COPD Guideline Updates

By Melissa Lipari, Pharm.D., BCACP

Reviewed by Jean Y. Moon, Pharm.D., FCCP, BCACP; and Ryan Petersen, Pharm.D., BCACP

LEARNING OBJECTIVES

1. Distinguish the differences between guideline approach and recommendations of the leading chronic obstructive pulmonary disease (COPD) guidelines.
2. Assess the use of biomarkers in the management of stable and acute exacerbation of COPD.
3. Design a pharmacologic treatment regimen that incorporates updated evidence-based COPD guidelines and patient-specific characteristics.
4. Evaluate factors that affect the assessment and management of patients with COPD at risk of or diagnosed with coronavirus disease 2019.
5. Assess the interventions that optimize the inhaled delivery of pharmacologic therapy in patients with COPD.

ABBREVIATIONS IN THIS CHAPTER

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
ATS	American Thoracic Society
CAT	COPD Assessment Test
CRP	C-Reactive protein
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
EOS	Blood eosinophil count
FEV_1	Forced expiratory volume at 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	Inhaled corticosteroid
LABA	Long-acting β_2-agonist
LAMA	Long-acting muscarinic antagonist
NICE	National Institute for Healthcare and Excellence
PFT	Pulmonary function test
SABA	Short-acting β_2-agonist
SABD	Short-acting bronchodilator
SAMA	Short-acting muscarinic antagonist

Table of other common abbreviations.

INTRODUCTION

Chronic lower respiratory diseases, which include chronic obstructive pulmonary disease (COPD), are the fourth leading cause of death in the United States (Kochanek 2020). Acute exacerbation of COPD (AECOPD) results in clinical worsening of disease and is a strong predictor of future exacerbations (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2022). Currently available pharmacotherapy for COPD may improve quality of life, respiratory symptoms, and reduce AECOPD. Emerging evidence for the use of biologic markers has changed treatment pathways and led to a more patient-specific approach to selecting appropriate pharmacotherapy. Clinical pharmacists are well positioned to optimize evidence-based pharmacotherapy that reduce negative outcomes of the disease. This chapter focuses on recent changes in the literature and evidence-based guidelines for the diagnosis, management, and delivery of care for patients with COPD.

BIOMARKERS

Research on the use of biomarkers to aid in therapeutic decision-making for patients with COPD has been of increasing interest in recent years. The data supporting the use of blood eosinophil count (EOS) to guide the management of stable disease are among the most compelling. As such, evidence-based guideline recommendations predominately address the role of EOS in initiation of inhaled corticosteroid (ICS) therapy. Although guidelines still promote the use of sputum purulence as a determining factor to initiate antibiotics in AECOPD, other biomarkers such as procalcitonin and C-reactive protein (CRP) may be useful in the future. Ambulatory care pharmacists can play an important role in ensuring the evidence-based use of biomarkers to design therapeutic care plans.

Blood Eosinophils

About 40% of patients with COPD have eosinophilic airway inflammation (Bafadhel 2017). Patients with high EOS are at a greater risk of more frequent AECOPD. Early studies investigating the effect of ICS monotherapy failed to demonstrate a benefit on outcomes such as lung function, exacerbations, and mortality (Vestbo 2016; Calverley 2007). These studies did not prospectively stratify patients by EOS concentration; however, post-hoc analyses have suggested that patients with a higher EOS may benefit from ICS therapy. In recent years, several studies have demonstrated a positive correlation between EOS and response to ICS therapy (Bafadhel 2018; Papi 2018; Lipson 2018; Vestbo 2017; Pascoe 2015; Siddiqui 2015). Therefore, stratification of therapy by EOS has been proposed as a way to identify patients who may benefit most from ICS therapy. The threshold of EOS at which to initiate ICS therapy is not well established; however, an EOS greater than 150 cells/mm^3 has been most often cited and is currently recommended in conjunction with other risk factors as one of the thresholds to initiate ICS therapy.

Procalcitonin and CRP

Historically, the presence of sputum purulence has been the gold standard to determine whether an antibiotic is indicated in patients experiencing AECOPD. Recently, however, procalcitonin and CRP, which are both acute inflammatory mediators, have been hypothesized to be useful biomarkers to aid in the initiation of antibiotics. Some studies have investigated the use of procalcitonin in both inpatient and outpatient settings with conflicting results (Schuetz 2012, 2009; Wang 2016). Therefore, the use of procalcitonin is not currently recommended.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology that leads to chronic obstructive pulmonary disease (COPD)
- Pulmonary function testing and lung markers used in COPD
- Drug knowledge of the oral and inhaled pharmacologic agents used to treat COPD

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Global Initiative for Chronic Obstructive Lung Disease Report. https://goldcopd.org/

Similarly, evidence is conflicting for the use of CRP to guide whether antibiotics should be initiated in patients experiencing AECOPD. Most of these studies investigated use of CRP in the inpatient setting. However, one recent multi-center open-label, randomized controlled trial in the United Kingdom investigated the use of point-of-care CRP to guide the addition of antibiotic therapy in the primary care setting (Butler 2019). The study enrolled a total of 653 patients into either the CRP- or the sputum purulence-directed arms, with sputum purulence as the standard of care. Patients in the CRP-directed arm were less likely to be prescribed an antibiotic within 4 weeks after randomization (57% vs. 77.4%; adjusted OR 0.31; 95% CI, 0.20–0.47). Health-related quality of life as assessed by the Clinical COPD Questionnaire improved for the CRP-driven group (Clinical COPD Questionnaire –0.19 score; 2-sided 90% CI, –0.33 to –0.05) 2 weeks after randomization. Although the results of this study are promising, more studies are necessary to justify the widespread use of CRP to determine whether to add antibiotics in ambulatory patients with AECOPD. Currently, evidence-based guidance advises against routine use of the CRP test in practice in favor of the symptomatic evaluation of sputum purulence (GOLD 2022a).

UPDATES IN THE PHARMACOLOGIC TREATMENT OF STABLE COPD

The management of stable COPD has evolved in recent years. Evidence-based guidelines have moved away from the widespread use of ICS therapy in all patients and encouraged an approach that is more patient centric. The inhaled agents for COPD commonly used in the United States are listed in Table 1.

Bronchodilators

Bronchodilators have long been the mainstay of therapy for patents with COPD. Bronchodilators improve lung function and quality of life. β_2-Agonists act on smooth muscle to promote bronchodilation, whereas muscarinic antagonists predominately inhibit the M3 receptor increasing cyclic adenosine monophosphate, resulting in bronchodilation (Matera 2020). β_2-Agonists and muscarinic antagonists are often used as monotherapy, but they may have synergistic effects when combined.

Short-acting bronchodilators (SABDs) can be used as initial therapy in less severe disease as needed (GOLD category A) or as scheduled to improve lung function and symptoms (GOLD 2022a). The evidence-based guidelines do not provide a preference for which SABD should be used in this category; however, some evidence suggests that ipratropium may have slightly superior efficacy compared with short-acting β_2-agonist (SABA) (Appleton 2006). The combination of both a short-acting muscarinic antagonist (SAMA) and a SABA is superior to monotherapy (Gross 1998). In addition, the risk of dose-related adverse effects (tachycardia and tremor) can be minimized by using dual SABD therapy versus using higher doses of one agent.

Table 1. Inhaled Pharmacotherapies for the Management of COPD

Drug Class	Pharmacologic Agent
SABA	Albuterol
SAMA	Ipratropium
Combination SABA + SAMA	Albuterol/ipratropium
LABA	Arformoterol Formoterol Indacaterol Olodaterol Salmeterol
LAMA	Aclidinium bromide Glycopyrrolate Tiotropium Umeclidinium Revefenacin
Combination LABA + LAMA	Formoterol/aclidinium Formoterol/glycopyrrolate Indacaterol/glycopyrrolate Vilanterol/umeclidinium Olodaterol/tiotropium
Combination LABA + ICS	Formoterol/beclomethasone Formoterol/budesonide Formoterol/mometasone Salmeterol/fluticasone Vilanterol/fluticasone furoate
Combination LABA + LAMA + ICS	Fluticasone/umeclidinium/vilanterol Budesonide/glycopyrrolate/formoterol

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β_2-agonist; SAMA = short-acting muscarinic antagonist.

Adapted with permission from: Global Initiative for Chronic Obstructive Lung Disease (GOLD). GOLD 2022 global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2022 report. Available at https://goldcopd.org/2022-gold-reports/.

Long-acting bronchodilators may be used instead of short-acting agents as another strategy to minimize the risk of adverse effects when greater symptom control is needed. In earlier stages of disease (GOLD categories A and B), data are lacking to support whether patients would benefit from long-acting muscarinic antagonist (LAMA) over long-acting β_2-agonist (LABA) therapy. However, LAMA is superior to LABA in reducing the risk of exacerbations and hospitalizations in moderate to very severe COPD (Decramer 2013; Vogelmeier 2011). One randomized, double-blind, double-dummy trial compared tiotropium 18 mcg inhaled once daily to salmeterol 50 mcg inhaled twice daily in patients with moderate to severe (GOLD stage II to IV) COPD (Vogelmeier 2011). Of 7376 study patients, 3707 received tiotropium and 3669 received salmeterol. Patients receiving tiotropium had a 17% reduction in risk of first exacerbation compared with those in the salmeterol arm (HR 0.83; 95% CI, 0.77–0.90; p<0.001). A significant reduction in moderate and severe exacerbations was also noted in the tiotropium arm. The INVIGORATE study, a multicenter, randomized, double-blind, double-dummy, parallel group noninferiority trial, confirmed these findings with a comparison of indacaterol and tiotropium (Decramer 2013). Although indacaterol met noninferiority criteria for improvement in lung function, tiotropium was superior to indacaterol in its reduction in the annualized rate of exacerbations (0.79 vs. 0.61, respectively; 1-sided 97.5% CI upper limit 1.44). No differences in overall and serious adverse effects were observed between groups.

The combination of LABA plus LAMA has demonstrated synergistic effects, similar to their short-acting counterparts. Combination therapy may be used in patients with significant symptoms, such as COPD Assessment Test (CAT) score greater than 20, on diagnosis or in patients with persistent symptoms or exacerbations despite bronchodilator monotherapy. Numerous studies have demonstrated the efficacy and safety of LAMA plus LABA versus long-acting bronchodilator monotherapy. Typically, these study patients had a low rate of exacerbations, which limits the external validity for patients at high risk of future exacerbations (GOLD 2022a). One recent meta-analysis compared dual bronchodilator therapy with monotherapy in a total of 6086 patients from 18 studies (Lipari 2020). Results showed an overall improvement in forced expiratory volume at 1 second (FEV_1) in patients receiving dual bronchodilator therapy versus monotherapy; however, this finding did not meet the minimal clinically important difference for lung volume. No differences between groups were found in symptoms scores as measured by the St. George Respiratory Questionnaire. The lack of significant symptom improvement may be attributed to the fact that the minimal clinically important difference for lung volume was not reached. No differences were observed in the rate of overall or serious adverse effects. The benefit of dual therapy appears to be greater compared with LABA than with LAMA monotherapy. A limitation to this analysis was that it did not assess exacerbation rates between the two treatments because of the heterogeneity of outcome data in the included trials. Dual bronchodilator therapy is a safe and effective strategy for therapy escalation in patients with persistent respiratory symptoms and should be considered before other therapeutic options.

Corticosteroids

The role of corticosteroids in the chronic management of COPD is somewhat controversial because the potential

benefits may be outweighed by the risk of adverse effects. The long-term use of systemic corticosteroids in the chronic management of COPD has not demonstrated benefit and is therefore not currently recommended by both the GOLD and American Thoracic Society (ATS) guidelines (GOLD 2022a; Nici 2020). The National Institute for Healthcare and Excellence (NICE) guidelines also do not endorse the routine use of oral corticosteroids for stable disease; however, these guidelines acknowledge that some patients may not be able to discontinue after an AECOPD. Use of inhaled therapy is more common; however, it is also not without the risk of potentially serious adverse events such as pneumonia. Therefore, ICS therapy is often reserved for patients with severe to very severe disease (GOLD stage III and IV) and those at a high risk of exacerbations. As previously mentioned, patients with increased EOS may have better outcomes when treated with combination ICS therapy; thus, this biomarker may help stratify patients who would experience the greatest benefit.

Use of ICS monotherapy is not recommended because of the potential risk of adverse events, particularly pneumonia (GOLD 2022a). Two landmark trials, TORCH and SUMMIT, investigated whether ICS plus LABA reduced the risk of mortality compared with their individual components and placebo (Vestbo 2016; Calverley 2007). The TORCH trial was a randomized, double-blind, placebo-controlled study of patients with COPD with the following inclusion criteria: age 40–80 years, current or former smoker, pre-bronchodilator FEV_1 less than 60% of predicted, increase in post-bronchodilator FEV_1 of less than 10% of the predicted value, and a ratio of prebronchodilator FEV_1 to forced vital capacity (FVC) less than or equal to 0.70. Study investigators compared the use of salmeterol 50 mcg plus fluticasone propionate 100 mcg twice daily to fluticasone plus placebo, salmeterol plus placebo, and placebo only, and their respective effects on mortality at 3 years. Final analysis included a total of 6117 patients, 875 of whom died at 3 years in the following groups: 16% treated with fluticasone, 13.5% with salmeterol, and 12.6% with fluticasone plus salmeterol, and 15.2% who received placebo only. On statistical analysis, however, no differences in mortality were shown between the fluticasone plus salmeterol group compared with the placebo-only group (HR 0.825; 95% CI, 0.681–1.002; p = 0.052). A major limitation of this study was that the study investigators did not require patients to have a history of AECOPD at enrollment. Therefore, it has been hypothesized that these patients would be less likely to benefit from ICS therapy because of their low risk of mortality at the time of enrollment (Calverley 2021). A post-hoc analysis of TORCH suggested that combination ICS plus LABA may reduce the risk of cardiovascular outcomes. Subsequently, the SUMMIT trial was designed to investigate this potential hypothesis.

The SUMMIT trial, a multicenter, randomized, placebo-controlled trial, was one of the largest survival studies ever conducted (Vestbo 2016). Similar to TORCH, it compared the effects of ICS plus LABA (fluticasone furoate and vilanterol) to their individual components on all-cause mortality. The study included a total of 16,485 patients; however, participants included those who had a history of cardiovascular disease or were at high risk of cardiovascular disease. No difference in all-cause mortality was noted between the groups. However, a reduction in the decline in FEV_1 in patients receiving combination therapy and a reduction in pneumonia risk in patients receiving vilanterol monotherapy were observed. Similar to TORCH, a history of exacerbations on enrollment was not an inclusion criterion and may have resulted in the inclusion of patients at lower risk of mortality. This study demonstrated that ICS plus LABA does not reduce mortality in patients with COPD and cardiovascular disease who do not have a history of exacerbations.

In contrast, one Cochrane review found that for patients with a history of at least one exacerbation in the past 12 months, ICS plus LABA therapy resulted in fewer exacerbations (Nannini 2012). The study investigators also found an increase in the risk of pneumonia in patients who were exposed to ICS therapy. This analysis further supports the hypothesis that patients who are at a higher risk of exacerbations are the most likely to benefit from combination ICS plus LABA therapy; however, this approach must be weighed against the risk of pneumonia.

Triple Therapy

Although ICS plus LABA therapy may not have demonstrated benefit in patients who had a low rate of exacerbations, emerging evidence has demonstrated that the use of triple therapy (LABA plus LAMA plus ICS) in patients who are highly symptomatic and have a history of moderate to severe exacerbations despite dual therapy may be beneficial. The FDA approval of a first triple inhaler for COPD in September 2017 has sparked renewed interest in its potential benefit. Three large trials compared triple therapy with LAMA (Singh 2016), LAMA plus LABA (Vestbo 2017), and ICS plus LABA (Papi 2018). The TRILOGY trial demonstrated that patients with more symptoms (CAT greater than 10), impaired lung function (FEV_1 less than 50% of predicted), and a history of exacerbations (at least 1 exacerbation in the past 12 months) receiving triple therapy had a greater improvement in lung function, but these patients did not demonstrate a statistically significant improvement in symptoms compared with those who received ICS plus LABA (Singh 2016). A lower rate of moderate to severe exacerbations at 26 weeks was observed. The TRINITY trial, which included patients with an FEV_1 less than 50% of predicted with at least 1 moderate to severe exacerbation, found that triple therapy when compared with LAMA monotherapy significantly reduced the annualized rate of moderate to severe exacerbations (Vestbo 2017). Lastly, the TRIBUTE trial similarly concluded that triple bronchodilator therapy compared with dual therapy reduced exacerbations rates in patients with an FEV_1 less than 50% of predicted with at least 1 moderate to severe exacerbation in the past

12 months (Papi 2018). The rate in adverse events was similar between groups. Triple therapy did not increase the rate of pneumonia compared with LAMA monotherapy or dual bronchodilator therapy.

The effect of triple therapy on mortality was further explored in two recent trials, IMPACT (Lipson 2018) and ETHOS (Rabe 2020). The IMPACT trial compared triple therapy to ICS plus LABA and dual bronchodilator therapy. The aim of the study was to determine if there was a benefit in escalating from dual to triple therapy in patients older than 40 years with symptomatic COPD (CAT score 10 or greater). A significant reduction was found in the annual rates of moderate to severe exacerbations, with a rate of 0.91 for triple therapy versus 1.07 in the ICS plus LABA group (rate ratio with triple therapy, 0.85; 95% CI, 0.80–0.90; 15% difference; p<0.001) and 1.21 in the LABA plus LAMA group (rate ratio with triple therapy, 0.75; 95% CI, 0.70–0.81; 25% difference; p<0.001). The incidence of mortality was lower in patients receiving triple therapy. This study is the first major trial since SUMMIT that attempted to investigate the risk of mortality, however, it was not the primary outcome of the trial. The rate of pneumonia was higher in patients receiving triple therapy. A major limitation of the IMPACT trial must be noted: Any patients on an ICS before randomization, but randomized to the dual bronchodilator group, were suddenly withdrawn from their ICS therapy. This withdrawal may, therefore, be an explanation for the increased rates of exacerbations in that trial arm.

Subsequently, ETHOS investigated two ICS doses in a triple inhaler therapy with dual bronchodilator or bronchodilator monotherapy in symptomatic patients with a history of moderate to severe exacerbations in the previous 12 months. Results were a reduction in moderate to severe exacerbations. Mortality, a pre-specified secondary end point, was lower in the higher dose ICS triple therapy arm compared with dual bronchodilator therapy.

These studies have demonstrated that in highly symptomatic patients with a history of exacerbations and low lung function, triple therapy may reduce exacerbations, improve lung function and symptoms, and decrease the risk of mortality. However, clinicians should escalate therapy with caution (with assessment of the risk of pneumonia) and ensure that dual therapy is optimized before making this change.

Withdrawal of ICS

Given the potential lack of benefit for the use of ICS plus LABA in patients at low risk of exacerbations, the potential for de-escalation of ICS therapy exists in practice. Three sets of guidelines—ATS, GOLD and NICE—support the withdrawal of ICS in patients who are not at risk of future exacerbations (GOLD 2022a; Nici 2020). Furthermore, GOLD suggests that patients who have experienced an episode of pneumonia may also be candidates for de-escalation of ICS therapy. In addition, ATS specifically makes this conditional recommendation in patients who are currently on triple therapy who have not had an exacerbation in the past 12 months.

The general recommendation that withdrawal of ICS therapy may be safe in patients with COPD is supported by the WISDOM trial. This randomized, double-blind, parallel-group active control study demonstrated noninferiority to triple therapy when fluticasone was withdrawn gradually over 12 weeks in patients taking tiotropium plus salmeterol who had at least 1 exacerbation in the past 12 months (Magnussen 2014). This study demonstrated that gradual ICS therapy withdrawal does not result in an increase of exacerbations. Pharmacists are well positioned to guide the appropriate withdrawal of ICS therapy where the risks of therapy may outweigh the benefit.

PHARMACOLOGIC THERAPY IN COPD EXACERBATIONS IN AMBULATORY PATIENTS

An estimated 80% of patients experiencing an AECOPD are treated in an outpatient setting where oral corticosteroids are often used in conjunction with a SABD. One analysis found no difference in outcomes for patients treated with oral versus intravenous prednisolone (de Jong 2007). Although this study was completed in the hospitalized patient population, there are limited reasons to use intravenous corticosteroids in the ambulatory setting. Therefore, oral corticosteroids are recommended in most patients being treated for AECOPD.

Oral Corticosteroid Use

Recent data investigating the appropriate duration of systemic corticosteroid therapy have resulted in a shift in recommendations to a shorter duration of therapy (GOLD 2022a; Nici 2020; NICE 2018). The REDUCE trial was a randomized noninferiority study conducted in Switzerland that compared the use of oral prednisone for 5 versus 14 days in patients who presented to the ED with an AECOPD (Leuppi 2013). The intention to treat analysis included a total of 311 patients. There was no difference in the time to next exacerbation at 6 months in patients receiving 5 versus 14 days of therapy. A Cox regression analysis demonstrated an HR of 0.95 (90% CI, 0.70–1.29; p=0.006 for noninferiority) for the time to re-exacerbation in the intention-to-treat analysis. No differences were noted in secondary outcomes, including time to death; the composite outcome of time to death or exacerbation, or both; and recovery of lung function. In addition, no differences were found in the rates of hyperglycemia and hypertension during the hospital stay. This study excluded patients with a history of asthma; therefore, it is unclear whether patients with asthma–COPD overlap syndrome would benefit from a shorter duration of therapy. One limitation of the study is that the assessment of hyperglycemia and hypertension only occurred during the acute hospital period and did not extend beyond discharge. Therefore, the assessment period was likely insufficient to observe a difference in effect. A recent observational cohort

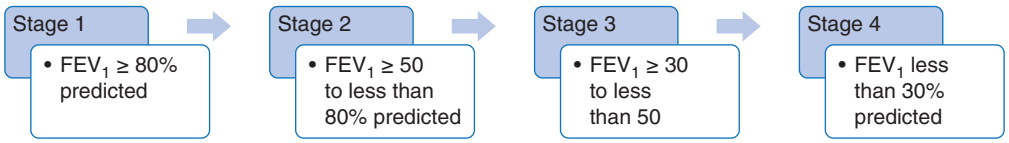

Figure 1. GOLD stages 1–4 by lung volume.

FEV_1 = forced expiratory volume at 1 second.

Information from Global Initiative for Chronic Obstructive Lung Disease (GOLD). GOLD 2022 global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2022 report. Available at https://goldcopd.org/2022-gold-reports/.

of Danish residents admitted for AECOPD assessed adverse effects of short (5 days) versus long duration of systemic (10 days) of prednisolone 25 mg/day over 12 months (Sivapalan 2019). The primary outcomes were the 1-year risk of pneumonia and all-cause mortality. The study authors concluded that patients receiving a shorter duration of corticosteroid therapy had a decreased incidence of pneumonia and all-cause mortality. This study confirms the findings of the REDUCE trial and further justifies the importance adhering to a short duration of systemic corticosteroids for AECOPD.

Antibiotic Use

The use of antibiotics to treat patients experiencing an AECOPD are common in practice. Despite this widespread use, the data surrounding the use of antibiotics in AECOPD are somewhat controversial. Given the mixed availability of data supporting the use of biomarkers to determine whether antibiotics are indicated, the gold standard remains to initiate antibiotic therapy in patients who present with the three cardinal symptoms (increased dyspnea, sputum purulence, and sputum volume) of AECOPD or two of the three symptoms if sputum purulence is present (GOLD 2022a; NICE 2019). Although GOLD recommends antibiotic therapy duration of 5 to 7 days, the American College of Physicians recommends 5 days of therapy (GOLD 2022a; Lee 2021). Pharmacists should ensure that the selection of antibiotics are appropriate based on resistance patterns in their area of practice.

CLINICAL GUIDELINE UPDATES IN COPD

The literature addressing inhaled pharmacotherapies has recently expanded, which has drastically changed how COPD is managed. Several international and national guidelines are published and updated regularly in the management of COPD. Pharmacists are well positioned to ensure the appropriate use of evidence-based pharmacotherapy in patients with COPD.

The GOLD report is updated annually and provides guidance on the diagnosis and management of stable and AECOPD. Although the GOLD report is updated yearly, the last major update to their recommendations was in 2018 and focused on the therapeutic management of stable COPD.

GOLD Report 2022: Updates in Approach

Recently, the GOLD report has shifted away from using lung function (post-bronchodilator FEV_1 percent of predicted) as the driver for pharmacotherapy selection (GOLD 2022a). The role of pulmonary function testing is to determine the severity of lung impairment at diagnosis and its progression of disease over time in patients with an FEV_1/FVC less than 0.7. The GOLD guideline classifies patients with COPD into four stages based on their FEV_1 percent of predicted volume (Figure 1).

To determine initial selection of pharmacotherapy, two primary patient assessments must be conducted to determine the patient's GOLD symptoms and risk of future exacerbations. The GOLD report endorses several validated symptom assessment tools, while placing an emphasis on using a tool that assesses effects of symptoms on quality of life as well as breathlessness. The gold standard tools for assessment are the St. George Respiratory Questionnaire and the Chronic Respiratory Questionnaire (Jones 1992; Guyatt 1987). However, the complexity of these assessments limits their practical use. The CAT and the COPD Control Questionnaire are shorter, more practical tools for assessment that correlate with the well validated gold standard tools (Jones 2009; van der Molen 2003). The Modified Medical Research Council questionnaire may also be used; however, this tool measures breathlessness only and is less preferred to assessment tests that also assess quality of life (Fletcher 1960).

The greatest risk of future exacerbations is a patient's history of exacerbations in the previous 12 months. The GOLD report states that a patient is considered high risk of future exacerbations if one of the following criteria is met: two or more exacerbations in the past 12 months or one or more exacerbations requiring a hospitalization in the preceding 12 months (GOLD 2022a). The GOLD report considers patients not meeting these criteria to be at low risk of future exacerbations. Patients at high risk of future exacerbations often require more aggressive therapy to reduce the risk of worsening disease that is caused by an episode. Once

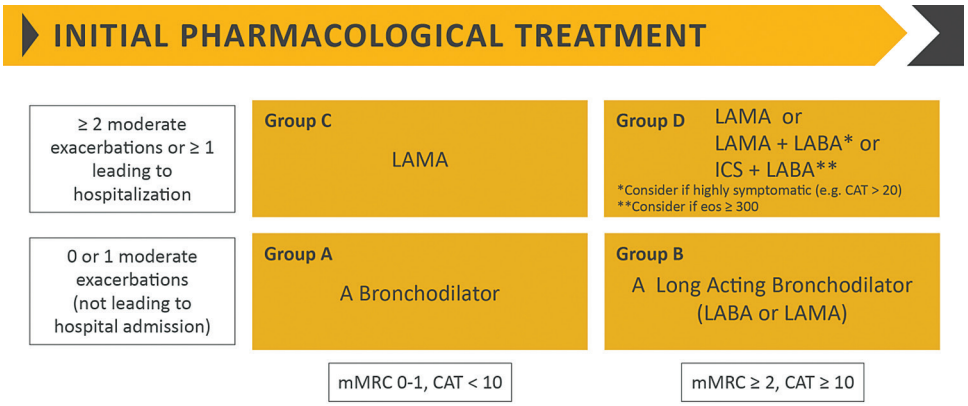

Figure 2. GOLD combined assessment and initial pharmacotherapy.

CAT = COPD Assessment Test; COPD = chronic obstructive lung disease; EOS = blood eosinophil count; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; mMRC = modified Medical Research Council Dyspnea Scale.

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symptoms and exacerbation risk are determined, patients can be placed into one of the four alphabetical GOLD groups (Figure 2).

In the treatment of stable COPD, the GOLD report divides the therapeutic management recommendations by initial and maintenance therapy. Initial therapy based on GOLD group is preferred (see Figure 2). Once patients are placed on initial therapy, they should be routinely assessed for response and worsening or improvement of symptoms and exacerbations. For example, a change in CAT score of 2 or more meets the criteria for the minimum clinically important difference (Kon 2014). The use of EOS can be used to guide whether ICS may be beneficial. Patients experiencing worsening symptoms or new exacerbations despite receiving initial therapy may be candidates for a therapy change once their adherence and inhaler technique are assessed (Figure 3). Patients who are using ICS therapy or who experienced an episode of pneumonia while on ICS therapy should be assessed for de-escalation to minimize the risk of adverse effects.

An *acute exacerbation of chronic obstructive pulmonary disease* is defined as worsening of a patient's symptoms beyond the typical daily variation as an episode that requires therapeutic intervention (GOLD 2022a). Most patients experiencing an AECOPD are treated in the ambulatory setting. Therefore, ambulatory care pharmacists are positioned to ensure the evidence-based treatment of AECOPD.

Patients who experience an AECOPD require treatment with a SABD and possibly systemic corticosteroids. Antibiotic therapy is warranted if the underlying cause is of a suspected bacterial origin (i.e., sputum purulence is present). Selection of antibiotic therapy should be based on local resistance patterns. The classification of AECOPD is mild, moderate, or severe. The severity of an AECOPD is defined by the level of pharmacotherapeutic treatment used (Table 2). The GOLD that the duration of systemic corticosteroid therapy should not exceed 5 days and emphasizes that oral corticosteroid therapy is as effective as intravenous therapy.

ATS COPD Practice Guidelines-Focused Approach

In 2020, ATS released a focused update for the chronic management of COPD (Nici 2020). The guideline sought to answer six questions regarding the management of COPD based on the literature available through 2019. The topics include the safety and efficacy of dual bronchodilator therapy versus monotherapy, dual bronchodilator therapy versus triple therapy, withdrawal of ICS therapy, use of eosinophils to add on ICS therapy, use of maintenance oral corticosteroids, and the use of opioids in advanced refractory dyspnea. The ATS recommendations on inhaled therapies compared with the GOLD report and NICE guidelines are listed in Table 3.

The ATS practice guidelines align with the GOLD report recommendations against the routine use of maintenance oral corticosteroids for patients with a history of severe exacerbations. The authors cite the lack of benefit in outcomes such as mortality, exacerbations, hospital admission and dyspnea with an increase in adverse events as rationale for this recommendation (NICE 2020). Lastly, the use of opioid therapy for advanced refractory dyspnea is conditionally recommended as a part of shared decision-making with the patient.

Together with the European Respiratory Society (ERS), ATS published their most recent guidance statement on the prevention and management of AECOPD in 2017 (Wedzicha 2017). This statement addresses several AECOPD

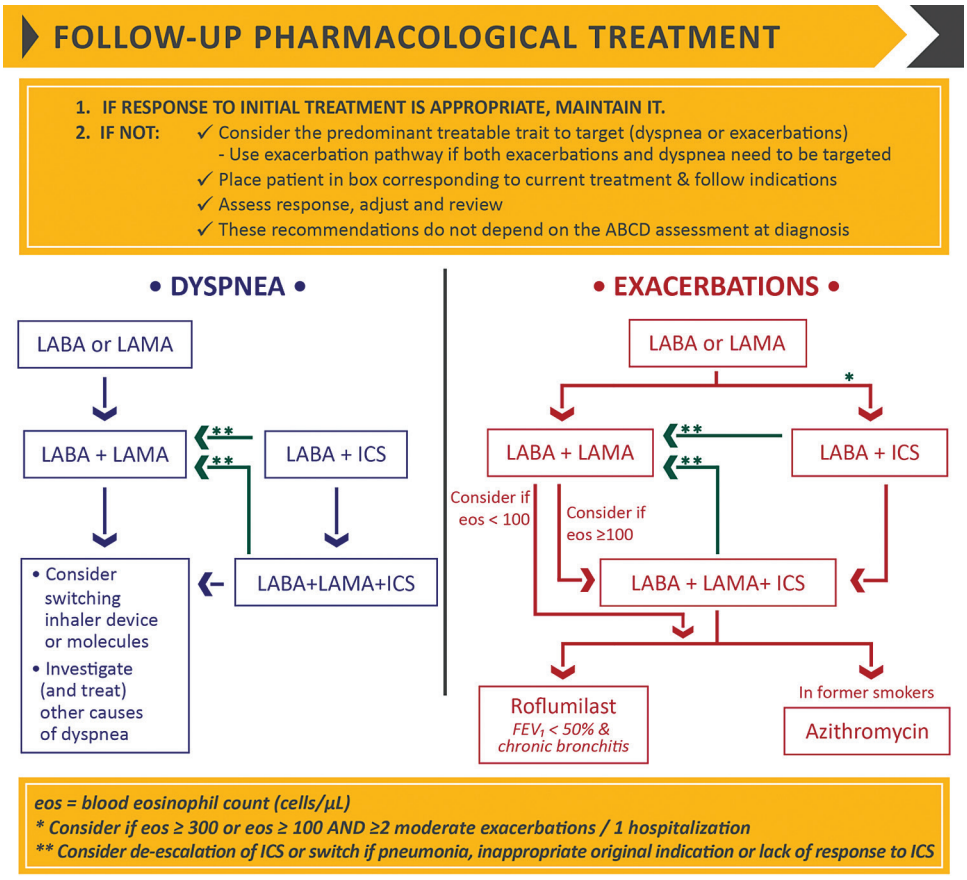

Figure 3. Follow-up pharmacologic therapy for worsening symptoms or new exacerbations of COPD.

COPD = chronic obstructive pulmonary disease; EOS = blood eosinophil count; FEV_1 = forced expiratory volume at 1 second; ICS = inhaled corticosteroids; LABA = long-acting β-2 agonist; LAMA = long-acting muscarinic antagonist.

Table 2. Severity of COPD Exacerbations

Severity	Definition
Mild	SABD only
Moderate	SABD + antibiotic therapy +/– systemic corticosteroids
Severe	Symptoms require ED visit or hospitalization

COPD = chronic obstructive pulmonary disease; SABD = short-acting bronchodilator.

Information from Global Initiative for Chronic Obstructive Lung Disease (GOLD). GOLD 2022 global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2022 report. Available at https://goldcopd.org/2022-gold-reports/.

management issues, including the use of oral corticosteroids and antibiotics in ambulatory patients, in addition to discussing the literature on the appropriate duration of systemic corticosteroids. Similar to the GOLD report, ATS endorses the use of oral corticosteroids for ambulatory patients experiencing an AECOPD. However, ATS is less specific in recommending a duration of therapy 14 days or less. Similarly, the ATS/ERS group suggests that the use of antibiotics may be beneficial in patients for AECOPD when sputum purulence is present. Furthermore, ATS/ERS acknowledges that patients with other risk factors may be candidates for antibiotic therapy.

NICE COPD Guideline

The NICE guideline was published in 2018 and last updated in July 2019. Similar to the GOLD report, NICE provides an algorithmic approach to initiating and escalating therapy with guidelines to de-escalate ICS therapy when appropriate. Although this guideline addresses the use of EOS counts to guide therapy decision-making, it predates more recent

Table 3. Comparison of COPD Drug Therapy Recommendations by Evidenced-Based Guideline

Recommended Therapy	GOLD	ATS	NICE
Dual bronchodilator therapy: LABA + LAMA	Initial therapy in highly symptomatic patients[a] —OR— Symptoms or exacerbations despite monotherapy	Exercise intolerance and dyspnea despite monotherapy	Initial scheduled therapy if no asthmatic features[b]
Dual therapy: LABA + ICS	EOS ≥ 300 cells/mm^3 —OR— EOS ≥ 100 cells/mm^3 AND ≥ 2 moderate exacerbations OR 1 hospitalization	Consider adding ICS if patient has an exacerbation requiring antibiotic or systemic corticosteroids	Asthmatic features[b]
Triple therapy: LABA + LAMA + ICS	Symptoms or exacerbations despite LABA + ICS therapy —OR— Exacerbations despite dual bronchodilator therapy and EOS ≥ 100 cells/mm^3	Exercise intolerance and dyspnea despite dual bronchodilator therapy —OR— ≥ 1 moderate or severe exacerbation in past 12 mo No guidance for or against using EOS > 150 cells/mm^3	1 severe or 2 moderate exacerbations in past 12 mo —OR— Symptoms that affect quality of life
Withdrawal of ICS therapy	If inappropriate initial indication, pneumonia, or lack of response	If exacerbation-free for 12 mo on triple therapy	If no response after 3 mo on triple therapy

[a]GOLD category D and CAT score greater than 20.

[b]History of asthma or atopy, higher EOS, greater than or equal to 400 mL variation in FEV_1 over time or greater than or equal to 20% daily variation in peak expiratory flow.

ATS = American Thoracic Society; COPD = chronic obstructive lung disease; EOS = blood eosinophil count; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist, LAMA = long-acting muscarinic antagonist; NICE = National Institute for Healthcare and Excellence.

Information from Global Initiative for Chronic Obstructive Lung Disease (GOLD). GOLD 2022 global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2022 report. Available at https://goldcopd.org/2022-gold-reports/; Nici L, Mammen MJ, Charbek E, et al. Pharmacologic management of COPD: an official ATS clinical practice guideline. Am J Respir Crit Care Med 2020;201:e56-369; National Institute for Healthcare and Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management; NICE guideline [NG 115] December 5, 2018. Available at www.nice.org.uk/guidance/ng115.

studies. Comparison of the guideline recommendations from GOLD, ATS and NICE highlighted in this chapter are listed in Table 3.

COVID-19 AND COPD

During the coronavirus disease 2019 (COVID-19) pandemic, patients with COPD have faced many challenges, such as sheltering in place, which has compromised their ability to seek routine care and potentially resulted in worsening of disease. It has also been hypothesized that patients with COPD are at greater risk of negative outcomes from COVID-19 infection. However, data are conflicting to support whether COPD is an independent risk factor for severe outcomes of COVID-19. A statement by GOLD authors addresses several key issues such as the role of spirometry, use of clinical monitoring with remote technology, need for alteration of pharmacotherapy, and use of nebulized therapy in patients with COPD during the COVID-19 pandemic (Halpin 2020).

Spirometry Testing

Spirometry testing is a high droplet-producing procedure that can place the patient and health care professionals at a greater risk of exposure to COVID-19. Given this potential risk, several guidance statements have been released on the safe and appropriate use of spirometry during the pandemic. The use of spirometry testing in areas of high community transmission should be avoided unless needed to make urgent therapeutic decisions (American Thoracic Society 2020). Patients should be referred to a full pulmonary laboratory if testing is absolutely needed and full personal protective equipment is available to the staff performing the testing.

Patient Care Scenario

A 64-year-old man with a 10-year history of COPD uses salmeterol/fluticasone 250/50 mcg 1 puff twice daily by dry powder inhaler. Post-bronchodilator spirometry shows an FEV_1/FVC of 0.64 and FEV_1 48% of predicted, with EOS of 90 cells/mm^3. His history includes one exacerbation that did not require hospitalization in the past year and treatment for community-acquired pneumonia.

Today, the patient presents to the primary care clinic with worsening dyspnea and an increase sputum production and purulence. After appropriate assessment, it is determined that he is experiencing AECOPD.

What is the best patient care plan for the acute and maintenance treatment of this patient's COPD?

ANSWER

This patient is experiencing a moderate AECOPD and requires systemic corticosteroid therapy. The patient should receive prednisone 40 mg/day for 5 days because a longer duration may increase the risk of adverse effects without any added benefit. Because the patient is presenting with sputum purulence, antibiotic therapy is indicated. Antibiotic selection should be based on local resistance patterns. In addition, because the patient has a recent history of treatment for pneumonia, it is reasonable to consider a gradual withdrawal of ICS to minimize the risk of subsequent episodes of pneumonia. The patient should be using dual bronchodilator therapy before withdrawal because this approach is proven to be safe.

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). GOLD 2022 global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2022 report. Available at https://goldcopd.org/2022-gold-reports/.
2. Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. JAMA 2013;309:2223-31.
3. Magnussen H, Watz H, Kirsten A, et al. Stepwise withdrawal of inhaled corticosteroids in COPD patients receiving dual bronchodilation: WISDOM study design and rationale. Respir Med 2014;108:593-99.

Remote Monitoring

During the COVID-19 pandemic, health-systems and outpatient clinics have limited their use of face-to-face visits to minimize the risk of COVID-19 transmission and have embraced the telehealth and remote monitoring to care for at-risk patients. The 2022 GOLD report includes a detailed checklist on completing a remote monitoring visit, either by telephone or virtually (GOLD 2022b). The checklist includes seven main topics to review with the patient during the encounter, as follows: 1) baseline symptoms, 2) COVID-19 assessment, 3) previous action plans, 4) recent admissions or ED visits, 5) COPD self-management, 6) main issues, and 7) summary intervention and plan. Although this checklist is mainly geared toward the management of COPD patients in the remote monitoring environment, it contains components that can be applied to any encounter type and serves as a useful tool for pharmacists participating in patient care.

Inhaled Therapy and COVID-19 Infection

Presently, no evidence is available to support alteration of pharmacologic therapies during the COVID-19 infection. However, the GOLD group recommends that patients should avoid the use of nebulized therapy specifically in an institutional setting to reduce the risk of COVID-19 transmission by this high droplet-producing treatment (McCormack 2020). In addition, no evidence suggests that patients with COPD and COVID-19 require different pharmacotherapy to treat their acute illness. Systemic corticosteroids and antibiotics should be used to treat AECOPD, either alone or as a co-infection of COVID, if indicated.

Pharmacists are well positioned to educate patients on differentiating between their normal daily COPD symptoms from potential COVID-19 symptoms. The main symptoms of mild COVID, defined as disease that does not require hospitalization or ED visit, that can be differentiated from COPD are fever, worsening shortness of breath (beyond baseline symptoms), dry cough, fatigue, and diarrhea (McCormack 2020). Patients experiencing these symptoms should seek medical attention for COVID-19 testing and appropriate care during their illness.

PHARMACIST-LED INTERVENTIONS

Pharmacists are among the most qualified health care professionals to develop care plans for COPD and select the appropriate inhaled pharmacologic therapies. Patient adherence and proper inhaler technique are of utmost importance in ensuring that patients are receiving the most benefit from their inhaled medications. Several studies have demonstrated the benefit of pharmacist-led interventions to promote proper technique and adherence.

One recent meta-analysis examined the benefit of pharmacist-led interventions on inhaler adherence and technique in patients with either COPD or adult asthma (Jia 2020). Studies were included if the design was a randomized controlled trial that enrolled adult patients with either COPD or asthma and if the primary intervention was pharmacist-led. A total of 13 studies were included in the final analysis. Of these, 10 studies reported data on medication adherence and seven reported data on inhalation technique. Despite heterogeneity in the method of reporting medication adherence (e.g., validated adherence scores, medication fill data),

Practice Points

- **Evidence supports a patient-centered approach to initiating and optimizing inhaled pharmacologic therapies in the management of stable COPD.**
- **The use of EOS to stratify which patients may benefit the most of ICS combination therapy (either dual or triple) is an emerging area of research.**
- **Bronchodilators remain the cornerstone of therapy and should be considered as initial therapy in most patients.**
- **Triple therapy may have a positive effect on lung function and symptoms and may reduce the risk of exacerbations and mortality in symptomatic patients with severe COPD who have a history of exacerbations.**
- **Patient adherence and inhaler technique should always be assessed and corrected, if necessary, before considering intensification of therapy.**

the authors found a significant improvement in medication adherence in patients receiving pharmacist-led interventions compared with usual care (risk ratio [RR] 1.34 [95% CI 1.18-1.52]). In the studies that reported inhaler technique, there was a significantly higher number of patients demonstrating proper inhaler technique in the pharmacist-led intervention arms compared with usual care (risk ratio 1.85; 95% CI 1.57–2.17). This analysis demonstrates the positive impact and important role pharmacists can play in the management of patients with COPD. Pharmacists should be included in the COPD care team to improve adherence and inhaler technique, known factors to improve patient outcomes.

CONCLUSION

The management of COPD is continuously evolving, with a recent and dramatic increase in emerging literature that explores the appropriate management. Given these data, a patient-centered approach is most appropriate. Pharmacists are well positioned to aid in the implementation of evidence-based therapy and to provide patient education.

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