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Practice Guideline

Update on guidelines for the treatment of COPD in Taiwan using evidence and GRADE system-based recommendations

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Chronic obstructive pulmonary disease (COPD) has significant contributions to morbidity and mortality world-wide. Early symptoms of COPD are not readily distinguishable, resulting in a low rate of diagnosis and intervention. Different guidelines and recommendations for the diagnosis and treatment of COPD exist globally. The first edition of clinical practice guidelines for COPD was published in 2016 by the Ministry of Health and Welfare in Taiwan in collaboration with the Taiwan evidence-based medicine association and Cochrane Taiwan, and was revised in 2019 in order to update recent diagnostic and therapeutic modalities for COPD and its acute exacerbation. This revised guideline covered a range of topics highlighted in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report, including strategies for the diagnosis, assessment, monitoring, and management of stable COPD and exacerbations, with particular focus on evidence from Taiwan. The recommendations included in the revised guideline were formed based on a comprehensive systematic review or meta-analysis of specific clinical issues identified by an expert panel that surveyed relevant scientific evidence in the literature and guidelines published by the clinical communities and organizations nationally and internationally.

The guidelines and recommendations are applicable to the clinical settings in Taiwan. We expect this revised guideline to facilitate the diagnosis, treatment and management of patients with COPD by physicians and health care professionals in Taiwan. Adaptations of the materials included herein for educational and training purposes is encouraged.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory disease with significant contributions to morbidity and mortality world-wide, and is a known risk factor of lung cancer.¹ Despite the enormous and increasing social-economic burden associated with COPD,^{2,3} this illness is preventable and treatable. Nevertheless, the general public has limited awareness of the symptoms of COPD which are often overlooked. The early symptoms of COPD are not readily distinguishable from diseases such as asthma and the common cold, which contributes to the low diagnostic rate. Furthermore, COPD disease progression is generally slow and unnoticeable resulting in delays in patients seeking medical assistance. Consequently, patients are often in the advanced disease stages at the time of initial screening.

Considering the poor diagnostic rate and delayed early intervention of COPD, a clinical practice guideline for COPD was published in 2016 by the Ministry of Health and Welfare in Taiwan (in Traditional Chinese). An update to the COPD guideline was made in 2019 to reinforce the importance of new diagnostic and therapeutic modalities for COPD and its acute exacerbation (AE) with a focus on Taiwan-specific evidence published since 2016. The management principles and recommendations included in this updated guidelines were formed based on a comprehensive systematic review or meta-analysis performed by the COPD guidelines writing group. Specific clinical issues identified by the expert panel included relevant scientific evidence and guidelines published by the clinical communities and organizations nationally and internationally, particularly with reference to topics highlighted in the Global Initiative for Chronic Obstructive Lung Disease (GOLD), Global Strategy for the Diagnosis, Management, and Prevention of COPD Report.^{4,5} Adjustments and modifications most suitable and applicable to the clinical setting in Taiwan as advised by the COPD writing group and the expert panel were also included. The guidelines were finalized after a thorough review by an external review board that included experts on evidence-based guideline development and COPD-related clinical practice. We expect these guidelines to assist medical professionals in their clinical practice, rather than be regarded as strict regulations. Adaptations of the materials included herein for educational and training purposes is encouraged.

COPD definition, regional epidemiology, and pathophysiology

COPD is a respiratory illness characterized by progressive, partially reversible airway obstruction and lung hyperinflation with systemic manifestations, sometimes followed

by exacerbations of increasing frequency and severity. COPD is suspected in individuals with a long or significant smoking history who show progressive exertional breathlessness, sputum production with/without cough, and frequent infections in the respiratory tract.¹ Spirometry is essential for the diagnosis of COPD, which is established by a FEV1/FVC ratio (forced expiratory volume in 1 s/forced vital capacity) of less than 0.70 post bronchodilator use.⁴ The WHO has defined a minimum set of intervention for the diagnosis of COPD in primary care.⁶

The prevalence of COPD in adults aged over 40 years ranges between 2.48 and 9.5%, based on telephone or database surveys conducted in Taiwan.^{7–9} However, the prevalence of COPD may be underestimated in Taiwan as limited data are available from large-scale screening of symptoms or lung function assessments. According to 2018 statistics published by the Ministry of Health and Welfare in Taiwan, chronic disease in the lower respiratory tract is the 7th leading cause of death, associated with an estimated mortality rate of 26.1 in every 100,000 persons. The same source in 2014 indicated that morbidity and mortality of COPD resulted in a total of 11 years of life lost (YLL) in individuals below the age of 70 years (the 10th leading cause in YLL in 2014). Admissions to intensive care units due to COPD increased from 12,384 persons in 2003 to 13,308 in 2013 in Taiwan, with the length of stay increasing from 21.58 days to 23.14 days.¹⁰ According to an analysis that adopted data from the Taiwan National Health Insurance database, the average spend in annual outpatient clinics for COPD-related visits increased by 29.3% from 2004 to 2010, and annual medical costs totaled 3434 US Dollars in 2005.¹⁰ Furthermore, the annual direct costs of inpatient admissions associated with moderate-to-severe COPD was between 38,000 and 288,000 New Taiwan Dollars. This did not account for any indirect economic and productivity loss (eg, caregiver-associated costs).¹¹

Chronic exposure to proinflammatory agents in cigarette smoke and environmental/occupational smog is considered to be the pathogenic trigger for COPD.^{12–14} Persistent inflammatory manifestations induced by these agents in the airways, as well as lung parenchyma and vasculature, lead to increased oxidative stress and protease overproduction in the lungs,¹⁵ and airway restriction and airflow limitation.¹⁶ The extent and progression of the inflammatory response may vary among individuals depending on genetic predisposition (ie, α -1 antitrypsin deficiency), age, gender, lung development, and comorbidities.⁴ Although disease symptoms associated with COPD are known to progress after cessation of smoking through unidentified mechanisms,¹⁷ early intervention measures including smoking abstinence, pulmonary rehabilitation, and prevention of respiratory infections are highly encouraged in patients with COPD.

Methodology

The guidelines were conducted in compliance with developmental processes as advised by several international organizations including the Global Initiative for Chronic Obstructive Lung Disease,^{4,5} the National Institute for Health and Clinical Excellence, and the Scottish Intercollegiate Guidelines Network, as well as regional governing and evidence-based research bodies such as the National Health Insurance Administration, and the National Health Research Institutes.^{18–20} Members of the expert panel and the writing group for the 2016 COPD practice guidelines were invited to participate in the 2019 update, and performed systematic literature reviews and meta-analyses with a focus on Taiwan-specific data in order to answer the clinical questions identified via the PICO framework. The quality of evidence was determined using the GRADE (ie, Grading of Recommendations, Assessment, Development and Evaluation) method and evaluated using our online software GRADE pro GDT (<http://gradpro.org/>).^{21,22} The quality of evidence and the strength of recommendations stated in the current guidelines are defined in [Supplementary Tables 1 and 2](#).

Diagnosis and assessment of COPD

Keypoints

Diagnosis

In any patient who has dyspnea, chronic cough or sputum production, regardless of history of exposure to risk factors for the disease, COPD should be considered and a spirometry test to establish diagnosis should be arranged. Post-bronchodilator $FEV_1/FVC < 0.7$ confirms pulmonary airflow obstruction. However, in the presence of comorbidities such as heart failure, pulmonary fibrosis, or severe obesity, a diagnosis of COPD should be based on a comprehensive evaluation of clinical symptoms that includes physical examination, imaging examination, and other cardiopulmonary function parameters.

Assessment - parameters

Parameters for assessing the COPD severity include: (I) symptom severity (modified MRC dyspnea scale (mMRC) and COPD assessment test (CAT)), (II) severity of airflow limitation, (III) exacerbation risk, (IV) concomitant chronic diseases/comorbidities, and (V) combined COPD assessment (refined 2019 GOLD ABCD assessment tool).⁴

- Evidence from the Taiwan TOLD study concluded that assessment of COPD must include overall assessment of symptoms, lung function, and comorbidities.²³
- Recent studies in Taiwan suggested CAT performed better than mMRC when evaluating patients' symptoms, comorbidities, and rate of ICU admission. When assessing patients' arrival to the emergency department and overall hospitalization status, mMRC performed better than CAT. When comparing health care resources utilization, CAT and mMRC have equal effectiveness in evaluating patients with regular medical treatment.²⁴

- Regarding concomitant chronic disease, studies from Taiwan reported that COPD patients with chronic kidney disease had a higher mortality rate. In addition, the risk of developing cancer in patients with COPD was 2.8 times higher than non-COPD patients.²⁵
- After a combined assessment of the severity of airway limitation and associated symptoms, COPD patients were grouped into four spirometric grades (1–4) and four groups (A through D according to symptoms burden and number of acute exacerbations), similar to the diagnostic classification used by the GOLD guidelines ([Fig. 1](#), Source: Ref.⁵).

Assessment – phenotypes

COPD is a heterogeneous disease with varied clinical presentations. Identification of clinical phenotypes is necessary in order to provide the most appropriate treatment.

- The GOLD treatment strategy uses an initial four-quadrant evaluation system to classify medications. The evaluation system is based on currently accepted phenotypes, including: (1) more symptomatic: may be a predictor of mortality; (2) Frequent exacerbator: the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study demonstrated this is the only predictor for the severity and frequency of exacerbations and the severity of COPD and the severity of all GOLD grade²⁶; (3) Chronic bronchitis: COPD studies have demonstrated a higher total mucin concentration and has two or more acute exacerbations per year.²⁷
- COPD exacerbator-phenotype (defined as patients with ≥ 2 exacerbations per year) should be included as a part of the COPD evaluation. The best predictor of frequent exacerbations is a history of previous treatment events.²⁸
- The prognosis of the exacerbator-phenotype is poor. Therefore, documenting the clinical records of these patients is very important, and patients may require anti-inflammatory treatment (eg, ICS) in addition to bronchodilators.
- For patients with COPD suspected of meeting the diagnosis of ACO diagnosis according to GINA/GOLD guidelines, blood eosinophil counts, and immunoglobulin tests are recommended in addition to bronchodilator tests.⁴
- Blood eosinophil count is a biomarker that has been more widely discussed in recent years. A high blood eosinophil may require the use of an inhaled corticosteroid (ICS) with long-acting β -agonists (LABA), which may result in a lower chance of exacerbations than LABA alone.^{29,30} A meta-analysis found that the use of ICS in COPD patients with $>2\%$ eosinophil counts reduced the incidence of acute exacerbations.³¹ Since, 2019, The GOLD clinical guidelines has recommend ICS for the initial treatment and follow-up treatment in patients with an eosinophil counts of 300 cells/uL; however, if the eosinophil count is below 100 cells/uL, use of ICS is not recommended.^{4,5}
- Additional clinical phenotypes and assessment indicators include: Alpha-1 antitrypsin deficiency (AATD)

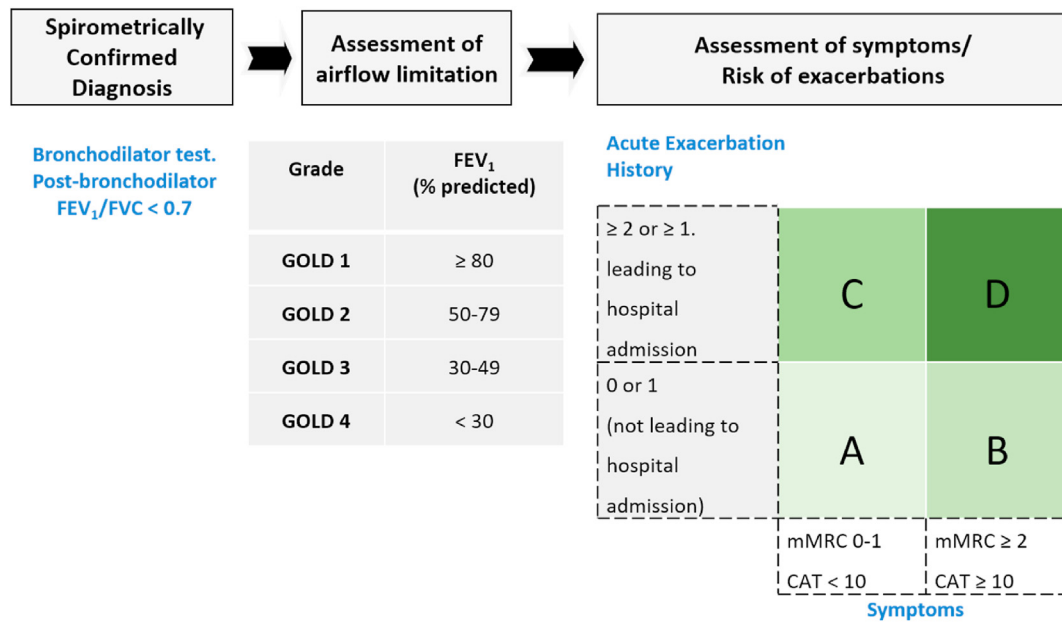


Figure 1 The Refined ABCD Assessment Tool Based on GOLD Classification. Abbreviations: CAT, COPD assessment test; FEV_1 , forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, Modified Medical Research Council Dyspnea Scale. Adapted from 2021, Global Initiative for Chronic Obstructive Lung Disease, <http://www.goldcopd.org/>, Fontana.

screening,³² FEV_1 and FEV_1 annual decline rates³³; wheezing³⁴; peripheral blood eosinophils counts,²⁹ BMI,³⁵ asthma-COPD overlap (ACO),³⁶ lung microbiome.³⁷

- Large-scale and long-term studies have demonstrated that frequent exacerbator phenotype and systemic inflammatory phenotype are correlated with prognosis. Rapid FEV_1 decline, chronic bronchitis and emphysema, wheezing, overweight, and obesity are correlated with disease progression and number of acute exacerbations. Peripheral blood eosinophil count, ACO, and lung microbiota are related to drug response and choice of drug treatments.

Screening

- Symptoms of COPD are easily missed. Screening for symptoms in high-risk populations may assist in the early detection of patients with moderate-to-severe COPD who can benefit from treatment.
- Lung function and imaging examinations should be arranged for patients with chronic cough, sputum production, dyspnea, wheezing, and other respiratory symptoms, and patients with a family history of antitrypsin deficiency.
- For patients without subjective awareness of symptoms, there is currently no evidence of clinical benefit in conducting screening questionnaires including the COPD Diagnostic Questionnaire (CDQ),³⁸ lung Function Questionnaire (LFQ),³⁹ COPD Population Screener (COPD-PS), or spirometry examinations.

Specific recommendations with supporting evidence

- The post-bronchodilator ratio of the first second of forced expiration (FEV_1) over the full, forced vital capacity (FVC) (FEV_1/FVC) is considered to reflect persistent airflow restriction as described by clinical practice guidelines published by well-known international organizations.^{4,40} GOLD guidelines advises using post-bronchodilator $FEV_1/FVC < 0.7$ as measured using spirometry for the diagnosis of COPD,⁴ whereas the American Thoracic Society and the European Respiratory Society suggest adopting the lower limit of normal for diagnostic purposes,⁴⁰ which is reflected by the single study-site data published by a research group in Taiwan.⁴¹ (Table 1, Recommendation 1.1).
- The spirometry measurements are strongly affected by the presence of comorbidities including heart failure,⁴² lung fibrosis,⁴³ lung emphysema,⁴⁴ and severe obesity,⁴⁵ and thus symptomology, physical examinations, radiographic imaging, and other cardiopulmonary assessment tools should be adopted to confirm suspected COPD (Table 1, Recommendation 1.2).
- The reversibility of FEV_1 has been demonstrated to vary significantly within the same patient when tested on different days,⁴⁶ and may be dependent on the type or dose of bronchodilator, as well as the patient's pre-bronchodilator baseline FEV_1 .^{46,47} Considering the lack of reproducibility and the poor association with patient clinical outcomes,^{46,47} the utilization of FEV_1 reversibility is currently not recommended for the diagnosis of COPD (Table 1, Recommendation 1.3).

Table 1 Recommendations for the diagnosis and assessment of COPD.

GRADE level of evidence	Recommendation
1A	1.1 We recommend adopting the post-bronchodilator FEV ₁ /FVC ratio for the diagnosis of COPD. (A strong recommendation with a high level of evidence)
1B	1.2 An accurate diagnosis of COPD in patients with concomitant conditions such as heart failure, lung fibrosis, or severe obesity should be made based on a multi-disciplinary evaluation involving clinical symptomatology, physical examination, radiographic imaging, and additional assessment of cardiopulmonary functions. (A strong recommendation with a moderate level of evidence)
1B	1.3 The reversibility of FEV ₁ should not be adopted to exclude the diagnosis of COPD. (A strong recommendation with a moderate level of evidence)
2A	1.4 For patients with a definite diagnosis of COPD, the qualitative indices of a chest CT can be adopted to distinguish different COPD phenotypes (eg, lung emphysema, air-trapping, and small-airway dysfunction) and the evaluation of AE, lung transplantation, the distribution of lung emphysema prior to a lung reduction surgery, the characteristics of comorbidities, and disease progression. (A weak recommendation with a high level of evidence)
1A	1.5 The clinical presentation of frequent exacerbations (with ≥ 2 exacerbations per year) should be included as a part of the COPD evaluation. (A strong recommendation with a high level of evidence)
1C	1.6 For patients with COPD who fulfill the ACO diagnostic criteria based on GINA/GOLD guidelines, bronchodilator tests, blood eosinophil counts, and immunoglobulin blood tests are recommended for advanced medical judgments. (A strong recommendation with a low level of evidence)
2B	1.7 For asymptomatic adults, questionnaires and spirometry are not recommended for the purposes of COPD screening. (A weak recommendation with a moderate level of evidence)

Abbreviations: ACO, asthma-COPD overlap syndrome; AE, acute exacerbation; COPD, chronic obstructive pulmonary disease; CT, computed tomography; FEV₁, the first second of forced expiration; FVC, forced vital capacity.

- Computed tomography (CT) examinations of the chest have not been routinely adopted to confirm the diagnosis of COPD, however it has been demonstrated that a chest CT can support subcategorizing distinct COPD phenotypes,^{48–50} determining comorbidities and the distribution of emphysema,^{33,51} as well as to predict risk of COPD exacerbation and disease progression.⁵² A study utilizing low-dose lung cancer screening via CT scan reported a sensitivity of 63% and specificity of 88% in the detection of COPD based on imaging evidence of lung emphysema and air-trapping.⁵³ (Table 1, Recommendation 1.4)
- The clinical phenotypes of COPD are extremely heterogeneous, and can dictate patient outcome and management strategies.⁵⁴ Patients who exhibit ≥ 2 exacerbations in a year are classified as having frequent exacerbations, and the best predictor for this is prior medication history for an exacerbating event.²⁸ These patients may have worse clinical outcomes and require treatments of systemic/inhaled corticosteroids, antibiotics, or bronchodilators.^{27,55} The level of evidence for this recommendation has been upgraded to high (from 1B to 1A) (Table 1, Recommendation 1.5).
- The expert consensus on asthma-COPD overlap syndrome (ACO) published by the Taiwan Society of Pulmonary and Critical Care Medicine adopted the definition of ACO as “patients having symptoms that fulfill the diagnostic criteria of either asthma or COPD, yet present with certain clinical characteristics of the other condition”.³⁶ as have been described in

the 2014 Global Initiative for Asthma report.⁵⁶ (Table 1, Recommendation 1.6)

- The sensitivity and specificity of several questionnaires for the detection of COPD were reported to range between 80% to 93% and 24%–49%, respectively, demonstrating moderate overall performance.^{57,58} Meanwhile, office-based screening of pulmonary function demonstrated a sensitivity ranging from 51% to 80% and a specificity ranging from 90% to 95%; however, no direct evidence was available to demonstrate the benefits and harms of screening asymptomatic adults.^{57,58}

Management of stable COPD

Keypoints

The WHO has defined a minimum set of interventions for the management of stable COPD in primary care.⁶

Pharmacological treatment

- The goal of management for stable COPD is to reduce symptoms and potential risks with minimal adverse effects from treatment. Appropriate treatments can reduce symptoms, the severity of exacerbations, and improve exercise tolerance and health status. Continuous patient monitoring and follow-up should ensure treatment goals are achieved.
- Different treatment options for the management of stable COPD can be categorized by the route of

administration [inhaled bronchodilators and inhaled corticosteroids] vs. oral medications).

- It is essential to provide instruction and demonstrate proper drug inhalation technique to patients who are being prescribed an inhaler device. Studies have reported that pharmacist-led interventions and lay health coaching improved inhalation technique and adherence in COPD patients.^{59,60}
- Inhaled bronchodilators (beta 2-agonists and anticholinergics) are recommended for the treatment of stable COPD. Treatment can be given alone or in combination, or in combination with inhaled corticosteroids (ICS) according to patient's disease severity and history of acute exacerbations.⁶¹
- Long-acting bronchodilators, including long-acting beta2-agonist (LABA) and anti-cholinergic drugs (long-acting muscarinic antagonists (LAMA) are recommended as first line maintenance therapy for stable COPD over short-acting agents.^{62,63} Both LAMA and LABA can be used as a single bronchodilator therapy; however, for patients with a greater risk of acute exacerbation, LAMA is the preferred bronchodilator.^{64–66}
- For patients with mild symptoms and a low risk of acute exacerbation, single LAMA- or LABA-based bronchodilator therapy is recommended as first-line treatment.^{67,68} If patients experience inadequate control of symptoms or repeated episodes of AE after bronchodilator monotherapy fixed-dose dual bronchodilator therapy (LABA + LAMA) can be considered. In contrast, for patients with severe initial symptoms, fixed-dose dual bronchodilator therapy is recommended as a first-line therapy.
- ICS are recommended for COPD patients with asthma, frequent acute exacerbations, or patients with high blood/sputum eosinophilic count (>300 cells/ μ L). For stable COPD patients without asthma, and with no increased eosinophil count (>300 cells/ μ L), discontinuation of ICS would not increase the risk of acute exacerbation but may cause reduced lung function. Potential adverse effects (e.g. higher prevalence of oral candidiasis, hoarse voice, skin bruising, decreased bone density, fracture and pneumonia may occur after long-term ICS treatment in some patients,^{69–71} if adverse events, occur consider discontinuing ICS gradually.^{4,5,72} In parallel, continued use of a fixed-dose dual bronchodilator therapy (LABA + LAMA), and close monitoring of lung function and evaluation for risk of acute exacerbation, is recommended.
- Fixed-dose triple therapy (inhaled treatment to LABA + LABA + ICS has been shown to improve lung function and reduce exacerbations compared to LAMA alone, LABA/LAMA and LABA/ICS; and have beneficial effect on mortality in COPD patients with frequent and/or severe exacerbations.^{73,74} Further study is needed to help determining the specific patient subgroups who would have greater survival benefit.⁵
- Oral medications, compared with inhaled medications, are used less for managing stable COPD; however, they are still commonly prescribed. These include oral corticosteroids, theophylline, type 4 phosphodiesterase inhibitors (PDE4 inhibitors), macrolides, antioxidant mucolytic agents, beta-adrenoceptor blockers (beta-

blockers), and opioids. Beta-blockers are an important drug for the treatment of heart disease. Use of cardiac-specific beta-blockers has been shown to improve prognosis for stable COPD patients with coronary artery disease or heart failure; however, there is no evidence that beta-blockers should be used in patients with COPD who do not have cardiovascular indications for their use (i.e. selective beta-blockers should not be used solely for the purpose of preventing exacerbations of COPD).⁷⁵ Furthermore, caution should be taken to monitor any reductions in lung function. In addition, for advanced COPD patients with refractory dyspnea, low-dose oral opiates can help with symptom relief.

- Initiation management: according to the GOLD diagnosis and treatment guidelines, COPD patients are divided into four groups (A through D) according to their symptoms and risk of acute exacerbation. First-line treatment should be based on their group (Fig. 2, Source: Ref.⁵),
- Follow-up management: patients should be reassessed for attainment of treatment goals. Treatment adjustments (escalate or de-escalate) may be needed based on the response to the initial therapy, including the improvement of symptoms and the risk of acute exacerbation. Note, follow-up treatment management algorithms and recommendations can be applied to any patient who is already taking maintenance treatments irrespective of their GOLD group allocation at treatment initiation. If treatment adjustments are necessary, the corresponding treatment algorithm for dyspnea or exacerbation should be selected (Fig. 3, Source: Ref.⁵).

Monitoring and follow-up

- Routine monitoring is important for patients with stable COPD. Monitoring should include a review of symptoms, lung function, and a history of acute exacerbations. Treatment strategies should be adjusted based on the monitoring results. Regular follow-up should assess patients' compliance with medications or non-drug treatments, treatment efficacy, complications, as well as common comorbidities common in patients with COPD.
- Follow-up assessment can vary depending on the severity of the patient. General recommendations are shown in Fig. 4 (Source: Ref.⁵).

Specific recommendations with supporting evidence

Pharmacological treatment

- Short-acting bronchodilators include those with agnostic activity towards β -adrenergic receptors (short-acting β -adrenergic agonists, SABA) and muscarinic receptors (short-acting muscarinic agonists, SAMA). SABA and SAMA can be used as monotherapy agents or in combination with each other.^{76,77} Although both have been shown to improve lung function and symptoms of COPD in patients, the use of either class of drug is associated with increased risk of heart disease.⁷⁶ Hence, SABA and SAMA

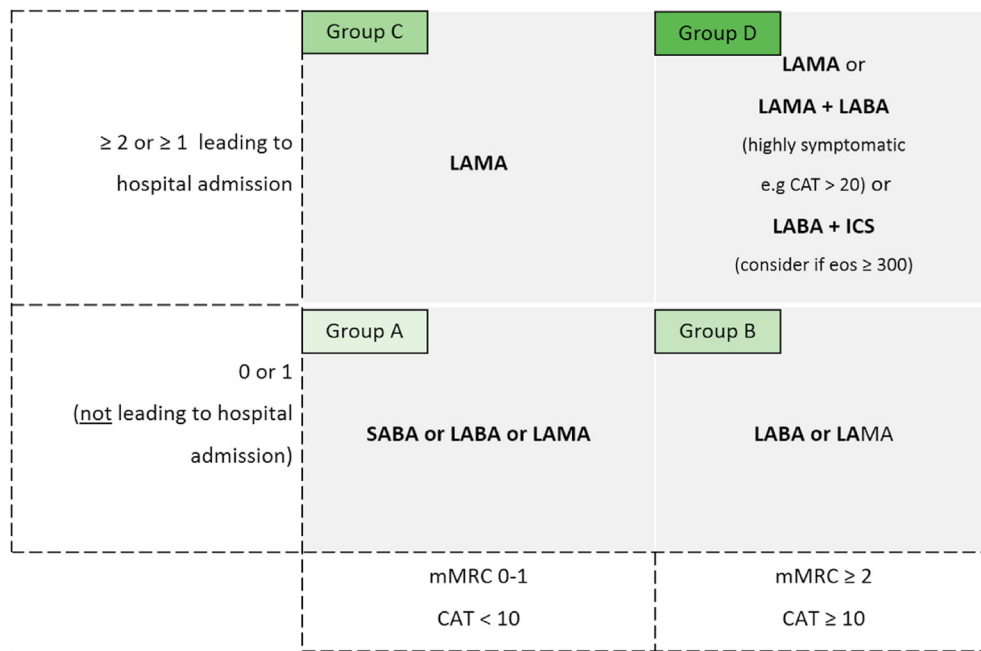


Figure 2 Initial Pharmacological Management of COPD Based on GOLD Classification. Abbreviations: CAT, COPD assessment test; eos, blood eosinophil count in cells per microliter; mMRC, Modified Medical Research Council Dyspnea Scale. Adapted from 2021, Global Initiative for Chronic Obstructive Lung Disease, www.goldcopd.org/, Fontana.

should only be administered in the event of an AE rather than routinely.⁶³ (Table 2, Recommendation 2.1).

- Indacaterol and olodaterol are two long-acting β -adrenergic agonists (LABA) approved as monotherapy in Taiwan, and have been shown to improve lung function,^{78,79} quality of life, and AEs in moderate-to-severe COPD patients.⁷⁹ On the other hand, tiotropium, glycopyrronium, and umeclidinium are the clinically available long-acting muscarinic agonists (LAMA) in Taiwan. Glycopyrronium has been demonstrated to be comparable to tiotropium in terms of efficacy and safety,⁸⁰ while umeclidinium is slightly better to tiotropium in efficacy.⁸¹ (Table 2, Recommendation 2.2).
- LAMAs and LABAs have been demonstrated by a meta-analysis using pooled results of 16 randomized controlled trials (RCT) to be comparable in the improvement of lung function (FEV1), symptoms (transition dyspnea index, TDI), and quality of life (St. George's Respiratory Questionnaire, SGRQ). In contrast, LAMAs are more effective in preventing AEs (OR = 0.84; 95% CI = 0.74 to 0.94; p = 0.003) with a better safety profile (OR = 0.92; 95% CI = 0.86 to 0.97; p = 0.005).⁶⁴ (Table 2, Recommendation 2.3).
- The safety and efficacy of fixed-dose dual bronchodilator therapies with combination LAMA and LABA (LAMA+LABA FDC) in comparison to LAMA or LABA alone in treating stable COPD have been evaluated in a meta-analysis.^{67,82} LAMA+LABA FDC are associated with improved FEV1, TDI score, and SGRQ score versus either agent alone.⁶⁷ The efficacy in improving lung function, lowering risk of exacerbation were demonstrated in patients with moderate-to-severe COPD,^{83,84} as well as in symptomatic patients with low exacerbation risk.⁸⁵ The level of evidence for this recommendation has

been upgraded to high (from 1B to 1A) (Table 2, Recommendation 2.4).

- A meta-analysis (included nine RCTs from 2013 to 2018)⁸⁶ demonstrated that, compared to LAMA monotherapy, LAMA+LABA FDC demonstrated lower risk in terms of all exacerbations (RR = 0.92; 95% CI = 0.86 to 1.00; p = 0.04). However, the efficacy in term of risk for moderate-to-severe exacerbations, severe exacerbations, or time to the first exacerbation were similar between LAMA+LABA FDC and LAMA monotherapy.^{67,68} Thus, for patients with a mild symptoms but higher risk of acute exacerbation, LAMA is the preferred initiation bronchodilator (Table 2, Recommendation 2.5).
- The efficacy and safety of four different groups of inhalers (ie, LAMA + LABA FDC, LABA plus ICS, and LAMA or LABA alone) have been examined extensively in patients with moderate-to-severe COPD, and a recently published meta-analysis demonstrated that LAMA + LABA FDC were better than LABA plus ICS in preventing moderate-to-severe-AEs and severe AEs,^{72,87,88} however, the benefit from ICS use in terms of lung function and exacerbation rate were lower in current or heavy smokers.⁸⁹ Recent studies have also demonstrated blood eosinophil count predicts exacerbation risk and the clinical response to ICS, patients with higher blood eosinophil counts (≥ 300 cells/ μ L) were found respond better to ICS + LABA.^{29,30,90} In patients with high exacerbation risk (≥ 2 exacerbations and/or 1 hospitalization in the previous year) LABA + ICS combination also showed greater extend of decrease in exacerbation than an LABA/LAMA combination at higher blood eosinophil concentrations.⁸⁷ Blood eosinophil counts should be considered at the same time when choosing the therapy. This recommendation has been modified and updated

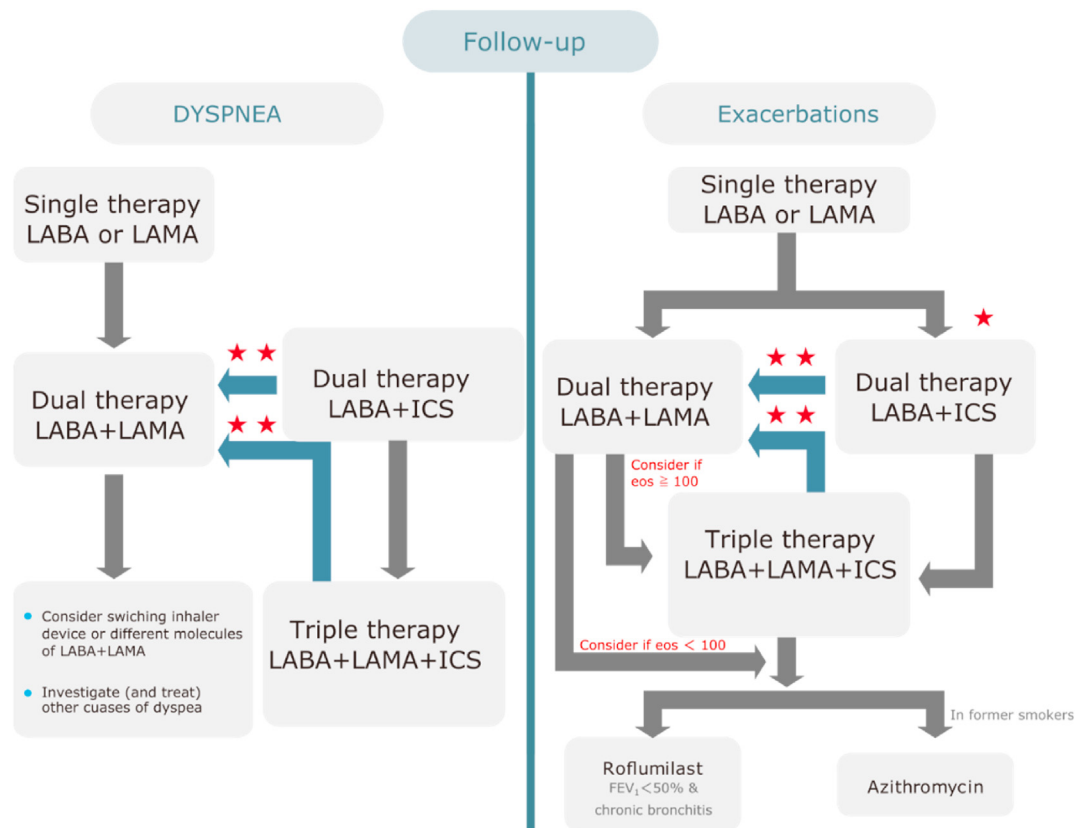


Figure 3 Follow-up pharmacological treatment strategies according to predominantly treatable traits (dyspnea or exacerbations). Eos, = blood eosinophil count in cells per microliter. *Consider if eos ≥ 300, or eos ≥ 100 AND ≥ 2 moderate acute exacerbations or ≥ 1 hospitalization. **Consider removing ICS or switch to LAMA + LABA if pneumonia, inappropriate original indications, or lack of response to ICS. Adapted from 2021, Global Initiative for Chronic Obstructive Lung Disease, www.goldcopd.org/, Fontana.

considering the recent clinical evidence (strength of recommendation from 2B to 1B) (Table 2, Recommendation 2.6).

- Regarding the withdrawal of ICS treatment in patients with stable COPD who have been receiving triple therapy – LABA + LAMA + ICS, a systematic review reported that patients with a blood eosinophil count of <300 cells/μL who had ICS withdrawn from their treatment did not show increased in risk of AEs after withdraw (OR = 1.11; 95% CI = 0.84 to 1.46).^{91,92} This finding is reflected in later studies in patients with low risk of AEs and patients with a prior history of COPD AEs.^{93,94} However, some published literature has reported a decrease in lung function and quality of life after cessation of ICS in COPD patients.^{94,95} Post-hoc analyses and later studies further showed a positive correlation between blood eosinophil counts (300 cells/μL or more) and decreased lung function and increased risk of AEs after withdrawal from ICS (strength of recommendation from 2B to 1B).^{96,97} (Table 2, Recommendation 2.7).
- A meta-analysis study pooled results from five observational studies (follow up duration range between 1 and 6 years) that focused on mortality in stable COPD patients and showed that the risk of mortality was increased (RR, 1.63; 95% CI, 1.19–2.23; p < 0.0001) in patients using

prednisolone (>5–10 mg per day) compared with controls.⁹⁸ Furthermore, it has been shown that among patients with COPD, long-term exposure to fluticasone and budesonide is consistently associated with a modest but statistically significant increased likelihood of fractures.⁷¹ In particular, increased risk of vertebral fracture also increased in patients treated with >5 mg prednisolone daily (RR = 2.31; 95% CI = 1.52 to 3.5; p = 0.03).^{99,100} (Table 2, Recommendation 2.8).

- A meta-analysis of 34 RCTs indicated that theophylline taken daily (maintained serum concentration at 5–20 μg/mL) significantly improved the FEV₁ (WMD, 90 mL; 95% CI 90–90 mL, arterial blood gas tensions and 6-minut walking distance (WMD, 38.9 m; 95% CI 21.5–56.2 m) while the incidence of drug-related adverse events is higher particularly gastrointestinal AE (OR, 4.08; 95% CI 2.84 to 5.86) and neurological AE (OR, 1.67; 95% CI 1.17 to 2.4).¹⁰¹ A meta-analysis of 7 observational cohorts suggests that theophylline (200–800 mg taken daily slightly increases all-cause death in COPD patients (HR, 1.07; 95% CI 1.04–1.18).¹⁰² Taken together use of oral theophylline improve lung function and exercise tolerance, however, it could accompany by a small increase in gastrointestinal, neurological, and cardiovascular adverse effects; and long-term use may be related

	GOLD 1-3 (predicted FEV ₁ ≥ 30%)	GOLD 4 (predicted FEV ₁ < 30%)
Frequency of assessment	At least once a year	At least once per 6 months
Clinical Assessment	• Smoking status and willingness to quit • Are symptoms well controlled? dyspnea, exercise tolerance, risk of acute exacerbation • Complications and/or comorbidities • Inhaler technique • Adherence to pharmacotherapy regimen • Side effects • Nutritional status assessment • Requiring pulmonary rehabilitation?	• Smoking status and willingness to quit • Are symptoms well controlled? dyspnea, exercise tolerance, risk of acute exacerbation • Complications and/or comorbidities • Inhaler technique • Adherence to pharmacotherapy regimen • Side effects • Nutritional status assessment • Requiring pulmonary rehabilitation? • Requiring oxygen therapy? • Requiring other intervention? (e.g., Non-invasive positive pressure ventilation, surgery etc.)
Measurements	• FEV₁ and FVC • BMI • mMRC or CAT	• FEV₁ and FVC • BMI • mMRC or CAT • SpO₂

Figure 4 Monitoring and Follow-up recommendations (Source: Ref.⁵).

to the increase in all-cause mortality. Therefore, for patients with poor lung function and exercise tolerance, oral theophylline can be used conditionally as an add-on treatment; however, caution should be taken, the minimum effective dose should be used to avoid potential adverse effects (Table 2, Recommendation 2.9).

- A Cochrane meta-analysis showed that treatments with phosphodiesterase 4 (PDE4) inhibitors, including roflumilast and cilomilast, could significantly increase FEV₁, FVC, peak expiratory flow, total SGRQ score, frequency of AE, and the rate of one or more AE in stable COPD patients compared with those treated with placebo. The improvement in FEV₁ attributable to PDE4 was observed regardless of the patients GOLD classification, but only roflumilast significantly decreased the frequency of AEs. No benefit associated with PDE4 inhibitors was observed in a 6-min walk test, symptom scores, and mortality.¹⁰³ These findings are partially in line with a post-hoc analysis that pooled results from 2 RCTs, both of which compared roflumilast with ICS or LABA alone. Benefits attributable to roflumilast were observed in COPD patients with chronic bronchitis (cough with sputum) with regards to FEV₁, AE frequency, and quality of life.¹⁰⁴ (Table 2, Recommendation 2.10–2.12)
- Two meta-analyses reported when treatments were supplemented with azithromycin, erythromycin, or clarithromycin for 3–36 months the rate of AEs and the annual frequency of AEs in patients (RR = 0.73; 95% CI = 0.58 to 0.91), and the total score in quality of life (MD = -1.78; 95% CI = -2.95 to -0.61) were reduced.^{105,106} Similarly, another pooled analysis reported that prophylactic oral macrolide therapy significantly inhibited the risk of AE events in stable COPD

patients. Adverse events associated with oral macrolide therapy were also observed to be higher compared with controls.¹⁰⁷ (Table 2, Recommendation 2.13).

- The Cochrane review published in 2015 compared the efficacy and safety of oral expectorants with placebo in COPD patients. Results revealed that oral expectorants, including n-acetylcysteine (NAC), reduced the number of AEs, the days of disability per person per month, and the risk of hospitalization, together with improved the quality of life without any added risk in adverse events.¹⁰⁸ (Table 2, Recommendation 2.14).
- Two meta-analyses using data from retrospective observational studies showed that long-term use of β -Adrenoceptor antagonists (β -blockers) in stable COPD patients with concurrent cardiovascular disease was significantly associated with decreased mortality,^{109,110} while cardioselective β -blockers also demonstrated benefits in FEV₁.¹¹¹ Results from Taiwan studies that utilized data from the National Health Insurance database also demonstrated improved outcomes with use of β -blockers after acute myocardial infarction.^{112,113} (Table 2, Recommendation 2.15).

Non-pharmacologic management

- Smoking cessation has the greatest capacity to influence the nature history of COPD. Irrespective of the presence of COPD and the state of patient lung function, cessation of smoking ameliorates respiratory symptoms and bronchial hyperresponsiveness, and prevents the deterioration of lung function.¹¹⁴ Furthermore, the benefits conferred by the cessation of smoking include reduced risks of AEs, morbidity, and mortality.^{115,116} However,

Table 2 Recommendations for the management of stable COPD.

GRADE level of evidence	Recommendations
1A	2.1 A prescription of short-acting bronchodilators is recommended for all COPD patients as a medication for AEs. (A strong recommendation with a high level of evidence)
1B	2.2 When symptoms are not controlled or disease severity remains advanced (including symptoms and the history of AEs) after an intermittent use of short-acting bronchodilators, the routine use of a long-acting bronchodilator is recommended. (A strong recommendation with a moderate level of evidence)
1A	2.3 For patients with stable COPD, either LAMA or LABA can be considered for bronchodilator monotherapy. In contrast, for patients with a high risk of AEs, LAMAs are recommended as a first-line therapy. (A strong recommendation with a high level of evidence)
1A	2.4 For patients with mild symptoms and a low risk of AEs, LAMA- or LABA-based bronchodilator monotherapy is recommended as the initial treatment. If patients experience inadequate control of symptoms or repeated episodes of AEs after bronchodilator monotherapy, a switch to fixed-dose dual bronchodilator therapy (LABA + LAMA) can be considered. In contrast, for patients with severe symptoms, fixed-dose dual bronchodilator therapy is recommended as a first-line therapy. (A strong recommendation with a high level of evidence)
1B	2.5 For patients with stable COPD, a LAMA-based bronchodilator monotherapy should be considered as the initial treatment for patients who have mild symptoms but a high risk of AEs. (A strong recommendation with a moderate level of evidence)
1B	2.6 For patients with stable COPD and a high risk of AEs, LABA + LAMA dual therapy is more effective than ICS + LABA in preventing AEs. However, blood eosinophil counts should be considered when choosing the therapy, as patients with higher blood eosinophil counts respond better to ICS + LABA. (A strong recommendation with a moderate level of evidence)
1B	2.7 For patients with stable COPD who achieve a blood eosinophil count of <300 cells/ μ L after the continued use of LABA + LAMA + ICS triple therapy, cessation of ICS may be considered after an evaluation. Lung function should be carefully followed-up to monitor for the risk of AEs. (A strong recommendation with a moderate level of evidence)
1C	2.8 For patients with stable COPD, the long-term use of oral corticosteroids for more than 1 year may increase the risk of mortality and vertebral fracture, therefore the treatment should not be used routinely. (A strong recommendation with a low level of evidence)
2B	2.9 For patients with stable COPD whose lung function remains inadequate after using any inhaled bronchodilators, an adjunctive therapy with oral theophylline at the minimum effective dose may be considered to improve the patient's lung function while paying attention to the associated AEs. (A weak recommendation with a moderate level of evidence)
2B	2.10 For patients with stable COPD and severe or extremely severe lung obstructions, an oral PDE4-inhibitor (roflumilast) therapy may be considered in the presence of chronic bronchitis. (A weak recommendation with a moderate level of evidence)
2B	2.11 For patients with stable COPD and clinical presentation of chronic bronchitis who have inadequate quality of life, an oral PDE4-inhibitor (roflumilast) therapy may be considered. (A weak recommendation with a moderate level of evidence)
1A	2.12 For patients with stable COPD and clinical presentations of chronic bronchitis who experience frequent AEs, an oral PDE4-inhibitor (roflumilast) therapy may be considered. (A strong recommendation with a high level of evidence)
1A	2.13 For patients with COPD who have experienced one or more episodes of AEs after a combination therapy of ICS + LABA + LAMA, an adjunct therapy with erythromycin or azithromycin may be considered to reduce the occurrence of AEs while paying attention to the associated AEs. (A strong recommendation with a high level of evidence)
2B	2.14 For patients with stable COPD, an oral expectorant (eg, NAC) may be used to reduce the risk of AEs, improve the quality of life, and reduce the risk of hospitalization. (A weak recommendation with a moderate level of evidence)
1C	2.15 For patients with stable COPD and concomitant coronary heart disease or heart failure, a cardioselective β -blockers may be considered to improve the clinical outcomes while paying attention to the deterioration of lung function. A high recommendation with a low level of evidence)
1A	2.16 For all COPD patients who smoke, the cessation of smoking is strongly recommended regardless of the disease severity. (A strong recommendation with a high level of evidence)
1B	2.17 For all COPD patients, annual influenza vaccination is recommended to reduce the risk of COPD AEs. (A strong recommendation with a moderate level of evidence)

(continued on next page)

Table 2 (continued)

GRADE level of evidence	Recommendations
1B	2.18 For all COPD patients, annual influenza vaccination is recommended to reduce the risk of severe complications (eg, hospitalization due to lower respiratory tract infections) and death. (A strong recommendation with a moderate level of evidence)
1B	2.19 For all COPD patients aged over 65 years, the pneumococcal vaccination (PCV13 and PPV23) is recommended. (A strong recommendation with a moderate level of evidence)
1B	2.20 For all COPD patients aged under 65 years with concomitant severe chronic diseases, the pneumococcal vaccination (PCV13 and PPV23) is recommended. (A strong recommendation with a moderate level of evidence)
1B	2.21 Patients with COPD are often malnourished, therefore nutritional status monitoring should be a part of the management procedures and appropriate nutritional supplementations should be given when needed. (A strong recommendation with a moderate level of evidence)
1A	2.22 Lung rehabilitation can enhance exercise capacity, reduce breathlessness, improve health-related quality of life, decrease the frequency and length of hospitalization, ameliorate COPD-related anxiety and depression, promote the recovery after hospitalization for AEs in these patients. Lung rehabilitation is recommended for patients with COPD. (A strong recommendation with a high level of evidence)
1B	2.23 Upper and lower limb muscle and endurance training are recommended as a part of lung rehabilitation. Lung rehabilitation can improve the survival rate and augment the efficacy of long-acting bronchodilators. (A strong recommendation with a moderate level of evidence)
1B	2.24 For COPD patients who are hospitalized for AEs, lung rehabilitation should be initiated within 4 weeks after discharge from the hospital as it prevents the risk of re-hospitalization and death. However, lung rehabilitation is not recommended immediately after AEs occur, as this may increase the risk of death from heart attacks. (A strong recommendation with a moderate level of evidence)
2B	2.25 For patients with stable COPD and concomitant hypercapnia, a routine treatment with a non-invasive positive pressure ventilator is not recommended. However, a treatment with a high intensity non-invasive positive pressure ventilator may be considered in patients with extremely severe disease after a careful evaluation of the benefits and risks, as well as the feasibilities. (A weak recommendation with a moderate level of evidence)

Abbreviations: β -blockers, β -Adrenoceptor antagonists; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 sympathomimetic agonists; LAMA, long-acting muscarinic agonists; NAC, n-acetylcysteine; PCV13, 13-valent pneumococcal conjugate vaccine; PDE4, phosphodiesterase 4; PPV23, 23-valent pneumococcal polysaccharide vaccine.

the effectiveness and safety of using electronic cigarettes as a smoking cessation aid is uncertain at present.^{117,118} (Table 2, Recommendation 2.16)

- Influenza vaccination reduces the risk of developing severe infections in the lower respiratory tract, hospitalization due to pneumonia, and death.^{119–121} Thus, the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recommend COPD patients receive an annual influenza vaccination to diminish the likelihood of AEs.^{114–116} Although there are currently no direct results supporting vaccination against pneumococcal pneumonia for the prevention of COPD AEs, both CDC and WHO recommend pneumococcal vaccination in adults over the age of 65 years,^{122,123} in individuals with comorbidities (including COPD) and aged between 19 and 64 years, and individuals with a high risk of pneumococcal infection based on the beneficial effects proven in the general population.^{114–116} While the clinical advantages of both 23-valent pneumococcal polysaccharide vaccine (PPV23) and 13-valent pneumococcal conjugate vaccine (PCV13) have been demonstrated in COPD patients,^{124,125} only limited data with respect to the optimal schedule or type of pneumococcal vaccination are available. The

level of evidence for recommendation 2.20 has been upgraded from 1C to 1B based on recent results (Table 2, Recommendation 2.17–20).

- Approximately 25–40% of severe COPD patients are malnourished, and is associated with being underweight with low fat-free mass, both of which are associated with a poor prognosis in COPD patients.¹²⁶ Nutritional supplementation has been shown to increase body-weight in severely malnourished COPD patients, significantly enhance performance in a 6-min walk test and the strength of respiratory muscles, and the overall health-related quality of life.^{127,128} (Table 2, Recommendation 2.21). Additional details regarding nutritional care can be found in the clinical nutritional care guideline published by the Taiwan Society of Pulmonary and Critical Care Medicine.¹²⁹
- Pulmonary rehabilitation is defined as “a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies” which aims to decrease patients’ disabilities in daily activities and their physical and psychological interactions with society in order to promote improved quality of life.^{130,131} Lung rehabilitation should be arranged within 4 weeks of hospital discharge.¹³² An effective lung rehabilitation

plan should last at least 6–8 weeks, preferably with 30-min sessions conducted twice weekly at minimum, involving respiratory and exercise training.¹³³ Continuous or intermittent endurance training would be beneficial to COPD patients regardless of exercise intensity. Exercise for the upper and lower limbs should also be considered in a pulmonary rehabilitation plan.¹³³ (Table 2, Recommendation 2.22–24)

- Efficacy of non-invasive positive pressure ventilation (NIPPV) for patients with severe stable COPD remains undetermined, as the outcome may be affected by hypercapnia ($\text{PaCO}_2 > 53$ mmHg).¹³⁴ The clinical performance of conventional low-intensity non-invasive positive pressure ventilation (NIPPV) in the management of stable COPD with severe clinical symptoms has been assessed by a Cochrane meta-analysis; results did not demonstrate benefit to hypercapnia, lung function, sleeping quality, life quality, or 6-min walk distance.¹³⁵ Recent publications have reported that nocturnal high-intensity NIPPV given in patients with severe stable COPD with concomitant hypercapnia was associated with decreased mortality and improved quality of life,¹³⁶ however, NIPPV with inspiratory positive airway pressure below 18 cmH₂O was insufficient to reverse hypercapnia.¹³⁷ A recent meta-analysis study reported NIV decreases mortality and risk of hospitalization with use of NIPPV in selected patients. However the most appropriate candidate subgroup remains unclear.¹³⁸ Thus, regular use of NIPPV was not recommended for stable COPD patients with comorbid hypercapnia. However, treatment with a high intensity non-invasive positive pressure ventilator could be considered in patients with severe stable disease after a careful evaluation of the benefits and risks, as well as the feasibilities (Table 2, Recommendation 2.25).

Management of COPD AEs

Keypoints

The WHO has defined a minimum set of intervention for the management of exacerbations.⁶

Definition of AE

The diagnosis of acute exacerbation of COPD is dependent on the acute changes in symptoms. When the clinical presentation exceeds the usual variability that occurs each day for the patient, including increased dyspnea severity, increased sputum volume, and thickened sputum, an acute deterioration of COPD should be considered.

Assessment

The use of biomarkers as a diagnostic tool for acute exacerbation is not currently recommended. Questionnaires may be considered as a tool to predict the risk of a patient's readmission.

Pharmacological treatment

The use of systemic corticosteroids is recommended to shorten recovery time, improve lung function and hypoxemia, and reduce the risk of early relapse, treatment

failure and long-term hospitalization. Antibiotics are recommended if patients concurrently present with dyspnea, increased sputum volume, and increased sputum thickness.

Non-pharmacological treatment

- Oxygen therapy is recommended when blood oxygen concentration is below 88%.
- When patients with COPD develop respiratory acidosis or severe dyspnea, treatment with a non-invasive positive pressure ventilator is recommended. This treatment can reduce the length of hospitalization for acute exacerbation and the rate of intubation rate and mortality caused by acute exacerbation.
- Pulmonary rehabilitation can shorten the number of hospital stays, reduce the proportion of mortality caused by acute exacerbations, and reduce the proportion of readmission for hospitalizations due to subsequent acute exacerbations.

Monitoring and follow-up

Specific conditions for the discharge of patients with acute exacerbation of COPD should be met. The items recommended for examination at discharge, and for follow-up evaluation after discharge, are shown in Fig. 5 (Source: Ref.⁵).

Specific recommendations with supporting evidence

- The major symptoms of COPD AEs include dyspnea, increase in sputum, and occurrence of sputum with increased consistency, while flu-like symptoms may also indicate an AE event. Two thirds of AEs are attributable to infection in the respiratory track and air pollution,¹³⁹ however the reasons for the remaining third are unknown. Apart from determining the cause of an AE, the presence of heart failure, arrhythmia, pneumonia, emphysema, pneumothorax, and pleural effusion should be excluded during differential diagnosis (Table 3, Recommendation 3.1).
- Routine clinical examinations assist in the diagnosis of polycythemia, anemia, leukocytosis, and eosinophilia in patients with COPD experiencing AEs.¹⁴⁰ Correlation between increased blood eosinophil counts with long-term mortality in COPD patients ($\text{HR} = 1.26$, 95% $\text{CI} = 1.14$ to 1.40 , $p < 0.001$) as been reported,¹⁴¹ a weak correlation has also been shown between elevated leukocyte and AEs.¹⁴² Further, results from a multicenter, open-label non-inferiority randomized control trial showed eosinophil-guided therapy reduced the duration of systemic corticosteroid exposure in patients admitted to hospital with COPD exacerbation.¹⁴³ (Table 3, Recommendation 3.2)
- Blood chemistry assays can be utilized to assess for concomitant conditions such as electrolyte imbalance and hyperglycemia when a COPD patient is experiencing AEs.¹⁴⁰ However, it should be noted that the clinical performance of blood chemistry tests has not been

- confirmed in large-scale studies (Table 3, Recommendation 3.3).
- Arterial gas analysis and blood oxygen monitoring can provide a timely follow-up of the change in blood pH, a vital factor for evaluating the use of mechanical ventilation upon concurrent presence of acute respiratory failure and the use of long-term oxygen therapy.¹⁴⁰ In contrast to PO₂ and PCO₂, venous pH and HCO₃ values correlate well with those of the artery, and could be used for determining the severity of hypercapnia in COPD patients presenting with an AE.^{144,145} (Table 3, Recommendation 3.4)
 - Infections of common bacteria such as *Hemophilus influenza*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* should be suspected in the event of a COPD AE, while *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* should also be considered in Taiwan as they have been found in sputum cultures of COPD patients obtained in the hospital.^{146,147} When empirical antibiotic treatments fail to work, clinicians should refer to the results of sputum cultures for further guidance to support their clinical decision-making.^{140,148} (Table 3, Recommendation 3.5)
 - While chest X-ray examinations can be utilized to exclude conditions such as diseases of the lung and the heart, x-rays should not be used routinely to assess COPD AEs.¹⁴⁰ However, the prevalence of COPD in patients with interstitial lung disease has been reported to be 8–9%, and these patients may have poorer survival than those without interstitial lung disease (HR = 2.7; 95% CI = 1.1 to 6.5; p = 0.03).¹⁴⁹ Similarly, COPD patients who present with lung emphysema upon CT scan also have higher hospitalization and rehospitalization rates associated with AEs.¹⁵⁰ The level of evidence has been updated based on recently published findings (from 1B to 1C) (Table 3, Recommendation 3.6)
 - The assessment of lung function may encounter technical issues and lead to inaccurate results during COPD AEs, and thus their routine use is not recommended in the indicated clinical scenario.¹⁴⁰ (Table 3, Recommendation 3.7)
 - An increase of blood neutrophils or eosinophils may worsen the inflammatory events in the airway, but their diagnostic value for COPD AEs is currently limited.^{151,152} Biomarkers including blood CRP, IL-1, CXCL10, and α 2-macroglobulin levels are associated with or are predictive of COPD AEs,^{153,154} however these findings remain to be confirmed in large-scale studies and are not recommended for the diagnosis of COPD AE.^{155,156} (Table 3, Recommendation 3.8)
 - Questionnaires including the COPD assessment test (CAT) and clinical COPD questionnaires (CCQ) are commonly adopted to evaluate the health status of COPD patients, and respective cut-off values of <10 and < 1 demonstrate good testing performance in detecting the risk of COPD AEs without a significant difference between questionnaires (area-under the curve: CAT = 0.65–0.86, CCQ = 0.58 to 0.94).^{157,158} Furthermore, several questionnaire-based evaluation tools including the Dyspnea, Eosinopenia, Consolidation, respiratory Acidosis and atrial Fibrillation (DECAF), Acute Physiology and Chronic Health Evaluation (APACHE) II have been shown to predict acute deterioration, survival, and risk of rehospitalization in COPD patients with AEs.^{159–161} (Table 3, Recommendation 3.9–10)
 - In the event of COPD AEs, the use of systemic corticosteroids is recommended.¹⁶² Systemic corticosteroids decrease the inflammatory response within the respiratory tract, and as a result ameliorate COPD AEs, improve lung function and hypoxemia, and reduce the days of hospitalization, risks of early relapse, treatment failure, and long-term hospitalization.^{163–165} Nevertheless, the side effects of high-dose corticosteroids should be considered. The benefit of systemic steroid in ameliorating AE of COPD patients compared with placebo, and that a low-dose corticosteroid treatment equivalent to prednisolone 80 mg daily have been reported to be sufficient.^{163,166,167} A systemic corticosteroid treatment for 5 days showed comparable efficacy to a 14-day corticosteroid treatment in preventing the occurrence of AEs.¹⁶⁷ Furthermore, a systemic corticosteroid therapy of 3–7 days did not increase the risk of AE reoccurrence.¹⁶⁸ (Table 3, Recommendation 3.11–12)
 - A limited number of placebo-controlled studies found that antibiotics could lower the rate of early death and treatment failure in COPD patients exhibiting sputum with increased consistency accompanied by dyspnea and/or increase in sputum.¹⁶⁹ Aminopenicillin alone or in combination with clavulanic acid or macrolide could be considered based on the bacteria isolates reported in major hospitals in Taiwan.^{146,170} Antibiotic treatments for COPD patients with frequent exacerbations, severe restriction of expiratory airflow, and those requiring mechanical ventilation due to AEs should be adjusted based on the common bacteria strains found in individual hospitals.¹³⁰ (Table 3, Recommendation 3.13–14)
 - Serum procalcitonin monitoring has been demonstrated to reduce COPD patients' exposure to antibiotics during AEs by 44% and the need of an antibiotic treatment for more than 5 days in published RCT reports.^{171,172} Another RCT supported these results and showed that monitoring serum procalcitonin during COPD AEs could lower the number of days of antibiotic treatments from 7.02 days to 2.10 days (p < 0.001).¹⁷³ However, conflicting results has been reported in recent studies. A systematic review and meta-analysis on the use of procalcitonin in hospitalized patients with COPD exacerbation found no significant reduction,¹⁷⁴ another study reported use of procalcitonin-based algorithm for initiating or stopping antibiotics was associated with higher mortality rate,¹⁷⁵ thus the use of procalcitonin-based protocols to make the decision on using antibiotics in patients with COPD exacerbations was not recommended (Table 3, Recommendation 3.15).
 - SABA alone or in combination with SAMA is recommended for the treatment of COPD AEs.⁵ Regarding the optimal delivery of inhaled short-acting bronchodilators, a meta-analysis indicated that wet nebulized and metered-dose inhalers showed equivalent performance in improving FEV₁, the former is more convenient to patients with severe airflow obstruction.¹⁷⁶ (Table 3, Recommendation 3.16)
 - Oxygen therapy is given to COPD patients exhibiting AEs in order to maintain blood oxygen saturation levels at

Discharge Criteria	
✓	Able to use LABA, LAMA or with ICS
✓	Frequency of medication: Inhaled SABA last 4 hours or longer.
✓	Patient has adequate physical and walking ability, and can walk across the room.
✓	Patient can eat and sleep well, without disruption by dyspnea.
✓	The patient is stable and asymptomatic for 12-24 hours
✓	Arterial blood gases have been stable for 12-24 hours.
✓	Patient and or caregiver fully understand correct use of medications
✓	Ensure follow-up and home-care arrangements have been arranged e.g. visiting nurse, oxygen delivery, meal provision
✓	Patient family and physical are confident that the patient can manage successfully at home
Recommended Checklist for Discharge	
✓	Ensure effective take-home medications for maintenance therapy
✓	Reassessment of inhaler technique
✓	Ensure understanding of the role of maintenance therapy
✓	Instruct patients to complete steroids and antibiotics, if prescribed
✓	Assess the requirement for continuing oxygen therapy °
✓	Arrange follow-up visits
✓	Provide management plan for comorbidities and follow-up
Recommended assessment at follow-up out-patient visit	
✓	Assess the ability to cope in his/her usual environment
✓	Measure FEV ₁ °
✓	Reassessment of inhaler technique
✓	Ensure patient's understanding of the treatment regimen
✓	Assess the need for long-term oxygen therapy or use of home nebulizer
✓	Assess the ability to perform physical activities and activities of daily living.
✓	Document symptoms using CAT or mMRC
✓	Determine the status of comorbidities

Figure 5 Discharge criteria and recommendations for follow-up assessment for COPD AEs (source: Ref. ⁵).

88–92%, and is recommended only when blood oxygen saturation levels are below 88%.^{177–179} Furthermore, arterial gas analysis or pulse oximeter analysis should be conducted as part of a follow-up to monitor oxygen saturation.¹⁷⁷ (Table 3, Recommendation 3.17)

- High-flow nasal cannula oxygen therapy reduces transcutaneous carbon dioxide and respiratory rate in COPD patients, and improves quality of life in those with hypercapnia.^{180,181} However, the effect of oxygen therapy via high-flow nasal cannula on mortality of COPD patients with AEs remains unclear despite being associated with a reduced intubation rate.^{182,183} (Table 3, Recommendation 3.18).
- Pooled data from 15 published RCTs, including a study from Taiwan found that NIPPV reduced the number of

hospitalized days in COPD patients by 3.24 days (95% CI = −4.42 to −2.06) compared with conventional treatments.¹⁸⁴ The benefits of NIPPV were especially evident in those who had a blood pH below 7.30 compared with those without respiratory acidosis, resulting in a reduction of 4.43 days of hospitalization.¹⁸⁵ In contrast, NIPPV did not significantly lessen the days of admission in COPD patients without respiratory acidosis (ie, blood pH between 7.30 and 7.35) when compared with general management strategies.^{186,187} (Table 3, Recommendation 3.19–20)

- In COPD patients with acute respiratory failure or hypercapnia after withdrawal from invasive mechanical ventilation, NIPPV has been shown to prevent re-intubation and death.^{188,189} Additionally, the mortality

Table 3 Recommendations for the management of COPD AEs.

GRADE level of evidence	Recommendations
1B	3.1 The diagnosis of COPD AEs are solely dependent on the acute alterations of symptoms. When the clinical presentations of patients exhibit a change from normal day-to-day symptoms, including increase in breathlessness and the amount and consistency of sputum, this may indicate a COPD AE. However, the diagnosis of heart failure, pulmonary embolism, acute coronary syndrome, pneumothorax, pneumonitis, lung collapse, and other conditions should be excluded. (A strong recommendation with a moderate level of evidence)
2B	3.2 In the event of a COPD AE, total blood cell count may be considered, as the eosinophil counts may be adopted as a reference when considering the use of systemic corticosteroids. (A weak recommendation with a moderate level of evidence)
2C	3.3 In the event of a COPD AE, a blood chemistry assay may be considered in order to evaluate the presence of concomitant conditions such as electrolyte imbalance and hyperglycemia. (A weak recommendation with low level evidence)
1C	3.4 In the event of a COPD AE, an arterial blood gas or an oximeter analysis may be adopted as a reference when considering oxygen or mechanical ventilation therapies. (A strong recommendation with a low level of evidence)
2C	3.5 In the event of a COPD AE with suspected infections, a sputum bacteria culture may be performed as a reference when considering the type of antibiotics. (A weak recommendation with a low level of evidence)
1C	3.6 In the event of a COPD AE, chest x-ray examinations may be adopted to exclude significant lung diseases other than COPD. (A strong recommendation with a low level of evidence)
1C	3.7 Upon encountering difficulties in performing lung function tests during a COPD AE and when this may lead to imprecise measurements, routine lung function tests are not recommended. (A strong recommendation with a low level of evidence)
2C	3.8 Biomarker analyses are not recommended for the diagnosis of AEs. (A weak recommendation with a low level of evidence)
2C	3.9 CAT and CCQ questionnaires may be adopted for evaluating the risk of COPD AEs. (A weak recommendation with a low level of evidence)
2B	3.10 During a COPD AE, questionnaires may be adopted to predict the risk of re-hospitalization and long-term survival. (A weak recommendation with a moderate level of evidence)
1B	3.11 In the event of a COPD AE, the use of systemic corticosteroids is recommended as it reduces recovery time, improves lung function and low hypoxemia, and reduces the risk of an early relapse, treatment failure, and long-term hospitalization. (A strong recommendation with a moderate level of evidence)
2B	3.12 Low-dose systemic corticosteroids are sufficient to improve the symptoms of COPD AEs. (A weak recommendation with a moderate level of evidence)
1B	3.13 When patients experience concurrent breathlessness, an increase in the amount of sputum, and an increase in thick sputum, the use of antibiotics is recommended. (A strong recommendation with a moderate level of evidence)
1C	3.14 When patients develop an increase of thick sputum and concomitant breathlessness or an increase in sputum, the use of antibiotics is recommended. (A strong recommendation with a low level of evidence)
2B	3.15 The level of serum procalcitonin may be considered as an indicator for the use of antibiotics during COPD AEs. (A weak recommendation with a moderate level of evidence)
1C	3.16 Short-acting inhalable β -blockers (or used in combination with short-acting anticholinergics) may be used for the treatment of COPD AEs. (A strong recommendation with a low level of evidence)
1B	3.17 For patients with a COPD AE whose blood oxygen saturation level is below 88%, oxygen therapy is recommended. (A strong recommendation with a moderate level of evidence)
2B	3.18 High-flow Nasal cannula oxygen therapy may be considered as a treatment option for COPD exacerbations as it may improve hypercapnia, but it has no significant effects on mortality rate. (A weak recommendation with a moderate level of evidence)
1B	3.19 In the event of respiratory acidosis or severe breathlessness in COPD patients, non-invasive positive pressure ventilator therapy is recommended as it may reduce the length of hospitalization for COPD AEs and the risk of intubation and death due to AEs. (A strong recommendation with a moderate level of evidence)
2B	3.20 Non-invasive positive pressure ventilator therapy is recommended as it may reduce the length of hospitalization for COPD exacerbations. The use of non-invasive positive pressure ventilator therapy significantly reduces the length of hospitalization especially in patients who

Table 3 (continued)

GRADE level of evidence	Recommendations
2B	develop respiratory acidosis. (A weak recommendation with a moderate level of evidence) 3.21 For COPD patients under invasive ventilation who exhibit signs of failure after exubation, the consideration of non-invasive positive ventilator therapy to assist in the weaning of the ventilator in those who do not have relevant contraindications is recommended as it may prevent re-intubation and reduce the risk of death. (A weak recommendation with a moderate level of evidence)
1B	3.22 Lung rehabilitation may reduce the length of hospitalization, reduce the proportion of death due to AEs, and concurrently decrease the likelihood of hospitalization during the next episode of AEs. (A strong recommendation with a moderate level of evidence)
2B	3.23 Lung rehabilitation including muscle stretching and moderate-to-high intensity exercise training should best be given within 48 h after discharge from the hospital, and this should reduce the likelihood of hospitalization during the next episode of AEs compared with lung rehabilitation given immediately upon hospital admission. (A weak recommendation with a moderate level of evidence)
2B	3.24 A comprehensive COPD care plan given to patients with frequent exacerbations, inadequate quality of life, decreased exercise capacity, and frequent occurrence of symptoms is recommended. (A weak recommendation with a moderate level of evidence)

Abbreviations: AE, acute exacerbation; COPD, chronic obstructive pulmonary disease.

rate of patients who received mechanical ventilation due to COPD AEs was lower than that due to acute respiratory distress syndrome.¹⁹⁰ (Table 3, Recommendation 3.21)

- According to results from a recent RCT that enrolled COPD patients who were experiencing AEs, patients who received pulmonary rehabilitation showed a reduced risk of future AEs requiring hospitalization (OR = 0.22; 95% CI = 0.08 to 0.5).^{191,192} A subsequent subgroup analysis found that patients who participated in pulmonary rehabilitation within 48 h after discharge from the hospital had significantly lower risk of being re-hospitalized due to COPD AEs compared with those who had no pulmonary rehabilitation.^{193,194} In contrast, in-hospital pulmonary rehabilitation did not benefit COPD patients who were hospitalized for AEs compared with no pulmonary rehabilitation at all (Table 3, Recommendation 3.22–23).
- A Cochrane systematic review reported the clinical outcomes of COPD patients managed by an integrated program, and showed that COPD patients have significantly improved quality of life and physical capacity as evaluated using a 6 min walking test compared with controls.¹⁹⁵ However, recent research conducted in the primary care setting in the Netherlands did not find a statistically significant difference between integrated management programs and conventional care strategies in improving the quality of life of COPD patients. These results remain to be confirmed by future studies.¹⁹⁶ (Table 3, Recommendation 3.24)

COPD and COVID-19

There is currently no evidence to suggest patients with COPD are at higher risk of infection with SARS-CoV-2. However, they may be at increased risk of developing severe disease. Results from a meta-analysis indicated the pooled odds ratio of COPD and the development of severe

COVID-19 was 4.38 (Fixed effect model, 95% CI: 2.34–8.20), while the OR of ongoing smoking was 1.98 (Fixed effect model, 95% CI: 1.29–3.05).^{197,198} The latest GOLD 2021 report stated that COPD patients who developed moderate to severe COVID-19, should be treated with evolving pharmacotherapeutics approaches as appropriate, and should be monitored more frequently than the usual COPD patients with particular attention to the need for oxygen therapy.⁵ Patients who develop asymptomatic or mild COVID-19 should be followed with the usual COPD protocols. In the absence of supporting reference, the GOLD report recommend that COPD patients infected with COVID-19 should be treated with the same standard of care treatment as other COVID-19 patients. Detailed recommendation on management of patients with COPD and suspected or proven COVID-19, and guidance on remote COPD patient follow-up during COVID-19 pandemic restrictions can be found in the full 2021 GOLD report and the 2020 GOLD Science Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease.¹⁹⁹

Conclusion

This updated COPD practice guidelines covered a range of topics highlighted in the GOLD report including recent updates in diagnostic and therapeutic modalities for COPD and its acute exacerbation. Adjustments and modifications most suitable and applicable to the clinical setting in Taiwan as advised by the COPD writing group and the expert panel were discussed.

This revised guidelines and recommendations are applicable to the clinical settings in Taiwan. We expect this guideline to facilitate the diagnosis, treatment and management of patients with COPD by physicians and health care professionals in Taiwan. Adaptations of the materials included herein for educational and training purposes is encouraged.

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Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

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