Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease

NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary

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PREFACE

Chronic obstructive pulmonary disease (COPD) is a major public health problem. It is the fourth leading cause of chronic morbidity and mortality in the United States (1) and is projected to rank fifth in 2020 as a worldwide burden of disease according to a study published by the World Bank/World Health Organization (2). Yet, COPD fails to receive adequate attention from the health care community and government officials. With these concerns in mind, a committed group of scientists encouraged the U.S. National Heart, Lung, and Blood Institute and the World Health Organization to form the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Among GOLD's important objectives are to increase awareness of COPD and to help the thousands of people who suffer from this disease and die prematurely from COPD or its complications.

The first step in the GOLD program was to prepare a consensus Workshop Report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*. The GOLD Expert Panel, a distinguished group of health professionals from the fields of respiratory medicine, epidemiology, socioeconomics, public health, and health education, reviewed existing COPD guidelines, as well as new information on pathogenic mechanisms of COPD as they developed a consensus document. Many recommendations will require additional study and evaluation as the GOLD program is implemented.

A major problem is the incomplete information about the causes and prevalence of COPD, especially in developing countries. While cigarette smoking is a major known risk factor, much remains to be learned about other causes of this disease. The GOLD Initiative will bring COPD to the attention of governments, public health officials, health care workers, and the general public, but a concerted effort by all involved in health care will be necessary to control this major public health problem.

I would like to acknowledge the dedicated individuals who prepared the Workshop Report and the effective leadership of the Workshop Chair, Professor Romain Pauwels. It is a privilege for the National Heart, Lung, and Blood Institute to serve as one of the cosponsors. We look forward to working with the

World Health Organization, and all other interested organizations and individuals, to meet the goals of the GOLD Initiative.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. COPD is currently the fourth leading cause of death in the world (3), and further increases in the prevalence and mortality of the disease can be predicted in the coming decades. A unified international effort is required to reverse these trends.

The **G**lobal Initiative for Chronic **O**bstructive **L**ung **D**isease (**GOLD**) is a collaborative project of the U.S. National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO). Its goals are to increase awareness of COPD and decrease morbidity and mortality from this disease. GOLD aims to improve prevention and management of COPD through a concerted worldwide effort of people involved in all facets of health care and health care policy, and to encourage a renewed research interest in this extremely prevalent disease.

TABLE 1. DESCRIPTION OF LEVELS OF EVIDENCE

Evidence Category	Sources of Evidence	Definition
A	RCTs. Rich body of data.	Evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	RCTs. Limited body of data.	Evidence is from endpoints of intervention studies that include only a limited number of patients, *post hoc* or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, or they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials. Observational studies.	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D	Panel Consensus Judgment.	This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.

Definition of abbreviation: RCT = randomized controlled trial.

The GOLD Workshop Report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*, presents a COPD management plan with four components: (*1*) Assess and Monitor Disease; (*2*) Reduce Risk Factors; (*3*) Manage Stable COPD; (*4*) Manage Exacerbations. The Workshop Report is based on the best-validated current concepts of COPD pathogenesis and the available evidence on the most appropriate management and prevention strategies. It has been developed by individuals with expertise in COPD research and patient care and extensively reviewed by many experts and scientific societies. Before its release for publication, the Workshop Report was reviewed by the NHLBI and the WHO. This Executive Summary provides key information about COPD; the full Workshop Report provides more details.

In Section 3, Four Components of COPD Management, levels of evidence are assigned to statements, where appropriate, using a system developed by the NHLBI (Table 1). Levels of evidence are indicated in parentheses after the relevant statement, e.g., (Evidence A).

DEFINITION AND CLASSIFICATION OF SEVERITY

Definition

COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

A diagnosis of COPD should be considered in any patient who has symptoms of cough, sputum production, or dyspnea, and/or a history of exposure to risk factors for the disease. The diagnosis is confirmed by spirometry. The presence of a post-bronchodilator $FEV_1 < 80\%$ of the predicted value in combination with an $FEV_1/FVC < 70\%$ confirms the presence of airflow limitation that is not fully reversible. Where spirometry is unavailable, the diagnosis of COPD should be made using all available tools. Clinical symptoms and signs, such as ab-

TABLE 2. CLASSIFICATION OF COPD BY SEVERITY

Stage	Characteristics
0: At Risk	Normal spirometry Chronic symptoms (cough, sputum production)
I: Mild COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geqslant 80\%$ predicted With or without chronic symptoms (cough, sputum production)
II: Moderate COPD	$FEV_1/FVC < 70\%$ $30\% \leqslant FEV_1 < 80\%$ predicted (IIA: $50\% \leqslant FEV_1 < 80\%$ predicted) (IIB: $30\% \leqslant FEV_1 < 50\%$ predicted) With or without chronic symptoms (cough, sputum production, dyspnea)
III: Severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ predicted, or the presence of respiratory failure,* or clinical signs of right heart failure

* Respiratory failure: $Pa_{O_2} < 8.0$ kPa (60 mm Hg) with or without $Pa_{CO_2} > 6.7$ kPa (50 mm Hg) while breathing air at sea level.

normal shortness of breath and increased forced expiratory time, can be used to help with the diagnosis. A low peak flow is consistent with COPD, but has poor specificity because it can be caused by other lung diseases and by poor performance. In the interest of improving the diagnosis of COPD, every effort should be made to provide access to standardized spirometry. Chronic cough and sputum production often precede the development of airflow limitation by many years, although not all individuals with cough and sputum production go on to develop COPD.

Classification of Severity

For educational reasons, a simple classification of disease severity into four stages is recommended (Table 2). The management of COPD is largely symptom-driven, and there is only an imperfect relationship between the degree of airflow limitation and the presence of symptoms. The staging, therefore, is a pragmatic approach aimed at practical implementation and should only be regarded as an educational tool, and a very general indication of the approach to management. All FEV_1 values refer to postbronchodilator FEV_1.

Stage 0: At Risk. Characterized by chronic cough and sputum production. Lung function, as measured by spirometry, is still normal.

Stage I: Mild COPD. Characterized by mild airflow limitation ($FEV_1/FVC < 70\%$ but $FEV_1 \geqslant 80\%$ predicted) and usually, but not always, by chronic cough and sputum production. At this stage, the individual may not even be aware that his or her lung function is abnormal.

Stage II: Moderate COPD. Characterized by worsening airflow limitation ($30\% \leqslant FEV_1 < 80\%$ predicted) and usually the progression of symptoms, with shortness of breath typically developing on exertion. This is the stage at which patients typically seek medical attention because of dyspnea or an exacerbation of their disease. The division in Stages IIA and IIB is based on the fact that exacerbations are especially seen in patients with an FEV_1 below 50% predicted. The presence of repeated exacerbations has an impact on the quality of life of patients and requires appropriate management.

Stage III: Severe COPD. Characterized by severe airflow limitation ($FEV_1 < 30\%$ predicted) or the presence of respiratory failure or clinical signs of right heart failure. Patients may have severe (Stage III) COPD even if the FEV_1 is $> 30\%$ predicted, whenever these complications are present. At this stage, quality of life is appreciably impaired and exacerbations may be life-threatening.

Poorly reversible airflow limitation associated with bronchiectasis, cystic fibrosis, tuberculosis, or asthma is not included except insofar as these conditions overlap with COPD. In many developing countries both pulmonary tuberculosis and COPD are common. Therefore, in all subjects with symptoms of COPD, a possible diagnosis of tuberculosis should be considered, especially in areas where this disease is known to be prevalent. In countries in which the prevalence of tuberculosis is greatly diminished, the possible diagnosis of this disease is sometimes overlooked.

Pathogenesis

COPD is characterized by chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature. Macrophages, T lymphocytes (predominately $CD8^+$), and neutrophils are increased in various parts of the lung. Activated inflammatory cells release a variety of mediators—including leukotriene B4 (LTB_4) (4), interleukin-8 (IL-8) (5–7), tumor necrosis factor-α (TNF-α) (5, 8), and others—capable of damaging lung structures or sustaining neutrophilic inflammation. In addition to inflammation, two other processes thought to be important in the pathogenesis of COPD are an imbalance of proteinases and antiproteinases in the lung, and oxidative stress. Inflammation of the lungs is caused by exposure to inhaled noxious particles and gases. Cigarette smoke can induce inflammation and directly damage the lungs (9–14). Although fewer data are available, it is likely that other COPD risk factors initiate a similar inflammatory process (15–19). It is believed that this inflammation can then lead to COPD.

Pathology

Pathologic changes characteristic of COPD are found in the central airways, peripheral airways, lung parenchyma, and pulmonary vasculature. In the central airways—the trachea, bronchi, and bronchioles greater than 2 to 4 mm in internal diameter—inflammatory cells infiltrate the surface epithelium (9, 20, 21). Enlarged mucus-secreting glands and an increase in the number of goblet cells are associated with mucus hypersecretion. In the peripheral airways—small bronchi and bronchioles that have an internal diameter of less than 2 mm—chronic inflammation leads to repeated cycles of injury and repair of the airway wall (22). The repair process results in a structural remodeling of the airway wall, with increasing collagen content and scar tissue formation, that narrows the lumen and produces fixed airways obstruction (23).

Destruction of the lung parenchyma in patients with COPD typically occurs as centrilobular emphysema. This involves dilatation and destruction of the respiratory bronchioles (24). These lesions occur more frequently in the upper lung regions in milder cases, but in advanced disease they may appear diffusely throughout the entire lung and also involve destruction of the pulmonary capillary bed. An imbalance of endogenous proteinases and antiproteinases in the lung resulting from genetic factors or the action of inflammatory cells and mediators, is thought to be a major mechanism behind emphysematous lung destruction. Oxidative stress, another consequence of inflammation, may also contribute (25).

Pulmonary vascular changes in COPD are characterized by a thickening of the vessel wall that begins early in the natural history of the disease. Thickening of the intima is the first structural change (26), followed by an increase in smooth muscle and the infiltration of the vessel wall by inflammatory cells (27). As COPD worsens, greater amounts of smooth muscle, proteoglycans, and collagen (28) further thicken the vessel wall.

Pathophysiology

Pathologic changes in the lungs lead to corresponding physiologic changes characteristic of the disease, including mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, and cor pulmonale. They usually develop in this order over the course of the disease. Mucus hypersecretion and ciliary dysfunction lead to chronic cough and sputum production. These symptoms can be present for many years before other symptoms or physiologic abnormalities develop. Expiratory airflow limitation, best measured through spirometry, is the hallmark physiologic change of COPD and the key to diagnosis of the disease. It is primarily caused by fixed airway obstruction and the consequent increase in airway resistance. Destruction of alveolar attachments, which inhibits the ability of the small airways to maintain patency, plays a smaller role.

In advanced COPD, peripheral airways obstruction, parenchymal destruction, and pulmonary vascular abnormalities reduce the lung's capacity for gas exchange, producing hypoxemia and, later on, hypercapnia. Pulmonary hypertension,

which develops late in the course of COPD (Stage III: Severe COPD), is the major cardiovascular complication of COPD and is associated with the development of cor pulmonale and a poor prognosis (29). The prevalence and natural history of cor pulmonale in COPD are not yet clear.

BURDEN OF COPD

Epidemiology

Most of the information available on COPD prevalence, morbidity, and mortality comes from developed countries. Even in these countries, accurate epidemiologic data on COPD are difficult and expensive to collect. Prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced. The imprecise and variable definitions of COPD have made it hard to quantify the morbidity and mortality of this disease in developed (30) and developing countries. Mortality data also underestimate COPD as a cause of death because the disease is more likely to be cited as a contributory than as an underlying cause of death, or may not be cited at all (31).

Prevalence. In the Global Burden of Disease Study conducted under the auspices of the WHO and the World Bank (2, 32), the worldwide prevalence of COPD in 1990 was estimated to be 9.34/1,000 in men and 7.33/1,000 in women. However, these estimates include all ages and underestimate the true prevalence of COPD in older adults. The prevalence of COPD is highest in countries where cigarette smoking has been, or still is, very common, whereas the prevalence is lowest in countries where smoking is less common, or total tobacco consumption per individual is low.

Morbidity. The limited data that are available indicate that morbidity due to COPD increases with age and is greater in men than women (1). COPD is responsible for a significant part of physician visits, emergency department visits, and hospitalizations.

Mortality. COPD is currently the fourth leading cause of death in the world (3), and further increases in the prevalence and mortality of the disease can be predicted in the coming decades (2, 32). In the United States, COPD death rates are very low among people younger than 45 yr of age but then increase with age, and COPD becomes the fourth or fifth leading cause of death among those over 45 (1).

Economic and Social Burden of COPD

Table 3 provides an understanding of the relative economic burden of COPD in four countries with Western styles of medical practice and social or private insurance structures. Similar data from developing countries are not available. The Global Burden of Disease Study (2, 32) estimated the fraction of mortality and disability attributable to major diseases and injuries using a composite measure of the burden of each health problem, the disability-adjusted life year (DALY = the sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of disability). According to projections, COPD will be the fifth leading cause of DALYs lost worldwide in 2020 (in 1990 it ranked twelfth), behind ischemic heart disease, major depression, traffic accidents, and cerebrovascular disease (Table 4).

TABLE 3. FOUR-COUNTRY COMPARISON OF COPD DIRECT AND INDIRECT COSTS

Country (Ref.)	Year	Direct Cost (*US$ Millions*)	Indirect Cost (*US$ Millions*)	Total (*US$ Millions*)	Per Capita* (*US$*)
U.K. (208)	1996	778	3,312	4,090	65
Netherlands (209)	1993	256	N/A†	N/A†	N/A†
Sweden (210)	1991	179	281	460	60
U.S. (1)	1993	14,700	9,200	23,900	87

* Per capita valuation based on 1993 population estimates from the United Nations Population Council and expressed in 1993 US dollars.

† N/A = not available; the authors did not provide estimates of indirect costs.

Risk Factors

Risk factors for COPD include both host factors and environmental exposures, and the disease usually arises from an interaction between these two types of factors. The host factor that is best documented is a rare hereditary deficiency of α_1-antitrypsin. Other genes involved in the pathogenesis of COPD have not yet been identified. The major environmental factors are tobacco smoke; heavy exposure to occupational dusts and chemicals (vapors, irritants, and fumes); and indoor/outdoor air pollution. The role of sex as a risk factor for COPD remains unclear. In the past, most studies showed that COPD prevalence and mortality were greater among men than women (33–36). More recent studies (1, 37) from developed countries show that the prevalence of the disease is almost equal in men and women, which probably reflects changing patterns of tobacco smoking. Some studies have in fact suggested that women are more susceptible to the effects of tobacco smoke than men (35, 38). This is an important question given the increasing rate of smoking among women in both developed and developing countries.

Host Factors

Genes. It is believed that many genetic factors increase (or decrease) a person's risk of developing COPD. The genetic risk factor that is best documented is a rare hereditary deficiency of α_1-antitrypsin (39–41). Premature and accelerated development of panlobular emphysema and decline in lung function occurs in many smokers and nonsmokers with the severe deficiency, although smoking increases the risk appreciably. Other genes involved in the pathogenesis of COPD have not yet been identified.

Airway hyperresponsiveness. Asthma and airway hyperresponsiveness, identified as risk factors that contribute to the development of COPD (42), are complex disorders related to a number of genetic and environmental factors. How they influence the development of COPD is unknown. Airway hyperresponsiveness may also develop after exposure to tobacco smoke or other environmental insults and thus may be a result of smoking-related airway disease.

TABLE 4. LEADING CAUSES OF DISABILITY-ADJUSTED LIFE YEARS (DALYs) LOST WORLDWIDE: 1990 AND 2020 (PROJECTED) (2, 32)

Disease or Injury	Rank 1990	Percent of Total DALYs	Rank 2020	Percent of Total DALYs
Lower respiratory infections	1	8.2	6	3.1
Diarrheal diseases	2	7.2	9	2.7
Perinatal period conditions	3	6.7	11	2.5
Unipolar major depression	4	3.7	2	5.7
Ischemic heart disease	5	3.4	1	5.9
Cerebrovascular disease	6	2.8	4	4.4
Tuberculosis	7	2.8	7	3.1
Measles	8	2.6	25	1.1
Road traffic accidents	9	2.5	3	5.1
Congenital anomalies	10	2.4	13	2.2
Malaria	11	2.3	19	1.5
COPD	12	2.1	5	4.1
Trachea, bronchus, lung cancer	33	0.6	15	1.8

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Lung growth. Lung growth is related to processes occurring during gestation, birth weight, and exposures during childhood (43–47). Reduced maximal attained lung function (as measured by spirometry) may identify individuals who are at increased risk for the development of COPD (48).

Exposures

Tobacco smoke. Cigarette smokers have a higher prevalence of lung-function abnormalities and respiratory symptoms, a greater annual rate of decline in FEV_1, and higher death rates for COPD than nonsmokers. Pipe and cigar smokers have higher COPD morbidity and mortality rates than nonsmokers, although their rates are lower than those for cigarette smokers (49). Not all smokers develop clinically significant COPD, which suggests that genetic factors must modify each individual's risk. Passive exposure to cigarette smoke may also contribute to respiratory symptoms and COPD by increasing the lungs' total burden of inhaled particulates and gases (33, 50, 51). Smoking during pregnancy may also pose a risk for the fetus, by affecting lung growth and development *in utero* and possibly the priming of the immune system (47, 52).

Occupational dusts and chemicals. When the exposures are sufficiently intense or prolonged, occupational dusts and chemicals (vapors, irritants, fumes) can cause COPD independently of cigarette smoking and increase the risk of the disease in the presence of concurrent cigarette smoking (53). Exposure to particulate matter, irritants, organic dusts, and sensitizing agents can cause an increase in airway hyperresponsiveness (54), especially in airways already damaged by other occupational exposures, cigarette smoke, or asthma.

Outdoor and indoor air pollution. High levels of urban air pollution are harmful to persons with existing heart or lung disease. The role of outdoor air pollution in causing COPD is unclear, but appears to be small when compared with cigarette smoking. Indoor air pollution from biomass fuel, burned for cooking and heating in poorly vented dwellings, has been implicated as a risk factor for the development of COPD (55–64).

Infections. A history of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood (48). However, viral infections may be related to another factor, e.g., low birth weight, that itself is related to COPD.

Socioeconomic status. There is evidence that the risk of developing COPD is inversely related to socioeconomic status (65). It is not clear, however, whether this pattern reflects exposures to indoor and outdoor air pollutants, crowding, poor nutrition, or other factors that are related to socioeconomic status (64, 66).

THE FOUR COMPONENTS OF COPD MANAGEMENT

Introduction

An effective COPD management plan includes four components: (*1*) Assess and Monitor Disease; (*2*) Reduce Risk Factors; (*3*) Manage Stable COPD; (*4*) Manage Exacerbations.

The goals of effective COPD management are to:

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Reduce mortality

These goals should be reached with a minimum of side effects from treatment, a particular challenge in patients with COPD where comorbidities are common. The extent to which these goals can be realized varies with each individual, and some treatments will produce benefits in more than one area. In selecting a treatment plan, the benefits and risks to the individual and the costs, direct and indirect, to the community must be considered. Patients should be identified before the end stage of the illness, when disability is substantial. However, the benefits of spirometric screening, of either the general population or smokers, are still unclear. Educating patients and physicians to recognize that cough, sputum production, and especially breathlessness are not trivial symptoms is an essential aspect of the public health care of this disease.

Reduction of therapy once symptom control has been achieved is not normally possible in COPD. Further deterioration of lung function usually requires the progressive introduction of more treatments, both pharmacologic and nonpharmacologic, to attempt to limit the impact of these changes. Acute exacerbations of signs and symptoms, a hallmark of COPD, impair patients' quality of life and decrease their health status. Appropriate treatment and measures to prevent further exacerbations should be implemented as quickly as possible.

Component 1: Assess and Monitor Disease

Key Points

- Diagnosis of COPD is based on a history of exposure to risk factors and the presence of airflow limitation that is not fully reversible, with or without the presence of symptoms.
- Patients who have chronic cough and sputum production with a history of exposure to risk factors should be tested for airflow limitation, even if they do not have dyspnea.
- For the diagnosis and assessment of COPD, spirometry is the gold standard as it is the most reproducible, standardized, and objective way of measuring airflow limitation. $FEV_1/FVC < 70\%$ and a postbronchodilator $FEV_1 < 80\%$ predicted confirms the presence of airflow limitation that is not fully reversible.
- Health care workers involved in the diagnosis and management of patients with COPD should have access to spirometry.

TABLE 5. KEY INDICATORS FOR CONSIDERING A DIAGNOSIS OF COPD*

Chronic cough:	Present intermittently or every day
	Often present throughout the day; seldom only nocturnal
Chronic sputum Production	Any pattern of chronic sputum production may indicate COPD
Dyspnea that is:	Progressive (worsens over time)
	Persistent (present every day)
	Described by the patient as: "increased effort to breathe," "heaviness," "air hunger," or "gasping"
	Worse on exercise
	Worse during respiratory infections
History of exposure to risk factors, especially:	Tobacco smoke
	Occupational dusts and chemicals
	Smoke from home cooking and heating fuels

* Consider COPD and perform spirometry if any of these indicators are present. These indicators are not diagnostic by themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is needed to establish a diagnosis of COPD.

- Measurement of arterial blood gas tensions should be considered in all patients with $FEV_1 < 40\%$ predicted or clinical signs suggestive of respiratory failure or right heart failure.

Diagnosis. A diagnosis of COPD (Table 5) should be considered in any patient who has cough, sputum production, dyspnea, or a history of exposure to risk factors for the disease. The diagnosis is confirmed by an objective measure of airflow limitation, preferably spirometry.

Assessment of symptoms. Chronic cough, usually the first symptom of COPD to develop (67), may initially be intermittent, but later is present every day, often throughout the day, and is seldom entirely nocturnal. In some cases, significant airflow limitation may develop without the presence of a cough. Small quantities of tenacious sputum are commonly raised by patients with COPD after coughing bouts. Dyspnea is the reason most patients seek medical attention and is a major cause of disability and anxiety associated with the disease. As lung function deteriorates, breathlessness becomes more intrusive. Wheezing and chest tightness are relatively nonspecific symptoms and may vary between days and over the course of a single day. An absence of wheezing or chest tightness does not exclude a diagnosis of COPD.

Medical history. A detailed medical history of a new patient known or thought to have COPD should assess:

1. Exposure to risk factors.
2. Past medical history, including asthma, allergy, sinusitis or nasal polyps, respiratory infections in childhood, and other respiratory diseases.
3. Family history of COPD or other chronic respiratory disease.
4. Pattern of symptom development.
5. History of exacerbations or previous hospitalizations for respiratory disorder.
6. Presence of comorbidities, such as heart disease and rheumatic disease, that may also contribute to restriction of activity.
7. Appropriateness of current medical treatments.
8. Impact of disease on patient's life, including limitation of activity; missed work and economic impact; effect on family routines; and feelings of depression or anxiety.
9. Social and family support available to the patient.
10. Possibilities for reducing risk factors, especially smoking cessation.

Physical examination. Though an important part of patient care, a physical examination is rarely diagnostic in COPD. Physical signs of airflow limitation are rarely present until significant impairment of lung function has occurred (68, 69), and their detection has a relatively low sensitivity and specificity.

Measurement of airflow limitation. To help identify patients earlier in the course of the disease, spirometry should be performed for patients who have chronic cough and sputum production and a history of exposure to risk factors, even if they do not have dyspnea. Spirometry should measure the maximal volume of air forcibly exhaled from the point of maximal inhalation (FVC) and the volume of air exhaled during the first second of this maneuver (FEV_1), and the ratio of these two measurements (FEV_1/FVC) should be calculated. Patients with COPD typically show a decrease in both FEV_1 and FVC. The presence of a postbronchodilator $FEV_1 < 80\%$ of the predicted value in combination with an $FEV_1/FVC < 70\%$ confirms the presence of airflow limitation that is not fully reversible. The FEV_1/FVC on its own is a more sensitive measure of airflow limitation, and an $FEV_1/FVC < 70\%$ is considered an early sign of airflow limitation in patients whose FEV_1 remains normal ($\geq 80\%$ predicted). This approach to defining airflow limitation is a pragmatic one in view of the fact that universally applicable reference values for FEV_1 and FVC are not available.

Assessment of severity. Assessment of severity (Table 2) is based on the level of symptoms, severity of the spirometric abnormality, and the presence of complications such as respiratory failure and right heart failure.

Additional investigations. For patients in Stage II: Moderate COPD and beyond, the following additional investigations may be useful:

1. *Bronchodilator reversibility testing.* Generally performed only once, at the time of diagnosis, this test is useful to help rule out a diagnosis of asthma, to establish a patient's best attainable lung function, to gauge a patient's prognosis, and to guide treatment decisions. However, even patients who do not show a significant FEV_1 response to a short-acting bronchodilator test can benefit symptomatically from long-term bronchodilator treatment.
2. *Glucocorticosteroid reversibility testing.* The simplest, and potentially safest, way to identify patients most likely to respond to long-term glucocorticosteroid treatment is with a treatment trial of inhaled glucocorticosteroids for 6 wk to 3 mo, using as criteria for glucocorticosteroid reversibility an FEV_1 increase of 200 ml and 15% above baseline (70, 71). The response to glucocorticosteroids should be evaluated with respect to the postbronchodilator FEV_1 (that is, the effect of treatment with inhaled glucocorticosteroids should be in addition to that of regular treatment with a bronchodilator).
3. *Chest X-ray.* A chest radiograph is seldom diagnostic in COPD unless obvious bullous disease is present, but it is valuable in excluding alternative diagnoses. Computed tomography (CT) of the chest is not routinely recommended. However, when there is doubt about the diagnosis of COPD, high-resolution CT (HRCT) might help in the differential diagnosis. In addition, if a surgical procedure such as bullectomy or lung volume reduction is contemplated, chest CT is helpful.
4. *Arterial blood gas measurement.* In advanced COPD, measurement of arterial blood gases is important. This test should be performed in patients with $FEV_1 < 40\%$ predicted or with clinical signs suggestive of respiratory failure or right heart failure. Clinical signs of respiratory failure or right heart failure include central cyanosis, ankle swelling, and an increase in the jugular venous pressure. Clinical signs of hypercapnia are extremely nonspecific outside of acute exacerbations. Respiratory failure is indicated by $Pa_{O_2} < 8.0$ kPa (60 mm Hg) with or without $Pa_{CO_2} > 6.0$ kPa (45 mm Hg) while breathing air at sea level. Measurement of arterial blood gases should be obtained by arterial puncture; finger or ear oximeters for assessing Sa_{O_2} are less reliable.
5. α_1-Antitrypsin deficiency screening. In patients who develop COPD at a young age (< 45 yr) or who have a strong family history of the disease, it may be valuable to identify coexisting α_1-antitrypsin deficiency. This could lead to family screening and appropriate counseling.

Differential diagnosis. A major differential diagnosis is asthma. In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiologic testing techniques. In these cases, current management is similar to that of asthma. Other potential diagnoses are usually easier to distinguish from COPD (Table 6).

Ongoing Monitoring and Assessment

Monitor disease progression and development of complications. COPD is usually a progressive disease, and a patient's lung function can be expected to worsen over time, even with the best available care. Symptoms and objective measures of airflow limitation should be monitored for development of complications and to determine when to adjust therapy.

Follow-up visits should include a discussion of new or worsening symptoms. Spirometry should be performed if there is a substantial increase in symptoms or a complication. Measurement of arterial blood gas tensions should be performed in all patients with an $FEV_1 < 40\%$ predicted or clinical signs of respiratory failure or right heart failure. Elevation of the jugular venous pressure and the presence of pitting ankle edema are often the most useful findings suggestive of right heart failure in clinical practice. Measurement of pulmonary arterial pressure is not recommended in clinical practice as it does not add practical information beyond that obtained from a knowledge of Pa_{O_2}.

TABLE 6. DIFFERENTIAL DIAGNOSIS OF COPD

Diagnosis	Suggestive Features*
COPD	Onset in mid-life Symptoms slowly progressive Long smoking history Dyspnea during exercise Largely irreversible airflow limitation
Asthma	Onset early in life (often childhood) Symptoms vary from day to day Symptoms at night/early morning Allergy, rhinitis, or eczema also present Family history of asthma Largely reversible airflow limitation
Congestive heart failure	Fine basilar crackles on auscultation Chest X-ray shows dilated heart, pulmonary edema Pulmonary function tests indicate volume restriction, not airflow limitation
Bronchiectasis	Large volumes of purulent sputum Commonly associated with bacterial infection Coarse crackles/clubbing on auscultation Chest X-ray/CT shows bronchial dilation, bronchial wall thickening
Tuberculosis	Onset all ages Chest X-ray shows lung infiltrate or nodular lesions Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Onset in younger age, nonsmokers May have history of rheumatoid arthritis or fume exposure CT on expiration shows hypodense areas
Diffuse panbronchiolitis	Most patients are male and nonsmokers Almost all have chronic sinusitis Chest X-ray and HRCT show diffuse small centrilobular nodular opacities and hyperinflation

* These features tend to be characteristic of the respective diseases, but do not occur in every case. For example, a person who has never smoked may develop COPD (especially in the developing world, where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even elderly patients.

Monitor pharmacotherapy and other medical treatment. In order to adjust therapy appropriately as the disease progresses, each follow-up visit should include a discussion of the current therapeutic regimen. Dosages of various medications, adherence to the regimen, inhaler technique, effectiveness of the current regime at controlling symptoms, and side effects of treatment should be monitored.

Monitor exacerbation history. Frequency, severity, and likely causes of exacerbations should be evaluated. Increased sputum volume, acutely worsening dyspnea, and the presence of purulent sputum should be noted. Severity can be estimated by the increased need for bronchodilator medication or glucocorticosteroids and by the need for antibiotic treatment. Hospitalizations should be documented, including the facility, duration of stay, and any use of critical care or intubation.

Monitor comorbidities. In treating patients with COPD, it is important to consider the presence of concomitant conditions such as bronchial carcinoma, tuberculosis, sleep apnea, and left heart failure. The appropriate diagnostic tools (chest radiograph, electrocardiogram [ECG], etc.) should be used whenever symptoms (e.g., hemoptysis) suggest one of these conditions.

Component 2: Reduce Risk Factors

Key Points

- Reduction of total personal exposure to tobacco smoke, occupational dusts and chemicals, and indoor and outdoor air pollutants are important goals to prevent the onset and progression of COPD.
- Smoking cessation is the single most effective—and cost-effective—way to reduce the risk of developing COPD and stop its progression (Evidence A).
- Brief tobacco dependence treatment is effective (Evidence A) and every tobacco user should be offered at least this treatment at every visit to a health care provider.
- Three types of counseling are especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment (Evidence A).
- Several effective pharmacotherapies for tobacco dependence are available (Evidence A), and at least one of these medications should be added to counseling if necessary and in the absence of contraindications.
- Progression of many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases (Evidence B).

TABLE 7. STRATEGIES TO HELP THE PATIENT WILLING TO QUIT SMOKING (75)

1. ASK: Systematically identify all tobacco users at every visit.
   Implement an office-wide system that ensures that, for every patient at every clinic visit, tobacco-use status is queried and documented.
2. ADVISE: Strongly urge all tobacco users to quit.
   In a clear, strong, and personalized manner, urge every tobacco user to quit.
3. ASSESS: Determine willingness to make a quit attempt.
   Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 d).
4. ASSIST: Aid the patient in quitting.
   Help the patient with a quit plan; provide practical counseling; provide intratreatment social support; help the patient obtain extratreatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.
5. ARRANGE: Schedule follow-up contact.
   Schedule follow-up contact, either in person or via telephone.

Smoking Prevention and Cessation. Comprehensive tobacco control policies and programs with clear, consistent, and repeated nonsmoking messages should be delivered through every feasible channel. Legislation to establish smoke-free schools, public facilities, and work environments should be encouraged by government officials, public health workers, and the public. Smoking cessation is the single most effective—and cost-effective—way to reduce the risk of developing COPD and stop its progression. Even a brief, 3-min period of counseling to urge a smoker to quit can be effective, and at the very least this should be done for every smoker at every visit (72, 73). Health education, public policy, and information dissemination programs are all vital components in a comprehensive cessation effort.

Guidelines for smoking cessation. Guidelines for smoking cessation were published by the U.S. Agency for Health Care Policy and Research (AHCPR) in 1996 (74) and updated in 2000 by the U.S. Public Health Service in *Treating Tobacco Use and Dependence: A Clinical Practice Guideline* (75).

Smoking cessation intervention process. The Public Health Service Report recommends a five-step program for intervention (Table 7), which provides a strategic framework helpful to health care providers interested in helping their patients stop smoking. Three types of counseling are especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment (74–79) (Evidence A).

Pharmacotherapy. Numerous effective pharmacotherapies for smoking cessation now exist (75, 79, 80) (Evidence A). Except in the presence of special circumstances, pharmacotherapy is recommended when counseling is not sufficient to help patients quit smoking. Numerous studies indicate that nicotine replacement therapy in any form (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge) reliably increases long-term smoking abstinence rates (75, 80). The antidepressants bupropion and nortriptyline have also been shown to increase long-term quit rates, although fewer studies have been conducted with these medications (75, 80). The effectiveness of the antihypertensive drug clonidine is limited by side effects (80). Special consideration should be given before using pharmacotherapy in selected populations: people with medical contraindications, light smokers (fewer than 10 cigarettes/day), and pregnant and adolescent smokers.

Occupational Exposures. Although it is not known how many individuals are at risk of developing respiratory disease from occupational exposures in either developing or developed countries, many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases (81). Emphasis should be on primary prevention, which is best achieved by the elimination or reduction of exposures to various substances in the workplace. Secondary prevention, achieved through epidemiologic surveillance and early case detection, is also of great importance.

Indoor/Outdoor Air Pollution. Individuals experience diverse indoor and outdoor environments throughout the day, each of which has its own unique set of air contaminants. Although outdoor and indoor air pollution are generally thought of separately, the concept of total personal exposure may be more relevant for COPD. Reducing the risk from indoor and outdoor air pollution requires a combination of public policy and protective steps taken by individual patients.

The health care provider should consider susceptibility (including family history, exposure to indoor/outdoor pollution) for each individual patient (82). Those who are at high risk should avoid vigorous exercise outdoors during pollution episodes. If various solid fuels are used for cooking and heating, adequate ventilation should be encouraged. Persons with severe COPD should monitor public announcements of air quality and should stay indoors when air quality is poor. Under most circumstances, health care providers should not suggest respiratory protection as a method for reducing the risks of ambient air pollution. Air cleaners have not been shown to have health benefits, whether directed at pollutants generated by indoor sources or at those brought in with outdoor air.

Component 3: Manage Stable COPD

Key Points

- The overall approach to managing stable COPD should be characterized by a stepwise increase in treatment, depending on the severity of the disease.
- For patients with COPD, health education can play a role in improving skills, ability to cope with illness, and health status. It is effective in accomplishing certain goals, including smoking cessation (Evidence A).
- None of the existing medications for COPD has been shown to modify the long-term decline in lung function that is the hallmark of this disease (Evidence A). Therefore, pharmacotherapy for COPD is used to decrease symptoms and complications.
- Bronchodilator medications are central to the symptomatic management of COPD (Evidence A). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms.
- The principal bronchodilator treatments are β_2-agonists, anticholinergics, theophylline, and a combination of one or more of these drugs (Evidence A).
- Regular treatment with inhaled glucocorticosteroids should only be prescribed for symptomatic patients with COPD with a documented spirometric response to glucocorticosteroids or for those with an $FEV_1 < 50\%$ predicted and repeated exacerbations requiring treatment with antibiotics or oral glucocorticosteroids (Evidence B).
- Chronic treatment with systemic glucocorticosteroids should be avoided because of an unfavorable benefit-to-risk ratio (Evidence A).
- All patients with COPD benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue (Evidence A).
- The long-term administration of oxygen (> 15 h per day) to patients with chronic respiratory failure has been shown to increase survival (Evidence A).

Introduction. The overall approach to managing stable COPD should be characterized by a stepwise increase in treatment, depending on the severity of the disease. The management strategy is based on an individualized assessment of disease severity and response to various therapies. Disease severity is determined by the severity of symptoms and airflow limitation, as well as other factors such as the frequency and severity of exacerbations, complications, respiratory failure, comorbidities (cardiovascular disease, sleep-related disorders, etc.), and the general health status of the patient. Treatment depends on the patient's educational level and willingness to apply the recommended management, on cultural and local conditions, and on the availability of medications.

Education. Although patient education alone does not improve exercise performance or lung function (83–86), it can play a role in improving skills, ability to cope with illness, and health status (87). In addition, patient education is effective in accomplishing certain specific goals, including smoking cessation (38) (Evidence A), initiating discussions and understanding of advance directives and end-of-life issues (88) (Evidence

TABLE 8. THERAPY AT EACH STAGE OF COPD

Stage	Characteristics	Recommended Treatment	
All		Avoidance of risk factors Influenza vaccination	
0: At risk	Chronic symptoms (cough, sputum) Exposure to risk factors Normal spirometry		
I: Mild COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ predicted With or without symptoms	Short-acting bronchodilator when needed	
II: Moderate COPD	IIA $FEV_1/FVC < 70\%$ $50\% \leq FEV_1 < 80\%$ predicted With or without symptoms	Regular treatment with one or more bronchodilators Rehabilitation	Inhaled glucocorticosteroids if significant symptoms and lung function response
	IIB $FEV_1/FVC < 70\%$ $30\% \leq FEV_1 > 50\%$ predicted With or without symptoms	Regular treatment with one or more bronchodilators Rehabilitation	Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations
III: Severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ predicted or presence of respiratory failure or right heart failure	Regular treatment with one or more bronchodilators Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations Treatment of complications Rehabilitation Long-term oxygen therapy if respiratory failure Consider surgical treatments	

B), and improving patient responses to acute exacerbations (89, 90) (Evidence B).

Education may take place in many settings: consultations with physicians or other health care workers, home care or outreach programs, and comprehensive pulmonary rehabilitation programs. It should be tailored to the needs and environment of the patient, interactive, directed at improving quality of life, simple to follow, practical, and appropriate to the intellectual and social skills of the patient and the caregiver. The topics that seem most appropriate for an education program to cover include: smoking cessation; basic information about COPD and pathophysiology of the disease; general approach to therapy and specific aspects of medical treatment; self-management skills; strategies to help minimize dyspnea; advice about when to seek help; self-management and decision-making in exacerbations; and advance directives and end-of-life issues.

Pharmacologic Treatment. Pharmacologic therapy (Table 8) is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. None of the existing medications for COPD has been shown to modify the long-term decline in lung function that is the hallmark of this disease (38, 91–94) (Evidence A). However, this should not preclude efforts to use medications to control symptoms.

Bronchodilators. Bronchodilator medications are central to the symptomatic management of COPD (95–98) (Evidence A) (Table 9). They are given either on an as-needed basis for relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms. Dose–response relationships using FEV_1 as the outcome are relatively flat with all classes of bronchodilators. Side effects are pharmacologically predictable and dose-dependent. Adverse effects are less likely and resolve more rapidly after treatment withdrawal with inhaled than with oral treatment. When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential.

The classes of bronchodilator drugs commonly used in treating COPD, β_2-agonists, anticholinergics, and methylxanthines, are shown in Table 10. The choice depends on the availability of the medication and the patient's response. All categories of bronchodilators have been shown to increase exercise capacity in COPD, without necessarily producing significant changes in

TABLE 9. BRONCHODILATORS IN STABLE COPD

Bronchodilator medications are central to symptom management in COPD.
Inhaled therapy is preferred.
The choice between β_2-agonist, anticholinergic, theophylline, or combination therapy depends on availability and individual response in terms of symptom relief and side effects.
Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.
Long-acting inhaled bronchodilators are more convenient.
Combining bronchodilators may improve efficacy and decrease the risk of side effects compared with increasing the dose of a single bronchodilator.

TABLE 10. COMMONLY USED BRONCHODILATOR DRUGS

Drug*	Metered-dose Inhaler (μg)†	Nebulizer (mg)†	Oral (mg)	Duration of Action (h)
β_2-agonists				
Fenoterol	100–200	0.5–2.0	—	4–6
Salbutamol (albuterol)‡	100–200	2.5–5.0	4	4–6
Terbutaline	250–500	5–10	5	4–6
Formoterol	12–24	—	—	12+
Salmeterol	50–100	—	—	12+
Anticholinergics				
Ipratropium bromide	40–80	0.25–0.5	—	6–8
Oxitropium bromide	200	—	—	7–9
Methylxanthines§				
Aminophylline (SR)	—	—	225–450	Variable, up to 24
Theophylline (SR)	—	—	100–400	Variable, up to 24

* Not all products are available in all countries.
† Doses: β_2-agonists refer to average dose given up to 4 times daily for short-acting and 2 times daily for long-acting preparations; anticholinergics are usually given 3–4 times daily.
‡ Name in parentheses refers to North American generic term.
§ Methylxanthines require dose titration depending on side effects and plasma theophylline levels.

FEV_1 (99–101) (Evidence A). Regular treatment with short-acting bronchodilators is cheaper but less convenient than treatment with long-acting bronchodilators. The long-acting, inhaled β_2-agonist salmeterol has been shown to improve health status significantly in doses of 50 μg twice daily (102) (Evidence B). Similar data for short-acting β_2-agonists are not available. Use of inhaled ipratropium (an anticholinergic) four times daily also improves health status (Evidence B) (103). Theophylline is effective in COPD, but because of its potential toxicity, inhaled bronchodilators are preferred when available. All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations.

Combining drugs with different mechanisms and durations of action might increase the degree of bronchodilation for equivalent or lesser side effects. A combination of a short-acting β_2-agonist and the anticholinergic drug ipratropium in stable COPD produces greater and more sustained improvements in FEV_1 than either alone and does not produce evidence of tachyphylaxis over 90 d of treatment (104–106) (Evidence A). Combination of a β_2-agonist, an anticholinergic, or theophylline may produce additional improvements in lung function (104, 107–109) and health status (101, 104, 107, 110). Increasing the number of drugs usually increases costs, and an equivalent benefit may occur by increasing the dose of one bronchodilator when side effects are not a limiting factor. Detailed assessments of this approach have not been carried out.

Increasing the dose of either a β_2-agonist or an anticholinergic, especially when given by a wet nebulizer, appears to provide subjective benefit in acute episodes (111) (Evidence B). Some patients may request regular treatment with high-dose, nebulized bronchodilators (112), especially if they have experienced subjective benefit from this treatment during an acute exacerbation. Clear scientific evidence for this approach is lacking, but one option is to examine the improvement in mean daily peak expiratory flow (PEF) recording during 2 wk of treatment in the home and continue with nebulizer therapy if a significant improvement occurs (112). In general, nebulized therapy for a stable patient is not appropriate unless it has been shown to be better than conventional dose therapy.

Glucocorticosteroids. Prolonged treatment with inhaled glucocorticosteroids does not modify the long-term decline in FEV_1 in patients with COPD (91–94). Regular treatment with inhaled glucocorticosteroids is only appropriate for symptomatic COPD patients with a documented spirometric response to inhaled glucocorticosteroids (*see* Component 1) or in those with $FEV_1 < 50\%$ predicted (Stage IIB: Moderate COPD and Stage III: Severe COPD) and repeated exacerbations requiring treatment with antibiotics or oral glucocorticosteroids (91–94) (Evidence B). The dose–response relationships and long-term safety of inhaled glucocorticosteroids in COPD are not known. The present guidelines recommend a trial of 6 wk to 3 mo with inhaled glucocorticosteroids to identify COPD patients who may benefit from long-term inhaled glucocorticosteroid therapy. Many existing COPD guidelines recommend the use of a short course (2 wk) of oral glucocorticosteroids to identify patients with COPD who might benefit from long-term treatment with oral or inhaled glucocorticosteroids. There is mounting evidence, however, that a short course of oral glucocorticosteroids is a poor predictor of the long-term response to inhaled glucocorticosteroids in COPD (93, 113).

Long-term treatment with oral glucocorticosteroids is not recommended in COPD (114–116) (Evidence A). There is no evidence of long-term benefit from this treatment. Moreover, a side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy (115, 116), which contributes to muscle weakness, decreased functionality, and respiratory failure in patients with advanced COPD.

Other Pharmacologic Treatments

Vaccines. Influenza vaccines can reduce serious illness and death in patients with COPD by approximately 50% (117). Vaccines containing killed or live, inactivated viruses are recommended (118), and should be given once (in autumn) or twice (in autumn and winter) each year (Evidence A). A pneumococcal vaccine containing 23 virulent serotypes has been used but sufficient data to support its general use in COPD patients are lacking (119–121) (Evidence B).

α_1-Antitrypsin augmentation therapy. Young patients with severe hereditary α_1-antitrypsin deficiency and established emphysema may be candidates for α_1-antitrypsin augmentation therapy. However, this therapy is very expensive, is not available in most countries, and is not recommended for COPD that is not related to α_1-antitrypsin deficiency (Evidence C).

Antibiotics. The use of antibiotics, other than in treating infectious exacerbations of COPD and other bacterial infections, is not recommended (122, 123) (Evidence A).

Mucolytic (mucokinetic, mucoregulator) agents. (ambroxol, erdosteine, carbocysteine, iodinated glycerol): Although a few patients with viscous sputum may benefit from mucolytics (124, 125), the overall benefits seem to be very small. Therefore, the widespread use of these agents cannot be recommended on the basis of the present evidence (Evidence D).

Antioxidant agents. Antioxidants, in particular *N*-acetylcysteine, have been shown to reduce the frequency of exacerbations and could have a role in the treatment of patients with recurrent exacerbations (126–129) (Evidence B). However, before their routine use can be recommended, the results of ongoing trials will have to be carefully evaluated.

Immunoregulators (immunostimulators, immunomodulators). A study using an immunostimulator in COPD showed a decrease in the severity (though not in the frequency) of exacerbations (130), but these results have not been duplicated. Thus, the regular use of this therapy cannot be recommended based on the present evidence (131) (Evidence B).

Antitussives. Cough, although sometimes a troublesome symptom in COPD, has a significant protective role (132). Thus, the regular use of antitussives is contraindicated in stable COPD (Evidence D).

Vasodilators. In patients with stable COPD, inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation-balance (133, 134) and thus is contraindicated.

Respiratory stimulants. The use of doxapram, a nonspecific respiratory stimulant available as an intravenous formulation, is not recommended in stable COPD (Evidence D). Almitrine bismesylate is not recommended for regular use in stable COPD patients (135–137) (Evidence B).

Narcotics. Narcotics are contraindicated in COPD because of their respiratory depressant effects and potential to worsen hypercapnia. Clinical studies suggest that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects (138–142). Codeine and other narcotic analgesics should also be avoided.

Others. Nedocromil, leukotriene modifiers, and alternative healing methods (e.g., herbal medicine, acupuncture, homeopathy) have not been adequately tested in COPD patients and thus cannot be recommended at this time.

Nonpharmacologic Treatment

Rehabilitation. The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and

increase physical and emotional participation in everyday activities. To accomplish these goals, pulmonary rehabilitation covers a range of nonpulmonary problems, including exercise deconditioning, relative social isolation, altered mood states (especially depression), muscle wasting, and weight loss. Patients with COPD at all stages of disease benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue (143) (Evidence A). Data suggest that these benefits can be sustained even after a single pulmonary rehabilitation program (144–146). Benefits have been reported from rehabilitation programs conducted in inpatient, outpatient, and home settings (147–149).

Ideally, pulmonary rehabilitation should involve several types of health professionals. A comprehensive pulmonary rehabilitation program includes exercise training, nutrition counseling, and education. Baseline and outcome assessments of each participant in a pulmonary rehabilitation program should be made to quantify individual gains and target areas for improvement and should include:

1. Detailed medical history and physical examination.
2. Measurement of spirometry before and after a bronchodilator drug.
3. Assessment of exercise capacity.
4. Measurement of health status and the impact of breathlessness.
5. Assessment of inspiratory and expiratory muscle strength and lower limb strength (e.g., quadriceps) in patients who suffer from muscle wasting (optional).

The first two assessments are important for establishing entry suitability and baseline status but are not used in outcome assessment. The last three assessments are essential baseline and outcome measures.

Oxygen therapy. The long-term administration of oxygen ($>$ 15 h per day) to patients with chronic respiratory failure has been shown to increase survival (123, 124, 150, 151) (Evidence A). It can also have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental state (152). Long-term oxygen therapy is generally introduced in Stage III: Severe COPD for patients who have: (*1*) Pa_{O_2} at or below 7.3 kPa (55 mm Hg) or Sa_{O_2} at or below 88%, with or without hypercapnia; or (*2*) Pa_{O_2} between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg) or Sa_{O_2} at or below 89%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive heart failure, or polycythemia (hematocrit $>$ 55%).

The goal of long-term oxygen therapy is to increase the baseline Pa_{O_2} to at least 8.0 kPa (60 mm Hg) or to produce Sa_{O_2} at least 90%, which will preserve vital organ function by ensuring an adequate delivery of oxygen. A decision about the use of long-term oxygen should be based on the waking Pa_{O_2} values. The prescription should always include the source of supplemental oxygen (gas or liquid), the method of delivery, duration of use, and the flow rate at rest, during exercise, and during sleep.

Ventilatory support. To date there is no convincing evidence that mechanical ventilatory support has a role in the routine management of stable COPD.

Surgical Treatments

Bullectomy. In carefully selected patients, this procedure is effective in reducing dyspnea and improving lung function (152) (Evidence C). A thoracic CT scan, arterial blood gas measurement, and comprehensive respiratory function tests are essential before making a decision regarding a patient's suitability for resection of a bulla.

Lung volume reduction surgery (LVRS). Although there are some encouraging reports (Evidence C), LVRS is still an unproven palliative surgical procedure (154, 155). Several large randomized studies are now underway to investigate the effectiveness and cost of LVRS in comparison to vigorous conventional therapy (156). Until the results of these studies are known, LVRS cannot be recommended for widespread use.

Lung transplantation. In appropriately selected patients with very advanced COPD, lung transplantation has been shown to improve quality of life and functional capacity (Evidence C) (157–160). Criteria for referral for lung transplantation include $FEV_1 < 35\%$ predicted, $Pa_{O_2} < 7.3$ to 8.0 kPa (55 to 60 mm Hg), $Pa_{CO_2} > 6.7$ kPa (50 mm Hg), and secondary pulmonary hypertension (161).

Component 4: Manage Exacerbations

Key Points

- Exacerbations of respiratory symptoms requiring medical intervention are important clinical events in COPD.
- The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution, but the cause of approximately one-third of severe exacerbations cannot be identified (Evidence B).
- Inhaled bronchodilators (particularly inhaled β_2-agonists or anticholinergics), theophylline, and systemic, preferably oral, glucocorticosteroids are effective for treatments for acute exacerbations of COPD (Evidence A).
- Patients experiencing COPD exacerbations with clinical signs of airway infection (e.g., increased volume and change of color of sputum, or fever) may benefit from antibiotic treatment (Evidence B).
- Noninvasive positive pressure ventilation (NIPPV) in acute exacerbations improves blood gases and pH, reduces in-hospital mortality, decreases the need for invasive mechanical ventilation and intubation, and decreases the length of hospital stay (Evidence A).

COPD is often associated with acute exacerbations of symptoms (162–165). The economic and social burden of COPD exacerbations is extremely high. The most common causes of an exacerbation are infection of the tracheobronchial tree (166–170) and air pollution (171), but the cause of approximately one-third of severe exacerbations cannot be identified (172). The role of bacterial infections, once believed to be the main cause of COPD exacerbations, is controversial (166–170, 173–175). Conditions that may mimic an acute exacerbation include pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism, and arrhythmia.

Diagnosis and Assessment of Severity. Increased breathlessness, the main symptom of an exacerbation, is often accompanied by wheezing and chest tightness, increased cough and sputum, change of the color or tenacity of sputum, and fever. Exacerbations may also be accompanied by a number of nonspecific complaints, such as malaise, insomnia, sleepiness, fatigue, depression, and confusion. A decrease in exercise tolerance, fever, or new radiologic anomalies suggestive of pulmonary disease may herald a COPD exacerbation. An increase in sputum volume and purulence points to a bacterial cause, as does a prior history of chronic sputum production (170).

The assessment of the severity of an acute exacerbation is based on the patient's medical history before the exacerbation, symptoms, physical examination, lung function tests, arterial blood gas measurements, and other laboratory tests. The medical history should cover how long worsening or new

TABLE 11. INDICATIONS FOR HOSPITAL ASSESSMENT OR ADMISSION FOR ACUTE EXACERBATIONS OF COPD*

Marked increase in intensity of symptoms, such as sudden development of resting dyspnea
Severe background COPD
Onset of new physical signs (e.g., cyanosis, peripheral edema)
Failure of exacerbation to respond to initial medical management
Significant comorbidities
Newly occurring arrhythmias
Diagnostic uncertainty
Older age
Insufficient home support

* Local resources need to be considered.

symptoms have been present, the frequency and severity of breathlessness and coughing attacks, sputum volume and color, limitation of daily activities, any previous episodes/exacerbations and whether they required hospitalization, and the present treatment regimen. When available, prior measurements of lung function and arterial blood gases are extremely useful for comparison with those made during the acute episode, as an acute change in these tests is more important than their absolute values. In patients with very severe COPD, the most important sign of severe exacerbation is a change in alertness and this signals a need for immediate evaluation in the hospital.

Lung function tests. Even simple lung function tests can be difficult for a sick patient to perform properly. In general, PEF $<$ 100 L/min or $FEV_1 < 1.00$ L indicates a severe exacerbation (176–178).

Assessment of arterial blood gases. In the hospital, measurement of arterial blood gases is essential to assess the severity of an exacerbation. $Pa_{O_2} < 8.0$ kPa (60 mm Hg) or $Sa_{O_2} <$ 90% (when breathing room air) indicates respiratory failure. In addition, $Pa_{O_2} < 6.7$ kPa (50 mm Hg), $Pa_{CO_2} > 9.3$ kPa (70 mm Hg), and pH $<$ 7.30 point toward a life-threatening episode that needs close monitoring or intensive care unit (ICU) management (179).

Chest X-ray and ECG. Chest radiographs (posterior/anterior plus lateral) are useful in identifying alternative diagnoses that can mimic the symptoms of an exacerbation. An ECG aids in the diagnosis of right ventricular hypertrophy, arrhythmias, and ischemic episodes. Pulmonary embolism can be very difficult to distinguish from an acute exacerbation, especially in severe COPD, because right ventricular hypertrophy and large pulmonary arteries lead to confusing ECG and radiographic results. Spiral CT scanning and angiography and perhaps specific D-dimer assays are the best tools presently available for diagnosis of pulmonary embolism in patients with COPD but ventilation–perfusion scanning is of no value. A low systolic blood pressure and an inability to increase the Pa_{O_2} above 8.0 kPa (60 mm Hg) despite high flow oxygen also suggest pulmonary embolism. If there are strong indications that pulmonary embolism has occurred, it is best to treat for this along with the exacerbation.

TABLE 12. INDICATIONS FOR ICU ADMISSION OF PATIENTS WITH ACUTE EXACERBATIONS OF COPD*

Severe dyspnea that responds inadequately to initial emergency therapy
Confusion, lethargy, coma
Persistent or worsening hypoxemia ($Pa_{O_2} < 6.7$ kPa, 50 mm Hg), or severe/worsening hypercapnia ($Pa_{CO_2} > 9.3$ kPa, 70 mm Hg), or severe/worsening respiratory acidosis (pH $<$ 7.30) despite supplemental oxygen and NIPPV

* Local resources need to be considered.

Other laboratory tests. The whole blood count may identify polycythemia (hematocrit $>$ 55%) or bleeding. White blood cell counts are usually not very informative. The presence of purulent sputum during an exacerbation of symptoms is sufficient indication for starting antibiotic treatment. *Streptococcus pneumoniae, Hemophilus influenzae*, and *Moraxella catarrhalis* are the most common bacterial pathogens involved in COPD exacerbations. If an infectious exacerbation does not respond to initial antibiotic treatment, a sputum culture and an antibiogram should be performed. Biochemical tests can reveal whether the cause of the exacerbation is an electrolyte disturbance (hyponatremia, hypokalemia, etc.), a diabetic crisis, or poor nutrition (low proteins), and may suggest a metabolic acid–base disorder.

Home Management. There is increasing interest in home care for patients with end-stage COPD, although economic studies of home care services have yielded mixed results. A major outstanding issue is when to treat an exacerbation at home and when to hospitalize the patient.

Bronchodilator therapy. Home management of COPD exacerbations involves increasing the dose or frequency of existing bronchodilator therapy (Evidence A). If not already used, an anticholinergic can be added until the symptoms improve. In more severe cases, high-dose nebulized therapy can be given on an as-needed basis for several days if a suitable nebulizer is available. However, long-term use of nebulizer therapy after an acute episode is not routinely recommended.

Glucocorticosteroids. Systemic glucocorticosteroids are beneficial in the management of acute exacerbations of COPD. They shorten recovery time and help to restore lung function more quickly (180–182) (Evidence A). They should be considered in addition to bronchodilators if the patient's baseline FEV_1 is $<$ 50% predicted. A dose of 40 mg prednisolone per day for 10 d is recommended (Evidence D).

Antibiotics. Antibiotics are only effective when patients with worsening dyspnea and cough also have increased sputum volume and purulence (Evidence B) (165). The choice of agents should reflect local patterns of antibiotic sensitivity among *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

Hospital Management. The risk of dying from an acute exacerbation of COPD is closely related to the development of respiratory acidosis, the presence of significant comorbidities, and the need for ventilatory support (183). Patients lacking

TABLE 13. MANAGEMENT OF SEVERE BUT NOT LIFE-THREATENING EXACERBATIONS OF COPD IN THE EMERGENCY DEPARTMENT OR THE HOSPITAL*

Assess severity of symptoms, blood gases, chest X-ray.
Administer controlled oxygen therapy and repeat arterial blood gas measurement after 30 min.
Bronchodilators:
Increase dose or frequency.
Combine β_2-agonists and anticholinergics.
Use spacers or air-driven nebulizers.
Consider adding intravenous aminophylline, if needed.
Add glucocorticosteroids oral or intravenous.
Consider antibiotics when signs of bacterial infection, oral or occasionally intravenous.
Consider noninvasive mechanical ventilation.
At all times:
Monitor fluid balance and nutrition.
Consider subcutaneous heparin.
Identify and treat associated conditions (e.g., heart failure, arrhythmias).
Closely monitor condition of the patient.

* Local resources need to be considered.

these features are not at high risk of dying, but those with severe underlying COPD often require hospitalization in any case. Attempts at managing such patients entirely in the community have met with only limited success (184), but returning them to their homes with increased social support and a supervised medical care package after an initial emergency room assessment has been much more successful (185). However, detailed cost-benefit analyses of these approaches are awaited.

Hospital assessment/admission should be considered for all patients who fit the criteria shown in Table 11. Some patients need immediate admission to an ICU (Table 12). Admission of patients with severe COPD exacerbations to intermediate or special respiratory care units may be appropriate if personnel, skills, and equipment are available to identify and manage acute respiratory failure successfully. The first actions when a patient reaches the emergency department are to provide controlled oxygen therapy and to determine whether the exacerbation is life-threatening. If so, the patient should be admitted to the ICU immediately. Otherwise, the patient may be managed in the emergency department or hospital as detailed in Table 13.

Controlled oxygen therapy. Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Adequate levels of oxygenation ($Pa_{O_2} > 8.0$ kPa, 60 mm Hg or $Sa_{O_2} > 90\%$) are easy to achieve in uncomplicated exacerbations, but CO_2 retention can occur insidiously with little change in symptoms. Once oxygen is started, arterial blood gases should be checked 30 min later to ensure satisfactory oxygenation without CO_2 retention or acidosis. Venturi masks are more accurate sources of controlled oxygen than are nasal prongs but are more likely to be removed by the patient.

Bronchodilator therapy. Short-acting, inhaled β_2-agonists are usually the preferred bronchodilators for treatment of acute exacerbations of COPD (Evidence A) (81, 123, 124). If a prompt response to these drugs does not occur, the addition of an anticholinergic is recommended, even though evidence concerning the effectiveness of this combination is rather controversial (186, 187). Despite its widespread clinical use, the role of aminophylline in the treatment of COPD exacerbations remains controversial. Most studies of aminophylline have demonstrated minor improvements in lung volumes but also worsening of gas exchange and hypoxemia (188, 189). In more severe exacerbations, addition of an oral or intravenous methylxanthine to the treatment can be considered. However, close monitoring of serum theophylline is recommended to avoid the side effects of these drugs (188, 190–192).

Glucocorticosteroids. Oral or intravenous glucocorticosteroids are recommended as an addition to bronchodilator therapy (plus eventually antibiotics and oxygen therapy) in the hospital management of acute exacerbations of COPD (180–182) (Evidence A). The exact dose that should be given is not known, but high doses are associated with a significant risk of side effects. Thirty to 40 mg of oral prednisolone daily for 10 to 14 d is a reasonable compromise between efficacy and safety (Evidence D). Prolonged treatment does not result in a greater efficacy and increases the risk of side effects.

Antibiotics. Antibiotics are only effective when patients with worsening dyspnea and cough also have increased sputum volume and purulence (165). The choice of agents should reflect local patterns of antibiotic sensitivity among *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

Ventilatory support. The primary objectives of mechanical support in patients with acute exacerbations in Stage III: Severe COPD are to decrease mortality and morbidity and to relieve symptoms. Ventilatory support includes both noninvasive mechanical ventilation using either negative or positive pressure devices, and invasive (conventional) mechanical ventilation by oro-/naso-tracheal tube or tracheostomy:

1. *Noninvasive mechanical ventilation.* NIPPV has been studied in many uncontrolled and five randomized controlled trials in acute respiratory failure (193). The studies show consistently positive results with success rates of 80 to 85% (194). Taken together they provide evidence that NIPPV increases pH, reduces Pa_{CO_2}, reduces the severity of breathlessness in the first 4 h of treatment, and decreases the length of hospital stay (Evidence A). More importantly, mortality—or its surrogate, intubation rate—is reduced by this intervention (195–198). However, NIPPV is not appropriate for all patients, as summarized in Table 14.
2. *Invasive (conventional) mechanical ventilation.* Patients who show impending acute respiratory failure and those with life-threatening acid–base status abnormalities or altered mental status despite aggressive pharmacologic therapy are likely to be the best candidates for invasive mechanical ventilation. The indications for initiating mechanical ventilation during exacerbations of COPD are shown in Table 15, the first being the commonest and most important reason. The three ventilatory modes most widely used are assisted-control ventilation, and pressure support ventilation alone or in combination with intermittent mandatory ventilation (199). The use of invasive ventilation in patients with

TABLE 14. SELECTION AND EXCLUSION CRITERIA FOR NIPPV

Selection criteria (at least two should be present)	Exclusion criteria (any may be present)
Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion	Respiratory arrest
Moderate to severe acidosis (pH 7.30–7.35) and hypercapnia (Pa_{CO_2} 6.0–8.0 kPa, 45–60 mm Hg)	Cardiovascular instability (hypotension, arrhythmias, myocardial infarction)
Respiratory frequency > 25 breaths/min	Somnolence, impaired mental status, uncooperative patient
	High aspiration risk; viscous or copious secretions
	Recent facial or gastroesophageal surgery
	Craniofacial trauma, fixed nasopharyngeal abnormalities
	Extreme obesity

From Kramer and coworkers (197).

TABLE 15. INDICATIONS FOR INVASIVE MECHANICAL VENTILATION

Severe dyspnea with use of accessory muscles and paradoxical abdominal motion
Respiratory frequency > 35 breaths/min
Life-threatening hypoxemia ($Pa_{O_2} < 5.3$ kPa, 40 mm Hg or $Pa_{O_2}/FI_{O_2} < 200$ mm Hg)
Severe acidosis (pH < 7.25) and hypercapnia ($Pa_{CO_2} > 8.0$ kPa, 60 mm Hg)
Respiratory arrest
Somnolence, impaired mental status
Cardiovascular complications (hypotension, shock, heart failure)
Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion)
NIPPV failure (or exclusion criteria, *see* Table 14)

Definition of abbreviation: FI_{O_2} = fractional concentration of oxygen in dry inspired gas.

end-stage COPD is influenced by the likely reversibility of the precipitating event, the patient's wishes, and the availability of intensive care facilities. Major hazards include the risk of ventilator-acquired pneumonia (especially when multiresistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation. Contrary to some opinions, mortality among COPD patients with respiratory failure is no greater than mortality among patients ventilated for non-COPD causes. When possible, a clear statement of the patient's own treatment wishes—an advance directive or "living will"—makes these difficult decisions much easier to resolve.

Weaning or discontinuation from mechanical ventilation can be particularly difficult and hazardous in patients with COPD, and the best method to wean patients from the ventilator remains a matter of debate (200, 201) Whether pressure support or a T-piece trial is used, weaning is shortened when a clinical protocol is adapted (Evidence A). Noninvasive ventilation (NIV) has been applied to facilitate the weaning process in COPD patients with acute or chronic respiratory failure (202). Compared with invasive pressure support ventilation, NIPPV during weaning shortened weaning time, reduced the stay in the ICU, decreased the incidence of nosocomial pneumonia, and improved 60-d survival rates (202). Similar findings have been reported when NIPPV is used after extubation for hypercapnic respiratory failure (203) (Evidence C).

Other Measures. Further treatment measures that can be used in the hospital include: fluid administration (accurate monitoring of fluid balance is essential); nutrition (supplementary when the patient is too dyspneic to eat); low-molecular-weight heparin in immobilized, polycythemic, or dehydrated patients with or without a history of thromboembolic disease; sputum clearance (by stimulating coughing and low-volume forced expirations as in home management). Manual or mechanical chest percussion and postural drainage may be beneficial in patients producing more than 25 ml sputum per day or with lobar atelectasis.

Hospital Discharge and Follow-up. Insufficient clinical data exist to establish the optimal duration of hospitalization for acute exacerbations of COPD (163, 204, 205). Consensus and limited data support the discharge criteria listed in Table 16. Table 17 provides items to include in a follow-up assessment 4 to 6 wk after discharge from the hospital. Thereafter, follow-up is the same as for stable COPD, including supervising smoking cessation, monitoring the effectiveness of each drug treatment, and monitoring changes in spirometric parameters (81). If hypoxemia developed during the exacerbation, arterial blood gases should be rechecked at discharge and at the follow-up visit. If the patient remains hypoxemic, long-term oxygen therapy should be instituted. Decisions about continuous domiciliary oxygen based on the severity of the acute hypoxemia during an exacerbation are frequently misleading.

The opportunities for prevention of future exacerbations should be reviewed before discharge with particular attention to future influenza vaccination plans, knowledge of current therapy including inhaler technique (206, 207), and how to recognize symptoms of exacerbations. Pharmacotherapy known to reduce the number of exacerbations should be considered. Social problems should be discussed and principal caregivers identified if the patient has a significant persisting disability.

FUTURE RESEARCH

A better understanding of molecular and cellular pathogenic mechanisms of COPD should lead to many new directions for both basic and clinical investigations. Improved methods for early detection, new approaches for interventions through targeted pharmacotherapy, possible means to identify the "susceptible" smoker, and more effective means of managing exacerbations are needed. Some research recommendations are provided; there are many additional avenues to explore.

1. Until there is a better understanding of the causal mechanisms of COPD, an absolutely rigid definition of COPD, and its relationship to other obstructive airway diseases, will remain controversial. Defining characteristics of COPD should be identified.
2. The stages of COPD and the disease course will vary from one patient to another. The GOLD Report describes four stages; their clinical utility needs to be evaluated.
3. Surrogate markers of inflammation, possibly derived from sputum (cells, mediators, enzymes) or exhaled condensates (lipid mediators, reactive oxygen species, cytokines), that may predict the clinical usefulness of new management and prevention strategies for COPD need to be developed.
4. Information is needed about the cellular and molecular mechanisms of inflammation in stable COPD and in exacerbations. Inflammatory responses in nonsmokers, exsmokers, and smokers with and without COPD should be compared. The mechanisms responsible for the persistence of the inflammatory response in COPD should be investigated. Why inflammation in COPD is poorly responsive to glucocorticosteroids and what treatments other than glucocorticosteroids are effective in suppressing inflammation in COPD are research topics that could lead to new treatment modalities.
5. There is a pressing need to develop drugs that control symptoms and prevent the progression of COPD. Some progress has been made and there are several classes of drugs that are now in preclinical and clinical development for use in patients with COPD.
6. Standardized methods for tracking trends in COPD prevalence, morbidity, and mortality over time need to be developed so that countries can plan for future increases in the need for health care services in view of predicted in-

TABLE 16. DISCHARGE CRITERIA FOR PATIENTS WITH ACUTE EXACERBATIONS OF COPD

Inhaled bronchodilator therapy is required no more frequently than every 4 h.
Patient, if previously ambulatory, is able to walk across room.
Patient is able to eat and sleep without frequent awakening by dyspnea.
Patient has been clinically stable for 12–24 h.
Arterial blood gases have been stable for 12–24 h.
Patient (or home caregiver) fully understands correct use of medications.
Follow-up and home care arrangements have been completed. (e.g., visiting nurse, oxygen delivery, meal provisions).
Patient, family, and physician are confident patient can manage successfully.

TABLE 17. FOLLOW-UP ASSESSMENT 4–6 WK AFTER DISCHARGE FROM HOSPITAL FOR AN ACUTE EXACERBATION OF COPD

Ability to cope in usual environment
Measurement of FEV_1
Reassessment of inhaler technique
Understanding of recommended treatment regimen
Need for long-term oxygen therapy or home nebulizer (for patients with severe COPD)

creases in COPD. This need is especially urgent in developing countries with limited health care resources.

7. Longitudinal studies demonstrating the course of COPD are needed in a variety of populations exposed to various risk factors. Such studies would provide insight into the pathogenesis of COPD, identify additional genetic bases for COPD, and identify how genetic risk factors interact with environmental risk factors in specific patient populations. Factors that determine why some, but not all, smokers develop COPD need to be identified.
8. Data are needed on the use, cost, and relative distribution of medical and nonmedical resources for COPD, especially in countries where smoking and other risk factors are prevalent. These data are likely to have some impact on health policy and resource allocation decisions. As options for treating COPD grow, more research will be needed to help guide health care providers and health budget managers regarding the most efficient and effective ways of managing this disease. Methods and strategies for implementation of COPD management programs in developing countries will require special attention.
9. While spirometry is recommended to assess and monitor COPD, other measures need to be developed and evaluated in clinical practice. Reproducible and inexpensive exercise-testing methodologies (e.g., stair-climbing tests) suitable for use in developing countries need to be evaluated and their use encouraged. Spirometers need to be developed that can ensure economical and accurate performance when a relatively untrained operator administers the test.
10. Because COPD is not fully reversible (with current therapies) and slowly progressive, it will become ever more important to identify early cases as more effective therapies emerge. Consensus on standard methods for detection and definition of early disease need to be developed. Data to show whether or not screening spirometry is effective in directing management decisions in COPD outcomes are required.
11. Primary prevention of COPD is one of the major objectives of GOLD. Investigations into the most cost-effective ways to reduce the prevalence of tobacco smoking in the general population and more specifically in young people are very much needed. Strategies to prevent people from starting to smoke and methods for smoking cessation require constant evaluation and improvement. Research is required to gauge the impact and reduce the risk from growing air pollution, urbanization, recurrent childhood infections, occupational exposures, and use of local cigarette equivalents. Programs designed to reduce exposure to biomass fuel in countries where this is used for cooking and domestic heating should be explored in an effort to reduce exposure and improve ventilation in the homes.
12. The specific components of effective education for patients with COPD need to be determined. It is not known, for example, whether patients with COPD should be given an individual management plan, or whether these plans are effective in reducing health care costs or improving the outcomes of exacerbations. Developing and evaluating effective tools for physician education concerning prevention, diagnosis, and management of COPD will be important in view of the increasing public health problem presented by COPD.
13. Studies are needed to determine whether education is an essential component of pulmonary rehabilitation. The cost-effectiveness of rehabilitation programs has not been assessed and there is a need to assess the feasibility, resource utilization, and health outcomes of rehabilitation programs that can be delivered outside the major teaching hospital setting. Criteria for selecting individuals for rehabilitation should be evaluated, along with methods to modify programs to suit the needs of individual patients.
14. Collecting and evaluating data to set levels of severity for COPD exacerbations would stimulate standardization of this outcome measure that is so frequently used in clinical trials. Better data on outcomes of COPD exacerbations would allow physicians to provide better advice to patients on possible outcomes and appropriateness of various types of treatment. Further exploration of the ethical principles of life support and greater insights into the behavioral influences that inhibit discussion of end-of-life issues are needed, along with studies to define the needs of patients with end-stage COPD.

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References

1. National Heart, Lung, and Blood Institute. Morbidity & Mortality: Chartbook on Cardiovascular, Lung, and Blood Diseases. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD. 1998. Available from: URL: www.nhlbi.nih.gov/nhlbi/seiin//other/cht-book/htm.
2. Murray CJL, Lopez AD. Evidence-based health policy—lessons from the Global Burden of Disease Study. *Science* 1996;274:740–743.
3. World Health Report. World Health Organization, Geneva. 2000. Available from URL: http://www.who.int/whr/2000/en/statistics.htm.
4. Hill AT, Bayley D, Stockley RA. The interrelationship of sputum inflammatory markers in patients with chronic bronchitis. *Am J Respir Crit Care Med* 1999;160:893–898.
5. Keatings VM, Collins PD, Scott DM, Barnes PJ. Differences in interleukin-8 and tumor necrosis factor-alpha in induced sputum from patients with chronic obstructive pulmonary disease or asthma. *Am J Respir Crit Care Med* 1996;153:530–534.
6. Pesci A, Balbi B, Majori M, Cacciani G, Bertacco S, Alciato P, Donner CF. Inflammatory cells and mediators in bronchial lavage of patients with chronic obstructive pulmonary disease. *Eur Respir J* 1998;12: 380–386.
7. Yamamoto C, Yoneda T, Yoshikawa M, Fu A, Tokuyama T, Tsukaguchi K, Narita N. Airway inflammation in COPD assessed by sputum levels of interleukin-8. *Chest* 1997;112:505–510.
8. Mueller R, Chanez P, Campbell AM, Bousquet J, Heusser C, Bullock GR. Different cytokine patterns in bronchial biopsies in asthma and chronic bronchitis. *Respir Med* 1996;90:79–85.
9. Mullen JB, Wright JL, Wiggs BR, Pare PD, Hogg JC. Reassessment of inflammation of airways in chronic bronchitis. *Br Med J (Clin Res Ed)* 1985;291:1235–1239.
10. Cosio M, Ghezzo H, Hogg JC, Corbin R, Loveland M, Dosman J, Macklem PT. The relations between structural changes in small airways and pulmonary-function tests. *N Engl J Med* 1978;298:1277–1281.
11. Niewoehner DE, Kleinerman J, Rice DB. Pathologic changes in the peripheral airways of young cigarette smokers. *N Engl J Med* 1974;291: 755–758.
12. Wright JL, Lawson LM, Pare PD, Wiggs BJ, Kennedy S, Hogg JC.

Morphology of peripheral airways in current smokers and ex-smokers. *Am Rev Respir Dis* 1983;127:474–477.
13. Ollerenshaw SL, Woolcock AJ. Characteristics of the inflammation in biopsies from large airways of subjects with asthma and subjects with chronic airflow limitation. *Am Rev Respir Dis* 1992;145:922–927.
14. Hunninghake GW, Crystal RG. Cigarette smoking and lung destruction: accumulation of neutrophils in the lungs of cigarette smokers. *Am Rev Respir Dis* 1983;128:833–838.
15. Li XY, Brown D, Smith S, MacNee W, Donaldson K. Short-term inflammatory responses following intratracheal instillation of fine and ultrafine carbon black in rats. *Inhal Toxicol* 1999;11:709–731.
16. Monn C, Becker S. Cytotoxicity and induction of proinflammatory cytokines from human monocytes exposed to fine (PM2.5) and coarse particles (PM10–2.5) in outdoor and indoor air. *Toxicol Appl Pharmacol* 1999;155:245–252.
17. Salvi S, Blomberg A, Rudell B, Kelly F, Sandstrom T, Holgate ST, Frew A. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. *Am J Respir Crit Care Med* 1999;159:702–709.
18. Von Essen SG, O'Neill DP, McGranaghan S, Olenchock SA, Rennard SI. Neutrophilic respiratory tract inflammation and peripheral blood neutrophilia after grain sorghum dust extract challenge. *Chest* 1995; 108:1425–1433.
19. Von Essen SG, Robbins RA, Thompson AB, Ertl RF, Linder J, Rennard SI. Mechanisms of neutrophil recruitment to the lung by grain dust exposure [published erratum appears in *Am Rev Respir Dis* 1989;139:1065]. *Am Rev Respir Dis* 1988;138:921–927.
20. O'Shaughnessy TC, Ansari TW, Barnes NC, Jeffery PK. Inflammation in bronchial biopsies of subjects with chronic bronchitis: inverse relationship of CD8+ T lymphocytes with FEV_1. *Am J Respir Crit Care Med* 1997;155:852–857.
21. Saetta M, Di Stefano A, Maestrelli P, Ferraresso A, Drigo R, Potena A, Ciaccia A, Fabbri LM. Activated T-lymphocytes and macrophages in bronchial mucosa of subjects with chronic bronchitis. *Am Rev Respir Dis* 1993;147:301–306.
22. Saetta M, Di Stefano A, Turato G, Facchini FM, Corbino L, Mapp CE, Maestrelli P, Ciaccia A, Fabbri LM. CD8+ T-lymphocytes in peripheral airways of smokers with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:822–826.
23. Leopold JG, Goeff J. Centrilobular form of hypertrophic emphysema and its relation to chronic bronchitis. *Thorax* 1957;12:219–235.
24. McLean KA. Pathogenesis of pulmonary emphysema. *Am J Med* 1958; 25:62–74.
25. Repine JE, Bast A, Lankhorst I. Oxidative stress in chronic obstructive pulmonary disease. Oxidative Stress Study Group. *Am J Respir Crit Care Med* 1997;156:341–357.
26. Wright JL, Lawson L, Pare PD, Hooper RO, Peretz DI, Nelems JM, Schulzer M, Hogg JC. The structure and function of the pulmonary vasculature in mild chronic obstructive pulmonary disease: the effect of oxygen and exercise. *Am Rev Respir Dis* 1983;128:702–707.
27. Peinado VI, Barbera JA, Abate P, Ramirez J, Roca J, Santos S, Rodriguez-Roisin R. Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159:1605–1611.
28. Riley DJ, Thakker-Varia S, Poiani GJ, Tozzi CA. Vascular remodeling. In: RG Crystal, JB West, PJ Barnes, ER Weibel, editors. The lung: scientific foundations, 2nd ed. Philadelphia: Lippincott-Raven; 1997. p. 1589–1597.
29. MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part Two. *Am J Respir Crit Care Med* 1994;150: 1158–1168.
30. Pride NB, Vermeire P, Allegra L. Diagnostic labels applied to model case histories of chronic airflow obstruction: responses to a questionnaire in 11 North American and western European countries. *Eur Respir J* 1989;2:702–709.
31. Mannino DM, Brown C, Giovino GA. Obstructive lung disease deaths in the United States from 1979 through 1993: an analysis using multiple-cause mortality data. *Am J Respir Crit Care Med* 1997;156:814–818.
32. Murray CJL, Lopez AD, editors. 1996. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020. Harvard University Press, Cambridge, MA.
33. Buist AS, Vollmer WM. Smoking and other risk factors. In: JF Murray, JA Nadel, editors. Textbook of respiratory medicine. WB Saunders; Philadelphia: 1994. p. 1259–1287.
34. Thom TJ. International comparisons in COPD mortality. *Am Rev Respir Dis* 1989;140:S27–34.
35. Xu X, Weiss ST, Rijcken B, Schouten JP. Smoking, changes in smoking habits, and rate of decline in FEV_1: new insight into gender differences. *Eur Respir J* 1994;7:1056–1061.
36. Feinleib M, Rosenberg HM, Collins JG, Delozier JE, Pokras R, Chevarley FM. Trends in COPD morbidity and mortality in the United States. *Am Rev Respir Dis* 1989;140:S9–18.
37. U.S. Centers for Disease Control and Prevention: Vital and Health Statistics: Current Estimates from the National Health Interview Survey. Department of Health and Human Service, Public Health Service. 1995. Publication No 96-1527.
38. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA Jr, Enright PL, Kanner RE, O'Hara P, *et al.* Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. The Lung Health Study. *JAMA* 1994;272:1497–1505.
39. Laurell CB, Eriksson S. The electrophoretic alpha-1 globulin pattern of serum in alpha-1 antitrypsin deficiency. *Scand J Clin Lab Invest* 1963;15:132–140.
40. Hubbard RC, Crystal RG. Antiproteases. In: RB Crystal, JB West, PJ Barnes, NS Cherniack, ER Weibel, editors. The lung: scientific foundations. New York: Raven Press; 1991. p. 1775–1787.
41. McElvaney NG, Crystal RG. Inherited susceptibility of the lung to proteolytic injury. In: RG Crystal, JB West, ER Weibel, PJ Barnes, editors. The Lung: Scientific Foundations, 2nd ed. Philadelphia: Lippincott-Raven; 1997. p. 2537–2553.
42. Orie NGM, Sluiter HJ, De Vreis K, Tammerling K, Wikop J. The host factor in bronchitis. In: NGM Orie, HG Sluiter, editors. Bronchitis, An International Symposium. Assen, Netherlands: Royal Vangorcum; 1961. p. 43–59.
43. Hagstrom B, Nyberg P, Nilsson PM. Asthma in adult life—is there an association with birth weight? *Scand J Prim Health Care* 1998;16: 117–120.
44. Svanes C, Omenaas E, Heuch JM, Irgens LM, Gulsvik A. Birth characteristics and asthma symptoms in young adults: results from a population-based cohort study in Norway. *Eur Respir J* 1998;12:1366–1370.
45. Todisco T, de Benedictis FM, Iannacci L, Baglioni S, Eslami A, Todisco E, Dottorini M. Mild prematurity and respiratory functions. *Eur J Pediatr* 1993;152:55–58.
46. Stein CE, Kumaran K, Fall CH, Shaheen SO, Osmond C, Barker DJ. Relation of fetal growth to adult lung function in South India. *Thorax* 1997;52:895–899.
47. Morgan WJ. Maternal smoking and infant lung function: further evidence for an in utero effect. *Am J Respir Crit Care Med* 1998;158: 689–690.
48. Tager IB, Segal MR, Speizer FE, Weiss ST. The natural history of forced expiratory volumes: effect of cigarette smoking and respiratory symptoms. *Am Rev Respir Dis* 1988;138:837–849.
49. U.S. Surgeon General. The Health Consequences of Smoking: Chronic Obstructive Pulmonary Disease. U.S. Department of Health and Human Services, Washington, DC. 1984. Publication No. 84-50205.
50. Leuenberger P, Schwartz J, Ackermann-Liebrich U, Blaser K, Bolognini G, Bongard JP, Brandli O, Braun P, Bron C, Brutsche M, *et al.* Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. *Am J Respir Crit Care Med* 1994;150:1222–1228.
51. Dayal HH, Khuder S, Sharrar R, Trieff N. Passive smoking in obstructive respiratory disease in an industrialized urban population. *Environ Res* 1994;65:161–171.
52. Holt PG. Immune and inflammatory function in cigarette smokers. *Thorax* 1987;42:241–249.
53. Kauffmann F, Drouet D, Lellouch J, Brille D. Twelve years spirometric changes among Paris area workers. *Int J Epidemiol* 1979;8:201–212.
54. Niewoehner DE. Anatomic and pathophysiological correlations in COPD. In GL Baum, JD Crapo, BR Celli, JB Karlinsky, editors. Textbook of Pulmonary Diseases. Philadelphia: Lippincott-Raven; 1998. p. 823–842.
55. Chen JC, Mannino MD. Worldwide epidemiology of chronic obstructive pulmonary disease. *Current Opin Pulmon Med* 1999;5:93–99.
56. Perez-Padilla R, Regalado U, Vedal S, Pare P, Chapela R, Sansores R. Exposure to biomass smoke and chronic airway disease in Mexican women. *Am J Respir Crit Care Med* 1996;154:701–706.
57. Dossing M, Khan Jal-Rabiah F. Risk factors for chronic obstructive lung disease in Saudi Arabia. *Respir Med* 1994;88:519–522.
58. Behera D, Jindal SK. Respiratory symptoms in Indian women using domestic cooking fuels. *Chest* 1991;100:385–388.
59. Amoli K. Bronchopulmonary disease in Iranian housewives chronically exposed to indoor smoke. *Eur Respir J* 1998;11:659–663.

60. Dennis R, Maldonado D, Norman S, Baena E, Martinez G. Woodsmoke exposure and risk for obstructive airways disease among women. *Chest* 1996;109:115–119.
61. Pandey MR. Prevalence of chronic bronchitis in a rural community of the Hill Region of Nepal. *Thorax* 1984;39:331–336.
62. Pandey MR. Domestic smoke pollution and chronic bronchitis in a rural community of the Hill Region of Nepal. *Thorax* 1984;39:337–339.
63. Samet JM, Marbury M, Spengler J. Health effects and sources of indoor air pollution. *Am Rev Respir Dis* 1987;136:1486–1508.
64. Tao X, Hong CJ, Yu S, Chen B, Zhu H, Yang M. Priority among air pollution factors for preventing chronic obstructive pulmonary disease in Shanghai. *Sci Total Environ* 1992;127:57–67.
65. Prescott E, Lange P, Vestbo J. Socioeconomic status, lung function and admission to hospital for COPD: results from the Copenhagen City Heart Study. *Eur Respir J* 1999;13:1109–1114.
66. Strachan DP. Epidemiology: A British perspective. In: PMA Calverley, NB Pride, editors. Chronic obstructive pulmonary disease. London: Chapman and Hall; 1995. p. 47–67.
67. Georgopoulas D, Anthonisen NR. Symptoms and signs of COPD. In: NS Cherniack, editor. Chronic obstructive pulmonary disease. Toronto: WB Saunders; 1991. p. 357–363.
68. Loveridge B, West P, Kryger MH, Anthonisen NR. Alteration in breathing pattern with progression of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986;134:930–934.
69. Kesten S, Chapman KR. Physician perceptions and management of COPD. *Chest* 1993;104:254–258.
70. Reis AL. Response to bronchodilators. In: Clausen J, editor. Pulmonary function testing: guidelines and controversies. New York: Academic Press; 1982.
71. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991; 144:1202–1218.
72. Wilson DH, Wakefield MA, Steven ID, Rohrsheim RA, Esterman AJ, Graham NM. "Sick of Smoking": evaluation of a targeted minimal smoking cessation intervention in general practice. *Med J Aust* 1990; 152:518–521.
73. Britton J, Knox A. Helping people to stop smoking: the new smoking cessation guidelines. *Thorax* 1999;54:1–2.
74. Fiore MC, Bailey WC, Cohen SJ. Smoking Cessation: Information for Specialists. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research and Centers for Disease Control and Prevention, Rockville, MD. 1996. AHCPR Publication No. 96-0694.
75. The tobacco use and dependence clinical practice guideline panel, staff, and consortium representatives. A clinical practice guideline for treating tobacco use and dependence. *JAMA* 2000;28:3244–3254.
76. American Medical Association. Guidelines for the Diagnosis and Treatment of Nicotine Dependence: How to Help Patients Stop Smoking. American Medical Association, Washington DC. 1994.
77. Glynn TJ, Manley MW, Pechacek TF. Physician-initiated smoking cessation program: the National Cancer Institute trials. *Prog Clin Biol Res* 1990;339:11–25.
78. Glynn TJ, Manley MW. How to Help Your Patients Stop Smoking. A National Cancer Institute Manual for Physicians. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, Bethesda, MD. 1990. NIH Publication No. 90-3064.
79. Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation: a meta-analysis. *JAMA* 1994; 271:1940–1947.
80. Lancaster T, Stead L, Silagy C, Sowden A. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. *BMJ* 2000;321:355–358.
81. The COPD Guidelines Group of the Standards of Care Committee of the BTS. BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997;52(Suppl 5):S1–28.
82. Samet J, Utell MJ. Ambient air pollution. In: L Rosenstock, M Cullen, editors. Textbook of occupational and environmental medicine. Philadelphia: WB Saunders; 1994. p. 53–60.
83. Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1995; 122:823–832.
84. Janelli LM, Scherer YK, Schmieder LE. Can a pulmonary health teaching program alter patients' ability to cope with COPD? *Rehabil Nurs* 1991;16:199–202.
85. Ashikaga T, Vacek PM, Lewis SO. Evaluation of a community-based education program for individuals with chronic obstructive pulmonary disease. *J Rehabil* 1980;46:23–27.
86. Toshima MT, Kaplan RM, Ries AL. Experimental evaluation of rehabilitation in chronic obstructive pulmonary disease: short-term effects on exercise endurance and health status. *Health Psychol* 1990;9: 237–252.
87. Celli BR. Pulmonary rehabilitation in patients with COPD. *Am J Respir Crit Care Med* 1995;152:861–864.
88. Heffner JE, Fahy B, Hilling L, Barbieri C. Outcomes of advance directive education of pulmonary rehabilitation patients. *Am J Respir Crit Care Med* 1997;155:1055–1059.
89. Stewart MA. Effective physician–patient communication and health outcomes: a review. *CMAJ* 1995;152:1423–1433.
90. Clark NM, Nothwehr F, Gong M, Evans D, Maiman LA, Hurwitz ME, Roloff D, Mellins RB. Physician–patient partnership in managing chronic illness. *Acad Med* 1995;70:957–959.
91. Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, Ohlsson SV. 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: 1948–1953.
92. Vestbo J, Sorensen 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; 353:1819–1823.
93. 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;320:1297–1303.
94. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease: *N Engl J Med* 2000;343:1902–1909.
95. Vathenen AS, Britton JR, Ebden P, Cookson JB, Wharrad HJ, Tattersfield AE. High-dose inhaled albuterol in severe chronic airflow limitation. *Am Rev Respir Dis* 1988;138:850–855.
96. Gross NJ, Petty TL, Friedman M, Skorodin MS, Silvers GW, Donohue JF. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease: A three-center study. *Am Rev Respir Dis* 1989;139:1188–1191.
97. Chrystyn H, Mulley BA, Peake MD. Dose response relation to oral theophylline in severe chronic obstructive airways disease. *BMJ* 1988;297:1506–1510.
98. Higgins BG, Powell RM, Cooper S, Tattersfield AE. Effect of salbutamol and ipratropium bromide on airway calibre and bronchial reactivity in asthma and chronic bronchitis. *Eur Respir J* 1991;4:415–420.
99. Jenkins SC, Heaton RW, Fulton TJ, Moxham J. Comparison of domiciliary nebulized salbutamol and salbutamol from a metered-dose inhaler in stable chronic airflow limitation. *Chest* 1987;91:804–807.
100. Ikeda A, Nishimura K, Koyama H, Tsukino M, Mishima M, Izumi T. Dose response study of ipratropium bromide aerosol on maximum exercise performance in stable patients with chronic obstructive pulmonary disease. *Thorax* 1996;51:48–53.
101. Guyatt GH, Townsend M, Pugsley SO, Keller JL, Short HD, Taylor DW, Newhouse MT. Bronchodilators in chronic air-flow limitation: effects on airway function, exercise capacity, and quality of life. *Am Rev Respir Dis* 1987;135:1069–1074.
102. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. *Am J Respir Crit Care Med* 1997;155:1283–1289.
103. Mahler DA, Donohue JF, Barbee RA, Goldman MD, Gross NJ, Wisniewski ME, Yancey SW, Zakes BA, Rickard KA, Anderson WH. Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest* 1999;115:957–965.
104. COMBIVENT Inhalation Aerosol Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone: an 85-day multicenter trial. *Chest* 1994;105:1411–1419.
105. The COMBIVENT Inhalation Solution Study Group. Routine nebulized ipratropium and albuterol together are better than either alone in COPD. *Chest* 1997;112:1514–1521.
106. Gross N, Tashkin D, Miller R, Oren J, Coleman W, Linberg S. Inhalation by nebulization of albuterol–ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease. Dey Combination Solution Study Group. *Respiration* 1998;65:354–362.
107. Ulrik CS. Efficacy of inhaled salmeterol in the management of smokers with chronic obstructive pulmonary disease: a single centre ran-

domised, double blind, placebo controlled, crossover study. *Thorax* 1995;50:750–754.
108. Taylor DR, Buick B, Kinney C, Lowry RC, McDevitt DG. The efficacy of orally administered theophylline, inhaled salbutamol, and a combination of the two as chronic therapy in the management of chronic bronchitis with reversible air-flow obstruction. *Am Rev Respir Dis* 1985;131:747–751.
109. van Noord JA, de Munck DR, Bantje TA, Hop WC, Akveld ML, Bommer AM. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. *Eur Respir J* 2000;15:878–885.
110. Murciano D, Auclair MH, Pariente R, Aubier M. A randomized, controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease. *N Engl J Med* 1989;320:1521–1525.
111. O'Driscoll BR, Kay EA, Taylor RJ, Weatherby H, Chetty MC, Bernstein A. A long-term prospective assessment of home nebulizer treatment. *Respir Med* 1992;86:317–325.
112. Tashkin DP, Bleecker E, Braun S, Campbell S, DeGraff AC Jr, Hudgel DW, Boyars MC, Sahn S. Results of a multicenter study of nebulized inhalant bronchodilator solutions. *Am J Med* 1996;100:62S–69.
113. Senderovitz T, Vestbo J, Frandsen J, Maltbaek N, Norgaard M, Nielsen C, Kampmann JP. Steroid reversibility test followed by inhaled budesonide or placebo in outpatients with stable chronic obstructive pulmonary disease. The Danish Society of Respiratory Medicine. *Respir Med* 1999;93:715–718.
114. Rice KL, Rubins JB, Lebahn F, Parenti CM, Duane PG, Kuskowski M, Joseph AM, Niewoehner DE. Withdrawal of chronic systemic corticosteroids in patients with COPD: a randomized trial. *Am J Respir Crit Care Med* 2000;162:174–178.
115. Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med* 1994;150:11–16.
116. Decramer M, Stas KJ. Corticosteroid-induced myopathy involving respiratory muscles in patients with chronic obstructive pulmonary disease or asthma. *Am Rev Respir Dis* 1992;146:800–802.
117. Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *N Engl J Med* 1994;331:778–784.
118. Edwards KM, Dupont WD, Westrich MK, Plummer WD Jr, Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. *J Infect Dis* 1994;169:68–76.
119. Simberkoff MS, Cross AP, Al-Ibrahim M, Baltch AL, Geiseler PJ, Nadler J, Richmond AS, Smith RP, Schiffman G, Shepard DS, *et al.* Efficacy of pneumococcal vaccine in high-risk patients: results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;315:1318–1327.
120. Williams JH Jr, Moser KM. Pneumococcal vaccine and patients with chronic lung disease. *Ann Intern Med* 1986;104:106–109.
121. Davis AL, Aranda CP, Schiffman G, Christianson LC. Pneumococcal infection and immunologic response to pneumococcal vaccine in chronic obstructive pulmonary disease: a pilot study. *Chest* 1987;92:204–212.
122. Isada CM, Stoller JK. Chronic bronchitis: the role of antibiotics. In: MS Niederman, GA Sarosi, J Glassroth, editors. Respiratory infections: a scientific basis for management. London: WB Saunders; 1994. p. 621–633.
123. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;152:S77–121.
124. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS, *et al.* Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. *Eur Respir J* 1995;8:1398–1420.
125. Poole PJ, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2000;2:Available from URL www.update-software.com or www.updatusa. com.
126. Hansen NC, Skriver A, Brorsen-Riis L, Balslov S, Evald T, Maltbaek N, Gunnersen G, Garsdal P, Sander P, Pedersen JZ, *et al.* Orally administered *N*-acetylcysteine may improve general well-being in patients with mild chronic bronchitis. *Respir Med* 1994;88:531–535.
127. British Thoracic Society Research Committee. Oral *N*-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airways obstruction. *Thorax* 1985;40:832–835.
128. Boman G, Backer U, Larsson S, Melander B, Wahlander L. Oral acetylcysteine reduces exacerbation rate in chronic bronchitis: report of a trial organized by the Swedish Society for Pulmonary Diseases. *Eur J Respir Dis* 1983;64:405–415.
129. Rasmussen JB, Glennow C. Reduction in days of illness after long-term treatment with *N*-acetylcysteine controlled-release tablets in patients with chronic bronchitis. *Eur Respir J* 1988;1:351–355.
130. Collet JP, Shapiro P, Ernst P, Renzi T, Ducruet T, Robinson A. Effects of an immunostimulating agent on acute exacerbations and hospitalizations in patients with chronic obstructive pulmonary disease. The PARI-IS Study Steering Committee and Research Group. Prevention of Acute Respiratory Infection by an Immunostimulant. *Am J Respir Crit Care Med* 1997;156:1719–1724.
131. Anthonisen NR. OM-8BV for COPD. *Am J Respir Crit Care Med* 1997;156:1713–1714.
132. Irwin RS, Boulet LP, Cloutier MM, Fuller R, Gold PM, Hoffstein V, Ing AJ, McCool FD, O'Byrne P, Poe RH, Prakash UB, Pratter MR, Rubin BK. Managing cough as a defense mechanism and as a symptom: a consensus panel report of the American College of Chest Physicians. *Chest* 1998;114:133S–181S.
133. Barbera JA, Roger N, Roca J, Rovira I, Higenbottam TW, Rodriguez-Roisin R. Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease. *Lancet* 1996;347:436–440.
134. Jones AT, Evans TW. NO: COPD and beyond. *Thorax* 1997;52(Suppl 3):S16–21.
135. Bardsley PA, Howard P, DeBacker W, Vermeire P, Mairesse M, Ledent C, Radermecker M, Bury T, Ansquer J. Two years treatment with almitrine bismesylate in patients with hypoxic chronic obstructive airways disease. *Eur Respir J* 1991;4:308–310.
136. Watanabe S, Kanner RE, Cutillo AG, Menlove RL, Bachand RT Jr, Szalkowski MB, Renzetti AD Jr. Long-term effect of almitrine bismesylate in patients with hypoxemic chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989;140:1269–1273.
137. Winkelmann BR, Kullmer TH, Kneissl DG, Trenk D, Kronenberger H. Low-dose almitrine bismesylate in the treatment of hypoxemia due to chronic obstructive pulmonary disease. *Chest* 1994;105:1383–1391.
138. Eiser N, Denman WT, West C, Luce P. Oral diamorphine: lack of effect on dyspnoea and exercise tolerance in the "pink puffer" syndrome. *Eur Respir J* 1991;4:926–931.
139. Young IH, Daviskas E, Keena VA. Effect of low dose nebulised morphine on exercise endurance in patients with chronic lung disease. *Thorax* 1989;44:387–390.
140. Rice KL, Kronenberg RS, Hedemark LL, Niewoehner DE. Effects of chronic administration of codeine and promethazine on breathlessness and exercise tolerance in patients with chronic airflow obstruction. *Br J Dis Chest* 1987;81:287–292.
141. Woodcock AA, Gross ER, Gellert A, Shah S, Johnson M, Geddes DM. Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. *N Engl J Med* 1981;305:1611–1616.
142. Poole PJ, Veale AG, Black PN. The effect of sustained-release morphine on breathlessness and quality of life in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1877–1880.
143. Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. *Am J Respir Crit Care Med* 1999;160:1248–1253.
144. Foglio K, Bianchi L, Bruletti G, Battista L, Pagani M, Ambrosino N. Long-term effectiveness of pulmonary rehabilitation in patients with chronic airway obstruction. *Eur Respir J* 1999;13:125–132.
145. Young P, Dewse M, Fergusson W, Kolbe J. Improvements in outcomes for chronic obstructive pulmonary disease (COPD) attributable to a hospital-based respiratory rehabilitation programme. *Aust N Z J Med* 1999;29:59–65.
146. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, Turner-Lawlor PJ, Payne N, Newcombe RG, Ionescu AA, Thomas J, Tunbridge J, Lonescu AA. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000;355:362–368.
147. Goldstein RS, Gort EH, Stubbing D, Avendano MA, Guyatt GH. Randomised controlled trial of respiratory rehabilitation. *Lancet* 1994;344:1394–1397.
148. Wijkstra PJ, Van Altena R, Kraan J, Otten V, Postma DS, Koeter GH. Quality of life in patients with chronic obstructive pulmonary disease improves after rehabilitation at home. *Eur Respir J* 1994;7:269–273.
149. McGavin CR, Gupta SP, Lloyd EL, McHardy GJ. Physical rehabilitation for the chronic bronchitic: results of a controlled trial of exercises in the home. *Thorax* 1977;32:307–311.

150. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980;93:391–398.
151. Report of the Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* 1981;1:681–686.
152. Tarpy SP, Celli BR. Long-term oxygen therapy. *N Engl J Med* 1995; 333:710–714.
153. Mehran RJ, Deslauriers J. Indications for surgery and patient work-up for bullectomy. *Chest Surg Clin North Am* 1995;5:717–734.
154. Benditt JO, Albert RK. Surgical options for patients with advanced emphysema. *Clin Chest Med* 1997;18:577–593.
155. Geddes D, Davies M, Koyama H, Hansell D, Pastorino U, Pepper J, Agent P, Cullinan P, MacNeill SJ, Goldstraw P. Effect of lung-volume-reduction surgery in patients with severe emphysema. *N Engl J Med* 2000;343:239–245.
156. The National Emphysema Treatment Trial Research Group. Rationale and design of The National Emphysema Treatment Trial: a prospective randomized trial of lung volume reduction surgery. *Chest* 1999; 116:1750–1761.
157. Trulock EP. Lung transplantation. *Am J Respir Crit Care Med* 1997; 155:789–818.
158. Theodore J, Lewiston N. Lung transplantation comes of age. *N Engl J Med* 1990;322:772–774.
159. Hosenpud JD, Bennett LE, Keck BM, Fiol B, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: fifteenth official report—1998. *J Heart Lung Transplant* 1998;17:656–668.
160. Annual Report of the U.S. Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network. Transplant data: 1988–1994. Division of Transplantation, Health Resources and Services Administration, U.S. Department of Health and Human Services, Washington, DC. 1995.
161. Maurer JR, Frost AE, Estenne M, Higenbottam T, Glanville AR. International guidelines for the selection of lung transplant candidates. The International Society for Heart and Lung Transplantation, the American Thoracic Society, the American Society of Transplant Physicians, the European Respiratory Society. *Transplantation* 1998; 66:951–956.
162. Regueiro CR, Hamel MB, Davis RB, Desbiens N, Connors AF Jr, Phillips RS. A comparison of generalist and pulmonologist care for patients hospitalized with severe chronic obstructive pulmonary disease: resource intensity, hospital costs, and survival. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. *Am J Med* 1998;10:366–372.
163. Gibson PG, Wlodarczyk JH, Wilson AJ, Sprogis A. Severe exacerbation of chronic obstructive airways disease: health resource use in general practice and hospital. *J Qual Clin Pract* 1998;18:125–133.
164. Warren PM, Flenley DC, Millar JS, Avery A. Respiratory failure revisited: acute exacerbations of chronic bronchitis between 1961–68 and 1970–76. *Lancet* 1980;1:467–470.
165. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106:196–204.
166. Wilson R. The role of infection in COPD. *Chest* 1998;113:242S–248S.
167. Soler N, Torres A, Ewig S, Gonzalez J, Celis R, El-Ebiary M, Hernandez C, Rodriguez-Roisin R. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 1998; 157:1498–1505.
168. Smith CB, Kanner RE, Golden CA, Klauber MR, Renzetti AD Jr. Effect of viral infections on pulmonary function in patients with chronic obstructive pulmonary diseases. *J Infect Dis* 1980;141:271–280.
169. MacFarlane JT, Colville A, Guion A, Macfarlane RM, Rose DH. Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. *Lancet* 1993;341:511–514.
170. Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest* 2000;117:1638–1645.
171. Anderson HR, Spix C, Medina S, Schouten JP, Castellsague J, Rossi G, Zmirou D, Touloumi G, Wojtyniak B, Ponka A, Bacharova L, Schwartz J, Katsouyanni K. Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. *Eur Respir J* 1997;10:1064–1071.
172. Chodosh S, McCarty J, Farkas S, Drehobl M, Tosiello R, Shan M, Aneiro L, Kowalsky S. Randomized, double-blind study of ciprofloxacin and cefuroxime axetil for treatment of acute bacterial exacerbations of chronic bronchitis. The Bronchitis Study Group. *Clin Infect Dis* 1998;27:722–729.
173. Walsh EE, Falsey AR, Hennessey PA. Respiratory syncytial and other virus infections in persons with chronic cardiopulmonary disease. *Am J Respir Crit Care Med* 1999;160:791–795.
174. Mogulkoc N, Karakurt S, Isalska B, Bayindir U, Celikel T, Korten V, Colpan N. Acute purulent exacerbation of chronic obstructive pulmonary disease and *Chlamydia pneumoniae* infection. *Am J Respir Crit Care Med* 1999;160:349–353.
175. Murphy TF, Sethi S, Klingman KL, Brueggemann AB, Doern GV. Simultaneous respiratory tract colonization by multiple strains of nontypeable *Haemophilus influenzae* in chronic obstructive pulmonary disease: implications for antibiotic therapy. *J Infect Dis* 1999;180: 404–409.
176. Emerman CL, Effron D, Lukens TW. Spirometric criteria for hospital admission of patients with acute exacerbation of COPD. *Chest* 1991; 99:595–599.
177. Emerman CL, Lukens TW, Effron D. Physician estimation of FEV_1 in acute exacerbation of COPD. *Chest* 1994;105:1709–1712.
178. Emerman CL, Cydulka RK. Use of peak expiratory flow rate in emergency department evaluation of acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med* 1996;27:159–163.
179. Emerman CL, Connors AF, Lukens TW, Effron D, May ME. Relationship between arterial blood gases and spirometry in acute exacerbations of chronic obstructive pulmonary disease. *Ann Emerg Med* 1989;18:523–527.
180. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med* 1996;154:407–412.
181. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet* 1999;354:456–460.
182. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, Anderson P, Morgan NA. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med* 1999;340:1941–1947.
183. Connors AF Jr, Dawson NV, Thomas C, Harrell FE Jr, Desbiens N, Fulkerson WJ, Kussin P, Bellamy P, Goldman L, Knaus WA. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators. *Am J Respir Crit Care Med* 1996;154:959–967.
184. Shepperd S, Harwood D, Gray A, Vessey M, Morgan P. Randomised controlled trial comparing hospital at home care with inpatient hospital care. II: cost minimisation analysis. *BMJ* 1998;316:1791–1796.
185. Gravil JH, Al-Rawas OA, Cotton MM, Flanigan U, Irwin A, Stevenson RD. Home treatment of exacerbations of chronic obstructive pulmonary disease by an acute respiratory assessment service. *Lancet* 1998; 351:1853–1855.
186. Moayyedi P, Congleton J, Page RL, Pearson SB, Muers MF. Comparison of nebulised salbutamol and ipratropium bromide with salbutamol alone in the treatment of chronic obstructive pulmonary disease. *Thorax* 1995;50:834–837.
187. Fernandez A, Munoz J, de la Calle B, Alia I, Ezpeleta A, de la Cal MA, Reyes A. Comparison of one versus two bronchodilators in ventilated COPD patients. *Intensive Care Med* 1994;20:199–202.
188. Barbera JA, Reyes A, Roca J, Montserrat JM, Wagner PD, Rodriguez-Roisin R. Effect of intravenously administered aminophylline on ventilation/perfusion inequality during recovery from exacerbations of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992; 145:1328–1333.
189. Mahon JL, Laupacis A, Hodder RV, McKim DA, Paterson NA, Wood TE, Donner A. Theophylline for irreversible chronic airflow limitation: a randomized study comparing n of 1 trials to standard practice. *Chest* 1999;115:38–48.
190. Lloberes P, Ramis L, Montserrat JM, Serra J, Campistol J, Picado C, Agusti-Vidal A. Effect of three different bronchodilators during an exacerbation of chronic obstructive pulmonary disease. *Eur Respir J* 1988;1:536–539.
191. Murciano D, Aubier M, Lecocguic Y, Pariente R. Effects of theophylline on diaphragmatic strength and fatigue in patients with chronic obstructive pulmonary disease. *N Engl J Med* 1984;311:349–353.
192. Emerman CL, Connors AF, Lukens TW, May ME, Effron D. Theophylline concentrations in patients with acute exacerbation of COPD. *Am J Emerg Med* 1990;8:289–292.
193. Meyer TJ, Hill NS. Noninvasive positive pressure ventilation to treat respiratory failure. *Ann Intern Med* 1994;120:760–770.

194. International Consensus Conferences in Intensive Care Medicine: noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 2001;163:283–291.
195. Bott J, Carroll MP, Conway JH, Keilty SE, Ward EM, Brown AM, Paul EA, Elliott MW, Godfrey RC, Wedzicha JA, *et al.* Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993;341:1555–1557.
196. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, Simonneau G, Benito S, Gasparetto A, Lemaire F. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995;333:817–822.
197. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 1995;151:1799–1806.
198. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet* 2000;355:1931–1935.
199. Esteban A, Anzueto A, Alia I, Gordo F, Apezteguia C, Palizas F, Cide D, Goldwaser R, Soto L, Budego G, Rodrigo C, Pimentel J, Raimondi G, Tobin MJ. How is mechanical ventilation employed in the intensive care unit? An international utilization review. *Am J Respir Crit Care Med* 2000;161:1450–1458.
200. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I, Fernandez R, de la Cal MA, Benito S, Tomas R, Carriedo D, Macias S, Blanco J, for the Spanish Lung Failure Collaborative Group. A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med* 1995;332:345–350.
201. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, Gasparetto A, Lemaire F. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1994;150;896–903.
202. Nava S, Ambrosino N, Clini E, Prato M, Orlando G, Vitacca M, Brigada P, Fracchia C, Rubini F. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease: a randomized, controlled trial. *Ann Intern Med* 1998;128:721–728.
203. Hilbert G, Gruson D, Portel L, Gbikpi-Benissan G, Cardinaud JP. Noninvasive pressure support ventilation in COPD patients with postextubation hypercapnic respiratory insufficiency. *Eur Respir J* 1998;11:1349–1353.
204. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159:158–164.
205. Mushlin AI, Black ER, Connolly CA, Buonaccorso KM, Eberly SW. The necessary length of hospital stay for chronic pulmonary disease. *JAMA* 1991;266:80–83.
206. Stoller JK, Lange PA. Inpatient management of chronic obstructive pulmonary disease. *Respir Care Clin North Am* 1998;4:425–438.
207. Peach H, Pathy MS. Follow-up study of disability among elderly patients discharged from hospital with exacerbations of chronic bronchitis. *Thorax* 1981;36:585–589.
208. NHS Executive. Burdens of Disease: A Discussion Document. Department of Health, London, UK.
209. Rutten-van Mölken MP, Postma MJ, Joore MA, Van Genugten ML, Leidl R, Jager JC. Current and future medical costs of asthma and chronic obstructive pulmonary disease in The Netherlands. *Respir Med* 1999;93:779–787.
210. Jacobson L, Hertzman P, Lofdahl C-G, Skoogh B-E, Lindgren B. The economic impact of asthma and COPD in Sweden 1980 and 1991. *Respir Med* 2000;94:247–255.