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Best Practice Management of Patients With Chronic Obstructive Pulmonary Disease: A Case-Based Review

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A B S T R A C T

Chronic obstructive pulmonary disease (COPD) is associated with a high clinical and economic burden and is the fourth leading cause of death in the United States. The management of patients with COPD aims to minimize and control symptoms, prevent exacerbations, and improve quality of life. We provide an illustrated case study of a female patient with typical progression of COPD and describe the diagnosis, assessment, and management strategy, referring to the evidence seen in recent studies that supports the treatment decisions.

Illustrated Case Study of a Patient

The patient is a 65-year-old female outpatient presenting with complaints of cough, chest congestion, and shortness of breath while walking uphill. She is a current smoker and works in a supermarket.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common and often preventable disease, characterized by chronic airflow limitation that causes persistent respiratory symptoms, including dyspnea, cough, and sputum production.[1] COPD was the third leading cause of death worldwide in 2016[2] and the fourth in the United States (US) in 2018.[3] Projections indicate that it will remain a leading cause of death by 2040.[4]

Disability in people with COPD is high, with COPD listed as the fifth leading cause of disability-adjusted life-years worldwide and the third leading cause in the US.[5] Thus, the individual burden of COPD is substantial, impacting health status, quality of life (QoL), and daily activities, as well as contributing to increased levels of anxiety and depression.[6] Acute exacerbations of COPD, defined as acute worsening of respiratory symptoms that warrant a change in regular medication,[1,7] often lead to physician visits or hospitalization as well as worsening morbidity and increasing the risk of death.[8] The burden of COPD is further exacerbated by the presence of concomitant conditions, such as cardiovascular disease, lung cancer, osteoporosis, muscle weakness, and cachexia, which impact a patient's health status and survival.[9]

COPD is also associated with a substantial and increasing economic burden.[1] Total direct costs vary between countries but are largely driven by inpatient hospitalization and medication,[10] with estimated costs of $32.1 billion in the US,[11] and €38.6 billion in the European Union.[12] Moreover, COPD and its associated comorbidities can lead to increased absenteeism or patients ceasing work owing to difficulties getting to work and worsening of symptoms that affect productivity.[13]

Diagnosis, Assessment, and Overview of Treatment of COPD

Illustrated case study: The female outpatient presents to the office with slowly increasing dyspnea on exertion, especially with climbing stairs. She reports symptoms including cough, chest congestion, and shortness of breath while walking uphill. Additionally, she complains of not being able to keep up with her friends when walking. To confirm a COPD diagnosis, spirometry is performed. Her postbronchodilator FEV_1/FVC ratio is 0.60, and her FEV_1 is 55% of predicted values. Over the past year she has experienced 1 exacerbation requiring a short course of antibiotics and systemic steroids. Based on her symptoms, treatment with a long-acting muscarinic antagonist (LAMA) is initiated.

A detailed medical history of patients known or suspected to have COPD should be conducted and include clarifying risk factors, such as smoking and exposure history, previous/family history of respiratory diseases, childhood history, including premature birth and respiratory events, presence of comorbidities, pattern of symptom development, including sleeping symptoms and changes in daily activities, and previous history of exacerbations or

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Table
Modified Medical Research Council Dyspnea Scale

mMRC Scale[15]	GOLD Modified mMRC Scale[1]	Impact
mMRC grade 1	mMRC grade 0	I only get breathless with strenuous exercise
mMRC grade 2	mMRC grade 1	I get short of breath when hurrying on the level or walking up a slight hill
mMRC grade 3	mMRC grade 2	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath after a mile or so (or after ¼ hour) when walking at my own pace on the level
mMRC grade 4	mMRC grade 3	I stop for breath after walking about 100 yards or after a few minutes on the level
mMRC grade 5	mMRC grade 4	I am too breathless to leave the house or I am breathless when undressing

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GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council.

hospitalizations.[1] However, detailed assessments are infrequent in primary care, and there are often discrepancies between clinicians and patients regarding the impression of care provided.[14]

In patients with symptoms suggestive of COPD (dyspnea, chronic cough or sputum production) and/or with a history of exposure to risk factors, such as tobacco smoke or other noxious substances, spirometry is required for a diagnosis.[1] Spirometry is an objective measure of airflow limitation that is the most reproducible, noninvasive, and readily available in clinical practice. A postbronchodilator FEV_1/FVC ratio of <0.70 confirms the presence of airflow limitation and, together with her symptoms, suggests a diagnosis of COPD.[1]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document classifies airflow limitation severity using spirometric cutoff points ranging from GOLD stage 1 (mild; FEV_1 ≥80% of predicted values) to GOLD stage 4 (severe; FEV_1 <30% of predicted values). Although FEV_1 is used to assess airflow limitation, the severity of limitation has not been shown to augment the COPD diagnosis, differentiate between COPD or asthma, or predict a patient's response to bronchodilator or corticosteroid therapy, and thus cannot be used alone to make treatment decisions for individual patients. Therefore, the GOLD strategy document recommends that treatment assignment be based on an assessment of both symptom burden and risk of exacerbation (based on prior exacerbation history).[1]

Assessing symptoms can be performed using short comprehensive measures that are suitable for routine clinical use, including the modified Medical Research Council (mMRC) questionnaire,[15] which assesses breathlessness (Table).[1,15] The patient reported walking slower than her friends, which would equate to an mMRC score of 2 according to the GOLD modified mMRC scale.[1] The COPD Assessment Test (CAT) is an 8-item questionnaire that assesses health status impairment in COPD. Each item is scored from 0 to 5 for a total score of 0 to 40, whereby a score of <10 indicates COPD symptoms are having a low impact on a patient's life, 10 to 20 a medium impact, >20 a high impact, and >30 a very high impact.[16]

When deciding on the initial pharmacologic treatment choice, patients can be classified according to the GOLD ABCD assessment (A: minimal symptoms and not much of a risk of having flare-ups; B: more symptoms but still a minimal risk for having flare-ups; C: minimal symptoms but a high risk for having flare-ups; D: severe symptoms and a high risk of having flare-ups), which considers both symptoms and exacerbation history.[1] The algorithm for the ABCD assessment can be seen in Figure 4.2 of the GOLD 2022 report.[1]

After symptom assessment, patients who have experienced 0 to 1 moderate exacerbation (ie, worsening of symptoms that did not lead to hospitalization) in the past year are placed in group A (if mMRC score 0–1 or CAT score <10) or group B (if mMRC score ≥2 or CAT score ≥10).[1] Initial treatment regimens for patients in GOLD group A or B include monotherapy with a LAMA or a long-acting β_2-agonist (LABA).[1] Initial treatment choice is not influenced by FEV_1, but should be guided by the ABCD assessment.

Respiratory Symptoms

Illustrated case study: *The patient has been receiving LAMA; however, after review, she advised that her breathlessness and cough have worsened and had an exacerbation requiring a short course of corticosteroids (oral prednisone 40 mg for 5 days). Symptom assessment found her mMRC and CAT scores have increased from 2 and 15, respectively, at her initial presentation to 3 and 20, respectively, suggesting step-up to dual bronchodilator therapy should be considered.*

The first symptom in patients with COPD is often chronic cough, and it can be a reason for them to seek medical care[17]; however, patients may often consider the cough to be related to smoking and/or environmental exposures.[1] Chronic cough in COPD may be productive (ie, producing phlegm) or unproductive.[17] Production of sputum may be associated with coughing or with chronic bronchitis, defined as regular production of sputum for ≥3 months over 2 consecutive years.[1,18]

The most characteristic symptom of COPD and a major driver of disability associated with the disease is dyspnea, which is a consequence of hyperinflation and gas trapping, reduced expiratory flow, and/or the presence of pulmonary bulla.[1] The term varies but is often described by patients as difficulty with breathing or "air hunger."[1] Increases in respiratory symptoms and decreases in lung function among patients with COPD is associated with deterioration in health-related QoL (HRQoL),[19,20] and symptoms may restrict patients' ability to participate in physical activity.[6]

Pharmacologic management, including monotherapy with β-agonists or anticholinergics, combination therapy with short- or long-acting β-agonists plus anticholinergics, combination therapy with long-acting β-agonists plus glucocorticoids, and treatment with methylxanthines, phosphodiesterase type 4 inhibitors, or mucolytic agents, should be reviewed to establish whether any adjustments to therapy are needed in the treatment of COPD.[1] This is achieved by assessing symptoms, such as dyspnea, cough, sputum production, wheezing, and chest tightness,[1] and risk factors for exacerbation, including exposure to air pollution, severe airflow limitation, high blood eosinophil count, history of prior exacerbations, severity of disease, and the presence of comorbidities, such as bronchiectasis, hyperglycemia, atherosclerosis, hypertension, dyslipidemia, and osteoporosis, and/or chronic bacterial or viral airway infection,[21] as well as adherence to treatment and inhaler technique.[1] Clinicians should highlight the importance of patients' adherence to their treatment and the correct use of their inhaler, and this should be part of an educative and comprehensive management program.[1]

On the basis of the frequency or severity of symptoms, assessed using mMRC or CAT, and exacerbations in the prior year, treatment can be stepped-up to dual therapy with LAMA/LABA or inhaled corticosteroid (ICS)/LABA, or to triple therapy with ICS/LAMA/LABA.[1] Once a patient has started treatment, their initial GOLD group (A, B, C, or D) is no longer relevant to determining therapy;

instead, the GOLD strategy document recommends that follow-up pharmacologic therapy be guided by treatment response, according to effects on symptoms, including dyspnea, exercise capacity, and/or exacerbations, and parameters such as blood eosinophil levels.[1] Changes to treatment require a review to ascertain clinical response and adverse effects, such as pneumonia, which may sometimes develop with long-term ICS use.[1]

Previous meta-analyses have demonstrated that dual bronchodilator therapy is more effective than monotherapy in improving trough FEV_1 and symptoms.[22-24] However, studies of dual- vs monobronchodilation can be complicated because some of the patients enrolled received ICS, which could confound the results and limit their generalizability. The recent Early MAXimisation of bronchodilation for improving COPD stability (EMAX) trial in 2,425 patients with symptomatic COPD at low risk of exacerbation who were naïve to ICS at enrolment, receiving treatment with umeclidinium plus vilanterol (UMEC/VI; n = 812), UMEC (n = 804), or salmeterol (n = 809), confirmed the benefits of dual- over monobronchodilator therapy for lung function and symptom improvement as well as short-term COPD worsening, with no additional safety concerns.[25] Change from baseline in trough FEV_1 at week 24 for UMEC/VI vs UMEC was 66 mL (95% confidence interval [CI], 43-89 mL) or 141 mL vs salmeterol (95% CI, 118-164 mL; both $P < .001$). The change from baseline in the self-administered computerized version of the transition dyspnea index at week 24 for UMEC/VI vs UMEC was 0.37 (95% CI, 0.06-0.68; $P = .018$) or 0.45 vs salmeterol (95% CI, 0.15-0.76; $P = .004$).

Furthermore, a task force under the guidance of the American Thoracic Society (ATS) made recommendations that included the use of dual therapy over LABA or LAMA monotherapy in patients with COPD and dyspnea or exercise intolerance.[24] Prospective randomized controlled trials have also shown benefits of single-inhaler triple therapy over dual therapy in patients with symptomatic COPD at risk of exacerbation in exacerbation reduction and improvements in lung function and symptoms.[26,27] However, in the observational DACCORD (Die ambulante Versorgung mit langwirksamen Bronchodilatatoren: COPD-Register in Deutschland) study of patients with COPD, 80% of whom had not exacerbated in the 6 months before entry, triple therapy did not appear to reduce exacerbations or improve health status compared with dual bronchodilation with LABA/LAMA, although differences in prior medication, disease severity, and exacerbation history likely influenced these results.[28]

Nonpharmacologic management is recommended in conjunction with pharmacologic therapy. Smoking is the main risk factor for developing COPD, and continued smoking results in worse respiratory symptoms and more severe disease[29]; therefore, smoking cessation is recommended for all patients with COPD.[1] In addition, patients with COPD are advised to receive recommended vaccinations, avoid environmental exposures, and receive pulmonary rehabilitation.[1] Pulmonary rehabilitation involves patient-tailored therapies, including exercise training, education, and behavior change interventions.[30] The benefits of pulmonary rehabilitation are extensive, leading to improvements in dyspnea, health status, and exercise tolerance, as well as reducing hospitalizations and symptoms.[1]

Exacerbations

Exacerbations are complex inflammatory events, often triggered by viral or bacterial infections or by environmental exposure such as pollution.[7] They are associated with increased airway inflammation, mucus production, and air trapping.[1] As a result, airflow limitation worsens and dynamic lung hyperinflation, the leading cause of dyspnea, develops.[31]

Frequent exacerbations are associated with worsening QoL[7] as well as an increased risk of hospitalization[32] and death.[33,34] An exacerbation that can be managed at home with an inhaled short-acting β_2-agonist may be considered mild,[1] whereas moderate exacerbations may require further treatment with antibiotics and/or oral corticosteroids.[1] However, severe and very severe exacerbations require an emergency department visit and/or hospitalization and often lead to acute respiratory failure,[1] whereas frequent exacerbations accelerate disease progression and lung function decline and are associated with worse QoL and decrease in exercise ability.[35]

Although hospitalizations for COPD exacerbations can occur in patients with all grades of airflow limitation, the severity of previous exacerbations is an important predictor of future hospitalizations for exacerbations and death. For instance, a retrospective population-based cohort study found that a history of ≥2 severe exacerbations increased the risk of a new severe exacerbation by nearly 7-fold (adjusted odds ratio [OR], 6.73; 95% CI, 3.53-2.83) and of death by nearly 8-fold (adjusted OR, 7.63; 95% CI, 3.41-17.05).[36] Furthermore, exacerbations can increase the risk of having a cardiovascular event.[37,38]

Illustrated case study: *Despite treatment with dual bronchodilation, the patient has experienced a severe exacerbation that required hospitalization. Her blood eosinophil count is 320 cells/μL, indicating a possible phenotype that requires close observation for acute exacerbations of COPD. After treatment for the exacerbation, the patient's treatment is escalated, with the inclusion of an ICS as part of a triple ICS/LAMA/LABA therapy.*

The GOLD strategy document recommends that patients experiencing exacerbations while on dual therapy should be escalated to triple therapy to lessen the risk of future exacerbations.[1] This is supported by large phase 3 studies that have shown efficacy for reducing exacerbations with triple therapy (ICS/LAMA/LABA) compared with dual therapies (LAMA/LABA or ICS/LABA).[26,27]

The Informing the Pathway of COPD Treatment (IMPACT) trial was a 52-week, randomized, double-bind phase 3 study that evaluated the effects of once-daily single-inhaler fluticasone furoate (FF)/UMEC/VI triple therapy vs once-daily FF/VI and UMEC/VI dual therapy on exacerbations in 10,355 patients with symptomatic COPD and a history of exacerbations.[27]

FF/UMEC/VI significantly reduced the annual rate of moderate/severe exacerbations by 15% vs FF/VI (rate ratio [RR], 0.85; 95% CI, 0.80-0.90; $P < .001$) and by 25% vs UMEC/VI (RR, 0.75; 95% CI, 0.70-0.81; $P < .001$). Moreover, FF/UMEC/VI significantly reduced the annual rate of severe exacerbations (those resulting in hospitalization or death) by 34% vs UMEC/VI (RR, 0.66; 95% CI, 0.56-0.78; $P < .001$), while a numerical reduction of 13% vs FF/VI was seen (RR, 0.87; 95% CI, 0.76-1.01; $P = .06$).

The Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) trial was a 52-week, randomized, double-bind phase 3 study that evaluated the effects of twice-daily single-inhaler budesonide/glycopyrrolate/formoterol (BUD/GLY/FOR) triple therapy at 2 doses of BUD (320 and 160 μg) vs twice-daily BUD/FOR and GLY/FOR dual therapy on exacerbations among 8,509 patients with symptomatic COPD and a history of exacerbations.[26] Similar to the IMPACT trial, the rate of moderate/severe exacerbations was significantly lower with triple therapy compared with dual therapy (BUD 320-μg triple therapy vs BUD/FOR: 13% reduction; RR, 0.87; 95% CI, 0.79-0.95; $P = .003$; BUD 320-μg triple therapy vs GLY/FOR: 24% reduction; RR, 0.76; 95% CI, 0.69-0.83; $P < .001$). With regards to severe exacerbations, BUD 320-μg triple therapy demonstrated a significant reduction of by 20% vs BUD/FOR (0.80; 95% CI, 0.66-0.97; $P = .02$) and a numerical reduction of 16% vs GLY/FOR (0.84; 95% CI, 0.69-1.03; $P = .09$).

Moreover, triple therapy has also shown improvements in other outcomes such as lung function and health status compared with LAMA/LABA or ICS/LABA dual therapy. In the IMPACT trial, FF/UMEC/VI led to improvements in lung function, symptoms, and patient-perceived HRQoL compared with FF/VI or UMEC/VI.[27,39] Similarly, improvements in lung function, symptoms, and HRQoL were seen in ETHOS with both doses of triple therapy vs dual therapies.[39]

Importantly, both IMPACT and ETHOS provide evidence for the role of ICS in reducing the risk of death in patients with symptomatic COPD at risk of exacerbation. In IMPACT, FF/UMEC/VI reduced on-treatment all-cause mortality by 42% compared with UMEC/VI (absolute risk reduction of 0.68%).[27] For the original on-/off-treatment analyses, 574 of 10,355 patients (5.5%) were missing vital status at week 52. A post hoc analysis after collection of additional vital status data up to week 52 for 99.6% of the intention-to-treat population confirmed the findings from the original analyses, showing that FF/UMEC/VI reduced the risk of on-/off-treatment all-cause mortality by 28% vs UMEC/VI (absolute risk reduction of 0.83%; $P = .042$).[40] In ETHOS, the original data set included 384 patients with incomplete vital status at database lock. A final retrieved data set was created at week 52, which included additional week 52 vital status information and comprised 99.6% of the 8,509 patients in the intention-to-treat population. In this final retrieved data set, BUD 320-μg triple therapy reduced the risk of on-/off-treatment all-cause mortality by 46% vs GLY/FOR (absolute risk reduction of 1.0%).[40]

Additional considerations when prescribing ICS use are smoking status and blood eosinophil counts.[1] Lighter or former smokers are more likely to benefit from ICS use than current or heavy smokers.[41] As shown in studies that evaluated outcomes in trials of ICS-containing therapy by continuous baseline blood eosinophil count, patients with low blood eosinophil counts (<100 cells/μL) are less likely to benefit from ICS use compared with patients with higher blood eosinophil counts, with regards to exacerbation rate reduction and improvements in lung function and health status.[42,43] This relationship between blood eosinophil and ICS benefits is also modified by smoking status.[43] As such, smoking status and blood eosinophil count can be used in clinical practice to help predict the likelihood of the beneficial effects of adding ICS to a bronchodilator maintenance treatment.

Assessing the Benefit vs Risk of Triple Inhaled Therapy

Although it is not possible to assess the benefit and risk of treatment on an individual patient basis, we can use the evidence gathered from randomized controlled trials to inform the benefit-risk profile of a given treatment option. ICS use is associated with an increased risk of pneumonia in patients with COPD.[44] As such, even though triple therapy has demonstrated significant benefits across multiple end points vs dual therapy, these benefits should be considered within the context of the ICS-related pneumonia risk for each individual patient when evaluating treatment escalation.

Clinical trials comparing triple therapy vs both dual ICS/LABA and LAMA/LABA therapy have shown a higher incidence of pneumonia in the ICS-containing arms compared with the LAMA/LABA treatment arm.[26,27] This risk was recognized in a 2016 report from the European Medicines Agency's Pharmacovigilance Risk Assessment Committee as a class effect of ICS-containing therapies, with no definitive evidence of intraclass differences.[45] Nevertheless, in a prespecified analysis of the IMPACT trial, the risk of combined pneumonia or moderate/severe exacerbation was reduced with FF/UMEC/VI compared with FF/VI or UMEC/VI, supporting a favorable benefit-risk profile of once-daily FF/UMEC/VI triple therapy compared with FF/VI and UMEC/VI dual therapy in symptomatic patients with COPD who are at risk of exacerbations.[46]

Summary

Initial pharmacotherapy should be selected based on the GOLD ABCD assessment, with long-acting bronchodilator monotherapy recommended for patients with low symptom and exacerbation burden.[1] For patients who continue to experience persistent breathlessness or exercise limitation, escalation to dual bronchodilation is advised by GOLD guidelines[1] and ATS guidelines.[24] Triple therapy with ICS/LAMA/LABA has shown favorable outcomes for patients with symptomatic COPD at risk of exacerbations, including a significant reduction in the rate of moderate/severe exacerbations compared with ICS/LABA or LAMA/LABA dual therapy.[26,27] GOLD guidelines and ATS guidelines recommend escalation to triple therapy for patients who continue to experience persistent breathlessness, exercise limitation, or exacerbations while receiving dual therapy,[1,24] as in our illustrated case study. Blood eosinophil counts of ≥100 cells/μL indicate a beneficial response with the addition of ICS.[1]

In addition to triple therapy, other clinical recommendations should be integrated into treatment management plans for this patient group, with smoking cessation recommended for all patients with COPD.[1] Patients should also receive general advice and encouragement regarding diet and physical activity.[1] These can be enhanced by participation in pulmonary rehabilitation programs. Finally, influenza and pneumococcal vaccinations are recommended to reduce the risk of exacerbation.[1]

Large phase 3 studies suggest a benefit of triple therapy on all-cause mortality among patients with COPD[40]; however, this needs to be further demonstrated in clinical practice, and additional research is required in patient populations beyond those at risk of frequent exacerbations to optimize triple therapy initiation.

Illustrated case study: *After treatment was escalated to triple therapy, the patient had no further exacerbations at her 18-month follow-up assessment. She continues with an annual vaccination program, she exercises regularly, has ceased smoking, and maintains a healthy diet. She continues with routine scheduled check-ups, in which treatment effectiveness and adverse events are monitored, and she reports that her symptoms now have less of an impact on her daily life.*

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