CHRONIC OBSTRUCTIVE PULMONARY DISEASE

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- November 2023

To the CHI Original Chronic Obstructive Pulmonary Disease Clinical Guidance- Issued January 2020

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Related Documents

Related SOPs

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Abbreviations

AATD	Alpha-1 Antitrypsin Deficiency
BMI	Body Mass Index
CADTH	Canadian Agency for Drugs and Technologies in Health
CAT	COPD Assessment Test
CHI	Council of Health Insurance
COPD	Chronic Obstructive Pulmonary Disease
CPG	Clinical Practice Guideline
CRQ	Chronic Respiratory Questionnaire
EMA	European Medicines Agency
EOS	Eosinophil
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GP	General Practitioners
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
ICS	Inhaled corticosteroids
IDF	Insurance Drug Formulary
IQWIG	Institute for Quality and Efficiency in Health Care
LABA	Long-Acting Beta-Agonist
LABD	Long-Acting Bronchodilators
LAMA	Long-Acting Muscarinic Antagonist
MMRC	Modified Medical Research Council dyspnea questionnaire
MRC	Medical Research Council dyspnea questionnaire
NAC	N-Acetylcysteine
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee

PFT	Pulmonary Function Test
RCT	Randomized Clinical Trial
SABA	Short-Acting Beta-Agonist
SABD	Short-Acting Bronchodilators
SAMA	Short-Acting Muscarinic Antagonist
SFDA	Saudi Food and Drug Authority
SGRQ	St. George's Respiratory Questionnaire
TB	Tuberculosis

Executive Summary

Chronic Obstructive Pulmonary Disease (COPD) is a diverse lung condition marked by persistent respiratory symptoms (such as dyspnea, cough, sputum production, and exacerbations). These symptoms are attributed to abnormalities in the airways (resulting in bronchitis or bronchiolitis) and/or the alveoli (leading to emphysema). COPD is characterized by chronic, frequently progressive, airflow obstruction[1].

COPD has become one of the leading causes of death globally, with 90% of these fatalities happening in low- and middle-income countries (LMICs). In 2012, over 3 million individuals lost their lives due to COPD, accounting for 6% of all global deaths.[1] COPD presents a significant public health issue that can be prevented and managed.[1] In 2019, the prevalence of COPD in Saudi Arabia was 2,053.04 cases per 100,000 population, which marked a 49% rise compared to 1990. This rate is lower than the global prevalence of 2,639.2 cases per 100,000 population[2].

COPD arises due to interactions between genetic factors (G) and environmental influences (E) that occur throughout an individual's lifespan (T). This interplay, often referred to as "GETomics," can lead to lung damage and/or disrupt their natural development and aging processes. The main factor responsible for COPD is the exposure to tobacco smoke. Furthermore, the most significant, although infrequent, genetic susceptibility factor for COPD that has been recognized so far involves mutations in the SERPINA1 gene, which result in α-1 antitrypsin deficiency[1].

The confirmation of COPD diagnosis relies on the identification of non-completely reversible airflow limitation, which is determined by spirometry showing a post-bronchodilation FEV1/FVC ratio of less than 0.7. Individuals with COPD commonly report symptoms like shortness of breath, restrictions in physical activities, and coughing with or without the production of sputum. Additionally, they may encounter acute respiratory episodes marked by heightened respiratory symptoms known as exacerbations, which necessitate specific preventive and treatment approaches. The symptom and risk components are combined to categorize patients into one of three groups: A, B and E according to CAT and mMRC assessment scores[1].

Smoking cessation continues to be the most important therapeutic intervention for COPD. Bronchodilators form the core of any treatment plan for COPD. The initial selection of medication depends on GOLD ABE assessment tool (detailed in figure 1 below). The choice of therapy can be influenced by initial clinical assessment, keeping in mind potential adverse effects. Other options for specific cases include oxygen therapy, alpha1-antitrypsin deficiency treatment, bullectomy, lung volume reduction surgery, lung transplantation and hospice care[3].

CHI issued Chronic Obstructive Pulmonary Disease guidance after thorough review of renowned international and national clinical guidelines in January 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an **addendum to the prior CHI Chronic Obstructive Pulmonary Disease clinical guidance** and seeks to offer guidance for the effective management of Chronic Obstructive Pulmonary Disease. It provides an **update on the** Chronic Obstructive Pulmonary Disease **Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized being the issuance of **updated versions** of previously reviewed guidelines namely **GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD) 2023**. Moreover, **new guidelines** are added to the report such as the COPD-X Plan: **Australian and New Zealand Guidelines** for the management of Chronic Obstructive Pulmonary Disease **2023, 2023 Canadian Thoracic Society Guideline** on Pharmacotherapy in Patients With Stable COPD, **Summary for Clinicians: Clinical Practice Guideline** on Pharmacologic Management of Chronic Obstructive Pulmonary Disease **(2021),** Management of COPD in Asia: **A position statement of the Asian Pacific Society of Respirology 2019** and **Spanish COPD guidelines (GesEPOC) 2021: Updated pharmacological treatment of stable COPD.**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to include the SFDA registered drugs **Budesonide/ Glycopyrrolate/Formoterol fumarate** (Breztri Aerosphere ®) and **Revefenacin** (YUPELRI ®) in the CHI formulary while removing **Umeclidinium** and **Ipratropium bromide/Salbutamol** as they are no longer registered on the SFDA Drug List of September 2023. There have been no changes or updates made to any of the previously listed drugs in terms of drug information and prescribing edits since February 2020.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Chronic Obstructive Pulmonary Disease therapeutic management.

Below is a table summarizing the major changes based on the different chronic obstructive pulmonary disease guidelines used to issue this report:

Table 1. Major Recommendations for the Management of Chronic Obstructive Pulmonary Disease (COPD)

Management of Chronic Obstructive Pulmonary Disease		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
The most vital step in averting the progression of COPD is to cease smoking.	II, Strong	Australian and New Zealand Guidelines 2023[4]
Receiving vaccinations reduces the risk of facing complications associated with influenza and pneumococcal infections.	I, Strong	Australian and New Zealand Guidelines 2023[4]
In Group A patients, characterized by their need for bronchodilator therapy to alleviate breathlessness, this can involve the use of either short-acting or long-acting bronchodilators.	Not graded	Global Initiative for Chronic Obstructive Lung Disease Global Strategy 2023[1]
In Group A patients, **if a long-acting bronchodilator is accessible and cost-effective, it is the preferred option, unless patients only encounter infrequent breathlessness.**	Not graded	Global Initiative for Chronic Obstructive Lung Disease Global Strategy 2023[1]
Patients in Group B should commence their treatment with a combination of a LABA* (Long-Acting Beta-Agonist) and a LAMA (Long-Acting Muscarinic Antagonist).	Not graded	Global Initiative for Chronic Obstructive Lung Disease Global Strategy 2023[1]
In Group B, if the LABA*+LAMA combination is not deemed suitable, there isn't a distinct preference for one category of long-acting bronchodilator (either LABA or LAMA) over the other for initial symptom relief in this patient group. The choice should be guided by the patient's perception of symptom relief.	Not graded	Global Initiative for Chronic Obstructive Lung Disease Global Strategy 2023[1]

For patients in Group E, a Cochrane systematic review and network meta-analysis have demonstrated that the LABA*+LAMA combination is the most effective at reducing COPD exacerbations. Consequently, if factors such as availability, cost, or side effects are not a concern, LABA+LAMA is the preferred initial therapy.	Not graded	Global Initiative for Chronic Obstructive Lung Disease Global Strategy 2023[1]
It may be prudent to consider LABA*+LAMA+ICS in Group E when the eosinophil count is 300 cells/μL or higher, in accordance with practical recommendations. Although there is no direct data on initiating triple therapy in newly diagnosed patients, it is reasonable to reserve this treatment for patients with a high eosinophil count (≥ 300 cells/μL).	Not graded	Global Initiative for Chronic Obstructive Lung Disease Global Strategy 2023[1]
When managing an exacerbation, it is advisable to initiate treatment with short-acting inhaled beta2-agonists, either as a standalone option or in combination with short-acting anticholinergics as the initial bronchodilators.	Evidence C	Global Initiative for Chronic Obstructive Lung Disease Global Strategy 2023[1]
In cases of severe exacerbations, systemic corticosteroids can improve lung function (FEV1), oxygen levels, and expedite recovery, including reducing the duration of hospitalization. The usual duration of corticosteroid treatment should not exceed 5 days.	Evidence C	Global Initiative for Chronic Obstructive Lung Disease Global Strategy 2023[1]
Antibiotics may be required when clinically indicated, as they can expedite recovery, reduce the risk of early relapse, prevent treatment failure, and shorten the length of hospital stay. The typical duration of antibiotic therapy is generally 5-7 days.	Evidence B	Global Initiative for Chronic Obstructive Lung Disease Global Strategy 2023[1]
For individuals with emphysema caused by Alpha-1 Antitrypsin Deficiency, it is	Weak, moderate	Global Initiative for Chronic

recommended to contemplate augmentation therapy, aiming to decelerate the decline in lung density as assessed through CT scans. However, it is essential to note that augmentation treatment has not demonstrated efficacy in alleviating symptoms or decreasing the frequency of exacerbations.		Obstructive Lung Disease Global Strategy 2023[1]
In patients with exacerbator phenotype that still suffer from COPD exacerbations despite receiving sufficient treatment, it is recommended to contemplate the inclusion of a high-dose mucolytic.	Weak, moderate	Spanish COPD Guidelines (GesEPOC) 2021[5]
Roflumilast has been suggested as an alternative treatment approach for reducing exacerbations in patients with the exacerbator phenotype, a group characterized by chronic bronchitis and substantial airflow limitation.	Weak, moderate	Spanish COPD Guidelines (GesEPOC) 2021[5]
Ideally, though not exclusively for individuals who used to smoke and are experiencing exacerbations despite receiving suitable treatment, macrolides, specifically azithromycin, may be considered.	Evidence B	Global Initiative for Chronic Obstructive Lung Disease Global Strategy 2023[1]
Combining bronchodilators in a single inhaler may be more convenient for the patients and can also increase compliance.	Not graded	Global Initiative for Chronic Obstructive Lung Disease Global Strategy 2023[1]
*As of the writing of this report, LABA as single agents are not available on the market in KSA.		

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in Chronic Obstructive Pulmonary Disease **clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI chronic obstructive pulmonary disease report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the January 2020 CHI Chronic Obstructive Pulmonary Disease Report and the corresponding recommendations:

Table 2. Clinical Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 Chronic obstructive pulmonary disease in over 16s: diagnosis and management **NICE guideline Published: 5 December 2018**	N/A*
1.2 **GOLD** Guidelines **2019**	1.1.1 **GOLD** Guidelines **2023**
1.3 **The Saudi Guidelines** for the Diagnosis and Management of COPD **2014**	N/A*

*****: *No updated versions available*

1.1.1 GOLD Report: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023)

The aim of the GOLD Report is to provide a non-biased review of the current evidence for the assessment, diagnosis, and treatment of people with COPD. The GOLD report is revised annually and has been used worldwide by healthcare professionals as a tool to implement effective management programs based on local healthcare systems[1]. Levels of evidence have been assigned to evidence-based recommendations where appropriate (table 3).

Table 3. Description of Levels of Evidence

Evidence Category	Sources of Evidence	Definition
A	Randomized controlled trials (RCTs)	Evidence is from endpoints of well-designed RCTs that provide consistent findings in the population for which the recommendation is made without any important limitations.
	Rich body of high-quality evidence without any significant limitation or bias	Requires high quality evidence from ≥ 2 clinical trials involving a substantial number of subjects, or a single high quality RCT involving substantial numbers of patient without any bias.
B	Randomized controlled trials (RCTs) with important limitations	Evidence is from RCTs that include only a limited number of patients, post hoc or subgroup analyses of RCTs or meta-analyses of RCTs.
	Limited body of evidence	Also pertains when few RCTs exist, or important limitations are evident (methodologic flaws, small numbers, short duration, undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent)
C	Non-randomized trials Observational studies	Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies
D	Panel consensus judgment	Provision of guidance is deemed valuable but clinical

		literature addressing the subject is insufficient. Panel consensus is based on clinical experience or knowledge that does not meet the above stated criteria.

A **new definition of COPD** has been proposed in the GOLD 2023 guidelines:

- Chronic Obstructive Pulmonary Disease (COPD) is a diverse lung condition marked by persistent respiratory symptoms (such as shortness of breath, cough, the production of sputum, and exacerbations) resulting from irregularities in the airways (including bronchitis and bronchiolitis) and/or the alveoli (emphysema). These irregularities lead to an ongoing, frequently worsening, restriction of airflow.

Causes and risk factors

- COPD is the result of interactions between genetics (G) and environmental (E) factors that occur throughout an individual's lifetime (referred to as GETomics). These interactions can harm the lungs or modify their natural development and aging processes.
- The primary environmental factors responsible for causing COPD include tobacco smoking and the inhalation of harmful particles and gases from indoor and outdoor air pollution. However, other environmental elements and host-related factors, such as abnormal lung development and accelerated lung aging, can also contribute to the development of COPD.
- While the most noteworthy genetic risk factor for COPD identified thus far is rare in the general population, involving mutations in the SERPINA1 gene resulting in α1-antitrypsin deficiency, there are other genetic variations with a relatively low individual impact that are linked to reduced lung function and an increased risk of COPD.

Diagnostic criteria

- In any patient presenting with symptoms like breathlessness, persistent cough, sputum production, or a history of exposure to COPD risk factors, it is important to contemplate the possibility of a COPD diagnosis. However, it is essential to confirm the diagnosis of COPD by performing forced spirometry and verifying the presence of a post-bronchodilator FEV1/FVC ratio less than 0.7.

Table 4. Clinical Indicators for Considering a Diagnosis of COPD. Adapted from the GOLD 2023 Guidelines.

Consider the diagnosis of COPD, and perform spirometry, if any of these clinical indicators are presents	
Dyspnea that is	• Progressive over time • Worse with exercise • Persistent
Recurrent wheeze	
Chronic cough	May be intermittent and may be unproductive
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.)
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.	

- In certain COPD patients, it can be challenging to differentiate the condition from asthma using current imaging and physiological testing methods. This difficulty arises because these two conditions exhibit overlapping characteristics and clinical presentations. However, it is generally more straightforward to distinguish COPD from most other potential differential diagnoses.
- A detailed medical history of a new patient who is known, or suspected, to have COPD should be conducted.
- While an integral component of patient care, a physical examination is seldom, if ever, conclusive in diagnosing COPD.

Initial Assessment

In the presence of FEV1/FVC ratio < 0.7 the assessment of airflow limitation severity in COPD (note that this may be different from severity of the disease) is based on the post-bronchodilator value of FEV1.

Table 5. GOLD Grades and Severity of Airflow Obstruction in COPD. Adapted from the GOLD 2023 Guideline 2023.

GOLD Grades and Severity of Airflow Obstruction 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

The modified Medical Research Council (mMRC) scale was the first questionnaire developed to measure breathlessness, which is a key symptom in many patients with COPD, although often unrecognized.

Table 6. Modified Medical Research Council MRC (mMRC) Dyspnea Scale. Adapted from the GOLD 2023 Guideline.

Modified MRC Dyspnea Scale	
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"

It is now recognized that COPD impacts patients beyond dyspnea. For this reason, multidimensional questionnaires are recommended. The most comprehensive disease-specific health status questionnaires such as the Chronic Respiratory Questionnaire (CRQ) and St. George's Respiratory Questionnaire (SGRQ) 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

COPD Control Questionnaire (CCQ©) have been developed and are suitable for use in the clinic.

The CAT™ is an 8-item questionnaire that assesses health status in patients with COPD.

Table 7. CAT Assessment. Adapted from the GOLD 2023 Guideline.

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	**Score**						**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	
Total score								

- In 2011, GOLD proposed to move from the simple spirometric grading system for disease severity assessment and treatment to a combined assessment strategy based on the level of symptoms (mMRC or CAT™), the severity of airflow limitation (GOLD grades 1-4), and the frequency of previous exacerbations.
- Now, in this 2023 document, GOLD proposes a further evolution of the ABCD combined assessment tool that recognizes the clinical relevance of exacerbations, independently of the level of symptoms of the patient. Figure 1 presents this new proposal. The A and B groups are unchanged, but the C and D groups are now merged into a single group termed "E" to highlight the clinical relevance of exacerbations. GOLD report acknowledges the need for this proposal to be validated by appropriate clinical research.

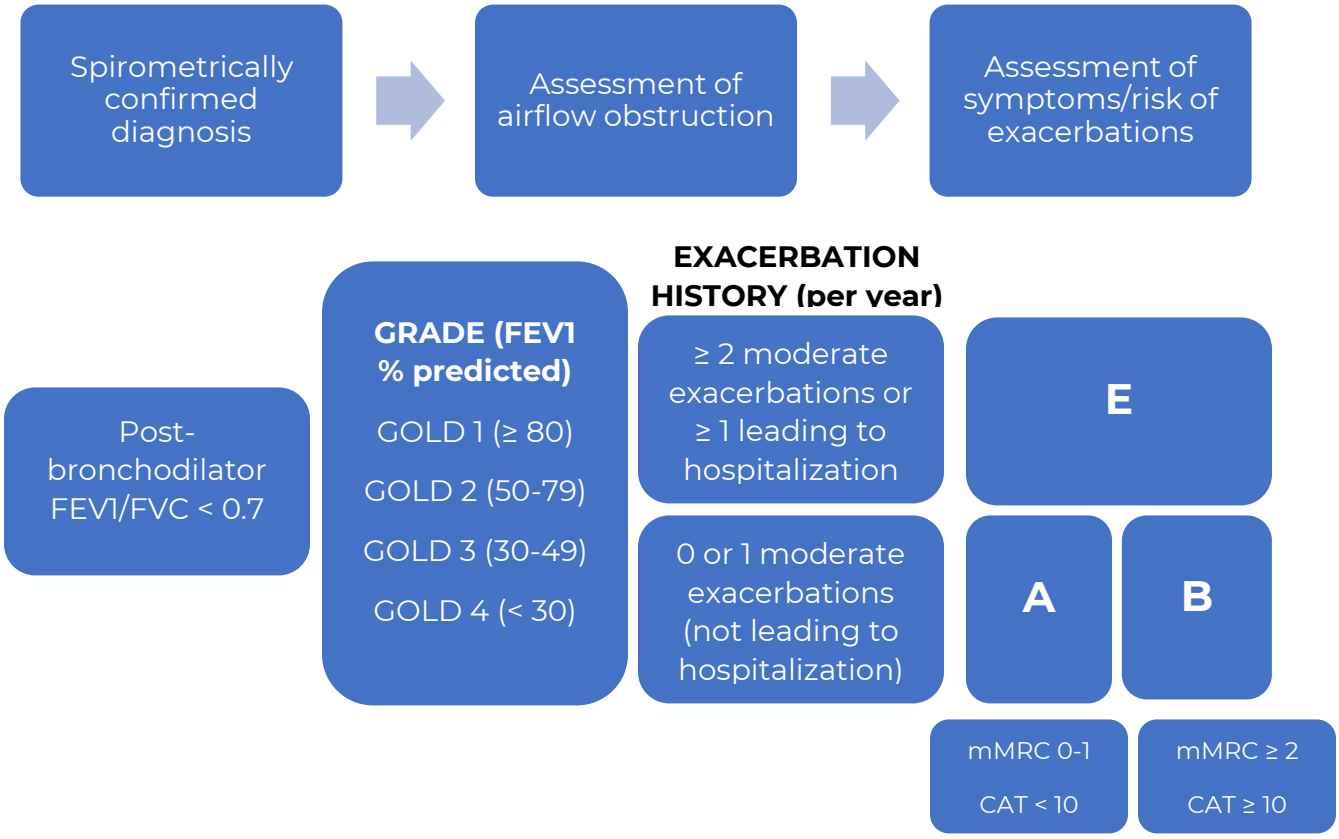

Figure 1. *GOLD ABE Assessment Tool. Adapted from the 2023 GOLD Guideline.*

Additional investigations

- Physiological tests include lung volumes, carbon monoxide diffusing capacity of the lungs (DLco), walking pulse oximetry and arterial blood gas measurement, exercise testing and assessment of physical activity.
- Imaging includes chest X-ray and computed tomography.
- The World Health Organization recommends that all patients with a diagnosis of COPD should be screened once for Alpha-1 antitrypsin deficiency (AATD), especially in areas with high AATD prevalence and COPD at younger age.

Clinical presentation

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

Prevention

- Quitting smoking is essential, and methods like nicotine replacement and medication have been proven to enhance long-term smoking cessation rates reliably.
- Influenza vaccination can reduce serious illness (such as lower respiratory tract infections requiring hospitalization) and death in people with COPD.
- Pneumococcal vaccinations, pneumococcal conjugated vaccine (PCV20 or PCV15) and pneumococcal polysaccharide vaccine (PPSV23), are approved for adults aged ≥ 65 years. They are also approved for adults aged 19-64 years if they have an underlying medical condition such as chronic lung disease (including COPD, emphysema, and asthma), cigarette smoking, solid organ transplant etc.
- In adults with COPD the US Centers for Disease Control (CDC) recommends the Tdap vaccination (also called dTaP/dTPa) to protect against pertussis (whooping cough), tetanus and diphtheria, in those who were not vaccinated in adolescence and the routine use of shingles vaccine. (45,46) People with COPD should have the COVID-19 vaccination in line with national recommendations.

Vaccination for stable COPD

- Influenza vaccinations is recommended in people with COPD (evidence B)
- The WHO and CDC recommend SARS-Cov-2 (COVID-19) vaccination for people with COPD (evidence B)
- The CDC recommends one dose of 20-valent pneumococcal conjugate vaccine (PCV20); or one dose of 15-valent pneumococcal conjugate vaccine (PCV15) followed by a 23-valent pneumococcal polysaccharide vaccine (PPSV23) in people with COPD (evidence B)
- The CDC recommends Tdap (dTaP/dTPa) vaccination to protect against pertussis (whooping cough) for people with COPD that were not vaccinated in adolescence (evidence B), and zoster vaccine to protect against shingles for people with COPD over 50 years (evidence B)

Pharmacological therapy for stable COPD

- Pharmacological therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and health status.
- Commonly used medications in COPD are:
    - Beta agonists: short acting (SABA) and long acting (LABA)
    - Anticholinergic drugs: long acting (LABA) and short acting (SABA)
    - Combination of short acting beta agonist + anticholinergic in one device SABA+SAMA
    - Combination of long-acting beta agonist + anticholinergic in one device LABA+LAMA
    - Methylxanthines
    - Combination of long-acting beta agonist + corticosteroids in one device LABA+ICS
    - Triple combination in one device
    - Phosphodiesterase -4 inhibitor
    - Mucolytics

    **As of the writing of this report, LABA as single agents are not available on the market in KSA.*

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 a LAMA increases FEV1 and reduces symptoms compared to monotherapy (evidence A)
- Combination treatment with a LABA and a 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)
- Single inhaler therapy may be more convenient and effective than multiple inhalers.

Anti-inflammatory therapy in stable COPD

Table 8. Anti-Inflammatory Therapy in Stable COPD

Recommendations	Evidence
Inhaled corticosteroids (ICS)	
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.	A
Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease.	A
Lower blood and sputum eosinophils are associated with greater presence of proteobacteria, notably *Haemophilus*, increased bacterial infections, and pneumonia.	-
Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of pneumonia.	C
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.	A
Recent data suggests a 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.	-
Single inhaler therapy may be more convenient and effective than multiple inhalers.	-
Oral glucocorticoids	
Long-term use of oral glucocorticoids has numerous side effects.	A
Long-term use of oral glucocorticoids has no evidence of benefits.	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	A
• A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA + ICS combinations.	A
Antibiotics	
Long-term azithromycin and erythromycin therapy reduces exacerbations over one year.	A

Mucoregulators and antioxidant agents	
Regular treatment with mucolytics such as erdosteine, carbocysteine and NAC reduces the risk of exacerbations in select populations.	B
Other anti-inflammatory agents	
Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy.	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.	C
Leukotriene modifiers have not been tested adequately in COPD patiens.	-

Factors to consider when initiating ICS treatment

Strongly favors use:

- History of hospitalization(s) for exacerbations of COPD, despite long-acting bronchodilator maintenance therapy
- ≥ 2 moderate exacerbations of COPD per year, despite long-acting bronchodilator maintenance therapy
- Blood eosinophils ≥ 300 cells/μL
- History of concomitant asthma

Favors use:

- 1 moderate exacerbations per year, despite long-acting bronchodilator maintenance therapy
- Blood eosinophils 100 to < 300 cells/μL

Against use:

- Repeated pneumonia events
- Blood eosinophils < 100 cells/μL
- History of active mycobacterial infection

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 people with COPD (evidence C)

Vasodilators:

- Vasodilators do not improve outcomes and may worsen oxygenation (evidence B)

Non-pharmacological therapy

- Non-pharmacologic therapies include:
    - Smoking cessation:
    - Pulmonary rehabilitation (PR)
    - Long term oxygen therapy (LTOT)
    - Non-invasive positive pressure ventilation (NPPV)
    - Lung transplantation and lung volume reduction surgery (LVRS)

Rehabilitation, education & self-management

Pulmonary rehabilitation:

- Pulmonary rehabilitation improves dyspnea, health status and exercise tolerance in stable patients (evidence A).
- Pulmonary rehabilitation reduces hospitalization among patients who have had a recent exacerbation (≤ 4 weeks from prior hospitalization) (evidence B).
- Pulmonary rehabilitation leads to a reduction in symptoms of anxiety and depression (evidence A).

Education and self-management:

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

Integrated care programs:

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

Supportive, palliative, end-of-life & hospice care

- 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).

Oxygen therapy and ventilatory support

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:

- Noninvasive positive pressure ventilation (NPPV) may improve hospitalization-free survival in selected patients after recent hospitalization, particularly in those with pronounced daytime persistent hypercapnia ($PaCO_2$ > 53 mmHg) (evidence B).

Interventional therapy in Stable COPD

- Lung volume reduction surgery improves survival in severe emphysema patients with upper-lobe emphysema and low post-rehabilitation exercise capacity (evidence A).
- In selected patients, bullectomy is associated with decreased dyspnea, improved lung function and exercise tolerance (evidence C).
- In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity (evidence C).

- In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, health status and lung function at 6-12 months following treatment. Endobronchial valves (evidence A); lung coils (evidence B); vapor ablation (evidence B).
- Phase III trials are currently being conducted to determine the efficacy of treatments for patients with refractory exacerbations and chronic bronchitis using cryospray, rheoplasty and targeted lung denervation technology.

Management of stable COPD

- Main goals of treatment are:
    - Reduce symptoms: relief symptoms, increase exercise tolerance, improve health status And
    - Reduce risk: prevent disease progression, prevent treat exacerbation, reduce mortality.

Risk factors identification and reduction

- 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).

Pharmacological treatment of stable COPD

- 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.
- When initiating treatment with long-acting bronchodilators, the preferred choice is a combination of a long-acting muscarinic antagonist and a long acting β2-agonist. In patients with persistent dyspnea on a single long-acting bronchodilator, treatment should be escalated to two (evidence A). The combination can be given as a single inhaler or multiple inhaler treatment.
- 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).

- Long-term monotherapy with ICS is not recommended (evidence A).
- The use of LABA + ICS combination in COPD is not encouraged. If there is an indication for an ICS, the combination LABA + LAMA + ICS has been shown to be superior to LABA + ICS.
- If patients with COPD have features of asthma, treatment should always contain an ICS.
- In patients with severe to very severe airflow limitation, chronic bronchitis and exacerbations, the addition of a PDE4 inhibitor to a treatment with long-acting bronchodilators with/without ICS can be considered (evidence B).
- Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, macrolides, in particular azithromycin, can be considered (evidence B).
- Statin therapy and/or beta-blockers are not recommended for prevention of exacerbations (evidence A).
- 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 treatment dyspnea in COPD patients with severe disease (evidence B).

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

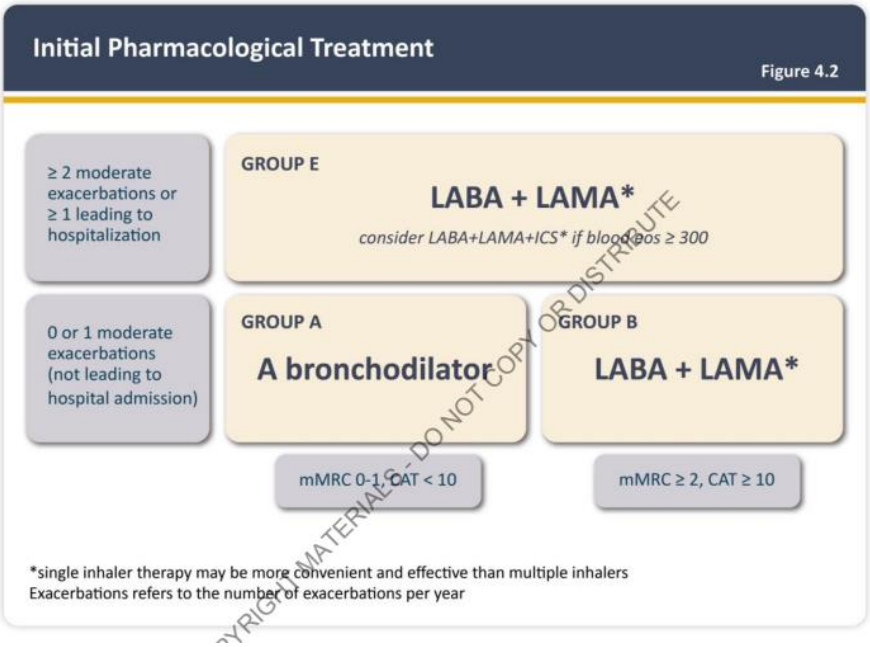

Figure 2. *Initial Pharmacological Treatment. Retrieved from the GOLD 2023 Guideline.*

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

Group A

- For all patients in Group A, bronchodilator treatment should be offered based on its effectiveness in alleviating breathlessness. This treatment can include either short-acting or long-acting bronchodilators. If a long-acting bronchodilator is available and affordable, it is the preferred choice, except for patients who experience very occasional breathlessness.
- This treatment should be continued if it proves beneficial.

Group B

- In Group B, treatment should commence with a combination of a LABA (Long-Acting Beta-Agonist) and a LAMA (Long-Acting Muscarinic Antagonist). Research has shown that in patients who had fewer than one moderate exacerbation in the year preceding the study and a CAT™ score of 10 or higher, the LABA+LAMA combination is superior to a LAMA or LABA alone in various aspects. Therefore, if there are no concerns about availability, cost, or side effects, the initial pharmacological choice should be LABA+LAMA.
- If a LABA+LAMA combination is not considered appropriate, there is no evidence favoring one class of long-acting bronchodilator (LABA or LAMA) over the other for initial symptom relief in this patient group. The choice

between the two should depend on the patient's perception of symptom relief.

- Group B patients often have comorbidities that can worsen their symptoms and affect their prognosis. Therefore, it is important to investigate and treat these comorbidities following national and international guidelines if they are present.

Group E

- In Group E, a Cochrane systematic review and network meta-analysis comparing dual combination therapy to single long-acting bronchodilators indicated that the LABA+LAMA combination was the most effective at reducing COPD exacerbations. Consequently, if there are no concerns regarding availability, cost, or side effects, LABA+LAMA is the preferred initial therapy for Group E patients.
- Consider using LABA+LAMA+ICS in Group E if the eosinophil count is 300 cells/μL or higher, following practical recommendations. While there are no direct data on initiating triple therapy in newly diagnosed patients, it is reasonable to reserve this treatment for patients with a high eosinophil count (≥ 300 cells/μL).
- The use of LABA+ICS (Inhaled Corticosteroid) in COPD is discouraged, but if there is a specific indication for an ICS, then LABA+LAMA+ICS has been demonstrated to be more effective than LABA+ICS and should be the preferred choice.
- If patients with COPD also have concomitant asthma, they should be managed as asthma patients, and the use of an ICS is essential in such cases.

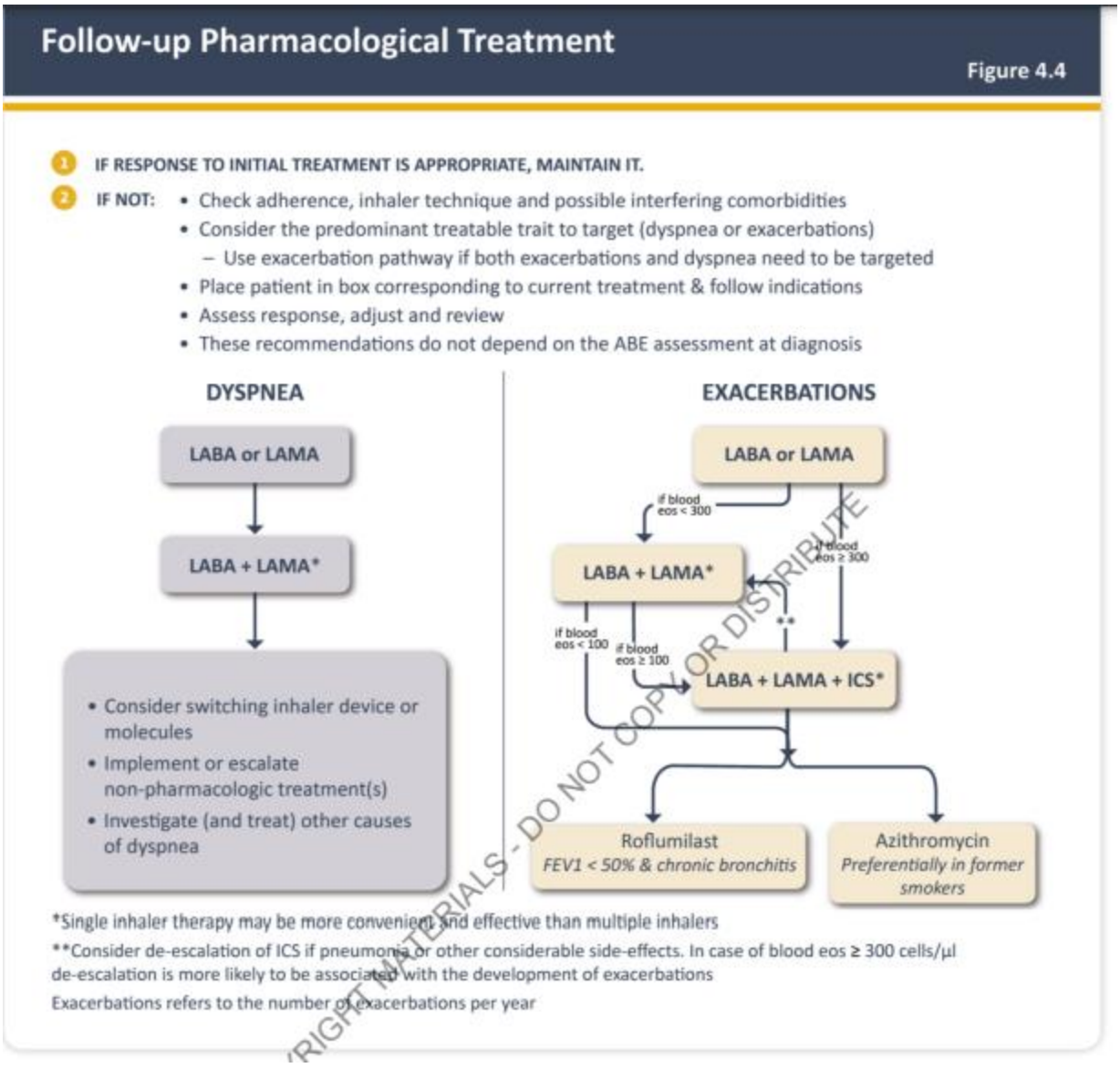

Figure 3. *Follow-up Pharmacological Treatment. Retrieved from the 2023 GOLD Guideline.*

- Follow up pharmacological management should be guided by the principles of first review and assess, then adjust if needed:
    1. Review: Review symptoms (dyspnea) and exacerbation risk (previous history, blood eosinophils).
    2. Assess: Assess inhaler technique and adherence, and the role of non-pharmacological approaches.
    3. Adjust: Adjust pharmacological treatment, including escalation or de-escalation. Switching inhaler device or molecules within the same class (e.g., using a different long-acting bronchodilator) may be considered

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

Dyspnea

- For patients with persistent breathlessness or exercise limitation on bronchodilator monotherapy, the use of two long-acting bronchodilators is recommended.
    - If the addition of a second long-acting bronchodilator does not improve symptoms, we suggest considering switching inhaler device or molecules.
- At all stages, dyspnea due to other causes (not COPD) should be investigated and treated appropriately. Inhaler technique and adherence should be considered as causes of inadequate treatment response.

Exacerbations

- For patients with persistent exacerbations on bronchodilator monotherapy, escalation to LABA+LAMA is recommended.
- Blood eosinophil counts may identify patients with a greater likelihood of a beneficial response to ICS. For patients who develop exacerbations under mono long-acting bronchodilator treatment and a blood eosinophil count ≥ 300 cells/μL escalation to LABA+LAMA+ICS may be considered.
- In patients who develop further exacerbations on LABA+LAMA therapy we suggest two alternative pathways. Blood eosinophil counts < 100 cells/μL can be used to predict a low likelihood of a beneficial ICS response:
    - Escalation to LABA+LAMA+ICS. A beneficial response after the addition of ICS may be observed at blood eosinophil counts ≥ 100 cells/μL, with a greater magnitude of response more likely with higher eosinophil counts.
- If patients treated with LABA+LAMA+ICS (or those with eosinophils < 100 cells/μL) still have exacerbations the following options may be considered:
    - Add roflumilast. This may be considered in patients with an FEV1 < 50% predicted and chronic bronchitis, 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.

- Withdrawing ICS can be considered if pneumonia or other considerable side-effects develop. If blood eosinophils are ≥ 300 cells/μL de-escalation is more likely to be associated with the development of exacerbations. Carefully consider the dose of ICS used to reduce the potential of ICS related side effects that are more frequent at higher doses.

Patients under treatment with LABA+ICS

- For patients who are well controlled in terms of symptoms and exacerbations, continuation with LABA+ICS is an option. However, for patients who experience further exacerbations, treatment should be escalated to LABA+LAMA+ICS.

Non-Pharmacological Treatment of Stable COPD

- Non-pharmacological interventions play a complementary role alongside pharmacological treatments and should be integrated into the comprehensive care of COPD patients.

Table 9. Non-Pharmacological Management of COPD. Adapted from the GOLD 2023 Guideline.

Patient group	Essential	Recommended	Depending on local guidelines
A	Smoking cessation (can include pharmacological treatment)	Physical activity	Flu vaccination Pneumococcal vaccination Pertussis vaccination COVID-19 vaccination Shingles vaccination
B and E	Smoking cessation (can include pharmacological treatment) Pulmonary rehabilitation	Physical activity	

Education, self-management, and pulmonary rehabilitation:

- Education is needed to change the patient's knowledge but there is no evidence that if used alone it will change 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). People with COPD should be encouraged to increase the level of physical activity although it is still unknown how to best insure the likelihood of success.

Vaccination:

- Influenza vaccination is recommended in people with COPD (evidence B).
- The WHO and CDC recommend SARS-CoV-2 (COVID-19) vaccination for people with COPD (evidence B).
- The CDC recommends one dose of 20-valent pneumococcal conjugate vaccine (PCV20); or one dose of 15-valent pneumococcal conjugate vaccine (PCV15) followed by a 23-valent pneumococcal polysaccharide vaccine (PPSV23) in people with COPD (evidence B).
- Pneumococcal vaccine has been shown to reduce the incidence of community-acquired pneumonia and exacerbations in people with COPD (evidence B).
- The CDC recommends Tdap (dTaP/dTPa) vaccination to protect against pertussis (whooping cough) for people with COPD that were not vaccinated in adolescence (evidence B), and zoster vaccine to protect against shingles for people with COPD over 50 years (evidence B).

Nutrition:

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

End of life and palliative care:

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

Treatment of hypoxemia:

- In patients with severe resting hypoxemia, PO2 less than 55 or < 60 in presence of polycythemia, cor-pulmonale or congestive heart failure 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).

Non-invasive ventilation

The initial choice of ventilation for individuals experiencing acute respiratory failure in COPD should be non-invasive mechanical ventilation, provided there are no absolute contraindications. This approach enhances gas exchange, lessens the respiratory effort and the necessity for intubation, shortens the duration of hospitalization, and enhances overall survival.Intervention bronchoscopy and surgery:

- Lung volume reduction surgery should be considered in selected patients with upper-lobe emphysema (evidence A).
- In selected patients with a large bulla, surgical bullectomy may be considered (evidence C).
- In selected patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, quality of life and lung function at 6-12 months following treatment. Endobronchial valves (evidence A); lung coils (evidence B); vapor ablation (evidence B).
- In patients with very severe COPD (progressive disease, BODE score 7 to 10, and not candidate for lung volume reduction), lung transplantation may be considered for referral with at least one of the following: (1) history of hospitalization for exacerbation associated with acute hypercapnia (PCO_2 > 50 mmHg); (2) pulmonary hypertension and/or cor pulmonale, despite oxygen therapy; or (3) FEV1 < 20% and either DLco < 20% or homogenous distribution of emphysema (evidence C).

Management of exacerbations

- COPD exacerbation is described as an episode marked by the worsening of dyspnea and/or cough along with sputum production within a period of fewer than 14 days. These exacerbations are frequently linked to heightened inflammation in the airways and throughout the body, triggered by factors such as airway infections, environmental pollution, or other lung-related insults.

- The goals for treatment of COPD exacerbations are to minimize the negative impact of the current exacerbation and to prevent subsequent events.
- To address an exacerbation, it is recommended to begin with short-acting inhaled beta2-agonists, either alone or in combination with short-acting anticholinergics as the initial bronchodilators (Evidence C).
- It's important to initiate maintenance therapy with long-acting bronchodilators as soon as possible. For patients who experience frequent exacerbations and have elevated blood eosinophil levels, the addition of inhaled corticosteroids to the double bronchodilator regimen should be considered.
- In cases of severe exacerbations, systemic corticosteroids can improve lung function (FEV1), oxygen levels, and reduce recovery time, including the duration of hospitalization. The typical duration of corticosteroid therapy should not exceed 5 days (Evidence C).
- Antibiotics may be necessary when indicated, as they can shorten recovery time, decrease the risk of early relapse, prevent treatment failure, and reduce the duration of hospitalization. The usual duration of antibiotic therapy is 5 days (Evidence B).
- The use of methylxanthines is discouraged due to their increased potential for side effects (Evidence B).
- In cases of acute respiratory failure in COPD patients without absolute contraindications, non-invasive mechanical ventilation should be the first-choice mode of ventilation. This approach improves gas exchange, reduces the effort required for breathing, decreases hospitalization duration, and enhances survival (Evidence A).
- The recovery time from an exacerbation can vary and may take up to 4-6 weeks, with some patients not fully returning to their pre-exacerbation functional state. Following an exacerbation, it is important to implement appropriate measures to prevent future exacerbations.

COPD and comorbidities

- COPD frequently occurs alongside other medical conditions, known as comorbidities, which can profoundly influence the course of the disease.
- As a general rule, the presence of comorbidities should not change the approach to COPD treatment. Comorbidities should be managed according to standard protocols, irrespective of whether COPD is present.
- Cardiovascular diseases are commonly observed and significant comorbidities in individuals with COPD.

- Lung cancer is a common occurrence in individuals with COPD and stands as a significant contributor to mortality.
- For individuals with COPD resulting from smoking, it is advisable to undergo an annual low-dose CT scan (LDCT) for lung cancer screening, following recommendations established for the general population.
- However, for individuals with COPD unrelated to smoking, annual LDCT screening for lung cancer is not recommended due to insufficient data to ascertain that the benefits outweigh the potential harm.
- Osteoporosis and depression/anxiety are frequently observed and significant comorbidities in COPD. These conditions are often underdiagnosed and are associated with reduced health status and prognosis. Gastroesophageal reflux (GERD) is linked to an elevated risk of exacerbations and decreased health status in individuals with COPD.
- When managing COPD as part of a broader multimorbidity care plan, it is essential to prioritize simplicity in treatment and aim to minimize polypharmacy, which involves taking multiple medications simultaneously.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI COPD report, along with their recommendations.

Table 10. List of Additional Guidelines

Additional Guidelines
The **COPD-X Plan**: Australian and New Zealand Guidelines for the Management of Chronic Obstructive Pulmonary Disease (**2023**)
Canadian Thoracic Society Guideline on Pharmacotherapy in Patients with Stable COPD (**2023**)
American Thoracic Society Clinical Practice Guideline on Pharmacologic Management of Chronic Obstructive Pulmonary Disease (**2020**)
Management of COPD in Asia: A Position Statement of the **Asian Pacific Society of Respirology** (**2019**)
Spanish COPD Guidelines (**GesEPOC**): Updated Pharmacological Treatment of Stable COPD (**2021**)

1.2.1 The COPD-X Plan: Australian and New Zealand Guidelines for the Management of Chronic Obstructive Pulmonary Disease (2023)

COPD-X provides guidance for **C**ase finding and confirming diagnosis, **O**ptimizing function, **P**revention of deterioration, **D**evelopment of care plans and management of e**X**acerbations. COPD-X highlights the critical role of reducing risk factors (particularly through smoking avoidance and cessation), optimizing function with multidisciplinary care, improving treatment of comorbidities and referring symptomatic patients to pulmonary rehabilitation. The guidelines promote the concept of 'stepwise management', beginning with one pharmacological intervention and evaluating response before adding another agent. The guidelines also emphasize the importance of non-pharmacological therapy for COPD. The recommendations made in the guidelines are applicable across multiple care settings. The guidelines recognize that a patient-centered approach involving a team of healthcare workers is required for optimal outcomes[4].

Table 11. National Heart, Lung, and Blood Institute (NHLBI) Categories and Levels of Evidence

NHLBI category	Sources of evidence	Definition
A	Randomized controlled trials (RCTs) extensive body of data.	Evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	Randomized controlled trials (RCTs) limited body of data.	Evidence is from endpoints of intervention studies that include only a limited number of patients, post-hoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.

C	Non-randomized trials, observational studies.	Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies.
D	Panel consensus, judgement.	The panel consensus is based on clinical experience or knowledge that does not meet the above criteria.

Table 12. National Health and Medical Research Council (NHMRC) Levels of Evidence and Corresponding National Heart, Lung, and Blood Institute (NHLBI) categories

NHLBI category	NHMRC level	Basis of evidence
A	I	Evidence obtained from a systematic review of all relevant randomized controlled trials.
B	II	Evidence obtained from at least one properly designed randomized controlled trial.
C	III-1	Evidence obtained from well-designed pseudorandomized controlled trials (alternate allocation or some other method).
C	III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomized, cohort studies, case-control studies, or interrupted time series with a control group.
C	III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel group.
C	IV	Evidence obtained from case series, either post-test or pre-test/post-test.

Table 13. Grading Scheme for Recommendations

Grading Scheme for Recommendations	
Strong recommendation	We recommend
Weak recommendation	We suggest

Case finding and confirm diagnosis

- The primary factor contributing significantly to the development of COPD is smoking (I, Strong).
- Smoking cessation reduces mortality (I, Strong).
- The initial stage in diagnosing COPD involves conducting a comprehensive assessment and examination of the patient's medical history (III-2, Strong).
- The diagnosis of COPD is established when there is a persistent restriction of airflow (with a post-bronchodilator FEV1/FVC ratio less than 0.7) (III-2, Strong).
- Upon diagnosing COPD, it is essential to routinely evaluate its level of severity (III-2, Strong).
- If FEV1 increases >400 mL following bronchodilator, consider asthma, or coexisting asthma and COPD (III-2, Strong).
- Further investigations may help a) confirm or exclude other conditions (either coexisting or with similar symptoms to COPD) and b) assess the severity of COPD (III-2, Strong).
- Referral to specialist respiratory services may be required (III-2, Strong).

Optimize Function

- Evaluating one's condition is the initial stage in maximizing their functionality (III-2, Strong).
- Optimize pharmacotherapy using a stepwise approach (I, Strong).
- Adherence and inhaler technique need to be checked on a regular basis (I, Strong).
- It is frequent for patients with COPD to have concurrent comorbid conditions (III-2, Strong).
- Early consideration of palliative care is essential, and it is best when administered by a diverse team, including the primary care team. This approach should involve the management of symptoms and the provision of support for psychosocial issues (II, Weak)
- Pulmonary rehabilitation improves quality of life and exercise capacity and reduces COPD exacerbations (I, Strong).
- Both surgical and endobronchial lung volume reduction procedures result in enhancements in lung function, exercise capacity, and quality of life (I, Weak).

- In individuals with moderate to severe COPD who experience frequent exacerbations, extended use of macrolide antibiotics has the potential to decrease the occurrence of exacerbations (I, Weak).
- In individuals with stable COPD who have hypercapnia, the consideration of prolonged non-invasive ventilation is advisable to lower mortality rates (I, Weak).

Prevent deterioration

- The most crucial action to prevent the deterioration of COPD is quitting smoking (II, Strong).
- The prevention of exacerbations plays a crucial role in averting deterioration (III-2, Strong).
- Vaccination lowers the likelihood of experiencing complications related to influenza and pneumococcal infections (I, Strong).
- Although data does not endorse the use of inhaled corticosteroids for all individuals with COPD, it does recommend their utilization for those with more advanced disease (FEV1 <50% predicted) who have a history of frequent exacerbations.
- Mucolytics can be advantageous for specific COPD patients (I, Strong).
- Prolonged oxygen therapy provides survival advantages to COPD patients experiencing hypoxemia (I, Strong).

Develop a care plan

- Effective management of chronic diseases involves anticipating the diverse needs of COPD patients (I, Strong).
- Collaboration between clinical support teams and the primary healthcare team can enhance the quality of life and reduce disability in COPD patients (III-2, Weak).
- Patients may find self-management support beneficial (I, Strong).
- Patients may benefit from participation in support groups and utilizing community services (III-2, Weak).
- The implementation of COPD exacerbation action plans can lead to a reduction in emergency department visits and hospital admissions (I, Strong).

Management of exacerbations

- A COPD exacerbation is characterized by a sudden change in the patient's baseline dyspnea, cough, and/or sputum that goes beyond their typical day-to-day variations and may require a modification in regular medication or hospitalization (III-2, Strong)
- Early diagnosis and prompt treatment of exacerbations can prevent hospitalization and delay the progression of COPD (III-2, Strong)
- A multidisciplinary approach may assist in managing some patients with exacerbations at home (I, Weak).
- Inhaled beta-agonist (e.g., salbutamol, 400–800mcg; terbutaline, 500–100mcg) and antimuscarinic agent (ipratropium, 80mcg) can be given by pressurized metered dose inhaler and spacer, or by jet nebulization (salbutamol, 2.5–5 mg; terbutaline, 5 mg; ipratropium, 500mcg).
- Oral corticosteroids expedite recovery and lower the chances of recurrence. A treatment duration of up to two weeks with prednisolone at a daily dosage of 40–50 mg is sufficient. Prolonged courses do not offer additional advantages and carry a greater risk of adverse effects.
- Antibiotics are given for purulent sputum to cover typical and atypical organisms.
- Controlled oxygen therapy is indicated in patients with hypoxia, with the aim of improving oxygen saturation to 88 to 92%.
- Ventilatory assistance is recommended for increasing hypercapnia and acidosis.
- Inhaled bronchodilators are effective as initial treatment for exacerbations (I, Strong).
- Systemic corticosteroids reduce the severity of exacerbations and expedite recovery (I, Strong).
- Exacerbations with signs of infection (such as increased sputum volume, change in color, and/or fever) benefit from antibiotic therapy (I, Strong).
- Controlled oxygen delivery (0.5-2.0 L/min) is recommended for patients with hypoxemia during exacerbations (II, Strong).
- When using supplemental oxygen for hypoxia during COPD exacerbations, targeting SpO2 levels between 88% and 92% improves survival (II, Strong).
- Non-invasive ventilation (NIV) is effective for patients with rising PaCO2 levels (I, Strong).

- Non-invasive ventilation enhances survival for individuals with COPD and acute hypercapnic respiratory failure (I, Strong).
- Consider the option of pulmonary rehabilitation at any time, including during the recovery phase following an exacerbation (I, Strong).
- Patients with COPD who are discharged from the hospital after an exacerbation should receive comprehensive follow-up care led by the primary healthcare team (I, Strong).

1.2.2 Canadian Thoracic Society Guideline on Pharmacotherapy in Patients with Stable COPD (2023)

This guideline provides recommendations from a comprehensive systematic review with a meta-analysis and expert-informed clinical remarks to optimize maintenance pharmacologic therapy for individuals with stable COPD, and a revised and practical treatment pathway based on new evidence since the 2019 update of the Canadian Thoracic Society (CTS) Guideline[6].

Table 14. CTS Levels of Evidence

Level of Evidence	
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Table 15. CTS Grading Scheme for Recommendations

Grading Scheme for Recommendations	
Strong recommendation	We recommend
Weak recommendation	We suggest

- For people with stable COPD who have a low likelihood of experiencing exacerbations, minimal symptoms and health-related quality of life issues (CAT score less than 10, mMRC score of 1), and only mild impairment in lung function (FEV1 equal to or greater than 80% of predicted), it is advisable to initiate monotherapy with either a LAMA or a LABA as the first treatment choice (Strong, Moderate to high certainty of greater improvements in dyspnea, exercise tolerance, and health status with LAMA or LABA compared to placebo).
- For individuals with stable COPD who have a low likelihood of experiencing exacerbations, but a moderate to high symptom burden or impaired health-related quality of life (CAT score of 10 or higher, mMRC score of 2 or higher), and reduced lung function (FEV1 less than 80% of predicted), it is recommended to begin dual therapy with a combination of LAMA and LABA as the initial maintenance treatment (Strong, Moderate to high certainty of greater improvements in dyspnea, exercise intolerance, and health status with LAMA/LABA compared to LAMA monotherapy, Moderate certainty of greater improvements in dyspnea, exercise intolerance, and health status with LAMA/LABA compared to LABA monotherapy)
    - LAMA/LABA dual therapy is preferred to ICS/LABA combination therapy due to significant improvement inlung function and lower rates of pneumonia. However, ICS/LABA combination therapy is preferred to LAMA/ LABA dual therapy in individuals who have COPD with concomitant asthma (Low certainty of greater improvements in dyspnea, exercise intolerance, and health status with LAMA/LABA compared to ICS/LABA combination therapy)
- In individuals with stable COPD, at low risk of exacerbations, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV1 < 80% predicted) despite LAMA/LABA dual therapy or ICS/LABA combination therapy, we recommend step-up to a LAMA/LABA/ICS triple combination therapy (Strong, Moderate certainty of greater improvements in dyspnea and health status with LAMA/LABA/ICS compared to LAMA/LABA dual therapy or ICS/ LABA combination therapy.).
    - The most effective approach to alleviate breathlessness, along with other symptoms and to enhance overall health status, involves combining optimal pharmacotherapy with pulmonary rehabilitation.
- In individuals with stable COPD, at low risk of exacerbations, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV1 < 80% predicted) despite LAMA/LABA/ICS triple combination therapy, we suggest not stepping down to LAMA/LABA

dual therapy (Weak, Low to moderate certainty of lack of harm from step down from LAMA/LABA/ICS to LAMA/LABA dual therapy).

- For patients taking LAMA/LABA dual therapy, we suggest not stepping down to LAMA or LABA monotherapy (Weak, insufficient evidence).
- In individuals with stable COPD, at low risk of exacerbations, currently on LAMA monotherapy, LABA monotherapy, or LAMA/LABA dual therapy, we do not suggest adding any of the following oral medications (Weak, *Low certainty* of no improvements in dyspnea, exercise tolerance, physical activity levels, and/or health status with oral therapies compared toplacebo):
    - Phosphodiesterase-4-inhibitors
    - Mucolytics
    - Statins
    - Anabolic steroids
    - Oral Chinese herbal medicines
    - Theophylline
- In all individuals with stable COPD and at a low risk of exacerbations, we recommend against treatment with ICS monotherapy (Strong, Low certainty of no improvements in dyspnea, exercise tolerance, physical activity levels, and/ or health status with ICS monotherapy compared to placebo).
- In individuals with stable COPD, at low risk of exacerbations, a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV1 < 80% predicted), we recommend starting LAMA/LABA dual therapy as initial maintenance therapy (Strong, Moderate certainty of greater reduction in rate of exacerbation with LAMA/LABA dual therapy compared to LAMA monotherapy).
    - LAMA/LABA dual therapy is preferred to ICS/LABA combination therapy due to significant improvement in lung function and lower rates of pneumonia. However, ICS/ LABA combination therapy is preferred to LAMA/LABA dual therapy in individuals who have COPD with concomitant asthma (Low to moderate certainty of greater reduction in rate of exacerbation with LAMA/LABA dual therapy compared to LABA monotherapy, Low to moderate certainty of greater reduction in rate of exacerbation with LAMA/LABA dual therapy compared to ICS/LABA combination therapy).
- In individuals with stable COPD, at high risk of exacerbations, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV1 < 80% predicted), we recommend the use

of LAMA/LABA/ICS triple combination therapy (Strong, Low to moderate certainty of greater reductionin rate of exacerbation with LAMA/LABA/ICS triple combination therapy compared to LAMA monotherapy).

- In individuals with stable COPD, at a high risk of exacerbations, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV1 < 80% predicted), we do not suggest step down from LAMA/LABA/ICS triple combination therapy to LAMA/LABA dual therapy (Weak, Low certainty of benefit of stepdown from LAMA/ LABA/ICS to LAMA/LABA).
- In individuals with stable COPD, at a high risk of exacerbations, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV1 < 80% predicted) who continue to exacerbate (either moderate or severe) despite being on LAMA/LABA/ICS triple combination therapy, we recommend the addition of macrolide maintenance therapy (Strong, Moderate certainty of greater reduction in rate of exacerbation with addition of oral macrolide to LAMA/LABA/ICS).
    - The benefits of macrolide maintenance therapy observed over a one-year period should be carefully considered in comparison to the potential risks of microbial resistance, hearing impairment, and cardiac arrhythmia associated with QT prolongation and drug interactions.
- In individuals with stable COPD, with a Chronic Bronchitic Phenotype at a high risk of exacerbations, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV1 < 80% predicted) who continue to exacerbate despite being on LAMA/ LABA/ICS triple combination therapy, we suggest the addition of either Roflumilast or N-acetylcysteine (Weak, Low certainty of greater reduction in rate of exacerbation with the addition of roflumilast compared to placebo?).
- In individuals with stable COPD, at a high risk of exacerbations, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV1 < 80% predicted), we recommend the use of LAMA/LABA/ICS triple combination therapy over LABA/LAMA dual therapy (Strong, Moderate certainty for greater reduction in mortality with LAMA/LABA/ICS triple combination compared to LABA/LAMA dual therapy).
- In individuals with stable COPD, at a high risk of exacerbations, with a moderate to high symptom burden/health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV1 < 80% predicted) we recommend the use of LAMA/LABA/ICS triple combination therapy over

ICS/LABA combination therapy (Weak, Moderate certainty for greater reduction in mortality with LAMA/LABA/ICS triple combination therapy compared to ICS/LABA combination therapy).

- While triple therapy has not demonstrated superiority in reducing mortality compared to ICS/LABA, it has exhibited more significant advantages in other crucial outcomes. This includes the prevention of moderate-to-severe acute exacerbations of chronic obstructive pulmonary disease (AECOPD), which was the primary outcome in these randomized controlled trials (RCTs). Additionally, triple therapy has shown improvements in dyspnea, health status, and lung function, which were secondary outcomes in this specific patient population.

1.2.3 American Thoracic Society Clinical Practice Guideline on Pharmacologic Management of Chronic Obstructive Pulmonary Disease (2020)

Evidence-based guidelines by the American Thoracic Society (ATS) for the pharmacological management of chronic obstructive pulmonary disease (COPD) were updated in 2020 by a multidisciplinary panel of experts. A comprehensive systematic review of the literature was performed to address the key clinical questions and critical patient-centered outcomes agreed on by the panel. These guideline recommendations focus on the pharmacological management of stable symptomatic COPD. The guideline has different implications for patients, clinicians, and policymakers (table 17)[7].

Table 16. ATS Levels of Evidence

Level of evidence	
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Table 17. Implications of Strong and Conditional Recommendations from the GRADE Working Group

	Strong Recommendation ("We Recommend . . .")	Conditional Recommendation ("We Suggest . . .")
For patients	The overwhelming majority of individuals in this situation would want the recommended course of action and only a small minority would not (it is the right course of action for >95% of patients).	The majority of individuals in this situation would want the suggested course of action, but a sizable minority would not (it is the right course of action for > 50% of patients)
For clinicians	The overwhelming majority of individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences (just do it).	Different choices will be appropriate for different patients, and you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision (slow down, think about it, and discuss it with the patient).
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators (the recommended course of action may be an appropriate performance measure).	Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place (the recommended course of action is not appropriate for a performance measure).

- The panel suggests opting for a combination therapy of long-acting β2-agonist (LABA) and long-acting muscarinic antagonist (LAMA) rather than choosing LABA or LAMA monotherapy on Patients with COPD Who Complain of Dyspnea or Exercise Intolerance and who are not on maintenance therapy (strong recommendation, moderate certainty evidence).
- The panel recommends the adoption of triple inhaler therapy, involving an inhaled corticosteroid (ICS), a long-acting β2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), instead of dual therapy (LABA/LAMA) for patients with COPD who have experienced one or more exacerbations in the previous year necessitating antibiotics, oral steroids, or hospitalization (conditional recommendation, moderate certainty evidence).
- The panel recommends considering discontinuation of inhaled corticosteroids (ICS) in patients with COPD who are receiving triple therapy (ICS/LABA/LAMA) if the patient has not experienced any exacerbations in the previous year (conditional recommendation, moderate certainty evidence).
- The panel did not provide a specific recommendation either in favor of or against the use of inhaled corticosteroids (ICS) as an additional treatment alongside long-acting bronchodilators for patients with COPD and blood eosinophilia, defined as having more than 2% blood eosinophils or exceeding 150 cells/ml. However, an exception was made for patients with a history of one or more exacerbations in the past year that necessitated antibiotics, oral steroids, or hospitalization, for whom the panel suggested considering the addition of ICS as part of their treatment (conditional recommendation, moderate certainty evidence).
- For individuals with COPD who have a history of severe and frequent exacerbations despite receiving otherwise optimal treatment, the panel advised against the utilization of maintenance oral corticosteroid therapy (conditional recommendation, low certainty evidence).
- For individuals with COPD who encounter severe, unmanageable breathlessness despite receiving otherwise effective treatment, the panel recommended the potential consideration of opioid-based therapy as a means of managing dyspnea. This decision should be made through a personalized approach involving shared decision-making (conditional recommendation, very low certainty evidence).

1.2.4 Management of COPD in Asia: A Position Statement of the Asian Pacific Society of Respirology (2019)

The following recommendations are retrieved from the clinical guidelines on the management of COPD in Asia issued by the Asian Pacific Society of Respirology in 2019[8]:

- It is crucial to highlight the significance of pulmonary function tests (PFT) to general practitioners (GPs).
- Teaching both general practitioners (GPs) and patients about the significance of inhalers is essential.
- A history of biomass smoke exposure should be taken.
- Parasitic infections should be ruled out in patients with high blood eosinophil counts.
- Doctors should offer guidance and provide nicotine replacement therapy and pharmacological recommendations.
- Monitoring air pollution levels is essential, and it is important to keep COPD patients informed. COPD patients should refrain from outdoor activities during periods of elevated air pollution.
- It's crucial to closely monitor potential drug side effects in patients with a low BMI. For patients with a low body mass index (BMI), considering a reduced dosage of roflumilast and inhaled corticosteroids (ICS) might be appropriate.
- ICS needs to be prescribed with caution in COPD combined with bronchiectasis.
- Patients with tuberculosis (TB) should be assessed for long-acting bronchodilator use. The presence and activity of TB should be assessed both before and after initiating inhaled corticosteroids (ICS) treatment.
- It is essential to exclude parasitic infections in individuals with elevated blood eosinophil counts.

1.2.5 Spanish COPD Guidelines (GesEPOC): Updated Pharmacological Treatment of Stable COPD (2021)

The Spanish COPD Guidelines (GesEPOC) were first published in 2012, and since then have undergone a series of updates incorporating new evidence on the diagnosis and treatment of COPD. GesEPOC was drawn up in partnership with scientific societies involved in the treatment of COPD and the Spanish Patients' Forum. Their recommendations are based on an evaluation of the evidence using

GRADE methodology, and a narrative description of the evidence in areas in which GRADE cannot be applied[5].

Table 18. Assessment of the Quality of Evidence and Modifying Factors

Study Design	Quality of evidence	Decrease if	Increase if
Randomized controlled trial	High	Design limitations: 1 Important 2 Very important	Strong association: 1 Strong 2 Very strong
	Moderate	Inconsistent results: 1 Inconsistent 2 Very inconsistent	Presence of a dose response gradient: 1 Evidence for a gradient
Observational study	Low	Absence of direct evidence: 1 Indirect 2 Very indirect	Potential confounders: 1 Would reduce a demonstrated effect or 1 Would suggest a spurious effect when results show no effect
	Very low	Inaccurate results: 1 Imprecise 2 Very imprecise Publication bias 1 Probable 2 Very likely	

Table 19. Implications of the Strength of Recommendations

	Strong recommendation	Weak recommendation
For patients	Most people would agree with the recommended intervention and only a small one part would not	Most people would agree with the recommended action but a significant number of them would not
For healthcare professionals	Most patients should receive the recommended intervention	It is recognized that different options are appropriate for different patients, and the doctor

		has to assist each patient in reaching the decision most consistent with their values and preferences.
For managers	The recommendation can be adopted as a health policy in most situations	There is a need for a significant debate involving stakeholders' participation.

- GesEPOC 2021 proposes a 4-step patient assessment process: 1) diagnosis of COPD and general measures; 2) risk stratification; 3) selection of inhaled treatment according to symptoms and clinical phenotype; and 4) identification and management of treatable traits.

Diagnosis

- The process begins with having a suspicion of diagnosis in an adult who is either a current smoker or has a history of smoking equivalent to more than 10 pack-years or prolonged exposure to harmful particles or gases. This suspicion arises when the individual presents respiratory symptoms, such as shortness of breath or persistent cough, with or without the production of phlegm.
- The diagnosis is then confirmed through spirometry testing conducted during periods of clinical stability. This test reveals a post-bronchodilator ratio of the forced expiratory volume in the first second (FEV1) to the forced vital capacity (FVC) of less than 0.7.
- Nonetheless, it is important to acknowledge that this value may underestimate airflow obstruction in younger individuals and potentially overdiagnose it in older individuals, as the ratio naturally decreases with age. Therefore, three criteria need to be fulfilled to make a diagnosis of COPD: prior exposure to risk factors, the presence of respiratory symptoms, and evidence of obstruction in spirometry performed after bronchodilation.
- Alpha-1 antitrypsin (AAT) should be determined in all patients.
- Following the diagnosis, several general measures should be taken for all COPD patients. These measures encompass quitting smoking, ensuring adequate nutrition, engaging in regular physical activity tailored to the patient's age and physical state, and assessing and addressing any accompanying medical conditions.

Risk stratification

- The evaluation of risk level is based on the likelihood of the patient experiencing exacerbations, disease progression, future complications, increased healthcare resource utilization, or higher mortality.
- GesEPOC suggests categorizing patients into two risk levels: low and high.
- Factors taken into account for risk assessment include post-bronchodilator FEV1 (%), the severity of dyspnea assessed using the modified Medical Research Council (mMRC) scale, and the number of exacerbations experienced in the previous year.

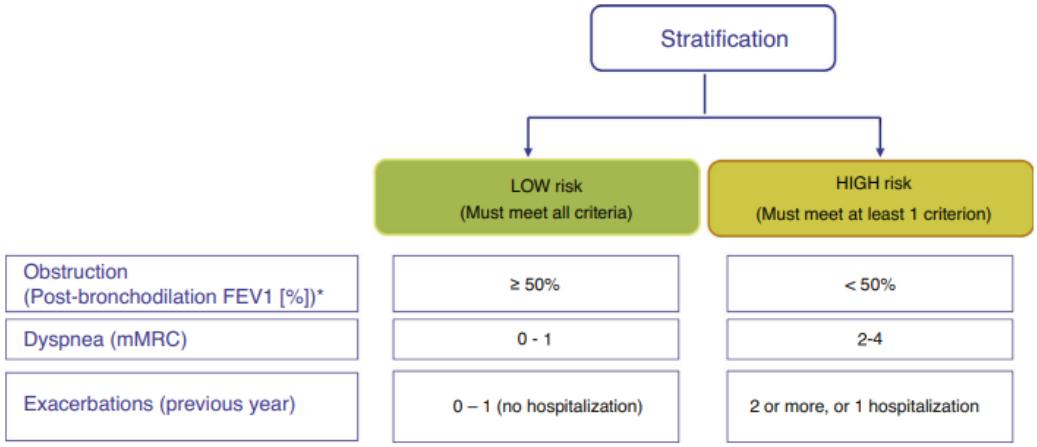

Figure 4. *Risk Stratification in COPD Patients. Retrieved from the GesEPOC 2021 Guideline.*

Table 20. Adaptation of the Care Level to Risk Levels. Retrieved from the GesEPOC 2021 Guideline.

	Therapeutic interventions	
Low risk	Smoking cessation	Counseling Specific treatment
	Therapeutic education	Structured therapeutic education program aimed at: • Promoting self-care • Therapeutic adherence Inhalation technique
	Physical activity	Regular exercise
	Vaccination	Anti-influenza Anti-pneumococcal (13-valent conjugate) Covid-19 Assess dTpa
	Alpha-1 antitrypsin deficiency	Augmentation treatment according to guidelines
	Pharmacological treatment	Bronchodilators
	Comorbidity	Treatment of the comorbidity
High risk	**Add to previous treatment:**	
	Pharmacological treatment	Guided by clinical phenotype Identify treatable traits
	Non-pharmacological treatment	Pulmonary rehabilitation Assess long-term home oxygen therapy Assess non-invasive ventilation Assess lung volume reduction in patients with extensive emphysema Assess lung transplant

Covid-19: coronavirus disease 2019; dTpa: Diphtheria, tetanus, acellular pertussis.

Treatment

- The general treatment objectives for COPD are to alleviate disease symptoms, reduce the frequency and severity of exacerbations, improve quality of life (QoL), and extend survival.
- The cornerstone of treatment for COPD in stable conditions lies in the use of inhalable medications, guided by symptoms in low-risk patients and by clinical phenotype in high-risk patients.
- For most patients, LABD (Long-Acting Bronchodilators) are the favored medications, and the choice of additional treatments to accompany LABD in initial therapy will be determined by the patient's risk group and clinical characteristics.
- For individuals with COPD who need a long-acting bronchodilator as their sole treatment, it is recommended to consider treatment with a LAMA (Weak, moderate).
- For patients at a low risk level who continue to experience symptoms despite using a long-acting bronchodilator, it is advisable to consider dual bronchodilation therapy (Strong, moderate).
- For high-risk patients who experience symptoms (with mMRC score greater than 2), it is recommended to opt for dual bronchodilation therapy rather than using a single bronchodilator. For patients who do not have eosinophilic exacerbations, it is suggested to initiate treatment with a combination of LABA and LAMA (Weak, low).
- An alternative approach for patients with a high frequency of exacerbations and blood eosinophilia levels nearing 300 cells/mm^3 is to consider treatment with LABA/ICS (Weak, low).
- In patients with exacerbations despite treatment with LABA/LAMA, triple therapy with LABA/LAMA/ICS is suggested. Using triple therapy involving LABA (Long-Acting Beta-Agonist), LAMA (Long-Acting Muscarinic Antagonist), and ICS (Inhaled Corticosteroid) provides a more significant reduction in the risk of exacerbations and a more substantial enhancement in symptom relief compared to dual bronchodilation with LABA and LAMA (Weak, moderate).
- Augmentation therapy is recommended for individuals with emphysema caused by Alpha-1 Antitrypsin Deficiency, with the objective of minimizing the decline in lung density as assessed by CT scans . Augmentation treatment, however, has not demonstrated efficacy in symptoms or reduction of exacerbations (Weak, moderate)

- In patients with the COPD exacerbator phenotype despite adequate treatment, it is suggested that a high-dose mucolytic be added (Weak, moderate).
- Roflumilast has been proposed as a secondary treatment option for preventing exacerbations in patients who exhibit the exacerbator phenotype, characterized by chronic bronchitis and significant airflow restriction (Weak, moderate).
- In patients with COPD with an exacerbator phenotype, with at least 3 exacerbations the previous year despite adequate treatment, long-term treatment with macrolides is suggested (Weak, moderate).
- Consider withdrawing ICS in patients with infrequent exacerbations (0∧1 moderate in the previous year) and < 300 eosinophils/mm3. Long-acting bronchodilator therapy should be maintained even after discontinuation (Weak, moderate).
- It is recommended not to withdraw ICS in eosinophilic exacerbator patients (Strong, moderate).

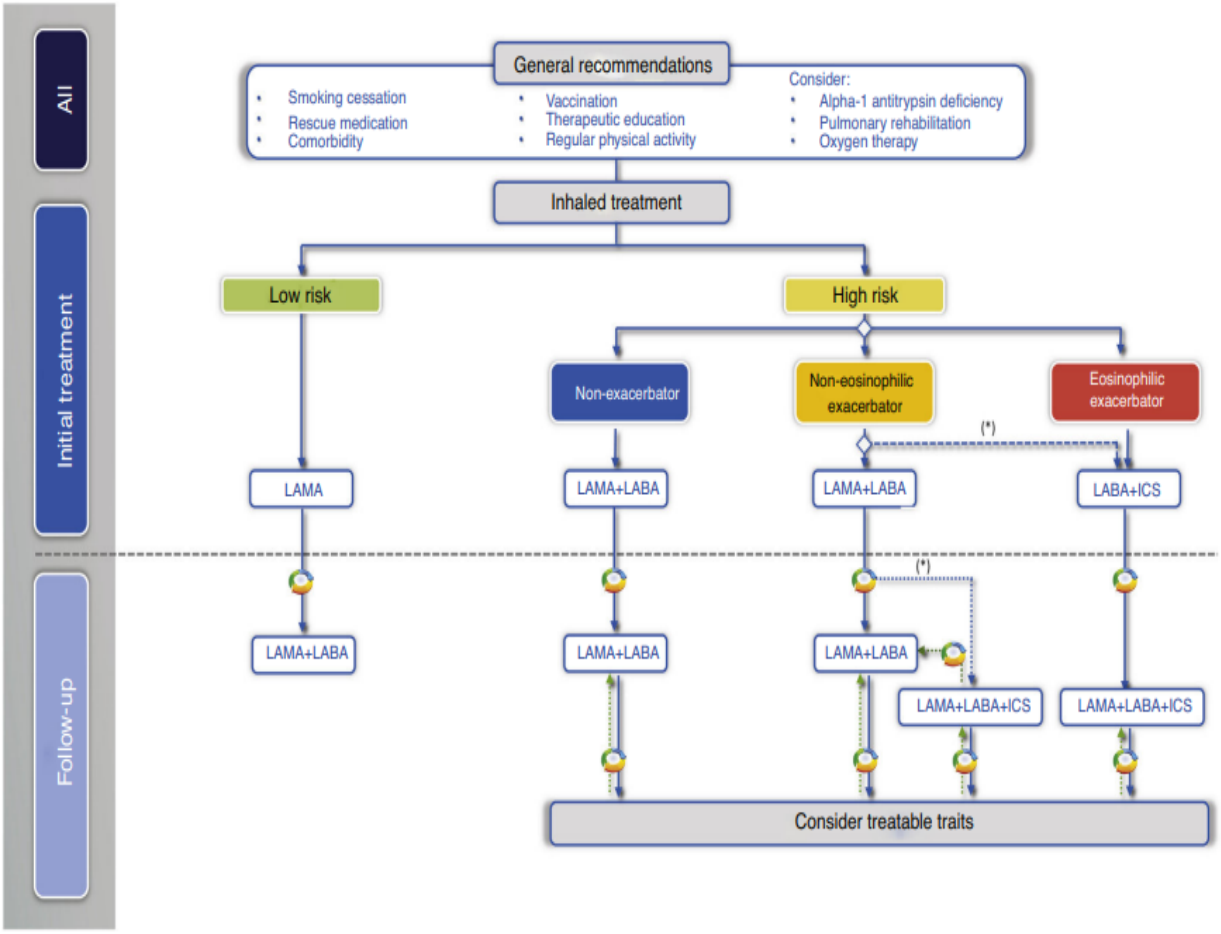

Figure 5. *Treatment of COPD Guided by Risk level and Phenotype. Retrieved from the GesEPOC 2021 Guideline.*

Section 2.0 Drug Therapy in Chronic Obstructive Pulmonary Disease

This section comprises three subsections: the first contains the newly recommended drugs, the second covers drug modifications, and the third outlines the drugs that have been withdrawn from the market.

2.1 Additions

There are two newly approved medications for the treatment of COPD by SFDA.

1. In July 2020, the combination of budesonide/glycopyrrolate/formoterol fumarate has been approved by the FDA for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).
2. Revefenacin received its first global approval on 9 November 2018 by the FDA for maintenance treatment of patients with COPD.

2.1.1 Budesonide/Glycopyrrolate/Formoterol Fumarate

This section includes pertinent information regarding the use of Budesonide/Glycopyrrolate/Formoterol fumarate in chronic obstructive disease as a maintenance treatment[9].

Table 21. Budesonide/Glycopyrrolate/Formoterol Fumarate Drug Information

SCIENTIFIC NAME Budesonide/Glycopyrrolate/Formoterol Fumarate	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	No
PMDA	Yes
Indication (ICD-10)	J44
Drug Class	Anticholinergic Agent; Long-Acting; $Beta_2$ Agonist; Corticosteroid, Inhalant (Oral)
Drug Sub-class	N/A
ATC Code	R03AL
Pharmacological Class (ASHP)	N/A

DRUG INFORMATION	
Dosage Form	Pressurised inhalation, suspension
Route of Administration	Inhalation use
Dose (Adult) [DDD]*	Chronic obstructive pulmonary disease: Oral inhalation: 2 inhalations twice daily; maximum dose: 2 inhalations twice daily.
Maximum Daily Dose Adults*	2 inhalations twice daily.
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal impairment:** CrCl > 45 mL/minute/1.73 m2: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). CrCl ≤ 45 mL/minute/1.73 m2: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); however, systemic glycopyrrolate exposure may be increased; use with caution. End-stage renal disease requiring dialysis: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); however, systemic glycopyrrolate exposure may be increased; use with caution. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); however, systemic budesonide and formoterol exposure may be increased in patients with severe impairment; use with caution and monitor closely.
Prescribing edits*	MD, ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	

G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a physician with experience in managing patients with advanced COPD.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): The choice of this combination therapy typically occurs in the later stages of COPD when symptoms are not adequately controlled with monotherapy with LABA or LAMA or when there is a significant component of airway inflammation that requires a corticosteroid.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Diarrhea, oral candidiasis, urinary tract infection, influenza, voice disorder, back pain, muscle spasm, cataract, cough, pneumonia, sinusitis, upper respiratory tract infection. **Most serious**: Bronchospasm, immunosuppression, hypersensitivity, adrenal suppression.
Drug Interactions	**Category X**: • Aclidinium • Aldesleukin • Anticholinergic Agents • Beta2-Agonists (Long-Acting) • Beta-Blockers (Nonselective) • Cimetropium • Desmopressin • Eluxadoline • Fexinidazole • Fusidic Acid (Systemic) • Glycopyrronium (Topical) • Ipratropium (Oral Inhalation) • Kratom • Levosulpiride • Loxapin • Oxatomide

	• Potassium Chloride • Potassium Citrate • Pramlintide • Revefenacin • Tiotropium • Umeclidinium
Special Population	N/A
Pregnancy	**Monograph:** There are no adequate and well-controlled studies with BREZTRI AEROSPHERE or with two of its individual components, glycopyrrolate or formoterol fumarate, in pregnant women to inform a drug associated risk; however, studies are available for the other component, budesonide. In animal reproduction studies, budesonide alone, administered by the subcutaneous route, caused structural abnormalities, was embryocidal, and reduced fetal weights in rats and rabbits at 0.3 and 0.75 times maximum recommended human daily inhaled dose (MRHDID), respectively, but these effects were not seen in rats that received inhaled doses up to 4 times the MRHDID. Studies of pregnant women who received inhaled budesonide alone during pregnancy have not shown increased risk of abnormalities. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans. Formoterol fumarate alone, administered by the oral route in rats and rabbits, caused structural abnormalities at 1500 and 61,000 times the MRHDID, respectively. Formoterol fumarate was also embryocidal, increased pup loss at birth and during

	lactation, and decreased pup weight in rats at 110 times the MRHDID. These adverse effects generally occurred at large multiples of the MRHDID when formoterol fumarate was administered by the oral route to achieve high systemic exposures. No structural abnormalities, embryocidal, or developmental effects were seen in rats that received inhalation doses up to 350 times the MRHDID. Glycopyrrolate alone, administered by the subcutaneous route in rats and rabbits, did not cause structural abnormalities or affect fetal survival at exposures approximately 2700 and 5400 times from MRHDID, respectively. Glycopyrrolate had no effects on the physical, functional, and behavioral development of rat pups with exposures up to 2700 times the MRHDID. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively[10].
Lactation	Budesonide is present in breast milk following oral inhalation; excretion of formoterol and glycopyrrolate are not known. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.

Contraindications	Hypersensitivity to budesonide, glycopyrrolate, formoterol, or any component of the formulation.
Monitoring Requirements	Monitor FEV1, peak flow, and/or other pulmonary function tests; bone mineral density; hypothalamic-pituitary-adrenal axis suppression; BP, heart rate; serum potassium; serum glucose; ocular changes; signs/symptoms of oral or systemic infection.
Precautions	**Concerns related to adverse effects:** • Adrenal suppression: May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Adult patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections. Do not use this

	product to transfer patients from oral corticosteroid therapy. • Asthma-related deaths: The use of long-acting beta-2 agonists (LABAs) as monotherapy has been associated with an increased risk of severe exacerbations and asthma-related deaths (SMART [Nelson 2006]; Walters 2007); additional data from other clinical trials suggest risk of asthma-related hospitalization may also be increased with LABA monotherapy in pediatric and adolescent patients. However, data from large, randomized, double-blind controlled trials do not show a significant increase in risk of serious asthma-related events (including hospitalizations, intubations, and death) in adults, adolescents, and pediatric patients (4 to 11 years of age) when fixed-dose LABAs are used with inhaled corticosteroids combined in a single inhaler compared with inhaled corticosteroid monotherapy • Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents and may be life-threatening; this should be distinguished from inadequate response. If paradoxical bronchospasm occurs, discontinue and institute alternative therapy. • Hypersensitivity: Immediate hypersensitivity reactions (eg,

	urticaria, angioedema, rash) have been reported; discontinue if a hypersensitivity reaction occurs and institute alternative therapy. • Immunosuppression: Prolonged use of corticosteroids may increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Avoid use, if possible, in patients with ocular herpes; tuberculosis (TB) infection (latent TB) or disease (active TB) of the respiratory tract; or untreated viral, fungal, or bacterial or parasitic systemic infections. Exposure to chickenpox or measles should be avoided; if the patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin or pooled IV immunoglobulin may be indicated; if chickenpox develops, treatment with antiviral agents may be considered. If exposure to measles occurs, prophylaxis with pooled IM immunoglobulin may be indicated. • Lower respiratory infections: Pneumonia and other lower respiratory tract infections have been reported in patients with COPD following the use of inhaled corticosteroids; monitor COPD patients closely since pneumonia symptoms may overlap symptoms of exacerbations.

	• Oral candidiasis: Local oropharyngeal *Candida* infection s may occur; treat appropriately while either continuing or interrupting (if necessary) therapy. • Serious effects/fatalities: Do not exceed recommended dose; serious adverse events, including fatalities, have been associated with excessive use of inhaled sympathomimetics. **Disease-related concerns:** • Bone mineral density: Use with caution in patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (eg, antiseizure medications, oral corticosteroids); long-term use of inhaled corticosteroids have been associated with decreases in bone mineral density. • Cardiovascular disease: Use with caution in patients with cardiovascular disease, especially coronary insufficiency, arrhythmias, and hypertension; beta-agonists may cause elevation in BP, heart rate, and increase risk of arrhythmias (eg, supraventricular tachycardia, extrasystoles); may also cause ECG changes (eg, flattening of the T wave, QTc prolongation, ST segment depression).

	• Diabetes: Use with caution in patients with diabetes mellitus; beta-2 agonists may increase serum glucose and aggravate preexisting diabetes mellitus and ketoacidosis. • Hepatic impairment: Budesonide and formoterol exposure may be increased in patients with severe hepatic impairment; use with caution in patients with severe impairment and monitor closely. • Hypokalemia: Use with caution in patients with hypokalemia; beta-2 agonists may decrease serum potassium (effect is usually transient). • Ocular disease: Use with caution in patients with increased intraocular pressure, cataracts, and/or glaucoma; increased intraocular pressure, glaucoma, and cataracts have occurred with prolonged use of inhaled corticosteroids. Consider routine eye exams in chronic users. • Prostatic hyperplasia/bladder neck obstruction: Glycopyrrolate may worsen the symptoms of prostatic hyperplasia and/or bladder neck obstruction (eg, painful urination, difficulty passing urine); use with caution. • Renal impairment: Use with caution in patients with severe renal impairment, including end-stage renal disease requiring dialysis; systemic exposure to glycopyrrolate may be increased.

	• Seizure disorders: Use with caution in patients with seizure disorders. • Thyrotoxicosis: Use with caution in patients with thyrotoxicosis. **Other warnings/precautions:** • Appropriate use: Do not use for acute episodes of COPD. Do not initiate in patients with significantly worsening, potentially life-threatening, or acutely deteriorating COPD. Do not exceed the recommended dose. After initiation of therapy, patients should use short-acting bronchodilators only on an as needed basis for acute symptoms. • Discontinuation of systemic corticosteroids: Withdraw systemic corticosteroid therapy with gradual tapering of dose (eg, patients on prednisone may decrease dose by 2.5 mg weekly during inhaled corticosteroid therapy). Monitor lung function, beta-agonist use, and COPD symptoms, and for signs and symptoms of adrenal insufficiency (eg, fatigue, lassitude, weakness, nausea and vomiting, hypotension) during withdrawal. • Transfer to oral inhaler: When transferring to oral inhaler, previously suppressed allergic conditions (eg, arthritis, rhinitis, conjunctivitis, eczema, eosinophilic conditions) may be unmasked.
Black Box Warning	N/A

REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of COPD treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Budesonide/Glycopyrrolate/Formoterol fumarate.**

Table 22. Budesonide/Glycopyrrolate/Formoterol Fumarate HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Budesonide/ Glycopyrrolate/ Formoterol Fumarate	NICE	Not available
	CADTH[11]	09/2021: CADTH recommends that Breztri Aerosphere **be reimbursed** by public drug plans for the treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema if certain conditions are met. Breztri Aerosphere should only be covered to treat patients who are not controlled on optimal dual inhaled therapy for COPD. Breztri Aerosphere should be reimbursed similar to Trelegy Ellipta. The price of Breztri Aerosphere should not exceed the drug program cost with the least-costly fixed-dose inhaled corticosteroid/long-acting muscarinic antagonist/long-acting beta2-agonist (ICS/LAMA/LABA) triple therapy combination for the same indication.
	HAS[12]	03/2021: Trixeo aerosphere (different brand name): **Favorable opinion** for reimbursement as maintenance treatment in adult patients with severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or combination of a

		long-acting beta2-agonist and a long-acting muscarinic antagonist. **Unfavorable opinion** for reimbursement as maintenance treatment in moderate COPD.
	IQWIG	Not available
	PBAC	Patient must have experienced at least one severe COPD exacerbation, which required hospitalization, or two or more moderate exacerbations in the previous 12 months, with significant symptoms despite regular bronchodilator therapy with a long-acting muscarinic antagonist (LAMA) and a long-acting beta-2 agonist (LABA) or an inhaled corticosteroid (ICS) and a LABA; OR Patient must have been stabilized on a combination of a LAMA, LABA and an ICS for this condition.

Conclusion Statement – Budesonide/Glycopyrrolate/Formoterol fumarate

Budesonide/Glycopyrrolate/Formoterol fumarate is recommended as an option for the maintenance treatment of chronic obstructive pulmonary disease (COPD). CADTH and PBAC recommend the reimbursement of this medication under specific circumstances. HAS had a favorable opinion for the use of Budesonide/Glycopyrrolate/Formoterol fumarate in the treatment of patients with severe chronic obstructive pulmonary disease (COPD) who do not experience sufficient relief from a combination of an inhaled corticosteroid and a long-acting beta2-agonist, or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist, however it had an unfavorable opinion for reimbursement when it comes to treating moderate COPD. However, no information could be retrieved from IQWIG and NICE regarding this medication.

2.1.2 Revefenacin

This section includes pertinent information regarding the use of Revefenacin in chronic obstructive disease as a maintenance treatment[9].

Table 23. Revefenacin Drug Information

SCIENTIFIC NAME **Revefenacin**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	J44
Drug Class	Anticholinergic Agent, Long-Acting
Drug Sub-class	N/A
ATC Code	N/A
Pharmacological Class (ASHP)	12:08.08 Antimuscarinics/Antispasmodics
DRUG INFORMATION	
Dosage Form	Inhalation solution
Route of Administration	Inhalation use
Dose (Adult) [DDD]*	**Chronic obstructive pulmonary disease, maintenance:** **Note:** Depending on symptoms and exacerbation risk, use monotherapy long-acting bronchodilator (long-acting beta agonist or long-acting muscarinic antagonist). In patients with more symptoms (eg, group B), use in combination with long-acting beta agonist. In addition, a short-acting bronchodilator is used for intermittent symptom relief. Nebulization solution: **Oral inhalation:** 175 mcg once daily.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A

Adjustment	**<u>Renal Impairment:</u>** No dosage adjustment necessary. **<u>Hepatic Impairment:</u>** Mild, moderate, or severe impairment: Use is not recommended.
Prescribing edits*	CU, MD, ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Should be used in combination with long-acting beta agonist.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a physician with experience in managing patients with advanced COPD.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): It is typically considered as a second-line or alternative therapy for COPD when patients do not respond well to or cannot tolerate other medications such as inhaled corticosteroids (ICS) or combination therapies like ICS/LABA (inhaled corticosteroid/long-acting beta2-agonist).	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**<u>Most common:</u>** Hypertension, dizziness, headache, back pain, bronchitis, nasopharyngitis, oropharyngeal pain, upper respiratory tract infection. **<u>Most serious:</u>** Bronchospasm, hypersensitivity.
Drug Interactions	**<u>Category X</u>**: • Aclidinium • Anticholinergic Agents • Cimetropium • Eluxadoline • Glycopyrrolate (Oral Inhalation) • Glycopyrronium (Topical) • Ipratropium (Oral Inhalation) • Leniolisib • Levosulpiride

	• OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors • Oxatomide • Potassium Chloride • Potassium Citrate • Pramlintide • Tiotropium • Umeclidinium
Special Population	**N/A**
Pregnancy	Adverse events were not observed in animal reproduction studies.
Lactation	It is not known if revefenacin is present in breast milk following oral inhalation. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity to revefenacin or any component of the formulation.
Monitoring Requirements	Monitor FEV1, peak flow (or other pulmonary function tests). Monitor for signs/symptoms of acute narrow angle glaucoma, hypersensitivity reactions, and urinary retention. Monitor for systemic antimuscarinic adverse effects in patients with severe renal impairment.
Precautions	**Concerns related to adverse effects:** • Bronchospasm: Paradoxical bronchospasm that may be life-threatening and may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response. If paradoxical bronchospasm occurs, manage with a short-acting bronchodilator, discontinue

	revefenacin, and institute alternative therapy. • CNS effects: Anticholinergic agents may cause dizziness and blurred vision; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). • Hypersensitivity: Immediate hypersensitivity reactions may occur. Discontinue therapy immediately if an allergic reaction occurs. **Disease-related concerns:** • Glaucoma: Use with caution in patients with narrow-angle glaucoma; may increase intraocular pressure. • Hepatic impairment: Use is not recommended in patients with hepatic impairment. • Prostatic hyperplasia/bladder neck obstruction: Use with caution in patients with prostatic hyperplasia or bladder neck obstruction; may cause and/or worsen urinary retention. • Renal impairment: Monitor for systemic antimuscarinic adverse effects in patients with severe renal impairment. **Other warnings/precautions:** Appropriate use: Revefenacin is intended as a once daily maintenance treatment and is not indicated for the initial (rescue) treatment of acute episodes of bronchospasm or with acutely deteriorating or potentially life-threatening COPD; after initiation of therapy, patients should use short-

	acting bronchodilators only on an as needed basis for acute symptoms. COPD may deteriorate acutely (over hours) or chronically (over days or longer); if revefenacin no longer controls bronchoconstriction symptoms, short-acting beta2-agonists becomes less effective, or the more inhalations of a short-acting beta2-agonist than usual are required, these may be indicators of COPD deterioration; re-evaluate the COPD treatment regimen. Increasing the daily revefenacin dose beyond the recommended dose is not appropriate in this situation.
Black Box Warning	N/A
REMS	N/A

Clinical trials – Revefenacin

Two double-blind, parallel-group studies, Phase III studies (Study 0126 and Study 0127), were conducted to evaluate the efficacy and safety of revefenacin in patients with moderate to very severe COPD.

In this study, individuals aged 40 years or older were randomly assigned to receive either revefenacin at a dose of 88 μg, revefenacin at a dose of 175 μg, or a placebo. The administration was done once daily using a standard jet nebulizer over a period of 12 weeks. The primary outcome measure was the 24-hour trough forced expiratory volume in 1 second (FEV1) on day 85. Secondary effectiveness measures included the overall treatment effect (OTE) on trough FEV1 and peak FEV1 (measured 0-2 hours after the first dose). Safety assessments were conducted to monitor any treatment-related adverse events.

Results of the study revealed that on day 85, both revefenacin at 88 µg and 175 µg doses demonstrated significant improvements in trough FEV1 compared to the placebo in Study 0126 (with increases of 79 mL [p=0.0003] and 146 mL [p<0.0001]) and Study 0127 (with increases of 160 mL and 147 mL; both p<0.0001). When data from both dosages of revefenacin were combined, there was a notable increase in OTE trough FEV1 by 115 mL and 142 mL (both p<0.001) and an increase in peak FEV1 by 127 mL and 129 mL (both p<0.0001) compared to the placebo. Notably, the 175 µg dose of revefenacin showed greater improvements in FEV1 among patients already using long-acting beta2-agonists and in patients with more severe COPD compared

to the 88 µg dose. Adverse events were generally minor and not a major cause for concern.

In conclusion, when administered once daily for 12 weeks to individuals with moderate to very severe COPD, revefenacin demonstrated clinically significant enhancements in both trough FEV1 and OTE FEV1. Furthermore, it was well-tolerated with no significant safety issues observed[13].

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of Revefenacin for the treatment of COPD**. Despite this, Revefenacin has been available on the American market since 2018. It is available now in the Saudi market since 2022.

CONCLUSION STATEMENT – REVEFENACIN

Revefenacin is recommended for COPD as maintenance treatment in specific situations, typically when other treatment options have been considered or tried. It is important to note that there is currently no available data or recommendations from HTA bodies specifically addressing the use of Revefenacin in COPD management, however, Revefenacin is recommended to be added to CHI formulary.

2.2 Modifications

No modifications have been made since January 2020.

2.3 Delisting

The medications below are no longer SFDA registered[14], therefore, it is advisable to delist the following drugs from CHI formulary.

- Umeclidinium
- Ipratropium bromide/Salbutamol

Section 3.0 Key Recommendations Synthesis

- Smoking is the predominant factor that plays a substantial role in the onset of COPD (II, Strong)[4].
- It is crucial to establish the diagnosis of COPD through the conduction of forced spirometry and confirming the presence of a post-bronchodilator FEV1/FVC ratio below 0.7[1].
- The most vital step in averting the progression of COPD is to cease smoking (II, Strong)[4].
- Receiving vaccinations reduces the risk of facing complications associated with influenza and pneumococcal infections (I, Strong)[4].
- Combinations of SABA (Short-Acting Beta-Agonist) and SAMA (Short-Acting Muscarinic Antagonist) prove more effective than either medication alone in enhancing FEV1 and alleviating symptoms (Evidence A)[1].
- Combining a LABA (Long-Acting Beta-Agonist) with a LAMA (Long-Acting Muscarinic Antagonist) increases FEV1 and reduces symptoms compared to monotherapy (Evidence A)[1].
- Combination treatment with a LABA and a LAMA reduces exacerbations compared to monotherapy (Evidence B)[1].
- When treating group A patients, characterized by their need for bronchodilator treatment to relieve breathlessness, this can involve either short-acting or long-acting bronchodilators[1].
- Group B patients should initiate treatment with a combination of a LABA and a LAMA[1].
- In Group B, if the LABA+LAMA combination is not deemed suitable, there is no clear preference for one class of long-acting bronchodilator (LABA or LAMA) over the other as initial symptom relief in this patient category. The choice should be based on the patient's perception of symptom relief[1].
- For patients in Group E, a Cochrane systematic review and network meta-analysis revealed that the LABA+LAMA combination was the most effective at reducing COPD exacerbations. Thus, if factors like availability, cost, or side effects are not of concern, LABA+LAMA is the preferred initial therapy[1].
- In Group E, the use of LABA+ICS (Inhaled Corticosteroid) for COPD is discouraged, but if there is a specific indication for an ICS, then LABA+LAMA+ICS has shown greater effectiveness than LABA+ICS and should be the preferred choice[1].

- Consider employing LABA+LAMA+ICS in Group E when the eosinophil count is 300 cells/μL or higher, following practical recommendations. While there is no direct data on initiating triple therapy in newly diagnosed patients, it is reasonable to reserve this treatment for patients with a high eosinophil count (≥ 300 cells/μL)[1].
- Dual therapy with LAMA/LABA is favored over using a combination of ICS/LABA because it results in substantial enhancements in lung function and reduced pneumonia rates. Nonetheless, if someone has COPD alongside asthma, it's better to opt for ICS/LABA combination therapy rather than LAMA/LABA dual therapy (Low certainty of greater improvements in dyspnea, exercise intolerance, and health status with LAMA/LABA compared to ICS/LABA combination therapy)[6].
- For patients experiencing exacerbations despite treatment with LABA/LAMA, it is suggested to consider triple therapy involving LABA (Long-Acting Beta-Agonist), LAMA (Long-Acting Muscarinic Antagonist), and ICS (Inhaled Corticosteroid). This triple therapy approach offers a more substantial reduction in the risk of exacerbations and greater relief from symptoms when compared to dual bronchodilation with LABA and LAMA (Weak, moderate)[5].
- When dealing with an exacerbation, it is advisable to start with short-acting inhaled beta2-agonists, either on their own or in combination with short-acting anticholinergics as the initial bronchodilators (Evidence C)[1].
- In cases of severe exacerbations, systemic corticosteroids can enhance lung function (FEV1), oxygen levels, and reduce recovery time, including the length of hospital stay. The typical course of corticosteroid treatment should not exceed 5 days (Evidence C)[1].
- Antibiotics may become necessary when clinically indicated, as they can expedite recovery, lower the risk of early relapse, avert treatment failure, and shorten the duration of hospitalization. The standard duration for antibiotic therapy is typically 5 days (Evidence B)[1].
- For individuals with emphysema due to Alpha-1 Antitrypsin Deficiency, it is recommended to consider augmentation therapy, aiming to slow the decline in lung density as assessed through CT scans. However, it's worth noting that augmentation treatment hasn't shown effectiveness in alleviating symptoms or reducing the frequency of exacerbations (Weak, moderate)[5].
- If patients continue to experience COPD exacerbations despite receiving adequate treatment, it is advisable to consider adding a high-dose mucolytic (Weak, moderate)[5].

- Roflumilast has been proposed as a secondary treatment option for preventing exacerbations in patients with the exacerbator phenotype, which is characterized by chronic bronchitis and significant airflow restriction (Weak, moderate)[5].
- For patients with COPD who exhibit the exacerbator phenotype and have had at least three exacerbations in the previous year despite receiving adequate treatment, it is suggested to consider long-term macrolide treatment (Weak, moderate)[5].
- Rehabilitation is recommended for all patients with applicable symptoms and/or a high risk of experiencing exacerbations (Evidence A)[1].
- Prolonged oxygen therapy offers survival benefits to COPD patients who have hypoxemia (I, Strong)[4].
- The consideration of nutritional supplementation is warranted for individuals with COPD who are malnourished (Evidence B)[1].
- Lung volume reduction surgery should be contemplated for specific patients with emphysema primarily in the upper lobes of the lungs (Evidence A)[1].
- In specific cases involving patients with a large bulla, surgical bullectomy may be considered (Evidence C)[1].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Chronic Obstructive Pulmonary Disease report** and aims to provide recommendations to aid in the management of Chronic Obstructive Pulmonary Disease report. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Chronic Obstructive Pulmonary Disease report. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Chronic Obstructive Pulmonary Disease

2020	Changes	2023	Rationale
Section 1.0 Chronic Obstructive Pulmonary Disease Clinical Guidelines			
Chronic obstructive pulmonary disease in over 16s: diagnosis and management NICE guideline Published: 5 December 2018	N/A		
GOLD Guidelines 2019	Updated	GOLD Guidelines 2023[1]	• The primary environmental factors responsible for causing COPD include tobacco smoking and the inhalation of harmful particles and gases from indoor and outdoor air pollution. However, other environmental elements and host-related factors, such as abnormal lung development and accelerated lung aging, can also contribute to the development of COPD. • In any patient presenting with symptoms like breathlessness, persistent cough, sputum production, or a history of exposure to COPD risk factors, it is important to contemplate the possibility of a COPD diagnosis. However, it is essential to confirm the diagnosis of COPD by performing forced spirometry and verifying the presence of a post-bronchodilator FEV1/FVC ratio less than 0.7.

			• The mMRC scale was the first questionnaire developed to measure breathlessness, which is a key symptom in many patients with COPD, although often unrecognized. • . Shorter comprehensive measures, such as the COPD Assessment Test (CAT™) and The COPD Control Questionnaire (CCQ©) have been developed and are suitable for use in the clinic. • Now, in this 2023 document, GOLD proposes a further evolution of the ABCD combined assessment tool that recognizes the clinical relevance of exacerbations, independently of the level of symptoms of the patient. Figure 5 presents this new proposal. The A and B groups are unchanged, but the C and D groups are now merged into a single group termed “E” to highlight the clinical relevance of exacerbations. We acknowledge that this proposal will have to be validated by appropriate clinical research. • Patients with COPD typically complain of dyspnea, wheezing, chest tightness, fatigue, activity limitation, and/or cough with or without sputum production, and may experience acute events characterized by increased respiratory symptoms called exacerbations that influence their health status and prognosis, and require specific preventive and therapeutic measures. • Quitting smoking is essential, and methods like nicotine replacement and medication have been

			proven to enhance long-term smoking cessation rates reliably. • Influenza vaccination decreases the incidence of lower respiratory tract infections. • Pneumococcal vaccination decreases the incidence of lower respiratory tract infections. • CDC recommends the Tdap vaccination (dTaP/dTPa; pertussis, tetanus and diptheria) for COPD patients who were not vaccinated in adolescence, as well as routine use of shingles vaccine in all COPD patients. • Pharmacological therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and health status. • Commonly used medications in COPD are: • Beta agonists: short acting (SABA) and long acting (LABA) • Anticholinergic drugs: long acting (LABA) and short acting (SABA) • Combination of short acting beta agonist + anticholinergic in one device SABA+SAMA • Combination of long-acting beta agonist + anticholinergic in one device LABA+LAMA • Methylxanthines • Combination of long-acting beta agonist + corticosteroids in one device LABA+ICS • Triple combination in one device • Phosphodiesterase -4 inhibitor

			• Mucolytics • Non-pharmacologic therapies include: • Smoking cessation: • Pulmonary rehabilitation (PR) • Long term oxygen therapy (LTOT) • Non-invasive positive pressure ventilation (NPPV) • Lung transplantation and lung volume reduction surgery (LVRS) • Pharmacologic and Non-Pharmacologic management of Stable COPD are detailed in the report. • Management of acute exacerbations is detailed in the report. • COPD frequently occurs alongside other medical conditions, known as comorbidities, which can profoundly influence the course of the disease. • COPD frequently occurs alongside other medical conditions, known as comorbidities, which can profoundly influence the course of the disease.
The Saudi Guidelines for the Diagnosis and Management of COPD 2014	N/A		
	Missing	The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic	**Case finding and confirm diagnosis** • The primary factor contributing significantly to the development of COPD is smoking (I, Strong). • Smoking cessation reduces mortality (I, Strong).

		Obstructive Pulmonary Disease 2023[4]	• The initial stage in diagnosing COPD involves conducting a comprehensive assessment and examination of the patient's medical history (III-2, Strong). • The diagnosis of COPD is established when there is a persistent restriction of airflow (with a post-bronchodilator FEV1/FVC ratio less than 0.7) (III-2, Strong). **Optimize Function** • All individuals with COPD should be offered non-pharmacological approaches, including pulmonary rehabilitation and consistent physical activity (I, Strong). • Pulmonary rehabilitation improves quality of life and exercise capacity and reduces COPD exacerbations (I, Strong). • Both surgical and endobronchial lung volume reduction procedures result in enhancements in lung function, exercise capacity, and quality of life (I, Weak). • In individuals with moderate to severe COPD who experience frequent exacerbations, extended use of macrolide antibiotics has the potential to decrease the occurrence of exacerbations (I, Weak). • In individuals with stable COPD who have hypercapnia, the consideration of prolonged non-invasive ventilation is advisable to lower mortality rates (I, Weak). **Prevent deterioration**

			• The most crucial action to prevent the deterioration of COPD is quitting smoking (II, Strong). • The prevention of exacerbations plays a crucial role in averting deterioration (III-2, Strong). • Vaccination lowers the likelihood of experiencing complications related to influenza and pneumococcal infections (I, Strong). • Although data does not endorse the use of inhaled corticosteroids for all individuals with COPD, it does recommend their utilization for those with more advanced disease (FEV1 <50% predicted) who have a history of frequent exacerbations. • Mucolytics can be advantageous for specific COPD patients (I, Strong). • Prolonged oxygen therapy provides survival advantages to COPD patients experiencing hypoxemia (I, Strong). **Develop a care plan** • Patients may find self-management support beneficial (I, Strong). • The implementation of COPD exacerbation action plans can lead to a reduction in emergency department visits and hospital admissions (I, Strong). **Management of exacerbations** • Inhaled bronchodilators are effective as initial treatment for exacerbations (I, Strong). • Systemic corticosteroids reduce the severity of exacerbations and expedite recovery (I, Strong).

			• Exacerbations with signs of infection (such as increased sputum volume, change in color, and/or fever) benefit from antibiotic therapy (I, Strong). • Controlled oxygen delivery (0.5-2.0 L/min) is recommended for patients with hypoxemia during exacerbations (II, Strong). • When using supplemental oxygen for hypoxia during COPD exacerbations, targeting SpO2 levels between 88% and 92% improves survival (II, Strong). • Non-invasive ventilation (NIV) is effective for patients with rising PaCO2 levels (I, Strong). • Non-invasive ventilation enhances survival for individuals with COPD and acute hypercapnic respiratory failure (I, Strong). • Consider the option of pulmonary rehabilitation at any time, including during the recovery phase following an exacerbation (I, Strong). • Patients with COPD who are discharged from the hospital after an exacerbation should receive comprehensive follow-up care led by the primary healthcare team (I, Strong)
	Missing	2023 Canadian Thoracic Society Guideline on Pharmacotherapy in Patients With Stable COPD[6]	• For people with stable COPD who have a low likelihood of experiencing exacerbations, minimal symptoms and health-related quality of life issues (CAT score less than 10, mMRC score of 1), and only mild impairment in lung function (FEV1 equal to or greater than 80% of predicted), it is advisable to initiate monotherapy with either a LAMA or a LABA as the first treatment choice (Strong, Moderate to

			high certainty of greater improvements in dyspnea, exercise tolerance, and health status with LAMA or LABA compared to placebo). • For individuals with stable COPD who have a low likelihood of experiencing exacerbations, but a moderate to high symptom burden or impaired health-related quality of life (CAT score of 10 or higher, mMRC score of 2 or higher), and reduced lung function (FEV1 less than 80% of predicted), it is recommended to begin dual therapy with a combination of LAMA and LABA as the initial maintenance treatment (Strong, Moderate to high certainty of greater improvements in dyspnea, exercise intolerance, and health status with LAMA/LABA compared to LAMA monotherapy, Moderate certainty of greater improvements in dyspnea, exercise intolerance, and health status with LAMA/LABA compared to LABA monotherapy) • In individuals with stable COPD, at low risk of exacerbations, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV1 < 80% predicted) despite LAMA/LABA dual therapy or ICS/LABA combination therapy, we recommend step-up to a LAMA/LABA/ICS triple combination therapy (Strong, Moderate certainty of greater improvements in dyspnea and health status with LAMA/LABA/ICS compared to LAMA/LABA dual therapy or ICS/ LABA combination therapy.).

			• In all individuals with stable COPD and at a low risk of exacerbations, we recommend against treatment with ICS monotherapy (Strong, Low certainty of no improvements in dyspnea, exercise tolerance, physical activity levels, and/ or health status with ICS monotherapy compared to placebo). • In individuals with stable COPD, at low risk of exacerbations, a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV1 < 80% predicted), we recommend starting LAMA/LABA dual therapy as initial maintenance therapy (Strong, Moderate certainty of greater reduction in rate of exacerbation with LAMA/LABA dual therapy compared to LAMA monotherapy). • In individuals with stable COPD, at a high risk of exacerbations, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV1 < 80% predicted), we recommend the use of LAMA/LABA/ICS triple combination therapy over LABA/LAMA dual therapy (Strong, Moderate certainty for greater reduction in mortality with LAMA/LABA/ICS triple combination compared to LABA/LAMA dual therapy).
	Missing	Summary for Clinicians: Clinical Practice Guideline on Pharmacologic	• The panel suggests opting for a combination therapy of long-acting β2-agonist (LABA) and long-acting muscarinic antagonist (LAMA) rather than choosing LABA or LAMA monotherapy on Patients with COPD

		Management of Chronic Obstructive Pulmonary Disease (2021)[5]	Who Complain of Dyspnea or Exercise Intolerance (strong recommendation, moderate certainty evidence). • The panel recommends the adoption of triple inhaler therapy, involving an inhaled corticosteroid (ICS), a long-acting β2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), instead of dual therapy (LABA/LAMA) for patients with COPD who have experienced one or more exacerbations in the previous year necessitating antibiotics, oral steroids, or hospitalization (conditional recommendation, moderate certainty evidence). • The panel recommends considering discontinuation of inhaled corticosteroids (ICS) in patients with COPD who are receiving triple therapy (ICS/LABA/LAMA) if the patient has not experienced any exacerbations in the previous year (conditional recommendation, moderate certainty evidence). • The panel did not provide a specific recommendation either in favor of or against the use of inhaled corticosteroids (ICS) as an additional treatment alongside long-acting bronchodilators for patients with COPD and blood eosinophilia, defined as having more than 2% blood eosinophils or exceeding 150 cells/ml. However, an exception was made for patients with a history of one or more exacerbations in the past year that necessitated antibiotics, oral steroids, or hospitalization, for whom the panel suggested considering the addition of ICS

			as part of their treatment (conditional recommendation, moderate certainty evidence). • For individuals with COPD who have a history of severe and frequent exacerbations despite receiving otherwise optimal treatment, the panel advised against the utilization of long-term oral corticosteroid therapy (conditional recommendation, low certainty evidence). • For individuals with COPD who encounter severe, unmanageable breathlessness despite receiving otherwise effective treatment, the panel recommended the potential consideration of opioid-based therapy as a means of managing dyspnea. This decision should be made through a personalized approach involving shared decision-making (conditional recommendation, very low certainty evidence).
	Missing	Management of COPD in Asia: A position statement of the Asian Pacific Society of Respirology* 2019[8]	• Doctors should offer guidance and provide nicotine replacement therapy and pharmaceutical products. • Monitoring air pollution levels is essential, and it is important to keep COPD patients informed. COPD patients should refrain from outdoor activities during periods of elevated air pollution. • It's crucial to closely monitor potential drug side effects in patients with a low BMI. For patients with a low body mass index (BMI), considering a reduced dosage of roflumilast and inhaled corticosteroids (ICS) might be appropriate.

			• ICS needs to be prescribed with caution in COPD combined with bronchiectasis.
	Missing	Spanish COPD guidelines (GesEPOC) 2021: Updated pharmacological treatment of stable COPD[5]	• For individuals with COPD who need a long-acting bronchodilator as their sole treatment, it is recommended to consider treatment with a LAMA (Weak, moderate). • For patients at a low risk level who continue to experience symptoms despite using a long-acting bronchodilator, it is advisable to consider dual bronchodilation therapy (Strong, moderate). • For high-risk patients who experience symptoms (with mMRC score greater than 2), it is recommended to opt for dual bronchodilation therapy rather than using a single bronchodilator. For patients who do not have eosinophilic exacerbations, it is suggested to initiate treatment with a combination of LABA and LAMA (Weak, low). • An alternative approach for patients with a high frequency of exacerbations and blood eosinophilia levels nearing 300 cells/mm^3 is to consider treatment with LABA/ICS (Weak, low). • In patients with exacerbations despite treatment with LABA/LAMA, triple therapy with LABA/LAMA/ICS is suggested. Using triple therapy involving LABA (Long-Acting Beta-Agonist), LAMA (Long-Acting Muscarinic Antagonist), and ICS (Inhaled Corticosteroid) provides a more significant reduction in the risk of exacerbations and a more substantial enhancement in symptom relief compared to dual

			bronchodilation with LABA and LAMA (Weak, moderate) • Augmentation therapy is recommended for individuals with emphysema caused by Alpha-1 Antitrypsin Deficiency, with the objective of minimizing the decline in lung density as assessed by CT scans. Augmentation treatment, however, has not demonstrated efficacy in symptoms or reduction of exacerbations (Weak, moderate) • In patients with the COPD exacerbator phenotype despite adequate treatment, it is suggested that a high-dose mucolytic be added (Weak, moderate). • Roflumilast has been proposed as a secondary treatment option for preventing exacerbations in patients who exhibit the exacerbator phenotype, characterized by chronic bronchitis and significant airflow restriction (Weak, moderate). • In patients with COPD with an exacerbator phenotype, with at least 3 exacerbations the previous year despite adequate treatment, long-term treatment with macrolides is suggested (Weak, moderate). • Consider withdrawing ICS in patients with infrequent exacerbations (0ʌ1 moderate in the previous year) and < 300 eosinophils/mm3. Long-acting bronchodilator therapy should be maintained even after discontinuation (Weak, moderate). • It is recommended not to withdraw ICS in eosinophilic exacerbator patients (Strong, moderate).

Appendix C. MeSH Terms PubMed

C.1 Pubmed Search for Chronic Obstructive Pulmonary Disease

The following is the result of the PubMed search conducted for chronic obstructive pulmonary disease guideline search:

Query	Filters	Search Details	Results
((((((((((Pulmonary Disease, Chronic Obstructive[MeSH Terms]) OR (Chronic Obstructive Lung Disease[Title/Abstract])) OR (Chronic Obstructive Pulmonary Diseases[Title/Abstract])) OR (COAD[Title/Abstract])) OR (COPD[Title/Abstract])) OR (Chronic Obstructive Airway Disease[Title/Abstract])) OR (Chronic Obstructive Pulmonary Disease[Title/Abstract])) OR (Airflow Obstruction, Chronic[Title/Abstract])) OR (Airflow Obstructions, Chronic[Title/Abstract])) OR (Chronic Airflow Obstructions[Title/Abstract])) OR (Chronic Airflow Obstruction[Title/Abstract])	Guideline, in the last 5 years	("pulmonary disease, chronic obstructive"[MeSH Terms] OR "chronic obstructive lung disease"[Title/Abstract] OR "chronic obstructive pulmonary diseases"[Title/Abstract] OR "COAD"[Title/Abstract] OR "COPD"[Title/Abstract] OR "chronic obstructive airway disease"[Title/Abstract] OR "chronic obstructive pulmonary disease"[Title/Abstract] OR "airflow obstruction chronic"[Title/Abstract] OR "airflow obstructions chronic"[Title/Abstract] OR "chronic airflow obstructions"[Title/Abstract] OR "chronic airflow obstruction"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	33

Appendix D. Treatment Algorithm

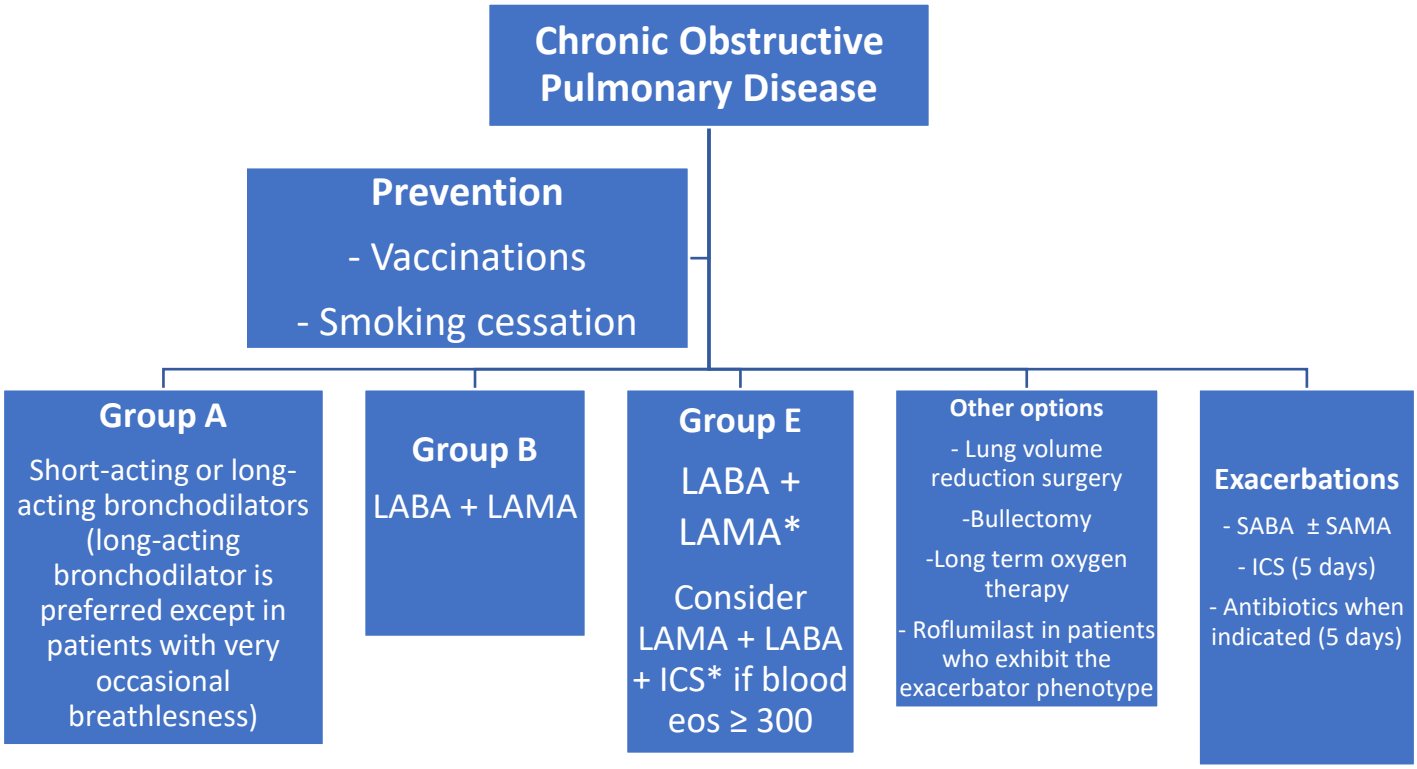

Figure 6. *Treatment Algorithm for Chronic Obstructive Pulmonary Disease*[1,4–8]