Strategies to Improve Outcomes in COPD

Barbara Yawn, MD, MSc, FAAFP

doi: 10.12788/jfp.0413

FACULTY

Barbara Yawn, MD, MSc, FAAFP, Department of Family and Community Health, Adjunct Professor, University of Minnesota.

DISCLOSURES

Dr. Yawn discloses that she serves on the advisory board of Boehringer Ingelheim, AstraZeneca, and GlaxoSmithKline. She also serves as a consultant to Boehringer Ingelheim and GlaxoSmithKline. Julie Akers, PharmD, discloses that she is on an advisory board for AstraZeneca.

ACKNOWLEDGMENT

Editorial support was provided by Julie Akers, PharmD.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and the Primary Care Respiratory Group and supported by funding from AstraZeneca.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease with no cure.[1] Despite being preventable and treatable, COPD is in the top 3 causes of mortality worldwide,[2] is the sixth leading cause of death in the United States,[1] and is a major cause of morbidity and healthcare expenditures.

COPD is expected to become more prevalent due to an aging population and risk factors such as smoking and air pollution.[3] While there are several risk factors for COPD, such as air pollution, exposure to fuel, and genetic or developmental abnormalities, smoking tobacco is the most common contributing factor in the United States[4] and is rapidly becoming a major risk factor in developing countries.[5,6]

COPD is estimated to contribute to nearly $40 billion in annual US healthcare expenditures.[7] The largest contributing factor to the economic burden of COPD is exacerbations, especially those frequent or severe enough to require emergency department visits or hospitalizations. In addition, cost of care directly correlates with disease progression and worsening symptoms with higher rates of comorbidities, polypharmacy, hospitalizations, and oxygen therapy.

This economic burden is also directly related to treatment for comorbidities, their impact on COPD progression, as well as the impact of COPD exacerbations on the comorbidities. Common comorbidities include diabetes, cardiovascular disease (CVD), lung cancer, gastroesophageal reflux disease, osteoporosis, depression, and anxiety.

According to the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) 2022 Report, several comorbid conditions can negatively impact COPD patient outcomes and vice versa.[8] Data spanning 35 years found that patients with COPD had a 2 to 5 times higher risk of ischemic heart disease than those without COPD.[9] In another study, the risk for a cardiovascular event was 10 times greater during the first 30 days following a COPD exacerbation that required hospitalization.[10] Therefore, the goals of management have shifted toward reducing symptoms, preventing exacerbations, and decreasing the risk of premature death.

DIAGNOSING AND ASSESSING THE SEVERITY OF COPD

Along with CVD, COPD has been shown to be an important primary consideration in the differential diagnosis of shortness of breath, frequent coughing or wheezing, sputum production, fatigue, and difficulty with deep inhalation.[8] While these symptoms plus smoking or other inhalation exposures, premature birth, age >40 years, and family history are key indicators, they are not diagnostic without spirometry confirmation.[8] The differential diagnoses include asthma, CVD, congestive heart failure, bronchiectasis, tuberculosis, lung cancer, cystic fibrosis, chronic allergic rhinitis, and gastroesophageal reflux disease.[8] Spirometry is the primary diagnostic tool to confirm COPD, with a postbronchodilator ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) of <0.7 indicative of COPD.[11] Spirometry will not rule out other comorbidities but is necessary to "rule in" COPD.

Patient-reported symptoms can be assessed using the modified Medical Research Council (mMRC) questionnaire, which measures breathlessness and assigns a grade of 0 to

4.[12] The COPD Assessment Test (CAT) is a comprehensive health status questionnaire that incorporates additional factors beyond breathlessness, such as frequency of cough and symptom impact on daily activities. CAT scores range from 0 to 40.[13] An mMRC grade of ≥2 or a CAT score of ≥10 indicates that the patient has a significant symptom burden. The mMRC is shorter but not as responsive to change as the CAT, but both are included in the GOLD 2022 ABCD Assessment Tool to guide treatment decisions.

GOLD recommendations are reviewed and updated annually based on emerging evidence; they recommend assessment of a patient's COPD status including airflow limitation, patient-reported symptoms, and exacerbation history to help predict patient outcomes and guide treatment decision-making.[8] Severity of airflow limitation is divided into 4 grades based on FEV_1: GOLD 1 (mild), an FEV_1 ≥80% predicted; GOLD 2 (moderate), an FEV_1 ≥50% and <80% predicted; GOLD 3 (severe), an FEV_1 ≥30% and <50% predicted; and GOLD 4 (very severe), an FEV_1 <30% predicted. These grades can be helpful in guiding timing for oxygen therapy evaluation.

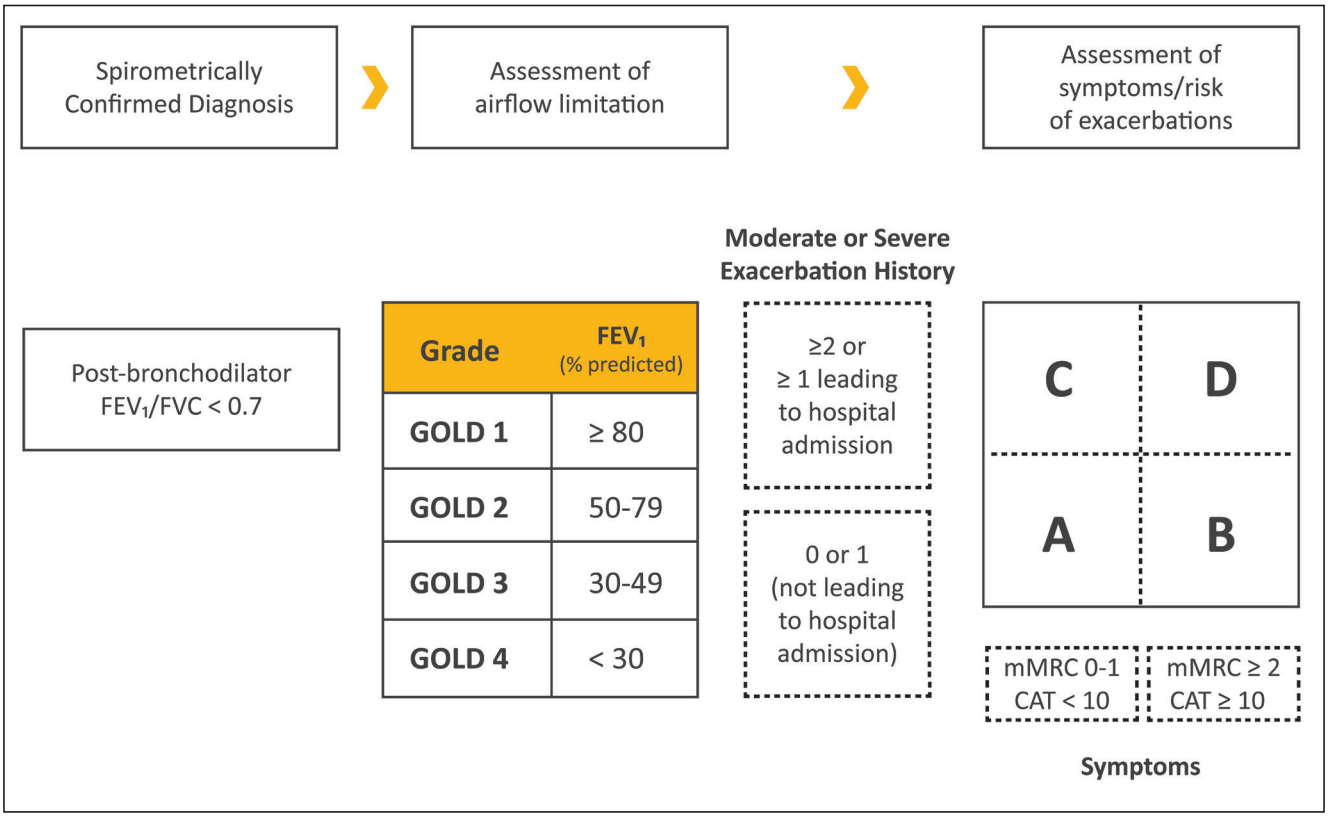
THE IMPORTANCE OF REDUCING COPD EXACERBATIONS

Exacerbations are defined as an acute worsening of respiratory symptoms, including dyspnea, cough, and wheeze, and increased sputum purulence and volume, which necessitate additional therapy. Exacerbations have a negative effect on lung function and mortality,[14-16] and a history of exacerbations is a strong predictor of future exacerbations.[8]

Exacerbation assessment is grouped into low and high risk of future events based primarily on history of previous exacerbations, with lower risk indicated by 0 to 1 exacerbations not requiring hospitalization in the prior 12 months. Higher risk is indicated by the occurrence of ≥2 exacerbations not requiring hospitalization in the prior 12 months or ≥1 exacerbation that led to a hospital admission. The results of patient-reported symptoms and exacerbation history are combined to determine placement into groups A, B, C, or D; the resultant grouping is then used to guide initial pharmacologic treatment decisions (**FIGURE 1**).[8]

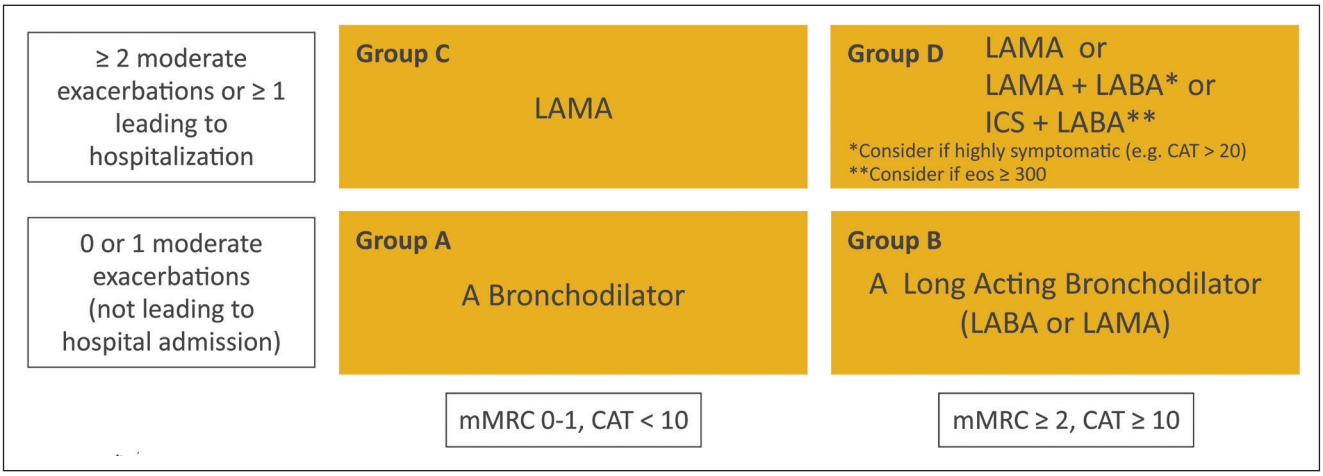
Exacerbation severity is classified by the treatments used to manage them. Mild exacerbations require only short-acting

FIGURE 1: **The refined ABCD assessment tool**



Source: Used with Permission © 2021, Global Initiative for Chronic Obstructive Lung Disease, available from www.goldcopd.org, published in Deer Park, IL.[8]

FIGURE 2. **Initial pharmacologic treatment**



Source: Used with Permission © 2021, Global Initiative for Chronic Obstructive Lung Disease, available from www.goldcopd.org, published in Deer Park, IL.[8]

beta agonist (SABA) or short-acting muscarinic antagonist (SAMA) therapy. Moderate exacerbations require oral corticosteroid and/or antibiotic therapy. Severe exacerbations require an emergency department (ED) visit or hospitalization.[8]

Both moderate and severe exacerbations reduce lung function in patients with COPD of all groups, with the greatest losses in those with milder disease.[14] Additionally, increasing frequency and severity of exacerbations is tied to an increased risk of death.[15] In 1 study, 43% of patients with 1 severe exacerbation died within 6 years posthospitalization, and that death rate increased to 56% for patients who experienced ≥2 severe exacerbations.[16]

MANAGING COPD EXACERBATIONS

COPD exacerbations can be brought on by several factors, with respiratory tract infections being the most common.[8] While management of acute exacerbations focuses on immediate symptom resolution, the long-term goal is to prevent future exacerbations and mortality. That prevention starts by ensuring a follow-up appointment within about 1 week of an exacerbation, especially a severe exacerbation, to reduce rehospitalization and ED visits. Those patients not seen within 30 days of an exacerbation have an increased 90-day mortality rate.[17]

The postexacerbation visits should address exacerbation prevention measures, such as reassessing inhaler technique, adherence, smoking status, and irritant exposures as well as monitoring patient-reported symptoms (mMRC/CAT).

This is also an excellent opportunity to discuss pulmonary rehabilitation and evaluate comorbid conditions. Studies report that only 20% to 30% of patients are adherent to their prescribed COPD regimen,[18,19] and inhaler technique errors may occur in >50% of cases.[20] For some people, medication therapy management and counseling or adherence coaching have been shown to be helpful.[21] This may also be a good time to schedule repeat spirometry testing to assess COPD progression.

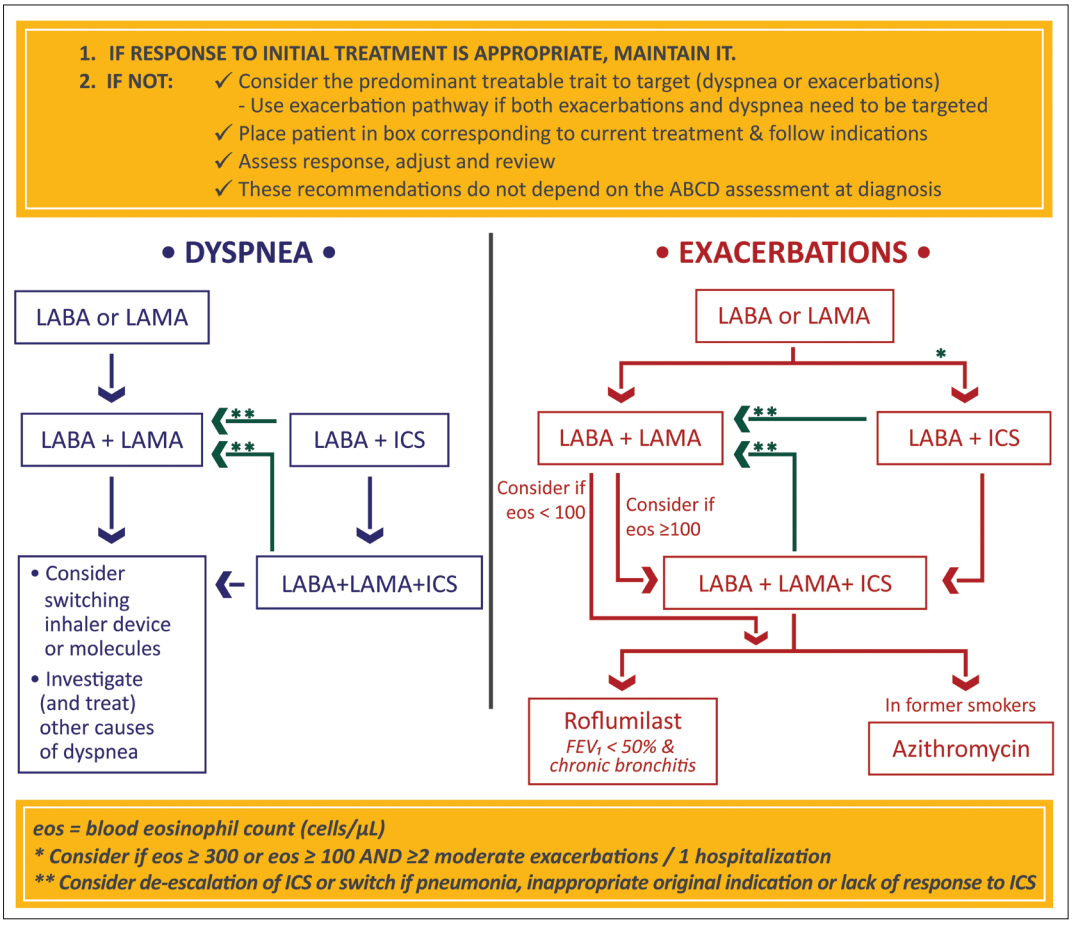
PHARMACOLOGIC TREATMENT OPTIONS

The goal of maintenance therapy is to reduce symptoms and exacerbations. The cornerstone of maintenance therapy is a pharmacologic approach based on symptoms, exacerbations, patient preference, side effects, costs, access, and patient ability to use the drug delivery device.

The GOLD ABCD Assessment Tool guides initial pharmacologic therapy choices (**FIGURE 2**).[8] All patients diagnosed with COPD should be prescribed a short-acting bronchodilator, such as a SABA or SAMA, for quick relief of increased shortness of breath or cough. For patients in group A, this can be the only therapy, but few people are diagnosed at this level of COPD. Patients in group B should be prescribed a long-acting bronchodilator, either a long-acting beta agonist (LABA) or long-acting muscarinic antagonist (LAMA) initially or in combination for those with greater breathlessness.

Patients in groups C and D have a greater risk of exacerbations, which guides their initial pharmacotherapy. Those in group C are recommended to begin therapy with a LAMA preferred over a LABA since LAMAs may be more effective in preventing exacerbations. Those in group D can be initiated on a LAMA, with dual therapy with LAMA + LABA if the CAT is >20 and adding an inhaled corticosteroid (ICS) if the blood eosinophil count is ≥300 cells/μL. ICS is used to prevent exacerbations, with recent recommendations noting that ICS is more effective in individuals with higher blood eosinophil counts.[22] Therefore, the choice to initiate ICS therapy is based on exacer-

FIGURE 3. **Follow-up pharmacologic treatment**



Source: Used with Permission © 2021, Global Initiative for Chronic Obstructive Lung Disease, available from www.goldcopd.org, published in Deer Park, IL.[8]

bation prevention, treatment of coexisting asthma, and blood eosinophilia, balanced against risks in those with repeated pneumonia events or mycobacterial infection. Depending on response to initial pharmacologic therapy, adjustments to the patient's regimen may be warranted. **FIGURE 3**[8] provides follow-up treatment guidance and is separated into 2 sections—one for patients presenting with continued or worsening dyspnea, and the other for those presenting with frequent new or continuing exacerbations. If the patient presents with both exacerbations and dyspnea, the exacerbation pathway is used. Additional therapies may include moving to 2 bronchodilators or adding ICS or a phosphodiesterase-4 inhibitor or long-term antibiotic therapy. The figure includes recommendations for de-escalating therapy, such as discontinuation of ICS in those without exacerbations.

The timing of pharmacologic adjustments may play an important role in reducing future risk. In the PRIMUS study published in 2022,[23] researchers evaluated exacerbation frequency, all-cause and COPD-related healthcare utilization, and costs among patients who had experienced ≥2 moderate or ≥1 severe exacerbation and who started triple therapy within 30 days of the exacerbation (prompt), between 31 and 180 days postexacerbation (delayed), and 181 and 365 days postexacerbation (very delayed). Results showed 11% increased odds for any exacerbation and 7% increased odds of a hospitalization for every 30-day delay in triple therapy. Additionally, both all-cause and COPD-related costs increased as a result of delayed triple therapy.

The PRIMUS study results reinforce the need for prompt patient-clinician communication regarding increased symptoms and follow-up visits within days after an ED visit or hospitalization for an exacerbation to ensure therapy is appropriately and promptly modified.

Two single-inhaler triple therapies (SITT) are available in the United States, making it easier to prescribe ICS + LAMA + LABA in a single inhaler. Two large, 52-week, phase 3 studies (IMPACT and ETHOS) evaluated the effect of SITT vs LABA + ICS or LAMA + LABA on exacerbations, lung function, quality of life, and all-cause mortality. In these studies of symptomatic patients with a history of frequent and/or severe exacerbations, triple therapies reduced the rate of moderate or severe exacerbations and COPD-related hospitalizations. Additionally, a beneficial effect on all-cause mortality was observed with triple therapies vs LAMA + LABA.[24,25]

NONPHARMACOLOGIC RECOMMENDATIONS FOR COPD

To address COPD holistically requires assessment of the

impact of COPD on patients' current and desired activity capabilities, exacerbations, and patient and family preferences, as well as comorbidities. Management includes prevention and maintenance interventions, which range from lifestyle modifications to prescription therapies.

A 2020 survey noted that the smoking rate among US patients with COPD was >45%, which is higher than among patients with other chronic diseases (23%), asthma (20%), and no chronic disease (18.9%).[26] Smoking cessation can greatly improve disease prognosis. Successful smoking cessation programs include a multimodal approach incorporating counseling, nicotine replacement therapy, and other prescription pharmacologic products. Electronic cigarettes are not recommended for nicotine replacement therapy, as several studies indicate a link to lung injury and death.[27-30]

While smoking abstinence is the primary preventative measure to reduce exacerbations and slow disease progression, other measures to avoid irritants and infections including COVID-19 (masking, hand washing, distancing) and vaccination against influenza, pneumonia, COVID-19, pertussis (Tdap), and shingles are important.[8]

Additionally, patients in GOLD ABCD groups B to D should be considered for pulmonary rehabilitation, which formalizes a physical activity plan with goal setting, supervised exercise, smoking cessation, nutrition education, and tools for self-management. When pulmonary rehabilitation is not available, activity goal setting can increase exercise and activities.

EDUCATION AND FOLLOW-UP

Patient education and routine follow-up are important elements of a COPD care plan. Rapid COPD assessment tools such as the CAT or mMRC can provide a quick assessment of continuing or new disease burden and can be done while the patient is waiting in the examination room. Developing a written action plan to address daily therapy and increase patient awareness of early symptom exacerbation are cornerstones of COPD self-management. At every visit it is important to assess the patient's ability to adhere to therapy by asking nonjudgmental questions such as, "How often are you able to take all of your medicines?" "Do you have any problems getting or paying for your medicines?" Reviewing and observing inhaler technique repeatedly is beneficial since technique adequacy often declines 3 to 6 months after the initial instructions. Ask patients to bring their inhalers to each visit since the exact type or brand of inhaler may vary from what was prescribed due to insurance or cost requirements. For people with low adherence, motivational interviewing techniques may help address issues. A quick assessment of adequate sleep, a healthy diet, and regular exercise can identify areas for future support and emphasize the importance of a more in-depth program such as pulmonary rehabilitation.

Discuss avoiding exacerbation triggers like upper respiratory infections and continually reinforce the importance of smoking abstinence and avoidance if the patient continues to smoke or is around others who smoke. Review vaccination history and make appropriate recommendations based on the Advisory Committee on Immunization Practices vaccine schedule, the GOLD 2022 Report, and Centers for Disease Control and Prevention recommentations.[31] Patients with COPD should be seen every 3 to 6 months, depending on disease severity and frequency of exacerbations. The schedule for repeating spirometry varies based on initial results and the course of the COPD. Those with a greater symptom burden and more frequent exacerbations should have more frequent spirometry testing, which may guide therapy and timing of referral to a pulmonologist or allergist.

CASE SCENARIO PART 1

A 67-year-old woman is new to your practice. She reports she was diagnosed with COPD 2 years prior, when she was experiencing dyspnea and a chronic cough. She had a CAT score of 12 and no exacerbation history, was categorized in group B, and was prescribed a SABA and a LAMA. Six months after diagnosis, she experienced an exacerbation that was treated with oral steroid therapy. At that time, her daily maintenance therapy was not changed—she says she was told to remain on the LAMA, which she says she uses most days. She presents today with a chief complaint of increased breathlessness and cough for approximately 2 weeks that is not manageable with the SABA, used as needed, in addition to her daily LAMA. Her past medical history includes hypertension (controlled with an angiotensin-converting enzyme inhibitor for the past 10 years) and osteoporosis (treated with bisphosphonate). She smoked for 30 years, quitting 2 years ago when diagnosed with COPD. She states she receives an annual influenza vaccination and has had her COVID-19 vaccines and a booster as well as recent Tdap and shingles vaccine series.

Spirometry: postbronchodilator FEV_1 = 47%
CAT = 24
Eosinophil = 150 cells/μL
Oxygen saturation = 91% at rest
CT = no infiltrates, no signs of bronchiectasis, significant emphysema, or lung masses. Cardiac size is not increased

CASE SCENARIO PART 2: CLINICAL RESPONSE

It is important to consider alternative reasons for her increased dyspnea, such as COVID-19 or new cardiovascular symptoms vs a COPD exacerbation. She reports getting a COVID test at the drug store last week and again yesterday and both were nega-

tive. She has no current arrhythmias or complaints of chest pains, weight gain, or edema. Since she complains primarily of dyspnea, this could be the start of an exacerbation. This is especially important to consider since her FEV_1 is lower than anticipated. Her pulse oxygen level falls in the 88% to 92% range targeted for most COPD patients[32] and does not suggest that immediate hospitalization is necessary.

Because this may be an exacerbation, therapy will be both short-term use of an oral corticosteroid burst and consideration of modifying her current therapy. Since she is already on pharmacotherapy, it is appropriate to use the follow-up therapy flow diagram (**FIGURE 3**) to decide on modifications. The next step would be to move to dual bronchodilator therapy with LAMA + LABA and continue the SABA as needed.

She may soon become a candidate for triple therapy by adding an ICS to her LAMA + LABA if she experiences another exacerbation and her eosinophil count remains >100 cells/μL. Triple therapy has been shown to improve lung function and patient-reported outcomes and reduce exacerbations when compared with LAMA, LABA + LAMA, and LABA + ICS. Azithromycin may also be considered as add-on therapy as the patient is a former smoker and does not have chronic bronchitis.

The patient needs to have a follow-up visit in 7 to 10 days and receive details on how to contact the physician's office if her dyspnea progresses. It would also be appropriate to retest her spirometry in 6 to 8 weeks to see if the values reflect an exacerbation or disease progression. The follow-up visit is an excellent time to discuss pulmonary rehabilitation opportunities, to develop a COPD action plan, and to provide additional education and support. ●

REFERENCES

1. Centers for Disease Control and Prevention. What is COPD? Published December 9, 2020. Accessed April 18, 2022. https://www.cdc.gov/copd/index.html
2. World Health Organization. The top 10 causes of death. Accessed April 18, 2022. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
3. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3(11):e442.
4. Centers for Disease Control and Prevention. Annual smoking-attributable mortality, years of potential life lost, and productivity losses—United States, 1997–2001. *MMWR Morb Mortal Wkly Rep*. 2005;54(25):625-628.
5. Lopez AD, Shibuya K, Rao C, et al. Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J*. 2006;27(2):397-412.
6. World Health Organization. Global Health Estimates: Life expectancy and leading causes of death and disability. Accessed July 2022. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates
7. Foster TS, Miller JD, Marton JP, Caloyeras JP, Russell MW, Menzin J. Assessment of the economic burden of COPD in the U.S.: a review and synthesis of the literature. *COPD*. 2006;3(4):211-218.
8. *Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: 2022 Report*. Global Initiative for Chronic Obstructive Lung Disease. Accessed April 19, 2022. https://goldcopd.org/wp-content/uploads/2021/12/GOLD-REPORT-2022-v1.1-22Nov2021_WMV.pdf
9. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med*. 2015;3:631-639.
10. Kunisaki KM, Dransfield MT, Anderson JA, et al. Exacerbations of chronic obstructive pulmonary disease and cardiac events. A post hoc cohort analysis from the SUMMIT Randomized Clinical Trial. *Am J Respir Crit Care Med*. 2018;198(1):51-57.
11. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet*. 2007;370(9589): 741-750.
12. mMRC (modified Medical Research Council) dyspnea scale. MD+CALC. Accessed April 18, 2020. https://www.mdcalc.com/mmrc-modified-medical-research-council-dyspnea-scale
13. The COPD Assessment Test (CAT). Accessed April 18, 2022. https://www.catestonline.org
14. Dransfield MT, Kunisaki KM, Strand MJ, et al; COPDGene Investigators. Acute exacerbations and lung function loss in smokers with and without chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2017;195(3):324-330.
15. Rothnie KJ, Müllerová H, Smeeth L, Quint JK. Natural history of chronic obstructive pulmonary disease exacerbations in a general practice-based population with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2018;198(4):464-471.
16. Blagev DP, Collingridge DS, Rea S, et al. Stability of frequency of severe chronic obstructive pulmonary disease exacerbations and health care utilization in clinical populations. *Chronic Obstr Pulm Dis*. 2018;5(3):208-220.
17. Gavish R, Levy A, Dekel OK, Karp e, Maimon N. The association between hospital readmission and pulmonologist follow-up visits in patients with COPD. *Chest*. 2015;148(2): 375-381.
18. Dhamane AD, Schwab P, Hopson S, et al. Association between adherence to medications for COPD and medications for other chronic conditions in COPD patients. *Int J Chron Obstruct Pulmon Dis*. 2016;12:115-122.
19. Neugaard BI, Priest JL, Burch SP, Cantrell CR, Foulis PR. Quality of care for veterans with chronic diseases: performance on quality indicators, medication use and adherence, and health care utilization. *Popul Health Manag*. 2011;14(2):99-106.
20. Molimard M, Raherison C, Lignot S, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. *Eur Respir J*. 2017;49(2):1601794.
21. Willard-Grace R, Chirinos C, Wolf J, et al. Lay health coaching to increase appropriate inhaler use in COPD: a randomized controlled trial. *Ann Fam Med*. 2020;18(1):5-14.
22. Singh D. Blood eosinophil counts in chronic obstructive pulmonary disease: a biomarker of inhaled corticosteroid effects. *Tuberc Respir Dis (Seoul)*. 2020;83(3):185-194.
23. Tkacz J, Evans KA, Touchette DR, et al. PRIMUS – prompt initiation of maintenance therapy in the US: a real-world analysis of clinical and economic outcomes among patients initiating triple therapy following a COPD exacerbation. Int J *Chron Obstruct Pulmon Dis*. 2022;17:329-342.
24. Lipson DA, Crim C, Criner GJ, et al. Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2020;201(12):1508-1516.
25. Rabe KF, Martinez FJ, Fergusun GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med*. 2020;383(1):35-48.
26. Montes de Oca M. Smoking cessation/vaccinations. *Clin Chest Med*. 2020;41(3):495-512.
27. He T, Oks M, Esposito M, Stienberg H, Makaryus M. "Tree-in-bloom": severe acute lung injury induced by vaping cannabis oil. *Ann Am Thorac Soc*. 2017;14(3):468-470.
28. Henry TS, Kanne JP, Klingerman SJ. Imaging of vaping-associated lung disease. *N Engl J Med*. 2019;381(15):1486-1487.
29. Layden JE, Ghinai I, Pray I, et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin–final report. *N Engl J Med*. 2020;382(10):903-916.
30. Centers for Disease Control and Prevention. Outbreak of lung injury associated with e-cigarette use, or vaping, products. Accessed April 18, 2020. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html
31. Centers for Disease Control and Prevention. Lung disease including asthma and adult vaccination. Accessed April 18, 2022. https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/lung-disease.html.
32. O'Driscoll BR, Howard LS, Earis J, Mak V. British Thoracic Society Guideline for oxygen use in adults in healthcare and emergency settings. *BMJ Open Respir Res*. 2017;4(1):e000170.