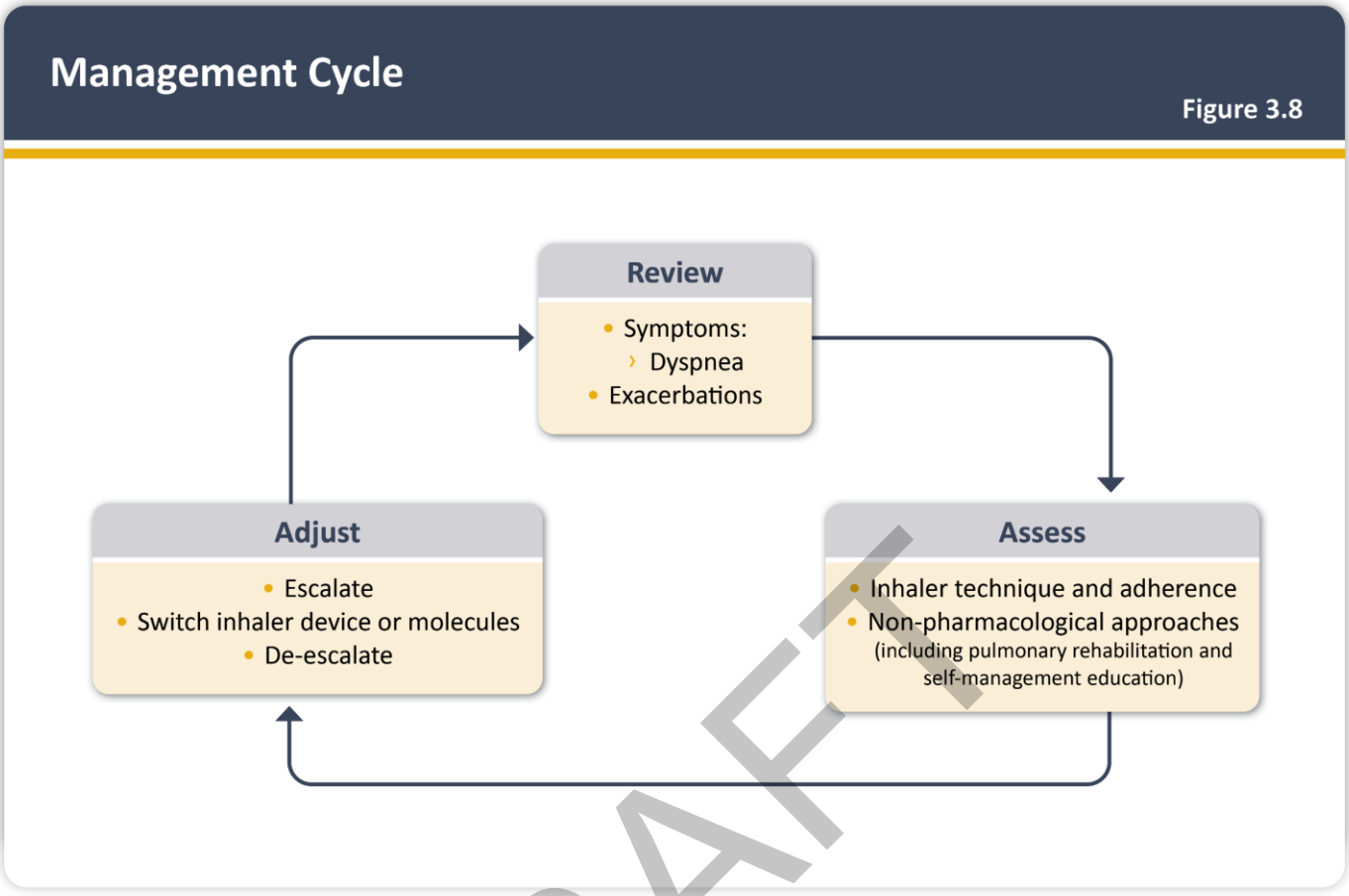
This is guided by the principles of first ***review*** and ***assess***, then ***adjust*** if necessary (**Figure 3.8**):

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

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

► **Adjust**
- Adjust pharmacological treatment, including escalation or de-escalation. Switching inhaler device or molecules within the same class (e.g., using a different long-acting bronchodilator) may be considered as

appropriate. Any change in treatment requires a subsequent ***review*** of the clinical response, including side effects.



Follow-up pharmacological management

A separate algorithm is provided for **FOLLOW-UP** treatment, where the management is based on two key treatable traits: persistence of dyspnea and occurrence of exacerbations (**Figure 3.9**).[75,110-112] These follow-up recommendations are designed to facilitate management of patients taking maintenance treatment(s), whether early after initial treatment or after years of follow-up. These recommendations incorporate the evidence from clinical trials and the use of peripheral blood eosinophil counts as a biomarker to guide the use of ICS therapy for exacerbation prevention (see more detailed information regarding blood eosinophil counts as a predictor of ICS effects later in **Chapter 3**).

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

The follow-up pharmacological treatment algorithm (**Figure 3.9**) can be applied to any patient who is already taking maintenance treatment(s) irrespective of the GOLD group allocated at treatment initiation. If response to initial treatment is appropriate, maintain it. If not:

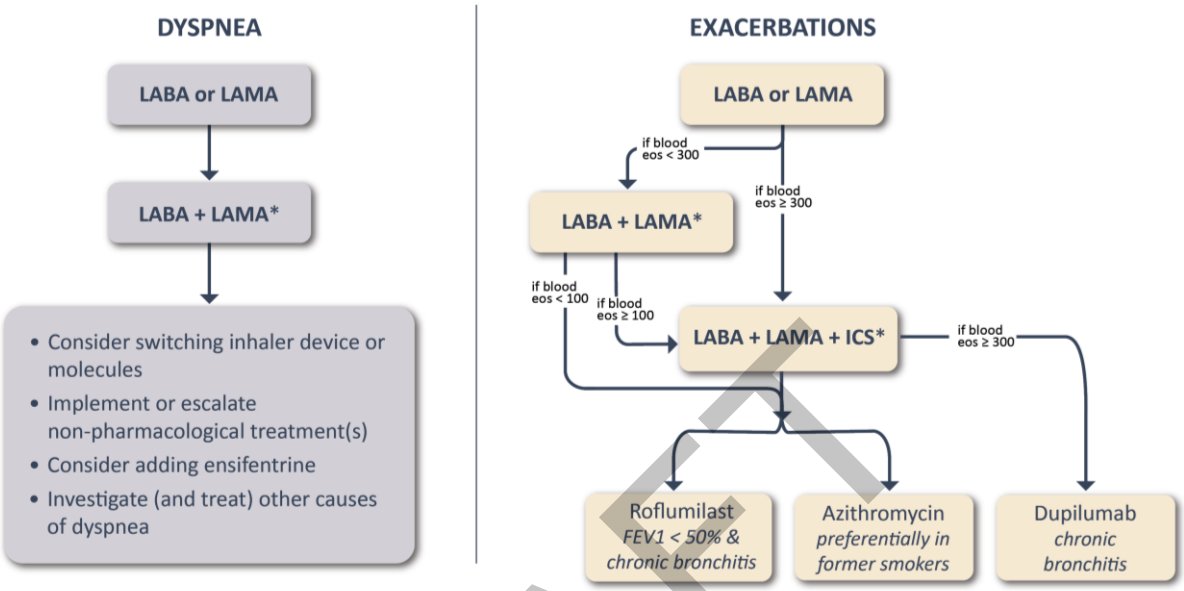
- Check adherence, inhaler technique and possible interfering comorbidities.
- The need to target primarily dyspnea/activity limitation or to prevent further exacerbations should be evaluated in each patient. Consider the predominant treatable trait to target (dyspnea or exacerbations).
    - Use the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

3.9 left column) or exacerbations (**Figure 3.9** right column)

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

Follow-up Pharmacological Treatment

Figure 3.9



*Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment.
Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eos ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations.
Exacerbations refers to the number of exacerbations per year.

Dyspnea

► For patients with persistent breathlessness or exercise limitation on ***bronchodilator*** monotherapy,[113] the use of two long-acting bronchodilators is recommended.

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

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

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

Exacerbations

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

► In patients who develop further exacerbations on **LABA+LAMA** therapy we suggest escalation to **LABA+LAMA+ICS.** A beneficial response after the addition of ICS may be observed at blood eosinophil counts ≥ 100 cells/µL, with a greater magnitude of response more likely with higher eosinophil counts.[70]

► If patients treated with **LABA+LAMA** and eosinophil counts < 100 cells/µL still have exacerbations the following options may be considered:

- Among those who are not currently smoking, consider adding azithromycin.[114,115] Consideration to the development of resistant organisms should be factored into decision-making.
- Among those with FEV1 < 50%, symptoms of chronic bronchitis and history of prior severe exacerbation, consider adding roflumilast.[116-118]

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

- Among those with eosinophils ≥ 300 cells/µl and symptoms of chronic bronchitis, consider adding dupilumab.[110,111]
- Among those who are not currently smoking, consider adding azithromycin.[114,115] Consideration to the development of resistant organisms should be factored into decision-making.
- Among those with FEV1 < 50%, symptoms of chronic bronchitis and history of prior severe exacerbation, consider adding roflumilast.[116-118]

►Patients treated with **LABA+LAMA+ICS** should not have the ICS component withdrawn unless the inhaled corticosteroids were started inappropriately, there has been no response to ICS, they experience significant side-effects, or severe or recurrent pneumonia. The risks and benefits of discontinuing ICS should be considered. If blood eosinophils are ≥ 300 cells/µL de-escalation is more likely to be associated with the development of exacerbations.[119,120]

Patients on treatment with LABA+ICS

► If a patient with COPD and **no features of asthma** has been treated – for whatever reason – with LABA+ICS and is well controlled in terms of symptoms and exacerbations, continuation with LABA+ICS is an option (**Figure 3.22**). However, if the patient has:

- **Further exacerbations:** treatment should be escalated to LABA+LAMA+ICS if the blood eosinophil count is ≥ 100 cells/µL or switched to LABA+LAMA if it is < 100 cells/µL.
- **Major symptoms:** change to LABA+LAMA or LABA+LAMA+ICS depending on previous treatment response to ICS (see 'Management of Patients Currently on LABA+ICS' Page 39 and **Figure 3.22** for further information).

Managing inhaled therapy

Most of the drugs used to treat COPD are inhaled. Thus, appropriate use of inhaler devices is crucial to optimize the benefit-risk ratio of inhaled therapy. Achieving this goal requires choosing the appropriate device, providing education, checking inhaler use regularly and, whenever necessary, adapting education and device (**Figure 3.10**).

Key Points for Inhalation of Drugs

Figure 3.10

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

There are currently at least 33 different inhaled therapies containing different bronchodilators (both short- and long-acting) and inhaled corticosteroids (ICS) alone or in combinations (**Figure 3.18**). In addition, at least 22 different inhaler devices are available,[121] including nebulizers, metered-dose inhalers (MDIs) used with or without valved holding chamber (VHC)/spacers, breath-actuated MDIs (BAIs), soft mist inhalers (SMIs) and dry powder inhalers (DPIs)[122] In multi-dose DPIs, the powder is contained in a reservoir or in individual blisters.[122] More information about inhalation devices is available on the Asthma + Lung UK website.[123]

NON-PHARMACOLOGICAL TREATMENT OF STABLE COPD

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

After receiving a diagnosis of COPD a patient should be given further information about the condition. Physicians should emphasize the importance of a smoke free environment, empower adherence to prescribed medication, ensure proper inhaler technique, promote physical activity, prescribe vaccinations, and refer patients to pulmonary rehabilitation.

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

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

Non-Pharmacological Management of COPD*

Figure 3.12

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

*Can include pharmacological treatment

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

Follow-up of Non-Pharmacological Treatment

Figure 3.13

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

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

Ensure

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

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

DYSPNEA

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

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
- Pulmonary rehabilitation (PR) program and/or maintenance exercise program post PR

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

Oxygen therapy and ventilatory support

Oxygen therapy

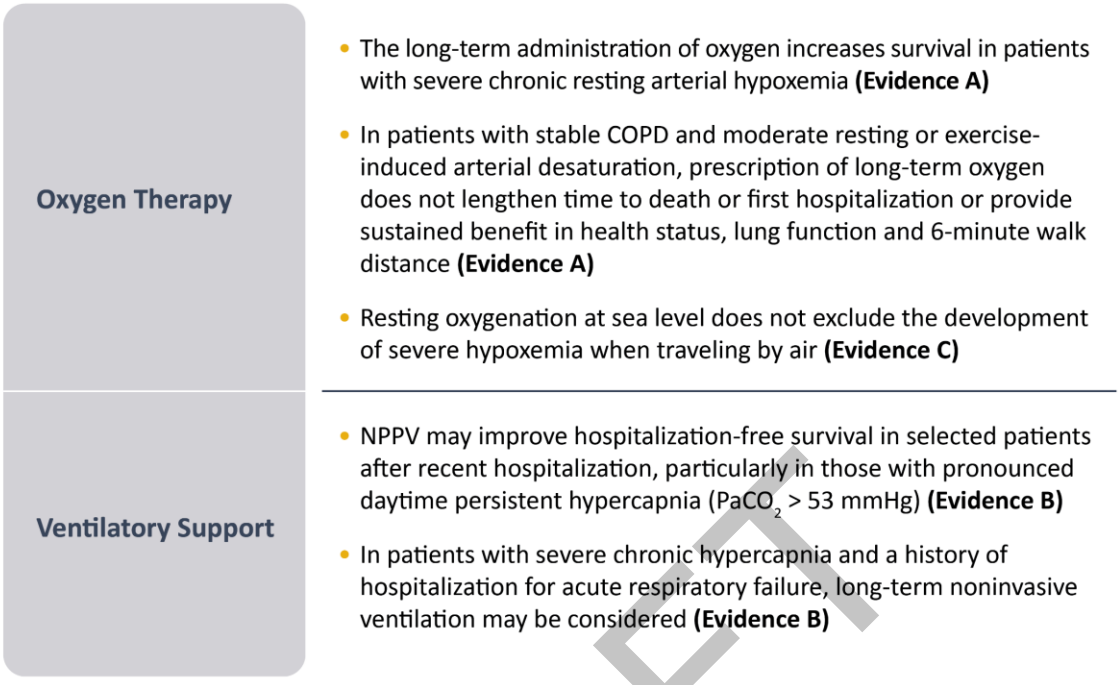
The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival in patients with severe resting hypoxemia.[124]

Ekström and colleagues[125] reported that among patients with severe hypoxemia agreeing to participate in a study, long-term oxygen therapy used for 24 hours per day did not result in a lower risk of hospitalization or death within one year compared to therapy for 15 hours per day, but the generalizability of this finding is unclear.

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.[126] Breathlessness may be relieved in COPD patients who are either mildly hypoxemic, or non-hypoxemic but do not otherwise qualify for home oxygen therapy, when oxygen is given during exercise training; however, studies have shown no improvement of breathlessness in daily life and no benefit on health-related quality of life (**Figure 3.14**).[126-128] There are contradictory studies although the majority do not demonstrate changes.[129]

Oxygen Therapy and Ventilatory Support in Stable COPD

Figure 3.14



Although air travel is safe for most patients with chronic respiratory failure who are on long-term oxygen therapy,[130] 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.[131] Those with a resting oxygen saturation > 95% and 6-minute walk oxygen saturation > 84% may travel without further assessment,[132] although it is important to emphasize that resting oxygenation at sea level does not exclude the development of severe hypoxemia when travelling by air.[130] 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.[133]

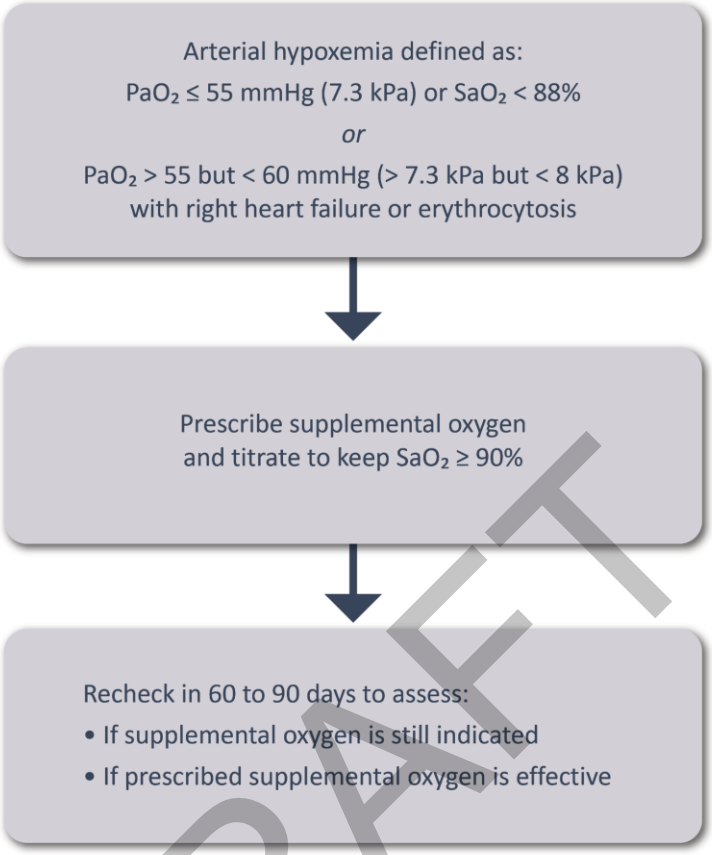
Long-term oxygen therapy (LTOT) is indicated for stable patients who have:

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

Once placed on LTOT the patient should be re-evaluated after 60 to 90 days with repeat arterial blood gas (ABG) or oxygen saturation measurements while inspiring room air and the level of oxygen flow that had been prescribed to determine if oxygen is still indicated and if so, therapeutic. An appropriate algorithm for the prescription of oxygen to COPD patients is shown in **Figure 3.15**.

Prescription of Supplemental Oxygen to COPD Patients

Figure 3.15



Ventilatory support

Noninvasive ventilation (NIV) is occasionally used in patients with stable very severe COPD.[134] NIV may be considered of some use in a selected group of patients, particularly in those with pronounced daytime hypercapnia and recent hospitalization, although a systematic review was unable to support or refute this.[135] In contrast, in patients with both COPD and obstructive sleep apnea there are clear indications for continuous positive airway pressure (CPAP).[136,137]

During exacerbations of COPD

NIV in the form of noninvasive positive pressure ventilation (NPPV) is the standard of care for decreasing morbidity and mortality in patients hospitalized with an exacerbation of COPD and acute respiratory failure[138-141] (see also **GOLD 2025 Report, Chapter 4**).

Stable patient

In patients with both COPD and obstructive sleep apnea there are clear benefits associated with the use of continuous positive airway pressure (CPAP) to improve both survival and the risk of hospital admissions.[136,137]

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.[142] A multicenter prospective RCT of COPD patients with persistent hypercapnia ($PaCO_2$ > 53 mmHg) after 2-4 weeks of hospital

discharge because an acute episode of exacerbation, compared the effects of home NIV plus oxygen compared to home oxygen alone on time to readmission or death.[142] Results showed that adding home NIV to oxygen therapy significantly prolonged the time to readmission or death within 12 months.[142] 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.[141]

Two previous retrospective studies[143,144] and two of three RCTs[142,145-148] 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.[146] 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.[149] NPPV when indicated should be instituted and monitored under the direction of personnel familiar with the process and the devices utilized.[150,151]

A meta-analysis suggested that in patients with chronic hypercapnic respiratory failure long-term treatment with HFNC may reduce acute exacerbations and improve SGRQ scores compared to standard care, but its effect on mortality and hospitalizations is uncertain.[152,153]

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

Palliative Care, End of Life and Hospice Care in COPD — Figure 3.16

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

Therapeutic interventions that reduce COPD mortality

COPD is the third leading cause of death worldwide, causing 3.23 million deaths in 2019. As we move towards targeting subgroups of COPD patients for specific therapy, it is important to know which modifiable factors (treatable traits) are associated with mortality. A large clinical database study of COPD in primary care has demonstrated that the highest magnitude of risk of all-cause mortality, COPD- and CVD-related mortality, was in individuals with increased severity and frequency of COPD exacerbations, GOLD groups B and D, and those with lower FEV1 (particularly GOLD 3 and 4).[154] We are still learning about the mechanisms that cause death in patients with COPD. Demonstrating benefits of

therapeutic modalities on mortality in RCTs has been difficult, requiring large populations and/or long follow-up duration and/or highly selected populations with a high but preventable risk of death during follow-up. In addition, the low number of events makes the analysis of disease specific mortality (e.g., respiratory or cardiovascular) in most trials difficult. **Figure 3.17** presents a summary of pharmacological and non-pharmacological therapies with evidence of efficacy in reducing the mortality of COPD patients.

Pharmacological therapy

Previous studies such as the TORCH clinical trial[155] and the SUMMIT trial[156] failed to provide evidence for the efficacy of a LABA+ICS combination compared to placebo in reducing mortality (primary outcome) in COPD patients. These trials had no requirement for a history of previous exacerbations. In the largest LAMA treatment trial UPLIFT, the intention to treat analysis, i.e., 30 days after completion of the study period, did not demonstrate a reduction in mortality (secondary outcome) compared to placebo. The majority of patients included in this study utilized an ICS.

Evidence has emerged from two large randomized clinical trials, IMPACT[70] and ETHOS,[109] that fixed-dose inhaled triple combinations (LABA+LAMA+ICS), reduce all-cause mortality compared to dual inhaled long-acting bronchodilation therapy. 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. These trials were enriched for symptomatic patients (CAT ≥ 10) with a history of frequent (≥ 2 moderate exacerbations) and/or severe exacerbations (≥ 1 exacerbation requiring a hospital admission) (**Figure 3.17**).

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

Figure 3.17

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

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

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

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

Non-pharmacological therapy

Smoking cessation. From the Lung Health Study, a randomized clinical trial (RCT) that included asymptomatic or mildly symptomatic COPD patients treated with a 10-week smoking cessation intervention program and followed up to 14.5 years, the overall mortality rate was reduced in the smoking cessation intervention group compared to the usual care group.[157]

Pulmonary rehabilitation (PR). A systematic review of RCTs reported a reduction in mortality for patients who had PR initiated during hospitalization or 4 weeks after discharge compared to those who did not have PR.[158-161] These results have been corroborated by real-world evidence, from a large population-based cohort of 190,000 patients hospitalized for COPD, in whom initiation of PR within 90 days of discharge, while rare, was associated with a statistically significant reduced mortality.[162]

Long term oxygen therapy (LTOT). Survival benefit of LTOT in COPD demonstrated in two studies in the early 1980s laid the foundation for long-term domiciliary management of hypoxemia. The Nocturnal Oxygen Therapy Trial (NOTT)(≥ 19 hours of continuous oxygen compared to ≤ 13 hours)[163] and the Medical Research Council (MRC)(≥ 15

hours compared to no oxygen),[164] two RCTs in COPD patients with resting $PaO_2 \leq 55$ mmHg or < 60 mmHg with *cor pulmonale* or secondary polycythemia showed a survival benefit. No significant benefit of LTOT was found in patients with moderate desaturation.[165]

Non-invasive positive pressure ventilation (NPPV). Recent meta-analyses[141,166] have shown positive results of long-term NPPV in patients with stable COPD. Although RCT results have being inconsistent on survival, larger trials with mortality as the primary outcome, enrolling patients with marked hypercapnia and applying higher IPAP levels demonstrated a reduction of mortality.[146,167]

Lung transplantation and lung volume reduction surgery (LVRS). Because of the absence of randomized trials, observational data has been used to estimate the survival benefit of lung transplantation, relative to remaining "untransplanted." The survival benefit of transplantation varied by disease group, with a 2-year expected benefit in 2/5 of transplanted COPD patients.[168]

LVRS has been shown to prolong survival compared to medical therapy in a very select group of patients with severe COPD, predominantly upper lobe emphysema, and low exercise capacity post-rehabilitation.[169] Among patients with non-upper-lobe emphysema and high exercise capacity post-rehabilitation, mortality was higher in the surgery group than in the medical-therapy group.

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

Overview of the evidence: Pharmacotherapy

Pharmacotherapies for smoking cessation

Pharmacological treatments for smoking cessation include controller medications aimed at achieving long-term abstinence (nicotine patch, bupropion, and varenicline) and those that rapidly relieve acute withdrawal symptoms (short-acting nicotine). Please see **Chapter 3** of the the **GOLD 2025 Report** for further information on Nicotine replacement products, Vaping/E-cigarettes, and Pharmacological products (nicotine replacement therapy, bupropion, nortriptyline and varenicline).

Pharmacotherapy to treat stable COPD

Pharmacotherapy for COPD is currently focused on symptoms and exacerbations. FEV1 decline has been considered a surrogate for the natural course of the disease. In this context, studies have been performed to evaluate if pharmacotherapy may have an impact on the change of FEV1 over time. Individual clinical trials have not been sufficiently conclusive to show that pharmacotherapy can reduce the rate of FEV1 decline.[170-174] However, a systematic review combining data from 9 studies demonstrated a reduction in the rate of FEV1 decline of 5.0 mL/year in active treatment arms compared with placebo arms.[175] The difference between long-acting bronchodilator containing treatment arms and placebo arms was 4.9 mL/year. The difference between inhaled corticosteroid containing treatment arms and placebo arms was 7.3 mL/year. Although we need to be aware of the potential benefit of pharmacotherapy in reducing the rate of lung function decline, further research is needed to know which patients are likely to benefit.

The classes of medications commonly used to treat COPD are shown in **Figure 3.18**. The choice within each class depends on the availability and cost of medication, and the clinical response balanced against side effects. Each

treatment regimen needs to be individualized as the relationship between severity of symptoms, airflow obstruction, and severity of exacerbations can differ between patients. The WHO has defined a minimum set of interventions for the management of stable COPD in primary care.[176]

Bronchodilators

Bronchodilators are medications that increase FEV1 and/or change other spirometric variables (**Figure 3.19**). They act by altering airway smooth muscle tone and the improvements in expiratory flow reflect widening of the airways rather than changes in lung elastic recoil. Bronchodilators tend to reduce dynamic hyperinflation at rest and during exercise,[177,178] and improve exercise performance. The extent of these changes, especially in patients with severe and very severe COPD, is not easy to predict from the improvement in FEV1 measured at rest.[179,180]

Bronchodilator dose-response (FEV1 change) curves are relatively flat with all classes of bronchodilators.[181-187] 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[188] but is not necessarily helpful in stable disease.[189] Bronchodilator medications in COPD are most often given on a regular basis to prevent or reduce symptoms. Toxicity is also dose-related (**Figure 3.18**). Use of short acting bronchodilators on a regular basis is not generally recommended.

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.[183,184] Regular and as-needed use of SABAs improve FEV1 and symptoms.[190] LABAs show duration of action of 12 or more hours and do not preclude additional benefit from as-needed SABA therapy.[191]

Formoterol and salmeterol are twice-daily LABAs that significantly improve FEV1 and lung volumes, dyspnea, health status, exacerbation rate and number of hospitalizations,[192] but have no effect on mortality or rate of decline of lung function. Indacaterol is a once daily LABA that improves breathlessness,[193,194] health status[194] and exacerbation rate.[194] Some patients experience cough following the inhalation of indacaterol. Oladaterol and vilanterol are additional once daily LABAs that improve lung function and symptoms.[195,196]

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,[197] and oxygen consumption can be increased under resting conditions in patients with chronic heart failure,[198] 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[199] 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.[192,200,201]

Maintenance Medications in COPD*

Figure 3.18

Generic Drug Name	Inhaler Type	Nebulizer	Oral/Injectable Delivery	Duration of Action
$BETA_2$-Agonists				
Short-acting (SABA)				
Fenoterol	MDI	✓	tablet, solution	variable
Levalbuterol	MDI	✓		variable
Salbutamol (albuterol)	MDI & DPI	✓	syrup, tablet	variable
Terbutaline	DPI		tablet	variable
Long-acting (LABA)				
Arformoterol		✓		12 hours
Formoterol	DPI	✓		12 hours
Indacaterol	DPI			24 hours
Olodaterol	SMI			24 hours
Salmeterol	MDI & DPI			12 hours
Anticholinergics				
Short-acting (SAMA)				
Ipratropium bromide	MDI	✓		6-8 hours
Oxitropium bromide	MDI	✓		7-9 hours
Long-acting (LAMA)				
Aclidinium bromide	DPI			12 hours
Glycopyrronium bromide	DPI		solution	variable
Tiotropium	DPI, SMI, MDI			24 hours
Umeclidinium	DPI			24 hours
Glycopyrronium		✓		12 hours
Revefenacin		✓		24 hours
Combination Short-Acting $Beta_2$-Agonist Plus Anticholinergic in One Device (SABA+SAMA)				
Fenoterol/ipratropium	SMI	✓		6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓		variable
Combination Long-Acting $Beta_2$-Agonist Plus Anticholinergic in One Device (LABA+LAMA)				
Formoterol/aclidinium	DPI			12 hours
Formoterol/glycopyrronium	MDI			12 hours
Indacaterol/glycopyrronium	DPI			12-24 hours
Vilanterol/umeclidinium	DPI			24 hours
Olodaterol/tiotropium	SMI			24 hours
Methylxanthines				
Aminophylline			solution, injectable	variable
Theophylline (SR)			tablet, capsule, elixir, solution, injectable	variable
Combination of Long-Acting $Beta_2$-Agonist Plus Corticosteroid in One Device (LABA+ICS)				
Formoterol/beclometasone	MDI, DPI			12 hours
Formoterol/budesonide	MDI, DPI			12 hours
Formoterol/mometasone	MDI			12 hours
Salmeterol/fluticasone propionate	MDI, DPI			12 hours
Vilanterol/fluticasone furoate	DPI			24 hours
Triple Combination in One Device (LABA+LAMA+ICS)				
Fluticasone/umeclidinium/vilanterol	DPI			24 hours
Beclometasone/formoterol/glycopyrronium	MDI, DPI			12 hours
Budesonide/formoterol/glycopyrrolate	MDI			12 hours
Phosphodiesterase-3 and/or -4 Inhibitors				
Roflumilast			tablet	24 hours
Ensifentrine		✓		12 hours
Mucolytic Agents				
Erdosteine			capsule, suspension	12 hours
Carbocysteine†			capsule, packet, solution,syrup	6-8 hours
N-acetylcysteine†		✓	solution, tablet	2-6 hours
Biologics				
Dupilumab			injectable	2 weeks

*This list is not exhaustive. Not all formulations are available in all countries. In some countries other formulations and dosages may be available. †Dosing regimens are under discussion. MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler. Note that glycopyrrolate & glycopyrronium are the same compound.

Bronchodilators in Stable COPD

Figure 3.19

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**
- Inhaled bronchodilators are recommended over oral bronchodilators (**Evidence A**)
- Regular and as-needed use of SABA or SAMA improves FEV1 and symptoms **(Evidence A)**
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV1 and symptoms **(Evidence A)**
- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea (**Evidence A**), and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**
- When initiating treatment with long acting bronchodilators the preferred choice is a combination of a LABA and a LAMA. In patients with persistent dyspnea on a single long-acting bronchodilator treatment should be escalated to two (**Evidence A**).
- Combination treatment with a LABA and a LAMA increases FEV1 and reduces symptoms compared to monotherapy **(Evidence A)**
- Combination treatment with a LABA+LAMA reduces exacerbations compared to monotherapy **(Evidence B)**
- Combinations can be given as single inhaler or multiple inhaler treatment. Single inhaler therapy may be more convenient and effective than multiple inhalers
- Ensifentrine significantly improves lung function **(Evidence A)**, dyspnea **(Evidence A)** and health status **(Evidence B)**
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**

Antimuscarinic drugs

Antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle.[202] Short-acting antimuscarinics (SAMAs), namely ipratropium and oxitropium, also block the inhibitory neuronal receptor M2, which potentially can cause vagally induced bronchoconstriction.[203] Long-acting muscarinic antagonists (LAMAs), such as tiotropium, aclidinium, glycopyrronium bromide (also known as glycopyrrolate), umeclidinium and revefenacin have prolonged binding to M3 muscarinic receptors, with faster dissociation from M2 muscarinic receptors, thus prolonging the duration of bronchodilator effect.[202]

A systematic review of RCTs concluded that ipratropium, a short acting muscarinic antagonist, alone provided small benefits over short-acting beta$_2$-agonist in terms of lung function, health status and requirement for oral steroids.[204] Among LAMAs, some are administered once a day (tiotropium, umeclidinium, revefenacin), others twice a day (aclidinium), and some are approved for once daily dosing in some countries and twice daily dosing in others (glycopyrrolate).[202,205] LAMA treatments improve symptoms, including cough and sputum and health status.[202,206,207] They also improve the effectiveness of pulmonary rehabilitation[208,209] and reduce exacerbations and related hospitalizations.[206] Clinical trials have shown a greater effect on exacerbation rates for LAMA treatment (tiotropium) versus LABA treatment.[210,211]

Adverse effects

Inhaled anticholinergic drugs are poorly absorbed which limits the troublesome systemic effects observed with atropine.[202,212] 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.[203,213] Although occasional urinary symptoms have been reported, there are no data to prove a true causal relationship.[214] 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.[215,216] In a large, long-term clinical trial in COPD patients, tiotropium added to other standard therapies had no effect on cardiovascular risk.[174] Although there were some initial concerns regarding the safety of tiotropium delivery via the Respimat®[217] 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.[218] 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.[219-221]

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.[222-224] 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,[222] 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.[225] Addition of theophylline to salmeterol produces a greater improvement in FEV1 and breathlessness than salmeterol alone.[226,227] Earlier studies reported contradictory evidence regarding the effect of low-dose theophylline on exacerbation rates.[228,229] 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.[230] A large placebo-controlled trial showed no effect of oral theophylline alone or in combination with prednisolone 5 mg daily on exacerbations of severe COPD.[231]

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.[223,225] Methylxanthines are non-specific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include atrial and ventricular arrhythmias (which can prove fatal) and *grand mal* convulsions (which can occur irrespective of prior epileptic history). Other side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum levels of theophylline. These medications have significant interactions with commonly used medications such as erythromycin (but not azithromycin), certain quinolone antibiotics (ciprofloxacin, but not ofloxacin), allopurinol, cimetidine (but not ranitidine), serotonin uptake inhibitors (fluvoxamine) and the 5-lipoxygenase inhibitor zileuton.

Combination bronchodilator therapy

Combining bronchodilators with different mechanisms and durations of action may increase the degree of

bronchodilation with a lower risk of side-effects compared to increasing the dose of a single bronchodilator.[232,233] Combinations of SABAs and SAMAs are superior compared to either medication alone in improving FEV1 and symptoms.[234] Treatment with formoterol and tiotropium in *separate inhalers* has a bigger impact on FEV1 than either component alone.[235] There are numerous combinations of a LABA and LAMA in a *single inhaler* available (**Figure 3.18**). These combinations improve lung function compared to placebo;[232] 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.[236] Single inhalers improve adherence to treatment.[237] 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.[238-241] 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.[242] 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.[105] The LABA+LAMA combination demonstrated favorable improvements compared with the monotherapies for the majority of outcomes irrespective of baseline HRQoL.[243] 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[244] (**Figure 3.19**). These findings have been shown in people across different ethnic groups (Asian as well as European).[245]

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.[246] 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.[247] Another study in patients with a history of exacerbations showed that a combination LABA+LAMA decreased exacerbations to a greater extent than an LABA+ICS combination.[248] However, another study in a population with high exacerbation risk (≥ 2 exacerbations and/or 1 hospitalization in the previous year) reported that LABA+ICS decreased exacerbations to a greater extent than a LABA+LAMA combination at higher blood eosinophil concentrations.[70] 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.[249]

Anti-inflammatory agents

To date, exacerbations (e.g., exacerbation rate, patients with at least one exacerbation, time-to-first exacerbation) represent the main clinically relevant end-point used for efficacy assessment of drugs with anti-inflammatory effects (**Figure 3.20**).

Inhaled corticosteroids (ICS)

General considerations

In vitro evidence suggests that COPD-associated inflammation has limited responsiveness to corticosteroids. Moreover, some drugs including beta$_2$-agonists, theophylline or macrolides may partially facilitate corticosteroid sensitivity in COPD.[250,251] The clinical relevance of this effect has not yet been fully established.

In vivo data suggest that the dose-response relationships and long-term (> 3 years) safety of ICS in people with COPD are unclear and require further investigation.[248] 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.[70,252]

Anti-Inflammatory Therapy in Stable COPD

Figure 3.20

Inhaled Corticosteroids	• Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)** • An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)** • We do not encourage the use of a LABA+ICS combination in COPD. If there is an indication for an ICS the combination LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice • Triple inhaled therapy of LABA+LAMA+ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA+ICS, LABA+LAMA or LAMA monotherapy **(Evidence A)**. Recent data suggesta beneficial effect of triple inhaled therapy versus fixed-dose LABA+LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations • If patients with COPD have features of asthma, treatment should always contain an ICS • Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of pneumonia **(Evidence C)** • Combinations can be given as single or multiple inhaler therapy. Single inhaler therapy may be more convenient and effective than multiple inhalers
Oral Glucocorticoids	• Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**
PDE Inhibitors	• In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations: ▪ Roflumilast improves lung function and reduces moderate and severe exacerbations **(Evidence A)** • Ensifentrine improves lung function **(Evidence A)** but an effect on exacerbations has not been evaluated in patients at increased exacerbation risk
Antibiotics	• Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)** • Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, azithromycin can be considered (**Evidence B**) • Treatment with azithromycin is associated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**
Mucoregulators & Antioxidant Agents	• Regular treatment with mucolytics such as erdosteine, carbocysteine and NAC reduces the risk of exacerbations in select populations **(Evidence B)** • Antioxidant mucolytics are recommended only in selected patients **(Evidence A)**
Biologics	• In patients with moderate to severe COPD with a history of exacerbations, chronic bronchitis and higher blood eosinophil counts (≥ 300 cells/µL): ▪ Dupilimab reduces exacerbations, improves lung function and quality of life **(Evidence A)**
Other Anti-Inflammatory Agents	• Statin therapy is not recommended for prevention of exacerbations (**Evidence A**) • Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy **(Evidence A)**. However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications **(Evidence C)** • Leukotriene modifiers have not been tested adequately in COPD patients

Efficacy of ICS (alone)

Most studies have found that regular treatment with ICS alone does not modify the long-term decline of FEV1 nor mortality in people with COPD.[253] Studies and meta-analyses assessing the effect of regular treatment with ICS alone on mortality in people with COPD have not provided conclusive evidence of benefit.[253] 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.[155] 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.[254] In moderate COPD, fluticasone furoate alone or in combination with vilanterol was associated with slower decline in FEV1 compared with placebo or vilanterol alone by on average 9 mL/year.[255] A number of studies have investigated whether there is a relationship between ICS treatment and risk of lung cancer with conflicting results.[256]

ICS in combination with long-acting beta agonist

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.[257,258] Clinical trials powered on all-cause mortality as the primary outcome failed to demonstrate a statistically significant effect of LABA+ICS combination therapy on survival.[155,254]

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.[65-70] 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.[75] Data modeling indicates that ICS containing regimens have little or no effect at a blood eosinophil count < 100 cells/µL,[65] therefore, this threshold can be used to identify patients with a low likelihood of treatment benefit with ICS. In addition, lower blood and sputum eosinophils are associated with greater presence of proteobacteria,[259-261] notably haemophilus, and increased bacterial infections and pneumonia.[262] Lower blood eosinophil counts therefore may identify individuals with microbiome profiles associated with increased risk of clinical worsening due to pathogenic bacterial species. The threshold of a blood eosinophil count ≥ 300 cells/µL identifies the top of the continuous relationship between eosinophils and ICS, and can be used to identify patients with the greatest likelihood of treatment benefit with ICS.

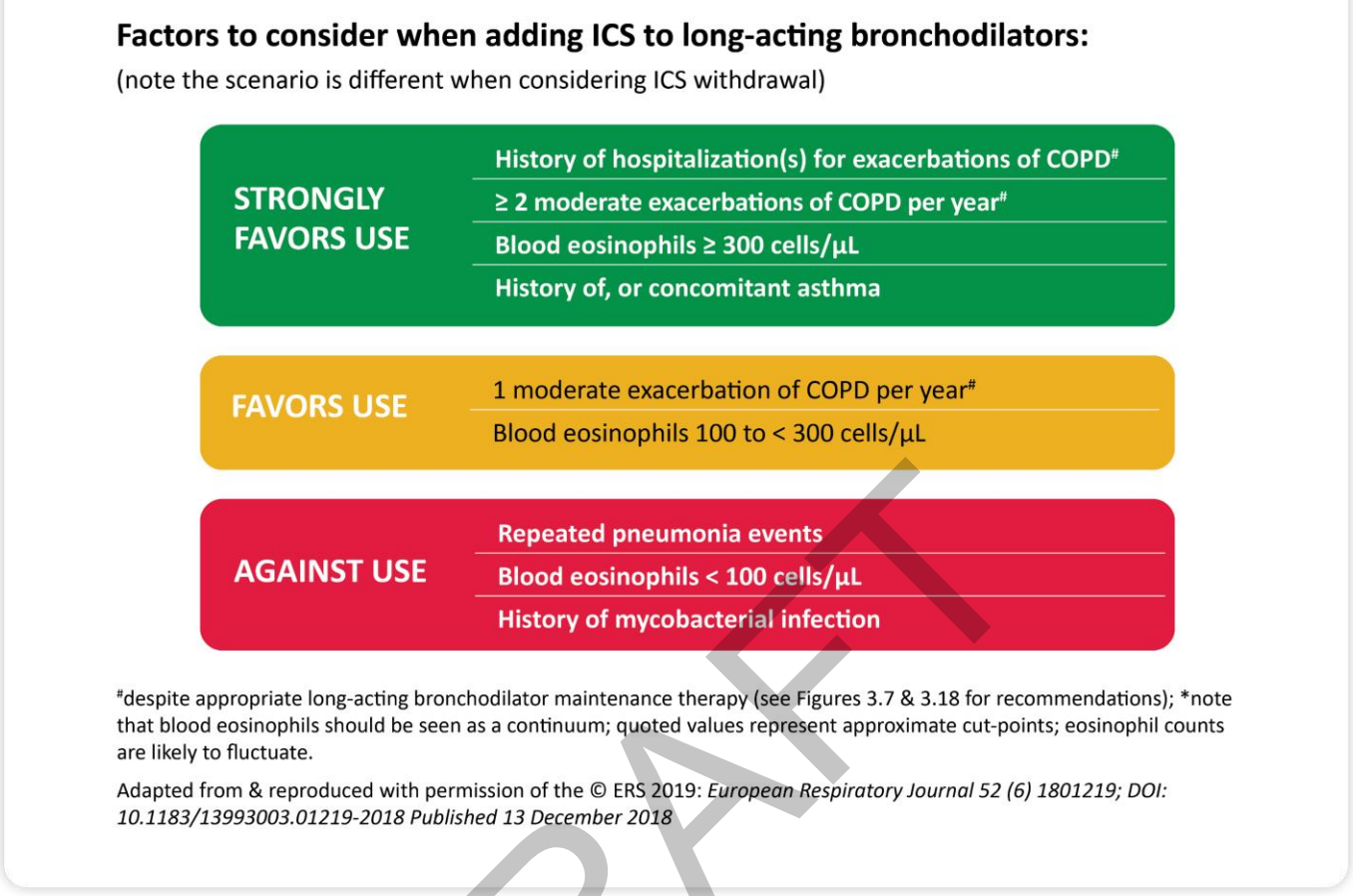
Sources of evidence include: 1) *post-hoc* analyses comparing LABA+ICS versus LABA[65,66,68]; 2) pre-specified analyses comparing triple therapy versus LABA+LAMA or LAMA[67,69,70]; and 3) other analyses comparing LABA+ICS versus LABA+LAMA[263] or studying ICS withdrawal.[119,120,264]

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).[67,70,248] Thus, the use of blood eosinophil counts to predict ICS effects should always be combined with clinical assessment of exacerbation risk (as indicated by the previous history of exacerbations). Other factors (smoking status, ethnicity, geographical location) could influence the relationship between ICS effect and blood eosinophil count but remains to be further explored.

Factors to consider when initiating ICS treatment in combination with one or two long-acting bronchodilators are shown in **Figure 3.21**.[265]

Factors to Consider when Initiating ICS Treatment

Figure 3.21



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

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Adverse effects

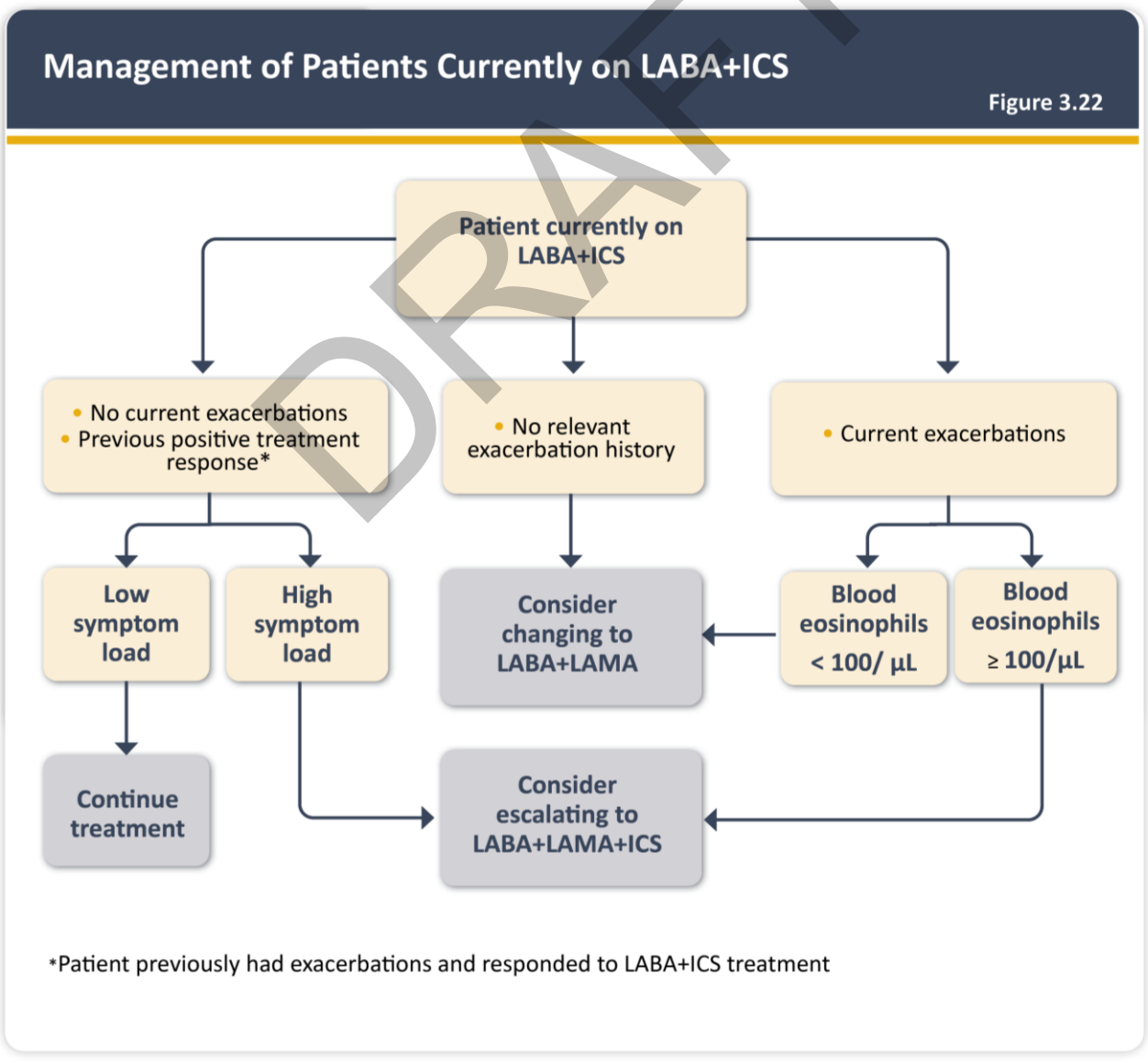
There is high quality evidence from RCTs that ICS use modifies the airway microbiome[266] and is associated with higher prevalence of oral candidiasis, hoarse voice, skin bruising and pneumonia.[253] This excess risk has been confirmed in ICS studies using fluticasone furoate, even at low doses.[267] Patients at higher risk of pneumonia include those who currently smoke, are aged ≥ 55 years, have a history of prior exacerbations or pneumonia, a body mass index (BMI) < 25 kg/m^2, a poor MRC dyspnea grade and/or severe airflow obstruction.[268,269] Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of developing pneumonia.[270] In studies of patients with moderate COPD, ICS by itself or in combination with a LABA did not increase the risk of pneumonia.[254,269]

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.[172,267,271-273] Results of observational studies suggest that ICS treatment could also be associated with increased risk of diabetes/poor control of diabetes,[274] cataracts,[275] and mycobacterial infection.[276] An increased risk of tuberculosis has been found in both observational studies and a meta-analysis of RCTs.[277-279] In the absence of RCT data on these issues, it is not possible to draw firm conclusions.[280] ICS and lung cancer incidence is discussed in **Chapter 5** of the **GOLD 2025 Report**.

Management of patients currently on LABA+ICS

In general, if there is an indication for ICS use then LABA+LAMA+ICS has been shown to be superior to LABA+ICS (**Figure 3.22**). For patients currently on LABA+ICS, it is important to review whether there was a relevant prior exacerbation history and whether there was a previous positive response to ICS treatment. Using this information, the following should be considered:

- If there was no relevant exacerbation history, then consider changing to LABA+LAMA (**Figure 3.22**).
- If there was a previous exacerbation history but currently there are no exacerbations this suggests a positive response to treatment.[281-286] If dyspnea persists despite treatment with LABA+ICS, escalation to LABA+LAMA+ICS should be considered.[287-290]
- If the patient is currently suffering with exacerbations, then blood eosinophil counts can be used to guide treatment; if < 100 cells/µl then consider changing to LABA+LAMA, while ≥ 100 cells/µl suggests that LABA+LAMA+ICS should be used (**Figure 3.22**).
- The benefits and risks of ICS withdrawal should be carefully considered, with a blood eosinophil count > 300 cells/µl being an indicator of increased risk of exacerbations with 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[291] and has been shown to improve lung function, patient reported outcomes and reduce exacerbations when compared to LAMA alone, LABA+LAMA and LABA+ICS.[67,69,70,292-299] A *post-hoc* analysis of one of the RCTs that evaluated the effects of LABA+LAMA+ICS showed that triple therapy improved clinical outcomes versus dual therapy regardless of smoking status.[300]

A *post-hoc* pooled analysis of three triple therapy clinical trials in COPD patients with severe airflow obstruction and a history of exacerbations showed a non-significant trend for lower mortality (assessed as a safety outcome) with triple inhaled therapy compared to non-ICS based treatments.[301] Two large one-year randomized controlled trials (named IMPACT and ETHOS) were reviewed earlier in Chapter 3 (see 'Therapeutic interventions that reduce COPD mortality') and provide new evidence on mortality reduction with fixed-dose inhaled triple combinations compared to dual bronchodilation.[109,302]

Oral glucocorticoids

Oral glucocorticoids have numerous side effects, including steroid myopathy[303] which can contribute to muscle weakness, decreased functionality, and respiratory failure in people with very severe COPD. Systemic glucocorticoids for treating acute exacerbations in hospitalized patients, or during emergency department visits, have been shown to reduce the rate of treatment failure, the rate of relapse and to improve lung function and breathlessness.[304] Conversely, prospective studies on the long-term effects of oral glucocorticoids in stable COPD are limited.[305,306] Therefore, while oral glucocorticoids play a role in the acute management of exacerbations, they have no role in the chronic daily treatment in COPD because of a lack of benefit balanced against a high rate of systemic complications.

Phosphodiesterase-4 (PDE4) inhibitor

The principal action of PDE4 inhibitors is to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP.[307] 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.[308] The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators,[309] and in patients who are not controlled on fixed-dose LABA+ICS combinations.[116] The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation.[115,118] There has been no study directly comparing roflumilast with an inhaled corticosteroid.

Adverse effects

Roflumilast has more adverse effects than inhaled medications for COPD.[310] 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[311,312] 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.[313] Later studies have shown that regular use of some antibiotics may reduce exacerbation rate.[314,315]

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.[114,316,317] Azithromycin use was associated with an increased incidence of bacterial resistance, prolongation of QTc interval, and impaired hearing tests.[114] A *post-hoc* analysis suggests lesser benefit in active smokers.[115] There are no data showing the efficacy or safety of chronic azithromycin treatment to prevent COPD exacerbations beyond one-year of treatment.

Pulse therapy with moxifloxacin (400 mg/day for 5 days every 8 weeks) in patients with chronic bronchitis and frequent exacerbations had no beneficial effect on the exacerbation rate overall.[318] Long-term doxycycline did not reduce exacerbations, although there may be responder subgroups.[319]

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

In COPD patients not receiving ICS, regular treatment with mucolytics such as carbocysteine and N-acetylcysteine (NAC) may reduce exacerbations and modestly improve health status.[320-323] In contrast, it has been shown that erdosteine may have a significant effect on (mild) exacerbations irrespective of concurrent treatment with ICS. Due to the heterogeneity of studied populations, treatment dosing and concomitant treatments, currently available data do not allow precise identification of the potential target population for antioxidant agents in COPD.[324]

Phosphodiesterase 3 and 4 (PDE 3 & PDE4) inhibitors

Ensifentrine is a novel, first-in-class, inhaled dual inhibitor of PDE3 and PDE4 with both anti-inflammatory activity and bronchodilator effects. PDE3 inhibition, through modulation of cyclic GMP levels, causes smooth muscle relaxation.[325] In parallel phase III studies, ensifentrine, delivered via standard jet nebulizer, significantly improved lung function[325] and dyspnea but had inconsistent effects on quality of life. A reduction in exacerbation rate was suggested but the patient populations were not enriched for exacerbation risk. In addition, the studies were not designed to assess the impact of ensifentrine on top of LABA+LAMA or LABA+LAMA+ICS making it difficult to fully position this agent in our treatment algorithm (**Figure 3.9**).[75,110-112] Studies did not find safety or tolerability issues.[326] Ensifentrine is currently only available in the United States.

Other drugs with potential to reduce exacerbations

Four large phase 3 studies have investigated the efficacy of the anti-IL-5 monoclonal antibody mepolizumab[327] and the anti-IL-5 receptor-α antibody benralizumab[328] in patients with COPD, who had a history of two or more exacerbations in the last year and increased blood eosinophil count. The studies showed inconsistent effects on exacerbation reduction, and none have received regulatory approval for treatment of COPD. Currently, large randomized trials are been conducted to investigate whether these and other biologic treatments are effective in a population who have more compelling evidence of eosinophilic or type II airway inflammation.[111]

Dupilumab is a fully human monoclonal antibody that blocks the shared receptor component for interleukin-4 and interleukin-13. In two large, phase 3, double-blind, randomized trials, patients with COPD, chronic bronchitis, a history of two or more moderate exacerbations or one or more severe exacerbation(s) in the last year despite treatment with LABA+LAMA+ICS, and blood eosinophil count of ≥ 300 cells/µL who received dupilumab had fewer exacerbations, better lung function and improved health status over 52 weeks.[110,111]

Nedocromil and leukotriene modifiers have not been tested adequately in COPD patients and the available evidence does not support their use. [329,330]

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.[331]

A recent Cochrane meta-analysis did not show sufficient evidence to support the use of immunostimulants.[332]

An RCT of the selective β1 receptor blocker metoprolol in patients with moderate or severe COPD, who did not have an established indication for beta-blocker use, showed it did not delay the time until the first COPD exacerbation compared to the placebo group and hospitalization for exacerbation was more common among the patients treated with metoprolol.[333,334] There is no evidence that beta-blockers should be used in people with COPD who do not have a cardiovascular indication for their use.

Simvastatin did not prevent exacerbations in people with COPD who had no metabolic or cardiovascular indication for statin treatment.[335] An association between statin use and improved outcomes (including decreased exacerbations and mortality) has been reported in observational studies of people with COPD who received them for cardiovascular and metabolic indications.[336]

There is no evidence that supplementation with vitamin D has a positive impact on exacerbations in unselected patients.[337] In a meta-analysis vitamin D supplementation reduced exacerbation rates in patients with low baseline vitamin D levels,[338] but a more recent study has shown no effect.[339]

Adherence to inhaled COPD medications

Adherence is defined as the process by which a person takes their medication as prescribed by a healthcare provider.[340] Adherence to therapy is a challenging issue in any chronic condition including COPD. Non-adherence to COPD medication has been associated with poor symptom control, increased risk of exacerbation, increased healthcare utilization and costs, decreased health-related quality of life and higher mortality risk.[341-351] Further information on this topic is available in **Chapter 3** of the **GOLD 2025 Report**.

Overview of the evidence: Non-pharmacological therapy

Pulmonary rehabilitation, self-management and integrative care in COPD

Pulmonary Rehabilitation, Self-Management and Integrative Care in COPD

Figure 3.24

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

MANAGEMENT OF EXACERBATIONS

KEY POINTS:

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

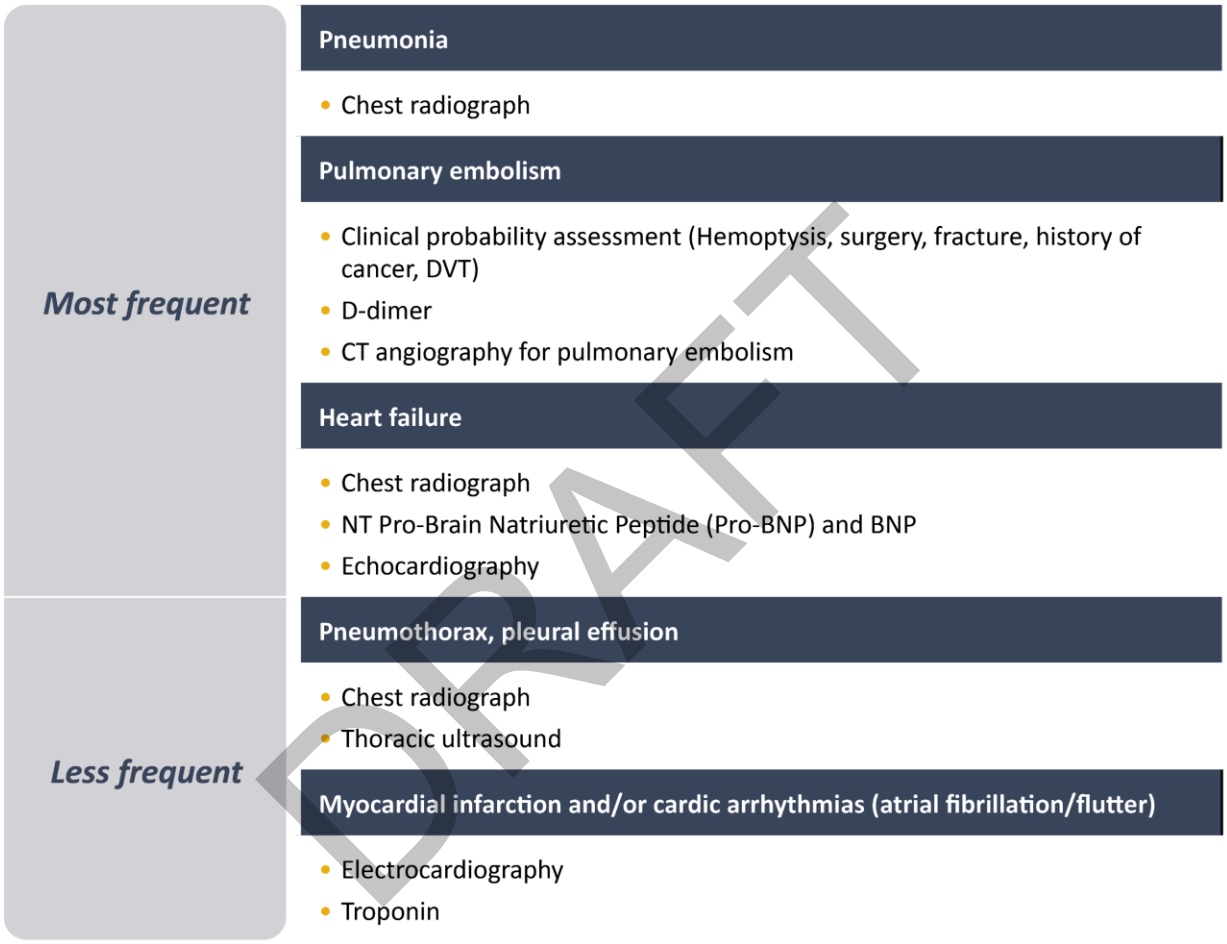
Considerations

Exacerbations of COPD are important events in the management of COPD because they negatively impact health status, rates of hospitalization and readmission, and disease progression.[56,57] COPD exacerbations are usually associated with increased airway inflammation, increased mucus production and marked gas trapping. These changes contribute to increased dyspnea that is the key symptom of an exacerbation. Other symptoms include increased sputum purulence and volume, together with increased cough and wheeze.[352,353] Patients with COPD are at increased risk of other acute events, particularly decompensated heart failure,[354,355] pneumonia,[356,357] pulmonary embolism[358,359] that may also mimic or aggravate an ECOPD. Thus, while worsening of dyspnea, particularly if

associated with cough and, purulent sputum, and no other symptoms or signs in a patient with COPD may be diagnosed as an ECOPD, other patients may have worsening of respiratory symptoms, particularly dyspnea without the classic characteristics of ECOPD, that should prompt careful consideration and/or search of those potential confounders, or contributors. In some patients one or more of these diagnoses may contribute to the clinical presentations and should be addressed appropriately (**Figure 4.1**).

Confounders or Contributors to be Considered in Patients Presenting with Suspected COPD Exacerbation

Figure 4.1



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

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

The current grading of the severity of an ECOPD, based on *post facto* use of healthcare resources, is a major limitation of the current definition. Because of global variability in the available resources to treat patients and local customs affecting the criteria for hospital visits and admissions, there is substantial variability in reported ECOPD outcomes.[360] **Figure 4.2** shows a proposed clinical approach based on the current best available evidence.[361]

Exacerbations: Diagnosis and Assessment

Figure 4.2

1.	Complete a thorough clinical assessment for evidence of COPD and potential respiratory and non-respiratory concomitant diseases, including consideration of alternative causes for the patient's symptoms and signs: primarily pneumonia, heart failure, and pulmonary embolism.
2.	**Assess:** a. Symptoms, severity of dyspnea that can be determined by using a VAS, and documentation of the presence of cough. b. Signs (tachypnea, tachycardia), sputum volume and color, and respiratory distress (accessory muscle use).
3.	Evaluate severity by using appropriate additional investigations such as pulse oximetry, laboratory assessment, CRP, arterial blood gases.
4.	Consider appropriate place of care.
5.	Establish the cause of the event (viral, bacterial, environmental, other).

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

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.[362] 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.[60,174,363]

Potential Indications for Hospitalization Assessment*

Figure 4.4

- 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

The indications for assessing the need for hospitalization during a COPD exacerbation are shown in **Figure 4.4**. When patients with a COPD exacerbation come to the emergency department, if hypoxemic they should be provided with supplemental oxygen and undergo assessment to determine whether the exacerbation is life-threatening and if increased work of breathing or impaired gas exchange requires consideration for non-invasive ventilation. If so, healthcare providers should consider admission to an area where proper monitoring and care can be provided. In less severe cases, the patient may be managed in the emergency department or hospital ward unit. In addition to pharmacological therapy, hospital management of exacerbations includes respiratory support (oxygen therapy, ventilation). The management of severe, but not life threatening, exacerbations is outlined in **Figure 4.5**.

The clinical presentation of COPD exacerbation is heterogeneous; thus, we recommend that in **hospitalized patients** the severity of the exacerbation should be based on the patient's clinical signs and recommend the following classification:[364]

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

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

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

Key points for the management of all exacerbations are given in **Figure 4.6.** Some patients need immediate admission to the respiratory care or intensive care unit (ICU) (**Figure 4.7**).

Management of Severe but not Life-threatening Exacerbations*

Figure 4.5

Assess severity of symptoms, blood gases, chest radiograph

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

Bronchodilators:

- Increase doses and/or frequency of short-acting bronchodilators
- Combine short-acting beta 2-agonists and anticholinergics
- Consider use of long-acting bronchodilators when patient becomes stable
- Use spacers or air-driven nebulizers when appropriate

Consider oral corticosteroids

Consider antibiotics (oral) when signs of bacterial infection are present

Consider noninvasive mechanical ventilation (NIV)

At all times:

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

*Local resources need to be considered

Key Points for the Management of Exacerbations

Figure 4.6

- Short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation **(Evidence C)**
- Systemic corticosteroids can improve lung function (FEV1), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not normally be more than 5 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 normally be 5 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)**

Indications for Respiratory or Medical Intensive Care Unit Admission*

Figure 4.7

- 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 < 40 mmHg) 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.

Respiratory Support

The indications for NIV[365] are summarized in **Figure 4.8**. The indications for initiating invasive mechanical ventilation during an exacerbation are shown in **Figure 4.9**.

Indications for Noninvasive Mechanical Ventilation (NIV)

Figure 4.8

At least one of the following:

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

Indications for Invasive Mechanical Ventilation

Figure 4.9

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

COPD AND COMORBIDITIES

KEY POINTS:

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

REFERENCES

The full list of references for this pocket guide can be found online at: www.goldcopd.org/pocketguidereferences.

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