Annals of Internal Medicine®

In the Clinic®

Chronic Obstructive Pulmonary Disease

Screening

Diagnosis

Treatment

Practice Improvement

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and progressive airflow obstruction. Tobacco smoking is the leading cause but not the only one. A postbronchodilator FEV_1–FVC ratio less than 0.70 is required for a diagnosis of COPD. Inhaler therapy is the backbone of treatment and should be complemented by a multifaceted management strategy that includes counseling and pharmacotherapy for smoking cessation, pulmonary rehabilitation, treatment of comorbidities, administration of influenza and pneumococcal immunizations, and prescription of long-term oxygen therapy in hypoxemic patients.

CME/MOC activity available at Annals.org.

Wassim W. Labaki, MD, MS
Sharon R. Rosenberg, MD, MS
From University of Michigan, Ann Arbor, Michigan (W.W.L.); and Northwestern University, Chicago, Illinois (S.R.R.).

doi:10.7326/AITC202008040

CME Objective: To review current evidence for screening, diagnosis, treatment, and practice improvement of chronic obstructive pulmonary disease.

Funding Source: American College of Physicians.

Acknowledgment: The authors thank Michael R. Littner, MD, author of the previous version of this In the Clinic.

Disclosures: Dr. Labaki, ACP Contributing Author, reports nonfinancial support from Pulmonx and personal fees from Konica Minolta outside the submitted work. Dr. Rosenberg, ACP Contributing Author, has nothing to disclose. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-0505.

With the assistance of additional physician writers, the editors of ***Annals of Internal Medicine*** develop **In the Clinic** using **MKSAP** and other resources of the American College of Physicians. The patient information page was written by Monica Lizarraga from the Patient and Interprofessional Partnership Initiative at the American College of Physicians.

In the Clinic does not necessarily represent official ACP clinical policy. For ACP clinical guidelines, please go to https://www.acponline.org/clinical_information/guidelines/.

ACP American College of Physicians®
Leading Internal Medicine, Improving Lives

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and progressive airflow obstruction documented on spirometry; it is associated with an abnormal inflammatory response of the lungs to noxious particles or gases (1–5). COPD affects close to 400 million people and is already the third leading cause of death worldwide, which the World Health Organization predicted would not occur until 2030 (6, 7). In the United States, the number of deaths from COPD in women has surpassed that in men since 2000. In fact, age-adjusted mortality rates for the disease in the United States decreased among men between 1999 and 2014 but have remained stable among women during that same period (8).

Although cigarette smoking is the leading cause of COPD, up to 25% of people with the disease have never smoked (9). Long-term exposure to other lung irritants—such as air pollution; chemical fumes; dust; and indoor products of biomass fuels, such as wood burned in stoves—may contribute to COPD. A rare genetic condition called α_1-antitrypsin deficiency can also cause the disease.

Screening

Which patient populations are at risk?

Patients younger than 40 years rarely develop COPD because susceptible persons develop the disease only after inhalational exposure to causative agents of sufficient intensity and duration. An estimated 80% of cases are due to cigarette smoking. A risk of 15% for clinically significant COPD among smokers is commonly cited, but this may be an underestimate (10). Risk factors among never-smokers include exposure to biomass fuels, air pollution, or secondhand smoke; workplace exposure to vapors, gases, dust, or fumes; asthma; maternal smoking in pregnancy; low birthweight; and a history of respiratory infections during childhood (11, 12). Genetic factors also play a role in susceptibility to COPD, the best defined being emphysema related to α_1-antitrypsin deficiency.

Should clinicians screen asymptomatic patients?

Screening asymptomatic patients with spirometry is not supported by convincing evidence. The U.S. Preventive Services Task Force recommends against screening for COPD in asymptomatic adults (13). However, epidemiologic data suggest that COPD is underdiagnosed (14). Furthermore, many patients with the disease report that they do not have symptoms but actually limit their daily physical activity to avoid or minimize them, and others attribute their symptoms to physical deconditioning or older age. A case-finding methodology in U.S. pulmonary and primary care clinics, which invoked 5 simple patient-reported questions and selective use of peak expiratory flow, identified patients in need of further diagnostic evaluation for COPD (15). Future study of performance in primary care settings will determine the utility of this approach.

1. Global Initiative for Chronic Obstructive Lung Disease website. Accessed at www.goldcopd.org on 10 January 2020.
2. Qaseem A, Wilt TJ, Weinberger SE, et al; American College of Physicians. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med. 2011;155:179-91. [PMID: 21810710]
3. U.S. Department of Veterans Affairs; U.S. Department of Defense. VA/DoD Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease. 2014. Accessed at www.healthquality.va.gov/guidelines/CD/copd on 12 January 2020.
4. National Institute for Health and Care Excellence. Chronic Obstructive Pulmonary Disease in Over 16s: Diagnosis and Management. 2018. Accessed at www.nice.org.uk/guidance/ng115 on 12 January 2020.
5. American Thoracic Society. ATS Official Documents. Accessed at www.thoracic.org/statements/copd.php on 10 January 2020.
6. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095-128. [PMID: 23245604]
7. Adeloye D, Chua S, Lee C, et al; Global Health Epidemiology Reference Group (GHERG). Global and regional estimates of COPD prevalence: systematic review and meta-analysis. J Glob Health. 2015;5:020415. [PMID: 26755942]
8. Centers for Disease Control and Prevention. Data and Statistics: COPD Death Rates in the United States. 2018. Accessed at www.cdc.gov/copd/data.html on 9 January 2020.
9. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet. 2009;374:733-43. [PMID: 19716966]
10. Rennard SI, Vestbo J. COPD: the dangerous underestimate of 15%. Lancet. 2006;367:1216-9. [PMID: 16631861]

Screening... The major risk factors for COPD are inhalational exposure to tobacco smoke (including secondhand smoke) and occupational or other exposure to biomass fuels, vapors, gases, dust, and fumes. The best-described genetic risk factor to consider is α_1-antitrypsin deficiency. Screening for COPD in asymptomatic adults is not recommended, but case-finding approaches may help identify undiagnosed persons.

CLINICAL BOTTOM LINE

Diagnosis

When should clinicians consider a diagnosis of COPD?

Clinicians should consider a diagnosis of COPD in adults aged 40 years or older who have risk factors and report chronic respiratory symptoms, such as shortness of breath, cough, or sputum production. Taking a thorough history is essential to capture the presence and burden of respiratory symptoms in at-risk persons. Clinicians should also remember that COPD is a heterogeneous condition. Some patients present predominantly with a chronic productive cough due to mucus hypersecretion (chronic bronchitis), whereas others present predominantly with progressive dyspnea secondary to lung hyperinflation (emphysema).

What is the role of pulmonary function testing in diagnosis?

In addition to the presence of relevant risk factors and chronic respiratory symptoms, a post-bronchodilator FEV_1–FVC ratio less than 0.70 is required for the diagnosis of COPD (1). Once the diagnosis is established, the FEV_1 percentage predicted informs the severity of lung function impairment, which is classified as mild (FEV_1 ≥80% of predicted), moderate (FEV_1 of 50%–79% of predicted), severe (FEV_1 of 30%–49% of predicted), or very severe (FEV_1 <30% of predicted). FEV_1 percentage predicted is strongly associated with mortality and is one of the components of the BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity) index, a well-validated tool for long-term prognosis in COPD (16). Other pulmonary function test measurements, such as lung volumes and the diffusing capacity for carbon monoxide (DLCO), may support the diagnosis but are not required. For example, a high total lung capacity indicating hyperinflation, a high residual volume indicating air trapping, and a low DLCO indicating impaired gas exchange are suggestive of emphysema.

What other tests should clinicians order when evaluating patients with COPD?

No test other than spirometry is required for the diagnosis of COPD, but some tests are helpful in clinical phenotyping and management, especially in patients with advanced disease. An arterial blood gas test can reveal chronic hypercapnia, which may prompt evaluation for home noninvasive ventilation in select patients (17). A 6-minute walk test should be ordered in patients with progressively worsening dyspnea or lung function, decreased DLCO, or significant emphysema on chest computed tomography (CT) to assess for hypoxia with exertion and candidacy for long-term oxygen ther-

11. Lamprecht B, McBurnie MA, Vollmer WM, et al; BOLD Collaborative Research Group. COPD in never smokers: results from the population-based Burden of Obstructive Lung Disease study. Chest. 2011;139:752-63. [PMID: 20884729]
12. Perez-Padilla R, Fernandez R, Lopez Varela MV, et al. Airflow obstruction in never smokers in five Latin American cities: the PLATINO study. Arch Med Res. 2012;43:159-65. [PMID: 22475778]
13. Siu AL, Bibbins-Domingo K, Grossman DC, et al; US Preventive Services Task Force (USPSTF). Screening for chronic obstructive pulmonary disease: US Preventive Services Task Force recommendation statement. JAMA. 2016;315:1372-7. [PMID: 27046365]
14. Soriano JB, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. Lancet. 2009;374:721-32. [PMID: 19716965]
15. Martinez FJ, Mannino D, Leidy NK, et al; High-Risk-COPD Screening Study Group. A new approach for identifying patients with undiagnosed chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2017;195:748-56. [PMID: 27783539]
16. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1005-12. [PMID: 14999112]
17. Coleman JM 3rd, Wolfe LF, Kalhan R. Noninvasive ventilation in chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2019;16:1091-8. [PMID: 31185181]
18. Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. Lancet Respir Med. 2018;6:117-26. [PMID: 29331313]
19. Rizkallah J, Man SFP, Sin DD. Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis. Chest. 2009;135:786-93. [PMID: 18812453]

20. American Thoracic Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168:818-900. [PMID: 14522813]
21. Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. Chronic Obstr Pulm Dis. 2016;3:668-82. [PMID: 28848891]
22. Chapman KR, Burdon JG, Piitulainen E, et al; RAPID Trial Study Group. Intravenous augmentation treatment and lung density in severe a1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;386:360-8. [PMID: 26026936]
23. Chen W, Thomas J, Sadatsafavi M, et al. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Lancet Respir Med. 2015;3:631-9. [PMID: 26208998]
24. Yohannes AM, Alexopoulos GS. Depression and anxiety in patients with COPD. Eur Respir Rev. 2014;23:345-9. [PMID: 25176970]
25. Woodruff PG, van den Berge M, Boucher RC, et al. American Thoracic Society/National Heart, Lung, and Blood Institute asthma-chronic obstructive pulmonary disease overlap workshop report. Am J Respir Crit Care Med. 2017;196:375-81. [PMID: 28636425]
26. Anthonisen NR, Skeans MA, Wise RA, et al; Lung Health Study Research Group. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005;142:233-9. [PMID: 15710956]
27. Jiménez-Ruiz CA, Andreas S, Lewis KE, et al. Statement on smoking cessation in COPD and other pulmonary diseases and in smokers with comorbidities who find it difficult to quit. Eur Respir J. 2015;46:61-79. [PMID: 25882805]
28. Cho-Reyes S, Celli BR, Dembek C, et al. Inhalation technique errors with metered-dose inhalers among patients with obstructive lung diseases: a systematic review and meta-analysis of U.S. studies. Chronic Obstr Pulm Dis. 2019;6:267-80. [PMID: 31342732]

apy. The eosinophil count on a complete blood count with differential can help guide the decision to initiate or discontinue inhaled corticosteroids (ICSs) because patients with higher eosinophil counts generally respond better to this class of inhalers (18). Obtaining a chest CT scan is important in the evaluation of patients with recurrent COPD exacerbations and those with persistent dyspnea despite maximal medical therapy to rule out pulmonary embolism and assess for the presence of other coexisting pulmonary abnormalities, such as bronchiectasis, interstitial lung disease, or lung mass (19).

Clinicians should also consider measuring the α_1-antitrypsin level in all symptomatic patients with fixed airflow obstruction, particularly those with COPD onset as early as the fifth decade of life; those with a family history of α_1-antitrypsin deficiency; and those with emphysema, bronchiectasis, liver disease, or panniculitis in the absence of a recognized risk factor or out of proportion to the culprit exposure (for example, smoking) (20, 21). Identifying this diagnosis is particularly important to urge current smokers to quit given that they are at high risk for accelerated lung function decline, and also to consider intravenous augmentation with pooled human α_1-antitrypsin, which has been shown to reduce declines in lung function and lung density measured on chest CT (22).

What other disorders should clinicians consider in patients with suspected COPD?

Clinicians should consider pulmonary disorders that can result in airflow obstruction, such as asthma or bronchiectasis, which can also coexist with COPD. In addition, patients with COPD are at higher risk for many other comorbidities, including coronary artery disease, heart failure with preserved or reduced ejection fraction, pulmonary hypertension, obstructive sleep apnea, osteoporosis, depression, and anxiety (23, 24). Physicians should regularly evaluate patients with COPD for these comorbidities.

How should clinicians distinguish patients with COPD from those with asthma?

It can be difficult to distinguish between asthma and COPD because both can present with airflow obstruction on spirometry and similar respiratory symptoms (such as dyspnea, cough, and wheeze). However, some clinical features may help differentiate between these disorders. In general, patients with asthma are less likely to be smokers; develop symptoms at a younger age; experience significant symptom variability (for example, between day and night, from day to day, or between seasons), as demonstrated by their often fluctuating peak flow measurements; have characteristic triggers for their symptoms, such as exercise, cold air, and aeroallergens (for example, dust mites, mold, pollen, and pets); and are more likely to have a personal or family history of atopy. In contrast, patients with COPD tend to have disease onset later in life, often have a significant smoking history (≥20 pack-years), have persistent dyspnea on exertion and productive cough, and generally have a less consistent response to inhalers. Patients with clinical features of both disorders are generally considered to have asthma–COPD overlap (25).

Diagnosis... In patients with chronic respiratory symptoms (dyspnea, cough, mucus production) and noxious exposures (cigarette smoking, indoor or outdoor pollution, occupational exposures), a postbronchodilator FEV_1–FVC ratio less than 0.70 is required for a diagnosis of COPD. Other tests and studies, such as full pulmonary function tests, an arterial blood gas test, a 6-minute walk test, a blood eosinophil count, and chest CT, may be helpful to clinically phenotype and guide the management of patients with COPD, especially those with advanced disease. Clinicians should measure α_1-antitrypsin level in all symptomatic patients with fixed airflow obstruction, especially those who have early-onset COPD; a family history of α_1-antitrypsin deficiency; or emphysema, bronchiectasis, liver disease, or panniculitis in the absence of a recognized risk factor or out of proportion to their known exposures. Cardiac comorbidities, osteoporosis, depression, and anxiety are common in patients with COPD and should be screened for on a regular basis.

CLINICAL BOTTOM LINE

Treatment

What is the evidence that smoking cessation benefits patients with COPD, and which interventions are most effective?

Clinicians should urge all current smokers with COPD to quit smoking and should address this with them at every clinic visit or hospital encounter. Persistence on the part of the treating physician is essential to maximize the chances of quitting. Smoking cessation has many important clinical benefits, including better response to bronchodilators, a reduced rate of lung function decline, and decreased mortality (26). A combination of counseling programs and pharmacotherapy is the most effective strategy to help patients quit smoking. Pharmacotherapy options include nicotine replacement therapy (patches, gums, lozenges, nasal sprays, and oral inhalers) and oral drugs, such as bupropion and varenicline (27).

How should clinicians approach drug therapy?

Inhaled medications, which include bronchodilators and corticosteroids, are the backbone of COPD management (**Table 1**). Bronchodilators come in short-acting (short-acting β_2-agonists and short-acting muscarinic antagonists) and long-acting (long-acting β_2-agonists [LABAs] and long-acting muscarinic antagonists [LAMAs]) formulations. Inhaler therapy should be considered part of a comprehensive management strategy that includes smoking cessation, pulmonary rehabilitation, treatment of comorbidities, and up-to-date influenza and pneumonia immunizations.

Symptom burden and exacerbation risk should guide initial inhaler therapy in patients with COPD, based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) ABCD staging system (1) (**Table 2**). Symptom burden can be evaluated using the modified Medical Research Council dyspnea severity scale (**Appendix Table 1**, available at Annals.org) or the more comprehensive COPD Assessment Test (CAT), which incorporates 8 symptom domains (www.catestonline.org). Exacerbation risk is determined by the frequency and severity of exacerbations in the preceding year (**Table 2**; also see the Box: Cri-

29. Tashkin DP, Celli B, Senn S, et al; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359:1543-54. [PMID: 18836213]
30. Vogelmeier C, Hederer B, Glaab T, et al; POET-COPD Investigators. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med. 2011;364:1093-103. [PMID: 21428765]
31. Oba Y, Keeney E, Ghatehorde N, et al. Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis. Cochrane Database Syst Rev. 2018;12:CD012620. [PMID: 30521694]
32. Lipson DA, Barnhart F, Brealey N, et al; IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med. 2018;378:1671-80. [PMID: 29668352]
33. Chapman KR, Hurst JR, Frent SM, et al. Long-term triple therapy de-escalation to indacaterol/glycopyrronium in patients with chronic obstructive pulmonary disease (SUNSET): a randomized, double-blind, triple-dummy clinical trial. Am J Respir Crit Care Med. 2018;198:329-39. [PMID: 29779416]
34. Albert RK, Connett J, Bailey WC, et al; COPD Clinical Research Network. Azithromycin for prevention of exacerbations of COPD. N Engl J Med. 2011;365:689-98. [PMID: 21864166]
35. Martinez FJ, Calverley PM, Goehring UM, et al. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. Lancet. 2015;385:857-66. [PMID: 25684586]
36. Poole PJ, Chacko E, Wood-Baker RW, et al. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006:CD002733. [PMID: 16437444]

Table 1. **Pharmacotherapy in COPD**

Drug Class	*Drug Names*	*Adverse Effects*	*Notes*
Bronchodilators			
Inhaled short-acting β_2-agonist	Albuterol Levalbuterol Terbutaline	Tachycardia, tremor, and hypokalemia (usually dose-dependent), but generally well tolerated by most patients	Generally used as needed for mild disease with low symptom burden or in more advanced disease for acute symptom relief in addition to maintenance inhalers
Inhaled short-acting anticholinergic	Ipratropium	Dry mouth, mydriasis on contact with eye, urine retention, palpitations, and (rarely) acute narrow-angle glaucoma, but generally well tolerated by most patients	Generally used as needed for mild disease with low symptom burden or in more advanced disease for acute symptom relief in addition to maintenance inhalers Avoid using both short- and long-acting anticholinergics
Inhaled long-acting β_2-agonist	Salmeterol Formoterol Arformoterol Indacaterol Olodaterol	Tachycardia, tremor; overdose can be fatal	Use as maintenance therapy when short-acting bronchodilators provide insufficient control of symptoms
Inhaled long-acting anticholinergic	Tiotropium Aclidinium Umeclidinium Glycopyrrolate Revefenacin	Dry mouth, mydriasis on contact with eye, urine retention, palpitations, and (rarely) acute narrow-angle glaucoma	Not to be used with ipratropium Use as maintenance therapy when short-acting bronchodilators provide insufficient control of symptoms or for patients at increased risk for exacerbations
Methylxanthine	Theophylline Aminophylline	Tachycardia, nausea, vomiting, insomnia; narrow therapeutic index; overdose can be fatal with arrhythmias and seizures (including status epilepticus)	Not recommended unless other long-acting bronchodilators are not tolerated or are unaffordable
Anti-inflammatory agents			
Inhaled corticosteroid	Fluticasone Budesonide Mometasone Ciclesonide Beclomethasone	Dysphonia, skin bruising, oral candidiasis, pneumonia, and (rarely) adverse effects of oral corticosteroids	Typically not used alone in COPD but in combination with a long-acting bronchodilator in patients at increased risk for exacerbations
Oral corticosteroid	Prednisone Prednisolone	Hyperglycemia, hypertension, fluid retention, osteoporosis, adrenal suppression, skin bruising, wound healing impairment, gastric ulcers, glaucoma, cataract, mood disturbance, insomnia, pneumonia, opportunistic infections, weight gain	Generally used for a limited period to treat exacerbations; avoid, if possible, in stable COPD given limited benefits and high risk for adverse effects Consider inhaled corticosteroids to facilitate weaning of oral corticosteroids
Oral macrolide	Azithromycin	Nausea, vomiting, diarrhea, hyperkalemia, hearing impairment	Used as a maintenance therapy for prevention of exacerbations Associated with QTc prolongation; avoid or prescribe with caution in patients with long QTc, those with a history of torsades de pointes or bradyarrhythmias, or those already using other QTc-prolonging drugs
Oral phosphodiesterase-4 inhibitor	Roflumilast	Weight loss, nausea, diarrhea, decreased appetite, insomnia, dizziness, back pain	Used as a maintenance therapy for prevention of exacerbations in patients with FEV_1 <50% of predicted and the chronic bronchitis phenotype Contraindicated when hepatic impairment (Child–Pugh class B or C) is present
Combination agents			
Combined inhaled short-acting β_2-agonist and short-acting anticholinergic in a single inhaler	Albuterol/ipratropium Fenoterol/ipratropium	Same/combined effects of both drug classes	Generally used as needed for mild disease with low symptom burden or in more advanced disease for acute symptom relief in addition to maintenance inhalers Avoid using both short- and long-acting anticholinergics
Combined inhaled long-acting β_2-agonist and long-acting anticholinergic in a single inhaler	Tiotropium/olodaterol Umeclidinium/vilanterol Glycopyrrolate/formoterol Glycopyrrolate/indacaterol	Same/combined effects of both drug classes	Recommended as maintenance therapy in highly symptomatic patients (e.g., those with CAT score ≥20) Avoid using both short- and long-acting anticholinergics
Combined inhaled long-acting β_2-agonist and corticosteroid in a single inhaler	Salmeterol/fluticasone propionate Formoterol/budesonide Vilanterol/fluticasone furoate	Same/combined effects of both drug classes	Recommended as maintenance therapy in symptomatic patients at high risk for exacerbations, especially if they have coexisting asthma or a blood eosinophil count ≥0.300 × 10^9 cells/L
Combined inhaled long-acting β_2-agonist, long-acting anticholinergic, and corticosteroid in a single inhaler	Umeclidinium/vilanterol/fluticasone furoate	Same/combined effects of all 3 drug classes	Recommended as escalation therapy in patients who remain symptomatic or continue to have exacerbations on dual inhaler therapy (either inhaled long-acting β_2-agonist plus inhaled long-acting anticholinergic, or inhaled long-acting β_2-agonist plus inhaled corticosteroid)

CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease.

teria for and Severity of Acute COPD Exacerbations). Recommended initial inhaler therapy consists of short-acting bronchodilators in GOLD group A, single long-acting bronchodilators (LABA or LAMA) in group B, LAMAs in group C, and either single (LAMA) or dual (LAMA + LABA) long-acting bronchodilator therapy or a combination of ICSs and LABAs in group D (1).

Criteria for and Severity of Acute COPD Exacerbations*

Criteria

More than day-to-day variation in respiratory symptoms:

- Worsening dyspnea
- Increase in sputum volume
- Increase in sputum purulence (generally yellow or green)

Severity

Mild exacerbation: treated with short-acting bronchodilators

Moderate exacerbation: treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids

Severe exacerbation: requires emergency department visit or hospitalization

** Adapted from reference 1.*

The choice of inhaler device and molecule within a given drug class must be individualized on the basis of such factors as access, cost, ease of use, and patient preference. Providing education on correct inhaler technique is essential because more than 75% of patients with COPD make at least 1 error during administration (28). Clinicians should assess inhaler technique and adherence on a regular basis. They should also review symptom burden and exacerbation frequency at each clinic visit to decide whether to maintain, switch, escalate, or deescalate current inhaler therapy.

What is the role of inhaled bronchodilators?

Short-acting bronchodilators have a duration of action of 3–6 hours and are typically used as needed for relief of respiratory symptoms. In contrast, long-acting bronchodilators should be used every day as maintenance therapy for their long-term benefits with regard to reducing dyspnea, improving lung function, and decreasing exacerbation frequency (29). LAMAs are superior to LABAs for prevention of exacerbations.

In a multinational randomized controlled trial (RCT), 7376 participants with COPD, a post-bronchodilator FEV_1 of no more than 70% of predicted, and at least 1 moderate or severe exacerbation in the previous year were randomly assigned to tiotropium, 18 mcg once daily, or salmeterol, 50 mcg twice daily (30). Tiotropium significantly increased the time to the first moderate or severe exacerbation compared with salmeterol (187 vs. 145 days; hazard ratio, 0.83 [95% CI, 0.77–0.90]; P < 0.001). Both groups experienced a similar rate of serious adverse events.

Dual LAMA and LABA bronchodilator therapy is more effective than monotherapy for symptom and lung function improvement (31). Therefore, clinicians should consider prescribing dual long-acting bronchodilator therapy in highly symptomatic patients (for example, those with a CAT score ≥20) or escalating to dual therapy in patients who remain symptomatic on monotherapy (1).

Table 2. **GOLD ABCD Staging to Guide Initial Pharmacologic Therapy in COPD**

Patient Category	*Characteristics*	*Exacerbations per Year*	*CAT Score*	*mMRC Dyspnea Scale Score*
A	Low risk, fewer symptoms	≤1	<10	0–1
B	Low risk, more symptoms	≤1	≥10	≥2
C	High risk, fewer symptoms	≥2/≥1 with hospitalization	<10	0–1
D	High risk, more symptoms	≥2/≥1 with hospitalization	≥10	≥2

CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council.

37. Centers for Disease Control and Prevention (CDC). Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). MMWR Morb Mortal Wkly Rep. 2010; 59:1102-6. [PMID: 20814406]
38. Matanock A, Lee G, Gierke R, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2019;68: 1069-75. [PMID: 31751323]
39. Walters JA, Tang JN, Poole P, et al. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;1:CD001390. [PMID: 28116747]
40. Wedzicha JA, Miravitlles M, Hurst JR, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2017;49. [PMID: 28298398]
41. Anthonisen NR, Manfreda J, Warren CP, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med. 1987;106:196-204. [PMID: 3492164]
42. Sethi S. Infectious exacerbations of chronic bronchitis: diagnosis and management. J Antimicrob Chemother. 1999;43 Suppl A:97-105. [PMID: 10225579]
43. Walters JA, Tan DJ, White CJ, et al. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014: CD001288. [PMID: 25178099]
44. Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. JAMA. 2013;309:2223-31. [PMID: 23695200]
45. McCarthy B, Casey D, Devane D, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2015:CD003793. [PMID: 25705944]

46. Puhan MA, Gimeno-Santos E, Cates CJ, et al. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2016;12: CD005305. [PMID: 27930803]
47. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93: 391-8. [PMID: 6776858]
48. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet. 1981;1:681-6. [PMID: 6110912]
49. Albert RK, Au DH, Blackford AL, et al; Long-Term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. N Engl J Med. 2016;375:1617-27. [PMID: 27783918]
50. Fishman A, Martinez F, Naunheim K, et al; National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med. 2003;348:2059-73. [PMID: 12759479]
51. Criner GJ, Sue R, Wright S, et al; LIBERATE Study Group. A multicenter randomized controlled trial of Zephyr Endobronchial Valve treatment in heterogeneous emphysema (LIBERATE). Am J Respir Crit Care Med. 2018;198:1151-64. [PMID: 29787288]
52. Criner GJ, Delage A, Voelker K, et al. Improving lung function in severe heterogenous emphysema with the Spiration Valve System (EMPROVE). A multicenter, open-label randomized controlled clinical trial. Am J Respir Crit Care Med. 2019;200: 1354-62. [PMID: 31365298]
53. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014–an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015;34:1-15. [PMID: 25085497]

When should clinicians prescribe corticosteroids?

ICSs should not be prescribed alone in COPD and are generally used in combination with long-acting bronchodilators. The combination of a LABA and an ICS is more effective than its individual components at improving health status, lung function, and exacerbation rate. A combination of a LABA and an ICS should be considered for initial inhaler therapy in patients with high symptom burden and high exacerbation frequency (GOLD group D), particularly if they have coexisting asthma or if their blood eosinophil count is 0.300×10^9 cells/L or higher (1). Recent studies have demonstrated that higher blood eosinophil counts are associated with better efficacy of ICSs at preventing exacerbations (18). Triple therapy with a LABA, a LAMA, and an ICS is superior to dual LABA/LAMA or LABA/ICS therapies at improving symptoms and lung function and reducing exacerbation frequency.

A multinational RCT enrolled 10 355 patients with COPD (FEV_1 <50% of predicted and ≥1 moderate or severe exacerbation in the previous year, or FEV_1 of 50%–80% of predicted and ≥2 moderate or severe exacerbations in the previous year) into the following single-inhaler groups: triple LABA/LAMA/ICS therapy with vilanterol/umeclidinium/fluticasone furoate, dual LABA/ICS therapy with vilanterol/fluticasone furoate, or dual LABA/LAMA therapy with vilanterol/umeclidinium (32). Over 52 weeks, the triple therapy group had a lower rate of moderate or severe exacerbations than either the dual LABA/ICS therapy group (rate ratio, 0.85 [CI, 0.80–0.90]; P < 0.001) or the dual LABA/LAMA therapy group (rate ratio, 0.75 [CI, 0.70–0.81]; P < 0.001).

It is important to note that ICSs have potential for several adverse effects, including higher risk for pneumonia, pulmonary nontuberculous mycobacterial infection, oral candidiasis, and skin bruising. Therefore, clinicians are encouraged to periodically review the risks and benefits of maintaining their patients with COPD on an ICS-containing regimen. Studies examining the effects of ICS withdrawal on clinical outcomes in patients with COPD have produced mixed results to date. In a study that included patients with infrequent exacerbations who were using triple inhaler therapy, deescalation to LABA/LAMA therapy resulted in a small decline in lung function and no difference in exacerbations (33). However, the subgroup of patients with baseline blood eosinophil counts of 0.300×10^9 cells/L or higher had significantly greater loss of lung function and frequency of exacerbations. These findings suggest that the decision on whether to maintain or withdraw an ICS requires clinicians to take several key factors into account, including exacerbation frequency, adverse effects, and blood eosinophil count.

Oral corticosteroids should be reserved for limited periods to treat acute exacerbations. In general, long-term therapy with oral corticosteroids should be avoided in stable disease because of limited, if any, benefits and a high potential for adverse effects, including osteoporosis.

When should clinicians consider adding long-term oral medications to inhaled drug therapy?

COPD exacerbations are detrimental events in the natural history of the disease and are associated with poor quality of life, loss of lung function, and increased mortality. Therefore, prevention of such events is an essential component of COPD

management. For patients receiving maximal inhaler therapy who continue to have frequent exacerbations, clinicians should consider adding long-term azithromycin or roflumilast for prophylaxis (**Table 1**).

In a multicenter RCT, 1142 former smokers with COPD who were at increased risk for exacerbations were randomly assigned to receive azithromycin, 250 mg daily, or placebo for 1 year in addition to usual care (34). The median time to the first exacerbation was 266 days in participants receiving azithromycin compared with 174 days in those receiving placebo ($P < 0.001$). Of note, hearing impairment affected 25% of participants in the azithromycin group compared with 20% in the placebo group ($P = 0.04$).

Roflumilast, a phosphodiesterase-4 inhibitor, has been shown to reduce the frequency of moderate and severe exacerbations in patients at high risk for exacerbations who have an FEV_1 less than 50% of predicted and the chronic bronchitis phenotype (35).

Theophylline is an oral drug with a small bronchodilator effect. However, given its modest symptomatic benefits, narrow therapeutic window, interactions with other medications, and adverse effects (including nausea, vomiting, tachyarrhythmias, and seizures), its use is generally not recommended.

What immunizations should clinicians administer?

The Advisory Committee on Immunization Practices (ACIP) recommends influenza and pneumococcal vaccinations for persons who have chronic pulmonary disorders, including COPD. Influenza vaccination significantly reduces the number of respiratory exacerbations and should be administered yearly to all patients with COPD (36). Adults aged 19–64 years who smoke or have COPD should be given the 23-valent pneumococcal polysaccharide vaccine, and it should be administered again at age 65 years if the previous vaccination was more than 5 years earlier (37). The ACIP no longer recommends vaccinating all adults aged 65 years or older with the 13-valent pneumococcal conjugate vaccine (PCV13) because universal PCV13 vaccination of children has led to a substantial decrease in infections attributed to PCV13 serotypes (38). Indications for PCV13 immunization include a history of invasive pneumococcal disease and the presence of an immunocompromised state, asplenia, a cerebrospinal fluid leak, or a cochlear implant. In the absence of these indications, shared patient–physician decision making regarding the administration of PCV13 is recommended.

In a Cochrane review of 12 RCTs that included a total of 2171 patients with COPD, those who received either pneumococcal vaccine were less likely to develop community-acquired pneumonia (odds ratio, 0.62 [CI, 0.43–0.89]; number needed to treat, 21) or have a COPD exacerbation (odds ratio, 0.60 [CI, 0.39–0.93]; number needed to treat, 8) (39).

How should clinicians manage acute exacerbations?

Although there is no single definition of a COPD exacerbation, the criteria shown in the first Box (Criteria for and Severity of Acute COPD Exacerbations) are commonly used. Acute exacerbations frequently occur after a bacterial or viral upper respiratory tract infection, exposure to an environmental irritant (such as high humidity, cold air, or aeroallergens), or a pulmonary embolism (19). Management includes prompt recognition. Inhaled short-acting bronchodilators are the mainstay of therapy for exacerbations because of their rapid onset of action. Additional management may also include initiation of antibiotics or oral corticosteroids and assessment of the need for hospitalization. Because the symptoms of an exacerbation are not

54. Siddiqui FM, Diamond JM. Lung transplantation for chronic obstructive pulmonary disease: past, present, and future directions. Curr Opin Pulm Med. 2018;24:199-204. [PMID: 29227305]
55. Thabut G, Christie JD, Ravaud P, et al. Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: a retrospective analysis of registry data. Lancet. 2008; 371:744-51. [PMID: 18313503]
56. Cerón Navarro J, de Aguiar Quevedo K, Ansótegui Barrera E, et al. Functional outcomes after lung transplant in chronic obstructive pulmonary disease. Arch Bronconeumol. 2015; 51:109-14. [PMID: 25151535]
57. Borro JM, Delgado M, Coll E, et al. Single-lung transplantation in emphysema: retrospective study analyzing survival and waiting list mortality. World J Transplant. 2016;6:347-55. [PMID: 27358780]
58. Schaffer JM, Singh SK, Reitz BA, et al. Single- vs double-lung transplantation in patients with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis since the implementation of lung allocation based on medical need. JAMA. 2015;313: 936-48. [PMID: 25734735]
59. Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2017;50. [PMID: 28889106]
60. Press VG, Au DH, Bourbeau J, et al. Reducing chronic obstructive pulmonary disease hospital readmissions. an official American Thoracic Society workshop report. Ann Am Thorac Soc. 2019;16: 161-70. [PMID: 30707066]

specific to COPD, relevant differential diagnoses should be considered, including acute myocardial infarction, pneumonia, arrhythmia, and exacerbation of congestive heart failure.

Clinicians should consider prescribing antibiotics for patients with an ambulatory COPD exacerbation. This recommendation is based on a pooled analysis of several studies that showed a decrease in treatment failure and an increase in the time between exacerbations with antibiotic therapy (40). Episodes that present with purulent sputum are most likely to benefit from antibiotic treatment (41). The severity of the exacerbation and the degree of lung function impairment are also important considerations when deciding whether to prescribe an antibiotic. The actual trigger of a COPD exacerbation is often not known in usual practice. Therefore, antibiotic therapy should cover the most common bacterial pathogens, such as *Haemophilus influenza*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*, while taking into account response to previous treatment and local bacterial resistance patterns (42). Antibiotic options include β-lactam/β-lactamase inhibitors, second- or third-generation cephalosporins, macrolides, fluoroquinolones, tetracyclines, and trimethoprim–sulfamethoxazole.

Oral corticosteroids should be strongly considered in patients with moderate to severe acute exacerbations. Several RCTs comparing corticosteroids administered orally or parenterally in exacerbations support a reduction in the likelihood of treatment failure and relapse by 1 month (43). These studies also show earlier improvement in symptoms and lung function and reduction in length of hospital stay. There is no evidence of benefit for parenteral versus oral corticosteroid treatment with regard to treatment failure, relapse, or mortality. Although adverse effects can result from administration of both parenteral and oral corticosteroids, they are less severe with oral treatment, which is therefore favored.

An RCT of 314 patients presenting to the emergency department with acute COPD exacerbations found no difference between a 5-day course of oral corticosteroids versus a 14-day course with regard to repeated exacerbation in 6 months (44). This supports the common practice of prescribing prednisone, 40 mg/d for 5 days, for patients not requiring admission to the intensive care unit.

It is important to recognize that some patients will have an inadequate response to outpatient management of an exacerbation; these patients may require hospitalization with possible noninvasive ventilation, intubation, and mechanical ventilation (Box: Indications for Hospital Assessment or Admission for COPD Exacerbations). A discussion of inpatient management of patients with COPD is beyond the scope of this review, and readers should consult other sources for further information (1, 40).

Indications for Hospital Assessment or Admission for COPD Exacerbations*

- Severe symptoms, such as sudden worsening of resting dyspnea, high respiratory rate, decreased oxygen saturation, confusion, or drowsiness
- Acute respiratory failure
- Onset of new physical signs (e.g., cyanosis or peripheral edema)
- Failure of exacerbation to respond to initial medical management
- Significant comorbid conditions (e.g., heart failure or newly occurring arrhythmias)
- Diagnostic uncertainty
- Insufficient home support

* *Adapted from reference 1.*

When should clinicians recommend pulmonary rehabilitation?

Pulmonary rehabilitation is a multidisciplinary program of care comprising various interventions that include exercise training (both aerobic and strength training), education, and psychological and nutritional counseling. Although these components are beneficial on an individual basis, the most effective approach is a comprehensive, integrated program (1, 3). A team of health care practitioners usually provides pulmonary rehabilitation in a structured program administered to groups of patients with COPD.

Clinicians should recommend pulmonary rehabilitation for all symptomatic patients with COPD as part of their overall treatment plan as pharmacotherapy is being optimized. Patients who are most likely to benefit are those with impaired quality of life due to COPD, those who experience breathlessness and anxiety that limit activity, and those who are willing to undertake an intensive education and exercise program (1, 3).

A 2015 Cochrane Collaboration review of 65 RCTs with a total of 3822 patients with COPD concluded that pulmonary rehabilitation reduced dyspnea and increased exercise ability and health-related quality of life (45). Another Cochrane Collaboration analysis of 1477 patients found that the effect of pulmonary rehabilitation after a COPD exacerbation on hospital readmission and mortality was heterogeneous, with some studies showing benefit and others not (46).

Future studies should examine factors responsible for this heterogeneity of effects, such as the duration and breadth of post-exacerbation rehabilitation programs.

What other adjunctive measures should clinicians consider?

Adjunctive therapies are commonly used, although little evidence supports their effectiveness. Relaxation techniques, diaphragmatic breathing, and pursed-lip breathing may reduce anxiety caused by shortness of breath. Nutritional interventions can help achieve ideal body weight and improve quality of life. Use of a flutter valve device and chest physiotherapy can enhance sputum clearance and alleviate dyspnea in patients with chronic bronchitis or coexisting bronchiectasis but have limited usefulness in the absence of excessive sputum production. Obstructive sleep apnea is common in patients with COPD and should be diagnosed and treated in a timely manner to improve overall cardiopulmonary health and enhance sleep quality.

When should clinicians prescribe oxygen therapy?

Long-term oxygen therapy decreases mortality in patients with severe resting hypoxemia (47, 48). Therefore, patients with moderate to severe COPD should be periodically evaluated to determine whether they need supplemental oxygen (see the Box: Criteria for Initiation of Long-Term Oxygen Therapy). Measurement of Pa_{O_2} after 30 minutes of breathing room air is the most accurate clinical standard for initiation of oxygen therapy. Pulse oximetry can be used to qualify patients for long-term oxygen therapy and to adjust oxygen flow rates. Patients can self-adjust the rate of oxygen flow using relatively inexpensive pulse oximeters, provided that they know to keep their Sa_{O_2} near 90%. This approach can be useful for patients to titrate oxygen flow at different altitudes. When long-term oxygen therapy is indicated for continuous use, it should be used for at least 15 hours, and ideally 24 hours a day.

In a multicenter RCT of long-term supplemental oxygen versus no long-term supplemental

oxygen in patients with COPD and moderate resting or exercise-induced desaturation, use of long-term supplemental oxygen did not improve mortality or time to first hospitalization compared with no long-term supplemental oxygen. The study did not find between-group differences in quality of life, lung function, or distance walked in 6 minutes (49).

Criteria for Initiation of Long-Term Oxygen Therapy*

Tested on room air at rest:

- Sa_{O_2} ≤88%, *or*
- Pa_{O_2} ≤55 mm Hg

Tested during exercise:

- Sa_{O_2} ≤88% or Pa_{O_2} ≤55 mm Hg *and*
- Documented improvement of hypoxemia during exercise with oxygen administration

Tested during sleep:

- Sa_{O_2} ≤88% or Pa_{O_2} ≤55 mm Hg for ≥5 minutes during sleep *or*
- Decrease in Sa_{O_2} >5% or decrease in Pa_{O_2} >10 mm Hg for ≥5 minutes associated with symptoms or signs attributable to hypoxemia (e.g., impaired cognition or restlessness)

** For patients with congestive heart failure, pulmonary hypertension/cor pulmonale, or erythrocytosis, Sa_{O_2} ≤89% or Pa_{O_2} of 56–59 mm Hg at rest, during exercise, or during sleep meets criteria for initiation of oxygen therapy.*

Taken together, these findings suggest that although long-term oxygen therapy decreases mortality in patients with COPD and severe resting hypoxia, it may not confer a survival benefit in those with moderate resting or exertional hypoxia. Therefore, shared decision making should guide the decision on whether to initiate oxygen therapy in these patients.

When should clinicians refer patients to a pulmonologist?

Clinicians should consider referring patients with COPD to a pulmonologist when there is diagnostic uncertainty or when patients are not responding well to treatment. Patients with COPD who average at least 2 annual exacerbations requiring treatment represent a specific subgroup associated with poor outcomes and may benefit from pulmonary subspecialty care. Patients with severe COPD undergoing high-risk surgeries based on the type, location, and urgency of the procedure may benefit from preoperative pulmonary optimization. Consideration of bronchoscopic or surgical lung volume reduction or lung transplant should also prompt referral to a pulmonologist. **Appendix Table 2** (available at Annals.org) lists referral recommendations adapted from professional society guidelines.

When should clinicians consider surgical or bronchoscopic therapies?

Lung volume reduction surgery

Lung volume reduction surgery (LVRS) involves resection of up to 30% of diseased or nonfunctioning emphysematous parenchyma to allow the remaining lung to function more efficiently. It may be considered in patients with COPD who have completed a pulmonary rehabilitation program and meet the following criteria: 1) evidence of upper lobe–predominant bilateral emphysema on chest CT; 2) total lung capacity and residual volume above 100% and 150% of predicted, respectively, on pulmonary function tests; 3) maximum postbronchodilator FEV_1 no greater than 45% of predicted; and 4) room air Pa_{CO_2} of no more than 60 mm Hg and Pa_{O_2} of at least 45 mm Hg. Patients with an FEV_1 of 20% of predicted or less and either homogeneous emphysema on CT or DLCO of

20% of predicted or less should not be considered for LVRS because they are unlikely to benefit from it and have a high risk for perioperative mortality (50). Select patients with upper lobe–predominant emphysema, low exercise capacity, and severe symptoms have experienced a mortality benefit along with improved symptoms and exercise capacity after LVRS (50).

Bronchoscopic lung volume reduction

Bronchoscopic approaches have also been developed to reduce lung volume through the placement of valves in select airways to produce targeted atelectasis of emphysematous portions of the lung. Two valve devices had been approved by the U.S. Food and Drug Administration as of 16 January 2020. Selection criteria for bronchoscopic lung volume reduction (BLVR) are generally similar to those for LVRS, with 2 exceptions: Emphysema distribution does not have to be upper lobe–predominant for BLVR, and the pulmonary fissure associated with the lobe to be targeted must be complete in BLVR so that atelectasis of that lobe can occur after valve placement. The rate of pneumothorax after BLVR can be as high as 30%, and most pneumothoraces occur in the first few days after the procedure. This requires that patients be hospitalized for a minimum of 3 days after the procedure for monitoring. Long-term mortality outcomes after BLVR remain to be determined.

A multicenter RCT to evaluate the efficacy and safety of the Zephyr Endobronchial Valve (Pulmonx) in patients with severe COPD with no collateral ventilation in the target lobe showed benefit for lung function, exercise tolerance, dyspnea, and quality of life over the standard of care medical therapy group to at least 12 months (51). Another multicenter, open-label RCT assessing the Spiration Valve System (Olympus) found that patients with severe heterogeneous emphysema who underwent BLVR had significant 6- and 12-month improvements in FEV_1 and 6-month improvements in dyspnea and quality of life compared with patients receiving optimal medical management alone (52).

Lung transplant

COPD-specific guidelines recommend lung transplant referral for patients with progressive disease despite maximal medical treatment that includes pharmacotherapy, pulmonary rehabilitation, and oxygen therapy if they are not candidates for bronchoscopic or surgical lung volume reduction and if they have a BODE index score of 5-6, a $PaCO_2$ greater than 50 mm Hg and/or a PaO_2 less than 60 mm Hg, and an FEV_1 less than 25% of predicted (53). Debate is ongoing about single versus bilateral lung transplant in COPD. Some studies have shown improved survival (54, 55) and functional results (56) with double versus single lung transplant, but others have demonstrated similar survival with fewer postoperative complications and lower mortality on the waiting list with single lung transplant (57). There was no difference in mortality at 5 years between single and double lung transplant in a propensity score–controlled analysis of more than 3000 recipients from the United Network for Organ Sharing database (58). Successful lung transplant results in improved pulmonary function, exercise capacity, quality of life, and possibly survival (2). Chronic allograft rejection (obliterative bronchiolitis) is the leading cause of long-term morbidity and mortality, with rates as high as 25%–55% after transplant.

Treatment... Inhaler therapy is the backbone of COPD treatment and should be complemented by a multifaceted management strategy that includes counseling and pharmacotherapy for smoking cessation, pulmonary rehabilitation, treatment of comorbidities, administration of influenza and pneumococcal immunizations, and prescription of long-term oxygen therapy in hypoxemic patients. Respiratory symptom burden and exacerbation frequency should guide initial and follow-up inhaler therapy. Acute exacerbations should be treated by optimizing bronchodilator therapy and adding systemic corticosteroids with or without antibiotics as clinically indicated. Patients with frequent exacerbations should be considered for long-term oral prophylactic therapies, such as azithromycin and roflumilast. Eligible patients with advanced COPD should be referred to a pulmonologist for consideration of interventional options, such as surgical or bronchoscopic lung volume reduction and lung transplant.

CLINICAL BOTTOM LINE

Practice Improvement

What do professional organizations recommend with regard to prevention, screening, diagnosis, and treatment?

Guidelines from professional organizations include those from GOLD (updated in 2020) (1); the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society on the diagnosis and management of stable COPD (updated in 2011) (2); the American Thoracic Society and European Respiratory Society on the prevention and management of COPD exacerbations (updated in 2017) (40, 59); the U.S. Department of Veterans Affairs and U.S. Department of Defense (updated in 2014) (3); and the National Institute for Health and Care Excellence (updated in 2019) (4). These guidelines present a comprehensive approach to diagnosis and management and draw information and evidence from various sources, including RCTs; cohort studies; case–control studies; expert opinion; and recommendations from public policy organizations, such as the ACIP.

What measures do stakeholders use to evaluate the quality of care for patients with COPD?

The Centers for Medicare & Medicaid Services instituted a penalty for 30-day readmissions as part of its Hospital Readmissions Reduction Program in October 2014. This prompted hospitals to develop readmission reduction programs with few published data on effectiveness. The American Thoracic Society recently released a workshop report on current best practices and models for addressing COPD hospital readmissions (60).

In the Clinic
Tool Kit

Chronic Obstructive Pulmonary Disease

Patient Information

https://medlineplus.gov/copd.html
https://medlineplus.gov/languages/copd.html
Patient information and handouts on COPD in English and other languages from the National Institutes of Health's MedlinePlus.

www.nhlbi.nih.gov/health-topics/copd
www.nhlbi.nih.gov/health-topics/espanol/epoc
Patient information on COPD in English and Spanish from the National Heart, Lung, and Blood Institute.

www.thoracic.org/patients/patient-resources/resources/copd-intro.pdf
Patient education handout on COPD from the American Thoracic Society.

Information for Health Professionals

https://goldcopd.org/gold-reports
2020 Global Strategy for Prevention, Diagnosis, and Management of COPD from the Global Initiative for Chronic Obstructive Lung Disease.

www.nice.org.uk/guidance/ng115
National Institute for Health and Care Excellence 2019 updated guideline on diagnosis and management of COPD.

www.thoracic.org/statements/resources/copd/prevention-copd-exacerbations.pdf
European Respiratory Society/American Thoracic Society 2017 updated guideline on prevention of COPD exacerbations.

www.aafp.org/afp/2017/0401/p433.html
Recommendations on diagnosis and management of COPD from the American Academy of Family Physicians.

WHAT YOU SHOULD KNOW ABOUT COPD

What Is Chronic Obstructive Pulmonary Disease (COPD)?

It is a common, preventable lung disease. People with COPD have a hard time getting air in and out of their lungs.

What Causes It?

Cigarette smoking is the leading cause of COPD. Breathing polluted air or chemical fumes over a long period of time may also cause it. In a small number of cases, it is caused by a rare genetic condition. It is usually diagnosed in middle-aged or older people.

What Are Common Symptoms?

- Shortness of breath, especially with activity
- Coughing a lot
- A cough that produces large amounts of mucus
- Wheezing
- Chest tightness
- Lack of energy or feeling tired

Your symptoms will depend on how severe your COPD is and how much damage has been done to your lungs. Some people have mild lung disease and only a few symptoms. Others have very severe lung disease and severe, frequent symptoms.

How Is It Diagnosed?

- Your doctor will listen to your chest with a stethoscope. He or she will ask about your symptoms and medical history.
- You will have a test called "spirometry." With this test, you blow into a machine called a spirometer that measures how well your lungs are working.
- Other tests and studies may be needed. These could include a CT scan of your chest, a blood test to measure the level of oxygen in your blood, or a walking test to measure how your body responds to activity.

How Is It Treated?

- One of the most important parts of COPD treatment is quitting smoking. This will improve your breathing, keep your COPD from getting worse, and lower your chances of dying. Your doctor will work with you to help you quit.
- Most symptoms are managed with inhaled medications, which improve breathing by relaxing airways or decreasing airway inflammation. Some inhalers are used every day; others are used only when your breathing gets worse. Talk to your doctor about the best inhalers for you based on cost, ease of use, and your personal preference.

- Your doctor may also prescribe steroids for short periods of time to help manage days when your symptoms are worse.
- If you have moderate or severe COPD, your doctor may prescribe oxygen. In rare cases, surgery or a lung transplant may be recommended.
- Your doctor may enroll you in a pulmonary rehabilitation program. This will teach you skills to live with COPD, manage symptoms, and improve your exercise tolerance.
- Managing other diseases, staying up-to-date on your vaccines, getting regular activity, and eating well are also important to keeping you healthy.
- You will need regular follow-up visits with your doctor. During these visits, your doctor will make sure you are using your inhaler correctly. They will review your symptoms and decide whether to make any changes to your medicine.

Questions for My Doctor

- What changes can I make in my life to help improve my symptoms?
- What will happen if I don't quit smoking? Can you help me quit?
- Is my lung damage reversible?
- Which inhaler is best for me?
- What are the risks or side effects of treatment?
- Would you watch me use my inhaler and tell me if I am using it correctly?
- Do I need oxygen therapy?
- Can I keep doing the things I like to do?
- How often should I have follow-up visits?
- Will I need to see any other doctors?

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

American Lung Association
www.lung.org/lung-health-diseases/lung-disease-lookup/copd

MedlinePlus
https://medlineplus.gov/copd.html

Live Well With COPD
http://acp-resources.com/COPD/index.php

Patient Information

Appendix Table 1. **Modified Medical Research Council Dyspnea Scale**

Score	*Description of Dyspnea*	*Severity*
0	I get breathless only with strenuous exercise.	None
1	I get short of breath when hurrying on level ground or walking up a slight hill.	Mild
2	On level ground, I walk slower than other people my age because of breathlessness, or I have to stop for breath when walking at my own pace.	Moderate
3	I stop for breath after walking approximately 100 yards or after a few minutes on level ground.	Severe
4	I am too breathless to leave the house or breathless when dressing.	Very severe

Appendix Table 2. **When to Consider Referral to a Pulmonary Specialist***

Disease onset before age 40 years
Frequent exacerbations (≥2 per year) despite adequate treatment
Rapidly progressive disease course (decrease in FEV_1, progressive dyspnea, decreased exercise tolerance, unintentional weight loss)
Severe COPD (FEV_1 <50% of predicted) despite optimal treatment
Need for oxygen therapy
Onset of comorbid condition (osteoporosis, heart failure, bronchiectasis, lung cancer)
Diagnostic uncertainty (e.g., coexisting COPD and asthma)
Symptoms disproportionate to the severity of airflow obstruction
Confirmed or suspected α_1-antitrypsin deficiency
Patient requests a second opinion
Patient is a potential candidate for lung transplant or bronchoscopic or surgical lung volume reduction
Patient has very severe disease and requires elective surgery that may impair respiratory function

COPD = chronic obstructive pulmonary disease.
** Adapted from references 3 and 5.*