



COPD UPDATE

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**Global Initiative for Chronic
Obstructive
Lung
Disease**

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



Chronic Obstructive Pulmonary Disease (COPD)

- ▶ COPD is currently the fourth leading cause of death in the world.¹
- ▶ COPD is projected to be the 3rd leading cause of death by 2020.²
- ▶ More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally.
- ▶ Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population.

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2095-128.

2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; **3**(11): e442.



GOLD 2019 Report: Chapters

Global Initiative for Chronic Obstructive Lung Disease



GLOBAL STRATEGY FOR THE DIAGNOSIS,
MANAGEMENT, AND PREVENTION OF
CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2019 REPORT

1. Definition and Overview
2. Diagnosis and Initial Assessment
3. Evidence Supporting Prevention & Maintenance Therapy
4. Management of Stable COPD
5. Management of Exacerbations
6. COPD and Comorbidities



COPD Definition

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



Etiology, pathobiology & pathology of COPD leading to airflow limitation & clinical manifestations

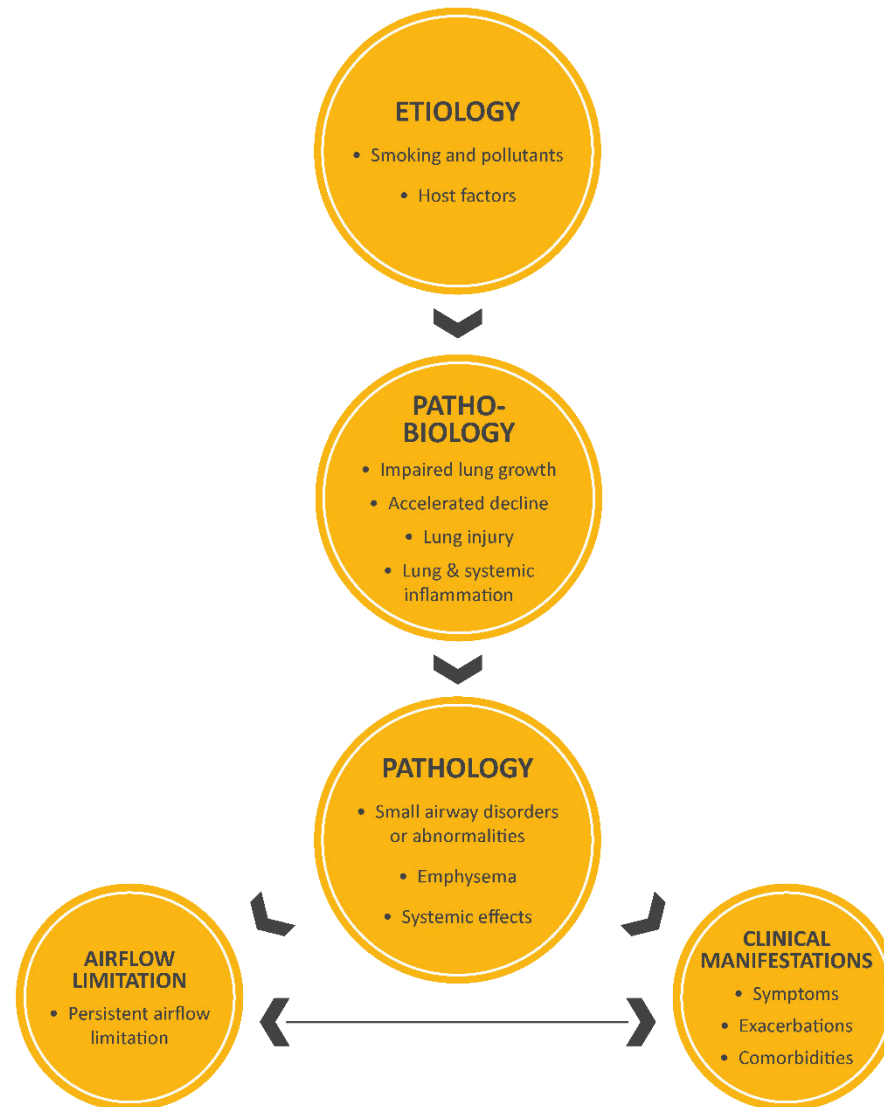


FIGURE 1.1



FEV₁ progression over time

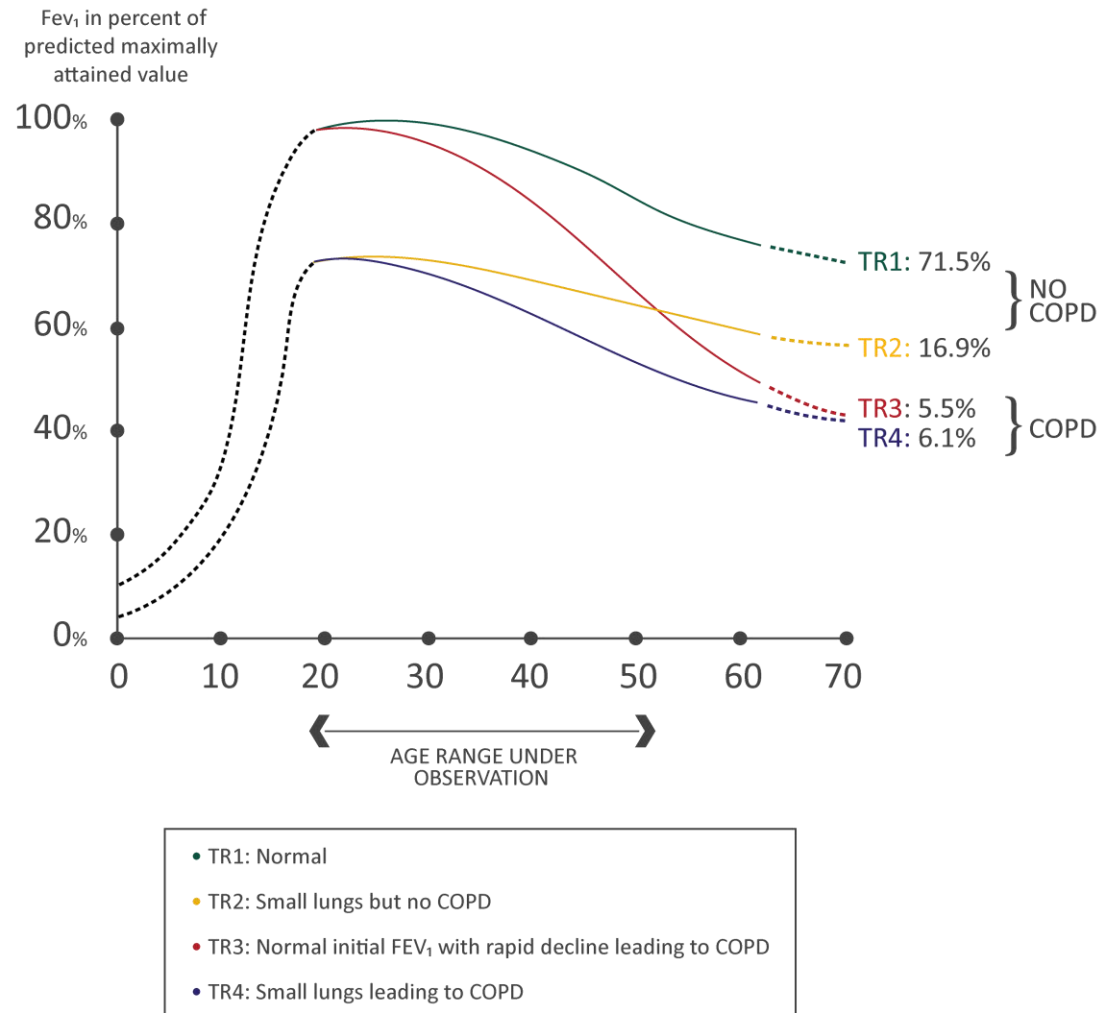


FIGURE 1.2



Definition and Overview

OVERALL KEY POINTS (1 of 2):

- ▶ Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.
- ▶ The most common respiratory symptoms include dyspnea, cough and/or sputum production. These symptoms may be under-reported by patients.
- ▶ The main risk factor for COPD is tobacco smoking but other environmental exposures such as biomass fuel exposure and air pollution may contribute.



Definition and Overview

OVERALL KEY POINTS (2 of 2):

- ▶ Besides exposures, host factors predispose individuals to develop COPD. These include genetic abnormalities, abnormal lung development and accelerated aging.
- ▶ COPD may be punctuated by periods of acute worsening of respiratory symptoms, called exacerbations.
- ▶ In most patients, COPD is associated with significant concomitant chronic diseases, which increase its morbidity and mortality.



Prevalence

Prevalence of COPD

- ▶ Prevalence of COPD was higher in smokers and ex-smokers compared to non-smokers
- ▶ Higher in ≥ 40 year group compared to those < 40
- ▶ Higher in men than women



Prevalence

Prevalence of COPD

- ▶ Estimated 384 million COPD cases in 2010.
- ▶ Estimated global prevalence of 11.7% (95% CI 8.4%–15.0%).
- ▶ Three million deaths annually.
- ▶ With increasing prevalence of smoking in developing countries, and aging populations in high-income countries, the prevalence of COPD is expected to rise over the next 30 years.
- ▶ By 2030 predicted 4.5 million COPD related deaths annually.



Economic and Social Burden

Economic burden of COPD

- ▶ COPD is associated with significant economic burden.
- ▶ COPD exacerbations account for the greatest proportion of the total COPD burden.

- ▶ European Union:
 - Direct costs of respiratory disease ~6% of the total healthcare budget
 - COPD accounting for 56% (38.6 billion Euros) of the cost of respiratory disease.

- ▶ USA:
 - Direct costs of COPD are \$32 billion
 - Indirect costs \$20.4 billion.



Factors that influence disease progression

- ▶ Genetic factors
- ▶ Age and gender
- ▶ Lung growth and development
- ▶ Exposure to particles
- ▶ Socioeconomic status
- ▶ Asthma & airway hyper-reactivity
- ▶ Chronic bronchitis
- ▶ Infections



Pathology, pathogenesis & pathophysiology

- ▶ Pathology
 - Chronic inflammation
 - Structural changes

- ▶ Pathogenesis
 - Oxidative stress
 - Protease-antiprotease imbalance
 - Inflammatory cells
 - Inflammatory mediators
 - Peribronchiolar and interstitial fibrosis

- ▶ Pathophysiology
 - Airflow limitation and gas trapping
 - Gas exchange abnormalities
 - Mucus hypersecretion
 - Pulmonary hypertension



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Diagnosis and Initial Assessment

OVERALL KEY POINTS (1 of 2):

- ▶ 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.
- ▶ Spirometry is required to make the diagnosis; the presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation.
- ▶ The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on the patient's health status, and the risk of future events (such as exacerbations, hospital admissions, or death), in order to guide therapy.



Diagnosis and Initial Assessment

OVERALL KEY POINTS (2 of 2):

- ▶ Concomitant chronic diseases occur frequently in COPD patients, including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety, and lung cancer. These comorbidities should be actively sought and treated appropriately when present as they can influence mortality and hospitalizations independently.



Diagnosis and Initial Assessment

▶ PATHWAYS TO THE DIAGNOSIS OF COPD

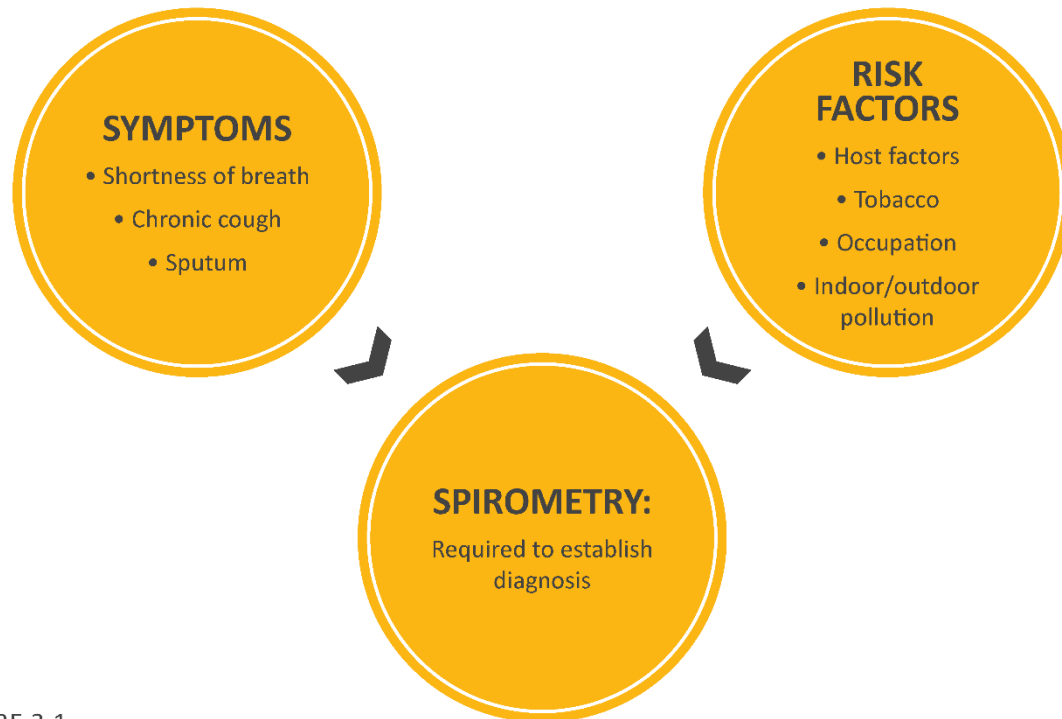


FIGURE 2.1



Diagnosis and Initial Assessment

▶ KEY INDICATORS FOR CONSIDERING A DIAGNOSIS OF COPD

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

Dyspnea that is:

Progressive over time.
Characteristically worse with exercise.
Persistent.

Chronic Cough:

May be intermittent and may be unproductive.
Recurrent wheeze.

Chronic Sputum Production: Any pattern of chronic sputum production may indicate COPD.

Recurrent Lower Respiratory Tract Infections**History of Risk Factors:**

Host factors (such as genetic factors, congenital/developmental abnormalities etc.).
Tobacco smoke (including popular local preparations).
Smoke from home cooking and heating fuels.
Occupational dusts, vapors, fumes, gases and other chemicals.

**Family History of COPD
and/or Childhood Factors:**

For example low birthweight, childhood respiratory infections etc.

TABLE 2.1



Diagnosis and Initial Assessment

► Symptoms of COPD

- Chronic and progressive dyspnea
- Cough
- Sputum production
- Wheezing and chest tightness
- Others – including fatigue, weight loss, anorexia, syncope, rib fractures, ankle swelling, depression, anxiety.



Diagnosis and Initial Assessment

▶ OTHER CAUSES OF CHRONIC COUGH

INTRATHORACIC

- Asthma
- Lung Cancer
- Tuberculosis
- Bronchiectasis
- Left Heart Failure
- Interstitial Lung Disease
- Cystic Fibrosis
- Idiopathic Cough

EXTRATHORACIC

- Chronic Allergic Rhinitis
- Post Nasal Drip Syndrome (PNDS)
- Upper Airway Cough Syndrome (UACS)
- Gastroesophageal Reflux
- Medication (e.g. ACE Inhibitors)

TABLE 2.2



Medical History

- ▶ Patient's exposure to risk factors
- ▶ Past medical history
- ▶ Family history of COPD or other chronic respiratory disease.
- ▶ Pattern of symptom development
- ▶ History of exacerbations or previous hospitalizations for respiratory disorder
- ▶ Presence of comorbidities
- ▶ Impact of disease on patient's life
- ▶ Social and family support available to the patient.
- ▶ Possibilities for reducing risk factors, especially smoking cessation.



Diagnosis and Initial Assessment

► CONSIDERATIONS IN PERFORMING SPIROMETRY

PREPARATION

- Spirometers need calibration on a regular basis.
- Spirometers should produce hard copy or have a digital display of the expiratory curve to permit detection of technical errors or have an automatic prompt to identify an unsatisfactory test and the reason for it.
- The supervisor of the test needs training in optimal technique and quality performance.
- Maximal patient effort in performing the test is required to avoid underestimation of values and hence errors in diagnosis and management.

BRONCHODILATION

- Possible dosage protocols are 400 mcg short-acting β_2 -agonist, 160 mcg short-acting anticholinergic, or the two combined.^a FEV₁ should be measured 10-15 minutes after a short-acting β_2 -agonist is given, or 30-45 minutes after a short-acting anticholinergic or a combination of both classes of drugs.

PERFORMANCE

- Spirometry should be performed using techniques that meet published standards.^b
- The expiratory volume/time traces should be smooth and free from irregularities. The pause between inspiration and expiration should be < 1 second.
- The recording should go on long enough for a volume plateau to be reached, which may take more than 15 seconds in severe disease.
- Both FVC and 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.

EVALUATION

- Spirometry measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex, and race.
- The presence of a postbronchodilator FEV₁/FVC < 0.70 confirms the presence of airflow limitation.

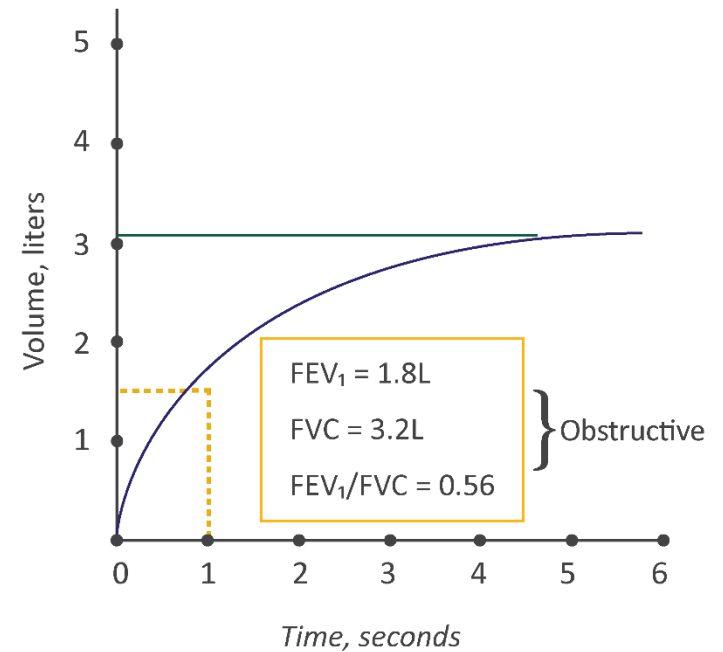
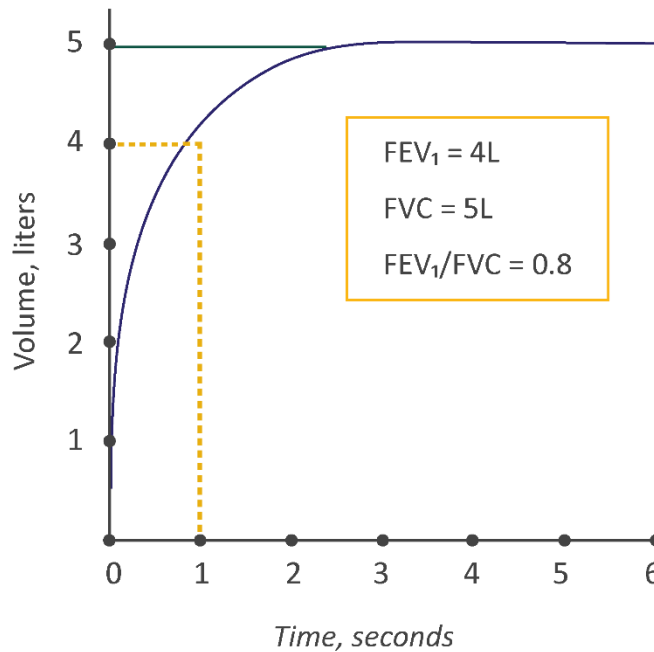
a Pellegrino et al. Eur Respir J 2005; 26(5): 948-68;

b Miller et al. Eur Respir J 2005; 26(2): 319-38.

Spirometry

SPIROMETRY - NORMAL TRACE

SPIROMETRY - OBSTRUCTIVE DISEASE



FVC = —————

FEV₁ = - - - - -

FIGURE 2.2A

FIGURE 2.2B



Post-bronchodilator FEV₁

CLASSIFICATION OF AIRFLOW LIMITATION SEVERITY IN COPD (BASED ON POST-BRONCHODILATOR FEV₁)

In patients with FEV₁/FVC < 0.70:

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

TABLE 2.4



Choice of thresholds

- ▶ COPD Assessment Test (CAT™)
- ▶ Chronic Respiratory Questionnaire (CCQ®)
- ▶ St George's Respiratory Questionnaire (SGRQ)
- ▶ Chronic Respiratory Questionnaire (CRQ)
- ▶ Modified Medical Research Council (mMRC) questionnaire



COPD Assessment Test (CAT™)

CAT™ ASSESSMENT

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

EXAMPLE: I am very happy	0	X	2	3	4	5	I am very sad	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.
FIGURE 2.3

TOTAL SCORE:



Modified MRC dyspnea scale

► MODIFIED MRC DYSPNEA SCALE^a

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

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

^a Fletcher CM. BMJ 1960; 2: 1662.

TABLE 2.5



Assessment of Exacerbation Risk

- ▶ COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy.
- ▶ Classified as:
 - **Mild** (treated with SABDs only)
 - **Moderate** (treated with SABDs plus antibiotics and/or oral corticosteroids) or
 - **Severe** (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure.
- ▶ Blood eosinophil count may also predict exacerbation rates (in patients treated with LABA without ICS).



ABCD assessment tool

THE REFINED ABCD ASSESSMENT TOOL

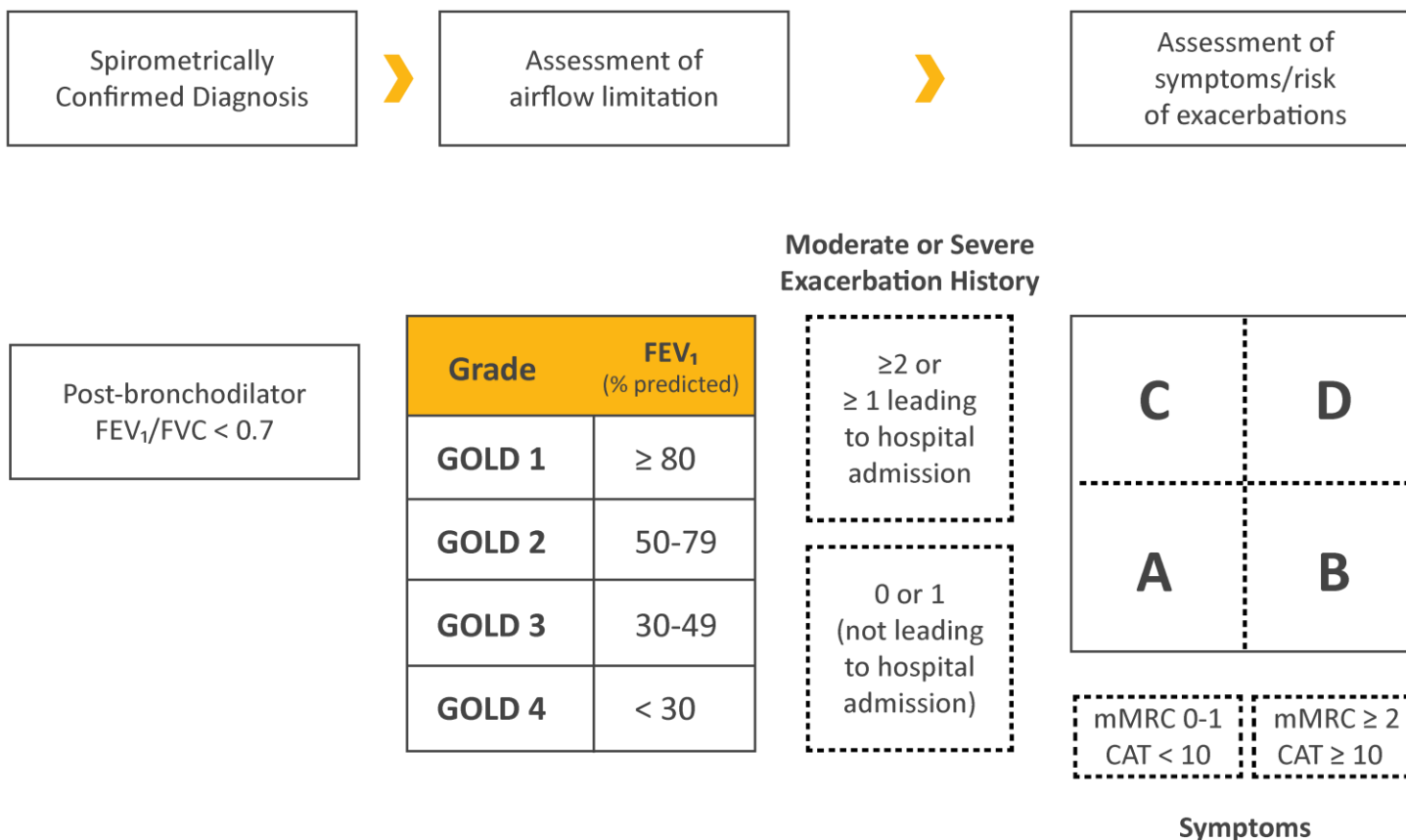


FIGURE 2.4



ABCD Assessment Tool

Example

- ▶ Consider two patients:
 - Both patients with $FEV_1 < 30\%$ of predicted
 - Both with CAT scores of 18
 - But, one with **0 exacerbations** in the past year and the other with **3 exacerbations** in the past year.
- ▶ Both would have been labelled **GOLD D** in the prior classification scheme.
- ▶ With the new proposed scheme, the subject with 3 exacerbations in the past year would be labelled **GOLD grade 4, group D**.
- ▶ The other patient, who has had no exacerbations, would be classified as **GOLD grade 4, group B**.



Summary

► ROLE OF SPIROMETRY

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

TABLE 2.6



Alpha-1 antitrypsin deficiency (AATD)

AATD screening

- ▶ The World Health Organization recommends that all patients with a diagnosis of COPD should be screened once especially in areas with high AATD prevalence.
- ▶ AATD patients are typically < 45 years with panlobular basal emphysema
- ▶ Delay in diagnosis in older AATD patients presents as more typical distribution of emphysema (centrilobular apical).
- ▶ A low concentration (< 20% normal) is highly suggestive of homozygous deficiency.



▶ DIFFERENTIAL DIAGNOSIS OF COPD

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

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

TABLE 2.7



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Prevention & Maintenance Therapy

OVERALL KEY POINTS (1 of 3):

- ▶ Smoking cessation is key. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates. Legislative smoking bans and counselling, delivered by healthcare professionals improve quit rates.
- ▶ The effectiveness and safety of e-cigarettes as a smoking cessation aid is uncertain at present.
- ▶ Pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.
- ▶ Each pharmacologic 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.



Prevention & Maintenance Therapy

OVERALL KEY POINTS (2 of 3):

- ▶ Inhaler technique needs to be assessed regularly.
- ▶ Influenza vaccination decreases the incidence of lower respiratory tract infections.
- ▶ Pneumococcal vaccination decreases lower respiratory tract infections.
- ▶ Pulmonary rehabilitation improves symptoms, quality of life, and physical and emotional participation in everyday activities.
- ▶ In patients with severe resting chronic hypoxemia, long-term oxygen therapy improves survival.



Prevention & Maintenance Therapy

OVERALL KEY POINTS (3 of 3):

- ▶ 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.



Smoking Cessation

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

▶ BRIEF STRATEGIES TO HELP THE PATIENT WILLING TO QUIT

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

TABLE 3.1



Vaccination

- ▶ Influenza vaccination can reduce serious illness (such as lower respiratory tract infections requiring hospitalization) and death in COPD patients.
- ▶ Pneumococcal vaccinations, PCV13 and PPSV23, are recommended for all patients ≥ 65 years of age.

▶ VACCINATION FOR STABLE COPD

- Influenza vaccination reduces serious illness and death in COPD patients (**Evidence B**).
- The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been shown to reduce the incidence of community - acquired pneumonia in COPD patients aged < 65 years with an $FEV_1 < 40\%$ predicted and in those with comorbidities (**Evidence B**).
- In the general population of adults ≥ 65 years the 13-valent conjugated pneumococcal vaccine (PCV13) has demonstrated significant efficacy in reducing bacteremia & serious invasive pneumococcal disease (**Evidence B**).

TABLE 3.2



Pharmacological therapy

Overview of the medications

- ▶ Pharmacological therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and health status.
- ▶ To date, there is no conclusive clinical trial evidence that any existing medications for COPD modify the long-term decline in lung function.
- ▶ The classes of medications commonly used to treat COPD are shown in **Table 3.3**.
- ▶ The choice within each class depends on the availability and cost of medication and favorable clinical response balanced against side effects.
- ▶ Each treatment regimen needs to be individualized as the relationship between severity of symptoms, airflow limitation, and severity of exacerbations can differ between patients.



Pharmacological therapy

COMMONLY USED MAINTENANCE MEDICATIONS IN COPD*

DELIVERY OPTIONS

Generic Drug Name	Inhaler Type	Nebulizer	Oral	Injection	Duration Of Action
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BETA₂-AGONISTS

SHORT-ACTING (SABA)

Fenoterol	MDI	√	pill, syrup		4-6 hours
Levalbuterol	MDI	√			6-8 hours
Salbutamol (albuterol)	MDI & DPI	√	pill, syrup, extended release tablet	√	4-6 hours 12 hours (ext. release)
Terbutaline	DPI		pill	√	4-6 hours

LONG-ACTING (LABA)

Arformoterol		√			12 hours
Formoterol	DPI	√			12 hours
Indacaterol	DPI				24 hours
Olodaterol	SMI				24 hours
Salmeterol	MDI & DPI				12 hours

ANTICHOLINERGICS

SHORT-ACTING (SAMA)

Ipratropium bromide	MDI	√			6-8 hours
Oxitropium bromide	MDI				7-9 hours

LONG-ACTING (LAMA)

Acclidinium bromide	DPI, MDI				12 hours
Glycopyrronium bromide	DPI		solution	√	12-24 hours
Tiotropium	DPI, SMI				24 hours
Umeclidinium	DPI				24 hours



Pharmacological therapy

COMBINATION SHORT-ACTING BETA ₂ -AGONIST PLUS ANTICHOLINERGIC IN ONE DEVICE (SABA/SAMA)					
Fenoterol/ipratropium	SMI	✓			6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓			6-8 hours
COMBINATION LONG-ACTING BETA ₂ -AGONIST PLUS ANTICHOLINERGIC IN ONE DEVICE (LABA/LAMA)					
Formoterol/acclidinium	DPI				12 hours
Formoterol/glycopyrronium	MDI				12 hours
Indacaterol/ glycopyrronium	DPI				12-24 hours
Vilanterol/umeclidinium	DPI				24 hours
Olodaterol/tiotropium	SMI				24 hours
METHYLYXANTHINES					
Aminophylline			solution	✓	Variable, up to 24 hours
Theophylline (SR)			pill	✓	Variable, up to 24 hours
COMBINATION OF LONG-ACTING BETA ₂ -AGONIST PLUS CORTICOSTEROIDS IN ONE DEVICE (LABA/ICS)					
Formoterol/beclometasone	MDI				
Formoterol/budesonide	MDI, DPI				
Formoterol/mometasone	MDI				
Salmeterol/fluticasone	MDI, DPI				
Vilanterol/fluticasone furoate	DPI				
TRIPLE COMBINATION IN ONE DEVICE (LABA/LAMA/ICS)					
Fluticasone/umeclidinium/vilanterol	DPI				
Beclometasone/formoterol/glycopyrronium	MDI				
PHOSPHODIESTERASE-4 INHIBITORS					
Roflumilast			pill		
MUCOLYTIC AGENTS					
Erdosteine			pill		

**Not all formulations are available in all countries. In some countries other formulations and dosages may be available.*

MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler.

TABLE 3.3



Pharmacological therapy

▶ BRONCHODILATORS IN STABLE COPD

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**.
- Regular and as-needed use of SABA or SAMA improves 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 significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**.
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**.
- Combination treatment with a LABA and LAMA increases FEV₁ and reduces symptoms compared to monotherapy **(Evidence A)**.
- Combination treatment with a LABA/LAMA reduces exacerbations compared to monotherapy **(Evidence B)**.
- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance **(Evidence B)**.
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**.

TABLE 3.4



Pharmacological therapy

▶ ANTI-INFLAMMATORY THERAPY IN STABLE COPD

INHALED CORTICOSTEROIDS

- An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD (**Evidence A**).
- Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease (**Evidence A**).
- Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms and health status and reduces exacerbations compared to ICS/LABA, LABA/LAMA or LAMA monotherapy (**Evidence A**).

ORAL GLUCOCORTICOIDS

- Long-term use of oral glucocorticoids has numerous side effects (**Evidence A**) with no evidence of benefits (**Evidence C**).

PDE4 INHIBITORS

- In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations:
 - » A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations (**Evidence A**).
 - » A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations (**Evidence A**).

ANTIBIOTICS

- Long-term azithromycin and erythromycin therapy reduces exacerbations over one year (**Evidence A**).
- Treatment with azithromycin is associated with an increased incidence of bacterial resistance (**Evidence A**) and hearing test impairments (**Evidence B**).

MUCOREGULATORS AND ANTIOXIDANT AGENTS

- Regular treatment with mucolytics such as erdosteine, carbocysteine and NAC reduces the risk of exacerbations in select populations (**Evidence B**).

OTHER ANTI-INFLAMMATORY AGENTS

- Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy (**Evidence A**). However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications (**Evidence C**).
- Leukotriene modifiers have not been tested adequately in COPD patients.

TABLE 3.5



Pharmacological therapy

▶ THE INHALED ROUTE

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

TABLE 3.6



Pharmacological therapy

▶ OTHER PHARMACOLOGICAL TREATMENTS

ALPHA-1 ANTITRYPSIN AUGMENTATION THERAPY

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

ANTITUSSIVES

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

VASODILATORS

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

TABLE 3.7



Rehabilitation, education & self-management

PULMONARY REHABILITATION, SELF-MANAGEMENT AND INTEGRATIVE CARE IN COPD

PULMONARY REHABILITATION

- Pulmonary rehabilitation improves dyspnea, health status and exercise tolerance in stable patients (**Evidence A**).
- Pulmonary rehabilitation reduces hospitalization among patients who have had a recent exacerbation (≤ 4 weeks from prior hospitalization) (**Evidence B**).

EDUCATION AND SELF-MANAGEMENT

- Education alone has not been shown to be effective (**Evidence C**).
- Self-management intervention with communication with a health care professional improves health status and decreases hospitalizations and emergency department visits (**Evidence B**).

INTEGRATED CARE PROGRAMS

- Integrated care and telehealth have no demonstrated benefit at this time (**Evidence B**).

TABLE 3.8



Palliative, end-of-life & hospice care

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

- Opiates, neuromuscular electrical stimulation (NMES), oxygen and fans blowing air on to the face can relieve breathlessness (**Evidence C**).
- In malnourished patients, nutritional supplementation may improve respiratory muscle strength and overall health status (**Evidence B**).
- Fatigue can be improved by self-management education, pulmonary rehabilitation, nutritional support and mind-body interventions (**Evidence B**).

TABLE 3.9



Oxygen therapy & ventilatory support in stable COPD

- ▶ ***During exacerbations of COPD.*** Noninvasive ventilation (NIV) in the form of noninvasive positive pressure ventilation (NPPV) is the standard of care for decreasing morbidity and mortality in patients hospitalized with an exacerbation of COPD and acute respiratory failure.

▶ OXYGEN THERAPY AND VENTILATORY SUPPORT IN STABLE COPD

OXYGEN THERAPY

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

VENTILATORY SUPPORT

- NPPV may improve hospitalization-free survival in selected patients after recent hospitalization, particularly in those with pronounced daytime persistent hypercapnia ($\text{PaCO}_2 \geq 52$ mmHg) (**Evidence B**).

TABLE 3.10



Interventional therapy in stable COPD

- ▶ **Lung volume reduction surgery (LVRS).** LVRS is a surgical procedure in which parts of the lungs are resected to reduce hyperinflation making respiratory muscles more effective pressure generators by improving their mechanical efficiency.

▶ INTERVENTIONAL THERAPY IN STABLE COPD

LUNG VOLUME REDUCTION SURGERY

- Lung volume reduction surgery improves survival in severe emphysema patients with an upper-lobe emphysema and low post-rehabilitation exercise capacity (**Evidence A**).

BULLECTOMY

- In selected patients bullectomy is associated with decreased dyspnea, improved lung function and exercise tolerance (**Evidence C**).

TRANSPLANTATION

- In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity (**Evidence C**).

BRONCHOSCOPIC INTERVENTIONS

- In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improves exercise tolerance, health status and lung function at 6-12 months following treatment. Endobronchial valves (**Evidence B**); Lung coils (**Evidence B**); Vapor ablation (**Evidence B**).



GOLD 2019 Report: Chapters

Global Initiative for Chronic Obstructive Lung Disease



GLOBAL STRATEGY FOR THE DIAGNOSIS,
MANAGEMENT, AND PREVENTION OF
CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2019 REPORT

1. Definition and Overview
2. Diagnosis and Initial Assessment
3. Evidence Supporting Prevention & Maintenance Therapy
4. Management of Stable COPD
5. Management of Exacerbations
6. COPD and Comorbidities



Management of stable COPD

OVERALL KEY POINTS:

- ▶ The management strategy for stable COPD should be predominantly based on the individualized assessment of symptoms and future risk of exacerbations.
- ▶ All individuals who smoke should be strongly encouraged and supported to quit.
- ▶ The main treatment goals are reduction of symptoms and future risk of exacerbations.
- ▶ Management strategies are not limited to pharmacologic treatments, and should be complemented by appropriate non-pharmacologic interventions.



Management of Stable COPD

- ▶ Once COPD has been diagnosed, effective management should be based on an individualized assessment to reduce both current symptoms and future risks of exacerbations.

▶ GOALS FOR TREATMENT OF STABLE COPD

- Relieve Symptoms
- Improve Exercise Tolerance
- Improve Health Status



REDUCE SYMPTOMS

and

- Prevent Disease Progression
- Prevent and Treat Exacerbations
- Reduce Mortality



REDUCE RISK

TABLE 4.1



Management of stable COPD

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

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

TABLE 4.2



Management of Stable COPD

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

▶ IDENTIFY & REDUCE RISK FACTOR EXPOSURE

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

TABLE 4.3



Treatment of Stable COPD

Pharmacological treatment

▶ KEY POINTS FOR THE USE OF BRONCHODILATORS ▶

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

TABLE 4.5



Treatment of Stable COPD

Pharmacological treatment

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

- Long-term monotherapy with ICS is not recommended (**Evidence A**).
- Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators (**Evidence A**).
- Long-term therapy with oral corticosteroids is not recommended (**Evidence A**).
- In patients with exacerbations despite LABA/ICS or LABA/LAMA/ICS, chronic bronchitis and severe to very severe airflow obstruction, the addition of a PDE4 inhibitor can be considered (**Evidence B**).
- In former smokers with exacerbations despite appropriate therapy, macrolides, in particular azithromycin, can be considered (**Evidence B**).
- Statin therapy is not recommended for prevention of exacerbations (**Evidence A**).
- Antioxidant mucolytics are recommended only in selected patients (**Evidence A**).

TABLE 4.6



Treatment of stable COPD

Pharmacological treatment

KEY POINTS FOR THE USE OF OTHER PHARMACOLOGICAL TREATMENTS

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

TABLE 4.7



Treatment of stable COPD

Pharmacological treatment algorithms

- ▶ A model for the **INITIATION** of pharmacological management of COPD according to the individualized assessment of symptoms and exacerbation risk following the ABCD assessment scheme is shown in **Figure 4.1**.
- ▶ There is a lack of high-quality evidence supporting initial pharmacological treatment strategies in newly diagnosed COPD patients.
- ▶ **Figure 4.1** is an attempt to provide clinical guidance using the best available evidence.
- ▶ Rescue short-acting bronchodilators should be prescribed to all patients for immediate symptom relief.



Treatment of stable COPD

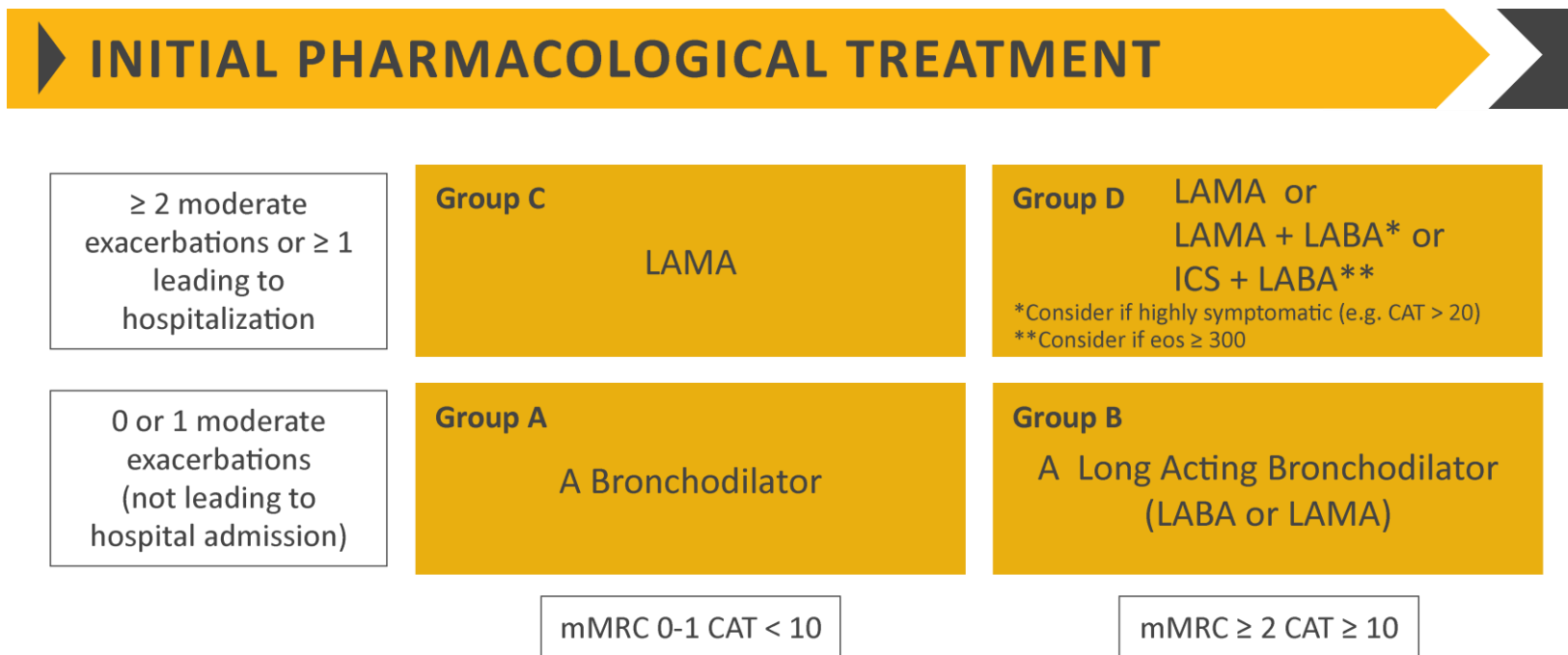


FIGURE 4.1

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

Treatment of stable COPD

- ▶ Following implementation of therapy, patients should be reassessed for attainment of treatment goals and identification of any barriers for successful treatment (**Figure 4.2**).
- ▶ Following review of the patient response to treatment initiation, adjustments in pharmacological treatment may be needed.

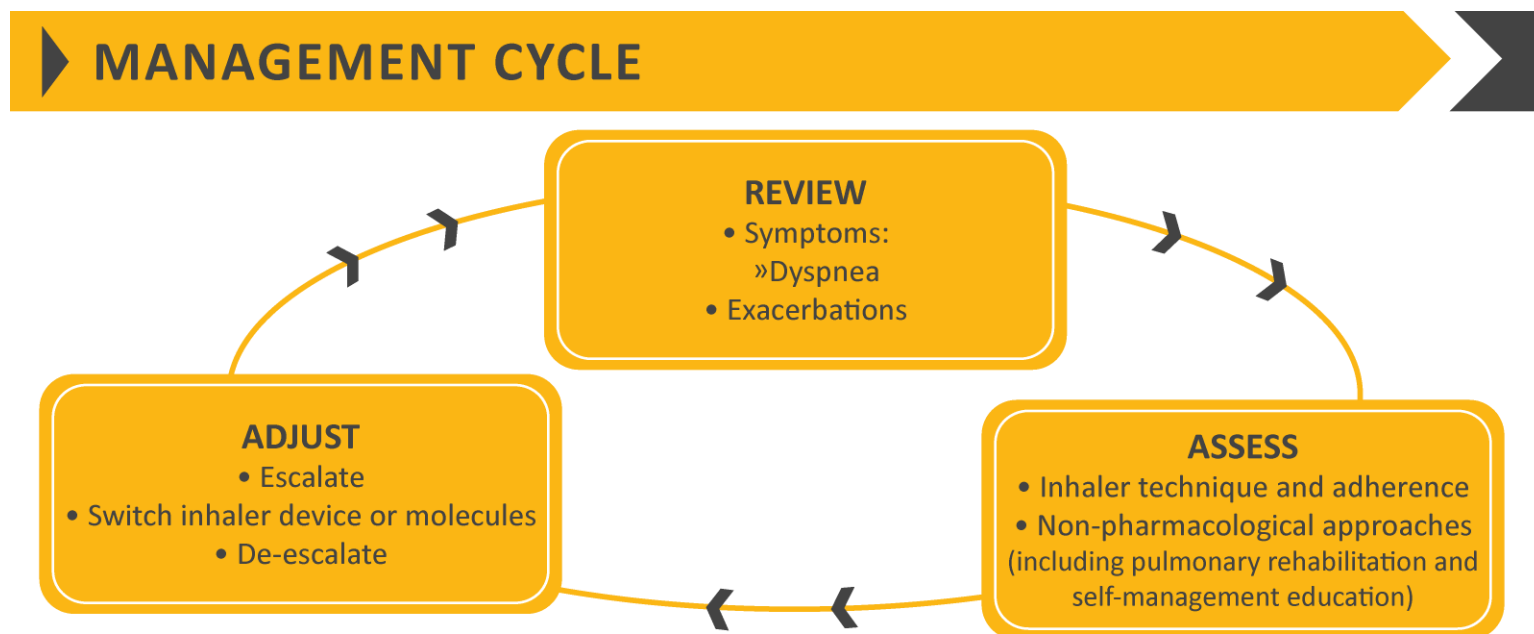


FIGURE 4.2



Treatment of stable COPD

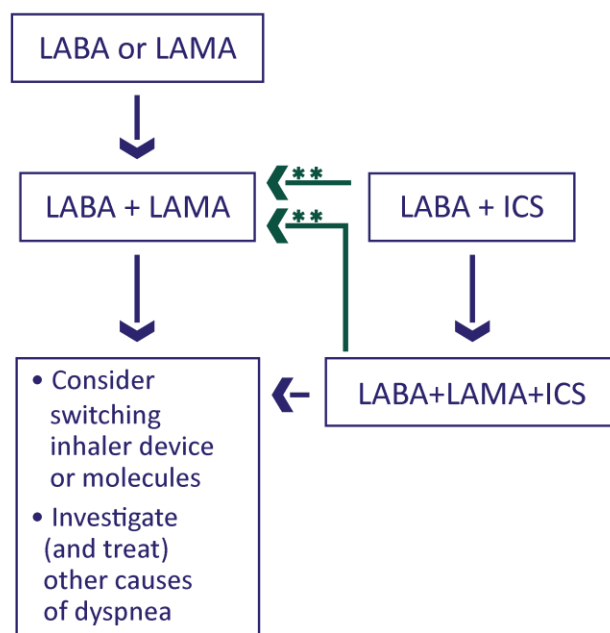
Follow-up pharmacological treatment

- ▶ A separate algorithm is provided for **FOLLOW-UP** treatment, where the management is still based on symptoms and exacerbations, but the recommendations do not depend on the patient's GOLD group at diagnosis (**Figure 4.3**).
- ▶ 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 recent 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.

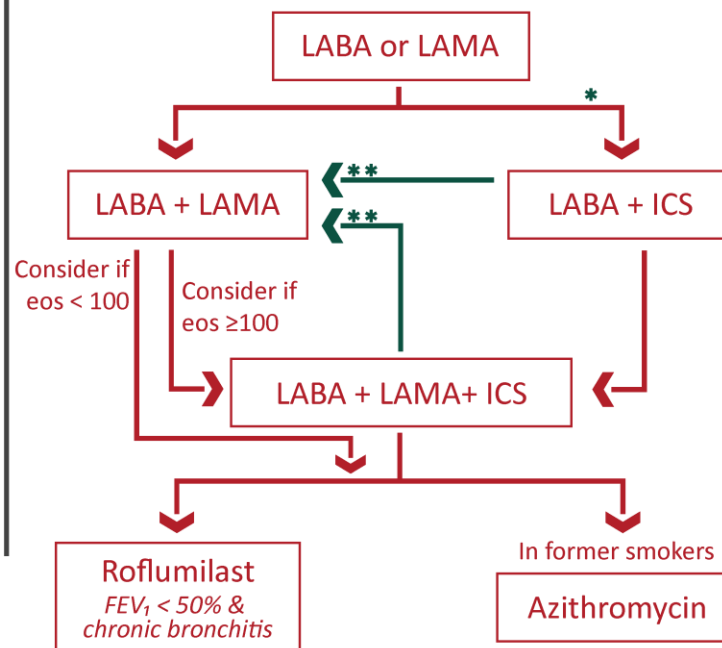
FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
2. IF NOT:
 - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
 - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
 - ✓ Place patient in box corresponding to current treatment & follow indications
 - ✓ Assess response, adjust and review
 - ✓ These recommendations do not depend on the ABCD assessment at diagnosis

• DYSPNEA •



• EXACERBATIONS •



eos = blood eosinophil count (cells/ μ L)

** Consider if eos ≥ 300 or eos ≥ 100 AND ≥ 2 moderate exacerbations / 1 hospitalization*

*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.3



Treatment of stable COPD

- ▶ **Figure 4.3** suggests escalation and de-escalation strategies based on available efficacy as well as safety data.
- ▶ The response to treatment escalation should always be reviewed, and de-escalation should be considered if there is a lack of clinical benefit and/or side effects occur.
- ▶ De-escalation may also be considered in COPD patients receiving treatment who return with resolution of some symptoms that subsequently may require less therapy.
- ▶ Patients, in whom treatment modification is considered, in particular de-escalation, should be undertaken under close medical supervision.
- ▶ We are fully aware that treatment escalation has not been systematically tested; trials of de-escalation are also limited and only include ICS.



Group A

- ▶ All **Group A** patients should be offered bronchodilator treatment based on its effect on breathlessness. This can be either a short- or a long-acting bronchodilator.
- ▶ This should be continued if benefit is documented.

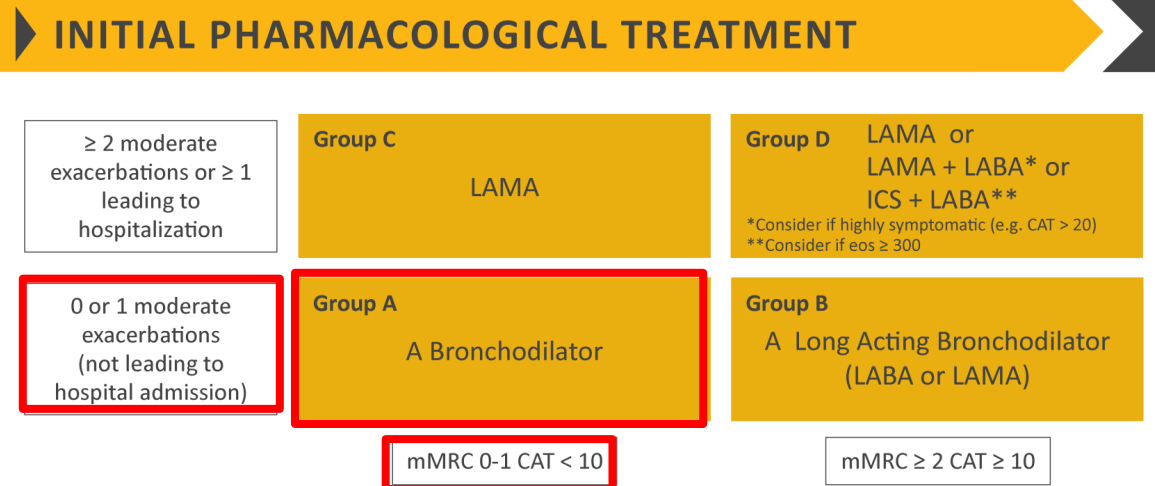


FIGURE 4.1



Group B

- ▶ Initial therapy should consist of a long acting bronchodilator (**LABA** or **LAMA**).
- ▶ Long-acting inhaled bronchodilators are superior to short-acting bronchodilators taken as needed i.e., *pro re nata* (prn) and are therefore recommended.

▶ INITIAL PHARMACOLOGICAL TREATMENT

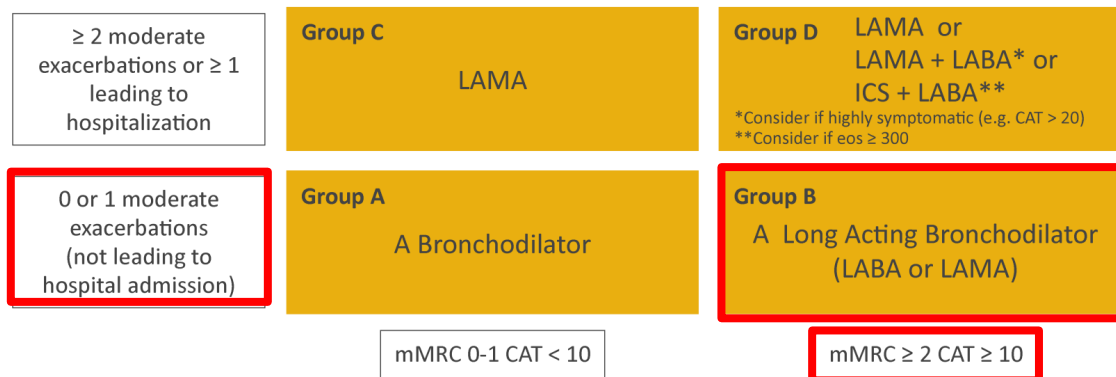


FIGURE 4.1



Group B

- ▶ There is no evidence to recommend one class of long-acting bronchodilators over another for initial relief of symptoms in this group of patients.
- ▶ In the individual patient, the choice should depend on the patient's perception of symptom relief.
- ▶ For patients with severe breathlessness initial therapy with two bronchodilators may be considered.
- ▶ **Group B** patients are likely to have comorbidities that may add to their symptomatology and impact their prognosis, and these possibilities should be investigated.



Group C

- ▶ Initial therapy should consist of a single long acting bronchodilator.
- ▶ In two head-to-head comparisons the tested LAMA was superior to the LABA regarding exacerbation prevention therefore we recommend starting therapy with a LAMA in this group.

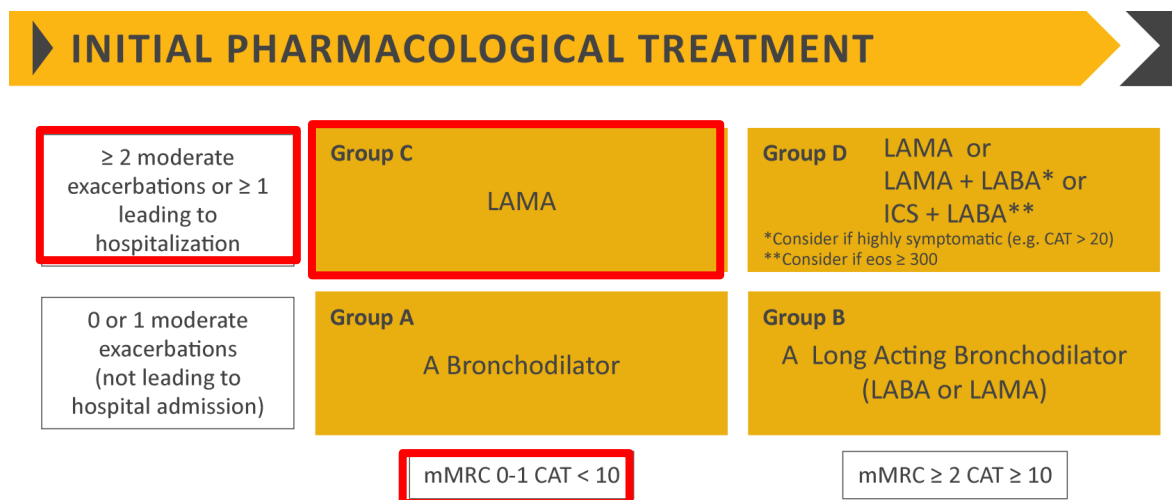


FIGURE 4.1



Group D

- ▶ In general, therapy can be started with a LAMA as it has effects on both breathlessness and exacerbations.
- ▶ For patients with more severe symptoms (order of magnitude of CAT™ ≥ 20), especially driven by greater dyspnea and/or exercise limitation, LAMA/LABA may be chosen as initial treatment based on studies with patient reported outcomes as the primary endpoint where LABA/LAMA combinations showed superior results compared to the single substances.
- ▶ An advantage of LABA/LAMA over LAMA for exacerbation prevention has not been consistently demonstrated, so the decision to use LABA/LAMA as initial treatment should be guided by the level of symptoms.

▶ INITIAL PHARMACOLOGICAL TREATMENT

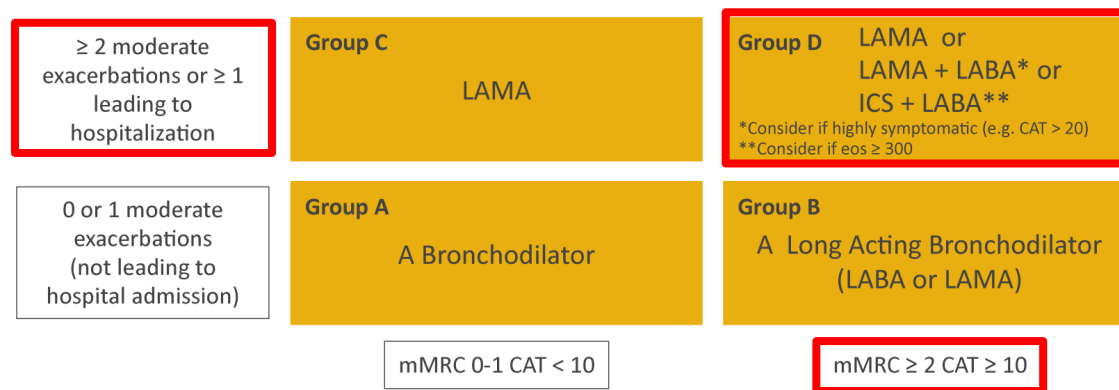


FIGURE 4.1



Group D

- ▶ In some patients, initial therapy with LABA/ICS may be the first choice.
- ▶ This treatment has the greatest likelihood of reducing exacerbations in patients with blood eosinophil counts ≥ 300 cells/ μ L.
- ▶ LABA/ICS may also be first choice in COPD patients with a history of asthma.
- ▶ ICS may cause side effects such as pneumonia, so should be used as initial therapy only after the possible clinical benefits versus risks have been considered.

▶ INITIAL PHARMACOLOGICAL TREATMENT

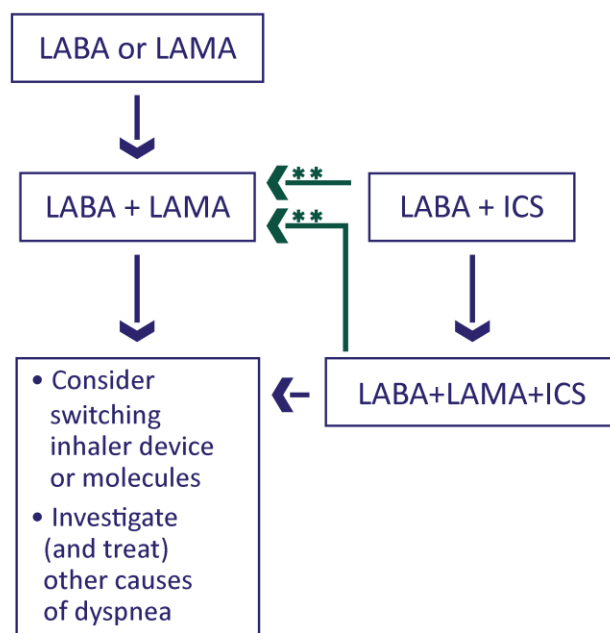


FIGURE 4.1

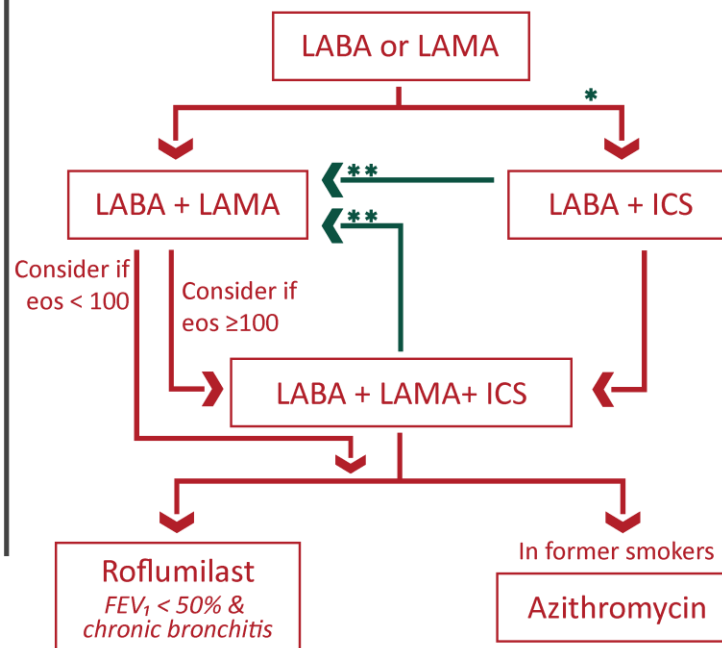
FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
2. IF NOT:
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 - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
 - ✓ Place patient in box corresponding to current treatment & follow indications
 - ✓ Assess response, adjust and review
 - ✓ These recommendations do not depend on the ABCD assessment at diagnosis

• DYSPNEA •



• EXACERBATIONS •



eos = blood eosinophil count (cells/μL)

** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*

*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.3



FOLLOW-UP pharmacological treatment

- ▶ The follow-up pharmacological treatment algorithm (**Figure 4.3**) can be applied to any patient who is already taking maintenance treatment(s) irrespective of the GOLD group allocated at treatment initiation.
- ▶ The need to treat primarily dyspnea/exercise limitation or prevent exacerbations further should be evaluated.
- ▶ If a change in treatment is considered necessary then select the corresponding algorithm for dyspnea or exacerbations.
- ▶ Identify which box corresponds to the patient's the current treatment.
- ▶ The exacerbation algorithm should also be used for patients who require a change in treatment for both dyspnea and exacerbations.



FOLLOW-UP pharmacological treatment

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

▶ MANAGEMENT CYCLE

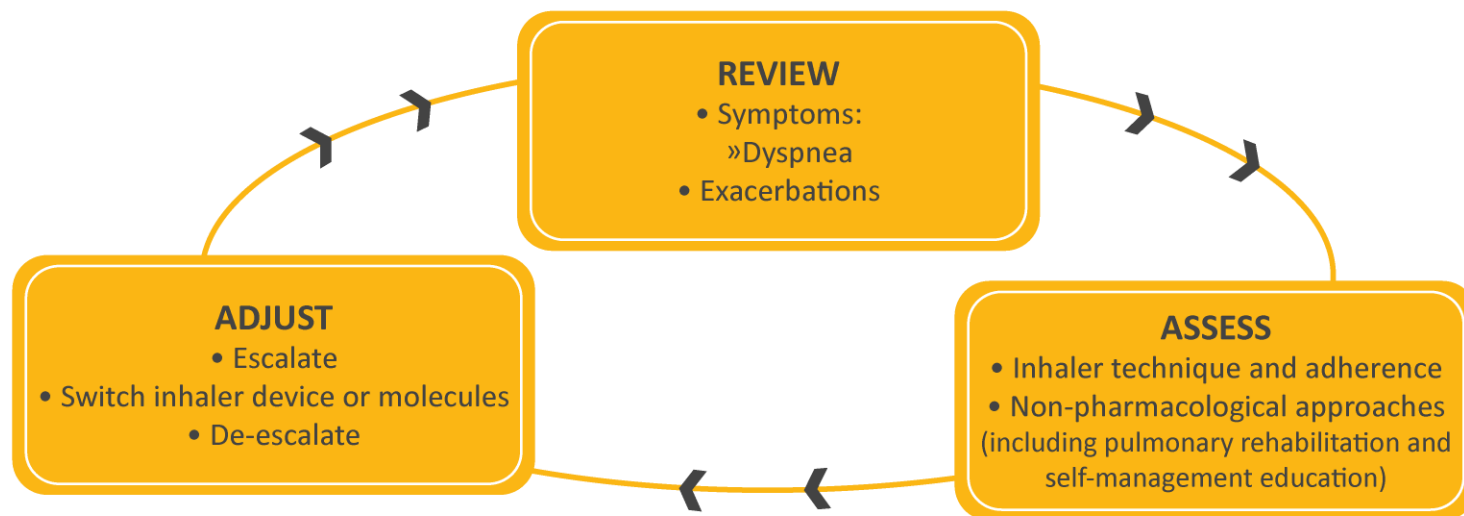


FIGURE 4.2



Review, Assess, Adjust

► Review

Review symptoms (dyspnea) and exacerbation risk.

► Assess

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

► Adjust

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



FOLLOW-UP pharmacological treatment

Dyspnea

- ▶ For patients with persistent breathlessness or exercise limitation on long acting bronchodilator monotherapy, the use of two bronchodilators is recommended.
- If the addition of a second long acting bronchodilator does not improve symptoms, we suggest the treatment could be stepped down again to monotherapy. Switching inhaler device or molecules can also be considered.



FOLLOW-UP pharmacological treatment

Dyspnea

- ▶ For patients with persistent breathlessness or exercise limitation on LABA/ICS treatment, LAMA can be added to escalate to triple therapy.
 - Alternatively, switching from LABA/ICS to LABA/LAMA should be considered if the original indication for ICS was inappropriate (e.g., an ICS was used to treat symptoms in the absence of a history of exacerbations), or there has been a lack of response to ICS treatment, or if ICS side effects warrant discontinuation.
- ▶ At all stages, dyspnea due to other causes (not COPD) should be investigated and treated appropriately. Inhaler technique and adherence should be considered as causes of inadequate treatment response.



FOLLOW-UP pharmacological treatment

Exacerbations

- ▶ For patients with persistent exacerbations on ***long acting bronchodilator*** monotherapy, escalation to either LABA/LAMA or LABA/ICS is recommended. LABA/ICS may be preferred for patients with a history or findings suggestive of asthma.
- ▶ Blood eosinophil counts may identify patients with a greater likelihood of a beneficial response to ICS.
- ▶ For patients with one exacerbation per year, a peripheral blood level ≥ 300 eosinophils/ μL identifies patients more likely to respond to LABA/ICS treatment.^{13,14}
- ▶ For patients with ≥ 2 moderate exacerbations per year or at least one severe exacerbation requiring hospitalization in the prior year, LABA/ICS treatment can be considered at blood eosinophil counts ≥ 100 cells/ μL , as ICS effects are more pronounced in patients with greater exacerbation frequency and/or severity.



FOLLOW-UP pharmacological treatment

Exacerbations

- ▶ In patients who develop further exacerbations on **LABA/LAMA** therapy we suggest two alternative pathways. Blood eosinophil counts < 100 cells/ μ L can be used to predict a low likelihood of a beneficial ICS response:
 - Escalation to LABA/LAMA/ICS. A beneficial response after the addition of ICS may be observed at blood eosinophil counts ≥ 100 cells/ μ L, with a greater magnitude of response more likely with higher eosinophil counts.
 - Add roflumilast or azithromycin if blood eosinophils < 100 cells/ μ L.



FOLLOW-UP pharmacological treatment

Exacerbations

- ▶ In patients who develop further exacerbations on **LABA/ICS** therapy, we recommend escalation to triple therapy by adding a LAMA.
- ▶ Alternatively, treatment can be switched to LABA/LAMA if there has been a lack of response to ICS treatment, or if ICS side effects warrant discontinuation.



FOLLOW-UP pharmacological treatment

Exacerbations

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



Non-Pharmacological Treatment

- ▶ Education and self-management
- ▶ Physical activity
- ▶ Pulmonary rehabilitation programs
- ▶ Exercise training
- ▶ Self-management education
- ▶ End of life and palliative care
- ▶ Nutritional support
- ▶ Vaccination
- ▶ Oxygen therapy



Non-pharmacological treatment

Education & self-management

- ▶ Based on GOLD groups, personalized design could include:
 - **Groups A, B, C & D** – addressing behavioral risk factors, including smoking cessation, maintaining or increasing physical activity, and ensuring adequate sleep and a healthy diet.
 - **Groups B & D** – learning to self-manage breathlessness, energy conservation techniques, and stress management strategies.
 - **Groups C & D** – avoiding aggravating factors, monitoring and managing worsening symptoms, having a written action plan and maintaining regular contact/communication with a healthcare professional.
 - **Group D** – discussing with their healthcare providers palliative strategies and advance care directives.



Non-pharmacological treatment

Physical activity

- ▶ Pulmonary rehabilitation, including community and home-based, is an approach with clear evidence of benefits. However, the challenge is promoting physical activity and maintaining it.
- ▶ There is evidence that physical activity is decreased in COPD patients. This leads to a downward spiral of inactivity which predisposes patients to reduced quality of life, increased rates of hospitalization and mortality.
- ▶ Behavior-targeted interventions with the aim of improving physical activity should be encouraged.
- ▶ Most published studies to date provide little guidance for adaptation of interventions for clinical care.



Non-pharmacological treatment

Pulmonary rehabilitation

- ▶ Patients with high symptom burden and risk of exacerbations (Groups B, C and D), should be encouraged to take part in a formal rehabilitation program that includes setting patient goals and is designed and delivered in a structured manner, taking into account the individual's COPD characteristics and comorbidities.
- ▶ The components of pulmonary rehabilitation may vary but evidence-based best practice for program delivery includes: structured and supervised exercise training, smoking cessation, nutrition counseling, and self-management education.



Non-pharmacological treatment

Exercise training

- ▶ A meta-analysis of RCTs found that exercise training alone, or with the addition of activity counseling, significantly improved physical activity levels in COPD patients.
- ▶ A combination of constant load or interval training with strength training provides better outcomes than either method alone.
- ▶ Where possible, endurance exercise training to 60-80% of the symptom-limited maximum work or heart rate is preferred, or to a Borg-rated dyspnea or fatigue score of 4 to 6 (moderate to severe).
- ▶ Exercise training can be enhanced by optimizing bronchodilators, since both LAMA and LABA have shown reduced resting and dynamic hyperinflation.



Non-pharmacological treatment

Oxygen therapy

- ▶ Long-term oxygen therapy is indicated for stable patients who have:
 - PaO_2 at or below 7.3 kPa (55 mmHg) or SaO_2 at or below 88%, with or without hypercapnia confirmed twice over a three-week period; or
 - PaO_2 between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO_2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%).
- ▶ Once placed on long-term oxygen therapy (LTOT) the patient should be re-evaluated after 60 to 90 days with repeat arterial blood gas (ABG) or oxygen saturation while inspiring the same level of oxygen or room air to determine if oxygen is therapeutic and still indicated, respectively.



Non-pharmacological treatment

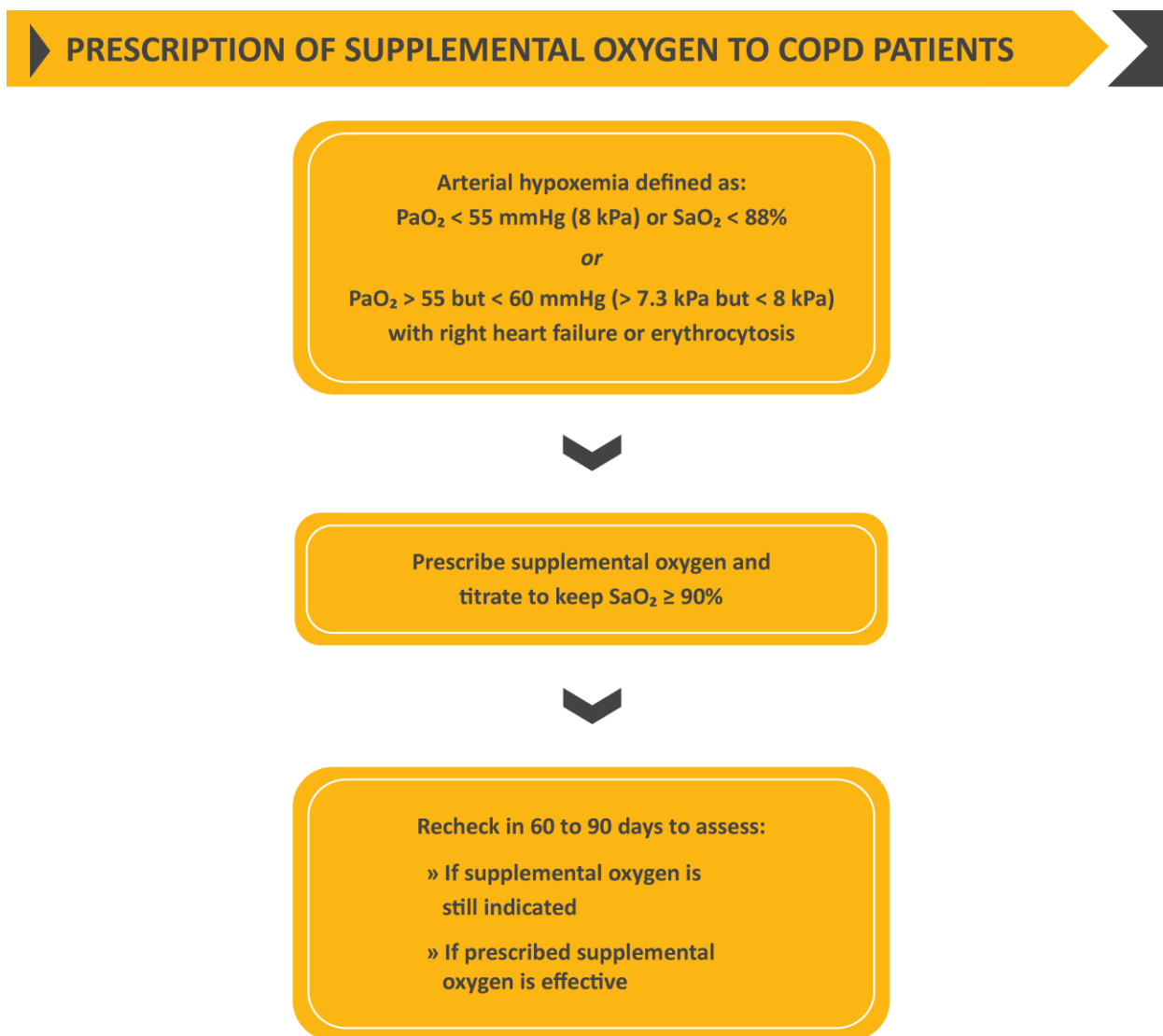


FIGURE 4.4



Non-pharmacological treatment

Oxygen therapy

- ▶ Long-term oxygen therapy is indicated for stable patients who have:
 - PaO_2 at or below 7.3 kPa (55 mmHg) or SaO_2 at or below 88%, with or without hypercapnia confirmed twice over a three-week period; or
 - PaO_2 between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO_2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%).
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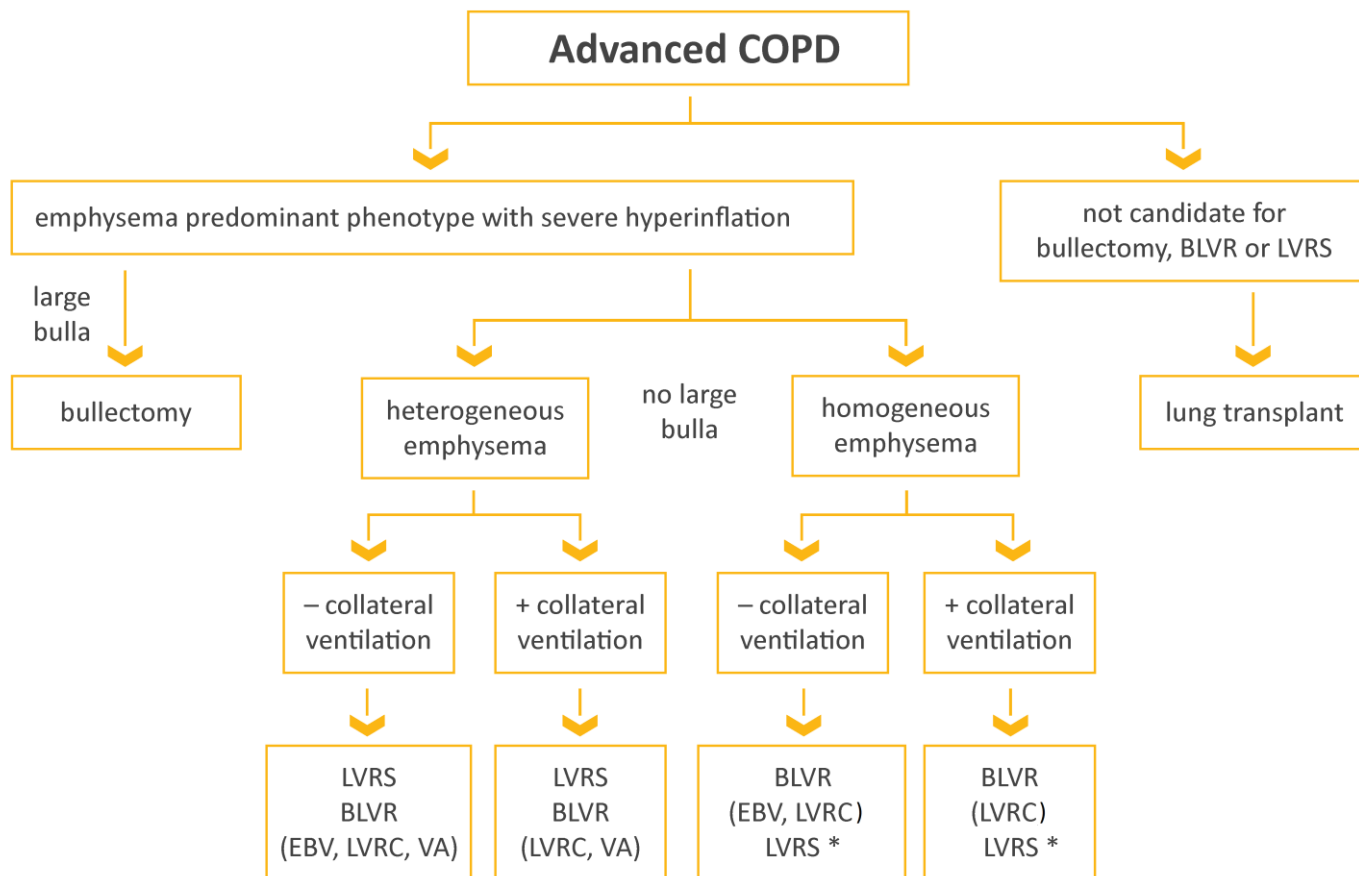
Non-pharmacological treatment

Interventional bronchoscopy & surgery

- ▶ In selected patients with heterogeneous or homogenous emphysema and significant hyperinflation refractory to optimized medical care, surgical or bronchoscopic modes of lung volume reduction (e.g., endobronchial one-way valves, lung coils or thermal ablation) may be considered.
- ▶ Some of these therapies (vapor ablation and lung coils) are not widely available for clinical care in many countries.
- ▶ In selected patients with a large bulla, surgical bullectomy may be considered.
- ▶ In selected patients with very severe COPD and without relevant contraindications, lung transplantation may be considered.

INTERVENTIONAL BRONCHOSCOPIC AND SURGICAL TREATMENTS FOR COPD

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



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

*at some but not all centers

FIGURE 4.5



Non-pharmacological treatment Summary

▶ KEY POINTS FOR THE USE OF NON-PHARMACOLOGICAL TREATMENTS

EDUCATION, SELF-MANAGEMENT AND PULMONARY REHABILITATION

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

VACCINATION

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

NUTRITION

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



Summary

END OF LIFE AND PALLIATIVE CARE

- All clinicians managing patients with COPD should be aware of the effectiveness of palliative approaches to symptom control and use these in their practice (**Evidence D**).
- End of life care should include discussions with patients and their families about their views on resuscitation, advance directives and place of death preferences (**Evidence D**).

TREATMENT OF HYPOXEMIA

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

TREATMENT OF HYPERCAPNIA

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

INTERVENTION BRONCHOSCOPY AND SURGERY

- Lung volume reduction surgery should be considered in selected patients with upper-lobe emphysema (**Evidence A**).
- Bronchoscopic lung volume reduction interventions may be considered in selected patients with advanced emphysema (**Evidence B**).
- In selected patients with a large bulla surgical bullectomy may be considered (**Evidence C**).
- In patients with very severe COPD (progressive disease, BODE score of 7 to 10, and not candidate for lung volume reduction) lung transplantation may be considered for referral with at least one of the following: (1) history of hospitalization for exacerbation associated with acute hypercapnia ($P_{CO_2} > 50$ mm Hg); (2) pulmonary hypertension and/or cor pulmonale, despite oxygen therapy; or (3) $FEV_1 < 20\%$ and either $DLCO < 20\%$ or homogenous distribution of emphysema (**Evidence C**).



Monitoring and Follow-up

Monitoring disease progression and development of complications and/or comorbidities

- ▶ **Measurements.** Decline in FEV_1 can be tracked by spirometry performed at least once a year.
- ▶ **Symptoms.** At each visit, information on symptoms since the last visit should be collected, including cough and sputum, breathlessness, fatigue, activity limitation, and sleep disturbances.
- ▶ **Exacerbations.** The frequency, severity, type and likely causes of all exacerbations should be monitored.
- ▶ **Imaging.** If there is a clear worsening of symptoms, imaging may be indicated.
- ▶ **Smoking status.** At each visit, the current smoking status and smoke exposure should be determined followed



Monitoring and Follow-up

Pharmacotherapy and other medical treatment

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

Monitoring should focus on:

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

Treatment modifications should be recommended.



GOLD 2019 Report: Chapters

Global Initiative for Chronic Obstructive Lung Disease



GLOBAL STRATEGY FOR THE DIAGNOSIS,
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2019 REPORT

1. Definition and Overview
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5. Management of Exacerbations
6. COPD and Comorbidities



Management of Exacerbations

OVERALL KEY POINTS (1 of 3):

- ▶ An exacerbation of COPD is defined as an acute worsening of respiratory symptoms that results in additional therapy.
- ▶ Exacerbations of COPD can be precipitated by several factors. The most common causes are respiratory tract infections.
- ▶ The goal for treatment of COPD exacerbations is to minimize the negative impact of the current exacerbation and to prevent subsequent events.
- ▶ Short-acting inhaled beta₂-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation.



Management of Exacerbations

OVERALL KEY POINTS (2 of 3):

- ▶ Maintenance therapy with long-acting bronchodilators should be initiated as soon as possible before hospital discharge.
- ▶ Systemic corticosteroids can improve lung function (FEV_1), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not be more than 5-7 days.
- ▶ Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be 5-7 days.
- ▶ Methylxanthines are not recommended due to increased side effect profiles.



Management of Exacerbations

OVERALL KEY POINTS (3 of 3):

- ▶ Non-invasive mechanical ventilation should be the first mode of ventilation used in COPD patients with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduces work of breathing and the need for intubation, decreases hospitalization duration and improves survival.
- ▶ Following an exacerbation, appropriate measures for exacerbation prevention should be initiated (see **GOLD 2019** Chapter 3 and Chapter 4).



Management of Exacerbations

COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy.

► They are classified as:

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



Management of Exacerbations

Classification of hospitalized patients

No respiratory failure:

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



Management of Exacerbations

Classification of hospitalized patients

Acute respiratory failure — non-life-threatening: Respiratory rate: > 30 breaths per minute; using accessory respiratory muscles; no change in mental status; hypoxemia improved with supplemental oxygen via Venturi mask 25-30% FiO₂; hypercarbia i.e., PaCO₂ increased compared with baseline or elevated 50-60 mmHg.



Management of Exacerbations

Classification of hospitalized patients

Acute respiratory failure — life-threatening:

Respiratory rate: > 30 breaths per minute; using accessory respiratory muscles; acute changes in mental status; hypoxemia not improved with supplemental oxygen via Venturi mask or requiring $FiO_2 > 40\%$; hypercarbia i.e., $PaCO_2$ increased compared with baseline or elevated > 60 mmHg or the presence of acidosis ($pH \leq 7.25$).



Management of Exacerbations

POTENTIAL INDICATIONS FOR HOSPITALIZATION ASSESSMENT*

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

*Local resources need to be considered.

TABLE 5.1



Management of Exacerbations

MANAGEMENT OF SEVERE BUT NOT LIFE-THREATENING EXACERBATIONS*

- Assess severity of symptoms, blood gases, chest radiograph.
- Administer supplemental oxygen therapy, obtain serial arterial blood gas, venous blood gas and pulse oximetry measurements.
- Bronchodilators:
 - » Increase doses and/or frequency of short-acting bronchodilators.
 - » Combine short-acting beta 2-agonists and anticholinergics.
 - » Consider use of long-active bronchodilators when patient becomes stable.
 - » Use spacers or air-driven nebulizers when appropriate.
- Consider oral corticosteroids.
- Consider antibiotics (oral) when signs of bacterial infection are present.
- Consider noninvasive mechanical ventilation (NIV).
- At all times:
 - » Monitor fluid balance.
 - » Consider subcutaneous heparin or low molecular weight heparin for thromboembolism prophylaxis.
 - » Identify and treat associated conditions (e.g., heart failure, arrhythmias, pulmonary embolism etc.).

*Local resources need to be considered.

TABLE 5.2



Management of Exacerbations

Pharmacological treatment

The three classes of medications most commonly used for COPD exacerbations are:

► **Bronchodilators**

- Although there is no high-quality evidence from RCTs, it is recommended that short-acting inhaled beta₂-agonists, with or without short-acting anticholinergics, are the initial bronchodilators for acute treatment of a COPD exacerbation.

► **Corticosteroids**

- Data from studies indicate that systemic glucocorticoids in COPD exacerbations shorten recovery time and improve lung function (FEV₁). They also improve oxygenation, the risk of early relapse, treatment failure, and the length of hospitalization.

► **Antibiotics**



Management of Exacerbations

INDICATIONS FOR RESPIRATORY OR MEDICAL INTENSIVE CARE UNIT ADMISSION*

- Severe dyspnea that responds inadequately to initial emergency therapy.
- Changes in mental status (confusion, lethargy, coma).
- Persistent or worsening hypoxemia ($\text{PaO}_2 < 5.3 \text{ kPa}$ or 40 mmHg) and/or severe/worsening respiratory acidosis ($\text{pH} < 7.25$) despite supplemental oxygen and noninvasive ventilation.
- Need for invasive mechanical ventilation.
- Hemodynamic instability - need for vasopressors.

*Local resources need to be considered.

TABLE 5.4



Management of Exacerbations

▶ INDICATIONS FOR NONINVASIVE MECHANICAL VENTILATION (NIV) ▶

At least one of the following:

- Respiratory acidosis ($\text{PaCO}_2 \geq 6.0$ kPa or 45 mmHg and arterial $\text{pH} \leq 7.35$).
- Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces.
- Persistent hypoxemia despite supplemental oxygen therapy.

TABLE 5.5



Management of Exacerbations

▶ INDICATIONS FOR INVASIVE MECHANICAL VENTILATION

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

TABLE 5.6



▶ DISCHARGE CRITERIA AND RECOMMENDATIONS FOR FOLLOW-UP

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

TABLE 5.7 (Part I)



1 – 4 WEEKS FOLLOW-UP



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

TABLE 5.7 (Part II)



12 – 16 WEEKS FOLLOW-UP



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

TABLE 5.7 (Part III)



Management of Exacerbations

INTERVENTIONS THAT REDUCE THE FREQUENCY OF COPD EXACERBATIONS	
INTERVENTION CLASS	INTERVENTION
Bronchodilators	LABAs
	LAMAs
	LABA + LAMA
Corticosteroid-containing regimens	LABA + ICS
	LABA + LAMA + ICS
Anti-inflammatory (non-steroid)	Roflumilast
Anti-infectives	Vaccines
	Long Term Macrolides
Mucoregulators	N-acetylcysteine
	Carbocysteine
Various Others	Smoking Cessation
	Rehabilitation
	Lung Volume Reduction

TABLE 5.8



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COPD and Comorbidities

OVERALL KEY POINTS (1 of 2):

- ▶ 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.
- ▶ Lung cancer is frequently seen in patients with COPD and is a main cause of death.
- ▶ Cardiovascular diseases are common and important comorbidities in COPD.



COPD and Comorbidities

OVERALL KEY POINTS (2 of 2):

- ▶ 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.



COPD and Comorbidities

Some common comorbidities occurring in patients with COPD with stable disease include:

- ▶ Cardiovascular disease (CVD)
- ▶ Heart failure
- ▶ Ischaemic heart disease (IHD)
- ▶ Arrhythmias
- ▶ Peripheral vascular disease
- ▶ Hypertension
- ▶ Osteoporosis
- ▶ Anxiety and depression
- ▶ COPD and lung cancer
- ▶ Metabolic syndrome and diabetes
- ▶ Gastroesophageal reflux (GERD)
- ▶ Bronchiectasis
- ▶ Obstructive sleep apnea