

Outpatient Chronic Obstructive Pulmonary Disease Management: Going for the GOLD

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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List of Design Committee Members: Christina R. Bellinger, MD, and Stephen P. Peters, MD, PhD

Activity Objectives

1. To understand the risks associated with stepping down asthma medications in ways that lead to a more informed decision with patients.
2. To incorporate specific patient characteristics into decisions about stepping down asthma medications.
3. To consider the multiple options regarding how to practically accomplish the step down of asthma medications.

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Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States with a burden of \$50 billion in direct health care costs. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines airflow obstruction as spirometry where the ratio of forced expiratory volume in the first second to forced vital capacity after

bronchodilation is less than 0.70. The guidelines also provided graded recommendations on current therapy for COPD. Treatment can be guided based on severity of disease and severity of symptoms. We review the GOLD guidelines to provide an overview of treatment modalities aimed at improving lung function, reducing hospitalization, and reducing mortality. © 2015 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2015;3:471-8)

Key words: COPD; Chronic obstructive pulmonary disease; GOLD guidelines

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease that affects more than 12 people nationwide and is the fourth leading cause of death in the United States. It results in a burden of \$50 billion in direct health care costs and indirect morbidity and mortality costs.¹ The main risk factor for the development of COPD is smoking although occupational exposures and wood burning stoves also contribute. Symptoms include a slow progression in worsening dyspnea, chronic cough, and chronic sputum production. Airflow obstruction is determined by spirometry where the ratio of forced expiratory volume in the first second to forced vital capacity (FEV₁/FVC) after bronchodilation is less than 0.70. Stable

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Abbreviations used

6MWT- Six-minute walk test
 CAT- COPD Assessment Test
 COPD- Chronic obstructive pulmonary disease
 DL_{CO}- Diffusing capacity
 FEV₁- Forced expiratory volume in the first second
 FVC- Forced vital capacity
 ICS- Inhaled corticosteroid
 LABA- Long-acting β -agonist
 LAMA- Long-acting antimuscarinic
 LVRS- Lung volume reduction surgery
 mMRC- Modified Medical Research Council Questionnaire
 PaO₂- Partial pressure of arterial oxygen
 PDE4-I- Phosphodiesterase-4 inhibitor
 QOL- Quality of life
 SABA- Short-acting β -agonist
 SAMA- Short-acting antimuscarinic

outpatient management of COPD focuses on smoking cessation assistance, preventative vaccinations, maintenance inhaler therapies, addition of oral medications if needed, pulmonary rehabilitation, and oxygen therapy. Additional considerations include the management of comorbidities and underlying depression.² The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has developed guidelines and recommendation grades incorporating a strategy that includes preventative care, maintenance therapy, and management of advanced disease and comorbidities. We present an overview of the GOLD guidelines and key trials that shape outpatient management of COPD.

ASSESSING SYMPTOMS AND SEVERITY

The symptoms of COPD include dyspnea, cough, sputum production, and wheezing. The validated COPD Assessment Test (CAT) is an 8-item questionnaire to measure symptoms. Scores range from 0 to 40 to determine the prevalence of more or less respiratory symptoms (<http://www.catestonline.org>). The higher the score, the more symptomatic a patient is. In addition, the Modified Medical Research Council Questionnaire (mMRC) assesses the symptoms of breathlessness. These 2 tools can be used to determine if patients have more or less symptoms to guide pharmacologic therapy (Figures 1 and 2). CAT scores less than 10 and mMRC grades 0-1 are categorized as "less symptoms," whereas CAT scores ≥ 10 and mMRC ≥ 2 are categorized as "more symptoms."²

The severity of airflow obstruction is based on the percent predicted FEV₁ (postbronchodilator) in the setting of an FEV₁/FVC < 0.70 (GOLD criteria). The severity based on FEV₁ can then be used to guide initial therapy and determine risk of exacerbations and mortality (Table I). GOLD groups 1 and 2 are the mild and moderate COPD and are classified as "low risk." GOLD groups 3 and 4 are severe and very severe COPD and are classified as "high risk."²

The subjective scores obtained from CAT and mMRC can then be combined with the objective spirometry categorization to obtain a group that reflects both risk and breathlessness (Figure 1). Group A have low risk and less symptoms, Group B have low risk and more symptoms, Group C have high risk and less symptoms, and Group D have high risk and high symptoms.² Medical management then can be guided by the group into which the patient falls (Figure 2).

NONPHARMACOLOGIC NONINVASIVE THERAPY**Smoking cessation**

Smoking cessation counseling should be offered to all patients with COPD who continue to smoke. Quitting smoking is the best intervention for COPD and the most cost effective.² Counseling should be given at every visit. Intense, structured programs can achieve quit rates of as high as 22%,³ but even brief counseling can help 5% to 10% of smokers quit.⁴

Preventative vaccines

The recommended vaccines for patients with COPD include influenza and pneumococcal vaccines. Vaccination against influenza can reduce respiratory illness and has a mortality benefit in patients with COPD. Pneumococcal polysaccharide vaccine can reduce community-acquired pneumonia in patients with severe or very severe COPD and younger than age 65.²

Oxygen therapy

In patients with COPD with resting hypoxemia, long-term supplemental oxygen > 15 hours/day has shown a mortality benefit. Oxygen therapy is recommended for patients with (a) saturations $\leq 88\%$ (or partial pressure of arterial oxygen [PaO₂] ≤ 55 mm Hg) or (b) patients with saturations $= 88\%$ (or PaO₂ 55-60 mm Hg) and coexisting pulmonary hypertension, congestive heart failure, or polycythemia. Testing should be reproducible twice over 3 weeks. In flight, oxygen may be necessary for some patients. Those with moderate to severe hypoxemia can be supplemented with 3 L/minute nasal cannula to maintain an in-flight PaO₂ of at least 50 mm Hg. If sea level PaO₂ is > 70 mm Hg, supplemental oxygen is infrequently needed.²

Pulmonary rehabilitation

Pulmonary rehabilitation offers exercise training and education. In patients with COPD, pulmonary rehabilitation has the ability to improve exercise capacity and endurance, improve quality of life (QOL), improve recovery after hospitalization for an exacerbation, enhance the effects of long-acting bronchodilators, and reduce anxiety and depression. To achieve these benefits, a program should be of at least 6 weeks or longer. Ongoing physical activity is recommended.²

PHARMACOLOGIC TREATMENT

Pharmacologic treatment of COPD is dependent on symptoms, airflow limitation, and exacerbations. Symptoms can be assessed with validated tools such as the CAT or the mMRC. These help determine if symptoms are more or less prevalent. Patients can then be stratified into low risk or high risk based on airflow limitation on spirometry (low risk: mild-to-moderate obstruction or FEV₁ $\leq 50\%$ predicted; high risk: severe or very severe with FEV₁ $< 50\%$ predicted) and based on frequency of exacerbation (low risk: 1 or less exacerbations per year; high risk: 2 or more exacerbations per year). Combining symptoms, airflow limitation, and exacerbation frequency can be used to determine which category a patient can be classified into to determine pharmacologic therapy (Figure 1).²

Bronchodilators

Bronchodilators improve expiratory flow by widening the airways and enabling lung emptying, reducing dynamic hyperinflation, and improving exercise capacity. Medications in this category include β_2 -agonists, anticholinergics (or antimuscarinics),

A	B	C	D
Low Risk FEV ₁ ≥ 50% predicted and/or ≤ 1 exacerbation per year	Low Risk FEV ₁ ≥ 50% predicted and/or ≤ 1 exacerbation per year	High Risk FEV ₁ < 50% predicted and/or ≥ 2 exacerbation per year	High Risk FEV ₁ < 50% predicted and/or ≥ 2 exacerbation per year
Less Symptoms mMRC 0-1 and/or CAT < 10	More Symptoms mMRC ≥ 2 and/or CAT ≥ 10	Less Symptoms mMRC 0-1 and/or CAT < 10	More Symptoms mMRC ≥ 2 and/or CAT ≥ 10

FIGURE 1. Assessment of COPD risk and breathlessness. Using COPD severity and symptom prevalence, a GOLD category can be applied (A through D) to guide therapeutic management. Adapted from GOLD Guidelines (Updated 2015).² CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in the first second; mMRC, Modified Medical Research Council Questionnaire.

A	B	C	D
Low Risk Less Symptoms	Low Risk More Symptoms	High Risk Less Symptoms	High Risk More Symptoms
		ICS/LABA or LAMA (ALT: LABA/LAMA or LAMA + PDE4-I or LABA + PDE4-I)	ICS/LABA and LAMA (ALT: ICS/LABA + PDE4-I or LABA/LAMA or LABA + PDE4-I)
	LAMA or LABA (ALT: LABA/LAMA)		
	Alternative or in addition to inhaled therapy: Theophylline Consider addition of anti-inflammatory macrolide therapy		
	Prevention: smoking cessation, physical activity, influenza vaccine, pneumococcal vaccine, education Add as needed short-acting bronchodilator (SABA or SAMA)		
	Consider Pulmonary Rehabilitation		
		Oxygen therapy if indicated (PaO ₂ ≤ 55 mmHg or SPO ₂ ≤ 88% with or without hypercapnea confirmed twice over a 3 week period)	
		Consider lung volume reduction surgery for very severe COPD with upper lobe predominant emphysema	
			Consider Palliative Care consultation

FIGURE 2. Outpatient COPD management. An escalating approach to the management of COPD based on GOLD guidelines incorporating severity and risk. Adapted from Global Initiative for Chronic Obstructive Lung Disease (Updated 2015).² COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting antimuscarinic; PDE4-I, phosphodiesterase-4 inhibitor; SABA, short-acting β_2 -agonist; SAMA, short-acting antimuscarinic.

TABLE I. Spirometry and GOLD category in relationship to exacerbations and mortality

	GOLD 1 Mild	GOLD 2 Moderate	GOLD 3 Severe	GOLD 4 Very severe
Spirometry (postbronchodilator)	FEV ₁ ≥ 80% Predicted	50% ≤ FEV ₁ < 80% predicted	30 % ≤ FEV ₁ < 50% predicted	FEV ₁ < 30% predicted
Number of exacerbations (per year per patient)	Unknown	0.7-0.9	1.1-1.3	1.2-2.0
Number of hospitalizations (per year per patient)	Unknown	0.11-0.2	0.25-0.3	0.4-0.54
Three-year mortality	Unknown	11%	15%	24%

FEV₁, Forced expiratory volume in the first second; GOLD, Global Initiative for Chronic Obstructive Lung Disease.
Adapted from Global Initiative for Chronic Obstructive Lung Disease (Updated 2015).²

and methylxanthines. These are prescribed in either long-acting daily or twice daily dosing or short-acting as needed dosing. There is a flat dose-response curve such that little additional benefit is seen with escalating dosages of either β_2 -agonists or

anticholinergics, but toxicity can worsen. The decision to use a β_2 -agonist, anticholinergic, or both is dependent on patient tolerance and response. Table II demonstrates possible variations in combinations of these medications.²

TABLE II. Inhalers for chronic obstructive lung disease

Medication	Trade name	Dosing
Short-acting β_2 -agonists (SABA)		
Fenoterol	Berotec N	100-200 μ g MDI or 1 mg/mL nebulized or 0.05% PO syrup
Levalbuterol	Xopenex	40-90 μ g MDI or 0.21, 0.42 mg/mL nebulized
Salbutamol (albuterol)	Ventolin	100, 200 μ g MDI & DPI or 5 mg/mL nebulized or 5 mg PO pill or 0.024% PO syrup 0.1, 0.5 mg injection
Terbutaline	Brethine, Bricanyl, Brethaire, Terbutin	400, 500 μ g DPI or 2.5, 5 mg PO pill
Long-acting β_2 -agonists (LABA)		
Formoterol	Foradil, Perforomist	4.5-12 μ g MDI and DPI or 0.01 mg/mL nebulized
Arformoterol	Brovana	0.0075 mg/mL nebulized
Indacaterol	Onbrez, Arcapta	75-300 DPI
Salmeterol	Serevent	25-50 μ g MDI and DPI
Tulobuterol	Hokunalin tape (Japan only)	2 mg transdermal patch
Short-acting anticholinergics (SAMA)		
Ipratropium bromide	Atrovent, Apotent, Ipraxa, Aerovent	20, 40 μ g MDI 0.25-0.5 mg/mL nebulized
Oxipropium bromide	Oxivent, Tersigan	100 μ g MDI 1.5 mg/mL nebulized
Long-acting anticholinergics (LAMA)		
Aclidinium bromide	Tudorza Pressair (in the USA) Eklira Genuar (in the UK)	322 μ g DPI
Glycopyrronium bromide		44 μ g DPI
Tiotropium	Spiriva	18 μ g DPI, 5 μ g SMI
Umeclidinium	Incruse Ellipta	62.5 μ g DPI
Combination SABA and SAMA		
Fenoterol/ipratropium	Beodual N	200/80 μ g MDI or 1.25/0.5 mg/mL nebulized
Salbutamol/ipratropium	Combivent, DuoNeb	100/20 μ g SMI
Combination LABA and LAMA		
Indacaterol/glycopyrronium	Ultibro Breezhaler	85/43 μ g DPI
Vilanterol/umeclidinium	Anora Ellipta	25/62.5 μ g DPI
Inhaled corticosteroids (ICS)		
Beclomethasone	Qvar	50-400 μ g MDI or DPI 0.2-0.4 mg/mL nebulized
Budesonide	Pulmicort Flexhaler	100, 200, 400 DPI 0.20, 0.25, 0.5 mg/mL nebulized
Fluticasone	Flovent HFA	50-500 μ g MDI or DPI
Combination ICS/LABA		
Formoterol/budesonide	Symbicort	4.5/160 μ g MDI or 9/320 μ g DPI
Formoterol/mometasone	Dulera	10/200, 10/400 μ g MDI
Salmeterol/fluticasone	Advair	50/100, 250, 500 μ g DPI or 25/50, 125, 250 μ g MDI
Vilanterol/fluticasone furoate	Breo Ellipta (in the USA) Relvar Ellipta (in Europe)	25/100 μ g MDI

DPI, Dry powder inhaler; MDI, metered dose inhaler; mg, milligrams; mL, milliliters; PO, by mouth; SMI, soft mist inhaler.

β_2 -Agonists. β_2 -Agonists activate adrenergic receptors resulting in a cyclic AMP-mediated airway smooth muscle relaxation. Short-acting β_2 -agonists (SABAs) counteract bronchoconstriction relatively quickly and last from 4 to 6 hours. Long-acting β_2 -agonists (LABAs) last for 12 hours. The onset is variable with formoterol

having a short onset among the LABAs. The side effects include tachycardia and arrhythmias, tremor, hypokalemia, and increased oxygen consumption. SABAs increase FEV₁ and decrease symptoms. LABAs also increase FEV₁ and decrease symptoms, but also reduce exacerbations. They do not impact mortality.²

Compared with placebo in patients with moderate to severe COPD indacaterol, a once daily LABA increased FEV₁ (>170 cm³) and reduced exacerbations (0.62-0.64, $P < .05$) with no adverse effects on electrocardiogram findings.⁵ It has also been shown to improve lung hyperinflation and physical activity.⁶ Salmeterol improves lung function,^{7,8} respiratory symptoms,⁷ and breathlessness.⁸ A meta-analysis of 26 studies revealed that LABAs improve QOL and lung function and reduce exacerbation.⁹

Anticholinergics. Anticholinergics (or antimuscarinics) inhibit the binding of acetylcholine to muscarinic receptors, thus preventing smooth muscle contraction and airway narrowing. Short-acting antimuscarinics (SAMAs) have a quick onset and last for up to 8 hours. Long-acting anticholinergics or antimuscarinics (LAMAs) last from 12 to 24 hours. The main side effects include dry mouth. Anticholinergics are avoided in patients with glaucoma, although only the use of anticholinergic solutions (not dry powder inhalation) was thought to have contributed to acute glaucoma.²

Ipratropium, a SAMA, is as effective or better in improving FEV₁ as SABA without the tachycardia side effects. SAMAs also decrease functional residual capacity and residual volume effectively reducing hyperinflation.¹⁰ A Cochrane Database meta-analysis of 11 studies demonstrated that lung function was better after ipratropium monotherapy or combined SAMA/SABA over SABA monotherapy. In addition, ipratropium monotherapy or combined SAMA/SABA reduced the requirement for inhaled corticosteroids (ICS) over SABA monotherapy.¹¹

Tiotropium, a LAMA, has a much higher affinity for muscarinic receptors compared with ipratropium, as well as more muscarinic receptor 3 (M₃) selectivity incurring a greater bronchodilator effect.¹⁰ The UPLIFT¹² (Understanding Potential Long-term Impacts on Function with Tiotropium) trial showed a slower decline in lung function, improved QOL, and reduction in COPD exacerbations in patients randomized to tiotropium over placebo. In patients with moderate to severe COPD, tiotropium has been shown to increase time to first exacerbation (187 days vs 145 days, $P < .001$) and first severe exacerbation (hazard ratio [HR] 0.72; 95% confidence interval [CI] 0.83-0.96, $P < .001$) over salmeterol. Tiotropium also reduced the annual number of moderate or severe exacerbations (0.64 vs 0.72, $P = .002$).¹³ Although tiotropium has been shown to outperform placebo and LABA, it is not superior to combination ICS/LABA therapy. In a randomized control trial of 1323 patients with COPD (mean FEV 39% predicted), the annual exacerbation rate was the same for tiotropium (1.32 exacerbations/year) and salmeterol/fluticasone (1.28 exacerbations/year, $P = .656$). Although more pneumonias were reported in the ICS/LABA group ($P = .008$), mortality was also lower (3% ICS/LABA group vs 6% tiotropium group, $P = .032$).¹⁴

Debate has been ongoing about cardiovascular risk and anticholinergic agents. Although a meta-analysis of 17 randomized trials found an increased risk of cardiovascular deaths,¹⁵ the UPLIFT trial did not.¹² Another database review actually found a reduction in cardiovascular events.¹⁶ Yet another meta-analysis, this time of the tiotropium mist inhaler (Respimat), found a 52% increase in mortality.¹⁷ A randomized double-blinded trial of more than 17,000 patients with COPD found no difference in the safety profile of tiotropium Handihaler as compared with tiotropium Respimat.¹⁸

Methylxanthines. The bronchodilator effect of methylxanthines is thought to be as a phosphodiesterase inhibitor (PDE-I). Theophylline has classically been used for COPD and has demonstrated a bronchodilator effect compared with placebo in stable COPD. It has also been shown to reduce exacerbations. It is metabolized by cytochrome P450, has decreased clearance with age, has a host of toxicities (arrhythmias, seizures, headaches, insomnia, nausea), and interacts with other medications. As such, theophylline is reserved for those who have not tolerated or had benefit from inhaled therapy or are already on maximal medical therapy.²

Combination bronchodilator therapy. Combining LABA and LAMA or SABA and SAMA have shown improvements in FEV₁ beyond that of single-agent therapy in patients with COPD.² There are now several combination inhaled LABAs/LAMAs on the market (Table II). As with tiotropium, these are once daily medications. Umeclidinium plus vilanterol was shown to be superior to vilanterol monotherapy or tiotropium monotherapy in improving lung function but had no difference in QOL or risk of exacerbation.¹⁹ In a double-blind, placebo-controlled trial of almost 1500 patients, umeclidinium plus vilanterol had greater improvement in lung function (FEV₁ increased 124-238 cm³ above placebo, $P < .001$) as well as improved health status and dyspnea compared with either drug in monotherapy and with placebo.²⁰

Corticosteroids

Inhaled corticosteroids. ICS are touted for their ability to reduce COPD exacerbations. Although they have some improvement in lung function and symptom reduction, they are not superior to bronchodilators in that respect. They should be added to high-risk patients who need a reduction in exacerbations (Figure 2).²

Combination ICS/LABA. Several available medications contain combined inhaled steroid and long-acting β_2 -agonist. The combination has shown improvements in lung function and frequency of exacerbations beyond that of single-agent therapy in patients with COPD.² This was well demonstrated in the TORCH²¹ (Toward Revolution in COPD Health) trial, a double-blind study of more than 6000 patients with COPD randomized to combined fluticasone/salmeterol (500/50 micrograms twice daily) or monotherapy with each or placebo. Combination therapy not only reduced exacerbation rates (1.13 to 0.85, $P < .001$) but also trended toward a mortality reduction—HR for death compared with placebo 0.825 (95% CI 0.681-1.002, $P = .052$). A meta-analysis of combination therapy found mortality benefit.²² An increased risk of pneumonia is seen with combined ICS/LABA therapy.² Triple therapy with ICS/LABA and tiotropium improves lung function, but more studies are needed to see if a reduction in exacerbations occurs.¹⁰

Once daily combined ICS/LABA therapy is also now available. Once daily medications carry the hope of improving medication adherence. Two clinical studies ($n = 1224$ and $n = 723$) in patients with moderate to severe COPD compared once daily fluticasone furoate/vilanterol in varying doses and against placebo. The once daily medication improved lung function, but the study duration was insufficient to determine the effect on exacerbation or mortality.^{23,24} A pooled parallel group study comparing fluticasone furoate/vilanterol in varying doses with vilanterol

TABLE III. COPD therapies' level of evidence according to GOLD guidelines

	Mortality reduction	Exacerbation reduction	Improved lung function	Improve symptoms and/or QOL
Oxygen therapy	B			
Pulmonary rehabilitation	B	A		A
Influenza vaccine	A			
Short-acting β_2 -agonist			B	B
Long-acting β_2 -agonist		A (formoterol and salmeterol)	A (formoterol, salmeterol, and indacaterol)	A (formoterol, salmeterol, and indacaterol)
Long-acting anticholinergics		A		A
Theophylline		B	A	
Combined bronchodilators			B	B
Inhaled corticosteroids		A	A*	A*
Combination ICS/LABA	B (in one meta-analysis)	A/B (moderate/severe)	B	B
Lung volume reduction surgery	A			

COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; QOL, quality of life.

*Although ICS improve lung function and symptoms, their indication in COPD is for reduction of exacerbations. Levels of evidence: A, randomized control trials with rich body of data, B, randomized control trials with limited data.

monotherapy over 1 year found improved lung function with once daily dual therapy and reduced exacerbations. Pneumonia was higher in the ICS/LABA groups, and pneumonia-related death was highest in the higher ICS dosing group.²⁵

Phosphodiesterase-4 inhibitors

Roflumilast (Daliresp) is a phosphodiesterase-4 inhibitor (PDE4-I) approved for the treatment of COPD and taken as a once daily pill. Through inhibition of PDE4, the breakdown of cyclic AMP is inhibited and inflammation is reduced. As it has no bronchodilator effects, it is for use in conjunction with at least one bronchodilator. In a randomized, placebo trial of patients with COPD, a subgroup with severe COPD (GOLD stage IV) has a lower annual exacerbation rate (1.01 vs 1.59, $P = .024$) with roflumilast.²⁶ In a subsequent randomized control trial of 1945 patients with severe COPD and symptoms of chronic bronchitis on appropriate combination inhaled therapy, roflumilast reduced exacerbations by 13.2% compared with placebo.²⁷ It is FDA approved for patients with severe COPD and chronic bronchitis (symptoms of cough and excess mucus) who are poorly controlled on inhaler therapy. The main side effect is gastrointestinal upset and subsequent weight loss. As such, it should not be used in underweight patients.²

Chronic macrolide therapy

GOLD guidelines currently do not support the use of chronic antibiotic therapy.² However, macrolide antibiotics have been incorporated for their anti-inflammatory effects in chronic respiratory disease. A randomized control trial that involved 1142 patients with COPD that met GOLD criteria for stage II, III or IV and on long-acting inhaled therapy (excluding those with cardiac problems and hearing deficits) found a reduction in exacerbations in patients on daily azithromycin therapy as compared with placebo (HR 0.73, 95% CI, 0.63 to 0.84; $P < .001$).²⁸ Because of QT-interval prolongation concern in patients on macrolide therapy, they are cautioned in patients with cardiovascular risk factors: QT-interval prolongation, hypokalemia, hypomagnesemia, bradycardia, and concomitant use of anti-arrhythmic agents.²⁹

NONPHARMACOLOGIC INVASIVE THERAPY

Lung volume reduction surgery

Removal of hyperinflated lobes can reduce diaphragmatic stretch, increase elastic recoil pressure, and improve lung mechanics. Careful patient selection for lung volume reduction surgery (LVRS) is required to ensure maximal benefit. LVRS has demonstrated mortality benefit in patients with upper-lobe predominant emphysema and low postrehabilitation exercise capacity. Improvement in QOL and exercise capacity was noted in patients with upper-lobe predominant emphysema and high postrehabilitation exercise capacity without a mortality benefit. Increased mortality was observed in patients undergoing LVRS with very severe COPD ($FEV_1 \leq 20\%$ predicted) and either homogeneous emphysema or severely reduced diffusing capacity ($DL_{CO} \leq 20\%$ predicted).²

Bronchoscopic lung volume reduction

Various modalities of bronchoscopic lung volume reduction (bronchial blocking devices, tissue remodeling, and airway bypass) have been studied, but many trials are ongoing.² Bronchial blocking devices—plugs/spigots and valves—reduce airflow into selected bronchioles to induce atelectasis in emphysematous lung. Trials of these blocking devices have at best had modest improvements in FEV_1 , 6-minute walk (6MWT) tests, or QOL.³⁰ The largest of these trials was the Zephyr Endobronchial Valve System that randomized 321 patients to standard care or endobronchial valves. FEV_1 increased by 6.8% and 6MWT by 5.8%.³¹ Tissue remodeling modalities attempt to collapse dysfunctional emphysematous lung and close collateral ventilation to these areas. These include the AeriSeal sealant (randomized trial closed but not yet published), PneumRx metal coil (randomized trial currently ongoing), and InterVapor heated water vapor.³⁰ Finally, the Exhale Drug-Eluting Stent was designed to create accessory pathways for air to escape hyperinflated lungs. However, an international randomized trial of 315 subjects found no improvement in mMRC scores, 6MWT, FEV_1 , or FVC.³²

Lung transplant

Patients with very severe COPD ($FEV_1 < 20\%$ predicted) may have benefit from lung transplant, but criteria are narrow, cost is high, and organ donors are sparse. Criteria for referring patients with COPD for lung transplantation include the BODE index (body mass index, airflow obstruction, dyspnea, and exercise capacity) of 5 (infers a 57% 4-year survival) as well as a history of (a) hypercapnea (partial pressure of arterial carbon dioxide > 50 mm Hg) in the setting of an exacerbation; (b) pulmonary hypertension, cor pulmonale, or both despite oxygen therapy; and (c) $FEV_1 < 20\%$ predicted with either a $DL_{CO} < 20\%$ predicted or homogeneous distribution of emphysema.²

COMORBIDITIES AND COPD

Comorbidities are rampant in COPD from a combination of life-style, chronic respiratory disease, and genetic susceptibility. Patients frequently have one or more of the following: congestive heart failure, coronary artery disease, obesity, diabetes, osteoporosis, and depression. Not surprisingly, lung cancer has a higher incidence in patients with COPD.²

Depression prevalence in patients with COPD is estimated to be 10% to 42%. It is associated with physical disability, long-term oxygen therapy, severe dyspnea, $FEV_1 < 50\%$ predicted, presence of other comorbidities, living alone, female gender, current smoker, and low socioeconomic status. Depression is under-recognized and undertreated in patients with COPD that can adversely affect medication compliance, physical activity, dyspnea, rehospitalization, and mortality. As such patients with COPD should be screened for depression and treated. A validated, commonly used tool for screening is the Patient Health Questionnaire³³ (phqscreeners.com/pdfs/02_PHQ-9/English.pdf).

PALLIATIVE CARE IN COPD

In its terminal phase, COPD is marked by downward spiraling symptoms, recurrent exacerbations, and declining health. Mortality following an acute exacerbation ranges from 23% to 80% depending on coexisting comorbidities such as cardiovascular disease and malignancy. Previously discussed comorbidities contribute to reduced QOL and mortality. Incorporating palliative inpatient and outpatient care can improve QOL, optimize function, reduce symptoms, and even prolong life.²

SUMMARY

The management of COPD is complex and requires a multitiered approach with preventative care and rehabilitation, inhaler regimen based on severity and symptoms (Figure 1), oxygen therapy, and referral for invasive treatments (lung volume reduction, transplant) when indicated. Table III demonstrates the level of evidence behind recommended therapies for COPD. Preventative care emphasizes smoking cessation and vaccination. Participation in pulmonary rehabilitation can speed the way to recovery following an exacerbation. Inhaler regimens must be carefully selected depending on the GOLD group (Figure 2). New once daily combination therapies may improve medication adherence. The addition of oral theophylline or macrolide anti-inflammatory therapy is based on the patient's failure to improve on standard therapy and his or her cardiovascular risk factors. The addition of roflumilast can be considered for patients who fail to improve on standard therapy and have chronic

bronchitis. Oxygen therapy has been shown to extend life and is indicated in patients who meet specific criteria. Finally, select patients may benefit from lung volume reduction surgery (upper lobe predominant emphysema) or lung transplantation ($FEV_1 < 20\%$ predicted).

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