The Saudi Thoracic Society Evidence-based guidelines for the diagnosis and management of chronic obstructive pulmonary disease

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Abstract:

The Saudi Thoracic Society (STS) developed an updated evidence-based guideline for diagnosing and managing chronic obstructive pulmonary disease (COPD) in Saudi Arabia. This guideline aims to provide a comprehensive and unbiased review of current evidence for assessing, diagnosing, and treating COPD. While epidemiological data on COPD in Saudi Arabia are limited, the STS panel believes that the prevalence is increasing due to rising rates of tobacco smoking. The key objectives of the guidelines are to facilitate accurate diagnosis of COPD, identify the risk for COPD exacerbations, and provide recommendations for relieving and reducing COPD symptoms in stable patients and during exacerbations. A unique aspect of this guideline is its simplified, practical approach to classifying patients into three classes based on symptom severity using the COPD Assessment Test and the risk of exacerbations and hospitalizations. The guideline provides the reader with an executive summary of recommended COPD treatments based on the best available evidence and also addresses other major aspects of COPD management and comorbidities. This guideline is primarily intended for use by internists and general practitioners in Saudi Arabia.

Keywords:

Chronic bronchitis, chronic obstructive pulmonary disease, emphysema, guidelines, Saudi Arabia

Executive summary

Question 1- should a long-acting muscarinic antagonist (LAMA) plus a long-acting beta2-adrenoceptor agonist (LABA) vs. LAMA alone be used in patients with stable chronic obstructive pulmonary disease (COPD)?

Recommendation:

1. In patients with stable COPD, the COPD Task Force suggests using LAMA plus LABA) over LAMA alone (Conditional recommendation, favours the intervention. Moderate certainty of the evidence)
2. Additional observation: The COPD Task Force suggests considering dual therapy with LAMA plus LABA for patients classified under COPD Class 2 and 3 (groups B and E).

Question 2: Should LAMA plus LABA plus an inhaled corticosteroid (ICS) vs. LABA plus LAMA be used in patients with stable COPD?

Recommendation:

1. In patients with stable COPD, the COPD Task Force suggests using triple therapy with LAMA plus LABA plus ICS over dual therapy with LABA plus

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LAMA (Conditional recommendation, favors the intervention. Moderate certainty of the evidence)
2. Additional observations: The COPD Task Force suggests using triple therapy with LAMA plus LABA plus ICS in patients with stable COPD and frequent exacerbations (2 or more exacerbation episodes, or one episode of hospitalization in the last year) (Class 3)(Group-E) or with elevated eosinophil counts (≥300 cells/μL)
3. In contrast, the COPD Task Force suggests using dual therapy with LABA plus LAMA in patients with stable COPD and low eosinophil counts.

Question 3: Should phosphodiesterase-4 (PDE4) inhibitors vs. no PDE4 inhibitors be used in patients with stable COPD?

Recommendation:
1. In patients with stable COPD, the COPD Task Force suggests using phosphodiesterase-4 (PDE4) inhibitors (Conditional recommendation, favours the intervention. Low certainty of the evidence)
2. Additional observation: The COPD Task Force suggests considering PDE4 inhibitors in particular in patients with chronic bronchitis or severe to very severe COPD with a history of exacerbations.

Question 4: Should mucolytic agents vs. placebo be used in patients with stable COPD?

Recommendation:
1. In patients with stable COPD, the COPD Task Force suggests adding mucolytic agents (Conditional recommendation, favours the intervention. Low certainty of the evidence)
2. **Additional observation:** The COPD Task Force suggests not using mucolytics as monotherapy.

Question 5: Should long-term oxygen therapy vs. no long-term oxygen therapy be used in subgroups of patients with stable COPD with moderate desaturation: (Not meeting the known criteria for oxygen indication):

Recommendation:
1. In subgroups of patients with stable COPD, particularly those who are mild to moderate hypoxemic or non-hypoxemic at rest, or have exercise-induced moderate desaturation, the COPD Task Force suggests not using long-term oxygen therapy (Conditional recommendation, favours the comparison. Very low certainty of the evidence)
2. Additional observations: Individual patient's factors including comorbidities should be considered when evaluating the patient's need for supplemental oxygen.

Question 6: Should shorter durations of ≤7 days of systemic corticosteroid treatment vs. longer treatments of >7 days be used in patients with an acute exacerbation of COPD (AECOPD)??

Recommendation:
1. In patients with an AECOPD, the COPD Task Force suggests using shorter durations of ≤7 days of systemic corticosteroid treatment over longer treatments of >7 days (Conditional recommendation, favours the intervention. Very low certainty of the evidence)
2. Additional observation: Long-term systemic corticosteroid use may be associated with serious side effects and/or sequelae (for example weight gain, increased risk of infection, adrenal insufficiency, osteoporosis, cataract, and/or aseptic joint necrosis).

Question 7: Should antimicrobial interventions vs. no antimicrobial interventions be used in patients with an acute exacerbation of COPD

Recommendation:
1. In patients with an AECOPD, the COPD Task Force suggests using antimicrobial interventions (Conditional recommendation, favours the intervention. Low certainty of the evidence)

Question 8: Should non-invasive ventilation vs. usual medical care be used in patients with an AECOPD and hypercapnic respiratory failure in the ward, High-Dependency Unit, or Intensive Therapy Unit?

Recommendation:
1. In patients with an acute exacerbation of COPD and hypercapnic respiratory failure, the COPD Task Force suggests using non-invasive ventilation in the ward, High-Dependency Unit, or Intensive Therapy Unit over usual care **(Conditional recommendation, favours the intervention. Very low certainty of the evidence)**.

Question 9: Should certain criteria to assess the suitability of and planning of home treatment or early discharge vs. no such criteria be used in patients with an acute exacerbation COPD?

Recommendation:
1. In patients with an AECOPD, the COPD Task Force suggests using certain criteria to assess the suitability of and planning of home treatment or early discharge **(Conditional recommendation, favors the intervention. Very low certainty of the evidence).**
2. Additional observations: The COPD Task Force suggests that before discharge the treating team should:

- Ensure that the patient is in a stable condition to be discharged home, with all comorbidities adequately managed and any laboratory and/or metabolic abnormalities corrected
- assess the patient's need for long-term oxygen therapy.
- Review with the patient all medication doses and durations, and the proper technique for using inhaler devices
- Give the patient a follow-up appointment within a few weeks
- Consider referring the patient to pulmonary rehabilitation.

Question 10: Should pulmonary rehabilitation vs. no pulmonary rehabilitation be used in patients with stable COPD?

Recommendation:

1. In patients with stable COPD, the COPD Task Force recommends using pulmonary rehabilitation **(Strong recommendation, favors the intervention. Moderate certainty of the evidence).**

Question 11: Should non-invasive ventilation vs. usual care be used in patients with stable COPD who have remained hypercapnic after an exacerbation?

Recommendation:

1. In patients with stable COPD who have remained hypercapnic after an exacerbation, the COPD Task Force suggests using non-invasive ventilation over usual care **(Conditional recommendation, favours the intervention. Very low certainty of the evidence).**
2. Additional observations:
   a. The COPD Task Force suggests considering non-invasive ventilation in patients who continue to experience hypercapnia two weeks after an exacerbation.
   b. While non-invasive ventilation is not appropriate in all patients, the Task Force highlights its potential to reduce hospital readmissions and mortality in this specific group of COPD patients.

Question 12: Should long-term prophylactic antibiotic therapy vs. no long-term prophylactic antibiotic therapy be used in patients with recurrent exacerbations of COPD?

Recommendation

1. In patients with recurrent exacerbations of COPD, the COPD Task Force suggests using long-term prophylactic antibiotic therapy **(Conditional recommendation, favours the intervention. Low certainty of the evidence).**
2. Additional observation: The COPD Task Force suggests considering an intermittent antibiotic approach (azithromycin 250 mg daily or 500 mg three times per week) in populations who have experienced one or more exacerbations and at least one hospitalization in the past year. Class 3 (Group E)

Introduction:

Chronic obstructive pulmonary disease (COPD) is a common noncommunicable disease characterized by persistent respiratory symptoms and airflow limitation, with a global prevalence ranging from 10.3% to 12.8%.[1]

COPD is among the leading causes of mortality worldwide and poses a significant economic burden.[2,3] The prevalence of COPD is projected to rise due to increasing smoking rates in low- and middle-income countries and aging populations in high-income countries.[2]

In Saudi Arabia, the overall prevalence of COPD is estimated at 4.2%, with a higher prevalence of 14.2% among current and former smokers.[4,5] Enhancing awareness, knowledge, and adherence to COPD guidelines among health-care providers in Saudi Arabia could improve the management and outcomes for COPD patients.[6-8]

Significant advancements have been made in COPD research and management since the publication of the previous Saudi Initiative for Chronic Airway Disease (SICAD) guidelines in 2014.[9] The current COPD guidelines aim to provide updated, evidence-based recommendations for managing stable and acute COPD exacerbations, reflecting the latest research and clinical practices.

Scope and Purpose

The Saudi Thoracic Society (STS) guidelines for the diagnosis and management of COPD aim to support pulmonologists, internists, family medicine practitioners, emergency medicine specialists, general practitioners, and their health-care teams in providing optimal care for patients with COPD. In addition, these guidelines seek to assist policymakers in clinical decision-making, improving patient outcomes, and efficiently allocating resources.

The current guidelines are designed to reflect the best practices in COPD management. However, they do not replace the clinician's decision-making capabilities in unique clinical situations involving COPD patients. Recognizing the importance of individualized care and shared decision-making, health-care professionals are encouraged to consider patients' preferences, values, and goals when implementing these recommendations. This approach ensures a patient-centered strategy in managing COPD.

Methods

A crucial aspect of the Saudi Ministry of Health (MoH) goal to achieve Vision 2030 is establishing a National Guidelines Program to ensure evidence-based clinical care for all diseases, including COPD. This guideline was developed through a collaborative effort between the MoH and the STS, involving a multidisciplinary group of 13 local experts. These experts were led by specialists who had previously contributed to the publication of the 2014 Saudi COPD guidelines.[9] The Elsevier Guidelines International team provided support to the COPD Task Force by gathering evidence and conducting a literature review.

At the outset of the guideline development process, the COPD Task Force members formulated a series of key questions to address various aspects of COPD diagnosis and treatment. Initially, 33 clinical questions were proposed, focusing on different facets of COPD management. These were then prioritized to 12 key questions, which served as a roadmap for the subsequent evidence search and synthesis. The expert panel thoroughly searched for relevant evidence from various sources, including published literature, existing guidelines, clinical trials, systematic reviews, and meta-analyses. The search process utilized established databases and incorporated input from experts in evidence grading.

The identified evidence was critically appraised and evaluated for its relevance, quality, and applicability to the clinical context. The expert panel carefully reviewed and analyzed the evidence, considering its strengths, limitations, and potential biases. Through a consensus-based approach, the panel synthesized the available evidence and formulated evidence-based recommendations. The discussions within the expert panel were structured and focused, with a balanced consideration of the available evidence, clinical expertise, and patient perspectives. Deliberations involved thorough evaluations of the benefits, risks, feasibility, and equity of various diagnostic and treatment approaches. The panel members engaged in constructive debates, allowing for the exploration of different viewpoints and the resolution of any discrepancies. The discussion also acknowledged the limitations of the evidence and potential areas for further research and refinement. Overall, the stringent review process, including the systematic evidence search and the collaborative efforts of the expert panel, ensures that these COPD guidelines are based on the best available evidence and expert consensus. To leverage recent high-quality efforts locally and internationally, the guideline development followed the Grading of Recommendations Assessment, Development, and Evaluation-ADOLOPMENT methodology, an internationally accepted approach for adopting, adapting, and creating new guidelines.[10]

In addition to the internal review process conducted by the expert panel, the guidelines underwent a crucial external review by three independent experts in COPD management. These reviewers were selected for their expertise and experience in the field. They were provided with the draft of the management guidelines and tasked with evaluating its content, methodology, and recommendations. The feedback and comments from these external reviewers were carefully considered and incorporated into the final version of the guidelines. This independent evaluation enhanced the overall robustness of the recommendations, increased the confidence in their applicability and relevance to clinical practice, and bolstered the credibility and reliability of the guidelines.

Moreover, the expert panel thoroughly reviewed and updated sections from the previous SICAD guidelines[9] that needed to be addressed by the current focused 12 questions on COPD management. These sections are epidemiology, diagnosis, clinical assessment of stable COPD patients, COPD exacerbation, addressing comorbidities, and other treatment strategies. The recommendations are summarized in the experts' executive summary.

The COPD Task Force adopted the same evidence criteria used in previous SICAD guidelines:

- Evidence Category A: Randomized controlled trials (RCTs) with a rich body of evidence
- Evidence Category B: RCTs with a limited body of evidence
- Evidence Category C: Nonrandomized trials and observational studies
- Evidence Category D: COPD Task Force consensus judgment.

Epidemiology

The pooled prevalence of COPD in the Eastern Mediterranean Region, based on a total of 92 studies, was 5.39%.[11] In the Middle East and North Africa (MENA) region, the pooled prevalence of COPD was 2.7% in the general population and 2.8% in hospital-based studies, with a higher frequency in men (5.2%) compared to women (1.8%).[12] COPD is one of the leading causes of death and disability in the MENA region, with hospitalizations being the most utilized health-care resource for this patient group.[13]

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region, with hospitalizations being the most utilized health-care resource for this patient group.[12]

The overall prevalence of COPD in Saudi Arabia among patients aged 40 years and older is 4.2%, with a higher prevalence in men (5.7%) compared to women (2.5%). The prevalence increases with age, reaching 11.4% in individuals aged 60 years and above, and 10.5% in those with a smoking history of over 20 pack-years.[4] In addition, the COPD prevalence among current or ex-smokers attending private primary health-care facilities in 2011 was reported to be 14.2%.[14] The intensive care unit (ICU) mortality rate for patients admitted with COPD exacerbation was 6%, while the hospital mortality rate was 11% in 2012.[15]

In general, the management of COPD faces several significant challenges:

1. Early diagnosis is crucial, as COPD often goes undetected in its initial stages
2. Appropriate treatment should be provided, including the proper use of medication devices
3. Patients' adherence to the prescribed COPD therapies must be ensured
4. Adherence to guidelines and access to specialized health care in COPD.

A study on managing COPD in the MENA region revealed that 31.8% of participants had received a COPD diagnosis from a physician, and only 20.6% had undergone spirometry in the previous year.[16] Furthermore, 15.7% reported receiving specific treatments for respiratory symptoms, 3.8% used inhaled long-acting bronchodilators together with corticosteroids, and 20.4% had been hospitalized overnight for their COPD, with a mean of 2.3 ± 3.7 hospitalizations per year.[16] A cross-sectional study in patients with severe COPD in the MENA region reported that 81.6% and 83.4% of patients experienced weekly and daily symptom variability, respectively. The number of exacerbations in the previous year, smoking cessation, and COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) D status were the most consistent factors associated with symptom variability.[17]

Patient adherence to COPD medication and inhaler technique has also been found to be suboptimal, with over 60% of Saudi patients reporting low medication adherence.[8] Over 70% of COPD patients make at least one critical error when demonstrating their inhaler technique, mainly when using dry powder inhalers.[7,18] A study on COPD medication adherence among Saudi and Turkish patients found an overall reported adherence of only 49%; of those, 74.7% reported high disease impact (COPD Assessment Test [CAT] >15) compared to 58.4% reporting medium–high adherence.[19]

Despite numerous high-quality, evidence-based guidelines published over the last decade, awareness of COPD guideline recommendations in Saudi Arabia remains insufficient.[8,20] In addition, the current secondary care services for COPD patients are limited, with many hospitals lacking respiratory departments, spirometry facilities, ICUs, and pulmonary rehabilitation programs.

Definitions of Chronic Obstructive Pulmonary Disease

COPD is a chronic lung disease that encompasses emphysema, chronic bronchitis, or a combination of both. Chronic bronchitis is defined by a chronic cough or expectoration lasting at least 3 months per year for 2 consecutive years. Emphysema, on the other hand, is a pathological condition marked by the permanent, destructive enlargement of airspaces distal to the terminal bronchioles, without prominent fibrosis.[9] COPD is characterized by chronic respiratory symptoms resulting from abnormalities in the airways or alveoli, leading to persistent and often progressive airflow obstruction. Patients with COPD commonly experience symptoms such as dyspnea, wheezing, chest tightness, fatigue, and cough, and they may suffer exacerbations marked by worsening symptoms triggered by factors such as respiratory infections and pollutants.[21] It is crucial to exclude other causes of chronic cough and expectoration, such as asthma or bronchiectasis.

Risk Factors

Cigarette smoking is by far the most significant risk factor for COPD.[21,22] Passive smoking and shisha (water pipe) smoking are other recognized risk factors for COPD.[23] Occupational exposure to organic or inorganic dust and heavy outdoor pollution are also notable risk factors.[22] In developing countries, the use of biomass fuel for indoor cooking with poor ventilation significantly exacerbates the risk of COPD.[24] Other major risk factors include male gender, advancing age, a history of airway diseases such as asthma and tuberculosis, HIV infection, recurrent childhood infections, and premature birth with underdeveloped lungs volumes.[21,25,26]

Epidemiological studies have demonstrated that lower socioeconomic status significantly increases the risk of developing COPD.[27] Furthermore, genetic and environmental factors may play a role in determining who develops the disease.[28]

Clinical Presentation

COPD should be considered in individuals aged 40 years and above who present with chronic cough, sputum production, or dyspnea during physical

exertion, especially if they have a history of smoking, are ex-smokers, or have been exposed to harmful particles. However, these symptoms alone are insufficient for accurately diagnosing airway obstruction; therefore, spirometry is essential for a definitive COPD diagnosis. The severity of symptoms directly correlates with the extent of smoking and lung function impairment, as measured by forced expiratory volume in 1 s (FEV1). Initially, shortness of breath occurs only during physical exertion, but as the disease progresses, it may be present even at rest. Coughing, typically accompanied by scanty sputum in the early stages, may become more frequent and produce larger volumes of sputum over time.[29,30]

Careful evaluation of COPD presentations is crucial to differentiate them from bronchiectasis, a common condition in Saudi Arabia.[31] Any changes in the amount or color of sputum in COPD patients may indicate an acute exacerbation and should be promptly recognized and treated to prevent a decline in clinical condition and lung function. Unlike asthma, audible wheezing is not a common presenting symptom in COPD.

Other symptoms of COPD include fatigue, loss of appetite, and weight loss, which typically manifest in the late stages of the disease and are associated with a poor prognosis, and increased risk of anxiety, depression, and disability.[32] Depression and anxiety are common in COPD patients and are linked to poor health status, more frequent exacerbations, and higher hospitalization rates.[33] Importantly, a normal physical examination does not exclude the presence of COPD, underscoring the need for thorough assessment and diagnostic testing.

In advanced cases of COPD, signs of lung hyperinflation and wheezing may only be audible during forced expiration. Severe and very severe chronic bronchitis can lead to ankle swelling due to right heart failure. Lower limb edema may indicate cor pulmonale, a recognized complication of severe COPD and chronic hypoxia. Clubbing is not typically associated with COPD, and its presence should raise suspicion for other conditions such as bronchiectasis, lung fibrosis, or lung cancer.

Recommendations

- The presence of cough, sputum production, dyspnea, and wheezing in an individual who is over 40 years of age and has a smoking history of more than 20 pack-years indicates a higher probability of having COPD (Evidence C).

Diagnostic Tools

Spirometry

Spirometry is essential for diagnosing COPD. It can be conveniently conducted in a clinic or as part of formal pulmonary function testing (PFT) in a laboratory. Handheld spirometry devices can serve as effective screening tools to measure spirometry parameters. However, if the results are abnormal, it is recommended to refer the patient for formal spirometry to confirm the diagnosis.

When spirometry is performed in a clinic, it is crucial to use a validated machine and ensure proper calibration according to the manufacturer's specifications when adhering to established procedural standards.[34] Given that spirometry results are effort-dependent, the best outcome from a minimum of three attempts should be selected to ensure accuracy.

It is recommended to evaluate reversibility by assessing the response to short-acting bronchodilators, if spirometry reveals a FEV1 to forced vital capacity (FVC) (FEV1/FVC ratio) of <70%. This can be achieved by administering a short-acting β2-adrenoceptor agonist, such as salbutamol (2 puffs of 100 μg/dose), or an anticholinergic, such as ipratropium bromide (2 puffs of 40 μg/dose), using a spacer device.

After administering salbutamol, spirometry should be performed 15–20 min later, while spirometry should be conducted 30 min after administering ipratropium bromide. Reversibility is defined as an improvement in FEV1 of at least 10% from the predose value, accompanied by an absolute increase in FEV1 of more than 200 ml.[34,35]

In COPD, PFT typically reveals airflow limitation, defined as a postbronchodilator FEV1/FVC ratio of <70%.[36] PFT also shows signs of air trapping and hyperinflation, indicated by elevated residual volume (RV) and total lung capacity (TLC), along with an increased RV/TLC ratio. Emphysema, characterized by the destruction of the lung parenchyma, is commonly associated with a reduction in diffusion capacity (DLco).[34]

Screening spirometry is not recommended for the general population, especially for individuals without symptoms or significant exposure to tobacco or other risk factors.[37-40] However, for those exhibiting symptoms or having risk factors such as a smoking history exceeding 20 pack-years, recurrent chest infections, or adverse early life events, spirometry is a valuable tool for early COPD detection.[21]

Recommendations

- Symptomatic individuals with risk factors such as a history of smoking and exposure to harmful particles should undergo spirometry testing (Evidence A)
- Handheld spirometry, which measures the ratio of FEV1 to FVC, can be utilized as a preliminary screening tool. If the results are abnormal, patients should be referred for formal PFT (Evidence D)

- In the appropriate clinical context and with exposure to risk factors, the presence of airflow limitation (FEV_1/FVC ratio <0.7 after bronchodilator use) confirms the diagnosis of COPD (Evidence A).

Screening and symptoms scoring questionnaires

Screening questionnaires can be valuable tools in diagnosing COPD, although they are not considered definitive diagnostic tests. They are typically designed to help identify individuals who are at a higher risk of having COPD and should be followed by additional diagnostic testing for confirmation.

There are a few commonly used self-administered screening questionnaires to detect COPD in primary and secondary care and the population for COPD. These questionnaires include CAT, COPD Diagnostic Questionnaire, International Primary Care Airways Group questionnaire, COPD Population Screener questionnaire, Lung Function Questionnaire, COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk, Dyspnea-12 (D-12) questionnaire, and PUMA questionnaire.[40-48] The PUMA questionnaire was developed for COPD detection in the primary care setting (PUMA Study) of four Latin American countries and has increased in popularity over the past few years. A PUMA score of ≥5 has a sensitivity of 74.2% and a specificity of 64.8% for diagnosing COPD.[46,47] All COPD screening questionnaires are easy to use; however, sensitivity and specificity values vary across populations, and the positive result needs to be confirmed by spirometry. Only CAT and D-12 are validated in the Arabic language.[45,49]

Recommendations

- Screening questionnaires for COPD are not definitive diagnostic tests. They can be valuable tools for screening and identifying individuals at a higher risk of COPD (Evidence C).

Chest radiography

The absence of abnormalities on a normal chest X-ray does not rule out the possibility of COPD. In more advanced cases, characteristic findings may include hyperinflation, diaphragmatic flattening, enlarged retrosternal airspace observed on the lateral view, and a tubular appearance of the heart. Occasionally, areas of increased lung transparency may be present. In addition, a chest X-ray can be valuable in excluding alternative conditions such as bronchiectasis, heart failure, lung fibrosis, and lung cancer.[21]

Recommendations

- Chest X-ray is not required for the diagnosis of COPD; however, it is valuable in excluding alternative conditions (Evidence C).

Chest computed tomography

Routine use of chest computed tomography (CT) is not recommended due to its cost and radiation hazards. However, high-resolution CT can be valuable in cases where there is uncertainty about the diagnosis of COPD, as it can confirm the condition or rule out other diseases like bronchiectasis, lung fibrosis, or lung cancer. CT imaging should be considered for patients with persistent exacerbations and symptoms that are disproportionate to the severity of the disease, especially if their FEV1 is below 45% of the predicted value and they exhibit significant hyperinflation and air trapping. In addition, patients who meet the criteria for lung cancer screening should also be considered for CT imaging.[21]

Recommendations

- CT chest should be considered in patients experiencing frequent exacerbations, exhibiting symptoms that are disproportionate to the severity of the disease, or meet the criteria for lung cancer screening (Evidence C).

Laboratory

Clinical evidence indicates that a higher eosinophil count in the blood is associated with an increased risk of future exacerbations in patients with a history of COPD exacerbations. These patients tend to respond better to treatment with inhaled corticosteroids (ICSs) in combination with long-acting bronchodilators. Therefore, blood eosinophil count serves as a potential biomarker for phenotyping COPD patients.[35,50] In addition, measuring alpha-1 antitrypsin (AAT) levels and conducting genetic testing should be considered for relatively young COPD patients with low smoking exposure to exclude the diagnosis of AAT deficiency.[51]

Recommendations

- Blood eosinophil count should be obtained as a biomarker for phenotyping COPD patients with exacerbations (Evidence B).

Chronic Obstructive Pulmonary Disease Assessment

COPD is a heterogeneous disease with diverse phenotypes, resulting in a wide range of clinical presentations. Some patients may predominantly experience symptoms such as dyspnea or a productive cough, while others face a higher risk of exacerbations. Therefore, it is crucial to conduct an individualized assessment of each patient's symptoms and identify those at greater risk of exacerbations during the initial evaluation. By considering these critical aspects, health-care providers can develop an effective management plan tailored to each patient's specific needs.

The comprehensive and personalized assessment for COPD should be based on the following components:

1. Confirming the diagnosis
2. Assessment of symptoms
3. Assessment of exacerbation risk
4. Classification of COPD based on the symptoms and risk of future exacerbations.

Confirming the diagnosis

Individuals aged 40 years and above who exhibit symptoms such as chronic cough, sputum production, or dyspnea during physical exertion should be evaluated for COPD, especially if they have a history of present or past smoking or exposure to harmful particles. The presence of these symptoms alone is not sufficient for a definitive diagnosis; therefore, spirometry is essential to accurately diagnose COPD and document its severity [Table 1].

Recommendations

- Spirometry is recommended to confirm the diagnosis and to assess severity of COPD (Evidence A)
- Airflow limitation (FEV_1/FVC) ratio of <70% after bronchodilator confirms the diagnosis of COPD (Evidence A).

Assessment of symptoms

The cardinal symptoms of COPD, including cough, sputum production, and dyspnea during exertion, should be thoroughly evaluated in all patients. It is recommended to use a validated tool for assessing the severity of dyspnea in patients with respiratory conditions, such as the COPD Modified Medical Research Council (mMRC) dyspnea scale [Table 2] or the CAT [Table 3] for an objective assessment of these symptoms.[48,52,53]

The CAT questionnaire comprehensively evaluates dyspnea and health status impairment in COPD patients and has been translated and validated in Arabic[49] [Figures 1 and 2]. Consisting of eight items rated on a Likert scale from 0 to 5, the CAT strongly correlates with the St. George's Respiratory Questionnaire, which measures health status. The CAT score ranges from 0 (completely asymptomatic) to 40 (extremely symptomatic) [Table 3]. A CAT score of ≥10 is associated with significantly impaired health status.[54]

Recommendations

- The severity of the symptoms based on CAT or mMRC score should be documented in patients with COPD (Evidence B).

Assessment of exacerbation risk

Exacerbations of COPD are marked by heightened inflammation in the airways and throughout the body, increased air trapping, hyperinflation, and reduced expiratory flow, leading to increased breathlessness and a decline in lung function.[55]

Table 1: Spirometry criteria for chronic obstructive pulmonary disease severity

Severity	Criteria
Mild	FEV_1 ≥80% predicted
Moderate	FEV_1 ≥50% and <80% predicted
Severe	FEV_1 ≥30% and <50% predicted
Very severe	FEV_1<30% predicted

FEV_1=Forced expiratory volume in 1 s

Table 2: Modified Medical Research Council dyspnea scale

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

mMRC=Modified Medical Research Council

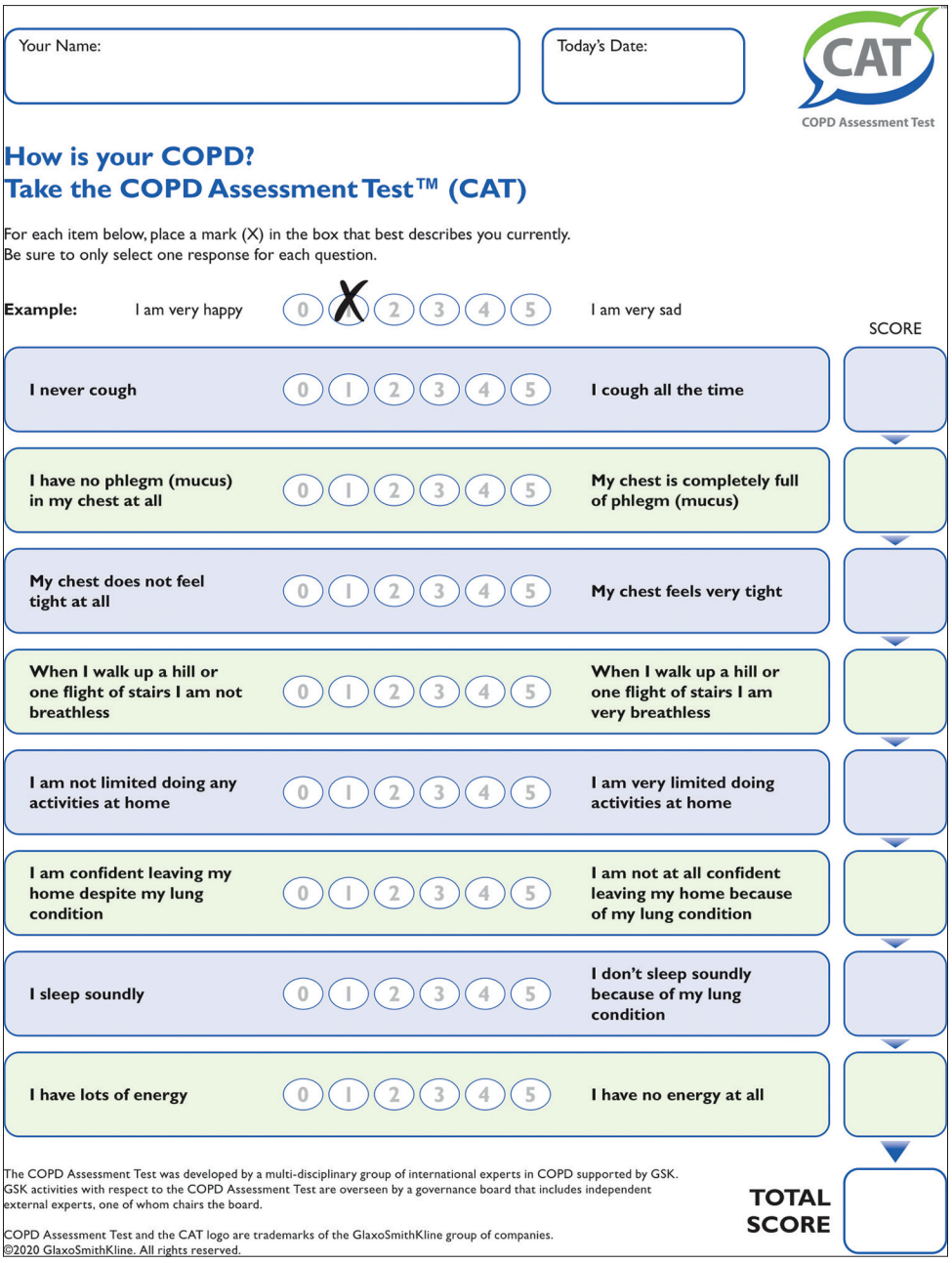
Table 3: Interpretation of the Chronic Obstructive Pulmonary Disease Assessment Test

Score of symptoms	Severity of symptoms
<10	Low
10–20	Medium
>20	High
>30	Very high

Various factors can trigger COPD exacerbations, including respiratory infections (both viral and bacterial), air pollution, exposure to irritants, and nonadherence to prescribed medications or treatment regimens. The definition of an exacerbation is complex; however, the most widely accepted criteria involve subjective elements such as increased dyspnea, cough, and sputum production beyond the patient's usual day-to-day variations.[56-58] These symptoms are nonspecific, making it essential to exclude other causes of acute dyspnea during the initial diagnosis of COPD exacerbations, as many COPD patients may have other chronic concomitant respiratory and nonrespiratory diseases.[58]

To assess the severity of COPD exacerbations, a recent proposal known as ROME recommends using specific measures such as a dyspnea visual score, respiratory rate, heart rate, resting room air oxygen saturation, and C-reactive protein (CRP) levels.[59] These objective criteria are crucial for evaluating the severity of exacerbations.[59]

An eosinophil count of more than 300 cells/μL in the blood is associated with an elevated risk of future exacerbations.[60-67] Recurrent COPD exacerbation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CAT
COPD Assessment Test

How is your COPD?
Take the COPD Assessment Test™ (CAT)

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

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

The COPD Assessment Test was developed by a multi-disciplinary group of international experts in COPD supported by GSK. GSK activities with respect to the COPD Assessment Test are overseen by a governance board that includes independent external experts, one of whom chairs the board.

Figure 1: English version of Chronic Obstructive Pulmonary Disease Assessment Test score[49]

is associated with a progressive decline in lung functions in approximately 25% of patients.[61,62] The average rate of recurrent exacerbation ranges from 0.5 to 3.5 per year.[63] Patients with two or more exacerbations per year tend to experience a more rapid decline in lung function, increased hospitalization, and increased risk of morbidity and mortality compared to those with infrequent exacerbations of <2 per year.[62,64] Studies have indicated that patients hospitalized for acute exacerbations of COPD (AECOPD) have a mortality rate of 25% and 65% at 1 year and 5 years, respectively.[62,65]

Furthermore, approximately 2%–19% of hospitalized patients with AECOPD require transfer to the ICU, with in-hospital mortality ranging from 12% to 25% and a readmission rate of 35% within 3 months.[62,66,67] Most of the patients admitted for COPD exacerbation typically have additional comorbidities. About 70% of readmissions following a hospitalization for exacerbation are due to the decompensation of these other medical conditions.[65]

Recommendations

- COPD exacerbation symptoms are nonspecific symptoms, and the initial diagnosis of COPD exacerbations should exclude other causes of acute symptoms as most of COPD patients have other chronic concomitant respiratory and nonrespiratory diseases (Evidence C)

Figure 2: Arabic version of Chronic Obstructive Pulmonary Disease Assessment Test score[49]

- Modified ROME [Figure 3] provides an objective criterion in evaluating the seriousness of COPD exacerbation (Evidence C)
- Eosinophil count should be obtained in patients with COPD exacerbation. It is helpful to phenotype patients who may respond to inhaled steroids (Evidence A)
- Risk of exacerbation should be documented in COPD patients based on the history of exacerbation or hospitalization due to COPD in the past year and symptoms severity CAT score (Evidence C)
- The risk of COPD exacerbation is defined as (Evidence A)
  - Low exacerbation risk (all the following should be fulfilled)
    1. At the most, one exacerbation in the past year
    2. No hospitalization due to COPD in the past year

- High exacerbation risk (one of the following should at least be fulfilled)
  1. Two or more exacerbations in the past year
  2. History of hospitalization due to COPD in the past year.

Chronic obstructive pulmonary disease classification

In 2014, the SICAD recommended three clinical classes for COPD by combining GOLD groups C and D.[9] The GOLD 2023 Report has further refined the ABCD assessment framework, introducing the ABE tool. This new approach merges the former C and D groups and places greater emphasis on the clinical impact of exacerbations, irrespective of symptom levels.[21,35]

In the current guidelines, the authors recommend three clinical classes for assessing symptoms and exacerbations in COPD patients [Table 4].

Recommendation

- Assessment of symptoms and exacerbations for COPD patients (Evidence D)
  - Class I (GOLD A)
    1. Less symptoms (CAT <10) or (mMRC 0–1)
    2. 0–1 exacerbation in the past year and no hospitalization
  - Class II (GOLD B)
    1. More symptoms (CAT ≥10) or mMRC ≥2
    2. 0–1 exacerbation in the past year and no hospitalization
  - Class III (GOLD E)
    1. At high risk of exacerbations regardless of symptoms
    2. ≥2 exacerbations in the past year and/or hospitalization.

Management of Chronic Obstructive Pulmonary Disease

Management of COPD is divided broadly into pharmacological and nonpharmacological treatment.

Pharmacological Therapy of Chronic Obstructive Pulmonary Disease

Pharmacological treatment for COPD focuses primarily on managing symptoms and preventing acute exacerbations. This approach aims to slow disease progression and reduce mortality. Inhaled therapy is the cornerstone of maintenance treatment for COPD and plays a crucial role in preventing exacerbations. These therapies improve airflow by altering smooth muscle tone, which enhances lung emptying and reduces hyperinflation at rest and during exercise. However, despite the symptomatic improvement, they do not change the progressive decline in FEV1 observed in COPD patients.[68-71]

Inhalation is the preferred route of administration, with various inhaler device options available in Saudi Arabia, including metered-dose inhalers, Evohaler, breath-actuated inhalers, and dry-powder inhalers. Nebulized bronchodilators may be beneficial for patients with poor inspiratory force and physical limitations that make them unable to use inhalers. However, due to cost and other practical concerns, regular use of nebulizers is generally not recommended. The medications available for treating COPD in the Saudi market are listed in Table 5.

Beta-2 agonists

The primary action of β2-agonists is to induce relaxation of airway smooth muscle by stimulating β2-adrenergic receptors and increasing the production of cyclic adenosine monophosphate (cAMP). Inhaled β2-agonists have a rapid onset of action, though this effect may be slower in COPD compared to asthma. These agents improve symptoms and FEV1.

The short-acting β2-agonists (SABAs) work within a few minutes, but the effects usually wear off within 4–6 h. SABA can be used on a regular and as-needed basis in COPD.[72-74] In contrast, LABAs have an effect lasting 12–24 h, allowing for once-daily or twice-daily dosing. LABA significantly improved FEV_1, lung volumes, dyspnea, quality of life (QoL), decreased exacerbation rate, and number of hospitalizations.[75-79] However, β2-agnostic therapies have not demonstrated an effect on mortality or the rate of decline in lung function over time.[78]

LABAs are recommended as maintenance therapy for COPD, as they are more effective and convenient than SABA treatment. The use of LABA should not preclude additional benefits from as-needed SABA.

Table 4: Saudi Thoracic Society guidelines chronic obstructive pulmonary disease classification: Assessment of symptoms and exacerbations

Class	Characteristics	CAT or mMRC score	Exacerbation in the past year	GOLD 2024 equivalent
I	Less symptoms: At low risk of exacerbation	CAT <10 or mMRC 1–2	0–1 and no hospitalization	Group A
II	More symptoms: At low risk of exacerbation	CAT ≥10 or mMRC≥2	0–1 and no hospitalization	Group B
III	At high risk of exacerbation regardless of symptoms	Any score	≥2 or ≥1 hospitalizations	Group E (C and D)

CAT=Chronic Obstructive Pulmonary Disease Assessment Test, mMRC=Modified Medical Research Council, GOLD=Global Initiative for Chronic Obstructive Lung Disease

Table 5: Medications used in the treatment of chronic obstructive pulmonary disease

Drug	Dose	Mode of administration
b2-agonists		
Short-acting b2-agonists		
Salbutamol	100, 200 µg	MDI
	5 mg/mL	Nebulizer solutation
Long-acting b2-agonists		
Unavailable as solo therapy in Saudi Arabia		
Anticholinergics		
Short acting anticholinergics		
Ipratropium bromide	20, 40 µg	MDI
	0.25–0.5 µg	Nebulizer solution
Long-acting anticholinergics		
Tiotropium	18 µg	DPI
	5 µg	DPI
Inhaled steroids		
Beclomethasone	50–400 µg	MDI, DPI
Budesonide	100, 200 µg	DPI
	0.25, 0.5 mg/mL	Nebulizer solution
Fluticasone propionate	50–500 µg	MDI, DPI
Ciclesonide	80–320 µg	MDI
Combination of long-acting b2-agonist and inhaled steroid		
Formoterol/budesonide	4.5/160 µg	DPI
Salmeterol/fluticasone	25/50, 25/125, 25/250 µg	MDI
	50/100, 50/250, 50/500 µg	DPI
Fluticasone furoate/vilanterol	100/25 µg	DPI
Beclometasone/formoterol	100/6 µg	MDI
Fluticasone propionate/formoterol fumerate	250/10 µg	MDI
Combination of long-acting b2-agonist and long acting anticholinergics		
Umeclidinium bromide and vilanterol	62.5/25 µg	DPI
Tiotropium/olodaterol	2.5/2.5 µg	Respimat
Glycopyrronium/indacaterol	110/50 µg	
Single inhaler triple therapy with ICSs, long-acting β2 agonist, and long-acting antimuscarinic agent		
Fluticasone furoate/umeclidinium bromide/vilanterol	100/62.5/25 µg	DPI
Formoterol fumarate/glycopyrronium bromide/budesonide	5/7.2/160 µg	MDI
Beclomethasone dipropionate/formoterol/glycopyrronium	87/5/9 µg	DPI
Methylxanthines		
Aminophylline	200–600 mg	Oral
Theophylline (SR)	100–600 mg	Oral
PDE4 inhibitors		
Roflumilast	500 µg	Oral
Systemic steroids		
Prednisolone/prednisone	5–60 mg	Oral

DPI=Dry powder inhaler, MDI=Metered-dose inhaler, ICSs=Inhaled corticosteroids, PDE4=Phosphodiesterase-4

The side effects are related to the stimulation of β2-adrenergic receptors that cause sinus tachycardia and rarely other cardiac rhythm abnormalities in susceptible patients. Symptomatic tremors may be troublesome in some older patients treated with high doses of β2-agonists. Hypokalemia can also occur, especially when treatment is combined with diuretics, and should be monitored in susceptible patients.[80] In general, β2-agonists are safe and well tolerated. The side effects are dose dependent and often resolve after treatment discontinuation.[81] However, COPD patients who are typically elderly and have cardiovascular comorbidities may be at a greater risk of developing clinically significant side effects.

Muscarinic antagonists

Antimuscarinic drugs, also known as anticholinergic medications, work by blocking the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors in airway smooth muscle.[82] The bronchodilation effect of a short-acting muscarinic antagonist (SAMA), such as inhaled ipratropium, can last up to 8 h. Long-acting muscarinic antagonists (LAMAs) have prolonged binding to M3 muscarinic receptors and faster dissociation

from M2 muscarinic receptors, thereby extending the bronchodilator effect. LAMAs are administered once or twice daily.[83-85]

Treatment with LAMA effectively reduces symptoms, improves QoL, and decreases exacerbations and hospitalizations at any stage in COPD patients.[85] Treatment with tiotropium is associated with reduced in mortality of COPD patients.[86] Moreover, treatment with LAMA improves the effectiveness of pulmonary rehabilitation. It may also reduce the rate of decline in lung function compared with a placebo in patients not on other maintenance drugs.[85-91] Clinical trials have shown greater protection from exacerbations for LAMA versus LABA treatment.[79,90,91]

A systematic review of RCTs concluded that ipratropium, a SAMA, provides the modest benefits over SABA in terms of lung function, health status, and the requirement for oral steroids.[89]

Anticholinergic drugs are generally safe, with dry mouth being the most common side effect. Although mild prostatic symptoms have been reported, no clear causal relationship has been established. In rare instances, the use of nebulized ipratropium with a facemask has been linked to the development of acute glaucoma.[92]

Recommendations

- The central role of bronchodilators in COPD is for symptom relief, rather than improving FEV_1 (Evidence A)
- Regular or as-needed SABA or SAMA provides relief of acute symptoms of COPD related to bronchospasm and improves FEV_1 (Evidence A)
- Regular treatment with LABAs is more effective and convenient compared to SABAs and has been shown to improve health status, QoL, and exercise tolerance in COPD patients (Evidence A)
- Regular treatment with LAMA as a monotherapy is better than LABA (Evidence A).

Combined bronchodilators

Combining bronchodilators with different mechanisms of action can provide greater bronchodilation than simply increasing the dose of a single bronchodilator.[93-95] Combinations of SABAs and SAMAs are superior to either medication alone in improving FEV1 and symptoms.[95-98] In addition, using a single inhaler therapy improves treatment adherence.[96]

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The COPD Task Force reviewed the evidence to determine whether combination therapy with LABAs and LAMAs is preferred over LAMA alone in patients with stable COPD. The review found little or no difference in the frequency of moderate or severe exacerbations (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.75–1.23) and (OR, 0.90; 95% CI, 0.59–1.36), respectively.[96-104] However, there were improvements in QoL (OR, 1.19; 95% CI, 1.04–1.35) and dyspnea index (OR, 0.21; 95% CI, 0.1–0.33).[92,97] LABA alone is not marketed in Saudi Arabia but is available in combination with LAMA.

Recommendations

- A combination of SABA and SAMA is superior to either in improving the symptoms and FEV_1 (Evidence A)
- Combined LABA/LAMA better than LABA or LAMA alone or LABA/ICS (Evidence A)
- A combination of LAMA and LABA preferably as a single inhaler is superior for symptomatic COPD patients (Evidence A).

Inhaled corticosteroids

The effects of oral and ICS in COPD are less well defined compared to their use in asthma. However, ICS may reduce COPD exacerbations, particularly in patients with high blood eosinophil count (>150 ells/μL) or overlap syndrome (OVS).[105] The use of ICS can increase the risk of pneumonia, so the benefits must be carefully weighed against risks such as pneumonia and fractures.[106-108]

Treatment with ICS alone does not significantly alter the long-term decline in FEV1 or mortality in patients with COPD.[109-112]

Inhaled corticosteroid and LABA combination

ICS and LABA combination reduces exacerbations compared to LABA alone, but not compared to LAMA. Furthermore, the LABA/LAMA combination significantly reduced exacerbations compared to ICS/LABA.[112-114] Clinical trials investigating ICS/LABA combinations in COPD patients failed to show a significant reduction in mortality as the primary outcome.[115-117]

Inhaled corticosteroid/LABA/long-acting muscarinic antagonist Triple Therapy

Triple therapy with ICS/LABA/LAMA is indicated for reducing exacerbations in patients not optimally controlled on dual bronchodilator therapy. The COPD Task Force reviewed the evidence and evaluated the effect of triple therapy in COPD. The rate of moderate-to-severe exacerbation reduction favored triple therapy (rate ratio [RR], 1.16; 95% CI, 1.11–1.20).[117-123] There was high certainty in the evidence

regarding the rate of severe exacerbations (RR, 1.22; 95% CI, 1.11–1.34).[121,122]

While the lack of a mortality benefit as the primary endpoint is an important consideration, two landmark studies showed a mortality advantage of triple therapy as a secondary endpoint.[121,122] A recent meta-analysis of 60 RCTs involving 103,034 COPD patients treated for more than 6 months concluded that inhaled therapy containing ICS, particularly triple therapy, was associated with reducing the all-cause mortality risk. Predictors of this association included eosinophil counts of ≥200/μL or a percentage of ≥2%, a history of ≥2 moderate or severe exacerbations in the previous year, COPD stages III or IV, age younger than 65 years, and a body mass index (BMI) of ≥25 kg/m².[117,122,123]

Recommendations

- Triple therapy (ICS/LABA/LAMA) is recommended for patients with a high risk of COPD exacerbation Class 3 (Group E) (Evidence A).

Phosphodiesterase-4 inhibitors (roflumilast)

Roflumilast, an oral PDE-4 inhibitor, is an anti-inflammatory drug that specifically inhibits the phosphodiesterase-4 enzyme responsible for breaking down intracellular cAMP. It has been approved for COPD patients with a chronic bronchitis phenotype who suffer from frequent exacerbations.

The COPD Task Force reviewed the evidence to determine the effects of phosphodiesterase-4 (PDE4) inhibitors in patients with stable COPD. Treatment with roflumilast was associated with a lower incidence of COPD exacerbations (OR, 0.78; 95% CI, 0.73–0.84), corresponding to 52 fewer events per 1000 patients. However, there was no significant effect on mortality (OR, 0.98; 95% CI, 0.77–1.24).[118,124-143]

The most common side effects of roflumilast include nausea, abdominal pain, diarrhea, reduced appetite, headache, and sleep disturbances. Most of these adverse effects improve over time. Mild weight reduction has also been reported.[144]

Recommendations

- Roflumilast is indicated in Class III COPD patients with chronic bronchitis phenotype (Evidence A).

Mucolytics

The regular use of mucolytics in COPD remains controversial. Mucolytics are often considered an "add-on" therapy for patients with severe COPD who have recurrent exacerbations and remain symptomatic despite maximum standard therapy.

The COPD Task Force reviewed the evidence to determine the efficacy of mucolytic agents in stable COPD patients. There was no effect on mortality (RR, 1.10; 95% CI, 0.56–2.16), FEV1 (MD, 0.05; 95% CI, 0.01–0.08), or St. George's Respiratory Questionnaire (−1.37; 95% CI, −2.85–0.11).[145-156] However, in a randomized, double-blind, placebo-controlled study, 1-year treatment with high-dose N-acetylcysteine (1200 mg/day) significantly improved small airway function and decreased frequency of exacerbations in stable COPD patients.[145]

Given that mucolytic agents are generally safe and well tolerated, the COPD Task Force concluded that, overall, the resources required for implementing the intervention of mucolytic agents in stable COPD resulted in negligible costs and potential savings and that cost-effectiveness probably favors the intervention.

Recommendations

- Mucolytics are not to be prescribed routinely for all patients with COPD (Evidence A)
- Mucolytics may be considered an "add-on" therapy in some selected patients of COPD who remain symptomatic despite maximum standard therapy (Evidence C).

Long-term prophylactic antibiotics

The prophylactic use of antibiotics is not routinely recommended for all patients with stable COPD, as the benefits do not always outweigh the risks. However, patients with severe COPD and frequent exacerbations, despite optimal treatment regimens, may benefit from macrolide prophylaxis.

The COPD Task Force reviewed the evidence on long-term prophylactic macrolide antibiotic therapy in patients with stable COPD and recurrent exacerbations. The review found a significant reduction in the number of exacerbations (OR, 0.57; 95% CI, 0.42–0.78), corresponding to 139 fewer events per 1000 patients.[157-164] Similarly, a Cochrane meta-analysis review of 2732 patients showed a reduction with macrolide exacerbations compared to placebo (OR 1.34, 95% CI, 1.19–1.50) with 127 fewer per 1000.[165]

For macrolide prophylaxis, azithromycin at a dose of 250–500 mg three times per week is recommended.[161,164] However, chronic use of azithromycin has been associated with adverse effects such as cardiovascular events, hearing loss, gastrointestinal symptoms, and mycobacterial resistance.[166,167] For macrolide prophylaxis, azithromycin at a dose of 250 daily or 500 mg three times per week is recommended.[160,163] However, chronic use of azithromycin has been associated with adverse effects such as cardiovascular events, hearing loss, gastrointestinal symptoms, and mycobacterial resistance.[165,166] Therefore, the benefits and risks of long-term azithromycin therapy must be carefully considered for each patient.

Recommendations

- Long-term prophylactic antibiotics are not recommended for all stable COPD patients (Evidence C)
- Consider an intermittent antibiotic approach (azithromycin 250 mg daily or 500 mg three times per week) in populations who have experienced one or more exacerbations and at least one hospitalization in the past year despite optimum therapy Class II (Group E) (Evidence A).

Biological therapies

Biological therapy has shown effectiveness in asthma management.[168] However, the impact of biologics on COPD outcomes has been inconsistent. Mepolizumab was evaluated in eosinophilic COPD patients in two trials.[169] Mepolizumab showed a slight reduction in moderate-to-severe exacerbations compared to a placebo. Benralizumab did not significantly reduce the COPD exacerbation rate compared to placebo.[170] On the other hand, dupilumab demonstrated a reduction in the annual rate of moderate-to-severe exacerbations and improved FEV1 in COPD patients with eosinophil counts >300 cells/μL and symptoms of chronic bronchitis.[171]

Recommendations

- Biological therapy may have potential benefits for a subset of COPD patients, but there is currently insufficient evidence to recommend their routine use (Evidence C)
- Dupilumab may have a potential role in eosinophilic COPD patients with chronic bronchitis phenotype and frequent exacerbations (Evidence B).

Nonpharmacological Therapy of Chronic Obstructive Pulmonary Disease

Smoking cessation

Smoking cessation has the most significant impact on the natural progression of COPD, slowing the accelerated decline in lung function and reducing mortality risk.[172-174] A study on smoking cessation among US adult smokers with and without COPD highlighted the essential benefits of reducing various health hazards associated with smoking.[173] The younger a smoker is when they quit, the more likely their rate of lung function decline will parallel that of nonsmokers.[175]

Quitting smoking is recommended at any age, as it can decrease COPD symptoms, reduce the number of exacerbations, and improve overall health status and exercise tolerance. Smoking cessation is one of the few interventions proven to decrease mortality in COPD patients, due to its beneficial effects on reducing the risks of lung cancer, cardiovascular disease, and other comorbid conditions.[176] The following strategies can help patients achieve their goal of quitting smoking.

Counseling

Obtaining a thorough smoking history from the patient and providing brief counseling by a health-care professional can result in quit rates ranging from 5% to 10%.[177] Tobacco dependence is a chronic condition, often requiring multiple attempts to quit successfully. More intensive interventions, however, can achieve long-term quit rates as high as 25%.[177] Combining a detailed smoking history with brief counseling, mindfulness-based therapy, and cognitive behavioral therapy acknowledges the chronic nature of tobacco dependence and can significantly support patients in their efforts to quit smoking.[178]

Pharmacological interventions

Pharmacological interventions are essential for smoking cessation in COPD patients. Nicotine replacement therapy (NRT) increases long-term quit rates and is more effective than placebo. However, NRT is contraindicated in patients with recent myocardial infarction, unstable angina, stroke, or untreated peptic ulcer disease. The most commonly used drugs for smoking cessation are varenicline and bupropion SR.[179,180] Varenicline is an effective partial agonist at nicotinic receptors,[181] while bupropion SR is an antidepressant that reduces withdrawal symptoms and cravings.[179] Combining different NRT forms or using varenicline with NRT can increase cessation rates.[179,180,182,183] Furthermore, professional counseling, group support, and pharmacotherapy significantly improve the success rate of smoking cessation efforts and slow the rate of decline of FEV1.[174,176,184]

Recommendations

- Smoking cessation is recommended at any age, as it improves health status and exercise tolerance and decreases COPD symptoms, exacerbations, and mortality. Quitting smoking is a crucial intervention that can provide significant benefits for COPD patients (Evidence A).

Long-term oxygen therapy

Approximately 7% of patients with moderate-to-severe COPD develop resting hypoxemia within 5 years.[185] The primary mechanisms leading to hypoxemia in COPD are ventilation–perfusion mismatch and destruction of the alveolar–capillary membrane due to emphysema. Pulmonary vasoconstriction occurs as a compensatory response to alveolar hypoxia. However, this ongoing vasoconstriction can result in pulmonary remodeling and pulmonary hypertension (PH), ultimately leading to right heart failure. Furthermore, persistent hypoxemia causes peripheral vasodilation, which triggers compensatory tachycardia and increased cardiac output to improve oxygen delivery. In addition, it may induce secondary erythrocytosis, increasing blood viscosity, leading

to muscle dysfunction, and causing neurocognitive impairment.[186]

These consequences contribute to increased hospitalization and increased mortality observed in COPD patients.[187] Strong evidence demonstrates that long-term oxygen therapy (LTOT) can improve survival and the QoL in COPD patients with significant hypoxemia.[188,189] LTOT is recommended when the patient's partial pressure of arterial oxygen (PaO_2) is <55 mmHg (<7.3 kPa), or the arterial oxygen saturation is <88% while breathing room air and in a stable clinical condition for at least 2 months with optimized medical therapy. LTOT is also indicated if the PaO_2 is between 55 and 60 mmHg (7.4–8 kPa) in a COPD patient with associated conditions such as cor pulmonale, peripheral edema, or a hematocrit of 55% or greater. In a randomized study, LTOT did not result in a longer time to death or first hospitalization or provided any sustained benefit concerning any of the other measured outcomes in stable COPD patients with moderate resting hypoxemia (arterial oxygen saturation 89%–93%).[190]

Although the supporting evidence is less robust, LTOT may also be considered for COPD patients with PaO_2 >60 mmHg (>8kPa) or arterial oxygen saturation > 88% who experience nocturnal hypoxemia or exercise-induced hypoxemia or in those with coexisting cardiovascular comorbidities.[186]

Once LTOT is initiated, it is recommended to regularly evaluate the patient at 3-month and 1-year intervals to optimize the oxygen prescription. The goal is maintaining a resting PaO_2 between 60 and 65 mmHg or an arterial oxygen saturation range of 88%–94%. The typical oxygen flow rate is 1–2.5 L/min, usually administered via nasal cannula, for a minimum of 18 h per day to achieve survival benefits. Home-based oxygen can be conveniently provided using an oxygen concentrator, and portable oxygen delivery systems are available for outdoor use.

Recommendations

- LTOT is recommended when the patient's PaO_2 is <55 mmHg (or <7.3 kPa) or PaO_2 is between 55 and 60 mmHg (7.4–8 kPa) and the patient has evidence of cor pulmonale, peripheral edema, or a hematocrit of 55% or higher in a stable clinical condition for at least 2 months with optimized medical therapy (Evidence A).

Noninvasive Ventilation

Noninvasive ventilation (NIV) provides ventilatory support to patients using a nasal or full facemask, eliminating the need for an endotracheal tube. The benefits of NIV in treating acute respiratory failure (ARF) due to COPD exacerbations and improving survival in COPD patients are well documented.[191-196]

A Cochrane review and meta-analysis did not find clear evidence of benefit from the long-term use of noninvasive positive pressure ventilation stable COPD patients.[191] However, more recent studies suggest that NIV may improve survival and QoL and reduce dyspnea in hypercapnic COPD patients, particularly when combined with pulmonary rehabilitation.[197] Despite these potential benefits, the overall certainty of the evidence on the outcomes of NIV for stable COPD patients with chronic respiratory failure remains low.[197]

The latest European Respiratory Society guidelines conclude that NIV may improve health outcomes in a subset of severe COPD patients with hypercapnia on maximal medical therapy, by targeting a reduction in carbon dioxide levels (PCO_2).[198] However, it is also important to consider the potential barriers and costs associated with NIV. Many insurers may not fully cover the cost of NIV, leading to high out-of-pocket costs for patients. This financial burden can limit accessibility. In addition, some patients struggle to tolerate NIV due to issues like claustrophobia or poor synchronization with the ventilation.[199]

High-flow nasal cannula (HFNC) is a respiratory support device used during the early, noninvasive management of ARF. Physiologically, HFNC has been shown to enhance oxygenation, promote alveolar recruitment, provide effective humidification and heating, facilitate secretion clearance, reduce dead space ventilation, and improve hypercapnia.[200,201] These combined benefits of HFNC can help prevent further deterioration of lung function and potentially avoid the need for endotracheal intubation in patients with ARF. Despite these results, little and limited evidence for improved clinical outcomes is currently available.[201,202]

Compared to NIV, HFNC has been associated with a higher reintubation rate and minimal impact on mortality.[201,202] While HFNC can slightly reduce the length of stay in the ICU and hospital, it offers only a modest increase in patient comfort compared to NIV. In addition, there is no significant difference between HFNC and NIV in terms of respiratory rate and gas exchange parameters.[202]

Recommendations

- NIV in the treatment of ARF due to COPD exacerbation is recommended (Evidence A)
- Based on the current evidence, the role of long-term NIV in stable COPD with chronic hypercapnic respiratory failure remains uncertain. NIV may be considered in a select group with severe COPD patients (Evidence C)

- Consider NIV in patients who experience hypercapnia 2 weeks after an exacerbation (Evidence B).

Vaccination

COPD exacerbations are associated with significant morbidity and mortality, leading to worsening airflow obstruction, increased hospitalizations, reduced QoL, accelerated disease progression, and even death. Notably, more than 70% of COPD exacerbations are triggered by infectious causes, with respiratory viruses identified in approximately 30% of cases.[203] Despite well-established recommendations for influenza and pneumococcal vaccinations in COPD patients, vaccination rates in this population remain suboptimal.[204]

Influenza vaccination has been shown to clearly reduce the risk of acute COPD exacerbations and may also help decrease hospitalizations and mortality in this patient population. Therefore, it is recommended that all COPD patients receive an annual influenza vaccination.[205]

The pneumococcal polysaccharide vaccine (PPSV23) has been shown to reduce the risk of pneumococcal pneumonia and invasive pneumococcal disease in COPD patients, particularly among smokers.[206,207] The pneumococcal 13-valent polysaccharide conjugate vaccine (PCV13) has proven effective in preventing vaccine-type pneumococcal bacteremia and nonbacteremic community-acquired pneumonia.[208] In one study, the protective effect of PCV13 was shown to last for 5 years.[207]

COVID-19 infection significantly increases the risk of COPD exacerbation, leading to higher complication rates and mortality.[209] Vaccination against COVID-19 is highly effective in preventing hospitalization and respiratory failure among COPD patients.[210]

Adults with chronic heart or lung disease compromised immune systems, and those living in long-term care facilities are at the highest risk for severe respiratory syncytial virus (RSV) illness.[211-213] Following the approval of RSV vaccines in the European Union, Canada, United States, United Kingdom, and Japan, the MoH in Saudi Arabia has approved the use of RSV vaccines for all individuals aged 60 years and older.

Herpes zoster (HZ) is a vaccine-preventable disease caused by the reactivation of latent varicella-zoster virus, which is present in >95% of adults ≥40 years of age.[214] In asthma and COPD, the risk of HZ infection increases by 24%–41% compared to the normal population.[215]

Recommendations

- All COPD patients should receive the annual influenza vaccine (Evidence A)
- All COPD patients should receive a pneumococcal vaccine (Evidence B)
- The RSV vaccine is recommended for all COPD patients >60 years of age (Evidence A)
- The COVID-19 vaccine is recommended for all COPD patients (Evidence C)
- The HZ vaccine is recommended for all COPD patients (Evidence C).

Pulmonary rehabilitation

Pulmonary rehabilitation is a multidisciplinary, individualized, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities.[216,217]

Pulmonary rehabilitation is an essential component of the comprehensive management strategy for patients with chronic lung diseases.[218] By addressing the functional and psychological challenges faced by these individuals, pulmonary rehabilitation aims to improve their overall well-being and QoL. The key objectives of pulmonary rehabilitation are to reduce symptoms, optimize functional status, increase participation in daily activities, and ultimately lower health-care costs by stabilizing or reversing the systemic effects of the chronic lung condition. Pulmonary rehabilitation, delivered as a supervised multidisciplinary program including exercise training, is one of the cornerstones in COPD management.[219,220]

Patients participating in pulmonary rehabilitation programs lasting 6–8 weeks experience significant improvements in symptoms, functional status, and QoL. Available evidence indicates that there are no additional benefits gained by extending the duration of these programs beyond 12 weeks.[221]

Pulmonary rehabilitation has demonstrated improvements in health-related QoL (HRQoL) and exercise capacity that are maintained for at least 12 months. However, there are no significant long-term effects on mortality.[222] Early pulmonary rehabilitation in patients hospitalized with a COPD exacerbation reduces the mortality, number of days in hospital, and number of readmissions.[223,224]

Patients with a high symptom burden and risk of COPD exacerbations (Class II and III Group B and E) should be referred to a well-structured pulmonary rehabilitation program. This evidence-based intervention should be tailored to the individual's specific COPD characteristics and any coexisting medical conditions. The rehabilitation program should incorporate patient-centered goal setting to ensure that it addresses each patient's unique needs and priorities.

Pulmonary rehabilitation remains significantly underresourced and underutilized across health-care systems. Despite its substantial clinical benefits, <5% of individuals with COPD who could potentially benefit from this intervention receive it.[225,226] In Saudi Arabia, the availability of pulmonary rehabilitation programs is limited in most hospitals. This lack of access to evidence-based, multidisciplinary therapy represents a significant gap and challenges in the comprehensive management of chronic respiratory diseases, which must be addressed to optimize patient outcomes.

Recommendations

- Pulmonary rehabilitation is recommended for COPD patients with an FEV_1 of at least 50% of the predicted value and those with moderate disease who have an FEV_1 between 50% and 80% of the predicted value (Evidence B)
- A typical pulmonary rehabilitation protocol is recommended to be at least three supervised visits per week over 8–12 weeks for approximately 20 visits (Evidence B)
- The COPD Task Force recommends early supervised pulmonary rehabilitation for patients hospitalized with COPD exacerbations (Evidence A)
- Pulmonary rehabilitation should be initiated during the hospital stay or within 4 weeks of discharge (Evidence A).

Lung volume reduction

Lung volume reduction surgery (LVRS) and bronchoscopic lung volume reduction (BLVR) with endobronchial valves can improve outcomes in appropriately selected COPD patients with emphysema phenotype. LVRS is reserved for highly selected patients with upper lobe predominant heterogeneous emphysema who do not improve significantly with a pulmonary rehabilitation program. It is contraindicated in very severely ill patients with either FEV_1 or diffusion lung capacity (DLCO) <20% of the predicted value.[227] Bronchoscopic techniques were introduced aiming at lung volume reduction by causing distal lung collapse via unidirectional valves or endobronchial glue.[228] Both techniques for lung volume reduction resulted in a clinically meaningful reduction in hyperinflation and similar improvements in patients with intact fissures.[229]

Recommendations

- LVRS is reserved for a highly selected small group of patients with upper lobe predominant heterogeneous emphysema who do not improve significantly from a pulmonary rehabilitation program (Evidence B)
- BLVR is an alternative procedure in patients without interlobar collateral ventilation (Evidence C).

Lung transplant

Lung transplantation is an option to increase the QoL and survival for highly selected patients with end-stage COPD, without obvious contraindications, when all possible treatments are optimized including optimal medication, O_2 therapy, NIV, controlling medical comorbidities, and pulmonary rehabilitation.[217]

COPD patients with clinical deterioration despite maximal treatment should be referred to a lung transplant center when the BODE score (BMI, obstruction, dyspnea, and exercise capacity) is 5 or higher, especially in the presence of frequent exacerbations, increase in BODE score >1 in the past 2 years, elevated pulmonary artery pressure, and an FEV_1 <25% predicted.[230]

The outcome of lung transplant for COPD is certainly acceptable and provides a better HRQoL and longer survival in most patients with a 5-year survival after transplantation of 70.4%.[231]

Recommendations

- Lung transplant should be considered for those with a high risk of death (>50%) due to COPD within 2 years if lung transplant is not performed and who have an FEV1 <25% of the predicted value, hypercapnia, associated PH, progressive deterioration, and frequent exacerbations (Evidence C).

Treatment for stable chronic obstructive pulmonary disease

The current management strategy for COPD primarily focuses on four key objectives:

- Controlling symptoms
- Preventing exacerbations
- Improving patients' QoL
- Reducing mortality.

In addition, health-care providers are recommended to focus on prevention, diagnosis, and appropriate treatment of any comorbidities associated with COPD, as these comorbidities are associated with higher risks of hospitalization and mortality.

Assessment of COPD patient includes using symptom scores (CAT or mMRC) to evaluate the severity of the patient's symptoms and inquiring about the history of exacerbations or hospitalizations in the past year, as shown in Table 4 and Figure 4. The treatment of COPD is stratified based on the COPD classification, as shown in Figure 5.

Class I (Group A)

Patients in this class are less symptomatic (CAT <10) and are at low risk of acute exacerbations or hospitalizations.

Recommendations

- First choice for COPD Class I: A short-acting bronchodilator such as SAMA or SABA on an as-needed basis (Evidence A)
- Second choice for COPD Class I: Combination of the two short-acting bronchodilators on as-needed basis (Evidence A)
- A long-acting bronchodilator is the preferred choice except in patients with very occasional breathlessness since LABA is not available in the Saudi market, we recommend LAMA (Evidence A)
- Short-acting bronchodilators on an as-needed basis are recommended with LAMA (Evidence B).

Class II (Group B)

Patients in this group are symptomatic with minimal exacerbations over the last year. In such individuals, symptom control is more appropriate and hence they would need more potent long-acting bronchodilators. It has been shown that LABA/LAMA is superior to LAMA in controlling the patient's symptoms.[232]

Recommendations

- Dual therapy with LAMA/LABA for Class II (Group B) (Evidence A)
- Other options include LAMA alone in COPD with no exacerbation. LABA alone is not available in Saudi Arabia and hence the task force cannot recommend it (Evidence A)
- Short-acting bronchodilators on an as-needed basis are recommended (Evidence B).

Class III (Group E)

In this group, patients have a high risk for recurrent exacerbation with 2 or more moderate exacerbations over the past year or one hospitalization due to AECOPD regardless of their symptom burden. The treatment strategy here is focused primarily on reducing exacerbation risk.

Recommendations

- Triple therapy with LAMA/LABA/ICS is recommended in COPD patients with eosinophil counts ≥300 cells/μL

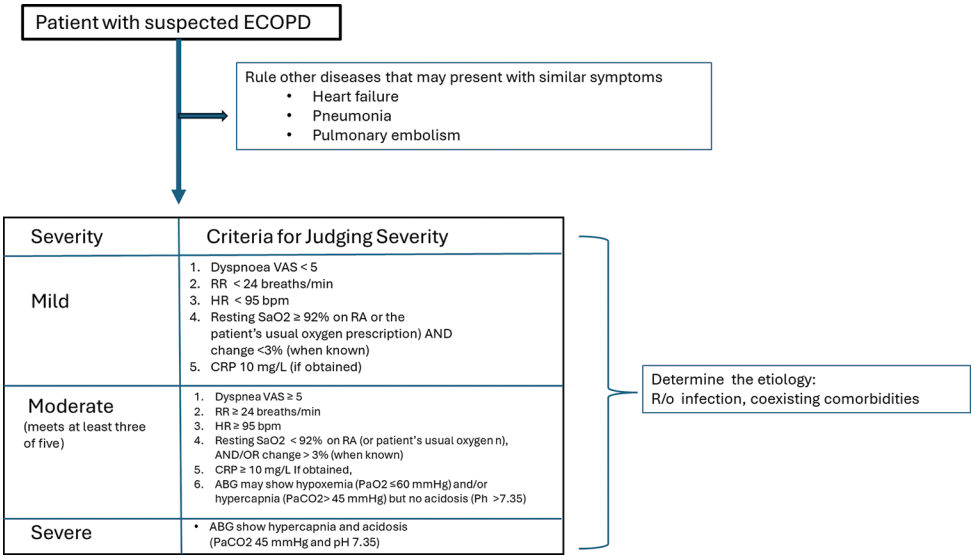

Figure 3: Diagnostic approach to a patient suspected of an exacerbation of chronic obstructive pulmonary disease. Modified from MacLeod *et al*.[59] VAS = Visual Assessment Score, CRP = C-reactive protein, ECOPD = Exacerbation of chronic obstructive pulmonary disease, HR = Hear rate, RR = Respiratory rate

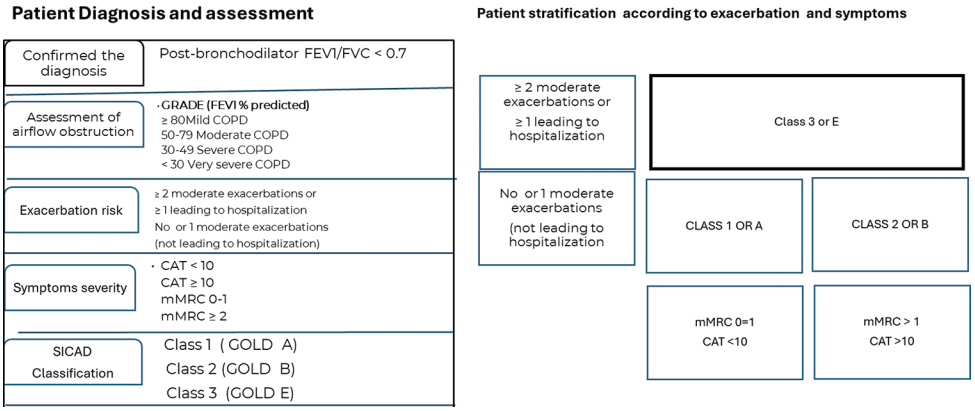

Figure 4: Classification based on diagnosis, assessment, and patient stratification

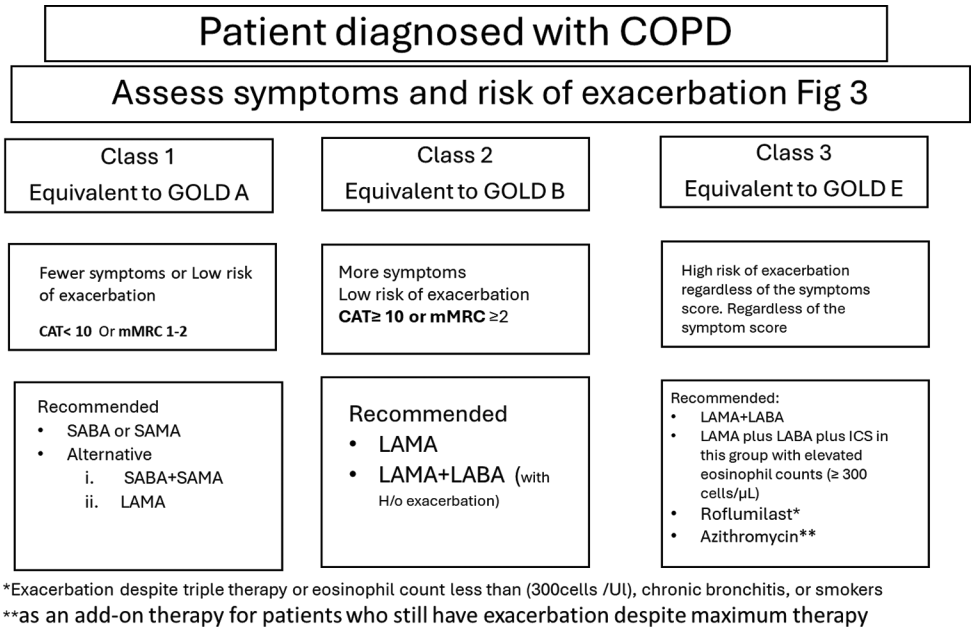

Figure 5: Algorithm for pharmacological treatment of stable chronic obstructive pulmonary disease. COPD = Chronic obstructive pulmonary disease, GOLD = Global Initiative for Chronic Obstructive Lung Disease, CAT = COPD Assessment Test, SABA = Short-acting β2-agonist, SAMA = Short-acting muscarinic antagonist, LABA = Long-acting beta agonist, LAMA = Long-acting muscarinic antagonist, mMRC = Modified Medical Research Council

- Dual therapy with LABA/LAMA is recommended in COPD patients with eosinophil counts <300 cells/μL (Evidence A)
- Phosphodiesterase-4 inhibitor (roflumilast) is recommended as an add-on therapy for patients who still have exacerbations despite triple therapy or eosinophil count <300 cells/μL and have chronic bronchitis phenotype (Evidence A)
- Maintenance azithromycin (250 mg daily or 500 mg three times per week) may be considered an add-on therapy for patients who still have exacerbations despite maximum therapy and low risk of side effects (Evidence A)
- Dupilumab may have potential benefits in a subset of COPD patients, but there is currently insufficient evidence to routinely recommend its use (Evidence C).

Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

The goals of treatment for AECOPD are to minimize the negative impact of the current exacerbation and prevent the development of future exacerbation. Management of the patient as an outpatient or need for hospitalization depends on the severity of the exacerbation and the severity of the underlying COPD and coexisting comorbidities.[233]

The main causes of hospital admission secondary to AECOPD are ARF with respiratory acidosis and hypercapnia, severe hypoxia, confusion or drowsiness, failure to respond to initial therapy, or uncontrolled coexisting comorbidities such as pneumonia, sepsis or heart failure.

Systemic steroids

Intravenous methylprednisolone or oral prednisolone should be routinely used for moderately severe or severe AECOPD. Studies have confirmed their efficacy in acute exacerbations, with a more rapid improvement of FEV_1 and shorter hospital stays. Oral corticosteroids are equally efficacious as intravenous corticosteroids for the treatment of most exacerbations of COPD.[234] The dose of systemic corticosteroids for treating a COPD exacerbation ranges from prednisone 30–60 mg once daily to methylprednisolone 60–125 mg 2–4 times daily.[235-238]

The COPD Task Force reviewed the evidence to determine the efficacy of shorter duration (i.e., ≤7 days) of corticosteroid treatment. Short duration of corticosteroid treatment has shown a noninferiority compared to longer duration (>7 days) in moderate-to-severe AECOPD and may lead to considerably better outcomes in milder exacerbations.[239-242] Long-term corticosteroid use may be associated with serious side effects, such as weight gain, hyperglycemia, increased risk of infection, adrenal insufficiency, osteoporosis, cataract, and/or aseptic joint necrosis.[243]

Recommendations

- Systemic steroids should be routinely used for moderately severe or severe AECOPD (Evidence A)
- The COPD Task Force suggests using shorter durations (5–7 days) of corticosteroid over a longer treatment (>7 days) (Evidence B)

Antimicrobial therapies

Approximately one-third of the exacerbations are associated with a viral infection. Bacterial colonization is reported in 20%–30% of cases during remissions and increases to 30%–50% during exacerbations. The COPD Task Force reviewed the evidence for antimicrobial intervention in AECOPD. The use of antibiotics for AECOPD is associated with a statistically significant[244,245] reduction in all-cause mortality, symptoms (dyspnea and cough), time to clinical cure, and improvement in infection cure rate.[246-253]

The usual organisms are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Branhamella catarrhalis*. *Pseudomonas aeruginosa* is occasionally present in severe or long-standing COPD. The following antibiotics are useful in COPD exacerbation: second-generation cephalosporins, amoxicillin–clavulanate, macrolide, quinolones such as moxifloxacin or levofloxacin, and doxycycline.[244,245,254-256]

Recommendations

- In patients with AECOPD, the COPD Task Force suggests using antimicrobial interventions (Evidence B).

Noninvasive ventilation

The COPD Task Force reviewed the evidence for utilization of NIV in patients with AECOPD. NIV is associated with a significant reduction in mortality, the need for endotracheal intubation, and hospital length of stay.[192-195,257-259]

Recommendations

- In patients with AECOPD and hypercapnic respiratory failure, the COPD Task Force suggests using NIV in the ward, high-dependency unit, or intensive therapy unit (Evidence B).

Discharge postacute exacerbations of chronic obstructive pulmonary disease

Four RCTs, one systematic review, and one meta-analysis were identified that compared the effects of using specific criteria to assess the suitability of patients for early discharge and planning for home treatment versus not using such criteria in patients with acute COPD exacerbations.[260-265]

The COPD Task Force reviewed the evidence using certain criteria to assess the suitability of and planning for home treatment or early discharge after AECOPD. The evidence indicates that using such criteria can impact mortality (RR, 0.76; 95% CI, 0.39–1.49) and reduce readmissions, including patients returning to the hospital within 2–6 months (RR, 0.72; 95% CI, 0.56–0.94).[260,262-265]

After stabilization of a patient post-AECOPD, the treating team should ensure the following:

- The patient is in a stable condition to be discharged home
- All comorbidities are adequately managed
- All laboratory and/or metabolic abnormalities corrected
- Assess the patient's need for long-term oxygen
- Review with the patient all medication doses and durations and the proper technique for using inhaler devices
- Give the patient a follow-up appointment within 2–4 weeks
- Consider referring the patient to pulmonary rehabilitation
- Assess the patient's need for home NIV.

Recommendations

- The COPD Task Force suggests using certain criteria to assess the suitability of and planning of home treatment or early discharge after AECOPD (Evidence C).

Systemic Effects of Chronic Obstructive Pulmonary Disease and Comorbidities

COPD is associated with low-grade, systemic inflammation with neutrophil elastase believed to be a key mediator of this process. This is evidenced by increased levels of various systemic inflammatory markers, such as leukocytosis, increased fibrinogen, and elevated CRP. Higher levels of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are also recognized in COPD patients.[266] The intensity of this systemic inflammation tends to increase during COPD exacerbations.[267]

Emerging evidence suggests that proinflammatory cytokines, particularly TNF-α, may be a driving force behind the pathogenesis of COPD.[268] However, the roles of inflammation and these proinflammatory cytokines may extend beyond the lungs, potentially contributing to the systemic effects of the disease and its associated comorbidities. This chronic, low-grade inflammation has also been implicated in contributing to several complications and comorbidities related to COPD, including weight loss, skeletal muscle dysfunction and wasting, cardiovascular disease, and depression.[267,269,270]

Sleep and chronic obstructive pulmonary disease

The interaction between sleep disorders and COPD is multifactorial and has a complex pathogenesis.[271,272] Epidemiological studies have estimated that the prevalence of various sleep disorders, including insomnia, restless leg syndrome, and sleep-disordered breathing, ranges from 34% to 78% among patients diagnosed with COPD.[273,274] The wide range of reported prevalence rates may reflect differences in study methodologies,

diagnostic criteria, and patient populations examined. Nonetheless, these findings underscore the high comorbidity of sleep disorders in the context of COPD, which has important implications for the comprehensive management of this patient group. Furthermore, the presence of sleep disorders in COPD patients may have a more deleterious impact on their health outcomes.

Physicians should be aware of the comorbid relationship between those two conditions and develop targeted interventions to optimize the management of patients afflicted by both sleep disorders and COPD.[275]

Overlap syndrome

OVS is characterized by the coexistence of obstructive sleep apnea (OSA) and COPD. In the general population, the prevalence of OVS falls within the range of 1%–3.6%. In patients with OSA, the prevalence of OVS falls between 7% and 55%.[276]

Patients with OVS experience more significant oxygen desaturation and are more prone to developing hypercapnia and PH, compared to COPD patients without concurrent OSA, despite similar degrees of airflow obstruction.[268,269] Furthermore, OVS is associated with an increased risk of COPD exacerbations, hospitalizations, and mortality.[277] Importantly, the treatment with continuous positive airway pressure (CPAP) has been shown to improve survival and decrease hospitalizations in patients with OVS and COPD.[278]

Clinicians should have a high level of suspicion for the coexistence of OSA (OVS) or obesity hypoventilation syndrome in COPD patients who exhibit the following characteristics:

a. Significant hypoxemia or hypercapnia disproportionate to the degree of airflow limitation
b. Presence of PH
c. Complaints of daytime sleepiness
d. Symptoms of sleep-disordered breathing, such as snoring, in the presence of a high BMI, need referral for a sleep study to evaluate for the presence of OSA syndrome (OVS).

Recommendations

- A comprehensive and multidisciplinary approach to the screening, diagnosis, and management of the OVS syndrome is recommended to optimize clinical outcomes for this high-risk patient group (Evidence B).

Lung cancer

Lung cancer is a major cause of death in COPD patients; COPD patients have a 3–4-fold increased risk of developing lung cancer when compared to smokers without COPD. The presence of COPD, especially severe COPD, is an independent risk factor for lung cancer.[279-281] Smoking cessation is the most effective measure to reduce lung cancer mortality.[176] Several studies have shown that lung cancer screening with low-dose CT scans can detect early-stage lung cancers in COPD patients and reduce lung cancer mortality in this high-risk group.[282-284] The GOLD guidelines recommend annual lung cancer screening with low-dose CT for COPD patients aged 55–80 years who have a ≥30 pack-years smoking history.[285] The US Preventive Services Task Force also recommends annual lung cancer screening with low-dose CT for adults aged 50–80 years who have a ≥20 pack-year smoking history and currently smoke or have quit within the past 15 years.[286] Many national and international guidelines specifically call out COPD as a high-risk condition that warrants lung cancer screening, often with eligibility criteria that are less stringent compared to the general population.[287-291]

Recommendations

- Annual lung cancer screening with low-dose CT for COPD for patients aged 55–80 years who have a ≥ 30 pack-year smoking history (Evidence B).

Cardiovascular diseases

COPD and heart failure share certain common risk factors, including cigarette smoking, advanced age, and systemic inflammation.[292]

The prevalence of COPD among individuals with heart failure ranges from 20 to 32%, and approximately 10% of hospitalized heart failure patients have concurrent COPD. Furthermore, heart failure is prevalent in more than 20% of patients with COPD and the risk of developing heart failure is 4.5 times higher in COPD patients compared to individuals without COPD. Finally, the prevalence of heart failure is three times greater among patients discharged from the hospital with COPD.[292-297]

The coexistence of heart failure and COPD in the same patient can present a significant diagnostic challenge, as the clinical symptoms and signs of these two common conditions often overlap. The use of biomarkers, like B-type natriuretic peptide (BNP), can help differentiate COPD exacerbations from heart failure episodes.[295,298]

Clinicians are encouraged to employ a combination of clinical assessment, spirometry, and echocardiography findings to accurately distinguish between these two conditions in patients suspected of having both.

Importantly, the use of beta-blockers for the treatment of heart failure appears to be safe and well tolerated in patients with coexisting COPD. Studies have suggested that beta-blocker therapy in this patient population may decrease the risk of COPD exacerbations, hospitalizations, and all-cause mortality.[299,300]

COPD patients have a significantly increased risk of ischemic heart disease given the common risk factors both conditions share. The mortality from myocardial infarction is more common in patients with frequent COPD exacerbations and worse lung function.[296,301-303]

PH in COPD is primarily driven by chronic hypoxia, leading to vasoconstriction, vascular remodeling, and increased pulmonary artery pressure. The incidence of PH in COPD patients varies widely, ranging from 6% to 60% of individuals, depending on the severity of their COPD and the diagnostic criteria used. However, most cases involve mild-to-moderate PH, with only 1%–3.7% experiencing severe PH.[304-307] COPD patients with hypoxia that is disproportionate to the degree of their airway obstruction should be screened for PH using transthoracic echocardiogram. Treatment for PH primarily involves managing COPD, including the use of oxygen supplementation.

COPD patients with severe PH should be referred to expert centers for further assessment, as routine use of PH target therapy in this group of patients is discouraged because of lack of efficacy and potential side effects.[308,309]

Finally, COPD patients have a higher risk of arrhythmias, particularly atrial fibrillation which is associated with lower FEV1.[310] Arrhythmias do not alter the treatment of COPD, though caution is advised when high-dose B2 agonist is used, especially during AECOPD.[311]

Recommendations

- Clinicians are encouraged to use a combination of clinical assessment, spirometry, and echocardiography findings to accurately distinguish between COPD and heart failure, as the symptoms and signs of these two conditions often overlap (Evidence C)
- The use of biomarkers like BNP can help differentiate COPD exacerbations from heart failure episodes (Evidence B)
- The use of beta-blockers for the treatment of heart failure appears to be safe and well tolerated in patients with coexisting COPD (Evidence C)
- COPD patients with hypoxia out of proportion to the degree of their airway obstruction should be screened for PH (Evidence B).

Nutrition

Malnutrition is a significant problem in COPD patients. The estimated prevalence of malnutrition and underweight is around 25%–40%, and 35% have a severely low fat-free mass index.[312] The studies revealed that patients who are underweight or lose weight during hospitalization due to COPD exacerbation are at high risk for future COPD exacerbations.[313,314] Studies also found a strong association between body weight, COPD events, and risk of death.[315,316] Malnourished COPD patients who received nutritional supplementation had significantly better respiratory muscle strength, but there was no significant improvement in the HRQoL or dyspnea.[312,317] The long-term benefit of supplementary nutrition needs further study, addressing underweight and weight loss in this patient population, and is yet to be determined.[317-319]

Recommendations

- Regular nutritional screening and supplementation for COPD patients are recommended, as malnutrition is prevalent and can increase the risk of exacerbations (Evidence C).

Vitamin D and osteoporosis

Vitamin D insufficiency and osteoporosis appear to be common problems affecting populations globally, even in sunny regions like Saudi Arabia.[320-323] Studies have linked Vitamin D deficiency to increased respiratory symptoms, decreased functional status, increased frequency of severe exacerbations, airway wall thickening on chest CT scans, and declines in lung function in COPD patients.[324,325] Vitamin D deficiency is also closely associated with the high prevalence of osteoporosis, which is particularly common in older COPD patients and those on chronic steroid therapy.[326] The factors leading to osteoporosis in COPD patients include systemic inflammation, corticosteroid use, Vitamin D deficiency, physical inactivity, tobacco exposure, lower bone mineral density, hypogonadism, hypoxia, sedentary lifestyle, and weight loss.[327-329]

Osteoporosis is considered one of the major systemic comorbidities of COPD. While the causal relationship and molecular link between COPD and osteoporosis are not fully established, recent epidemiological data found that osteoporosis is highly prevalent in COPD patients.[327,330] There is no clear evidence that Vitamin D supplementation has a beneficial impact on exacerbations in unselected patient populations.[331] However, studies about Vitamin D supplementation showed conflicting results in reducing COPD exacerbation rates in patients with low baseline Vitamin D levels.[332,333]

Recent endocrine society recommends against routine 25(OH)D testing for the general population aged 50–74 years.[334] Given the higher prevalence of osteoporosis in the Saudi population compared to Western countries and the increased risk of osteoporosis and osteopenia in COPD patients, Vitamin D level measurements and screening for osteoporosis should be considered in high-risk patients.

Recommendations

- For COPD patients with risk factors for osteoporosis, we recommend measuring 25-hydroxyvitamin

D levels and performing dual-energy X-ray absorptiometry scans (Evidence C)
- Vitamin D supplementation is not routinely recommended for patient with COPD; however, Vitamin D deficiency should be identified and treated (Evidence C).

Depression and anxiety

Depression and anxiety are common comorbidities experienced by COPD patients. Studies estimate that up to 40% of COPD patients also suffer from clinical depression,[335,336] and a similar proportion experience clinically significant anxiety.[337,338] The burden of COPD, including breathlessness, activity limitations, and fear of exacerbations, can contribute to the development of mood disorders in this population.[339-341] Furthermore, depression and anxiety in COPD patients are associated with poorer treatment adherence, more frequent hospitalizations, and decreased QoL.[339,342]

Effectively screening for and managing these mental health conditions is an important part of comprehensive COPD care. Strategies may include counseling, support groups, and appropriate pharmacological interventions.[343] Addressing the psychological impacts of COPD can help improve overall health outcomes for this vulnerable patient population.

Recommendation

- COPD Task Force recommends regular screening and management of depression and anxiety should be an integral part of comprehensive COPD care (Evidence B).

Surgery in chronic obstructive pulmonary disease

Surgery and general anesthesia are generally not contraindicated in patients with COPD. However, the risk of postoperative complications is higher in COPD patients compared to healthy individuals, and the specific surgical site plays a significant role during the postoperative period. Upper abdominal and thoracic surgeries have more postoperative complications compared to lower abdominal surgeries.[344-346] Other important risk factors for postoperative complications include active smoking, the presence of bronchospasm, excessive secretions, and severity and class of COPD.

Patients with COPD undergoing surgery must be carefully assessed for symptoms of ongoing infection, bronchospasm, smoking, and the site of surgery. Comorbidity risks that need to be assessed include hypoxia, hypercapnia, risk for thromboembolism, PH, and associated cardiac comorbidities, such as coronary artery disease and heart failure.

Postlung resection pulmonary complications are unpredictable.[347] The individual patient's risk factors should be identified for lung resection procedures through a comprehensive clinical history, physical examination, chest imaging, and pulmonary function tests.[348,349]

COPD patients at high risk for surgical complications due to poor lung function should undergo further assessment, such as diffusion capacity (DLco), regional perfusion distribution using ventilation-perfusion scans, and evaluation of exercise capacity.[348,349]

Before any elective surgery, COPD patients should be advised to stop smoking for at least 6–8 weeks and receive maximal therapy for their COPD, including pulmonary rehabilitation.[350] Furthermore, early mobilization, chest physiotherapy, and incentive spirometry may help reduce postoperative complications in this patient population.[351]

Recommendations

- The COPD Task Force recommends the following measures for COPD patients undergoing elective surgery
  - Comprehensive evaluation before surgery including clinical history, physical examination, chest radiography, and pulmonary function tests (Evidence C)
  - COPD patients should be advised to abstain from smoking for at least 6–8 weeks and receive optimal treatment for their COPD, including pulmonary rehabilitation (Evidence C)
  - Quantitative ventilation–perfusion lung scan to assess predicted postoperative lung function should be considered in COPD patients going for lung resection (Evidence C)
  - Early mobilization, chest physiotherapy, and incentive spirometry may help reduce the risk of postoperative complications in this patient population (Evidence C).

Air travel

Compared to healthy individuals, patients with moderate-to-severe COPD patients are at risk of developing potentially serious oxygen desaturation during long commercial flights.[352] However, air travel is generally safe for most patients with chronic respiratory failure who are provided with oxygen supplementation during travel.[353] It is recommended to maintain a PaO2 above 50 mmHg (6.7 kPa) in COPD patients during flight.[354]

Studies indicate that this can be achieved in those with moderate-to-severe hypoxemia at sea level by supplementary oxygen at 3 liters by nasal mask or 32% venturi mask.[354] Patients with oxygen saturation of more than 95% or oxygen saturation during a 6-min

walking test of more than 84% do not need oxygen supplements during travel.[354-356] Patients with COPD are recommended to ask their doctors to fill out the oxygen supplement request form provided by airlines. Attention also should be paid to coexisting conditions that could preclude air travel like unstable angina, severe anemia, uncontrolled heart failure, large emphysematous bullae, or pneumothorax.

Recommendations

- COPD management should be optimized before air travel (Evidence C)
- Oxygen supplements should be considered in COPD patients with oxygen saturation <95% or <84% during a 6-min walking test (Evidence C).

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Conflicts of interest

There are no conflicts of interest.

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