

## REVIEW ARTICLE

## CURRENT CONCEPTS

# Management of Chronic Obstructive Pulmonary Disease

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**C**HRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IS A SYNDROME OF progressive airflow limitation caused by chronic inflammation of the airways and lung parenchyma.<sup>1</sup> The primary physiological abnormality in COPD is an accelerated decline in the forced expiratory volume in one second (FEV<sub>1</sub>) from the normal rate in adults over 30 years of age of approximately 30 ml per year to nearly 60 ml per year.<sup>2</sup> As shown in Figure 1, the disease course begins with an asymptomatic phase in which lung function deteriorates without associated symptoms. The onset of the subsequent symptomatic phase is variable but often does not occur until the FEV<sub>1</sub> has fallen to approximately 50 percent of the predicted normal value.<sup>3</sup> Since substantial deterioration in airflow has already occurred by the time most patients present with symptoms, it is reasonable to conclude that the degree of airflow limitation is only one of many factors that govern the onset of symptoms.

Hyperinflation, which occurs at rest and worsens with exercise (Fig. 2), is an additional physiological abnormality that is commonly seen in patients with moderate-to-severe COPD. It is manifested primarily by an increase in the functional residual capacity, which places the muscles of respiration at a mechanical disadvantage, thereby increasing the work of breathing and reducing exercise tolerance. Additional physiological abnormalities include a reduction in the diffusing capacity for carbon monoxide, hypoxemia, and alveolar hypoventilation.

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## DIAGNOSIS, STAGING, AND PROGNOSIS

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Because the majority of cases occur in patients who have smoked,<sup>4</sup> all current or former smokers should be considered at increased risk for COPD. Other risk factors, which account for far fewer cases, include  $\alpha_1$ -antitrypsin deficiency,<sup>5</sup> airway hyperresponsiveness,<sup>6</sup> and indoor air pollution.<sup>7</sup> Since symptoms may not occur until lung function is substantially reduced, early detection is enhanced by spirometric evaluation of FEV<sub>1</sub> and forced vital capacity (FVC). Guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) state that the airflow limitation in COPD is characterized by an FEV<sub>1</sub> value that is less than 80 percent of the predicted normal value and an FEV<sub>1</sub>:FVC ratio of less than 0.70.<sup>3</sup>

Currently, most guidelines recommend that practitioners use a combination of information about symptoms and evidence of impairment of physiological function in determining the severity of the disease,<sup>3,8-10</sup> although the guidelines differ somewhat with regard to setting thresholds for mild, moderate, and severe disease (Table 1). The stage of the disease suggests the prognosis, and follow-up data from longitudinal studies indicate that moderate and severe stages of the disease are associated with higher mortality.<sup>11</sup> However, in the largely asymptomatic group of patients that GOLD<sup>3</sup> categorizes as "stage 0, at risk," only 18.5 percent of the patients progress to more severe

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airflow limitation at 15 years,<sup>12</sup> which suggests that more information is required to predict which patients with incipient disease will progress rapidly to a more advanced stage.

Most guidelines also state that in addition to airflow limitation, patients with COPD have an incomplete response to albuterol (change in FEV<sub>1</sub>, <200 ml and 12 percent)<sup>3,13</sup> and typically do not have evidence of airway hyperresponsiveness (i.e., an abnormal bronchoconstrictor response to a stimulus such as methacholine). Although these features are helpful in distinguishing COPD from asthma,<sup>3</sup> the distinctions are not entirely clear-cut. Indeed, there is responsiveness to a bronchodilator in 23 to 42 percent of patients with COPD, depending on the criteria used.<sup>14</sup> Furthermore, data from the Lung Health Study indicate that 59 percent of men and 85 percent of women with moderate disease (mean [±SD] FEV<sub>1</sub>:FVC ratio, 0.63±0.055 percent) have airway hyperresponsiveness.<sup>15</sup> Thus, although guideline-based spirometric criteria are useful starting points, differentiation of COPD from asthma requires careful integration of epidemiologic risk factors (including the patient's age, smoking status, and family history), clinical status

(including both the indolent and progressive nature of symptoms), and a knowledge of the distribution and potential overlap of physiological disturbances.

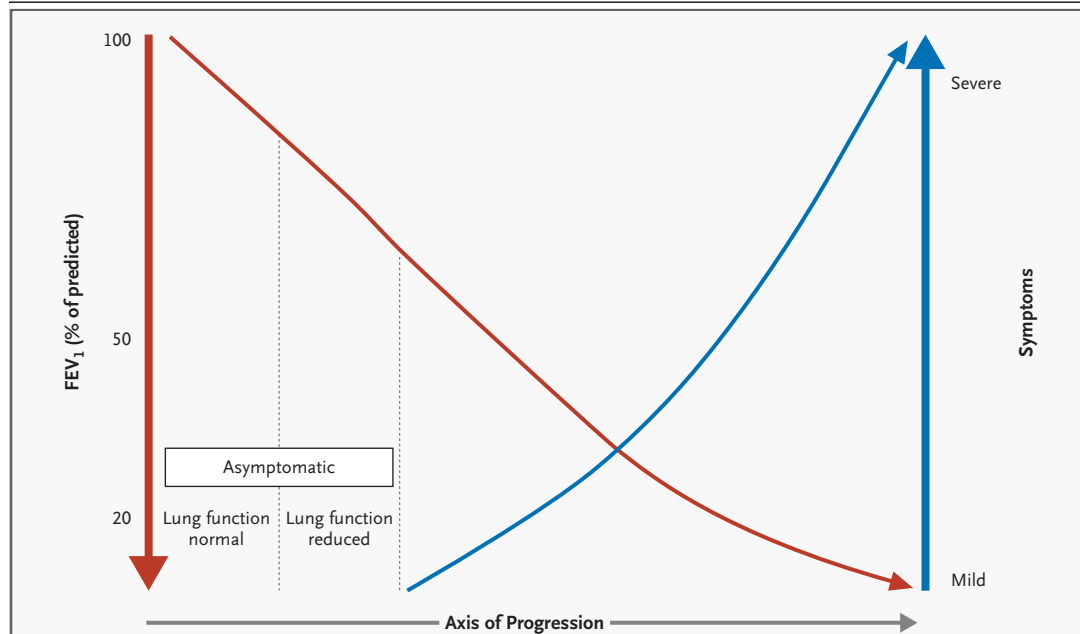
MANAGEMENT OF STABLE COPD

The major goals of therapy include smoking cessation, symptom relief, improvement in physiological function, and limitation of complications, such as abnormal gas exchange and exacerbations of the disease. As summarized in Figure 3, an integrated approach to treatment combines health care maintenance and use of drug and supplemental therapies in a stepwise fashion as the disease progresses.

HEALTH CARE MAINTENANCE

Regular Assessment of Lung Function

It is not yet known whether spirometric screening for COPD is cost effective, and evidence-based criteria for the optimal frequency of such testing in patients with established disease need to be established. Until more data become available, we recommend that spirometry be performed in all



**Figure 1. Deterioration in Lung Function in Patients with COPD.** Symptoms generally develop only after a significant decline in forced expiratory volume in one second (FEV<sub>1</sub>) has occurred; they progress as lung function deteriorates further.

patients at risk to detect asymptomatic airflow limitation; in patients with established disease, spirometry should be performed at least annually, and more frequently if needed, to assess clinical status or the response to therapy.

#### Smoking Cessation

Abstinence from smoking results in a sustained 50 percent reduction in the rate of lung-function decline in patients with COPD,<sup>2</sup> and smoking cessation is the only intervention known to be so effective in modifying the disease. Unfortunately, achieving and maintaining smoking cessation in patients with COPD is a challenge. Approximately 35 percent of the subjects in the Lung Health Study achieved abstinence at one year, but only 22 percent reported continued abstinence at five years with a regimen combining nicotine replacement (available in the form of chewing gum, inhaler, spray, and transcutaneous patch), behavioral counseling, and frequent maintenance visits.<sup>16</sup> Sustained-release bupropion is also effective, although the likelihood of sustained abstinence among patients who have COPD is lower with bupropion than with nicotine replacement.<sup>17</sup>

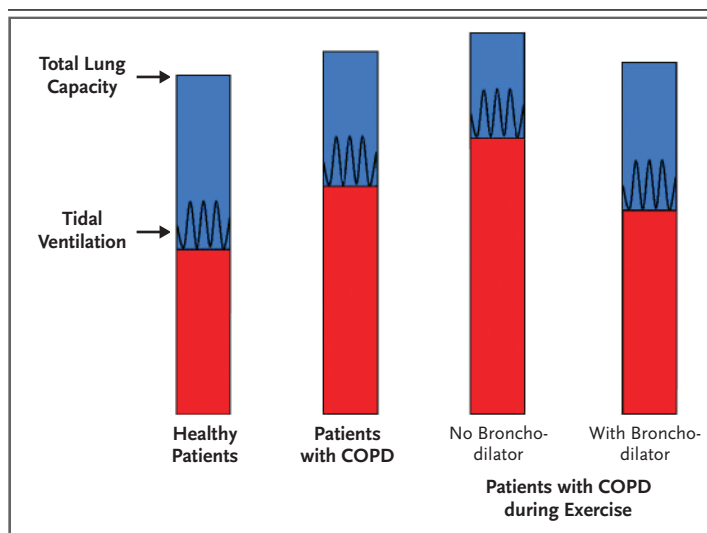
#### Vaccination

Although there is little evidence of a direct benefit of vaccination in patients with COPD, we recommend that pneumococcal vaccination and annual influenza vaccination be offered to all patients in an attempt to reduce both disease-specific mortality and mortality from all causes.<sup>18,19</sup> Administration of the influenza vaccine does not appear to increase adverse outcomes in patients with COPD in the short term.<sup>20</sup>

#### DRUG THERAPY

##### Inhaled Bronchodilators

Inhaled bronchodilators are the foundation of pharmacotherapy for COPD because of their capacity to alleviate symptoms, decrease exacerbations of disease, and improve the quality of life.<sup>21-25</sup> These drugs also improve airflow and hyperinflation (Fig. 2),<sup>26,27</sup> thereby decreasing the work of



**Figure 2. Pulmonary Hyperinflation in Patients with COPD.**

As compared with healthy patients, patients with COPD have pulmonary hyperinflation with an increase in functional residual capacity (red) and a decrease in inspiratory capacity (blue). This condition increases the volume at which tidal ventilation (oscillating line) occurs and places the muscles of respiration at mechanical disadvantage. Hyperinflation worsens with exercise and therefore reduces exercise tolerance (dynamic hyperinflation). Inhaled bronchodilators improve dynamic hyperinflation, as well as hyperinflation at rest (not shown), thereby reducing the work of breathing and increasing exercise tolerance.

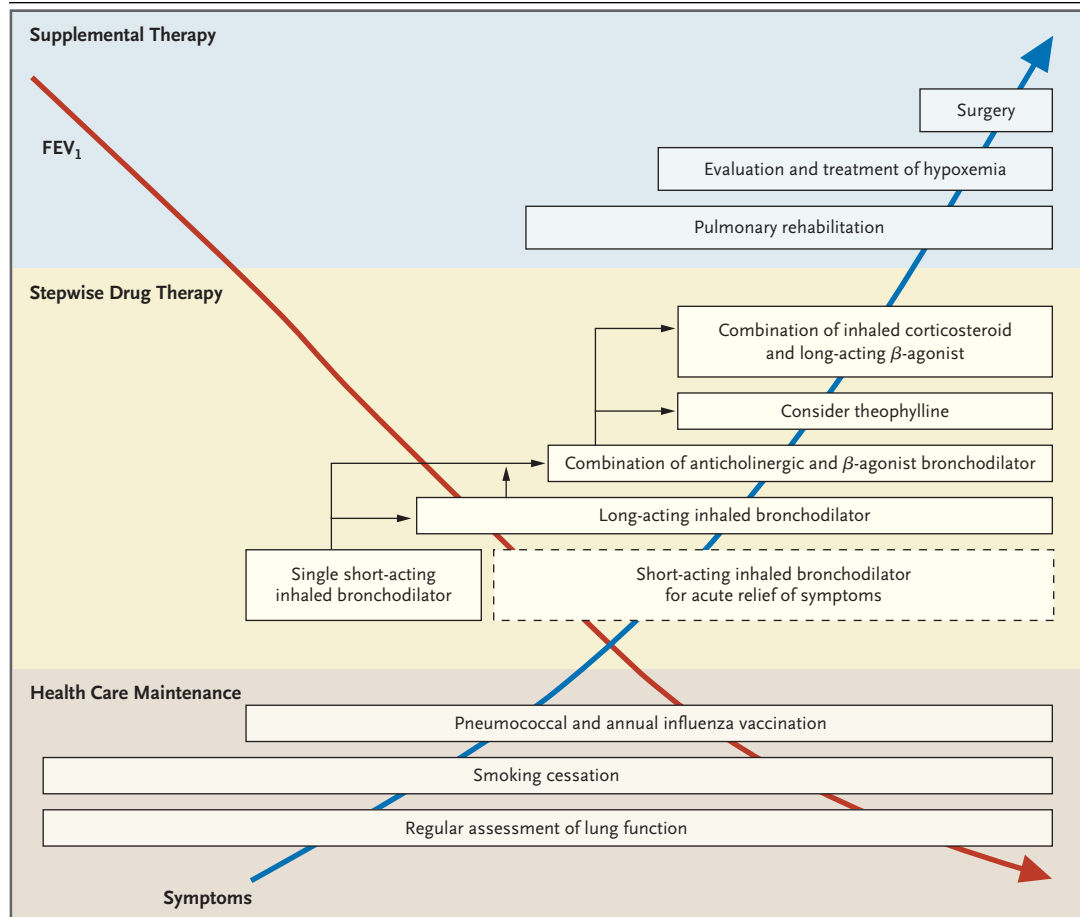
**Table 1. A Comparison of Four Sets of Staging Criteria for COPD.\***

Stage	American Thoracic Society (1995) <sup>8</sup>		European Respiratory Society (1995) <sup>9</sup>		British Thoracic Society (1997) <sup>10</sup>		GOLD (2003) <sup>3</sup>	
	FEV <sub>1</sub> %	Symptoms	FEV <sub>1</sub> %	Symptoms	FEV <sub>1</sub> %	Symptoms	FEV <sub>1</sub> %	Symptoms
0 (at risk)							≥80	–
I (mild)	≥50	NA	70	NA	60–80	±	≥80	±
II (moderate)	35–49	NA	50–69	NA	40–59	+	50–79	+
III (severe)	<35	NA	<50	NA	<40	++	30–49	++
IV (very severe)							<30	+++

\* GOLD denotes Global Initiative for Chronic Obstructive Lung Disease, and FEV<sub>1</sub> forced expiratory volume in one second (shown as a percentage of the predicted normal value). In the Symptoms columns, NA denotes not applicable (staging is based on physiology only), – no symptoms, ± variable symptoms, + mild-to-moderate symptoms, ++ symptoms that limit exertion, and +++ symptoms that limit daily activities.

breathing and improving exercise tolerance. Paradoxically, improvement in function resulting from the administration of bronchodilators is not always reflected by changes in FEV<sub>1</sub> and FVC, and measurement of lung volumes or inspiratory capacity may be necessary to document physiological improvement.<sup>27</sup>

Inhaled bronchodilators can be grouped according to mechanism or duration of action (Table 2). Short-acting  $\beta_2$ -adrenergic-receptor agonists (e.g., albuterol sulfate) and cholinergic-receptor antagonists (e.g., ipratropium bromide) result in bronchodilation for four to six hours.<sup>28</sup> Long-acting  $\beta_2$ -adrenergic-receptor agonists such as for-



**Figure 3. An Algorithm for the Treatment of COPD.**

The components of COPD therapy include health care maintenance, drug therapy, and supplemental therapy. Because patients with reduced lung function may be asymptomatic, spirometry is indicated to diagnose asymptomatic reduction in lung function in at-risk patients. Treatment should be initiated when reduced lung function is demonstrated, with or without the presence of symptoms. Smoking cessation should be aggressively pursued in patients across the severity spectrum, and vaccination is an important addition to health care maintenance. Patients may initially require only as-needed therapy with a single short-acting anticholinergic agent or  $\beta$ -agonist. For patients with moderate-to-severe disease, or for those with persistent or increasing symptoms with as-needed bronchodilators, a single regularly scheduled, long-acting inhaled bronchodilator of either pharmacologic class or the regularly scheduled combination of a short- or long-acting anticholinergic agent and a  $\beta$ -agonist is preferred. For patients treated with a long-acting inhaled bronchodilator, a short-acting agent should be prescribed concurrently for rapid treatment of acute symptoms (box with dashed outline). The addition of pulmonary rehabilitation to treatment regimens will reduce symptoms and improve exercise performance, and the addition of theophylline or an inhaled corticosteroid (or both) to optimal inhaled bronchodilator therapy may provide additional benefits. Patients with moderate or severe disease should be tested for hypoxemia, and it should be aggressively treated if present. Lung-volume-reduction surgery and transplantation are options for a subgroup of patients with very severe disease.

meterol fumarate and salmeterol xinafoate have an effect for 8 to 12 hours, and the long-acting anticholinergic agent tiotropium bromide has a duration of effect of more than 24 hours. In stable disease, administration by means of a metered-dose or dry-powder inhaler is preferred.

For patients with mild airflow limitation and intermittent symptoms, a single short-acting inhaled bronchodilator relieves symptoms and improves airflow. Albuterol and ipratropium are equally effective with regard to bronchodilation, symptom scores, and the rates of treatment failure and can be used interchangeably for mild disease as the first step in a series of measures for treating patients with COPD (Fig. 3).<sup>28-31</sup>

Since most patients have at least moderate airflow limitation when first evaluated, they are likely to require regularly scheduled bronchodilation<sup>3</sup> and to derive benefit from a long-acting bronchodilator as initial therapy. Formoterol, salmeterol, and tiotropium all have an equivalent peak bronchodilator effect but have a prolonged duration of effect, which may explain the superiority of these drugs to short-acting bronchodilators in reducing symptoms and the frequency of exacerbations and in improving the quality of life.<sup>22,23,25</sup> Treatment may be initiated with either a long-acting anticholinergic agent or a  $\beta$ -agonist, since there is little evidence to suggest clinically significant differences between pharmacologic classes. Long-acting inhaled bronchodilators are not appropriate for the treatment of acute symptoms, so a short-acting bronchodilator should also be prescribed for acute relief of symptoms (Fig. 3).

Combination bronchodilator therapy (an anticholinergic agent plus a  $\beta$ -agonist) may be considered for patients in whom a single inhaled bronchodilator has failed to provide adequate relief. The combination of albuterol and ipratropium provides greater bronchodilation than either drug used alone,<sup>28</sup> and similar benefits are obtained by combining long-acting  $\beta$ -agonists with ipratropium.<sup>32,33</sup> Although the combination of albuterol and ipratropium is commonly prescribed for regularly scheduled use, regularly scheduled ipratropium combined with albuterol on an as-needed basis has been reported to be equally effective.<sup>34</sup>

#### Theophylline

If symptoms continue despite combined inhaled-bronchodilator therapy, theophylline may be prescribed because of its capacity to provide addition-

al improvement in lung function and symptoms when added to inhaled bronchodilators.<sup>35,36</sup> Since theophylline may be toxic, frequent monitoring for supratherapeutic levels, adverse drug reactions, and drug interactions is critical.

#### Inhaled Corticosteroids

The appropriate role of inhaled corticosteroids in COPD is controversial. Many studies have shown that inhaled corticosteroids do not substantially modify airway inflammation in COPD, and four large, long-term clinical trials<sup>37-40</sup> comparing inhaled corticosteroids with placebo found that these drugs do not appreciably alter the rate of decline in lung function. This absence of physiological effects, as well as differences in inflammatory phenotype between COPD and asthma,<sup>41</sup> has led many investigators to conclude that these drugs are ineffective in COPD.

However, some of the same trials have demonstrated that treatment with inhaled corticosteroids alleviates patients' symptoms,<sup>40</sup> reduces the frequency of exacerbations,<sup>39</sup> and improves health status.<sup>42</sup> These studies relied on FEV<sub>1</sub> as the primary outcome variable and did not evaluate such physiological variables as hyperinflation, which may have a greater effect on clinical status than the FEV<sub>1</sub> does. Moreover, these studies may not have been powered adequately to detect small differences in the rate of decline in the FEV<sub>1</sub>.<sup>43</sup> In fact, the effect of cigarette smoking in blunting the spirometric response to corticosteroids, as was recently observed in a study involving patients with asthma,<sup>44</sup> may have affected the response to inhaled corticoste-

**Table 2. Duration and Administration of Inhaled Bronchodilators.**

Drug	Duration	Usual Dose*
<b>Short-acting</b>		
Albuterol sulfate	4–6 hr	Two puffs every 4 hr (MDI, 90 $\mu$ g/puff)
Ipratropium bromide	4–6 hr	Two puffs every 4 hr (MDI, 18 $\mu$ g/puff)
<b>Long-acting</b>		
Formoterol fumarate	8–12 hr	One inhalation twice daily (DPI, 12 $\mu$ g/inhalation)
Salmeterol xinafoate	8–12 hr	One inhalation twice daily (DPI, 50 $\mu$ g/inhalation)
Tiotropium bromide	More than 24 hr	One inhalation once daily (DPI, 18 $\mu$ g/inhalation)

\* MDI denotes metered-dose inhaler, and DPI dry-powder inhaler.

roids in the studies of COPD, in which smokers made up 39 to 100 percent of the study population. Thus, the medical literature suggests that inhaled corticosteroids provide clinical benefit to some patients with COPD and that this effect is independent of the patients' FEV<sub>1</sub> response, perhaps operating through an improvement in hyperinflation or a reduction in the frequency of exacerbations.

Guidelines recommend that inhaled corticosteroids be considered for patients with moderate-to-severe airflow limitation who have persistent symptoms despite optimal bronchodilator therapy.<sup>3</sup> This recommendation is based in large part on the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) trial, in which subjects with a mean FEV<sub>1</sub> of approximately 50 percent of the predicted normal value had a 25 percent relative reduction in frequency of exacerbations when treated with inhaled fluticasone propionate.<sup>39</sup> Exacerbations appear to accelerate the rate of lung-function decline in COPD,<sup>45</sup> and the reduction in exacerbations seen in the ISOLDE trial supports the use of inhaled corticosteroids to modify the frequency of exacerbations, independently of the drugs' effects on underlying airway inflammation. In addition, the observation that the combination of inhaled corticosteroids and long-acting  $\beta$ -agonists is superior to placebo or either drug alone with regard to lung function, frequency of exacerbations, symptoms, and health status<sup>46,47</sup> suggests that the use of inhaled corticosteroids should be restricted to patients in whom optimal bronchodilator therapy has failed to improve the symptoms, physiological findings, or frequency of exacerbations.

It is important to recognize that in older patients the side effects of inhaled corticosteroids are not well understood, and the use of these drugs should be carefully considered. Since it is difficult to predict accurately which patients will benefit from therapy, clinical and spirometric responses should be assessed in the months after the initiation of inhaled corticosteroids. Treatment should be discontinued if no substantial clinical or physiological improvement is seen, since there is no evidence that continuing treatment with inhaled corticosteroids provides any long-term benefit in such cases.

#### *Oral Corticosteroids*

Assessing the spirometric response to a trial of oral corticosteroids has been advocated as a means of identifying patients who have a response to inhaled corticosteroids. In the ISOLDE trial, all subjects

received oral prednisolone before fluticasone.<sup>39</sup> The overall response to prednisolone was minimal (a mean increase in FEV<sub>1</sub> of 69 ml) and was unrelated to the patients' baseline FEV<sub>1</sub>, responsiveness to a bronchodilator, subsequent decline in FEV<sub>1</sub>, or response to inhaled fluticasone.<sup>48</sup> Thus, although a trial of oral corticosteroids may be useful in detecting coexisting asthma, it is a poor predictor of the response to inhaled corticosteroids among patients with COPD. Oral corticosteroids should not be used in the routine management of stable disease.

#### **SUPPLEMENTAL THERAPY**

##### *Pulmonary Rehabilitation*

Pulmonary rehabilitation improves patients' exercise capacity, reduces dyspnea, improves the quality of life,<sup>49</sup> and reduces the number and duration of hospitalizations related to respiratory disease.<sup>50</sup> It is appropriate for patients with clinically significant exertional symptoms and is most effective when delivered as a multifaceted program incorporating individually tailored aerobic physical training, comprehensive education about the disease, psychosocial counseling, and nutritional support.<sup>51</sup> Although having a low body-mass index is associated with increased mortality from respiratory disease among patients with COPD,<sup>52</sup> there is no evidence that enhanced nutrition improves body weight, lung function, exercise capacity, or survival.<sup>53</sup>

##### *Treatment of Abnormal Gas Exchange*

Hypoxemia develops as a result of a worsening ventilation-perfusion mismatch, and aggressive testing for hypoxemia is critical, since clinical trials have shown that mortality is reduced by treatment with supplemental oxygen for 15 or more hours per day.<sup>54,55</sup> In stable patients, Medicare guidelines suggest that oxygen therapy should be initiated if the resting partial pressure of arterial oxygen is 55 mm Hg or lower or if the oxygen saturation is 88 percent or less. However, these recommendations are based in large part on the inclusion criteria for the Medical Research Council study<sup>54</sup> and the Nocturnal Oxygen Therapy Trial<sup>55</sup> and may not identify all patients who would benefit from supplemental oxygen. For example, supplemental oxygen substantially improves training intensity and exercise tolerance even in patients in whom desaturation does not occur during exercise.<sup>56</sup>

Supplemental oxygen should be adjusted to maintain an oxygen saturation of at least 90 per-

cent at all times. Since patients may have normal oxygen saturation at rest but hypoxemia with exertion or sleep, pulse oximetry and oxygen titration should be performed during all three conditions. Worsening hypoxemia during air travel must be considered, and a general recommendation is that patients requiring oxygen should increase their oxygen flow rate by 2 liters per minute during flight.<sup>57</sup>

In advanced disease, hypoxemia and hypercapnia (alveolar hypoventilation) may occur as a result of an increase in the dead-space fraction, a ventilation-perfusion mismatch, or an increase in the work of breathing with enhanced production of carbon dioxide. Inhaled bronchodilators can help reduce the work of breathing and improve gas exchange in some patients with alveolar hypoventilation. Trials of noninvasive positive-pressure ventilation have been conducted in patients with stable COPD, and although hypercapnia can be improved,<sup>58</sup> improvement often comes at the cost of increased hyperinflation.<sup>59</sup> A two-year trial of noninvasive positive-pressure ventilation in addition to supplemental oxygen in patients with alveolar hypoventilation demonstrated improvements in dyspnea and the quality of life but only small improvements in arterial carbon dioxide levels.<sup>60</sup>

### Surgery

Lung-volume-reduction surgery can reduce hyperinflation and should be considered in patients with severe upper-lobe emphysema and reduced exercise tolerance who are not faring well with medical

therapy alone. In 2000, a small randomized, controlled trial that compared lung-volume-reduction surgery with medical therapy in patients with severe emphysema demonstrated improved lung function, exercise capacity, and quality of life 6 to 12 months after surgery.<sup>61</sup> Subsequently, the National Emphysema Treatment Trial found that the addition of lung-volume-reduction surgery to optimal medical therapy and rehabilitation led to an overall improvement in exercise tolerance and survival in a subgroup of patients with reduced exercise tolerance and predominantly upper-lobe emphysema.<sup>62</sup> Overall mortality did not improve, however, and mortality was increased in a subgroup of patients with severe physiological impairment ( $FEV_1$ ,  $\leq 20$  percent of the predicted normal value) and homogeneous emphysema or a carbon monoxide diffusing capacity no more than 20 percent of the predicted normal value.<sup>63</sup>

Single-lung transplantation is an alternative surgical option for patients with end-stage emphysema who have an  $FEV_1$  that is less than 25 percent of the predicted normal value after the administration of a bronchodilator and who have such complications as pulmonary hypertension, marked hypoxemia, and hypercapnia.<sup>64</sup> The surgery does not appear to improve survival significantly in these patients, however.<sup>65</sup>

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