Annals of Internal Medicine | Clinical Guidelines

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

Amir Qaseem, MD, PhD, MHA; Vincenza Snow, MD; Paul Shekelle, MD, PhD; Katherine Sherif, MD; Timothy J. Wilt, MD, MPH; Steven Weinberger, MD; and Douglas K. Owens, MD, MS, for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians*

**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 $FEV_1$ 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 $FEV_1$ 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 $FEV_1$ less than 60% predicted. (Grade: weak recommendation, moderate-quality evidence.)

**Recommendation 5:** Clinicians should prescribe oxygen therapy in patients with COPD and resting hypoxemia ($Pao_2$ ≤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 $FEV_1$ less than 50% predicted. (Grade: weak recommendation, moderate-quality evidence.)

*Ann Intern Med.* 2007;147:633-638. www.annals.org
For author affiliations, see end of text.

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 disease 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-

*See also:*

**Print**
Related article . . . . . 639
Summary for Patients . . . . . I-41

**Web-Only**
CME quiz
Conversion of graphics into slides
Audio summary

*This paper, written by Amir Qaseem, MD, PhD, MHA; Vincenza Snow, MD; Paul Shekelle, MD, PhD; Katherine Sherif, MD; Timothy J. Wilt, MD, MPH; Steven Weinberger, MD; and Douglas K. Owens, MD, MS, was developed for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians (ACP): Douglas K. Owens, MD, MS (*Chair*); Donald E. Casey Jr., MD, MPH, MBA; J. Thomas Cross Jr., MD, MPH; Paul Dallas, MD; Nancy C. Dolan, MD; Mary Ann Forciea, MD; Lakshmi Halasyamani, MD; Robert H. Hopkins Jr., MD; and Paul Shekelle, MD, PhD. Approved by the ACP Board of Regents on 14 July 2007.

 

*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 $FEV_1$ less than 60% predicted or $FEV_1$–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 $FEV_1$ 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 $FEV_1$ 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 |
|---|---|
| **GOLD** | |
| Mild | $FEV_1$–FVC ratio <0.70<br>$FEV_1$ ≥80% predicted |
| Moderate | $FEV_1$–FVC ratio <0.70<br>≤50% $FEV_1$ <80% predicted |
| Severe | $FEV_1$–FVC ratio <0.70<br>≤30% $FEV_1$ <50% predicted |
| Very severe | $FEV_1$–FVC ratio <0.70<br>$FEV_1$ ≤30% predicted or $FEV_1$ <50% predicted plus chronic respiratory failure |
| **ATS/ERS** | |
| At risk† | $FEV_1$–FVC ratio >0.7<br>$FEV_1$ ≥80% predicted |
| Mild | $FEV_1$–FVC ratio ≤0.7<br>$FEV_1$ ≥80% predicted |
| Moderate | $FEV_1$–FVC ratio ≤0.7<br>$FEV_1$ of 50% to 80% predicted |
| Severe | $FEV_1$–FVC ratio ≤0.7<br>$FEV_1$ ≥30% to 50% predicted |
| Very severe | $FEV_1$–FVC ratio ≤0.7<br>$FEV_1$ <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 β-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 β-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 β-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 β-agonists were slightly superior to dual $D_2$ dopamine receptor–$\beta_2$-agonist (sibenadet) (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 β-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 β-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 β-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 $FEV_1$ less than 50% predicted (17–21). Combination therapy with long-acting β-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 β-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 β-agonist may reduce exacerbations compared with long-acting β-agonist monotherapy (3). The combination of a short-acting β-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 hospitalizations 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 β-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 β-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 β-agonists (34).

### Adverse Effects

Evidence for withdrawals from treatment and nonadherence showed that individuals using long-acting β-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 β-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 β-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 β-agonists in symptomatic individuals with $FEV_1$ 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 $FEV_1$ 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 $Pa_{O_2}$ greater than 60 mm Hg reduced deaths in individuals who have very severe AO ($FEV_1$ <30% predicted) and resting hypoxemia (mean resting $Pa_{O_2}$ ≤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 $Pa_{O_2}$ 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 $FEV_1$ 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 ($FEV_1$ <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 $FEV_1$ 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 $FEV_1$ 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 ($PaO_2$ ≤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.

From the American College of Physicians and Drexel University College of Medicine, Philadelphia, Pennsylvania; Veterans Affairs Greater Los Angeles Healthcare System and RAND, Santa Monica, California; Veterans Affairs Palo Alto Health Care System and Stanford University, Stanford, California; and Minnesota Veterans Affairs Medical Center, Minneapolis, Minnesota.



**Grant Support:** Financial support for the development of this guideline comes exclusively from the ACP operating budget.

**Potential Financial Conflicts of Interest:** *Stock ownership or options (other than mutual funds):* S. Weinberger (GlaxoSmithKline). *Grants received:* V. Snow (Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, Novo Nordisk, Pfizer Inc., Merck & Co. Inc., Bristol-Myers Squibb, Atlantic Philanthropies, Sanofi Pasteur).

**Requests for Single Reprints:** Amir Qaseem, MD, PhD, MHA, American College of Physicians, 190. N. Independence Mall West, Philadelphia, PA 19106; e-mail, aqaseem@acponline.org.

Current author addresses are available at www.annals.org.

## References

1. **Murray CJ, Lopez AD.** Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet. 1997;349:1498-504. [PMID: 9167458]

2. **National Heart, Lung, and Blood Institute.** Data Fact Sheet: Chronic Obstructive Pulmonary Disease. Bethesda, MD: National Institutes of Health; 2003. Accessed at www.nhlbi.nih.gov/health/public/lung/other/copd_fact.pdf on 15 March 2007. NIH publication no. 03-5229.

3. **Wilt TJ, Niewoehner D, MacDonald R, Kane RL.** Management of stable chronic obstructive pulmonary disease: a systematic review for a clinical practice guideline. Ann Intern Med. 2007;147:639-53.

4. **Wilt TJ, Niewoehner D, Kim CB, Kane RL, Linabery A, Tacklind J, et al.** Use of spirometry for case finding, diagnosis, and management of chronic obstructive pulmonary disease (COPD). (Prepared by the Minnesota Evidence-based Practice Center under contract 290-02-0009.) Rockville, MD: Agency for Healthcare Research and Quality; September 2005. AHRQ publication no. 05-E017-2.

5. **Schulz KF, Chalmers I, Hayes RJ, Altman DG.** Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995;273:408-12. [PMID: 7823387]

6. **Higgins JP, Thompson SG, Deeks JJ, Altman DG.** Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60. [PMID: 12958120]

7. **DerSimonian R, Laird N.** Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88. [PMID: 3802833]

8. **Mannino DM, Gagnon RC, Petty TL, Lydick E.** Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med. 2000; 160:1683-9. [PMID: 10847262]

9. **Holleman DR Jr, Simel DL.** Does the clinical examination predict airflow limitation? JAMA. 1995;273:313-9. [PMID: 7815660]

10. **Holleman DR Jr, Simel DL, Goldberg JS.** Diagnosis of obstructive airways disease from the clinical examination. J Gen Intern Med. 1993;8:63-8. [PMID: 8441077]

11. **Badgett RG, Tanaka DJ, Hunt DK, Jelley MJ, Feinberg LE, Steiner JF, et al.** Can moderate chronic obstructive pulmonary disease be diagnosed by historical and physical findings alone? Am J Med. 1993;94:188-96. [PMID: 8430714]

12. **Bohadana AB, Mohankumar T.** Symptoms and signs in the assessment of chronic airflow obstruction. Indian J Chest Dis Allied Sci. 1982;24:133-42. [PMID: 7166350]

13. **Hepper NG, Hyatt RE, Fowler WS.** Detection of chronic obstructive lung disease. An evaluation of the medical history and physical examination. Arch Environ Health. 1969;19:806-13. [PMID: 5351681]

14. **Mannino DM, Etzel RA, Flanders WD.** Do the medical history and physical examination predict low lung function? Arch Intern Med. 1993;153:1892-7. [PMID: 8250649]

15. **Pardee NE, Winterbauer RH, Morgan EH, Allen JD, Olson DE.** Combinations of four physical signs as indicators of ventilatory abnormality in obstructive pulmonary syndromes. Chest. 1980;77:354-8. [PMID: 7357938]

16. **Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al.** 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]

17. **Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H.** Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J. 2003;22:912-9. [PMID: 14680078]

18. **Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, et al.** Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2003;361:449-56. [PMID: 12583942]

19. **Hanania NA, Darken P, Horstman D, Reisner C, Lee B, Davis S, et al.** The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. Chest. 2003;124: 834-43. [PMID: 12970006]

20. **Mahler DA, Wire P, Horstman D, Chang CN, Yates J, Fischer T, et al.** Effectiveness of fluticasone propionate and salmeterol combination delivered via

the Diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2002;166:1084-91. [PMID: 12379552]
21. **Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, et al.** Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J. 2003;21:74-81. [PMID: 12570112]
22. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. COMBIVENT Inhalation Aerosol Study Group. Chest. 1994;105:1411-9. [PMID: 8181328]
23. Routine nebulized ipratropium and albuterol together are better than either alone in COPD. The COMBIVENT Inhalation Solution Study Group. Chest. 1997;112:1514-21. [PMID: 9404747]
24. **Tashkin DP, Ashutosh K, Bleecker ER, Britt EJ, Cugell DW, Cummiskey JM, et al.** Comparison of the anticholinergic bronchodilator ipratropium bromide with metaproterenol in chronic obstructive pulmonary disease. A 90-day multi-center study. Am J Med. 1986;81:81-90. [PMID: 2947465]
25. **Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S.** Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax. 2003;58: 399-404. [PMID: 12728159]
26. **Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, et al.** A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J. 2002;19:217-24. [PMID: 11866001]
27. **Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, Korducki L, et al.** Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med. 2005;143:317-26. [PMID: 16144890]
28. **Dusser D, Bravo ML, Iacono P.** The effect of tiotropium on exacerbations and airflow in patients with COPD. Eur Respir J. 2006;27:547-55. [PMID: 16507855]
29. **Vincken W, van Noord JA, Greefhorst AP, Bantje TA, Kesten S, Korducki L, et al.** Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. Eur Respir J. 2002;19:209-16. [PMID: 11871363]
30. **Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, 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]
31. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med. 2000;343:1902-9. [PMID: 11136260]
32. **Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al.** Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356:775-89. [PMID: 17314337]
33. **Salpeter SR, Buckley NS, Salpeter EE.** Meta-analysis: anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. J Gen Intern Med. 2006;21:1011-9. [PMID: 16970553]
34. **Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al.** Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356:775-89. [PMID: 1714337]
35. **Rossi A, Kristufek P, Levine BE, Thomson MH, Till D, Kottakis J, et al.** Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. Chest. 2002;121: 1058-69. [PMID: 11948033]
36. **Stockley RA, Chopra N, Rice L.** Addition of salmeterol to existing treatment in patients with COPD: a 12 month study. Thorax. 2006;61:122-8. [PMID: 16443706]
37. **Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK.** Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ. 2000;320:1297-303. [PMID: 10807619]
38. **Pauwels RA, Löfdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, et al.** Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med. 1999;340:1948-53. [PMID: 10379018]
39. **Barr RG, Bourbeau J, Camargo CA, Ram FS.** Inhaled tiotropium for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005: CD002876. [PMID: 15846642]
40. **Salpeter SR, Ormiston TM, Salpeter EE.** Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. Chest. 2004;125: 2309-21. [PMID: 15189956]
41. **Wouters EF, Postma DS, Fokkens B, Hop WC, Prins J, Kuipers AF, et al.** Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax. 2005;60:480-7. [PMID: 15923248]
42. **Vestbo J, Sørensen T, Lange P, Brix A, Torre P, Viskum K.** Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 1999;353:1819-23. [PMID: 10359405]
43. **Finnerty JP, Keeping I, Bullough I, Jones J.** The effectiveness of outpatient pulmonary rehabilitation in chronic lung disease: a randomized controlled trial. Chest. 2001;119:1705-10. [PMID: 11399694]
44. **Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al.** Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet. 2000;355:362-8. [PMID: 10665556]
45. **Wedzicha JA, Bestall JC, Garrod R, Garnham R, Paul EA, Jones PW.** Randomized controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients, stratified with the MRC dyspnoea scale. Eur Respir J. 1998;12:363-9. [PMID: 9727786]
46. **Sin DD, McAlister FA, Man SF, Anthonisen NR.** Contemporary management of chronic obstructive pulmonary disease: scientific review. JAMA. 2003; 290:2301-12. [PMID: 14600189]
47. **Puhan MA, Scharplatz M, Troosters T, Steurer J.** Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality —a systematic review. Respir Res. 2005;6:54. [PMID: 15943867]
48. **Taylor SJ, Candy B, Bryar RM, Ramsay J, Vrijhoef HJ, Esmond G, et al.** Effectiveness of innovations in nurse led chronic disease management for patients with chronic obstructive pulmonary disease: systematic review of evidence. BMJ. 2005;331:485. [PMID: 16093253]
49. 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]
50. 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]
51. **Górecka D, Gorzelak K, Sliwiński P, Tobiasz M, Zieliński J.** Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. Thorax. 1997;52:674-9. [PMID: 9337824]
52. **Chaouat A, Weitzenblum E, Kessler R, Charpentier C, Enrhart M, Schott R, et al.** A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. Eur Respir J. 1999;14:1002-8. [PMID: 10596681]
53. **Eaton T, Garrett JE, Young P, Fergusson W, Kolbe J, Rudkin S, et al.** Ambulatory oxygen improves quality of life of COPD patients: a randomised controlled study. Eur Respir J. 2002;20:306-12. [PMID: 12212960]
54. **McDonald CF, Blyth CM, Lazarus MD, Marschner I, Barter CE.** Exertional oxygen of limited benefit in patients with chronic obstructive pulmonary disease and mild hypoxemia. Am J Respir Crit Care Med. 1995;152:1616-9. [PMID: 7582304]

**Current Author Addresses:** Drs. Qaseem, Snow, and Weinberger: 190 N. Independence Mall West, Philadelphia, PA 19106.
Dr. Shekelle: 1776 Main Street, Santa Monica, CA 90401.
Dr. Sherif: 219 North Broad Street, 6th Floor, Philadelphia, PA 19107.
Dr. Wilt: 1 Veterans Drive (111-0), Minneapolis, MN 55417.
Dr. Owens: 117 Encina Commons, Stanford, CA 94305.