

In the Clinic

Chronic Obstructive Pulmonary Disease

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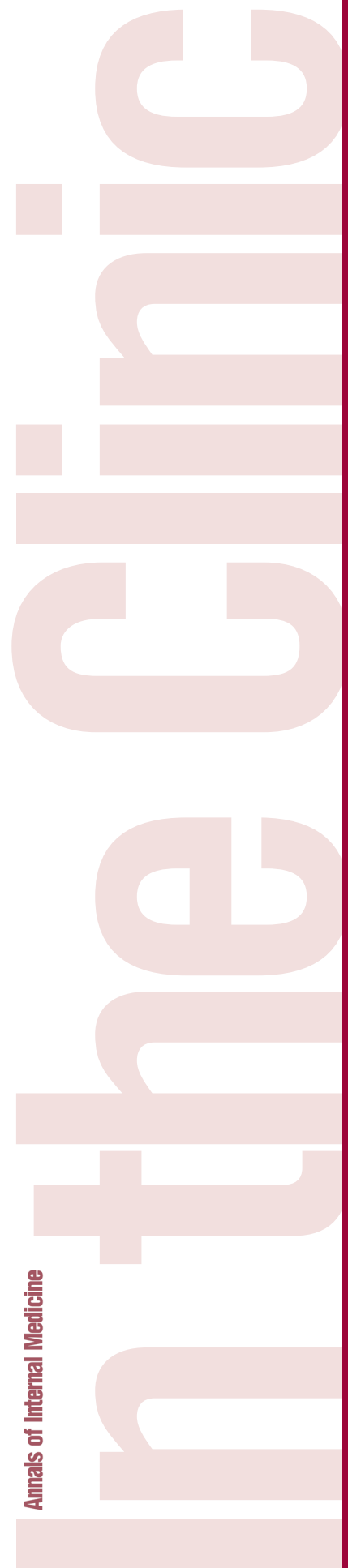
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CME Objective: To review current evidence for the screening, diagnosis, treatment and practice improvement of chronic obstructive pulmonary disease.

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Chronic obstructive pulmonary disease (COPD) is a treatable, preventable, and partially reversible disease characterized by progressive airflow obstruction documented by spirometry; it is associated with an abnormal inflammatory response of the lungs to noxious particles or gases (1–4).

Between 10% and 20% of COPD in the United States is estimated to be caused by occupational or other exposure to chemical vapors, irritants, and fumes. However, a recent review suggested that the percentage of patients with COPD who never smoked is 25% in the United States and may vary worldwide between about 15% (Japan) and 48% (South Africa), with higher rates in women (5). More information is needed to determine the role of inhaled irritants other than cigarette smoke, such as those found in outdoor air pollution, and with indoor products of biomass fuels, such as wood-burning stoves.

Screening

Which patient populations are at risk?

Patients younger than 35 years rarely get COPD because susceptible individuals develop the disease only after inhalational exposure to causative agents of sufficient intensity and duration. An estimated 80% to 90% of COPD is due to cigarette smoking. A risk of 15% for clinically significant COPD among smokers is commonly cited, but this may be an underestimate (6). The effect of environmental, or “second-hand,” smoke in the development of COPD is less clear (7, 8). Genetic factors clearly play a role in susceptibility to COPD, the best defined being emphysema related to α_1 -antitrypsin deficiency.

COPD is a common cause of morbidity and mortality worldwide. Unlike the sharp reduction in death from heart disease, there has been an almost 100% increase in age-adjusted mortality from COPD between 1970 and 2002. As of 2006, COPD was the fourth-leading cause of death in the United States, accounting for 5.1% (124 583) of all deaths. In 2000, the number of deaths from COPD in women was equal to that in men. Although COPD deaths continue to represent a large proportion of deaths from all causes, recent trends suggest that the incidence of new cases is decreasing and mortality rates may have peaked (9).

Should clinicians screen asymptomatic patients?

Screening asymptomatic patients for COPD with spirometry is not supported by convincing evidence. The U.S. Preventive Services Task Force and the Global Initiative for Obstructive Lung Disease (GOLD) (1, 10) recommend against screening for COPD in the general population. On the other hand, epidemiologic evidence suggests that one half of the current population with COPD has not been identified (7), and patients who smoke or have other risk factors may have COPD without being symptomatic.

A potential benefit of early detection is the opportunity to motivate patients to stop smoking, but data to support this are conflicting. Some studies show that simply informing patients that they have abnormal spirometry does not lead to smoking cessation, while other data suggest that providing patients with an estimate of their “lung age” is effective (11,12).

Some professional organizations recommend a case-finding approach in patients with symptoms who present with risk factors, such as smoking and age older than 35 years. For example, the updated 2009 GOLD guidelines suggest that clinicians perform spirometry

1. Global Initiative for Chronic Obstructive Lung Disease. Accessed at www.goldcopd.org on 4 December 2010.
2. American Thoracic Society. COPD Guidelines. Accessed at www.copd-at-ers.org/copddoc.pdf on 20 November 2010.
3. Department of Veterans Affairs and Department of Defense. COPD Guidelines. Accessed at www.healthquality.va.gov/Chronic_Obstructive_Pulmonary_Disease_CO PD.asp on 27 November 2010.
4. National Institute of Clinical Excellence. Management of chronic obstructive pulmonary disease in adults in primary and secondary care. Accessed at <http://guidance.nice.org.uk/CG101/Guidance/pdf/English> on 26 November 2010.
5. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet*. 2009;374:733-43. [PMID: 19716966]
6. Rennard SJ, Vestbo J. COPD: the dangerous underestimate of 15%. *Lancet*. 2006;367:1216-9. [PMID: 16631861]
7. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet*. 2007;370:765-73. [PMID: 17765526]
8. Eisner MD, Anthonisen N, Coultas D, et al. Committee on Nonsmoking COPD, Environmental and Occupational Health Assembly. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Resp Crit Care Med* 2010;182:693-718. [PMID: 20802169]
9. Chronic Obstructive Pulmonary Disease Prevalence and Mortality. Accessed at the United States Environmental Protection Agency at <http://cfpub.epa.gov/eroe/index.cfm?fuseaction=detail.viewIncl&v=list.listByAlpha&r=216638&subtop=381> on 4 December 2010.

to look for COPD in patients with symptoms, such as chronic cough and sputum production or shortness of breath (1). The United

Kingdom's National Institute for Clinical Excellence and the Veterans Affairs COPD guidelines have similar recommendations (3, 4).

Screening... The major risk factors for COPD are inhalational exposure to tobacco smoke, which may include second-hand smoke, and occupational or other exposure to dust, vapors, irritants, and fumes. α_1 -antitrypsin deficiency is the best-described genetic risk factor to consider, especially when patients develop COPD before age 50 years. Screening for COPD in the asymptomatic general population is not recommended. Some professional organizations recommend spirometry in specific patient groups as a case-finding measure and to encourage patients to stop smoking.

CLINICAL BOTTOM LINE

When should clinicians consider a diagnosis of COPD?

COPD should be considered in patients with a history of significant exposure to tobacco smoke, especially when they have such symptoms as cough, sputum production, dyspnea, and decreased exercise tolerance. The physical examination may be normal. In more advanced disease, there may be evidence of hyperinflation, such as hyperresonance and distant breath sounds. Chronic bronchitis, defined as at least 90 days of cough and sputum production in each of 2 consecutive years, and emphysema, a pathologic diagnosis suggested by hyperinflation on examination and confirmed by imaging studies, are commonly associated with COPD. However, neither is required to make the diagnosis.

What is the role of pulmonary function testing in diagnosis?

Spirometry is essential for diagnosis and classification of COPD. A post-bronchodilator FEV_1 -FVC ratio < 0.70 is generally considered the diagnostic threshold, although this may be present in normal elderly persons. The FEV_1 percentage predicted is used to classify COPD as mild ($>80\%$), moderate (50% – 80%), severe (30% – 50%), or very severe ($<30\%$) (1–4). It is important to note that the degree of reversibility of

airflow limitation (e.g., improvement in FEV_1 after bronchodilator or glucocorticosteroids) is not recommended for diagnosis, differential diagnosis with asthma, or for prediction of response to long-term treatment with bronchodilators or glucocorticosteroids (1, 4).

Measurement of lung volume and diffusing capacity may support the diagnosis but are not generally required. Arterial blood gases and pulse oximetry are usually used to determine whether a patient is a candidate for long-term oxygen therapy or if chronic hypercapnia is present. These tests may also be helpful in further characterizing the severity of COPD; suggesting the presence of emphysema, and excluding other lung diseases, such as restrictive lung disease.

Spirometric measurements can also be used to calculate the BODE index (Table 1) (13), which stands for Body mass index; Obstruction as measured by FEV_1 ; Dyspnea as measured by the Modified Medical Research Council dyspnea questionnaire (14); and Exercise, as determined by a 6-minute walk test. Increasing BODE index is associated with higher risk for hospitalization and worse long-term prognosis. It is also used in evaluation of patients for lung transplantation (15).

Diagnosis

10. U.S. Preventive Services Task Force. Screening for Chronic Obstructive Pulmonary Disease Using Spirometry: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med.* 2008;148:535-43. [PMID: 18316746]
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15. Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2006; 25:745-55. [PMID: 16818116]

Table 1. The MMRC Dyspnea Severity Scale* for Calculation of the BODE Index

Severity	Score	Degree of Breathlessness Related to Activities
None	0	Not troubled with breathlessness except with strenuous exercise
Mild	1	Troubled by shortness of breath when hurrying or walking up a slight hill
Moderate	2	Walks slower than people of the same age due to breathlessness or has to stop for breath when walking at own pace on level ground
Severe	3	Stops for breath after walking approximately 100 meters or after a few minutes on level ground
Very severe	4	Too breathless to leave the house or breathless when dressing or undressing

Variable	Points on BODE Index†			
	0	1	2	3
FEV ₁ (percentage predicted)	≥65	50–64	36–49	≤35
Distance walked in 6 min, m	≥350	250–349	150–249	≤149
MMRC dyspnea scale score	0–1	2	3	4
Body mass index	>21	≤21		

* Adapted from Veterans' Affairs and Department of Defense guidelines (3). BODE = Body mass index, Obstruction, Dyspnea, and Exercise; COPD = chronic obstructive pulmonary disease; MMRC = Modified Medical Research Council.

† Points for each variable are summed with a possible range from 0 to 10. Higher numbers indicate worse prognosis. Adapted from (10).

The BODE index was validated prospectively in 625 patients with COPD. The average FEV₁ percentage predicted varied from 39% to 47%. For each 1-point increase in the BODE index, there was a 1.34 increase in the hazard ratio for subsequent death from any cause and a 1.62 increase for death from respiratory failure (13).

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

Apart from the specific pulmonary function tests described previously, no other tests are routinely recommended in diagnosing COPD, classifying its severity, or helping to determine prognosis. However, chest radiographs may show flattened diaphragms and hyperlucency and computed tomography (CT) scanning may show destruction of pulmonary parenchyma in patients with emphysema. In addition, echocardiography may indicate the possibility of cor pulmonale from pulmonary hypertension. Treatment of such pulmonary hypertension with vasodilators is off-label, may not be effective in improving exercise tolerance and reducing pulmonary arterial blood pressure, and frequently leads to a reduction in arterial oxygen hemoglobin saturation (16–18).

Clinicians should consider measuring the α_1 -antitrypsin level in patients who have documented COPD with onset as early as the fifth decade of life or in the absence of a recognized risk factor, such as smoking and occupational dust exposure. It should also be considered in patients with a family history of emphysema or α_1 -antitrypsin deficiency, bronchiectasis, liver disease, or panniculitis.

Exercise testing may also be useful in the differential diagnosis of patients with dyspnea when it is unclear whether symptoms are pulmonary or cardiac in origin.

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

In the proper setting, clinicians should consider any condition that produces airflow obstruction, including asthma; bronchiectasis; cystic fibrosis; bronchiolitis; and upper airway obstruction due to tumors of the trachea, tracheal stenosis, tracheomalacia, and vocal cord dysfunction. Less common diagnoses include other pulmonary conditions that cause dyspnea, such as interstitial lung disease; pulmonary arterial hypertension; chest wall disorders, such as kyphoscoliosis;

16. Blanco I, Gimeno E, Munoz PA, et al. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Am J Respir Crit Care Med*. 2010;181:270-8. [PMID: 19875684]
17. Rietema H, Holverda S, Bogaard HJ, et al. Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. *Eur Respir J*. 2008;31:759-64. [PMID: 18094009]
18. Stolz D, Rasch H, Linka A, et al. A randomised, controlled trial of bosentan in severe COPD. *Eur Respir J*. 2008;32:619-28. [PMID: 18448495]
19. National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Accessed at www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf on 24 December 2010.

and cardiac causes. Some of these may also coexist with COPD.

How should clinicians distinguish between patients with COPD and those with asthma?

Because spirometric obstruction, cough, wheeze, and dyspnea are common to both COPD and asthma, it is sometimes difficult to distinguish between the disorders. In general, patients with asthma develop symptoms at a younger

age; are less likely to be smokers; and experience symptoms intermittently and with more variability, which may be demonstrated by monitoring daily peak flow (19). Those with COPD tend to have onset of disease later in life; commonly have chronic productive cough; have more persistent dyspnea; and generally have a less consistent response to drugs, such as inhaled corticosteroids and bronchodilators.

Diagnosis... Clinicians should suspect COPD in patients with a smoking history or substantial exposure to inhaled irritants who have chronic cough, sputum, or dyspnea. Confirm the diagnosis by spirometry with a FEV₁-FVC ratio < 0.70 measured after administration of a bronchodilator. Use the FEV₁ and clinical data to determine disease severity and to exclude other disorders. Consider measuring the α_1 -antitrypsin level in patients who present with early-onset COPD or in those with a compatible family history.

CLINICAL BOTTOM LINE

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

Clinicians should urge all patients with COPD who smoke to quit and to enroll in a smoking cessation program. There is excellent evidence that patients with COPD who stop smoking have a reduced rate of decline in pulmonary function (20) and reduced mortality (21).

In a multicenter, randomized, controlled trial (RCT) of an intensive smoking cessation program that included behavioral modification and nicotine gum versus placebo, middle-aged smokers in the intervention group had a slower rate of decline in FEV₁ (34 mL/y) than those in the placebo group (63 mL/y) over a 5-year period (21). A follow-up study found that after 14.5 years, all-cause mortality was significantly lower in the smoking cessation group than in the usual care group (8.83 per 1000 person-years vs. 10.38 per 1000 person-years; P = 0.03) (21).

Smoking cessation therapies range from brief interventions in

physicians' offices to more structured programs, which typically include 2 to 3 longer advice sessions and medications, such as nicotine preparations, bupropion, or varenicline. These programs are effective in up to 30% of patients at 1 year.

How should clinicians approach drug therapy?

Inhaled medications—including β_2 -agonists, anticholinergics, and corticosteroids—are the cornerstones of pharmacotherapy for COPD and should be considered part of an overall treatment strategy that includes smoking cessation, education, pulmonary rehabilitation, and long-term oxygen therapy (LTOT) in hypoxemic patients. Of these therapies, only smoking cessation convincingly reduces the rate of decline in pulmonary function, and only smoking cessation and LTOT decrease mortality. The goal of treatment should be symptom relief, particularly dyspnea, prevention of exacerbations, and improvement in long-term respiratory health status.

Treatment

20. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV₁. The Lung Health Study. *JAMA*. 1994;272:1497-505. [PMID: 7966841]
21. Anthonisen NR, Skeans MA, Wise RA, et al. 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]
22. Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2007;147:633-8. [PMID: 17975186]

23. Calverley PM, Anderson JA, Celli B, et al. TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356:775-89. [PMID: 17314337]
24. Tashkin DP, Celli B, Senn S, et al. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2008;359:1543-54. [PMID: 18836213]
25. Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med*. 2008;178:332-8. [PMID: 18511702]
26. Troosters T, Celli B, Lystig T, et al. Tiotropium as a first maintenance drug in COPD: secondary analysis of the UPLIFT trial. *Eur Respir J*. 2010;36:65-73. [PMID:20185426]
27. van Noord JA, Aumann JL, Janssens E, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. *Eur Respir J*. 2005;26:214-22. [PMID: 16055868]
28. Aaron SD, Vandemheen KL, Ferguson D et al; Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*. 2007;146:545-55. [PMID: 17310045]
29. Puhan MA, Bachmann LM, Kleijnen J, et al. Inhaled drugs to reduce exacerbations in patients with chronic obstructive pulmonary disease: a network meta-analysis. *BMC Med*. 2009;7:2-15. [PMID: 19144173]

Before therapy is initiated, it is important to assess the severity of disease by the level of FEV₁ and by asking about baseline symptoms and the nature and frequency of exacerbations. Validated instruments, like the Modified Medical Research Council scale of dyspnea (Table 1), may provide additional information. Symptoms do not necessarily correlate with the level of FEV₁, and dyspnea may respond to drug therapy at any level. However, most studies of the effectiveness of drug therapy with endpoints of health status and frequency of COPD exacerbations were performed in symptomatic patients with an FEV₁ < 60% of the predicted level. In view of this, the American College of Physicians (ACP) recommended that long-acting bronchodilator and inhaled corticosteroid treatment for stable COPD be reserved as primary therapy for patients who have respiratory symptoms and an FEV₁ < 60% of predicted (22). However, these

interventions are often indicated for symptom relief in patients with a higher FEV₁.

What is the role of inhaled bronchodilators?

There are no data to recommend initial use of one bronchodilator over another, and the choice should be based on patient preference, potential side effects, and cost. Treatment should begin with a single bronchodilator and step up to combination bronchodilator therapy if additional symptomatic relief is required (1–4). The Figure outlines the guidelines to step therapy from the American Thoracic Society/European Respiratory Society (2) and is consistent with other recommendations (1–4).

Short-acting bronchodilators with durations of action of 3 to 6 hours are preferred in patients with mild COPD, for treatment of intermittent symptoms, and for rescue treatment for breakthrough symptoms in patients taking long-acting medications. The short-acting bronchodilators include β_2 -agonists or the anticholinergic agent ipratropium (Table 2). Ipratropium has a slower onset of action but can be used for rescue as monotherapy or in combination with albuterol. Metered-dose inhalers, dry-powder inhalers, and nebulizers are equally effective but require patient education regarding proper technique to ensure adequate drug delivery. For example, the open-mouth technique is not recommended for any hydrofluoroalkane propellant-driven inhaler because of the slow speed of aerosol delivery, or with any anticholinergic metered-dose inhaler due to the potential for pupillary dilatation.

Monotherapy with long-acting bronchodilators significantly reduces the frequency of exacerbations and improves overall respiratory health status but does not significantly reduce hospitalizations or mortality (23, 24). Post hoc analyses have suggested that a

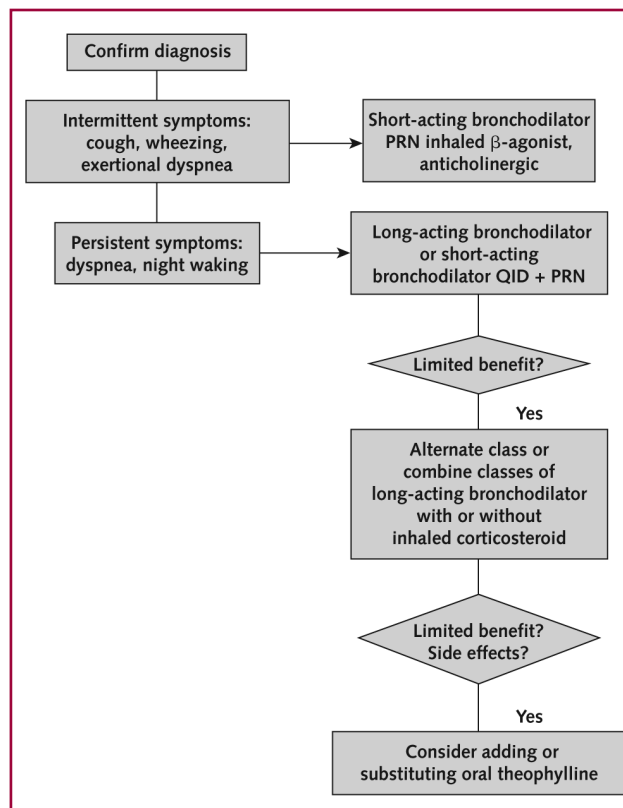


Figure. Step therapy for patients with COPD from the American Thoracic Society/European Respiratory Society guidelines.

Table 2. Drug Treatment for COPD*

Agent	Dosage	Side Effects	Notes
Bronchodilator agents			
Inhaled short-acting β_2 -agonist: albuterol levalbuterol metaproterenol pirbuterol	2 inhalations as needed, up to 12 inhalations per day	Sympathomimetic symptoms, such as tremor and tachycardia	Generally used as needed
Inhaled short-acting anticholinergic: ipratropium	2 inhalations qid, increase as tolerated	Dry mouth, mydriasis on contact with eye	Approved by the FDA as maintenance therapy. Not to be used with tiotropium.
Inhaled long-acting anticholinergic: tiotropium	18 μ g/d	Dry mouth, mydriasis on contact with eye	Approved by the FDA as maintenance therapy and to prevent COPD exacerbations. Not to be used with ipratropium
Inhaled long-acting β_2 -agonist: salmeterol formoterol aformoterol	Salmeterol, 42 μ g bid by MDI and 50 μ g bid by DPI; formoterol, 12 μ g bid by DPI and 20 μ g by nebulized solution; aformoterol, 15 μ g bid by nebulized solution	Sympathomimetic symptoms, such as tremor and tachycardia	Use as maintenance therapy. Overdose can be fatal. Not to be used to treat COPD exacerbations or acute bronchospasm.
Oral theophylline aminophylline: generic and brand name sustained and short acting	Aim for serum levels between 5 and 14 μ g/mL	Tachycardia, nausea, vomiting, disturbed pulmonary function, and sleep. Overdose can be fatal with seizures and arrhythmias	Use as maintenance therapy. May also improve respiratory muscle function.
Oral β_2 -agonists: albuterol metaproterenol terbutaline	Albuterol, 4 mg bid; metaproterenol, 5 to 10 mg tid to qid; terbutaline, 2.5 to 5 mg tid	Sympathomimetic symptoms, such as tremor and tachycardia	Use as maintenance therapy. Rarely used because of side effects but may be beneficial to patients who cannot use inhalers.
Oral phosphodiesterase 4 inhibitors	Roflumilast, 500 mcg daily	Diarrhea, weight loss, nausea, influenza, insomnia, headache, backache, decreased appetite, dizziness	Use to reduce risk for COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Roflumilast is not a bronchodilator and is not indicated for relief of acute bronchospasm.
Anti-inflammatory agents			
Inhaled corticosteroids: fluticasone budesonide mometasone ciclesonide	Maximum daily recommended doses of the following: fluticasone, 880 mcg, budesonide 720 mcg, mometasone, 880 mcg, ciclesonide, 640 mcg; all in divided doses.	Skin bruising, oral candidiasis, rarely adrenal suppression possibly glaucoma, decreased bone density, diabetes systemic hypertension, pneumonia and cataracts	Most effective in patients with a history of frequent exacerbations and when used in conjunction with long-acting bronchodilators. Not approved by the FDA for treatment of COPD.
Oral corticosteroids: prednisone prednisolone	Varying doses	Skin bruising, adrenal suppression, glaucoma, osteoporosis	Avoid use, if possible, in stable COPD. Pulmonary function improved in 10%–20% of patients. Reduce to lowest effective indose, cluding transition to inhaled corticosteroids, alternate day oral corticosteroids, or both. Intravenous or oral corticosteroids are standard therapy and are effective for acute exacerbations.
Combination agents			
Combined inhaled long-acting β_2 -agonist and inhaled corticosteroid: in a single inhaler	Each dose is given twice daily. fluticasone 250 mcg/salmeterol 50 mcg dry powder Diskus fluticasone 230 mcg/salmeterol 42 mcg budesonide 320 mcg/formoterol 10 mcg MDI Combination of comparable doses of inhaled corticosteroids and long-acting β_2 -agonists in separate inhalers	See long-acting β_2 agonist and inhaled corticosteroid	Fluticasone 250 mcg/salmeterol 50 mcg Diskus is approved by the FDA as maintenance therapy for COPD and prevention of COPD exacerbations. Budesonide 320/ formoterol 9 mcg MDI is approved by FDA as maintenance therapy for COPD. All other combinations and doses including those not listed are not approved by the DFDA for COPD. Combinations are not to be used for treatment of acute bronchospasm. Overdosage of combination can be fatal because of long-acting β_2 -agonist.

*COPD = chronic obstructive pulmonary disease; DPI = dry-powder inhaler; FDA = Food and Drug Administration; MDI = metered-dose inhaler; qid = four times daily; tid = three times daily.

long-acting β_2 -agonist (LABA) reduces the rate of decline of pulmonary function in patients with a prebronchodilator $FEV_1 \leq 60\%$ of predicted (25), as did a long-acting anticholinergic in patients with a postbronchodilator $FEV_1 \leq 70\%$ of predicted (26).

Approved LABAs include salmeterol, formoterol, and aformoterol, all of which require twice-daily dosing. The only long-acting anticholinergic agent currently available is tiotropium, which is given once daily. Salmeterol and tiotropium have a slow onset of action, whereas formoterol and aformoterol have a rapid onset of action. Long-acting bronchodilators should never be used as rescue therapy or in doses greater than those indicated on package inserts.

Oral β_2 -agonists have not been well-studied in COPD. They may be effective but are slower in onset, have more side effects (1), and are generally avoided.

If monotherapy is insufficient, clinicians should consider using inhaled combination therapy with a LABA and long-acting anticholinergic. Some studies show that such combinations may improve FEV_1 (27), but few data indicate that combination therapy is significantly better than monotherapy in alleviating dyspnea, improving exercise tolerance, and reducing COPD exacerbations. One study suggests that combination therapy with tiotropium and salmeterol improves disease-specific quality of life (29).

When should clinicians prescribe corticosteroids?

Clinicians should consider adding inhaled corticosteroids to regimens of inhaled long-acting bronchodilators in patients with moderate or severe COPD (usually when FEV_1 is $< 50\%$ of predicted) who remain symptomatic or have repeated exacerbations. When paired with a LABA, inhaled corticosteroids afford greater improvement in pulmonary function and clinical outcomes than

either agent alone (23). Post hoc analysis of one study suggested that an inhaled corticosteroid alone or combined with a LABA compared with placebo reduced the rate of decline of pulmonary function (25).

A meta-analysis of 26 786 patients in RCTs to November 2007 compared the combination of an inhaled corticosteroid and a LABA with the LABA alone. The combination significantly reduced the incidence of exacerbations in patients with an $FEV_1 \leq 40\%$ of predicted but not in patients with a higher FEV_1 (29). Other, more recent RCTs document the efficacy of combination therapy in preventing exacerbations compared with a LABA alone in patients with a prebronchodilator $FEV_1 \leq 50\%$ predicted and a COPD exacerbation in the past year (30, 31).

Combining a long-acting anticholinergic with a LABA plus an inhaled corticosteroid improves quality of life compared with monotherapy with a long-acting anticholinergic (28). A retrospective analysis of a long-acting anticholinergic when used with an inhaled corticosteroid and a LABA suggested that this combination reduced mortality, COPD exacerbations, and COPD hospitalizations compared with an inhaled corticosteroid combined with a LABA. Other combinations that included a long-acting anticholinergic and a short-acting anticholinergic together seemed to increase mortality, exacerbations, and hospitalizations (32).

An RCT compared salmeterol plus fluticasone with placebo, salmeterol alone, or fluticasone alone for a period of 3 years in 6112 patients with an $FEV_1 < 60\%$ of predicted. The study found that the combination decreased the annual rate of moderate-to-severe exacerbations compared with either salmeterol or fluticasone alone. A statistically significant effect on mortality was not seen (23).

Side effects of inhaled corticosteroids are listed in Table 2. The incidence of pneumonia is reported to be increased with the use of inhaled corticosteroids; a meta-analysis of RCTs comprising over 23 000 patients shows a relative risk of pneumonia of

30. Ferguson GT, Anzueto A, Fei R, et al. Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. *Respir Med*. 2008;102:1099-108. [PMID: 18614347]
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35. 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]
36. 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]
37. Sethi S. Infectious exacerbations of chronic bronchitis: diagnosis and management. *J Antimicrob Chemother*. 1999;43 Suppl A:97-105. [PMID: 10225579]

1.56 ($P < 0.0001$) in patients taking inhaled corticosteroids compared with those who did not (33). Although safety concerns prompted the U.S. Food and Drug Administration (FDA) to recommend against the use of LABAs without concomitant administration of inhaled corticosteroids, these recommendations did not apply to COPD.

Oral corticosteroids should be reserved for limited periods to treat acute exacerbations of COPD. In general, ongoing use of oral corticosteroids should be avoided in stable disease because of limited, if any, benefits and a high potential for side effects.

When should clinicians consider adding oral theophylline to inhaled drug therapy?

The bronchodilator effects of methylxanthines, such as aminophylline or theophylline, are relatively modest, and side effects, especially nausea and tachyarrhythmia, are common. These drugs can be used in patients with refractory symptoms even if they are receiving inhaled bronchodilators and/or inhaled corticosteroids. In such patients, theophylline can be started at a low dose and titrated to effect, aiming for a blood level between 5 and 14 micrograms/mL (2, 3). Theophylline should be discontinued if symptoms do not improve after several weeks and should not be used in treating acute exacerbations of COPD. The narrow therapeutic window, multiple interactions with other medications, and potential toxicity necessitate frequent monitoring of serum drug levels.

What immunizations should clinicians administer?

The Advisory Committee on Immunization Practices recommends influenza and pneumococcal vaccinations for persons who have chronic pulmonary or cardiovascular disorders, including COPD (34).

Influenza vaccination should be administered yearly to all patients with COPD.

In a Cochrane review of 11 RCTs, 6 of which were done in patients with COPD, use of inactivated influenza vaccine resulted in a significant reduction in the total number of exacerbations per vaccinated person compared with those who received placebo (weighted mean difference, -0.37 [95% CI, -0.64 to -0.11]; $P = 0.006$) (35).

Adults aged 19 to 64 who smoke or who have COPD should be given pneumococcal vaccination once, and again after age 65 years if the previous vaccination was given more than 5 years earlier. If the patient was not vaccinated before age 65, then a one-time vaccination is recommended (34).

How should clinicians manage acute exacerbations?

Although there is no single definition of a COPD exacerbation, the criteria shown in the Box are used commonly (Criteria and Classification of Acute COPD Exacerbation).

Acute exacerbations frequently develop after an upper respiratory infection. Management includes prompt recognition and may also involve adjustment of bronchodilator and steroid therapy, initiation of antibiotics, and assessment of the need for hospitalization. If pneumonia is suspected, a chest radiograph should be obtained for confirmation.

Clinicians should strongly consider prescribing antibiotics for patients with a moderate or severe exacerbation. Exacerbations may be due to bacterial or viral infection or inhaled irritants; the inciting factor is typically not known in usual practice, so therapy is given for the most common bacterial pathogens, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* (36, 37), taking into account local bacterial resistance patterns. Several meta-analyses and systematic reviews support the utility of antibiotics in this setting because they improve peak flow, reduce mortality, and

Criteria and Classification of Acute COPD Exacerbation

Major criteria

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

Additional criteria

- Upper respiratory infection in the past 5 days
- Fever of no apparent cause
- Increase in wheezing and cough
- Increase in respiratory rate or heart rate 20% above baseline

Mild exacerbation = 1 major criterion plus 1 or more additional criteria

Moderate exacerbation = 2 major criteria

Severe exacerbation = all 3 major criteria

(Adapted from ref. 30)

38. McCrory DC, Brown C, Gelfand SE, et al. Management of acute exacerbations of COPD: a summary and appraisal of published evidence. *Chest*. 2001;119:1190-209. [PMID: 11296189]
39. Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and meta-analysis. *Chest*. 2008;133:756-66. [PMID: 18321904]
40. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med*. 1999;340:1941-7. [PMID: 10379017]
41. Hurst JR, Vestbo J, Anzueto A, Locantore N, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363:1128-38. [PMID: 2084324730]

Indications for Hospital Assessment or Admission for Exacerbations of COPD

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea
- Severe underlying COPD
- Onset of new physical signs (for example, cyanosis or peripheral edema)
- Failure of exacerbation to respond to initial medical management
- Significant comorbid conditions
- Frequent exacerbations
- Newly occurring arrhythmias
- Diagnostic uncertainty
- Older age
- Insufficient home support

(Adapted from ref. 1)

reduce treatment failure, especially in patients with more severe exacerbations (38, 39).

The severity of the exacerbation, the degree of impaired pulmonary function, the history of exacerbations, and the response to previous treatment should be used to guide therapy. Sputum Gram stain and culture are usually not initially needed to treat acute exacerbations. Rather, the severity of the exacerbation and baseline pulmonary function is useful to guide therapy. For patients with moderate or severe exacerbations, a β -lactam/ β -lactamase inhibitor, an extended-spectrum macrolide, a second- or third-generation cephalosporin, or a fluoroquinolone can be used. Mild exacerbations can be managed with a tetracycline or trimethoprim-sulfamethoxazole. In any case, always consider antibiotics in patients with purulent sputum (1, 4).

Oral corticosteroids should be considered in patients with moderate-to-severe acute exacerbations of COPD. Although the appropriate dose is not well-defined, 30 to 60 mg/d for up to 2 weeks is commonly used. There is good evidence to suggest that a 6-week course of systemic steroids is no more beneficial than a 2-week course, and the longer course increases the risk for adverse effects (40).

A meta-analysis of 959 patients treated for COPD exacerbations found a reduction in treatment failures with the use of systemic corticosteroids (39).

Tailoring therapy to prevent future COPD exacerbations is difficult because there are several factors that determine risk. The frequency of an exacerbation in the past year has an overall sensitivity of 43% and a specificity of 87% for predicting the frequency of an exacerbation in the following year. The best predictor of future exacerbations is 2 or more exacerbations in the past year. Others include a baseline FEV_1 <50% of predicted and a history of gastroesophageal reflux or heartburn (41).

Preliminary information suggests that use of a proton-pump inhibitor may help prevent exacerbations in older patients with COPD (42).

Recent studies suggest that use of prophylactic antibiotics may prevent future exacerbations of COPD (43, 44); however, this approach is not established and awaits more definitive information. One concern is that it may promote antibacterial resistance. Some patients with chronic bronchitis may have fewer exacerbations with use of mucolytics; this effect seems to be absent in patients using inhaled corticosteroids (45, 46).

It is important to recognize patients in whom outpatient management of a COPD exacerbation is inadequate and hospitalization with possible intubation and mechanical ventilation may be necessary (see the Box: Indications for Hospital Assessment or Admission for Exacerbations of COPD). A discussion of inpatient management of COPD patients is beyond the scope of this review. For more information, the reader is referred to other sources (1, 4).

When should clinicians recommend pulmonary rehabilitation?

Pulmonary rehabilitation is a multidisciplinary program of care comprising various interventions that include exercise 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 (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 drug treatment is being optimized. Patients who are most likely to benefit are those with impaired quality of life from COPD, who experience

42. Sasaki T, Nakayama K, Yasuda H, et al. A randomized, single-blind study of lansoprazole for the prevention of exacerbations of chronic obstructive pulmonary disease in older patients. *J Am Geriatr Soc.* 2009;57:1453-7. [PMID: 19515110]
43. Sethi S, Jones PW, Theron MS, et al. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Respir Res.* 2010;11:10-22. [PMID: 20109213]
44. Seemungal TA, Wilkinson TM, Hurst JR, et al. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med.* 2008;178:1139-47. [PMID: 1872343744]
45. Poole P, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2010 Feb 17;(2):CD001287. [PMID 20166060]

breathlessness and anxiety that limit activity, and who are willing to undertake an intensive education and exercise program (1, 3). Most studies involve patients with more severe COPD, but patients with mild-to-moderate disease may also benefit.

A meta-analysis of 20 RCTs of 979 patients, including studies to the year 2000, concluded that pulmonary rehabilitation increased exercise ability and health-related quality of life and reduced dyspnea. Inspiratory muscle training by itself was not effective. Patients with severe COPD required a program lasting at least 6 months to achieve benefit, while patients with mild-to-moderate COPD could benefit from shorter programs (47).

A Cochrane collaboration analysis of 219 patients to 2008 found that pulmonary rehabilitation following a COPD exacerbation significantly reduced future hospital admissions and mortality and improved health-related quality of life compared with conventional community care without rehabilitation. The improvement in health-related quality of life was well above the minimal important difference. In all trials, pulmonary rehabilitation improved exercise capacity. No adverse events were reported (2 studies) (48).

What other adjunctive measures should clinicians consider?

Adjunctive therapies are used commonly, although little evidence supports their effectiveness. Relaxation techniques may reduce anxiety due to shortness of breath, pursed-lip breathing and diaphragmatic breathing are used to reduce shortness of breath, and nutritional interventions aim to achieve ideal body weight and improve the ability to perform daily activities and exercise (1, 3, 4). Chest physiotherapy, percussion and vibration, and postural drainage are used to enhance clearance of sputum and alleviate shortness of breath, but have limited usefulness in the absence of excessive sputum production and inadequate bronchial clearance.

When should clinicians prescribe oxygen therapy?

Patients with moderate-to-severe COPD should be periodically evaluated to determine whether they

need supplemental oxygen. The Box lists criteria for initiation of long-term oxygen therapy (Criteria for Initiation of Long-Term Oxygen Therapy). Measurement of PaO₂ after 30 minutes of breathing room air is the most accurate clinical standard for initiating therapy. Pulse oximetry can be used to qualify patients for long-term oxygen therapy and to adjust oxygen flow rates after the initial diagnosis and over time. Inexpensive pulse oximeters allow patients to self-adjust the rate of oxygen flow, provided the patient is instructed in the use of the oximeter and keeps SaO₂ above and near 90%. This approach can also be useful for patients to titrate oxygen flow at different altitudes.

When long-term oxygen therapy is indicated, it should be used for at least 15 hours and ideally 24 hours a day. Patients should have an initial follow-up within 3 months and yearly thereafter to guide subsequent oxygen therapy (49). However, the criteria of the Centers for Medicare & Medicaid Services do not generally require follow-up assessment if the qualifying PaO₂ was 55 mm Hg or less or the qualifying SaO₂ was 88% or less (50).

In patients who do not qualify for continuous therapy, oxygen therapy can be used to reduce dyspnea during exercise in persons with exertional desaturation (51, 52) and during sleep in those who desaturate at night (52). However, it is unclear whether the use of nocturnal oxygen in patients without daytime hypoxemia has benefits in mortality, health-related quality of life, or daytime function (52, 53).

In a Cochrane review, meta-analysis of 6 RCTs showed that long-term home oxygen therapy improved survival in a select group of patients with COPD and severe hypoxemia (arterial PaO₂ < 55 mm Hg [8.0 kPa]). Home oxygen therapy did not improve survival in patients with mild-to-moderate hypoxemia or in those with only arterial desaturation at night (53).

Criteria for Initiation of Long-Term Oxygen Therapy

- Room air PaO₂ no greater than 55 mm Hg or between 56 to 59 mm Hg with cor pulmonale or signs of tissue hypoxia, such as polycythemia; or an SaO₂ no greater than 88%, or 89% with cor pulmonale and/or signs of tissue hypoxia;
- Nocturnal hypoxemia with an SaO₂ no greater than 88% (use oxygen only at night); or
- Exercise hypoxemia with a PaO₂ 55 mm Hg or less or an SaO₂ 88% or less (use oxygen only with exertion).

46. Decramer M, Rutten-van Mölken M, Dekhuijzen PN, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet*. 2005;365:1552-60. [PMID:15866309]
47. Salzman GF, Mosier MC, Beasley BW, et al. Rehabilitation for patients with chronic obstructive pulmonary disease: meta-analysis of randomized controlled trials. *J Gen Intern Med*. 2003;18:213-21. [PMID: 12648254]
48. Puhan MA, Scharplatz M, Troosters T, et al. Respiratory rehabilitation after acute exacerbation of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Ar. No.:CD005305. DOI:10.1002/14651858. CD005305.pub2. [PMID: 19160250]
49. Guyatt GH, Nonoyama M, Lacchetti C, et al. A randomized trial of strategies for assessing eligibility for long-term domiciliary oxygen therapy. *Am J Respir Crit Care Med*. 2005;172:573-80. [PMID: 15901604]

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. Table 3 lists referral recommendations adapted from professional society guidelines.

Patients with COPD have a 2.7- to 4.7-fold increase in the risk for postoperative pulmonary complications depending on the severity of COPD and the type, location, and urgency of the surgical procedure. Patients undergoing thoracic and upper abdominal procedures are at greatest risk. Patient-related risk factors include age, American Society of Anesthesiologists class, and cigarette smoking (54).

A systematic review of interventions to reduce postoperative pulmonary complications after noncardiothoracic surgery found that some are effective in preventing atelectasis, pneumonia, and respiratory failure. These include early ambulation, lung expansion maneuvers, such as incentive spirometry, deep breathing exercises, and continuous positive airway pressure. Teaching patients about lung expansion maneuvers increases efficacy. Data that favor use of nasogastric tubes, epidural anesthesia and analgesia, laparoscopic operations, and enteral nutrition interventions are less clear-cut (54, 55).

When should clinicians consider surgical therapies?

Lung-volume reduction surgery

Lung-volume reduction surgery involves resection of up to 30% of diseased or nonfunctioning 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 bilateral emphysema on CT scan; 2) post-bronchodilator total lung capacity and residual volume > 150% and 100% of predicted, respectively; 3) maximum FEV₁ no greater than 45% of predicted; and 4) room air PaCO₂ no more than 60 mm Hg and a PaO₂ of at least 45 mm Hg. Patients with an FEV₁ ≤20% of predicted and either homogenous emphysema on CT scan or carbon monoxide-diffusing capacity ≤20% of predicted should not be considered for lung-volume reduction surgery as they are unlikely to benefit and have a high risk for perioperative mortality (56).

In patients with COPD who meet specific clinical criteria, lung-volume reduction surgery increases the chance for improved exercise capacity, lung function, dyspnea, and quality of life but does not improve overall survival compared with medical therapy alone. In a subgroup of

Table 3. When to Consider Referral to a Pulmonary Specialist*

Disease onset before 40 years of age
Frequent exacerbations (2 or more per year) despite adequate treatment
Rapidly progressive course of disease (decline in FEV ₁ , progressive dyspnea, decreased exercise tolerance, unintentional weight loss)
Severe COPD (FEV ₁ <50% predicted) despite optimal treatment
Need for oxygen therapy
Onset of comorbid condition (osteoporosis, heart failure, bronchiectasis, lung cancer)
Diagnostic uncertainty (for example, coexisting COPD and asthma)
Symptoms disproportionate to the severity of the airflow obstruction
Confirmed or suspected α ₁ -antitrypsin deficiency
Patient requests a second opinion
Patient is a potential candidate for lung transplantation or lung-volume reduction surgery
Patient has very severe disease and requires elective surgery that may impair respiratory function

*Adapted and modified from American Thoracic Society/European Respiratory Society and Veterans' Affairs/Department of Defense guidelines (2, 3). COPD = chronic obstructive pulmonary disease.

patients with upper lobe emphysema and low exercise capacity, lung-volume reduction surgery may improve survival, but definitive long-term data are not yet available (56).

More recently, endobronchial approaches to reduce lung volume by creating atelectasis of emphysematous portions of the lung are in development. These may include one-way valves, introduction of biologic materials, or creation of nonanatomical pathways to decompress hyperinflated portions of the lung (57). None of these approaches is approved by the FDA as of 4 December 2010.

Lung transplantation

COPD disease-specific guidelines for candidate selection for lung transplantation include patients with a BODE index of 7 to 10 and at least 1 of the following: 1) history of hospitalization for an exacerbation

associated with acute hypercapnia ($\text{PCO}_2 > 50$ mm Hg); 2) pulmonary hypertension, cor pulmonale, or both despite oxygen therapy; and 3) $\text{FEV}_1 < 20\%$ of predicted and either a carbon monoxide–diffusing capacity $< 20\%$ of predicted or homogenous distribution of emphysema (15).

Successful lung transplantation results in improved pulmonary function, exercise capacity, quality of life, and possibly survival (2). Actuarial survival following single lung transplantation for patients with COPD is approximately 83%, 60%, and 43% at 1, 3, and 5 years, respectively. Double-lung transplantation survival is similar or slightly higher (58). By 5 years after lung transplantation, the prevalence of chronic allograft rejection (obliterative bronchiolitis), the leading cause of long-term morbidity and mortality, is as high as 50% to 70% among survivors (59).

Treatment... All patients with COPD who smoke should be urged to stop and to enter a smoking cessation program. Patients who have symptoms, such as dyspnea, can be treated with inhaled β -agonists or anticholinergic agents alone or in combination. The greatest benefit from treatment with long-acting bronchodilators is achieved in patients with an $\text{FEV}_1 < 60\%$ of predicted, and benefits include improved health status and reduced COPD exacerbations. These benefits may be enhanced with the addition of an inhaled corticosteroid. Acute exacerbations should be treated by optimizing bronchodilator therapy and adding systemic corticosteroids and/or antibiotics when clinically indicated. All patients should be encouraged to exercise. Pulmonary rehabilitation should be offered to patients with moderate-to-severe COPD to improve dyspnea and health status. Continuous long-term oxygen therapy is recommended for patients with hypoxemia. Eligible patients should be evaluated for lung-volume reduction surgery or lung transplantation.

CLINICAL BOTTOM LINE

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

Guidelines from professional organizations include those from the Global Initiative for Chronic Obstructive Lung Disease, updated in 2009 (1); the American Thoracic Society/European Respiratory Society, updated in 2005 (2); the Veterans Affairs and Department of Defense, updated in

2007 (3); the National Institute of Clinical Excellence, updated in 2010 (4); and the ACP, published in 2007 (22). The first 4 present a comprehensive approach to the diagnosis and management of COPD and draw information and evidence from a variety of sources, including RCTs; cohort studies; case-control studies; recommendations from public policy organizations, such as the Advisory Committee on Immunization Practices;

Practice Improvement

50. Centers for Medicare & Medicaid Services. Evidence of medical necessity oxygen claims. Accessed at www.cms.hhs.gov/transmittals/downloads/r1742B3.pdf on 20 November 2010.
51. Bradley JM, O'Neill B. Short-term ambulatory oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2005;CD004356. [PMID: 16235359]
52. Cranston JM, Crockett AJ, Moss JR, et al. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2005;CD001744. [PMID: 16235285]
53. Lewis CA, Fergusson W, Eaton T, et al. Isolated nocturnal desaturation in COPD: prevalence and impact on quality of life and sleep. *Thorax*. 2009;64:133-8. [PMID: 18390630]
54. American College of Physicians. Preoperative pulmonary risk stratification for non-cardiothoracic surgery: systematic review for the American College of Physicians. *Ann Intern Med*. 2006;144:581-95. [PMID: 16618956]
55. Ferreira IM, Brooks D, Lacasse Y, et al. Nutritional supplementation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2005;CD000998. [PMID: 15846608]
56. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med*. 2003;348:2059-73. [PMID: 12759479]
57. Berger RL, DeCamp MM, Criner GJ, and Celli BR. Lung volume reduction therapies for advanced emphysema: an update. *Chest*. 2010;138:407-17. [PMID: 20682529]
58. United Network for Organ Sharing. The organ procurement and transplantation network. Accessed at <http://optn.transplant.hrsa.gov/ar2009/> on 20 November 2010.

59. Heng D, Sharples LD, McNeil K, et al. Bronchiolitis obliterans syndrome: incidence, natural history, prognosis, and risk factors. *J Heart Lung Transplant*. 1998;17:1255-63. [PMID: 9883768]
60. 2010 PQRI Measures List. Accessed at https://www.cms.gov/PQRI/Downloads/2010_PQRI_Measures-List_111309.pdf on 4 December 2010.

and expert opinion. The ACP guidelines are based almost solely on RCTs (22). Although most guidelines suggest treating patients with COPD when they become symptomatic, the contribution of the ACP meta-analysis and guideline is to emphasize that the evidence indicates that inhaled drug therapy is most effective in patients in whom FEV₁ is < 60% predicted.

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

The Centers for Medicare & Medicaid Services issued specifications for

measures for the 2010 Physicians Quality Reporting Initiative (60). Of these measures, 2 relate to COPD. The first measure evaluates the percentage of patients age 18 years or older with a diagnosis of COPD who had spirometry evaluation documented in the measurement year. The second measure evaluates the percentage of patients age 18 years or older with a diagnosis of COPD, an FEV₁-FVC ratio < 0.70, and such symptoms as dyspnea, cough, sputum, or wheezing who were prescribed an inhaled bronchodilator.

In the Clinic Tool Kit

Chronic Obstructive Pulmonary Disease

PIER Modules

<http://pier.acponline.org/physicians/diseases/d631/d631.html>

PIER modules on chronic obstructive pulmonary disease (COPD), smoking cessation, and preoperative pulmonary risk assessment from the American College of Physicians (ACP). PIER modules provide evidence-based, updated information on current diagnosis and treatment in an electronic format designed for rapid access at the point of care.

Patient Information

www.acponline.org/fgi/pierpi.pl?module=d153

Access the Patient Information material on the following page for duplication and distribution to patients.

www.nlm.nih.gov/medlineplus/copdchronicobstructivepulmonarydisease.html

www.nlm.nih.gov/medlineplus/tutorials/copd/btm/index.htm

www.nlm.nih.gov/medlineplus/spanish/tutorials/copds spanish/btm/index.htm

Information on COPD from National Institutes of Health's MedlinePLUS, including an interactive tutorial in English and Spanish.

www.acponline.org/patients_families/diseases_conditions/copd/

<http://copd.acponline.org/>

www.acponline.org/fgi/pierpi.pl?module=d153

Information for patients on COPD from the ACP, plus access to the ACP's COPD Portal and HEALTH TIPS patient handout.

www.nhlbi.nih.gov/health/dci/Diseases/Copd/Copd_WhatIs.html

Information on COPD, in question and answer format, from the National Heart, Lung, and Blood Institute.

Clinical Guidelines

www.annals.org/content/147/9/633.long

Diagnosis and management of stable COPD from the ACP in 2007.

www.healthquality.va.gov/Chronic_Obstructive_Pulmonary_Disease_COPD.asp

Management of COPD from the U.S. Department of Veterans Affairs in 2007.

<http://guidance.nice.org.uk/CG101/NICEGuidance/pdf/English>

Management of COPD in adults in primary and secondary care from the British National Institute for Health and Clinical Excellence in 2010.

<http://goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=996>

Global strategy for the diagnosis, management, and prevention of COPD from the Global Initiative for Chronic Obstructive Lung Disease in 2008.

Quality-of-Care Guidelines

www.annals.org/content/148/7/529.full

Advises against screening for COPD using spirometry from the U.S. Preventive Services Task Force in 2008.

THINGS YOU SHOULD KNOW ABOUT COPD

In the Clinic
Annals of Internal Medicine

What is chronic obstructive pulmonary disease (COPD)?

- It is a lung disease that makes it hard to breathe.
- Most people with COPD have both emphysema and chronic bronchitis.
- Emphysema damages the walls between the lung's air sacs and causes the air sacs to lose elasticity. This leads to shortness of breath.
- Chronic bronchitis inflames the lung's airways and causes them to become clogged with mucus. This makes breathing hard, and causes a chronic cough with mucus.

Who gets COPD?

- It is most common in cigarette smokers.
- It can also occur in persons exposed to lung irritants like air pollution, chemical fumes, second-hand smoke, or dust.
- A rare genetic condition called α_1 -antitrypsin deficiency makes some people vulnerable to lung damage from lung irritants.
- It is usually diagnosed in middle-aged or older adults.

What are the symptoms?

- Coughing up large amounts of mucus.
- Wheezing.
- Shortness of breath.
- Chest tightness.
- Symptoms develop slowly and often worsen over time.
- When severe, symptoms may make routine activities, like walking, difficult.

How is it diagnosed?

- Your doctor will listen to your chest with a stethoscope and ask about your symptoms, medical history, and possible causes of COPD.



- The doctor may order a test called "spirometry." You blow into a machine called a spirometer that measures how well your lungs are functioning.
- Other tests may include a chest x-ray or CT scan, which can reveal signs of COPD, and an arterial blood gas test, which measures the level of oxygen in your blood.

How is COPD treated?

- Smoking cessation is the most effective treatment.
- Medications can improve breathing, including bronchodilators, corticosteroids, antibiotics, and theophylline.
- Supplemental oxygen therapy increases the level of oxygen in blood.
- Your doctor may enroll you in a pulmonary rehabilitation program, which teaches patients skills for living with COPD.
- In severe cases, a surgery called "lung-volume reduction" can improve breathing by removing damaged tissue from the lungs. Rarely, patients may receive lung transplants.

For More Information

www.lungusa.org/lung-disease/copd/
Information for patients on COPD, including information on lifestyle changes, management tools, and support groups, from the American Lung Association.

www.cancer.gov/cancertopics/factsheet/tobacco/cessation
Information on quitting smoking, including how to get help, from the National Cancer Institute.

www.alpha-1foundation.org/publications/
Publications from the Alpha-1 Foundation, including education brochures titled "What Is Alpha-1 Antitrypsin Deficiency?" and "What Does It Mean To Be an Alpha-1 Carrier?"

ACP

AMERICAN COLLEGE OF PHYSICIANS
INTERNAL MEDICINE | Doctors for Adults®

1. A 72-year-old woman is evaluated for fatigue and decreased exercise capacity. The patient has severe chronic obstructive pulmonary disease (COPD), which was first diagnosed 10 years ago, and was hospitalized for her second exacerbation 1 month ago. She is a former smoker, having quit 5 years ago. She has no other significant medical problems. Her medications are albuterol as needed, an inhaled corticosteroid, a long-acting bronchodilator, and oxygen 2 L/min by nasal cannula.

On physical examination, vital signs are normal. Breath sounds are decreased, and there is 1+ bilateral pitting edema. Spirometry done 1 month ago showed an FEV₁ of 28% of predicted, and blood gases measured at that time (on supplemental oxygen) showed pH 7.41, PCO₂ 43 mm Hg, and PO₂ 64 mm Hg; DLCo is 30% of predicted. There is no nocturnal oxygen desaturation. Chest radiograph at this time shows hyperinflation. CT scan of the chest shows homogenous distribution of emphysema.

Which of the following would be the most appropriate management for this patient?

- A. Lung transplantation
 - B. Lung volume-reduction surgery
 - C. Nocturnal assisted ventilation
 - D. Pulmonary rehabilitation
2. A 65-year-old woman is evaluated in a follow-up examination for dyspnea, chronic cough, and mucoid sputum; she was diagnosed with COPD 3 years ago. The patient has a 40-pack-year history of cigarette smoking, but quit smoking 1 year ago. She is otherwise healthy, and her only medication is inhaled albuterol as needed.

On physical examination, vital signs are normal. Breath sounds are decreased, but there is no edema or jugular venous distention. Spirometry shows an FEV₁ of 62% of predicted and an FEV₁/FVC ratio of 65%. Chest radiograph shows mild hyperinflation.

Which of the following is the most appropriate therapy for this patient?

- A. Add a long-acting inhaled bronchodilator
 - B. Add an inhaled corticosteroid
 - C. Add an oral corticosteroid
 - D. Add theophylline and montelukast
 - E. Continue current albuterol therapy
3. A 60-year-old man is evaluated during routine follow-up in November. The patient has severe COPD, with dyspnea on minimal exertion and a chronic cough. He has a 40-pack-year history of cigarette smoking, but he quit smoking 3 years ago. His medications are albuterol as needed, inhaled corticosteroids, and tiotropium.

On physical examination, the patient is afebrile, blood pressure is 140/88 mm Hg, pulse rate is 90/min, and respiration rate is 20/min. Oxygen saturation with the patient at rest and breathing ambient air is 86%. Jugular venous distention and a loud P₂ are present. The chest is hyperinflated and breath sounds are diminished. There is 1+ pedal edema.

Hemoglobin concentration is 16.5 g/dL (165 g/L). Arterial blood gases show pH 7.35, PCO₂ 55 mm Hg, and PO₂ 55 mm Hg on ambient air. Spirometry shows an FEV₁ of 25% of predicted. Chest radiograph shows hyperinflation but no infiltrates.

Which of the following is the most appropriate therapy for this patient?

- A. Continuous oxygen
 - B. Nocturnal oxygen
 - C. Oxygen as needed
 - D. Oxygen during exercise
4. A 70-year-old woman is evaluated for a 6-month history of fatigue, unintentional weight loss of 4.4 kg (10 lb), increase in chronic cough with sputum production, and decreased exercise capacity. The patient has a 40-pack-year history of cigarette smoking but stopped smoking 10 years ago when COPD was diagnosed. She has no other symptoms and reports

no abdominal pain, nausea, vomiting, diarrhea, or change in bowel habits. Her medications are albuterol as needed, an inhaled corticosteroid, and salmeterol. She has been on stable dosages of these drugs for 18 months. Age- and sex-appropriate cancer screening tests done 6 months ago were normal. On physical examination, her temperature is 37.5°C (99.5°F), blood pressure is 128/76 mm Hg, pulse is 94/min and regular, respiration rate is 16/min, and BMI is 20. Heart sounds are distant, and breath sounds are diminished bilaterally. There are no abdominal masses or organomegaly and no peripheral edema. Laboratory studies yield the following results: hemoglobin, 15 g/dL (150 g/L); albumin, 3.0 g/dL (30 g/L); creatinine, 0.8 mg/dL (70.7 μmol/L); and thyroid-stimulating hormone, 2.0 μU/mL (2.0 mU/L).

Spirometry shows an FEV₁ of 40% of predicted and an FEV₁/FVC ratio of 45%. Chest radiograph shows hyperinflation.

Which of the following is the most likely reason for this patient's weight loss?

- A. Breast cancer
- B. Cervical cancer
- C. Colon cancer
- D. COPD

Questions are largely from the ACP's Medical Knowledge Self-Assessment Program (MKSAP, accessed at http://www.acponline.org/products_services/mksap/15/?pr31). Go to www.annals.org/intheclinic/ to complete the quiz and earn up to 1.5 CME credits, or to purchase the complete MKSAP program.