

# Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline from the American College of Physicians

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**Recommendation 1:** In patients with respiratory symptoms, particularly dyspnea, spirometry should be performed to diagnose airflow obstruction. Spirometry should not be used to screen for airflow obstruction in asymptomatic individuals. (Grade: strong recommendation, moderate-quality evidence.)

**Recommendation 2:** Treatment for stable chronic obstructive pulmonary disease (COPD) should be reserved for patients who have respiratory symptoms and FEV<sub>1</sub> less than 60% predicted, as documented by spirometry. (Grade: strong recommendation, moderate-quality evidence.)

**Recommendation 3:** Clinicians should prescribe 1 of the following maintenance monotherapies for symptomatic patients with COPD and FEV<sub>1</sub> less than 60% predicted: long-acting inhaled  $\beta$ -agonists, long-acting inhaled anticholinergics, or inhaled corticosteroids. (Grade: strong recommendation, high-quality evidence.)

**Recommendation 4:** Clinicians may consider combination inhaled therapies for symptomatic patients with COPD and FEV<sub>1</sub> less than 60% predicted. (Grade: weak recommendation, moderate-quality evidence.)

**Recommendation 5:** Clinicians should prescribe oxygen therapy in patients with COPD and resting hypoxemia (PaO<sub>2</sub>  $\leq$  55 mm Hg). (Grade: strong recommendation, moderate-quality evidence.)

**Recommendation 6:** Clinicians should consider prescribing pulmonary rehabilitation in symptomatic individuals with COPD who have an FEV<sub>1</sub> less than 50% predicted. (Grade: weak recommendation, moderate-quality evidence.)

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Chronic obstructive pulmonary disease (COPD) is a slowly progressive lung disease involving the airways and/or pulmonary parenchyma, resulting in a gradual loss of lung function. The symptoms of COPD range from chronic cough, sputum production, and wheezing to more severe symptoms, such as dyspnea, poor exercise tolerance, and signs or symptoms of right-sided heart failure. In the United States, COPD affects more than 5% of the adult population and is the 4th leading cause of death and the 12th leading cause of morbidity (1, 2).

The purpose of this guideline is to present the available evidence on the diagnosis and management of COPD. The target audience for this guideline is all physicians, and the target patient population is all adults with COPD. These recommendations are based on the systematic evidence review in this issue by Wilt and colleagues (3) and the Agency for Healthcare Research and Quality–sponsored Minnesota Evidence-based Practice Center evidence report (4).

## METHODS

The literature search included studies from MEDLINE and the Cochrane database from 1966 to May 2005 (4). In addition, searches for oxygen, inhaled therapies, and dis-

ease management were updated through March 2007. The exclusion criteria were children or individuals with asthma, restrictive lung disease, or  $\alpha_1$ -antitrypsin deficiency. The methods of Schulz and colleagues (5) were used to assess the quality of randomized, controlled trials. Results from the individual studies were aggregated to produce pooled estimates. Heterogeneity was assessed by using the chi-square and  $I^2$  tests (6), and the DerSimonian–Laird random-effects model was used (7). Details about the methods used for the systematic evidence review may be found in detail in the background paper by Wilt and colleagues in this issue (3).

This guideline grades the evidence and recommenda-

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**Table 1. American College of Physicians' Clinical Practice Guidelines Grading System\***

Quality of Evidence	Strength of Recommendation	
	Benefits Do or Do Not Clearly Outweigh Risks	Benefits, Risks, and Burdens Are Finely Balanced
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or harms	I recommendation	

\* Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

tions by using the American College of Physicians' clinical practice guidelines grading system adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup (Table 1).

The objective of this guideline is to analyze the evidence for the following questions:

1. What is the value of clinical examination for prediction of airflow obstruction (AO)?
2. What is the incremental value of spirometry for case finding and diagnosis of adults who are COPD treatment candidates?
3. What management strategies are effective for the treatment for COPD (inhaled therapies, pulmonary rehabilitation programs, and supplemental long-term oxygen therapy)?

### CLINICAL EXAMINATION FOR PREDICTION OF AIRFLOW OBSTRUCTION

The National Health and Nutrition Examination Survey III and a systematic review of 19 studies examining the accuracy of clinical examination to predict AO were used to estimate the prevalence of COPD and AO and clinical diagnostic accuracy (8, 9). Cigarette smoking is the most common cause of COPD. A 70-pack-year history of smoking was the best predictor of AO, with a positive likelihood ratio of 8.0 but a sensitivity of only 40%. The literature showed that findings from physical examination also had high specificity (>90%) but poor sensitivity. In addition, sputum production or wheezing was also associated with an increased likelihood of AO. Evidence to assess the utility of combining items that were included in a clinical examination to predict AO showed that combinations of findings were more helpful for diagnosing the presence of AO (10–15). The best combination to exclude COPD included never having smoked, no reported wheezing, and no wheezing on examination. A patient with any combination of 2 findings (≥70-pack-year history of smoking, history of COPD, or decreased breath sounds)

can be considered likely to have AO (defined as FEV<sub>1</sub> less than 60% predicted or FEV<sub>1</sub>–FVC ratio less than 0.60) (positive likelihood ratio, 34) (9–15).

### INCREMENTAL VALUE OF SPIROMETRY

Spirometry may be useful to identify patients who may benefit from initiating therapy (Table 2). The evidence supports inhaled treatment in patients who have symptoms and FEV<sub>1</sub> less than 60% predicted. The literature also showed that respiratory symptom status is not a reliable indicator of the presence of AO. However, as spirometric values worsened, individuals reported more respiratory symptoms, such as cough, sputum, wheezing, or dyspnea. But 33% of individuals with normal spirometric values reported respiratory symptoms. In addition, 21% of individuals who had severe to very severe AO by spirometry reported no symptoms. Nearly 80% of persons reporting any respiratory symptom had normal airflow, and only 3% to 4% had severe to very severe AO (8).

Evidence is insufficient to support widespread use of spirometry for testing adults with no respiratory symptoms, including those with current and past exposure to COPD risk factors. Spirometry may be beneficial in symptomatic adults who have an FEV<sub>1</sub> greater than 60% predicted for determining when to initiate therapy. The evidence does not support periodic spirometry after initiation of therapy to monitor ongoing disease status or to modify therapy. Furthermore, no high-quality evidence supports the use of obtaining and providing spirometry results to

**Table 2. Spirometric Classifications of Chronic Obstructive Pulmonary Disease\***

Classification	Definition
<b>GOLD</b>	
Mild	FEV <sub>1</sub> –FVC ratio <0.70 FEV <sub>1</sub> ≥80% predicted
Moderate	FEV <sub>1</sub> –FVC ratio <0.70 ≤50% FEV <sub>1</sub> <80% predicted
Severe	FEV <sub>1</sub> –FVC ratio <0.70 ≤30% FEV <sub>1</sub> <50% predicted
Very severe	FEV <sub>1</sub> –FVC ratio <0.70 FEV <sub>1</sub> ≤30% predicted or FEV <sub>1</sub> <50% predicted plus chronic respiratory failure
<b>ATS/ERS</b>	
At risk†	FEV <sub>1</sub> –FVC ratio >0.7 FEV <sub>1</sub> ≥80% predicted
Mild	FEV <sub>1</sub> –FVC ratio ≤0.7 FEV <sub>1</sub> ≥80% predicted
Moderate	FEV <sub>1</sub> –FVC ratio ≤0.7 FEV <sub>1</sub> of 50% to 80% predicted
Severe	FEV <sub>1</sub> –FVC ratio ≤0.7 FEV <sub>1</sub> ≥30% to 50% predicted
Very severe	FEV <sub>1</sub> –FVC ratio ≤0.7 FEV <sub>1</sub> <30% predicted

\* ATS/ERS = American Thoracic Society/European Respiratory Society; GOLD = Global Initiative for Chronic Obstructive Lung Disease.  
† Patients who smoke or have exposure to pollutants; have cough, sputum, or dyspnea; or have family history of respiratory disease.

improve smoking cessation, identify and treat asymptomatic individuals to prevent future respiratory symptoms, or reduce spirometric decline in lung function.

## INHALED THERAPIES

### Exacerbations

The literature showed that monotherapy with long-acting inhaled  $\beta$ -agonists, a long-acting inhaled anticholinergic, or inhaled corticosteroids was superior to placebo or short-acting anticholinergics in reducing exacerbations. Tiotropium (relative risk, 0.84 [95% CI, 0.78 to 0.90]), long-acting  $\beta$ -agonists (relative risk, 0.87 [CI, 0.82 to 0.93]), and corticosteroids (relative risk, 0.85 [CI, 0.75 to 0.96]) reduce the relative risk for at least 1 exacerbation compared with placebo. However, ipratropium, a short-acting anticholinergic, was not superior to placebo (relative risk, 0.95 [CI, 0.78 to 1.15]). In comparison studies, long-acting  $\beta$ -agonists were as effective as ipratropium (relative risk, 0.89 [CI, 0.72 to 1.10]), corticosteroids (relative risk, 1.06 [CI, 0.84 to 1.34]), or a long-acting anticholinergic (tiotropium) (relative risk, 1.11 [CI, 0.93 to 1.33]). Also, long-acting  $\beta$ -agonists were slightly superior to dual  $D_2$  dopamine receptor- $\beta_2$ -agonist (sibena-det) (relative risk, 0.80 [CI, 0.63 to 1.02]), and tiotropium was more effective than ipratropium (relative risk, 0.77 [CI, 0.62 to 0.95]). Compared with tiotropium alone, the combination of tiotropium with a long-acting  $\beta$ -agonist and inhaled corticosteroid has been shown to improve respiratory symptoms related to quality of life and lung function (16). Patients treated with tiotropium plus a long-acting  $\beta$ -agonist and inhaled corticosteroid had an increase of greater than 4 points on the St. George Respiratory Questionnaire, which is considered to be clinically significant (16).

Evidence comparing the combination of inhaled corticosteroids and long-acting  $\beta$ -agonists with either monotherapy or placebo was evaluated in 5 multigroup studies that lasted from 6 to 23 months in patients with a mean baseline FEV<sub>1</sub> less than 50% predicted (17–21). Combination therapy with long-acting  $\beta$ -agonists and inhaled corticosteroids showed an absolute risk decrease in the percentage of individuals with at least 1 exacerbation compared with placebo. The combination of long-acting  $\beta$ -agonists and corticosteroid therapy did not reduce the percentage of individuals with at least 1 exacerbation compared with inhaled corticosteroid monotherapy (17, 18, 20, 21). However, adding an inhaled corticosteroid to a long-acting  $\beta$ -agonist may reduce exacerbations compared with long-acting  $\beta$ -agonist monotherapy (3). The combination of a short-acting  $\beta$ -agonist (albuterol) and ipratropium reduced exacerbations compared with albuterol alone (22–24).

### Hospitalizations and Death

Use of tiotropium (absolute risk difference, –2% [CI, –4% to –1%]) (25–28) and ipratropium (absolute risk difference, –4% [CI, –10% to 1%]) reduced hospitaliza-

tions for patients with COPD (29). However, the Lung Health Study I and II trials showed no significant difference in hospitalizations per 100 person-years of exposure between ipratropium and placebo or between inhaled corticosteroids and placebo (30, 31). The TORCH (Towards a Revolution in COPD Health) study (32) showed that use of a combination of a long-acting  $\beta$ -agonist and an inhaled corticosteroid reduces deaths compared with use of an inhaled corticosteroid alone (relative risk, 0.79 [CI, 0.67 to 0.94]). Results from a meta-analysis by Salpeter and colleagues (33) showed an increase in respiratory deaths with long-acting  $\beta$ -agonists and a decrease with anticholinergics. However, a recently released TORCH study found no difference in deaths due to pulmonary causes between placebo and salmeterol (34). In addition, serious adverse effects occurred in 10% of the persons receiving inhaled corticosteroids as monotherapy or combination therapy compared with 6% of persons receiving placebo or long-acting  $\beta$ -agonists (34).

### Adverse Effects

Evidence for withdrawals from treatment and nonadherence showed that individuals using long-acting  $\beta$ -agonists, tiotropium, or inhaled corticosteroids were less likely to withdraw from treatment for any reason compared with those receiving placebo (17, 18, 21, 26, 27, 29, 35, 36). In trials of combination therapy with corticosteroids and long-acting  $\beta$ -agonists, withdrawals were lower for combination therapy than for placebo but were similar to either type of monotherapy (17, 18, 21, 26, 27, 29, 35, 36). Adverse events during follow-up also were minor and were similar to those with placebo. The main adverse reactions included oropharyngeal candidiasis and a moderate to severe degree of easy bruising with inhaled corticosteroids (18, 37, 38), dry mouth with tiotropium (39), and minor cardiovascular events with  $\beta$ -agonists (40). Results from 2 randomized, controlled trials (37, 38) showed that the incidence of fracture during 3 years was similar with inhaled corticosteroids and with placebo (1.4% vs. 2.0%, respectively). However, after 3 years, lumbar spine and femur bone density was lower in the triamcinolone group of the Lung Health Study II (31).

## RELATIONSHIP BETWEEN SPIROMETRY AND EFFECTIVENESS OF INHALED THERAPY

The evidence is not sufficient to evaluate the effectiveness of long-acting  $\beta$ -agonists in symptomatic individuals with FEV<sub>1</sub> greater than 50% predicted or in asymptomatic individuals regardless of spirometric values. Evidence on other inhaled therapies used for at least 1 year found little or no improvement in respiratory outcomes or deaths among individuals with mild or moderate AO or in those with normal airflow but chronic sputum production (18, 30, 31, 41, 42). Modifying existing therapy for COPD or monitoring disease status according to spirometric values was not evaluated in trials.

## PULMONARY REHABILITATION PROGRAMS

The main components of most pulmonary rehabilitation programs included endurance or exercise training, education, behavioral modification, and outcome assessment. Three studies found clinically significant improvement in dyspnea and fatigue (43–45). Pulmonary rehabilitation did not result in reduction in deaths, but the studies had small sample sizes and short durations (46). A review of 6 small RCTs in patients with baseline FEV<sub>1</sub> less than 40% predicted showed a reduction in hospitalizations and clinically significant improvement in health status and exercise capacity (47).

## DISEASE MANAGEMENT AND PATIENT EDUCATION

The evidence did not show any effect of disease management programs or patient education on deaths, COPD exacerbations, reduction in all-cause readmissions, hospital length of stay, visits to primary care physicians, clinically meaningful improvement in the St. George Respiratory Questionnaire health status score, patient satisfaction, self-management skills, or adherence to treatment (46, 48).

## SUPPLEMENTAL LONG-TERM OXYGEN THERAPY AND DEATH

Two trials showed that supplemental oxygen used 15 or more hours daily to maintain a PaO<sub>2</sub> greater than 60 mm Hg reduced deaths in individuals who have very severe AO (FEV<sub>1</sub> <30% predicted) and resting hypoxemia (mean resting PaO<sub>2</sub> ≤55 mm Hg) (49, 50). Two other studies showed no effect on relative risk for death with use of supplemental oxygen (9 to 13 hours daily) during the day or at night in patients with similar severity of AO but with daytime PaO<sub>2</sub> greater than 60 mm Hg (51, 52). In addition, studies showed no effect of ambulatory oxygen on respiratory health status measures (53, 54).

## SUMMARY

History and clinical examination are poor predictors of AO and its severity. Evidence does not support using spirometry as a diagnostic strategy for individuals not reporting respiratory symptoms. However, adding spirometry to clinical examination for individuals with respiratory symptoms, especially dyspnea, has demonstrated benefits. Treatment benefits for COPD are primarily related to reduced exacerbations among patients who are more likely to have exacerbations, dyspnea that limits activity, or severe to very severe AO. Inhaled corticosteroids and long-acting bronchodilators are more effective in reducing exacerbations than are short-acting inhalers. The reduction in deaths is associated with the use of long-term supplemental oxygen therapy for patients with very severe AO and resting hypoxemia.

## RECOMMENDATIONS

*Recommendation 1: In patients with respiratory symptoms, particularly dyspnea, spirometry should be performed to diagnose airflow obstruction. Spirometry should not be used to screen for airflow obstruction in asymptomatic individuals. (Grade: strong recommendation, moderate-quality evidence.)*

Targeted use of spirometry for diagnosis of AO is beneficial for individuals with respiratory symptoms, particularly dyspnea. Evidence does not support the use of spirometry to screen for AO in asymptomatic individuals, including those who have risk factors for COPD. No high-quality evidence supports obtaining and providing spirometry results to improve smoking cessation, or to identify and treat asymptomatic individuals to prevent future respiratory symptoms or reduce spirometric decline in lung function.

*Recommendation 2: Treatment for stable COPD should be reserved for patients who have respiratory symptoms and FEV<sub>1</sub> less than 60% predicted as documented by spirometry. (Grade: strong recommendation, moderate-quality evidence.)*

Evidence shows that individuals who will benefit the most from therapy are those who have respiratory symptoms and clinically significant AO (FEV<sub>1</sub> <60% predicted). No evidence supports treating asymptomatic patients, because treatment does not improve outcomes. The evidence does not support periodic spirometry after initiation of therapy to monitor ongoing disease status or to modify therapy. This recommendation does not address the occasional use of bronchodilators for acute symptomatic relief.

*Recommendation 3: Clinicians should prescribe 1 of the following maintenance monotherapies for symptomatic patients with COPD and FEV<sub>1</sub> less than 60% predicted: long-acting inhaled β-agonists, long-acting inhaled anticholinergics, or inhaled corticosteroids. (Grade: strong recommendation, high-quality evidence.)*

Monotherapy with a long-acting inhaled β-agonist, a long-acting inhaled anticholinergic, or an inhaled corticosteroid is beneficial in reducing exacerbations. Inhaled corticosteroids and long-acting inhaled bronchodilators have similar effectiveness but differ in adverse effects, reductions in deaths, and hospitalizations. The review did not systematically evaluate all other outcomes. Evidence is insufficient to recommend 1 monotherapy over another.

*Recommendation 4: Clinicians may consider combination inhaled therapies for symptomatic patients with COPD and FEV<sub>1</sub> less than 60% predicted. (Grade: weak recommendation, moderate-quality evidence.)*

When to use combination therapy instead of monotherapy has not been clearly established. In the TORCH trial (32), combination therapy with long-acting β-agonists and corticosteroids reduced exacerbations more than did monotherapy. Although deaths with combination therapy decreased in the trial compared with monotherapy, the reduction did not reach the predetermined level of statisti-

cal significance. In a recent randomized trial (16), addition of salmeterol–fluticasone to tiotropium therapy did not statistically influence rates of COPD exacerbation but did improve lung function, quality of life, and hospitalization rates in patients with moderate to severe COPD. However, studies of combination therapies do not consistently demonstrate benefits of combination therapy over monotherapy.

**Recommendation 5:** Clinicians should prescribe oxygen therapy in patients with COPD and resting hypoxemia ( $PaO_2 \leq 55$  mm Hg). (Grade: strong recommendation, moderate-quality evidence.)

Use of supplemental oxygen for 15 or more hours daily can help improve survival in patients with severe AO ( $FEV_1 < 30\%$  predicted) and resting hypoxemia.

**Recommendation 6:** Clinicians should consider prescribing pulmonary rehabilitation in symptomatic individuals with COPD who have an  $FEV_1$  less than 50% predicted. (Grade: weak recommendation, moderate-quality evidence.)

Evidence supports the use of pulmonary rehabilitation programs for patients with severe AO, because they reduce hospitalizations and improve health status and exercise capacity. However, the evidence is not clear for individuals with  $FEV_1$  greater than 50% predicted.

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**Note:** Clinical practice guidelines are guides only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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