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Outpatient treatment of chronic obstructive pulmonary disease: Comparisons with asthma

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Chronic obstructive pulmonary disease (COPD) is a progressive syndrome of expiratory airflow limitation caused by chronic inflammation of the airways and lung parenchyma. The airway inflammatory response in COPD is initiated by smoking in the overwhelming majority of cases, and chronic exposure to cigarette smoke initiates a series of events that cause damage to central airways, peripheral airways, and terminal airspaces, leading to physiologic and clinical abnormalities. The contrasting inflammatory phenotypes of asthma and COPD have important implications for clinical and physiologic manifestations of disease, as well as for therapy. The outpatient treatment of COPD differs from the approach used in asthma and can be divided into 3 subgroups: health care maintenance, drug therapy, and nondrug therapy. Smoking cessation, regular spirometry, and immunization are important components of health care maintenance. Drug therapy consists of optimal bronchodilator therapy supplemented, when necessary, with either inhaled corticosteroids or theophylline. Nondrug therapies include pulmonary rehabilitation, supplemental oxygen, and surgery. (*J Allergy Clin Immunol* 2004;114:715-24.)

Key words: *Chronic obstructive pulmonary disease, asthma, therapy*

Chronic obstructive pulmonary disease (COPD) is a disorder of progressive airflow limitation caused by chronic inflammation of the airways and lung parenchyma and associated with symptoms such as cough, sputum production, and dyspnea. Smoking is the primary risk factor for the development of COPD,¹ and all current or former smokers should be considered to be at increased risk for COPD. Other risk factors, such as α_1 -antitrypsin deficiency,² airway hyperresponsiveness,³ and indoor air

Abbreviations used

COPD: Chronic obstructive pulmonary disease

FVC: Forced volume capacity

ISOLDE: Inhaled Steroids in Obstructive Lung Disease in Europe

pollution,⁴ have been described but account for far fewer cases. Although COPD and asthma share many clinical features, characteristic features of asthma, such as airway hyperresponsiveness and bronchodilator-responsive expiratory airflow limitation, are less commonly observed in patients with COPD, and significant differences in airway inflammatory phenotype exist between the two.⁵ These pathologic and physiologic differences have a direct effect on the choice of pharmacologic therapy for these disorders.

AIRWAY INFLAMMATION

In patients with COPD, chronic exposure to cigarette smoke causes inflammation in the central airways,⁶ peripheral airways,⁷ and alveoli.⁸ Neutrophils and macrophages play a major role in the pathogenesis of COPD, whereas eosinophils play a minor role, except in the setting of exacerbations.⁹ These differences in inflammatory phenotype are particularly important when considering the role of anti-inflammatory agents, such as inhaled corticosteroids, in asthma versus COPD.

In patients with COPD, neutrophils mediate tissue destruction through the release of elastases, and sputum neutrophilia in smokers has been shown to be associated with chronic cough, sputum production, and an accelerated decrease in FEV₁ over time.¹⁰ Although neutrophil influx is required for cigarette smoke-induced connective tissue-matrix breakdown in mouse models and has been described in clinical studies, it appears to be dependent on the presence of macrophage-derived matrix metalloproteinase,¹¹ suggesting that both neutrophils and macrophages are required for the development of emphysema after smoke exposure.¹² In mouse models of the acute

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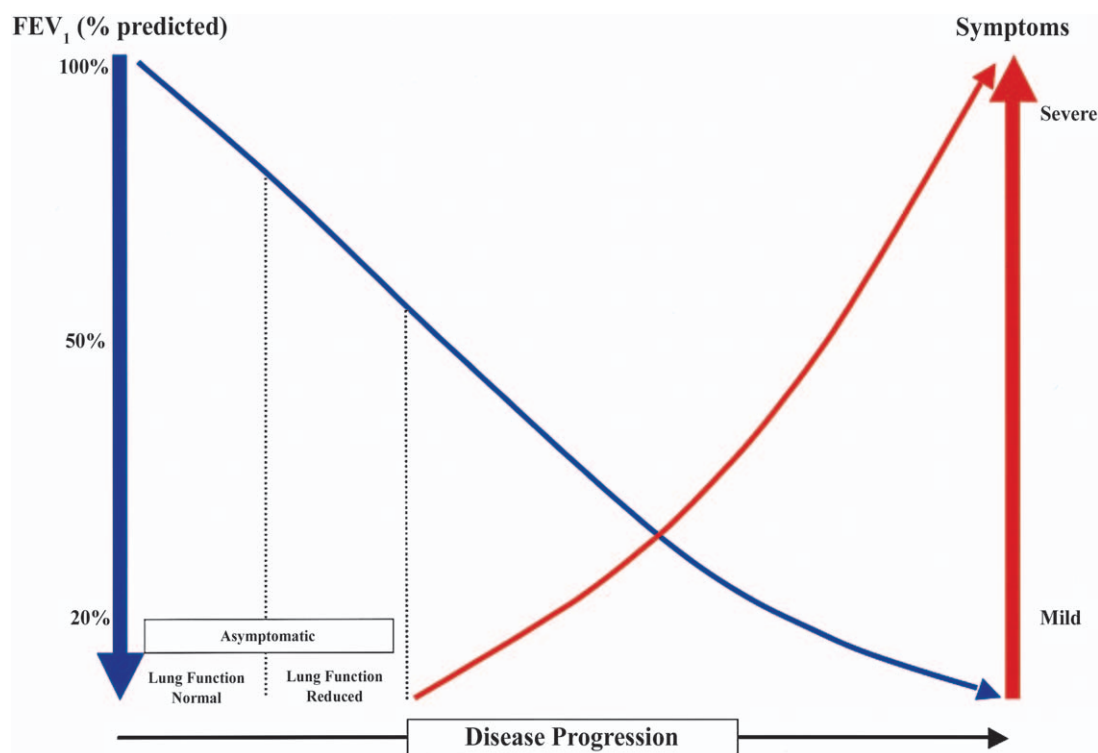


FIG 1. Natural history of COPD. The early course of disease is marked by an asymptomatic decrease in lung function. Progressive symptoms generally develop only after a significant decrease in FEV₁ has occurred and worsen as lung function deteriorates further. Reprinted with permission from Sutherland ER, Cherniack RM. Management of chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:2689-97. © 2004 Massachusetts Medical Society. All rights reserved.

response to tobacco smoke, the secretion of matrix metalloproteinase¹¹ from macrophages has been reported to cause macrophages to release TNF- α , resulting in neutrophil influx, possibly through activation of vascular endothelial cells.¹¹

Much of the airflow limitation in COPD occurs in airways of less than 2 mm in diameter,¹³ and small airway inflammation is a significant contributor to the physiologic impairment seen in patients with COPD.^{14,15} In the small airways in patients with COPD, there is a significant negative correlation between the number of CD8⁺ T lymphocytes and FEV₁ percent predicted, with an r value of -0.63 ($P = .01$) and a significant inverse relationship between airway smooth muscle area and FEV₁ percent predicted ($r = -0.67$; $P = .01$).⁷

CLINICAL PHENOTYPES

Traditionally, the terms chronic bronchitis and emphysema have been used to describe the 2 major clinical phenotypes of COPD.¹⁶ Chronic bronchitis results from inflammation of the small- and medium-sized airways and presents with airflow limitation, dyspnea, chronic cough, and sputum production. Emphysema occurs as a result of destruction of elastic tissue in the terminal airspaces and parenchyma, resulting in loss of lung elastic recoil, airflow

limitation, dyspnea, and hypoxemia. Centrilobular emphysema is most commonly associated with cigarette smoking and is seen predominantly in the upper lobes of the lung, occurring as a result of inflammatory destruction of the respiratory bronchioles. Panlobular emphysema, seen primarily in patients with α_1 -antitrypsin deficiency, occurs as a result of a more uniform destruction of the secondary lobule and predominantly involves the lower lobes.¹⁷

LUNG FUNCTION

Airflow limitation is a cardinal feature of both COPD and asthma. An accelerated loss of lung function defines the natural history of COPD, with a doubling of the rate of annual FEV₁ decline from approximately 30 mL/y to nearly 60 mL/y.¹⁸ Early COPD is marked by an asymptomatic phase in which lung function deteriorates without leading to significant symptoms, and symptoms often do not ensue until the FEV₁ has decreased to nearly 50% of predicted value (Fig 1).¹⁹ Whereas expiratory airflow limitation in asthma typically responds significantly (ie, $\geq 12\%$ and 200 mL)²⁰ to inhaled bronchodilators, airflow limitation in COPD is generally described as poorly bronchodilator responsive. However, bronchodilator responsiveness has been reported in up to 23% to 42% of patients with COPD, depending on the criteria used.²¹

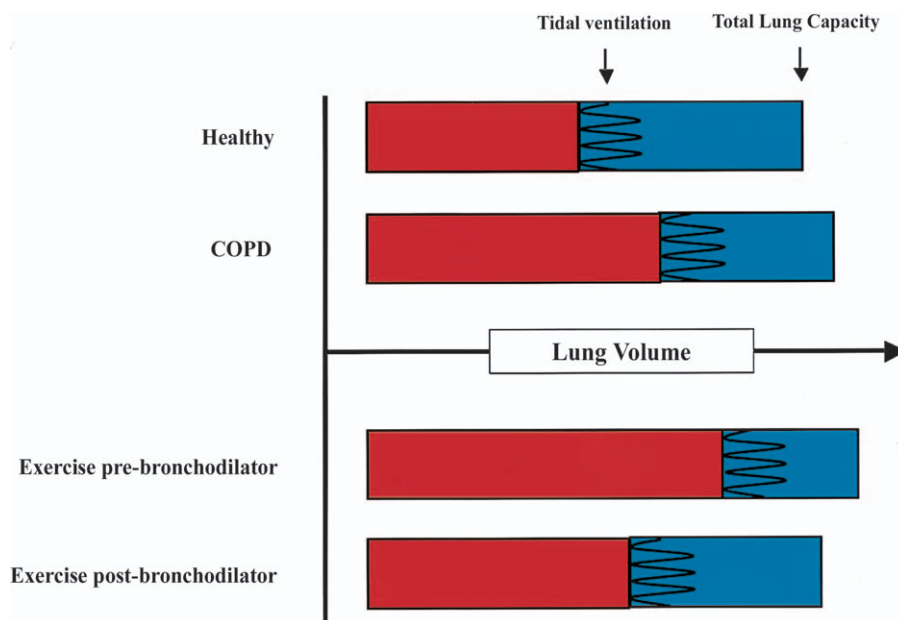


FIG 2. Compared with healthy individuals (*upper panel, top*), patients with COPD (*upper panel, bottom*) demonstrate hyperinflation with increased functional residual capacity (*red*) and total lung capacity and a decreased inspiratory capacity (*blue*). This increases the lung volume at which tidal ventilation occurs, places the respiratory musculature at mechanical disadvantage, and increases work of breathing. Hyperinflation worsens with exercise (*bottom panel, top*) but is improved by the use of inhaled bronchodilators.

Airway hyperresponsiveness, a hallmark of asthma, is seen in COPD as well. Long-term follow-up has revealed that in COPD airway hyperresponsiveness is an important predictor of progression in airflow limitation independent of features such as age, sex, baseline lung function, baseline smoking history, and changes in smoking status.³ The Lung Health Study evaluated airway hyperresponsiveness in smokers with COPD and moderate airflow limitation (FEV_1 /forced vital capacity [FVC] ratio, $63\% \pm 5.5\%$ [mean $\pm$ SEM]) and demonstrated that the overall prevalence of airway hyperresponsiveness (defined as a methacholine PC_{20} value of <25 mg/mL) ranged from 58.9% in men to 85.1% in women and that the severity of baseline airflow limitation was correlated with the degree of airway hyperresponsiveness. However, airway hyperresponsiveness was defined as a methacholine PC_{20} value of less than 25 mg/mL, an upper limit of provocative concentration higher than that typically observed in asthmatic patients.²²

An additional critical physiologic abnormality in moderate-to-severe COPD is hyperinflation, which occurs at rest and increases with exercise (Fig 2). Hyperinflation, which results in increased lung volumes, is manifested by an increase in the functional residual capacity. Total lung capacity increases as well, and tidal ventilation occurs at a higher percentage of total lung capacity. This places the muscles of respiration at a mechanical disadvantage, resulting in increased work of breathing and reduced exercise tolerance. Other physiologic abnormalities seen in patients with COPD include both a reduction in the diffusing capacity for carbon monoxide and hypoxemia,

which are due to destruction of the alveolar-capillary interface, as well as alveolar hypoventilation, which can occur as a result of an increased dead-space fraction of tidal ventilation or as a result of increased carbon dioxide production in the setting of increased work of breathing.

DETERMINING SEVERITY

Major guidelines use a combination of symptoms or physiologic impairment to stage disease severity,^{19,23-25} although they differ somewhat with regard to thresholds for mild, moderate, and severe disease (Table I). Guidelines from the Global Initiative for Obstructive Lung Disease state that airflow limitation in COPD is characterized by a post-bronchodilator FEV_1 of less than 80% of predicted and an FEV_1 /FVC ratio of less than 70%.¹⁹ Disease stage suggests prognosis, and follow-up data from longitudinal studies indicate that moderate and severe stages of disease are associated with increased mortality.²⁶

TREATMENT

The major goals of therapy of COPD include smoking cessation, symptom relief, improvement of airflow, and hyperinflation and limiting complications, such as exacerbations. A general classification of treatment into health care maintenance, drug therapy (Table II), and nondrug therapy is useful.²⁷

TABLE I. Spirometric staging criteria for COPD

Stage	American Thoracic Society, ²⁵ European Respiratory Society, ²⁵ GOLD ¹⁹		British Thoracic Society ²³		Canadian Thoracic Society ²⁴	
	FEV ₁ /FVC	FEV ₁ %	FEV ₁ /FVC	FEV ₁ %	FEV ₁ /FVC	FEV ₁ %
At risk	>0.7	≥80	—	—	≥0.7	≥80
Mild	≤0.7	≥80	<0.7	60-80	<0.7	60-79
Moderate	≤0.7	50-80	<0.7	40-59	<0.7	40-59
Severe	≤0.7	30-49	<0.7	<40	<0.7	<40
Very severe	≤0.7	<30	—	—	—	—

GOLD, Global Initiative for Chronic Obstructive Lung Disease.

TABLE II. Principal effects and use of drug therapy in COPD versus asthma

COPD		Asthma
Short-acting anticholinergic	Reduction in hyperinflation; symptom relief; improvement in airflow	No currently defined role in stable disease
Long-acting anticholinergic	Reduction in hyperinflation; symptom relief; improvement in airflow; reduction in exacerbations	No currently defined role
Short-acting β -agonist	Reduction in hyperinflation; symptom relief; improvement in airflow	Improvement in airflow; symptom relief
Long-acting β -agonist	Reduction in hyperinflation; symptom relief; improvement in airflow; reduction in exacerbations	Improvement in airflow; symptom relief; only used with concurrent inhaled corticosteroid
Anticholinergic/ β -agonist combination	Symptom relief; reduction in hyperinflation; improvement in airflow; reduction in exacerbations	No currently defined role in stable disease
Inhaled corticosteroid	No significant effects on long-term progression of airflow; reduction of exacerbations, improvement of symptoms, and health status; bronchodilation; indicated in moderate-to-severe disease not responsive to optimal bronchodilation	Principal anti-inflammatory controller therapy for persistent disease
Inhaled corticosteroid/long-acting β -agonist combination	Reduce exacerbations; improve symptoms; improve health status; indicated in moderate-to-severe disease not responsive to optimal bronchodilation	Combination controller therapy for persistent disease
Theophylline	Bronchodilation, putative anti-inflammatory effects	Bronchodilating controller therapy, putative anti-inflammatory effects
Leukotriene modifiers	No currently defined role	Anti-inflammatory and bronchodilating controller therapy

HEALTH CARE MAINTENANCE

Liberal use of spirometry is critical to the diagnosis and management of COPD. Because patients can have moderately impaired lung function before they become symptomatic, spirometric screening to detect early disease should be considered in all adults with a smoking history of more than 10 pack-years. Buffels et al²⁸ reported in 2004 that office spirometry, when used as an adjunct to evaluation of symptoms in the general practice setting, resulted in improved rate of detection of early-stage COPD, reinforcing the importance of spirometry as an important tool for early diagnosis. For those patients with established disease, regular spirometry is useful for following the course and prognosis of COPD, as well as for evaluating changes in lung function during periods of changing clinical status or in response to alterations in therapy.

Smoking cessation is a critical component of health care maintenance, as it is the only intervention known to modify the long-term natural history of lung function decrease in patients with COPD. Eleven-year follow-up data from the Lung Health Study suggest that in individuals with COPD, abstinence from tobacco results in a sustained improvement in the rate of lung function decrease in patients with COPD, returning the rate of decrease to near normal.¹⁸ Unfortunately, as with all smokers, achieving and maintaining smoking cessation in patients with COPD is a challenge. Approximately 35% of subjects in the Lung Health Study achieved abstinence at 1 year, and only 22% reported continued abstinence at 5 years, with a regimen combining nicotine replacement, behavioral counseling, and frequent maintenance visits.²⁹ Quit rates are increased by adding sustained-release bupropion to the combination of nicotine replacement and behavioral counseling.³⁰

As in asthma, immunization against influenza and pneumococcus should be offered to all patients with COPD.^{31,32}

INHALED BRONCHODILATORS

Inhaled bronchodilators are the foundation of pharmacotherapy in COPD because of their ability to improve symptoms and quality of life and decrease exacerbations.³³⁻³⁷ These drugs also improve the physiologic manifestations of COPD, including airflow limitation and hyperinflation,³⁸⁻⁴⁰ thus reducing the work of breathing and increasing exercise tolerance. Because bronchodilators can improve lung volumes without changing the FEV₁ and FVC values, measurement of lung volumes or inspiratory capacity might also be necessary to identify physiologic improvement.³⁹

Inhaled bronchodilators can be grouped by duration or mechanism of action, and duration of action is an important variable in determining patient response. Short-acting β_2 -adrenergic receptor agonists (eg, albuterol sulfate) and cholinergic receptor antagonists (eg, ipratropium bromide) bronchodilate for 4 to 6 hours.⁴¹ Long acting β -agonists, such as formoterol fumarate and salmeterol xinafoate, have an effect for 8 to 12 hours, and the long-acting anticholinergic tiotropium bromide has an effect for more than 24 hours.

For those patients with mild airflow limitation or symptoms, intermittent use of a single short-acting inhaled bronchodilator can be sufficient. Because albuterol and ipratropium are equally effective with regard to their ability to bronchodilate, to improve symptom scores, and to reduce treatment failures, either drug can be used as initial therapy for mild disease.⁴¹⁻⁴⁴ These drugs can also be used in combination (see below).

Patients who present with moderate airflow limitation and persistent symptoms at first evaluation are more likely to require regularly scheduled bronchodilation¹⁹ and to derive greater benefit from a long-acting bronchodilator as initial therapy. Formoterol, salmeterol, and tiotropium demonstrate equivalent peak bronchodilator effects^{34,35,45} but have a prolonged duration of effect versus short-acting agents, which might explain the superiority of these drugs versus short-acting bronchodilators in reducing symptoms and exacerbation frequency and improving quality of life.^{34,35,37} Treatment with long-acting inhaled bronchodilators can be initiated with either an anticholinergic agent or a β -agonist because there is currently little evidence to suggest that there are significant clinical differences between pharmacologic classes. Long-acting inhaled bronchodilators are not appropriate for the treatment of acute symptoms, and patients should also be prescribed a short-acting bronchodilator for acute symptoms.

Combination bronchodilator therapy (anticholinergic plus β -agonist) can be considered for patients in whom a single inhaled bronchodilator has failed to provide adequate relief. The combination of albuterol and ipra-

tropium provides greater bronchodilation than either drug used alone,⁴¹ and similar benefits are obtained by combining long-acting β -agonists with ipratropium.⁴⁶ Few studies thus far have evaluated the combination of a long-acting anticholinergic agent with a long-acting β -agonist, although a study by Cazzola et al⁴⁷ published in 2004 suggested that the combination of formoterol and tiotropium did not result in increased bronchodilation over that seen with either drug used alone. Although the combination of albuterol and ipratropium is commonly prescribed for regularly scheduled use, regularly scheduled ipratropium combined with as-needed albuterol has been reported to be equally effective.⁴⁸

Short-acting β -agonists are used as quick-relief medications in the treatment of asthma and are recommended for use in all asthma severity stages. These drugs provide significant bronchodilation and can normalize lung function in some patients with asthma, but adult patients with persistent asthma should also be treated with inhaled corticosteroids.⁴⁹ In patients with asthma, long-acting β -agonists both bronchodilate and confer protection against airways responsiveness to methacholine, nonspecific irritants (eg, exercise and cold air),⁵⁰⁻⁵⁴ and allergen-induced bronchoconstriction.⁵⁵ Unlike in COPD, the use of long-acting β -agonists as monotherapy for long-term control of asthma is not recommended because these drugs are inferior to inhaled corticosteroids as long-term controller medications.⁵⁶ Current recommendations are that long-acting β -agonists be used as second-line controller medications when inhaled corticosteroids alone are inadequate.⁴⁹ A number of clinical trials⁵⁷⁻⁶⁰ have reported that in asthma the addition of a long-acting β -agonist used twice daily to inhaled corticosteroids is at least as effective in the control of asthma as doubling the dose of inhaled corticosteroids.

INHALED CORTICOSTEROIDS

Inhaled corticosteroids exhibit anti-inflammatory properties at both the molecular and cellular levels. Glucocorticoids diffuse readily across cell membranes, where they bind the intracytoplasmic glucocorticoid receptor. This complex is then translocated into the nucleus, where it binds to glucocorticoid response elements.⁶¹ Up to 100 genes with glucocorticoid response elements have been identified,⁶² and either upregulation or downregulation of transcription might occur as a result of glucocorticoid binding.⁶³ In some cases the gene products are proinflammatory cytokines that are downregulated by glucocorticoid binding to the glucocorticoid response element.⁶⁴ Glucocorticoids also inhibit the ability of nuclear transcription factors to upregulate the immune response.⁶⁵ At the cellular level, glucocorticoids result in a reduction in the number of eosinophils and activated T lymphocytes in bronchoalveolar lavage fluid and airway epithelium^{66,67} in asthmatic subjects, and this beneficial effect is likely the result of a reduction in transcription of proinflammatory cytokine genes. Corticosteroids inhibit

many of the inflammatory processes at work in the asthmatic airway,⁶⁸ improve lung function, reduce the number of asthma exacerbations, reduce the number of acute care hospitalizations for asthma,⁶⁹ and reduce asthma mortality.⁷⁰ Because of these effects, corticosteroids are the mainstay of therapy for patients with all forms of persistent asthma.

In contrast, the benefit of corticosteroids in COPD is less clear, and resistance to corticosteroids at the molecular level has been postulated as an important issue in the management of this disorder.⁷¹ Four large, long-term clinical trials⁷²⁻⁷⁵ comparing inhaled corticosteroid monotherapy with placebo reported that these drugs do not alter lung function, and smaller studies have shown that inhaled corticosteroids do not significantly modify airway inflammation in COPD. Some of these trials, however, have shown that inhaled corticosteroid therapy improves symptoms,⁷⁵ exacerbation frequency,⁷⁴ and health status,⁷⁶ suggesting clinical benefit that occurs independently of effects on airflow. Additionally, many subjects (39% to 100%) in the trials of inhaled corticosteroid use in COPD smoked, and the recent observation in asthmatic patients that cigarette smoking blunts the spirometric response to oral corticosteroids⁷⁷ might also be relevant to these studies.

The Global Initiative for Chronic Obstructive Lung Disease guidelines suggest that the use of inhaled corticosteroids should be considered in patients with moderate-to-severe airflow limitation with persistent symptoms despite optimal bronchodilator therapy.¹⁹ 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 FEV₁ of approximately 50% of predicted value experienced a 25% relative reduction in exacerbations in response to inhaled fluticasone propionate.⁷⁴ Exacerbations contribute to accelerated lung function decrease in patients with COPD,⁷⁸ and the reduction in exacerbations seen in ISOLDE supports the use of inhaled corticosteroids in an attempt to modify exacerbation frequency independent of the effects on underlying airway inflammation. In the United States inhaled corticosteroids are not approved as monotherapy for the treatment of COPD.

Although inhaled corticosteroids have a much lower risk of inducing many of the adverse events seen with oral corticosteroids, their use has been associated with dose-dependent accelerated bone loss,⁷⁹ oral candidiasis,⁸⁰ dysphonia,⁸¹ and depression of the hypothalamic-pituitary-adrenal axis.⁸² These risks are likely to be increased in older patients with COPD, and the use of these drugs in patients with COPD should be carefully considered. Because it is difficult to predict which patients with COPD will benefit from inhaled corticosteroids, clinical and spirometric response should be assessed in the months after initiation of inhaled corticosteroids. Treatment should be discontinued if significant clinical or physiologic improvement is not seen because there is no evidence that continuing inhaled corticosteroids in the absence of significant clinical or physiologic improvement provides any long-term benefit.

INHALED CORTICOSTEROID/LONG-ACTING β -AGONIST COMBINATIONS

The combination of inhaled corticosteroids and long-acting β -agonists (both budesonide-formoterol and fluticasone-salmeterol) has been reported to be superior to placebo or either drug alone with regard to lung function, frequency of exacerbations, symptoms, and health status^{83,84} in patients with COPD, and the combination of fluticasone (250 μ g twice daily) and salmeterol (50 μ g twice daily) has been approved by the US Food and Drug Administration for the treatment of COPD.⁸⁵ The addition of inhaled corticosteroids appears to provide added bronchodilator effect and supported a treatment strategy in which bronchodilator therapy is optimized first, with the addition of inhaled corticosteroids restricted to patients in whom optimal bronchodilator therapy has failed to improve symptoms, physiology, or exacerbation frequency.

ORAL CORTICOSTEROIDS

In patients with lung disease, the use of oral corticosteroids is associated with a dose-dependent increase in the odds of vertebral, hip, rib, or sternal fracture; cataracts; muscle weakness; bruising; and opportunistic infections, such as oral candidiasis.⁸⁶ Because of these side effects, the use of oral corticosteroids in asthma is generally restricted to those patients with severe persistent asthma whose symptoms are not controlled despite aggressive treatment with inhaled corticosteroids, other long-term controller agents, and aggressive treatment of environmental factors and comorbid conditions. Similarly, oral corticosteroids should not be used in the routine management of stable COPD.

Assessing spirometric response to an oral corticosteroid trial in COPD is not a useful technique for identifying patients who will respond to inhaled corticosteroids. In a secondary analysis of data from ISOLDE (in which all subjects received oral prednisolone before fluticasone), Burge et al⁷⁴ reported that the overall response to prednisolone was minimal (mean increase in FEV₁, 69 mL) and unrelated to baseline FEV₁, bronchodilator responsiveness, and subsequent decrease in FEV₁ or response to inhaled fluticasone.⁸⁷

THEOPHYLLINE

Theophylline has a role in the treatment of both COPD and asthma. The exact mechanism by which theophylline has its effect remains unclear, but it is likely related to molecular effects that include phosphodiesterase inhibition, blockade of the adenosine receptor, and effects on calcium flux in the airway smooth muscle.⁸⁸ Renewed interest in theophylline has been generated by increased evidence that it has specific anti-inflammatory effects.⁸⁹ The use of low-dose theophylline appears to reduce the

number of activated lymphocytes in the peripheral blood after allergen challenge,⁹⁰ and in subjects with nocturnal asthma, theophylline results in significant reductions in the percentage of bronchoalveolar lavage neutrophils and eosinophils at 4 AM.⁹¹ Theophylline also protects against airway responsiveness in asthma,^{92,93} but despite the anti-inflammatory effects of theophylline, the results from multiple clinical trials indicate that methyl xanthines are inferior to inhaled corticosteroids in the treatment of chronic asthma.

In patients with COPD, theophylline can be considered as an addition to inhaled bronchodilator therapy because of its ability to provide additional improvement in lung function and symptoms when added to inhaled bronchodilators.^{94,95} Because it has significant toxic potential, particularly in older patients with multiple comorbidities treated with multiple medications, frequent monitoring for supratherapeutic levels, adverse drug reactions, and drug-drug interactions is critical. Oral phosphodiesterase 4 inhibitors are currently being evaluated in patients with COPD. Early clinical trials have demonstrated that members of this class of drugs are effective bronchodilators, but additional safety and efficacy data are needed before the role of these medications in COPD pharmacotherapy can be determined.⁹⁶

LEUKOTRIENE MODIFIERS

Leukotriene modifiers do not currently have a defined role in the treatment of COPD. Montelukast has been shown in one study of subjects with moderate and severe COPD to attenuate the bronchoconstrictor response to hypertonic saline, an effect that appears to be greater in more severe disease,⁹⁷ and zafirlukast has been demonstrated in a small study to provide modest bronchodilation in patients with COPD.⁹⁸

NONDRUG THERAPIES FOR THE TREATMENT OF COPD

In patients with moderate or severe COPD, pulmonary rehabilitation improves exercise capacity, dyspnea, and quality of life⁹⁹ and reduces the number and duration of respiratory disease-related hospitalizations.¹⁰⁰ Rehabilitation, which is most effective when delivered as a multifaceted program incorporating individually tailored aerobic physical training, comprehensive disease education, psychosocial counseling, and nutritional support, is appropriate for patients who are experiencing significant exertional symptoms.¹⁰¹ Although nutritional support is important for patients with COPD and reduced body mass index, as suggested by an inverse relationship between body mass and respiratory mortality,¹⁰² there is as of yet no evidence that enhanced nutrition improves body weight, lung function, exercise capacity, or mortality.¹⁰³

Abnormal gas exchange is an important complication of advanced COPD. Hypoxemia, which develops as

a result of worsening ventilation-perfusion mismatch, is the most important complication for which the clinician should be vigilant. Two important studies demonstrated that mortality is reduced by treatment with supplemental oxygen for more than 15 hours per day,^{104,105} and physicians must be aware of and test for hypoxemia in patients with moderate-to-severe disease. Most guidelines suggest that oxygen should be initiated in stable patients if the resting arterial partial pressure of oxygen is less than 55 mm Hg or if the oxygen saturation is 88% or less. However, these recommendations might not identify all patients who benefit from supplemental oxygen. For example, even in patients in whom desaturation does not occur during exercise, the use of supplemental oxygen substantially improves training intensity and exercise tolerance.¹⁰⁶ Supplemental oxygen should be titrated to maintain an oxygen saturation of 90% or greater at all times. Because patients might be normoxic at rest but desaturate with exertion or sleep, pulse oximetry should be performed during all 3 conditions, with oxygen prescribed to maintain normal saturation at all times.

In advanced disease hypercapnia (alveolar hypoventilation) occurs as a result of increased dead space or increased work of breathing with enhanced carbon dioxide production. Inhaled bronchodilators can help reduce work of breathing and improve gas exchange in some patients with alveolar hypoventilation. Noninvasive positive-pressure ventilation can improve hypercapnia over the short term,¹⁰⁷ but this improvement often comes at the cost of added hyperinflation.¹⁰⁸ A 2-year study of noninvasive positive-pressure ventilation plus supplemental oxygen in patients with alveolar hypoventilation demonstrated improvements in shortness of breath and quality of life but yielded only small reductions in arterial carbon dioxide.¹⁰⁹

Surgery is an option for patients with end-stage emphysema. The National Emphysema Treatment Trial reported that the addition of lung volume reduction surgery to optimal medical therapy and rehabilitation led to an overall improvement in exercise capacity and survival in a subgroup of patients with reduced exercise capacity and predominantly upper-lobe emphysema.¹¹⁰ Overall mortality did not improve, however, and increased mortality was observed in a subgroup of patients with FEV₁ values of 20% of predicted value or less and homogenous emphysema or diffusion capacity for carbon monoxide of less than 20% of predicted value.¹¹¹ Single-lung transplantation is an alternative surgical option for patients with end-stage emphysema with a postbronchodilator FEV₁ value of 25% of predicted value or less and complications such as pulmonary hypertension, marked hypoxemia, and hypercapnia.¹¹²

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