

Global Initiative for Chronic Obstructive Lung Disease



**GLOBAL STRATEGY FOR THE DIAGNOSIS,
MANAGEMENT, AND PREVENTION OF
CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

UPDATED 2004

EXECUTIVE SUMMARY

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(Based on an April 1998 NHLBI/WHO Workshop)



Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: NHLBI/WHO Workshop

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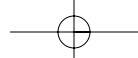
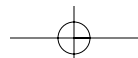


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PREFACE

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 States¹ 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 Organization². 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 US 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. We look forward to working with all interested organizations and individuals to meet the goals of the GOLD Initiative.

Development of the Workshop Report was supported through educational grants to the Department of Respiratory Diseases of the Ghent University Hospital, Belgium (WHO Collaborating Center for the Management of Asthma and COPD) from Altana, Andi-Ventis, AstraZeneca, Aventis, Bayer, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Sharp & Dohme, Mitsubishi Pharma, Nikken Chemicals, Novartis, Pfizer, Schering-Plough, and Zambon.

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Methodology and Summary of Recommendations (2004 Update)

The GOLD Workshop Report, *Global Strategy for Diagnosis, Management and Prevention of COPD* presented in 2001 was based on the scientific literature available at that time. To assure that the recommendations for management of COPD remained as current as possible, the GOLD Executive Committee established a Science Committee* to review published research and to post an updated report yearly on the GOLD website. The first update (2003) was posted on July 1, 2003. This second update (2004) includes review of publications from April through December 2003 (January to March 2003 publications were included in the 2003 update). A revision of the entire document has been implemented and is scheduled to be completed in 2006.

Methods: The process used for the 2004 update, identical to that described for the 2003 update, included a Pub Med search using search fields established by the Committee: 1) COPD OR chronic bronchitis OR emphysema, All Fields, All Adult, 19+ years, only items with abstracts, Clinical Trial, Human, sorted by Authors; and 2) COPD OR chronic bronchitis OR emphysema AND systematic, All fields, All adult, 19+ years, only items with abstracts, Human, sorted by Author. In addition, publications in peer review journals not captured by Pub Med could be submitted to individual members of the Committee providing an abstract and the full paper were submitted in (or translated into) English.

All members of the Committee received a summary of citations and all abstracts. Each abstract was assigned to 2 Committee Members (members were not assigned to a paper where he/she appears as an Author), although any member was offered the opportunity to provide an opinion on any abstract. Members evaluated the abstract or, up to her/his judgment, the full publication, by answering specific written questions from a short questionnaire, and to indicate if the scientific data presented impacted on recommendations in the GOLD Workshop report. If so, the member was asked to specifically identify modifications that should be made. The entire GOLD Science Committee met on a regular basis to discuss each individual publication that was indicated to have an impact on COPD management by at least 1 member of the Committee, and to reach a consensus on the changes in the report. Disagreements were decided by vote.

*Members: L. Fabbri, *Chair*, P. Barnes, S. Buist, P. Calverley, Y. Fukuchi, W. MacNee, R. Pauwels, K. Rabe, R. Rodriguez-Roisin, J. Zielinski

GOLD Executive Summary (2004 Update): Summary of Recommendations

Between April 1 and December 2003, 140 articles met the search criteria. Of these, 16 papers were identified to have an impact on the GOLD report, either by: 1) confirming, that is, adding or replacing an existing reference, or 2) modifying, that is, changing the text or introducing a concept that required a new recommendation to the report.

The most important changes can be summarized as follows:

- Page 14: A statement was added to indicate that withdrawal from treatment with inhaled glucocorticosteroids can lead to exacerbations in some patients.
- Page 14: Two new references have been added to further support the recommendation that inhaled glucocorticosteroids combined with a long acting β_2 -agonist is more effective than the individual components in symptomatic COPD patients with an FEV₁ < 50% predicted (*Stage III: Severe COPD* and *Stage IV: Very Severe COPD*) and repeated exacerbations (Evidence A).
- Page 16: The recommendation for lung volume reduction surgery (LVRS) has been modified, reporting that it does not improve life expectancy but improves exercise capacity in patients with predominant upper lobe emphysema and a low post rehabilitation exercise capacity, and may improve global health status in patients with heterogeneous emphysema.
- Page 16: Based on a retrospective review of the literature triggered by new articles appearing after 2001, a new section has been added on recommendations for surgery in COPD.

Two additional issues were covered in the Workshop Report (updated 2004). On page 75, after a retrospective

review of the literature triggered by a 2003 publication, a statement regarding the use of walking aids in patients with COPD has been added. On page 77, the role of oxygen supplementation before, during or after exercise has been discussed with the suggestion that there is no evidence of benefit from using short burst oxygen for symptom -matic relief before or after exercise.

The GOLD Science Committee acknowledged the publication of the ATS/ERS position paper on COPD¹ that overall confirms almost all recommendations of the GOLD Workshop, but also expands some topics not covered or only marginally touched by the GOLD Reports. Prior to its release, the proposed modifications for the GOLD Workshop Report (Updated 2004) were submitted to the GOLD Executive Committee for approval.

The GOLD Workshop Report (Updated 2004), the GOLD Executive Summary(Updated 2004), and the GOLD Pocket Guide (Updated 2004) along with the complete list of references examined by the Committee are available on the GOLD website (www.goldcopd.org).

Reference

1. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23(6):932-46.

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 world³, 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 **Global Initiative for Chronic Obstructive Lung Disease (GOLD)** is conducted in collaboration with the US 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.

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. Prior to 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 boldface enclosed in parentheses after the relevant statement – e.g., (**Evidence A**).

Evidence Category	Sources of Evidence	Definition
A	Randomized controlled trials (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	Randomized controlled trials (RCTs). Limited body of data.	Evidence is from endpoints of intervention studies that include only a limited number of patients, posthoc 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, 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.

1. 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 postbronchodilator FEV₁ < 80% of the predicted value in combination with an FEV₁/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 abnormal 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 since 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 FEV₁ values refer to postbronchodilator FEV₁.

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 (FEV₁/FVC < 70% but FEV₁ ≥ 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 (50% ≤ FEV₁ < 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.

Table 2 - Classification of Severity*

Stage	Characteristics
0: At Risk	<ul style="list-style-type: none"> • normal spirometry • chronic symptoms (cough, sputum production)
I: Mild COPD	<ul style="list-style-type: none"> • FEV₁/FVC < 70% • FEV₁ ≥ 80% predicted • with or without chronic symptoms (cough, sputum production)
II: Moderate COPD	<ul style="list-style-type: none"> • FEV₁/FVC < 70% • 50% ≤ FEV₁ < 80% predicted • with or without chronic symptoms (cough, sputum production)
III: Severe COPD	<ul style="list-style-type: none"> • FEV₁/FVC < 70% • 30% ≤ FEV₁ < 50% predicted with or without chronic symptoms (cough, sputum production)
IV: Very Severe COPD	<ul style="list-style-type: none"> • FEV₁/FVC < 70% • FEV₁ < 30% predicted or FEV₁ < 50% predicted plus chronic respiratory failure

*Classification based on postbronchodilator FEV₁
 FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO₂) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO₂ (PaCO₂) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.

Stage III: Severe COPD - characterized by further worsening of airflow limitation ($30\% \leq FEV_1 < 50\%$ predicted), increased shortness of breath, and repeated exacerbations which have an impact on patients' quality of life.

Stage IV: Very Severe COPD - Characterized by severe airflow limitation ($FEV_1 < 30\%$ predicted) or the presence of chronic respiratory failure. Patients may have very severe (Stage IV) 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 (LTB₄)⁴, interleukin 8 (IL-8)⁵⁻⁷, tumor necrosis factor α (TNF- α)^{5,8}, and others – capable of damaging lung structures and/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 lungs⁹⁻¹⁴. Although fewer data are available, it is likely that other COPD risk factors initiate a similar inflammatory process¹⁵⁻¹⁹. It is believed that this inflammation can then lead to COPD.

PATHOLOGY

Pathological 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 2-4 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 wall²². 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 obstruction²³.

Destruction of the lung parenchyma in COPD patients typically occurs as centrilobular emphysema. This involves dilatation and destruction of the respiratory bronchioles²⁴. 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 – due to 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 contribute²⁵.

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 change²⁶, followed by an increase in smooth muscle and the infiltration of the vessel wall by inflammatory cells²⁷. As COPD worsens, greater amounts of smooth muscle, proteoglycans, and collagen²⁸ further thicken the vessel wall.

PATHOPHYSIOLOGY

Pathological changes in the lungs lead to corresponding physiological 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 physiological abnormalities develop.

Expiratory airflow limitation, best measured through spirometry, is the hallmark physiological change of COPD³ and the key to diagnosis of the disease. It is primarily

due to fixed airways obstruction and the consequent increase in airways 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 IV: Very Severe COPD*), is the major cardiovascular complication of COPD and is associated with the development of cor pulmonale and a poor prognosis²⁹. The prevalence and natural history of cor pulmonale in COPD are not yet clear.

2. BURDEN OF COPD

EPIDEMIOLOGY

Most of the information available on COPD prevalence, morbidity, and mortality comes from developed countries. Even in these countries, accurate epidemiological 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 developed³⁰ 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 all³¹.

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, while 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 women¹. COPD is responsible for a significant part of physician visits, emergency department visits, and hospitalizations.

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\$)
UK ³³	1996	778	3,312	4,090	65
The Netherlands ³⁴	1993	256	N/A	N/A	N/A [#]
Sweden ³⁵	1991	179	281	460	60
US 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.
The authors did not provide estimates of indirect costs.

Mortality: COPD is currently the fourth leading cause of death in the world², and further increases in the prevalence and mortality of the disease can be predicted in the coming decades^{2,32}. In the US, COPD death rates are very low among people under age 45 but then increase with age, and COPD becomes the fourth or fifth leading cause of death among those over 45¹.

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 pre-

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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mature 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**).

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 alpha-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, fumes); and indoor/outdoor air pollution.

The role of gender as a risk factor for COPD remains unclear. In the past, most studies showed that COPD prevalence and mortality were greater among men than women³⁶⁻³⁹. More recent studies^{1,40} 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^{38,41}. 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 alpha-1 antitrypsin⁴²⁻⁴⁴. 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 COPD⁴⁵, 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 airways disease.

Lung Growth: Lung growth is related to processes occurring during gestation, birth weight, and exposures during childhood⁴⁶⁻⁵⁰. Reduced maximal attained lung function (as measured by spirometry) may identify individuals who are at increased risk for the development of COPD⁵¹.

Exposures

Tobacco Smoke: Cigarette smokers have a higher prevalence of lung-function abnormalities and respiratory symptoms, a greater annual rate of decline in FEV₁, 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 smokers⁵². 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^{36,53,54}. 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^{50,55}.

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 smoking⁵⁶. Exposure to particulate matter, irritants, organic dusts, and sensitizing agents can cause an increase in airway hyperresponsiveness⁵⁷, 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 COPD⁵⁸⁻⁶⁷.

Infections: A history of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood⁵¹. 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

status⁶⁸. 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^{67,69}.

3. 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 COPD patients 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 community-based 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. 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 COPD patients should have access to spirometry.
- 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, or dyspnea, and/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 develop⁷⁰, 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 COPD patients 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 non-specific 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.

Table 5 - Key Indicators for Considering a Diagnosis of COPD	
<i>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.</i>	
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.

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

- Exposure to risk factors
- Past medical history, including asthma, allergy, sinusitis or nasal polyps, respiratory infections in childhood, and other respiratory diseases
- Family history of COPD or other chronic respiratory disease
- Pattern of symptom development
- History of exacerbations or previous hospitalizations for respiratory disorder
- Presence of comorbidities, such as heart disease and rheumatic disease, that may also contribute to restriction of activity
- Appropriateness of current medical treatments
- 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

- Social and family support available to the patient
- 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^{71,72}, 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 (forced vital capacity, FVC) and the volume of air exhaled during the first second of this maneuver (forced expiratory volume in one second, FEV₁), and the ratio of these two measurements (FEV₁/FVC) should be calculated. Patients with COPD typically show a decrease in both FEV₁ and FVC. The presence of a postbronchodilator FEV₁ < 80% of the predicted value in combination with an FEV₁/FVC < 70% confirms the presence of airflow limitation that is not fully reversible. The FEV₁/FVC on its own is a more sensitive measure of airflow limitation, and an FEV₁/FVC < 70% is considered an early sign of airflow limitation in patients whose FEV₁ remains normal (≥ 80% predicted). This approach to defining airflow limitation is a pragmatic one in view of the fact that universally applicable reference values for FEV₁ 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.

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 FEV₁ response to a short-acting bronchodilator test may benefit symptomatically from long-term bronchodilator treatment.

Chest X-ray: A chest X-ray 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.

Arterial blood gas measurement: In advanced COPD, measurement of arterial blood gases is important. This test should be performed in patients with FEV₁ < 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 exacerbations. Respiratory failure is indicated by a PaO₂ < 8.0 kPa (60 mm Hg) with or without PaCO₂ > 6.7 kPa (50 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 arterial oxygen saturation (SaO₂) are less reliable.

Alpha-1 antitrypsin deficiency screening: In patients who develop COPD at a young age (< 45 years) or who have a strong family history of the disease, it may be valuable to identify coexisting alpha-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 physiological 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

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, and/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.

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 PaO_2 .

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, 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 – intervention 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 the 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**).

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-minute 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^{75,76}. 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 US Agency for Health Care Policy and Research (AHCPR) in 1996⁷⁷ and updated in 2000 by the US Public Health Service in *Treating Tobacco Use and Dependence: A Clinical Practice Guideline*⁷⁸.

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 treatment⁷⁷⁻⁸¹ (**Evidence A**).

Pharmacotherapy: Numerous effective pharmacotherapies for smoking cessation now exist^{78,82,83} (**Evidence A**). Except in the presence of special circumstances, pharma-

cotherapy 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^{78,83}. The antidepressants bupropion⁸⁴ and nortriptyline have also been shown to increase long-term quit rates, although fewer studies have been conducted with these medications^{78,83}. The effectiveness of the antihypertensive drug clonidine is limited by side effects⁸³. 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 gases⁸⁵. 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 patient⁸⁶. 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.

Table 7 - Strategies to Help the Patient Willing to Quit Smoking⁷⁸
<p>1. ASK: Systematically identify all tobacco users at every visit. <i>Implement an office-wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco-use status is queried and documented.</i></p>
<p>2. ADVISE: Strongly urge all tobacco users to quit. <i>In a clear, strong, and personalized manner, urge every tobacco user to quit.</i></p>
<p>3. ASSESS: Determine willingness to make a quit attempt. <i>Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).</i></p>
<p>4. ASSIST: Aid the patient in quitting. <i>Help the patient with a quit plan; provide practical counseling; provide intra-treatment social support; help the patient obtain extra-treatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.</i></p>
<p>5. ARRANGE: Schedule follow-up contact. <i>Schedule follow-up contact, either in person or via telephone.</i></p>

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/or 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 long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators, but more expensive (**Evidence A**).
- The addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate for symptomatic COPD patients with an $FEV_1 < 50\%$ predicted (*Stage III: Severe COPD* and *Stage IV: Very Severe COPD*) and repeated exacerbations (**Evidence A**).
- Chronic treatment with systemic glucocorticosteroids should be avoided because of an unfavorable benefit-to-risk ratio (**Evidence A**).
- All COPD patients 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 hours 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 function⁸⁷⁻⁹⁰, it can play a role in improving skills, ability to cope with illness, and health status⁹¹. In addition, patient education is effective in accomplishing certain specific goals, including smoking cessation⁴¹ (**Evidence A**), initiating discussions and understanding of advance directives and end-of-life issues⁹² (**Evidence B**), and improving patient responses to exacerbations^{93,94} (**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 (**Table 10**) has been shown to modify the long-

term decline in lung function that is the hallmark of this disease^{41,95-98} (**Evidence A**). However, this should not preclude efforts to use medications to control symptoms.

BRONCHODILATORS

Bronchodilator medications are central to the symptomatic management of COPD⁹⁹⁻¹⁰² (**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 the FEV₁ 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.

Bronchodilator drugs commonly used in treating COPD include: β_2 -agonists, anticholinergics, and methylxanthines.

Table 9 - Bronchodilators in Stable COPD
<ul style="list-style-type: none"> • 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 effective and convenient, but more expensive. • Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

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 FEV₁^{103,104} (**Evidence A**).

Table 8 - Therapy at Each Stage of COPD					
Old	0: At Risk	I: Mild	II: Moderate		III: Severe
New	0: At Risk	I: Mild	II: Moderate	III: Severe	IV: Very Severe
Characteristics	<ul style="list-style-type: none"> • Chronic symptoms • Exposure to risk factors • Normal spirometry 	<ul style="list-style-type: none"> • FEV₁/FVC < 70% • FEV₁ \geq 80% • With or without symptoms 	<ul style="list-style-type: none"> • FEV₁/FVC < 70% • 50% \leq FEV₁ < 80% • With or without symptoms 	<ul style="list-style-type: none"> • FEV₁/FVC < 70% • 30% \leq FEV₁ < 50% • With or without symptoms 	<ul style="list-style-type: none"> • FEV₁/FVC < 70% • FEV₁ < 30% or FEV₁ < 50% predicted plus chronic respiratory failure
	Avoidance of risk factor(s); influenza vaccination				
		Add short-acting bronchodilator when needed			
			Add regular treatment with one or more long-acting bronchodilators Add rehabilitation		
				Add inhaled glucocorticosteroids if repeated exacerbations	
					Add long-term oxygen if chronic respiratory failure Consider surgical treatments

Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators, but more expensive¹⁰⁵⁻¹⁰⁷ (**Evidence A**). Regular use of a long-acting β_2 -agonist¹⁰⁵ or long-acting anticholinergic improves health status¹⁰⁵⁻¹⁰⁷. Theophylline is effective in COPD, but due to its potential toxicity, inhaled bronchodilators are preferred when avail-

able. 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 an anticholinergic produces

Table 10 - Commonly Used Formulations of Drugs for COPD					
Drug	Inhaler (μ g)	Solution for Nebulizer (mg/ml)	Oral	Vials for injection (mg)	Duration of Action (hours)
β_2-agonists					
Short-acting					
Fenoterol	100-200 (MDI)	1	0.05% (Syrup)		4-6
Salbutamol (albuterol)	100, 200 (MDI & DPI)	5	5mg (Pill) Syrup 0.024%	0.1, 0.5	4-6
Terbutaline	400, 500 (DPI)	-	2.5, 5 (Pill)	0.2, 0.25	4-6
Long-acting					
Formoterol	4.5-12 (MDI & DPI)				12+
Salmeterol	25-50 (MDI & DPI)				12+
Anticholinergics					
Short-acting					
Ipratropium bromide	20, 40 (MDI)	0.25-0.5			6-8
Oxipropium bromide	100 (MDI)	1.5			7-9
Long-acting					
Tiotropium	18 (DPI)				+24
Combination short-acting β_2-agonists plus anticholinergic in one inhaler					
Fenoterol/Ipratropium	200/80 (MDI)	1.25/0.5			6-8
Salbutamol/Ipratropium	75/15 (MDI)	0.75/4.5			6-8
Methylxanthines					
Aminophylline			200-600 mg (Pill)	240 mg	Variable, up to 24
Theophylline (SR)			100-600 mg (Pill)		Variable, up to 24
Inhaled glucocorticosteroids					
Beclomethasone	50- 400 (MDI & DPI)	0.2-0.4			
Budesonide	100, 200, 400 (DPI)	0.20, 0.25, 0.5			
Fluticasone	50-500 (MDI & DPI)				
Triamcinolone	100 (MDI)	40		40	
Combination long-acting β_2-agonists plus glucocorticosteroids in one inhaler					
Formoterol/Budesonide	4.5/80, 160 (DPI) (9/320) (DPI)				
Salmeterol/Fluticasone	50/100, 250, 500 (DPI) 25/50, 125, 250 (MDI)				
Systemic glucocorticosteroids					
Prednisone			5-60 mg (Pill)		
Methyl-prednisolone	10-2000 mg		4, 8, 16 mg (Pill)		

MDI=metered dose inhaler; DPI=dry powder inhaler

greater and more sustained improvements in FEV₁ than either alone and does not produce evidence of tachyphylaxis over 90 days of treatment¹⁰⁸⁻¹¹⁰ (**Evidence A**).

Combination of a β_2 -agonist, an anticholinergic, and/or theophylline may produce additional improvements in lung function^{108,111-115} and health status^{104,108,111,116}. 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 episodes¹¹⁷ (**Evidence B**). Some patients may request regular treatment with high-dose, nebulized bronchodilators¹¹⁸, especially if they have experienced subjective benefit from this treatment during an exacerbation. Clear scientific evidence for this approach is lacking, but one option is to examine the improvement in mean daily peak expiratory flow recording during 2 weeks of treatment in the home and continue with nebulizer therapy if a significant improvement occurs¹¹⁸. In general, nebulized therapy for a stable patient is not appropriate unless it has been shown to be better than conventional dose therapy.

GLUCOCORTICOSTEROIDS

Regular treatment with inhaled glucocorticosteroids does not modify the long-term decline of FEV₁ in patients with COPD⁹⁵⁻⁹⁸. However, regular treatment with inhaled glucocorticosteroids is appropriate for symptomatic COPD patients with an FEV₁ < 50% predicted (Stage III: Severe COPD and Stage IV: Very Severe COPD) and repeated exacerbations (for example, 3 in the last three years)¹¹⁹⁻¹²² (**Evidence A**). This treatment has been shown to reduce the frequency of exacerbations and improve health status (**Evidence A**), and withdrawal from treatment with inhaled glucocorticosteroids can lead to exacerbations in some patients²²³. Inhaled glucocorticosteroid combined with a long-acting β_2 -agonist is more effective than the individual components^{119,121,122,224,225} (**Evidence A**).

Many existing COPD guidelines recommend the use of a short course (two weeks) of oral glucocorticosteroids to identify COPD patients 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^{97,123}. Long-term treatment with oral glucocorticosteroids is not

recommended in COPD¹²⁴⁻¹²⁶ (**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^{125,126}, 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 COPD patients by about 50%^{127, 226}. Vaccines containing killed or live, inactivated viruses are recommended¹²⁸, 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 lacking¹²⁹⁻¹³¹ (**Evidence B**).

Alpha-1 Antitrypsin Augmentation Therapy: Young patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy. However, this therapy is very expensive, is not available in most countries, and is not recommended for COPD that is unrelated to alpha-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^{132,133} (**Evidence A**).

Mucolytic (Mucokinetic, Muco regulator) Agents (ambroxol, erdosteine, carbocysteine, iodinated glycerol): Although a few patients with viscous sputum may benefit from mucolytics^{134,135}, 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 exacerbations¹³⁶⁻¹³⁹ (**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 exacerbations¹⁴⁰, but these results have not been duplicated. Thus, the regular use of this

therapy cannot be recommended based on the present evidence¹⁴¹ (**Evidence B**).

Antitussives: Cough, although sometimes a troublesome symptom in COPD, has a significant protective role¹⁴². 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-perfusion balance^{143,144} 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 patients¹⁴⁵⁻¹⁴⁷ (**Evidence B**).

Narcotics: The use of oral and parenteral opioids are effective for treating dyspnea in COPD patients with advanced disease. There are insufficient data to conclude whether nebulized opioids are effective¹⁴⁸. However, there are some clinical studies suggesting that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects¹⁴⁹⁻¹⁵³.

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.

NON-PHARMACOLOGIC 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. COPD patients at all stages of disease benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue¹⁵⁴ (**Evidence A**). The minimum length of an effective rehabilitation program is two months; the longer the program continues, the more effective the results¹⁵⁵⁻¹⁵⁷ (**Evidence B**). However, as yet,

no effective structure has been developed to maintain the effects over time¹⁵⁸. Benefits have been reported from rehabilitation programs conducted in inpatient, outpatient, and home settings¹⁵⁹⁻¹⁶¹.

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:

- Detailed medical history and physical examination
- Measurement of spirometry before and after a bronchodilator drug
- Assessment of exercise capacity
- Measurement of health status and the impact of breathlessness
- 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 baseline and outcome measures.

OXYGEN THERAPY

The long-term administration of oxygen (>15 hours per day) to patients with chronic respiratory failure has been shown to increase survival¹⁶²⁻¹⁶⁴ (**Evidence A**). It can also have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental state¹⁶⁴.

Long-term oxygen therapy is generally introduced in *Stage IV: Very Severe COPD* for patients who have:

- PaO₂ at or below 7.3 kPa (55 mm Hg) or SaO₂ at or below 88%, with or without hypercapnia; or
- PaO₂ between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg) or SaO₂ 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 PaO₂ to at least 8.0 kPa (60 mm Hg) at sea level and rest, and/or produce SaO₂ 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 PaO₂ 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 function¹⁶⁵ (**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): LVRS is a surgical procedure in which parts of the lung are resected to reduce hyperinflation. Results from large multicenter studies indicate that LVRS does not improve life expectancy but improves exercise capacity in patients with predominant upper lobe emphysema and a low post-rehabilitation exercise capacity²²⁷, and may improve global health status in patients with heterogeneous emphysema²²⁸. In some centers, with adequate experience, perioperative mortality of LVRS has been reported to be less than 5%. However, hospital costs associated with LVRS are high and it remains an experimental palliative surgical procedure not 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 capacity¹⁶⁰⁻¹⁶³ (**Evidence C**). Criteria for referral for lung transplantation include FEV₁ < 35% predicted, PaO₂ < 7.3-8.0 kPa (55-60 mm Hg), PaCO₂ > 6.7 kPa (50 mm Hg), and secondary pulmonary hypertension¹⁷⁰.

SPECIAL CONSIDERATIONS

Surgery in COPD: Postoperative pulmonary complications are as important and common as postoperative cardiac complications and, consequently, are a key component of increased risk of surgery in COPD patients. The principal potential factors contributing to the risk include smoking, poor general health status, age, obesity and COPD severity. A comprehensive definition of postoperative pulmonary complications should include only major pulmonary respiratory complications, namely lung

infections, atelectasis and/or increased airflow obstruction, all potentially resulting in acute respiratory failure and aggravation of underlying COPD²²⁹⁻²³⁴.

The surgical site is the most important predictor, and risk increases as the incision approaches the diaphragm. Upper abdominal and thoracic surgery represents the greatest risk, the latter being uncommon after interventions outside the thorax or abdomen. Most reports conclude that epidural or spinal anesthesia have a lower risk than with general anesthesia, although the results are not totally uniform. Patient-risk factors are identified by careful history, physical examination, chest radiography, and pulmonary function tests.

Several studies in high risk COPD patients suggest that there is threshold beyond which the risk of surgery is prohibitive. Surgery should be postponed if an exacerbation is present. Surgery in patients with COPD needs to be differentiated from that aimed to improve function and symptoms for COPD. This includes bullectomy, lung volume reduction surgery and lung transplantation²³⁴.

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 about one-third of severe exacerbations cannot be identified (**Evidence B**).
- Inhaled bronchodilators (particularly inhaled β_2 -agonists and/or anticholinergics), theophylline, and systemic, preferably oral, glucocorticosteroids are effective treatments for 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, and/or fever) may benefit from antibiotic treatment (**Evidence B**).
- Noninvasive intermittent positive pressure ventilation (NIPPV) in 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 exacerbations of symptoms¹⁷¹⁻¹⁷⁴. The economic and social burden of COPD exacerbations is extremely high. The most common causes of an exacerbation are infection of the tracheobronchial tree¹⁷⁵⁻¹⁷⁹ and air pollution¹⁸⁰, but the cause of about one-third of severe exacerbations cannot be identified. The role of bacterial infections, once believed to be the main cause of COPD exacerbations, is controversial^{175-179,181-184}. Conditions that may mimic the symptoms of an 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 and/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, and/or new radiological 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 production¹⁷⁹.

The assessment of the severity of an 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 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 of the patient 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, a PEF < 100 L per minute or an FEV₁ < 1.00 L indicates a severe exacerbation¹⁸⁵⁻¹⁸⁷.

Assessment of Arterial Blood Gases: In the hospital, measurement of arterial blood gases is essential to assess the severity of an exacerbation. A PaO₂ < 8.0 kPa (60 mm Hg) and/or SaO₂ < 90% with or without PaCO₂ > 6.7 kPa, 50 mmHg (when breathing room air) indicates respiratory failure. In addition, PaO₂ < 6.7 kPa (50 mm Hg), PaCO₂ > 9.3 kPa (70 mm Hg), and pH < 7.30 point towards a life-threatening episode that needs close monitoring or critical management¹⁸⁸.

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 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 PaO₂ 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.

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(s) (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 end-stage COPD patients, 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 and/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 exacerbations of COPD. They shorten recovery time and help to restore lung function more quickly¹⁸⁹⁻¹⁹¹ (**Evidence A**), and may reduce the risk of early relapse²³⁵. They should be considered in addition to bronchodilators if the patient's baseline FEV₁ is < 50% predicted. A dose of 40 mg prednisolone per day for 10 days is recommended (**Evidence D**). One large study indicates that nebulized budesonide may be an alternative to oral glucocortico-steroids in the treatment of nonacidotic exacerbations¹⁹².

Antibiotics: Antibiotics are only effective when patients with worsening dyspnea and cough also have increased

Table 11 - Indications for Hospital Assessment or Admission for Exacerbations of COPD*
<ul style="list-style-type: none"> • 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

Table 12 - Indications for ICU Admission of Patients with Exacerbations of COPD*
<ul style="list-style-type: none"> • Severe dyspnea that responds inadequately to initial emergency therapy. • Confusion, lethargy, coma. • Persistent or worsening hypoxemia (PaO₂ < 5.3 kPa, 40 mm Hg), and/or severe/worsening hypercapnia (PaCO₂ > 8.0 kPa, 60 mm Hg), and/or severe/worsening respiratory acidosis (pH < 7.25) despite supplemental oxygen and NIPPV.

* Local resources need to be considered

sputum volume and purulence¹⁷⁴ (**Evidence B**). 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 exacerbation of COPD is closely related to the development of respiratory acidosis, the presence of significant comorbidities, and the need

Table 13 - Management of Severe but Not Life-threatening Exacerbations of COPD in the Emergency Department or the Hospital*
<ul style="list-style-type: none"> • Assess severity of symptoms, blood gases, chest X-ray. • Administer controlled oxygen therapy and repeat arterial blood gas measurement after 30 minutes. • Bronchodilators: <ul style="list-style-type: none"> — Increase doses or frequency. — Combine β₂-agonists and anticholinergics. — Use spacers or air-driven nebulizers. — Consider adding intravenous methylxanthine, if needed. • Add glucocorticosteroids <ul style="list-style-type: none"> — Oral or intravenous. • Consider antibiotics <ul style="list-style-type: none"> — When signs of bacterial infection, oral or occasionally intravenous. • Consider noninvasive mechanical ventilation. • At all times: <ul style="list-style-type: none"> — 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

for ventilatory support¹⁹³. Patients lacking 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 success¹⁹⁴, 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 successful¹⁹⁵. However, detailed cost-benefit analyses of these approaches are awaited.

A range of criteria to consider for hospital assessment/admission for exacerbations of COPD are shown in **Table 11**. Some patients need immediate admission to an intensive care unit (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 ($\text{PaO}_2 > 8.0$ kPa, 60 mm Hg or $\text{SaO}_2 > 90\%$) 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 minutes 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 the treatment of exacerbations of COPD^{85,133,134} (**Evidence A**). 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 controversial^{196,197}. 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 without showing gas exchange deterioration^{198,199}. 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^{198,200,201}. Possible beneficial effects in lung function, and clinical endpoints, are modest and inconsistent, whereas adverse effects are significantly increased²³⁶.

Glucocorticosteroids: Oral or intravenous glucocorticosteroids are recommended as an addition to bronchodilator therapy (plus eventually antibiotics and oxygen therapy) in the hospital management of exacerbations of COPD¹⁸⁹⁻¹⁹¹ (**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 days 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 purulence¹⁴¹. 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 exacerbations in *Stage IV: Very 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-/nasotracheal tube or tracheostomy.

Table 14 - Indications and Relative Contraindications for NIPPV^{203,204}

Selection criteria

- Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion.
- Moderate to severe acidosis ($\text{pH} < 7.35$) and hypercapnia ($\text{PaCO}_2 > 6.0$ kPa, 45mm Hg)²⁰⁹.
- Respiratory frequency > 25 breaths per minute.

Exclusion criteria

- Respiratory arrest.
- Cardiovascular instability (hypotension, arrhythmias, myocardial infarction).
- 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.

Noninvasive Mechanical Ventilation: Noninvasive intermittent positive pressure ventilation (NIPPV) has been studied in many uncontrolled and five randomized controlled trials in acute respiratory failure^{202,203}. The studies show consistently positive results with success rates of 80-85%²⁰⁴. Taken together they provide evidence that NIPPV increases pH, reduces PaCO_2 , reduces the severity of breathlessness in the first 4 hours of treatment, and decreases the length of hospital stay (**Evidence A**). More importantly, mortality – or its surrogate, intubation rate – is reduced by this intervention²⁰⁵⁻²⁰⁸. However, NIPPV is not appropriate for all patients, as summarized in **Table 14**.

Invasive (Conventional) Mechanical Ventilation: Patients who show impending acute respiratory failure and those with life-threatening acid-base status abnormalities and/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-

Table 15 - Indications for Invasive Mechanical Ventilation
<ul style="list-style-type: none"> • Severe dyspnea with use of accessory muscles and paradoxical abdominal motion. • Respiratory frequency > 35 breaths per minute. • Life-threatening hypoxemia ($\text{PaO}_2 < 5.3 \text{ kPa}$, 40 mm Hg or $\text{PaO}_2/\text{FiO}_2^* < 200 \text{ mm Hg}$). • Severe acidosis ($\text{pH} < 7.25$) and hypercapnia ($\text{PaCO}_2 > 8.0 \text{ kPa}$, 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).

control ventilation, and pressure support ventilation alone or in combination with intermittent mandatory ventilation²¹⁰.

The use of invasive ventilation in end-stage COPD patients 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^{211,212}. Whether pressure support or a T-piece trial is used, weaning is shortened when a clinical protocol is adopted (**Evidence A**). Noninvasive ventilation (NIV) has been

applied to facilitate the weaning process in COPD patients with acute or chronic respiratory failure²¹³. Compared with invasive pressure support ventilation, noninvasive intermittent positive pressure ventilation (NIPPV) during weaning shortened weaning time, reduced the stay in the intensive care unit, decreased the incidence of nosocomial pneumonia, and improved 60-day survival rates²¹³.

Similar findings have been reported when NIPPV is used after extubation for hypercapnic respiratory failure²¹⁴ (**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 > 25 ml sputum per day or with lobar atelectasis.

Table 16 - Discharge Criteria for Patients with Exacerbations of COPD
<ul style="list-style-type: none"> • Inhaled β_2-agonist therapy is required no more frequently than every 4 hrs. • 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 hrs. • Arterial blood gases have been stable for 12-24 hrs. • 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 Weeks After Discharge from Hospital for Exacerbations of COPD
<ul style="list-style-type: none"> • 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 and/or home nebulizer (for patients with very severe COPD).

HOSPITAL DISCHARGE AND FOLLOW-UP

Insufficient clinical data exist to establish the optimal duration of hospitalization for acute exacerbations of COPD^{171,215,216}. 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 weeks 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 parameters⁸⁵. Home visits by a community nurse may permit earlier discharge of patients hospitalized with a nonacidotic exacerbation of COPD, without increasing readmission rate.²¹⁷⁻²²⁰

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^{221,222}, 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.

4. 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.

■ Until there is a better understanding of the causal mechanisms of COPD, an absolutely rigid definition of COPD, and its relationship to other obstructive airways diseases, will remain controversial. Defining characteristics of COPD should be better identified.

■ The stages of COPD and the disease course will vary from one patient to another. The GOLD Report describes four stages and their clinical utility needs to be evaluated.

■ 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.

■ Information is needed about the cellular and molecular mechanisms of inflammation in stable COPD and in exacerbations. Inflammatory responses in nonsmokers, ex-smokers, 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.

■ 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 COPD patients.

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

■ 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.

■ 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.

■ 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.

■ Since 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 needs to be developed. Data to show whether or not screening spirometry is effective in directing management decisions in COPD outcomes are required.

■ 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.

■ The specific components of effective education for COPD patients need to be determined. It is not known, for example, whether COPD patients 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.

■ 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.

■ 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 end-stage COPD patients.

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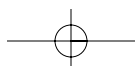
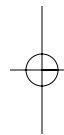
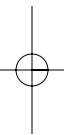
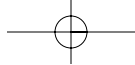
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