ABSTRACT

- **Objective:** Objective: To review the management of stable chronic obstructive pulmonary disease (COPD).
- **Methods:** Review of the peer-reviewed literature.
- **Results:** Effective management of stable COPD requires the physician to apply a stepwise intensification of therapy depending on patient symptoms and functional reserve. Bronchodilators are the cornerstone of management. In addition to pharmacologic therapies, nonpharmacologic therapies, including smoking cessation, vaccinations, proper nutrition, and maintaining physical activity, are an important part of long-term management. Those who continue to be symptomatic despite appropriate maximal therapy may be candidates for lung volume reduction. Palliative care services for COPD patients, which can aid in reducing symptom burden and improving quality of life, should not be overlooked.
- **Conclusion:** Successful management of stable COPD requires a multidisciplinary approach that utilizes various medical therapies as well as nonpharmacologic interventions.

Key words: chronic obstructive pulmonary disease; exacerbation; bronchodilator; lung volume reduction; cough.

COPD management is guided by disease severity that is measured using a multimodal staging system developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). The initial classification adopted by GOLD 2011 report encompassed 4 categories based on symptoms, number of exacerbations, and degree of airflow limitation on pulmonary function testing. However, in 2017 the GOLD ABCD classification was modified to consider only symptoms and risk of exacerbation in classifying patients regardless of performance on spirometry and FEV1 [7,8] (Figure 1). This approach was intended to make therapy more individualized based on the patient clinical profile. The Table displays a summary of the recommended treatments according to classification based on the GOLD 2017 report.

CASE 1

A 65-year-old male with COPD underwent pulmonary function testing (PFT), which demonstrated an obstructive ventilatory defect (forced expiratory volume in 1 second/forced vital capacity ratio [FEV1/FVC], 0.45; FEV1, 2 L [65% of predicted]; and diffusing capacity of the lung for carbon monoxide [DLCO], 15 [65% of predicted]). He has dyspnea with strenuous exercise but is comfortable at rest and with minimal exercise. He has had 1 exacerbation in the last year that was treated on an outpatient basis with steroids and antibiotics. His medication regimen includes inhaled tiotropium once daily and inhaled albuterol as needed that he uses roughly twice a week.

- **What determines the appropriate therapy for a given COPD patient?**

Chronic obstructive pulmonary disease (COPD) is a systemic inflammatory disease characterized by irreversible obstructive ventilatory defects [1–4]. It is a major cause of morbidity and mortality affecting 5% of the population in the United States and was the third leading cause of death in 2008 [5,6]. The goals in COPD management are to provide symptom relief, improve the quality of life, preserve lung function, and reduce the frequency of exacerbations and mortality. In this review, we will discuss the management of stable COPD in the context of 3 common clinical scenarios.
The patient in our clinical scenario can be classified as GOLD category B.

**What is the approach to building a pharmacologic regimen for the patient with COPD?**

The backbone of the pharmacologic regimen for COPD includes short- and long-acting bronchodilators. They are usually given in an inhaled form to maximize local effects on the lungs and minimize systemic side effects. There are 2 main classes of bronchodilators, beta agonists and muscarinic antagonists, and each targets specific receptors on the surface of airway smooth muscle cells. Beta agonists work by stimulating beta-2 receptors, resulting in bronchodilation, while muscarinic antagonists work by blocking the bronchoconstrictor action of M3 muscarinic receptors. Inhaled corticosteroids can be added to long-acting bronchodilator therapy but cannot be used as stand-alone therapy. Theophylline is an oral bronchodilator that is used infrequently due to its narrow therapeutic index, toxicity, and multiple drug interactions.

Figure 2 presents an approach to building a treatment plan for the patient with stable COPD.

• **Who should be on short-acting bronchodilators? What is the best agent? Should it be scheduled or used as needed?**

All patients with COPD should be on an inhaled short-acting bronchodilator as needed for relief of symptoms [7]. Both short-acting beta agonists (albuterol and levalbuterol) and short-acting muscarinic antagonists (ipratropium) have been shown in clinical trials and meta-analyses to improve symptoms and lung function in patients with stable COPD [9,10] and seem to have comparative efficacy when compared head-to-head in trials [11]. However, the airway bronchodilator effect achieved by both classes seems to be additive when used in combination and is also associated with less exacerbations compared to albuterol alone [12]. On the other hand, adding albuterol to ipratropium increased the bronchodilator response but did not reduce the exacerbation rate [11–13]. Inhaled short-acting beta agonists when used as needed rather than scheduled are associated with less medication use without any significant difference in symptoms or lung function [14].

The side effects related to using recommended doses of a short-acting bronchodilator are minimal. In retro-
spective studies, short-acting beta agonists increased the risk of severe cardiac arrhythmias [15]. Levalbuterol, the active enantiomer of albuterol (R-albuterol) developed for the theoretical benefits of reduced tachycardia, increased tolerability, and better or equal efficacy compared to racemic albuterol, failed to show a clinically significant difference in inducing tachycardia [16]. Beta agonist overuse is associated with tremor and in severe cases hypokalemia, which happens mainly when patients try to achieve maximal bronchodilation; the clinically used doses of beta agonists are associated with fewer side effects but achieve less than maximal bronchodilation [17]. Ipratropium can produce systemic anticholinergic side effects, urinary retention being the most clinically significant especially when combined with long-acting anticholinergic agents [18].

In light of the above discussion, a combination of short-acting beta agonist and muscarinic antagonist is recommended in all patients with COPD unless the patient is on a long-acting muscarinic antagonist [7,18]. In the latter case, a short-acting beta agonist used as a rescue inhaler is the best option. In our patient, albuterol was the choice for his short-acting bronchodilator as he was using the long-acting muscarinic antagonist tiotropium.

**• Are short-acting bronchodilators enough? What do we use for maintenance therapy?**

All patients with COPD who are category B or higher according to the modified GOLD staging system should be on a long-acting bronchodilator [7,19]: either a long-acting beta agonist (LABA) or long-acting muscarinic antagonist (LAMA). Long-acting bronchodilators work on the same receptors as their short-acting counterparts but have structural differences. Salmeterol is the prototype for long-acting selective beta-2 agonist. It is structurally similar to albuterol but has an elongated side chain that allows it to bind firmly to the area of beta receptors and stimulate them repetitively, resulting in an extended duration of action [20]. Tiotropium on the other hand

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**Table. GOLD Suggested Treatment Regimens Based on Severity of Disease [7]**

<table>
<thead>
<tr>
<th>Category</th>
<th>Suggested Regimen</th>
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| A (Less Symptoms, Low risk) | **First choice:** short-acting bronchodilator when needed; anticholinergic alone or beta-agonist alone  
**Second choice:** long-acting anticholinergic or long-acting beta agonist or short-acting beta-agonist and short-acting anticholinergic as needed  
**Alternative:** theophylline |
| B (More Symptoms, Low Risk) | Short-acting bronchodilator when needed and pulmonary rehabilitation  
**First choice:** regular treatment with a long-acting bronchodilator  
**Second choice:** regular treatment with a long-acting anticholinergic and long-acting beta agonist  
**Alternatives:** short-acting beta-agonist and/or short-acting anticholinergic, theophylline |
| C (Less Symptoms, High risk) | Short-acting bronchodilator when needed and pulmonary rehabilitation  
**First choice:** regular treatment with a combination long-acting beta agonist and inhaled glucocorticoid or a long-acting anticholinergic  
**Second choice:** regular treatment with a long-acting anticholinergic and a long-acting beta agonist  
**Alternatives:** phosphodiesterase-4 inhibitor, SABA and/or SAMA, theophylline  
Consider surgical treatments |
| D (More Symptoms, High risk) | Short-acting bronchodilator when needed and pulmonary rehabilitation  
**First choice:** regular treatment with combination inhaled glucocorticoid and a long-acting beta agonist and/or long-acting anticholinergic  
**Second choice:** regular treatment with one of the following combinations:  
Inhaled glucocorticoid and a long-acting beta agonist PLUS a long acting anticholinergic  
Inhaled glucocorticoid and a long-acting beta agonist PLUS a phosphodiesterase-4 inhibitor  
Long-acting anticholinergic and a long-acting beta agonist  
Long-acting anticholinergic and a phosphodiesterase-4 inhibitor  
**Alternatives:** carbocysteine, short-acting beta-agonist and/or short-acting anticholinergic, theophylline  
Consider surgical treatments |
is a quaternary ammonium of ipratropium that is a nonselective muscarinic antagonist [21]. Compared to ipratropium, tiotropium dissociates more quickly from M2 receptors, which is responsible for the undesired anticholinergic effects, while at the same time it binds M1 and M3 receptors for a prolonged time, resulting in extended duration of action [21].

The currently available long-acting beta agonists include salmeterol, formoterol, aformoterol, olodaterol, and indacaterol. The last two have the advantage of once-daily dosing rather than twice [22,23]. LABAs have been shown to improve lung function, exacerbation rate, and quality of life in multiple clinical trials [22–24]. Vilanterol is another LABA that has a long duration of action and can be used

Figure 2. Flowchart describing approach to treatment of a patient with stable COPD.
once daily [25], but is only available in a combination with umeclidinium, a LAMA. Several LAMAs are approved for use in COPD, including the prototype tiotropium in addition to aclidinium, umeclidinium, and glycopyrronium. These have been shown in clinical trials to improve lung function, symptoms, and exacerbation rate [26–29].

Patients can be started on either a LAMA or LABA depending on patient needs and side effects [7]. Both have comparable side effects and efficacy as detailed below. Concerning side effects, there is conflicting data concerning an association of cardiovascular events with both classes of long-acting bronchodilators. While clinical trials failed to show an increased risk [24,30,31], several retrospective studies showed an increased risk of emergency room visits and hospitalizations due to tachyarrhythmias, heart failure, myocardial infarction, and stroke upon initiation of long-acting bronchodilators [32,33]. There was no difference in risk for adverse cardiovascular events between LABA and LAMA in one Canadian study, and slightly more with LABA in a study using an American database [32,33]. Urinary retention is another possible complication of LAMA supported by evidence from meta-analyses and retrospective studies but not clinical trials and should be discussed with patients upon initiation [34,35]. There have been concerns about increased mortality with the soft mist formulation of tiotropium that were put to rest by the tiotropium safety and performance in Respimat (TIOSPIR) trial, which showed no increased mortality compared to Handihaler [36].

As far as efficacy and benefits, tiotropium and salmeterol were compared head-to-head in a clinical trial, and tiotropium increased the time before developing first exacerbation and decreased the overall rate of exacerbations [37]. No difference in hospitalization rate or mortality was noted in one meta-analysis, although tiotropium was more effective in reducing exacerbations [38]. The choice of agent should be made based on patient comorbidities and side effects. For example, an elderly patient with severe benign prostatic hyperplasia and urinary retention should try a LABA while for a patient with severe tachycardia induced by albuterol, LAMA would be a better first agent.

**What is the role of inhaled corticosteroids in COPD?**

Inhaled corticosteroids (ICS) are believed to work in COPD by reducing airway inflammation [39]. ICS should not be used alone for COPD management and are always combined with LABA [7]. Several inhaled corticosteroid formulations are approved for use in COPD, including budesonide and fluticasone. ICS has been shown to decrease symptoms and exacerbations with modest effect on lung function and no change in mortality [40]. Side effects include oral candidiasis, dysphonia, and skin bruising [41]. There is also an increased risk of pneumonia [42]. ICS are best reserved for patients with a component of asthma or asthma–COPD overlap syndrome (ACOS) [43]. ACOS is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD [44].

**What if the patient is still symptomatic on a LABA or LAMA?**

For patients whose symptoms are not controlled on one class of long-acting bronchodilator, recommendations are to add a bronchodilator from the other class [7]. There are also multiple combined LAMA-LABA inhalers that are approved in the US and can possible improve adherence to therapy. These include tiotropium-oladeterol, umeclidinium-vilanterol, glycopyronnium-indacaterol, and glycopyrrolate-formoterol. In a large systematic review and meta-analysis comparing LABA-LAMA combination to either agent alone, there was a modest improvement in post bronchodilator FEV1 and quality of life with no change in hospital admissions, mortality, or side effects [45]. Interestingly, adding tiotropium to LABA reduced exacerbations although adding LABA to tiotropium did not [45].

Current guidelines recommend that patients in GOLD categories C and D that are not well controlled should receive a combination of LABA-ICS [7]. However, a new randomized trial showed better reduction of exacerbations and decreased occurrence of pneumonia in patients receiving LAMA-LABA compared to LABA-ICS [46]. In light of this new evidence, it is prudent to use a LAMA-LABA combination before adding ICS.

Triple therapy with LAMA, LABA, and ICS is a common approach for patients with severe uncontrolled disease and has been shown to decrease exacerbations and improve quality of life [7,47]. Adding tiotropium to LABA-ICS decreased exacerbations and improved quality
of life and airflow in the landmark UPLIFT trial [26]. In another clinical trial, triple therapy with LAMA, LABA, and ICS compared to tiotropium alone decreased severe exacerbations, pre-bronchodilator FEV1, and morning symptoms [48].

• Is there a role for theophylline? Other agents?

Theophylline
Theophylline is an oral adenosine diphosphate antagonist with indirect adrenergic activity, which is responsible for the bronchodilator therapeutic effect in patients with obstructive lung disease. It is also thought to work by an additional mechanism that decreases inflammation in the airways [49]. It has a serious side effect profile that includes ventricular arrhythmias, seizures, vomiting, and tremor [50]. It is metabolized in the liver and has multiple drug interactions and a narrow therapeutic index. It has been shown to improve lung function, gas exchange and symptoms in meta-analysis and clinical trials [51,52].

In light of the nature of the adverse effects and the wide array of safer and more effective pharmacologic agents available, theophylline should be avoided early on in patients with COPD. Its use can be justified as an add-on therapy in patients with refractory disease on triple therapy for symptomatic relief [50]. If used, the therapeutic range for COPD is 8–12 mcg/mL peak level measured 3 to 7 hours after morning dose and is usually achieved using a daily dose of 10 mg per kilogram of body weight for nonobese patients [53].

Systemic Steroids
Oral steroids are used in COPD exacerbations but should never be used chronically in COPD patients regardless of disease severity as they increase morbidity and mortality without improving symptoms or lung function [54,55]. The dose of systemic steroids should be tapered and finally discontinued.

Mucolytics
Classes of mucolytics include thiol derivatives, inhaled dornase alpha, hypertonic saline, and iodine preparations. Thiol derivatives such as N-acetylcysteine are the most widely studied [56].

There is no consistent evidence of beneficial role of mucolytics in COPD patient [7,56]. The PANTHEON trial showed decreased exacerbations with N-acetylcysteine (1.16 exacerbations per patient-year compared to 1.49 exacerbations per patient-year in the placebo group; risk ratio 0.78, 95% CI 0.67–0.90; P = 0.001) but had methodologic issues including high drop-out rate, exclusion of patients on oxygen, and a large of proportion of nonsmokers [57].

Chronic Antibiotics
There is no role for chronic antibiotics in the management of COPD [7]. Macrolides are an exception but are used for their anti-inflammatory effects rather than their antibiotic effects. They should be reserved for patient with frequent exacerbations on optimal therapy and will be discussed later in the review [58].

• What nonpharmacologic treatments are recommended for COPD patients?

Smoking cessation, oxygen therapy for severe hypoxemia (resting O2 saturation ≤ 88 or PaO2 ≤ 55), vaccination for influenza and pneumococcus, and appropriate nutrition should be provided in all COPD patients. Pulmonary rehabilitation is indicated for patients in GOLD categories B, C, and D [7]. It improves symptoms, quality of life, exercise tolerance and health care utilization. Beneficial effects last for about 2 years [59,60].

• What other diagnoses should be considered in patients who continue to be symptomatic on optimal therapy?

Other diseases that share the same risk factors as COPD and can contribute to dyspnea, including coronary heart disease, heart failure, thromboembolic disease, and pulmonary hypertension, should be considered. In addition, all patients with refractory disease should have a careful assessment of their inhaler technique, continued smoking, need for oxygen therapy, and associated deconditioning.

CASE 2

A 70-year-old male with severe COPD on oxygen therapy and obstructive sleep apnea treated on nocturnal CPAP was seen in the pulmonary clinic for
evaluation of his dyspnea. He was symptomatic with minimal activity and had chronic cough with some sputum production. He had been hospitalized 3 times over the past 12 months and had been to the emergency department (ED) the same number of times for dyspnea. Pertinent medications included as-needed albuterol inhaler, inhaled steroids, and tiotropium 18 mcg inhaled daily. He demonstrated good inhaler technique. On examination, his vital signs were pulse 99 bpm, SpO₂ 94% on 2L/min oxygen by nasal cannula, blood pressure 126/72 mm Hg, respiratory rate 15, and BMI 35 kg/m². He appeared chronically ill but in no acute distress. No wheezing or rales were heard. He had no lower extremity edema. The remainder of the exam was within normal limits. His last pulmonary function test demonstrated moderate obstruction with significant bronchodilator response to 2 puffs of albuterol. The side effects of chronic steroid therapy were impressed upon the patient and 500 mg of roflumilast was started daily. Over the course of the next 3 months, he had no further exacerbations. Roflumilast was continued. He has not required any further hospitalizations, ED visits, or oral steroid use since the last clinic visit.

• What is the significance of acute exacerbations of COPD?

Acute exacerbation of COPD (AECOPD) is a frequently observed complication for many patients with COPD [61,62]. AECOPD is associated with accelerated disease progression, augmented decline in health status and quality of life, and increased mortality [63]. Exacerbations account for most of the costs associated with COPD. Estimates suggest that the aggregate costs associated with the treatment of AECOPDs are between $3.2 and $3.8 billion, and that annual health care costs are 10-fold greater for patients with COPD associated with acute exacerbations than for patients with COPD but without exacerbations [64]. Hence, any intervention that could potentially minimize or prevent this complication will have far-reaching benefits to patients with COPD as well as provide significant cost saving.

• How do acute exacerbations affect the course of the disease?

In general, as the severity of the underlying COPD increases, exacerbations become both more severe and more frequent. The quality of life of patients with frequent exacerbations is worse than patients with a history of less frequent exacerbations [68]. Frequent exacerbations have also been linked to a decline in lung function, with studies suggesting that there might be a decline of 7 mL in FEV1 per lower respiratory tract infection per year [59,69] and approximately 8 mL per year in patients with frequent exacerbations as compared to those with sporadic exacerbations [70].

• What are the triggers for COPD exacerbation?

COPD exacerbation is defined as a baseline change of the patient’s dyspnea, cough, and/or sputum that is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD [65]. Exacerbation in clinical trials has been defined on the basis of whether an increase in the level of care beyond regular care is required primarily in the hospital or ED [66]. Frequent exacerbations are defined as 3 symptom-defined exacerbations per year or 2 per year if defined by the need for therapy with corticosteroids, antibiotics, or both [67].

• What is the underlying pathophysiology?

AECOPD is associated with enhanced upper and lower airway and systemic inflammation. The bronchial mucosa of stable COPD patients have increased numbers of CD8⁺ lymphocytes and macrophages. In mild AECOPD, eosinophils are increased in the bronchial mucosa and modest elevation of neutrophils, T lymphocytes (CD3), and TNF alpha positive cells has also been reported [62]. With more severe AECOPD, airway neutrophils are increased. Oxidative stress is a key factor in the development of airway inflammation in COPD [61]. Patients with severe exacerbations have augmented large airway interleukin-8 (IL-8) levels and increased oxidative stress as demonstrated by markers such as hydrogen peroxide and 8-isoprostane [66].
Respiratory infections are estimated to trigger approximately two-thirds of exacerbations [62]. Viral and bacterial infections cause most exacerbations. The effect of the infective triggers is to increase inflammation, cause bronchoconstriction, edema, and mucus production, with a resultant increase in dynamic hyperinflation [71]. Thus, any intervention that reduces inflammation in COPD reduces the number and severity of exacerbations, whereas bronchodilators have an impact on exacerbation by their effects on reducing dynamic hyperinflation. The triggers for the one-third of exacerbations not triggered by infection are postulated to be related to other medical conditions, including pulmonary embolism, aspiration, heart failure, and myocardial ischemia [66].

**What are the pharmacologic options available for prevention of AECOPD?**

In recognition of the importance of preventing COPD exacerbations, the American College of Chest Physicians and Canadian Thoracic Society [65] have published an evidence-informed clinical guideline specifically examining the prevention of AECOPD, with the goal of assisting clinicians in providing optimal management for COPD patients. The following pharmacologic agents have been recognized as being effective at reducing the frequency of acute exacerbations without any impact on the severity of COPD itself.

**Roflumilast**

Phosphodiesterase 4 (PDE4) inhibition appears to have inflammatory modulating properties in the airways, although the exact mechanism of action is unclear. Some have proposed that it reduces inflammation by inhibiting the breakdown of intracellular cyclic adenosine monophosphate [72]. In 2 large clinical trials [73,74], daily use of a PDE4 inhibitor (roflumilast) showed a significant (15%–18%) reduction in yearly AECOPD incidence (approximate number needed to treat: 4). This benefit was seen in patients with GOLD stage 3–4 disease (FEV1 < 50% predicted) with the chronic bronchitic phenotype and who had experienced at least 1 exacerbation in the previous year.

Importantly, these clinical trials specifically prohibited the use of ICS and LAMAs. Thus, it remains uncertain if PDE4 inhibition should be used as an add-on to ICS/LAMA therapy in patients who continue to have frequent AECOPD or whether PDE4 inhibition could be used instead of these standard therapies in patients with well-controlled daily symptoms without ICS or LAMA therapy but who experience frequent exacerbations.

Of note, earlier trials with roflumilast included patients with ICS and LAMA use [73,75]. These trials were focused on FEV1 improvement and found no benefit. It was only in post ad hoc analyses that a reduction in AECOPD in patients with frequent exacerbations was found among those taking roflumilast, regardless of ICS or LAMA use [76]. While roflumilast has documented benefit in improving lung function and reducing the rate of exacerbations, it has not been reported to decrease hospitalizations [64]. This indicates that although the drug reduces the total number of exacerbations, it may not be as useful in preventing episodes of severe exacerbations of COPD.

Although PDE4 inhibitors are easy to administer (a once-daily pill), they are associated with significant GI side effects (diarrhea, nausea, reduced appetite), weight loss, headache, and sleep disturbance [77]. Adverse effects tend to occur early during treatment, are reversible, and lessen over time with treatment [66]. Studies reported an average unexplained weight loss of 2 kg, and monitoring weight during treatment is advised. In addition, it is important to avoid roflumilast in underweight patients. Roflumilast should also be used with caution in depressed patients [65].

**N-acetylcysteine**

N-acetylcysteine (NAC) reduces the viscosity of respiratory secretions as a result of the cleavage of the disulfide bonds and has been studied as a mucolytic agent to aid in the elimination of respiratory secretions [78]. Oral NAC is quickly absorbed and is rapidly present in an active form in lung tissue and respiratory secretions after ingestion. NAC is well tolerated except for occasional patients with GI adverse effects. The role of NAC in preventing AECOPD has been studied for more than 3 decades [79–81], although the largest clinical trial to date was reported in 2014 [57]. Taken together, the combined data demonstrate a significant reduction in the rate of COPD exacerbations associated with the use of NAC when compared with placebo (OR, 0.61; CI, 0.37–0.99). Clinical guidelines suggest that in patients with moderate to severe COPD (FEV1/FVC < 0.7, and FEV1 < 80% predicted) receiving maintenance bronchodilator therapy
combined with ICS and history of 2 more exacerbations in the previous 2 years, treatment with oral NAC can be administered to prevent AECOPD.

**Macrolides**
Continuous prophylactic use of antibiotics in older studies had no effect on the frequency of AECOPD [82,83]. But it is known that macrolide antibiotics have several antimicrobial, anti-inflammatory and immunomodulating effects and have been used for many years in the management of other chronic airway disease, including diffuse pan-bronchiolitis and cystic fibrosis [65]. One recent study showed that the use of once-daily, generic azithromycin 5 days/week appeared to have an impact on AECOPD incidence [84]. In this study, AECOPD was reduced from 1.83 to 1.48 per patient-year (RR, 0.83; 95% CI, 0.72–0.95: P = 0.01). Azithromycin also prevented severe AECOPD. Greater benefit was obtained with milder forms of the disease and in the elderly. Azithromycin did not appear to provide any benefit in those who continued to smoke (hazard ratio, 0.99) [85]. Other studies have shown that azithromycin was associated with an increased incidence of bacterial resistance and impaired hearing [86]. Overall data from the available clinical trials are robust and demonstrate that regular macrolide therapy definitely reduces the risk of AECOPD. But due to potential side effects macrolide therapy is an option rather than a strong recommendation [65]. The prescribing clinician also needs to consider the potential of prolongation of the QT interval [84].

**Immunostimulants**
Immunostimulants have also been reported to reduce frequency of AECOPD [87,88]. Bacterial lysates, reconstituted mixtures of bacterial antigens present in the lower airways of COPD patients, act as immunostimulants through the induction of cellular maturation, stimulating lymphocyte chemotaxis, and increasing opsonization when administered to individuals with COPD [66]. Studies have demonstrated a reduction in the severe complications of exacerbations and hospital admissions in COPD patients with OM-85, a detoxified oral immunoactive bacterial extract [87,88]. However, most of these trials were conducted prior to the routine use of long-acting bronchodilators and ICS in COPD. A recent study by Braidol et al evaluated the efficacy of ismigen, a bacterial lysate, in reducing AECOPD [89] and found no difference in the exacerbation rate between ismigen and placebo or the time to first exacerbation. Additional studies are needed to examine the long-term effects of this therapy in patients receiving currently recommended COPD maintenance therapy [66].

**β Blockers**
Observational studies of beta-blocker use in preventing AECOPD have yielded encouraging results, with one study showing a reduction in AECOPD risk (incidence risk ratio, 0.73; CI 0.60–0.90) in patients receiving beta blockers versus those not on beta blockers [90]. Based on these findings, a clinical trial investigating the impact of metoprolol on risk of AECOPD is ongoing [91].

**Proton Pump Inhibitors**
Gastroesophageal reflux disease is an independent risk factor for exacerbations [92]. Two small, single-center studies [93,94] have shown that use of lansoprazole decreases the risk and frequency of AECOPD. However, data from the Predicting Outcome using Systemic Markers in Severe Exacerbations of COPD (PROMISE-COPD) study [66], which was a multicenter prospective observational study, suggested that patients with stable COPD receiving a proton pump inhibitor were at high risk of frequent and severe exacerbations [95]. Thus, at this stage, their definitive role needs to be defined, possibly with a randomized, placebo-controlled study.

**CASE 3**
A 65-year-old male with severe COPD (FEV1/FVC 27, FEV1 25% of predicted, residual volume 170% of predicted for his age and height) was seen in the pulmonary clinic. His medications include a LABA/LAMA combination that he uses twice daily as advised. He uses his rescue albuterol inhaler roughly once a week. The patient complains of severe disabling shortness of breath with exertion and severe limitation of his quality of life because of his inability to lead a normal active life. He is on 2 L/min of oxygen at all times. He has received pulmonary rehabilitation in hopes of improving his quality of life but can only climb a flight of stairs before he must stop to rest. He asks about options but does not want to consider lung transplantation today. His most recent chest CT scan demonstrates upper lobe predominant emphysematous changes with no masses or nodules.
Lung volume reduction surgery (LVRS) attempts to reduce space-occupying severely diseased, hyperexpanded lung, thus allowing the relatively normal adjoining lung parenchyma to expand into the vacated space and function effectively [96]. Hence, such therapies are suitable for patients with emphysematous lungs and not those with bronchitic-predominant COPD. LVRS offers a greater chance of improvement in exercise capacity, lung function, quality of life, and dyspnea in the correctly chosen patient population as compared with pharmacologic management alone [97]. However, the procedure is associated with risks, including higher short-term morbidity and mortality [97]. Patients with predominantly upper-lobe emphysema and a low maximal workload after rehabilitation were noted to have lower mortality, a greater probability of improvement in exercise capacity, and a greater probability of improvement in symptoms if they underwent surgery compared to medical therapy alone [97]. On the contrary, patients with predominantly non–upper-lobe emphysema and a high maximal workload after rehabilitation had higher mortality if they underwent surgery compared to receiving medical therapy alone [97]. Thus, a subgroup of patients with homogeneous emphysema symmetrically affecting the upper and lower lobes are considered to be unlikely to benefit from this surgery [97,98].

Valves and other methods of lung volume reduction such as coils, sealants, intrapulmonary vents, and thermal vapor in the bronchi or subsegmental airways have emerged as new techniques for nonsurgical lung volume reduction [99–104]. Endobronchial-valve therapy is associated with improvement in lung function and with clinical benefits that are greatest in the presence of heterogeneous lung involvement. This works by the same principle as with LVRS, by reduction of the most severely diseased lung units, expansion of the more viable, less emphysematous lung results in substantial improvements in lung mechanics [105,106]. The most important complications of this procedure include pneumonia, pneumothorax, hemoptysis and increased frequency of COPD exacerbation in the following thirty days. The fact that high-heterogeneity subgroup had greater improvements in both the FEV1 and distance on the 6-minute walk test than did patients with lower heterogeneity supports the use of quantitative high-resolution computed tomography (HRCT) in selecting patients for endobronchial-valve therapy [107]. The HRCT scans also help in identifying those with complete fissures; a marker of lack of collateral ventilation (CV+) between different lobes. Presence of CV+ state predicts failure of endobronchial valve and all forms of endoscopic lung volume reduction strategies [108]. Bronchoscopic thermal vapor ablation (BTVA) therapy can potentially work on a subsegmental level and be successful for treatment of emphysema with lack of intact fissures on CT scans. Other methods that have the potential to be effective in those with collateral ventilation would be endoscopic coil therapy and polymeric lung volume reduction [106,109]. Unfortunately there are no randomized controlled trial data demonstrating clinically meaningful improvement following coil therapy or polymeric lung volume reduction in this CV+ patient population. Vapor therapy is perhaps the only technique that has been found to be effective in upper lobe predominant emphysema even with CV+ status [108].

Our patient has evidence of air trapping and emphysema based on a high residual volume. A CT scan of the chest can determine the nature of the emphysema (heterogeneous versus homogenous) and based on these findings, further determination of the best strategy for lung volume reduction can be made.

Is there a role for long-term oxygen therapy?

Long-term oxygen therapy (LTOT) used for > 15 hours a day is thought to reduce mortality among patients with chronic obstructive pulmonary disease (COPD) and severe resting hypoxemia [110–113]. More recent studies have failed to show similar beneficial effects of LTOT. A recent study examined the effects of LTOT in randomized fashion and determined that supplemental oxygen for patients with stable COPD and resting or exercise-induced moderate desaturation did not affect the time to death or first hospitalization, time to first COPD exacerbation, time to first hospitalization for a COPD exacerbation, the rate of all hospitalizations, the rate of all COPD exacerbations, or changes in measures of quality of life, depression, anxiety, or functional status [114].

Our patient is currently on long-term oxygen therapy and in spite of some uncertainty as to its benefit, it is prudent to order oxygen therapy until further clarification is available.
• What is the role of pulmonary rehabilitation?

Pulmonary rehabilitation is an established treatment for patients with chronic lung disease [115]. Benefits include improvement in exercise tolerance, symptoms, and quality of life, with a reduction in the use of health care resources [116]. A Spanish population-based cohort study that looked at the influence of regular physical activity on COPD showed that patients who reported low, moderate, or high physical activity had a lower risk of COPD admissions and all-cause mortality than patients with very low physical activity after adjusting for all confounders [117].

As previously mentioned, patients in GOLD categories B, C, and D should be offered pulmonary rehabilitation as part of their treatment [7]. The ideal patient is one who is not too sick to undergo rehabilitation and is motivated to his or her quality of life.

• What is the current scope of lung transplantation in the management of severe COPD?

There is a indisputable role for lung transplantation in end-stage COPD. However, lung transplantation does not benefit all COPD patients. There is a subset of patients for whom the treatment provides a survival benefit. It has been reported that 79% of patients with an FEV1 < 16% predicted will survive at least 1 year additional after transplant, but only 11% of patients with an FEV1 > 25% will do so [118]. The pre-transplant BODE (body mass index, airflow obstruction/FEV1, dyspnea, and exercise capacity) index score is used to identify the patients who will benefit from lung transplantation [119,120]. International guidelines for the selection of lung transplant candidates identify the following patient characteristics [121]:

- The disease is progressive, despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy
- The patient is not a candidate for endoscopic or surgical LVRS
- BODE index of 5 to 6
- The partial pressure of carbon dioxide is greater than 50 mm Hg or 6.6kPa and/or partial pressure of oxygen is less than 60 mm Hg or 8kPa
- FEV1 of 25% predicted

The perioperative mortality of lung transplantation surgery has been reduced to less than 10%. Risk of complications from surgery in the perioperative period, such as bronchial dehiscence, infectious complications, and acute rejection, have also been reduced but do occur. Chronic allograft dysfunction and the risk of lung cancer in cases of single lung transplant should be discussed with the patient before surgery [122].

• How can we incorporate palliative care into the management plan for patients with COPD?

Among patients with end-stage COPD on home oxygen therapy who have required mechanical ventilation for an exacerbation, only 55% are alive at 1 year [123]. COPD patients at high risk of death within the next year of life as well as patients with refractory symptoms and unmet needs are candidates for early palliative care. Palliative care and palliative care specialists can aid in reducing symptom burden and improving quality of life among these patients and their family members and is recommended by multiple international societies for patients with advanced COPD [124,125]. In spite of these recommendations, the utilization of palliative care resources has been dismally low [126,127]. Improving physician-patient communication regarding palliative services and patients’ unmet care needs will help ensure that COPD patients receive adequate palliative care services at the appropriate time.

CONCLUSION

COPD is a leading cause of morbidity and mortality in the United States and represents a significant economic burden for both individuals and society. The goals in COPD management are to provide symptom relief, improve the quality of life, preserve lung function, and reduce the frequency of exacerbations and mortality. COPD management is guided by disease severity that is measured using the GOLD multimodal staging system and requires a multidisciplinary approach. Several classes of medication are available for treatment, and a stepwise approach should be applied in building an effective...
pharmacologic regimen. In addition to pharmacologic therapies, nonpharmacologic therapies, including smoking cessation, vaccinations, proper nutrition, and maintaining physical activity, are an important part of long-term management. Those who continue to be symptomatic despite appropriate maximal therapy may be candidates for lung volume reduction. Palliative care services for COPD patients, which can aid in reducing symptom burden and improving quality of life, should not be overlooked.

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