Diagnosis and treatment of patients with chronic obstructive pulmonary disease in the primary care setting: focus on the role of spirometry and bronchodilator reversibility

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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease. The pulmonary function component of COPD is characterized by progressive airflow limitation that is not fully reversible, defined by postbronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <0.70 and postbronchodilator FEV_1 <80% predicted.[1] The disease is associated with an abnormal inflammatory response to tobacco smoke and other noxious particles, leading to narrowing of the small airways and destruction of the lung parenchyma.[1] Significant extrapulmonary effects may contribute to disease severity in some patients.[1]

COPD currently is the third leading cause of death in the United States[2] and is associated with substantial morbidity and economic costs.[3] In 2008, an estimated 12.1 million adults at least 18 years old in the United States reported having a physician diagnosis of COPD, including chronic bronchitis and/or emphysema, with greater prevalence reported in women than in men.[3] Based on data from the National Health and Nutrition Examination Survey (NHANES) III (1988–1994), however, an estimated 24.1 million people had impaired pulmonary function indicative of obstructive lung disease (FEV_1/FVC <0.70).[4] The discrepancy between these prevalence estimates suggests that a substantial number of patients with COPD are undiagnosed.[3,4]

Primary care physicians play a critical role in ensuring that an accurate diagnosis of COPD occurs early in the disease process and that adverse health outcomes are minimized through appropriate treatment. The present review discusses important factors for identifying and diagnosing patients with COPD in the primary care setting, with a focus on the role of spirometry and the clinical relevance of acute bronchodilator reversibility testing in patients with COPD.

Identify patients for whom a diagnosis should be considered

Primary care physicians are often the first point of medical contact for patients presenting with symptoms of diseases and other health care concerns, including COPD; each visit, however,

FIGURE 1 Example algorithm for differential diagnosis of COPD
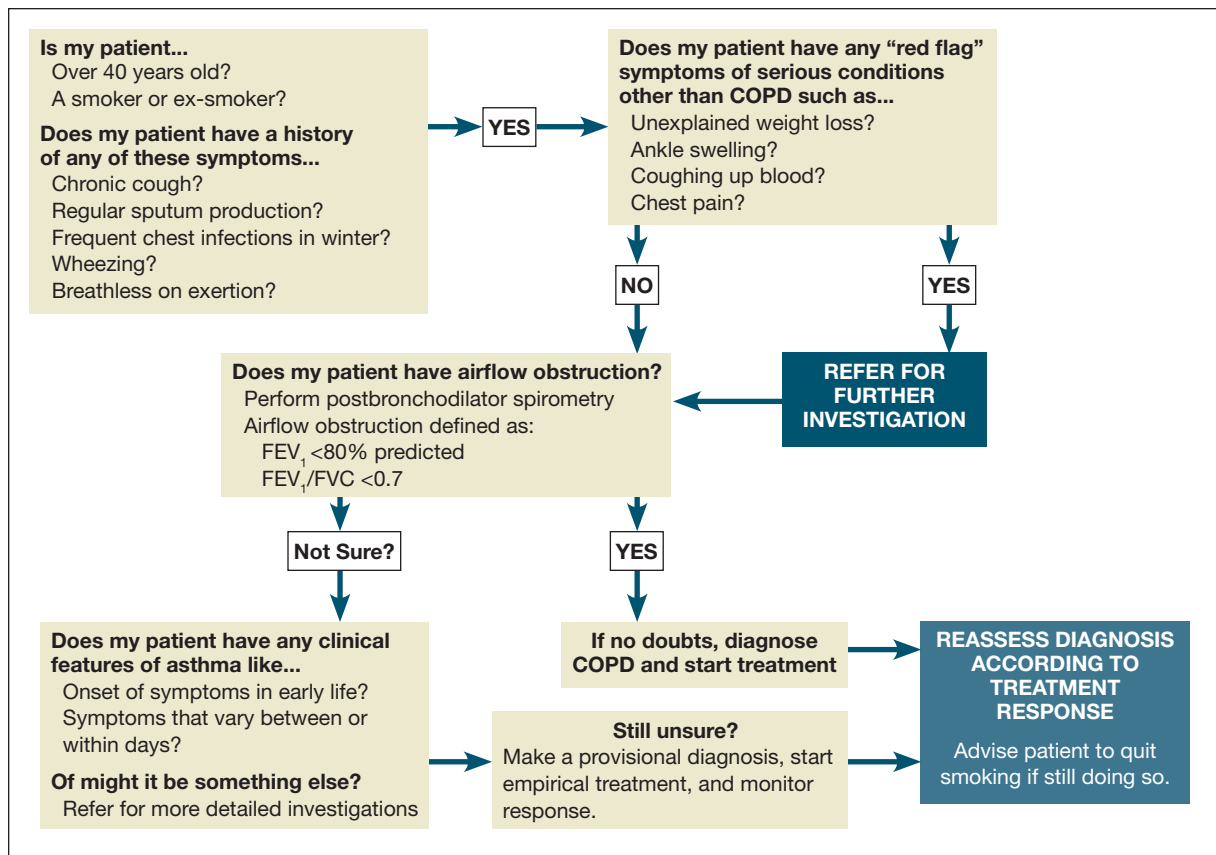
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

From Price DB, Yawn BP, Jones RCM. Improving the differential diagnosis of chronic obstructive pulmonary disease in primary care. *Mayo Clin Proc*. 2010;85:1122-1129.[6] Copyright © 2010. Reprinted with permission from Dowden Health Media.

typically consists of a short consultation, which may limit in-depth diagnostic assessment.[5] Key symptoms of COPD include chronic and persistent dyspnea that worsens over time and with exercise, chronic cough that may be intermittent or unproductive, and chronic sputum production.[1] Because patients often do not recognize symptoms of COPD or report them to their physicians, the first indication of COPD may occur when a patient presents with an exacerbation at a more advanced stage of the disease.[6,7]

Recognition of indicative symptoms and history and exposure to risk factors, such as tobacco,[1] early in the course of COPD may facilitate more targeted disease screening in primary care.[7] Brief validated questionnaires that evaluate patient symptoms and history could serve as a first-level screen to aid physicians in quickly identifying patients who may be at risk for COPD and could benefit from further assessment using spirometry.[8,9] Algorithms incorporating symptoms, clinical features, and lung function also have been developed to aid in the diagnosis of COPD (**FIGURE 1**).[6]

Screening may help identify patients at early stages of COPD. Although trials comparing the clinical effects of early treatment vs treatment after patients manifest symptoms have not been conducted,[10] recent evidence from large clinical trials suggests clinical benefits from COPD treatment initiated as early as Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II.[1,11,12] In a subanalysis of 2739 stage II COPD patients from the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study, patients receiving tiotropium 18 µg once daily had a lower rate of postbronchodilator FEV_1 decline (*P*=.024), longer median time to first exacerbation (*P*<.0001), and better health status at all time points (*P*<.0001) compared with those receiving placebo.[11] Similarly, a post hoc analysis assessed treatment effects by disease severity in patients from the TOwards a Revolution in COPD Health (TORCH) study. In 2156 stage II COPD patients, twice-daily fluticasone propionate/salmeterol 500/50-µg treatment was associated with improved pulmonary function, reduced exacerbations, greater improvements in health status, and reduced mortality compared with placebo.[12] Moreover, comorbidities such as cardiovascular disease, osteoporosis, and diabetes may present in early stages of COPD, share a common inflammatory etiology, and contribute

to decreased functional abilities.[10,13] In particular, the risk of a cardiac event is present early in the course of the disease and increases as COPD severity worsens.[13] Although not clearly established, physical inactivity may be involved in the pathogenesis of these comorbidities[10]; thus, the effect of COPD treatments on physical inactivity could aid in slowing the progression of comorbidities. These findings suggest that patients may benefit from early recognition and treatment of COPD.

Identifying individual aspects of medical history that accurately predict risk for COPD may be a simple and effective approach for screening. Ohar et al evaluated respiratory symptoms and spirometric data from a large cohort of subjects (N=3955) who underwent work-related medical evaluations between 1980 and 2008 to identify factors with positive predictive values for development of airway obstruction.[14] In that study, a smoking history of ≥20 pack-years was the strongest predictor of airway obstruction (adjusted odds ratio, 3.59; 95% confidence interval [CI], 2.80–4.61), with the addition of symptoms of cough, dyspnea, sputum, or wheeze adding little to the predictive value of smoking history.[14] Data from a survey in a random sample of adults in Sweden (n=4851) identified age of at least 45 years, smoking, and family history of obstructive airway disease as risk factors for COPD, with smoking (ever) being the strongest predictor.[15] These data suggest that smoking history, age, and family history may be useful in identifying a population of patients in clinical practice who may be at risk for fixed airflow obstruction.

Perform spirometry for an accurate diagnosis of COPD

The GOLD guidelines recognize spirometry as essential for a definitive and confident diagnosis of COPD.[1] Spirometry remains the gold standard for monitoring disease progression[1,16]; evidence suggests, however, that it is underused or used inconsistently in clinical practice.[7,17-19]

In a study assessing use of spirometry in patients hospitalized and discharged with a diagnosis of COPD, only 31% had spirometry testing completed within the previous 8 years.[17] In a survey of 523 primary care physicians caring for patients with COPD in the United States between 2003 and 2004, 51% used spirometry to test for bronchodilator responsiveness before diagnosis, 77% used spirometry always or most of the time for a diagnosis of COPD, and 43% used spirometry to monitor patients with COPD.[18] Data from that survey also showed that only 54% of primary care physicians were aware of professional guidelines for COPD diagnosis and management, and only 5% of those physicians specifically recognized GOLD guidelines.[18] In a 2006 survey of 278 family clinicians in the United States, including physicians (n=178) and nonphysicians (nurse practitioners and physician assistants, n=100), 76% of respondents indicated that they used spirometry for diagnosing COPD, while only 31% stated that they used spirometry for all COPD diagnoses.[19] In that study, staff in offices that had spirometers, which comprised 52% of respondents, were significantly more likely to use spirometry for diagnosis (odds ratio, 3.7) and to consult GOLD or American Thoracic Society (ATS) guidelines (odds ratio, 2.4).[19] Data also show that primary care physicians can perform spirometry accurately and effectively after 2 days of spirometry training, with treatment changes consistent with GOLD guidelines.[20]

The advent of newer, handheld spirometers that are accurate, reproducible, and inexpensive should facilitate use of spirometry in primary care.[21-24] Handheld digital spirometers, developed as inexpensive alternatives to conventional spirometry apparatus,[25] can be convenient and practical for use in primary care, as they provide accurate, reproducible, and robust measurements; portability; and ease of storage.[21] Portable spirometers have been shown to generate reproducible FEV_1 measurements[22] that correlate with data obtained from conventional spirometry apparatus[25] and to retain calibration stability.[26] Handheld spirometers have been used in conjunction with questionnaires to measure the prevalence of COPD and associated risk factors in large studies in major Latin American cities[27,28] and worldwide.[21,29] Details about handheld spirometers that meet National Lung Health Education Program criteria[30] are shown in TABLE 1. Other handheld spirometers include the Micro-Plus (CareFusion, San Diego, California), Mini-Wright Digital (Clement Clarke International Ltd, Harlow, United Kingdom), PF 100 (Microlife AG Swiss Corporation, Widnau, Switzerland), PiKo-1 (nSpire Health, Inc, Longmont, Colorado), and Vitalograph Micro (Vitalograph Ltd, Buckingham, United Kingdom, and Lenexa, Kansas). In addition, spirometry is reimbursable,[23] and current procedural terminology (CPT) codes are available for spirometry recordings and tests of responsiveness to bronchodilators, regardless of spirometer type (TABLE 2).[24] International Classification of Diseases (ICD-9-CM, ninth revision, Clinical Modification) codes that are related to diagnosis or treatment of COPD that support use of spirometry also are available (eg, 490, bronchitis; 496, COPD; 491.21, COPD with acute exacerbation; 786.0, dyspnea; 786.05, shortness of breath; 786.2, chronic cough; 486.07, wheezing; 305.1, smoking).[31]

Interpreting reversibility of airflow obstruction

COPD is characterized by airflow limitation that is not fully reversible,[1] although significant reversibility has been demonstrated in patients with COPD.[32-34] For this reason, reversibility of airflow obstruction is no longer recommended for distinguishing asthma from COPD.[1] Confusion exists surrounding the concept of bronchodilator reversibility for several reasons, including variability in patients' responsiveness to bronchodilator treatment

TABLE 1 Examples of currently available handheld spirometers that meet National Lung Health Education Program criteria[30]

Spirometer	Manufacturer	Lung function measures	Data storage	Web site	Estimated price[a]
EasyOne Plus	ndd Medical Technologies Inc., Andover, MA	FEV$_1$, FVC, PEF, and others	Readings from 700 subjects	http://www.nddmed.com/index/easy one-plus	• $1290 (includes 2000-1 Frontline Spirometer, 2010-4 cradle, 2020-1 color printer)[b] • $1990 (includes 2001-1 Diagnostic Spirometer, 2010-4 cradle, 2020-1 color printer)[b] • $326 for 200 disposable Spirette mouthpieces[b]
SDI Astra 300	SDI Diagnostics, Easton, MA	Over 40 parameters of FVC, VC, and MVV	Data exported to printer or computer via cable or wireless via Bluetooth module	http://www.sdidiagnostics.com/spirometers/astra300.php	• $1825; $375 for 300 disposable mouthpieces[c]

[a]List price ($US), which was accurate at publication and may vary based on choice of accessories.

[b]http://www.opsmedical.com/EasyOne.htm; [c]http://www.medicaldevicedepot.com/SearchResults.asp?Search=sdi+astra+300+spirometer+mouthpiece.

Abbreviations: FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; MVV, maximal voluntary ventilation; PEF, peak expiratory flow; VC, vital capacity.

over time[35] and lack of a standardized definition or procedure for testing.[36] Significant bronchodilator reversibility has been defined by the ATS and European Respiratory Society (ERS) as an increase in FEV$_1$ and/or FVC of ≥12% and ≥200 mL compared with control values.[36] Other definitions of reversibility, based on absolute or percentage changes in FEV$_1$ and/or FVC, also exist (**TABLE 3**).[1,36-39]

Results of bronchodilator reversibility testing can vary by the criterion used and over time. Calverley et al studied bronchodilator responsiveness 30 minutes after administration of treatment (salbutamol 400 μg followed 30 minutes later by ipratropium 80 μg via spacer) in a subset of 660 patients with COPD aged 40–75 years from a randomized placebo-controlled study.[35] According to the combined ATS threshold, 42% of patients exhibited reversibility of airflow obstruction, compared with 23% of patients when the ERS criterion was used at the first visit.[35] Within-subject variability over time also was apparent; bronchodilator reversibility status changed in 52% and 38% of patients classified using ATS and ERS criteria, respectively, when tested on subsequent study visits.[35]

In a study by Anthonisen et al, bronchodilator responsiveness was assessed 10 minutes after administration of 2 inhalations of isoproterenol 200 μg in smokers aged 35–59 years with airway obstruction (n=4194) in the 11-year Lung Health Study cohort.[40] Approximately 20% of patients exhibited reversibility, defined as >200 mL in-

crease in FEV$_1$ from baseline.[40] When defined based on improvement of >15% from prebronchodilator FEV$_1$ or ≥12% of the predicted normal FEV$_1$ value, reversibility was reported in 3% and 1% of patients, respectively.[40]

Tashkin et al assessed reversibility of airflow obstruction at baseline using near maximal bronchodilation 30 minutes after bronchodilator treatment (administration of ipratropium 80 μg metered-dose inhaler [MDI] followed 60 minutes later by albuterol 400 μg) in the UPLIFT study (n=5993).[34] Reversibility of airflow obstruction was common in this cohort, but varied depending on the criterion used, with 54% to 73% exhibiting reversibility based on an increase in FEV$_1$ of ≥12%, ≥15%, ≥12% and ≥200 mL, or ≥200 mL, and 39% showing reversibility based on a ≥10% absolute improvement in percent predicted FEV$_1$.[34] Significant improvements in FEV$_1$ were observed in patients initially classified as responsive and in those classified as poorly responsive; improvement in FEV$_1$ was significantly greater, however, in "responsive" patients, regardless of the criteria used ($P<.001$).[34] In that study, the percentage of patients exhibiting bronchodilator reversibility based on the combined ATS criteria decreased as COPD severity (GOLD stage) increased, but percentages were similar across COPD severity categories when using the ≥15% FEV$_1$ improvement criterion.[34]

In a post hoc analysis[41] of data pooled from common treatment arms in 2 randomized, double-blind, mul-

TABLE 2 Examples of CPT codes for spirometry related to diagnosis and treatment of COPD[24]

Code[a]	Description[b]	Reimbursement[b]
94010	Spirometry, including graphic record, total and timed vital capacity, expiratory flow rate measurement(s), with or without maximal voluntary ventilation	$36.65
94060	Bronchodilation responsiveness, spirometry as in 94010, pre- and post-bronchodilator administration	$63.00
94375	Respiratory flow volume loop	$39.64
94620	Pulmonary stress testing; simple (eg, 6-minute walk test, prolonged exercise test for bronchospasm with pre- and post-spirometry and oximetry)	$65.44
94664	Demonstration and/or evaluation of patient utilization of an aerosol generator, nebulizer, metered-dose inhaler or IPPB device	$16.68
99211	Office or other outpatient visit for the evaluation and management of an established patient that may not require the presence of a physician. Usually, the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services.	$9.34

[a]This table provides examples of codes related to spirometry. Comprehensive lists of CPT and ICD-9-CM codes should be consulted in clinical practice.

[b]CPT code descriptions and reimbursement amounts (costs based on 2011 CPT codes and Medicare payment information for Nevada).[24]

Abbreviations: COPD, chronic obstructive pulmonary disease; CPT, current procedural terminology; ICD-9-CM, International Classification of Diseases, ninth revision, Clinical Modification; IPPB, intermittent positive pressure breathing.

ticenter studies,[42,43] FEV_1 reversibility was assessed 30 minutes after administration of formoterol-containing treatment (budesonide/formoterol 320/9 µg or 160/9 µg pressurized MDI [pMDI] or formoterol 9 µg dry powder inhaler [DPI]) on the day of randomization.[41,44] Reversibility of airflow obstruction was achieved by 51% to 54% of patients after formoterol-containing treatment when using ATS criteria (≥12% and ≥200 mL FEV_1 improvement) and 66% to 73% when using the ≥15% FEV_1 improvement threshold.[41,44] Similar to results observed in the post hoc analysis of the UPLIFT study, the percentage of patients exhibiting reversibility of airflow obstruction decreased with increasing COPD severity category when using ATS criteria, but not when using the ≥15% FEV_1 improvement threshold.[44]

Factors that contribute to variability in reported reversibility of airflow obstruction in studies of patients with COPD include differences in the definition used for bronchodilator reversibility and the inherent variation in the degree of bronchodilator reversibility between and within patients over time and by choice of bronchodi-

lator.[36] Because of these limitations, ATS/ERS guidance recommends testing a patient's response to a particular bronchodilator after a single dose or after 2–8 weeks of treatment.[36] Additionally, both the GOLD and ATS/ERS guidelines indicate that lack of an acute bronchodilator response during reversibility testing does not preclude a clinical response to long-term bronchodilator treatment.[1,36] Overall, evidence suggests that patients with COPD can exhibit significant reversibility of airflow obstruction in response to bronchodilators, supporting their use in treating patients with COPD.

Assessing and treating hyperinflation

Hyperinflation is a physiological change characteristic of patients with moderate to severe COPD.[1,45] Inflammation and other pathogenetic factors contribute to lung function decline and airway obstruction, which leads to a progressive trapping of air during expiration and hyperinflation.[1] These changes, which manifest as an increase in the volume of air remaining in the lungs at the end of exhalation (functional residual capacity) and

TABLE 3 Guidelines with criteria commonly used to assess reversibility in patients with COPD following bronchodilator administration

Guideline	Publication date	Spirometry measurement	Criteria[a]
ACCP[37]	1974	FEV_1	≥15%
ATS[38]	1991	FEV_1 or FVC	≥12% and ≥200 mL
ERS[39]	1995	Percentage predicted FEV_1	>10%
ATS/ERS[36]	2005	FEV_1 and/or FVC	>12% and >200 mL
GOLD[1]	2009	FEV_1	>12% and >200 mL

[a]Improvement compared with predose values.

Abbreviations: ACCP, American College of Chest Physicians; ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

FIGURE 2 **Patients with COPD have pulmonary hyperinflation with corresponding increase in functional residual capacity (black) and a decrease in inspiratory capacity (white)**
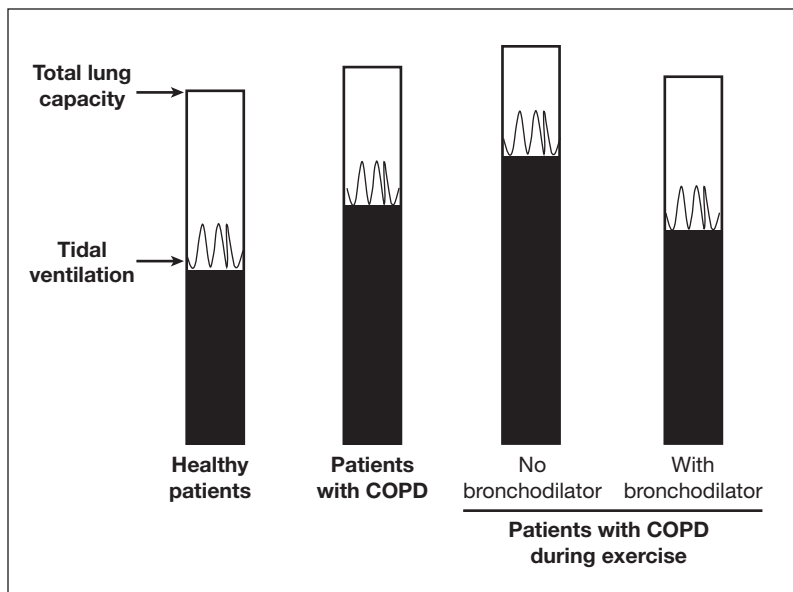

The volume at which tidal ventilation (oscillating line) occurs subsequently increases, putting the muscles of respiration at a mechanical disadvantage. Hyperinflation worsens with exercise and reduces exercise tolerance (dynamic hyperinflation). Inhaled bronchodilators improve dynamic hyperinflation as well as hyperinflation at rest (not shown), and improve exercise tolerance.[45]

Abbreviation: COPD, chronic obstructive pulmonary disease.

From Sutherland ER, Cherniack RM. Management of chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350:2689-2697.[45] Copyright © 2004. Reprinted with permission from the Massachusetts Medical Society.

FIGURE 3 **Lung volume measurements over time**
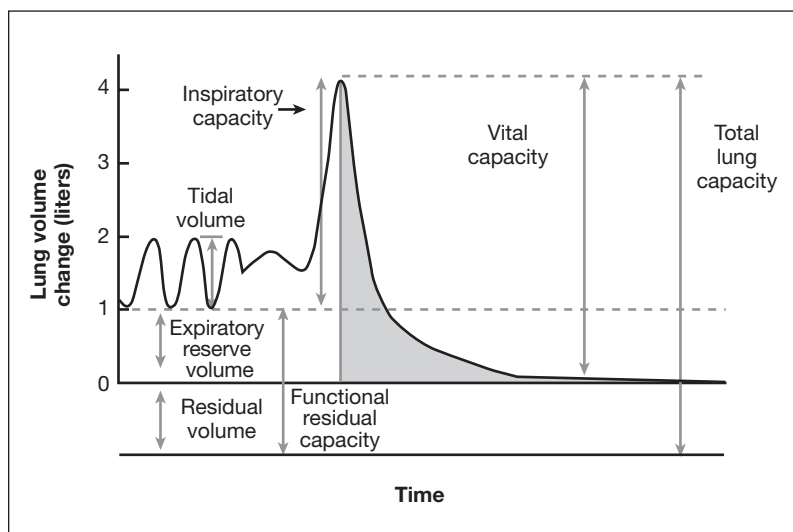
Adapted from Guyton AC, Hall JE. Respiratory insufficiency—pathophysiology, diagnosis, oxygen therapy. In: Guyton AC, Hall JE. *Textbook of Medical Physiology.* 11th ed. Philadelphia, PA: Elsevier Saunders; 2006:526.[48] Copyright © 2006. With permission from Elsevier.

a corresponding decrease in the volume of air that can be drawn into the lungs (inspiratory capacity [IC]),[1] increase the work of breathing and reduce exercise tolerance (**FIGURE 2**).[45] Dynamic hyperinflation has been shown to be an independent predictor of decreased daily physical activity[46] and mortality due to all causes and respiratory failure[47] in patients with COPD. While simple spirometry may identify a patient with COPD, lung volume measurements (described in **FIGURE 3**)[48] provide important information about the disease in individual patients (eg, delineation of hyperinflation and emphysema).[1]

Bronchodilators improve lung emptying and reduce hyperinflation at rest and during exercise.[1] Evidence suggests that patients with COPD who do not show a significant response to bronchodilators based on flow (FEV$_1$) can show a significant lung volume response based on improvements in the spirometric parameters of FVC[33,49] or IC.[49] Improvement in IC has been associated with decreased hyperinflation and improved exercise tolerance,[49-53] the latter of which is recognized as an important goal for effective management of COPD.[1]

In studies in patients with COPD, daily treatment with tiotropium 18 µg resulted in significant improvements in IC and FVC compared with placebo (*P*<.01) after 4 weeks[51] and was associated with significantly reduced lung hyperinflation (as measured by increases in IC and decreases in forced residual capacity and residual volume) and improvement in exercise test parameters compared with placebo (*P*<.05) after 6 weeks of treatment.[54] In a study by O'Donnell et al, patients with COPD treated with fluticasone/salmeterol DPI 250/50 µg for 8 weeks showed significant improvements in IC and FVC from baseline compared with placebo (*P*<.05) and had corresponding improvements in exercise measures.[55] Data from the UPLIFT study showed a significant increase in FVC from baseline of 471 mL (20.1%; *P*<.001) after treatment

with ipratropium and albuterol on the day of randomization.[34] Greater improvements in IC and FVC also were observed following formoterol-containing treatment (budesonide/formoterol 320/9 µg pMDI, budesonide/formoterol 160/9 µg pMDI, or formoterol 9 µg DPI) compared with placebo (FVC 350–410 mL vs 100 mL, respectively; IC 250–330 mL vs 100 mL, respectively) on the day of randomization in a post hoc analysis of 2 clinical studies described previously.[56]

The results from the studies highlight the benefits of bronchodilator therapy in improving lung volume, even in the absence of a flow response (ie, FEV_1), and reducing hyperinflation. Given the association between hyperinflation and decreased daily activity and increased mortality, it is essential that patients with COPD receive appropriate bronchodilator treatment as early as possible.
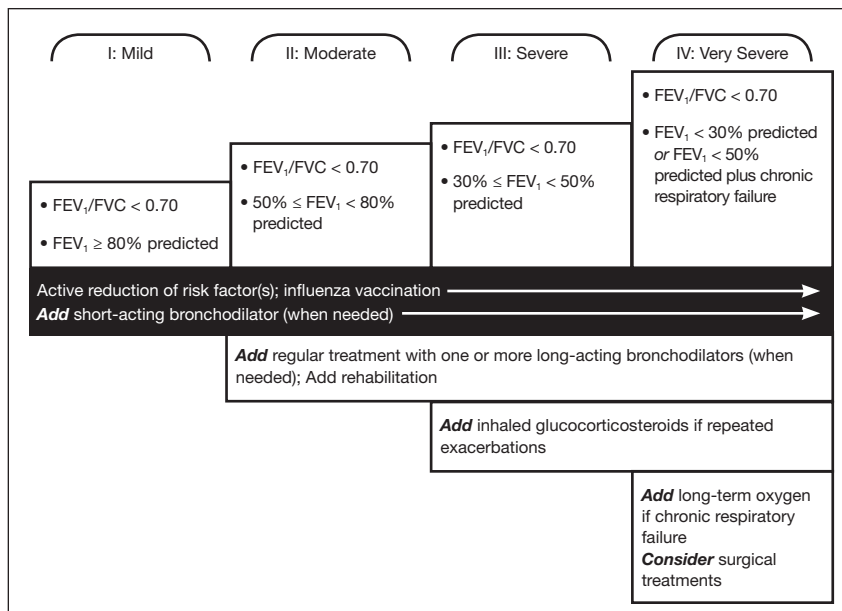

FIGURE 4 Global initiative for chronic Obstructive Lung Disease (GOLD) stepwise algorithm for therapy at each stage of COPD

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

From Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for Diagnosis, Management, and Prevention of COPD.* http://www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=989. Accessed November 22, 2010.[1] Copyright © 2009. Reprinted with permission from Global Initiative for Chronic Obstructive Lung Disease, all rights reserved.

Treat COPD according to disease severity

Types of medications commonly used to treat COPD include bronchodilators (short- and long-acting β_2-adrenergic agonists, anticholinergics, and methylxanthines) and inhaled and systemic corticosteroids.[1,16] Combinations of short-acting β_2-agonists (SABAs) with anticholinergics and long-acting β_2-adrenergic agonists (LABAs) with corticosteroids also have been developed.[1] Within each treatment class, choice of a specific medication depends on drug availability and the patient's response, which may vary among individuals.[1] The 2009 GOLD guidelines recommend long-term maintenance treatment of COPD, with the addition of more medications as disease severity worsens; patients should be monitored and therapy should be altered in response to side effects or disease worsening.[1] The algorithm recommended by the 2009 GOLD guidelines for treatment of COPD is shown in **FIGURE 4**.[1] Stages of disease severity are based on spirometry assessment[1]; therefore, assessment of spirometry is essential for monitoring and treating COPD appropriately.

Conclusions

COPD is a prevalent condition in the adult population in the United States and is widely underdiagnosed in primary care and other medical settings.[3,4] Factors such as smoking history may be predictive of airway obstruction[14] and may facilitate identification and screening of patients at risk for COPD. Spirometry is necessary to make a definitive diagnosis of COPD[1,16]; handheld spirometers were developed as convenient and inexpensive alternatives to traditional spirometers and may facilitate performance of spirometry in the primary care setting.[21-24] While the definition of COPD includes lack of full reversibility, many patients have exhibited substantial bronchodilator response.[34,35,40,41,44] Notably, even in the absence of a flow response (FEV_1), patients can show a significant volume response (eg, IC, FVC).[34,49] Bronchodilator treatment has been shown to decrease hyperinflation and increase exercise tolerance, important goals of therapy in patients with COPD.[1,54,55] Because primary care physicians are the first point of contact for patients, it is critical that physicians identify patients at risk for COPD, use spirometry to accurately diagnose the disease, and provide proper treatment to patients as early as possible. ■

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