

# Global Initiative for Chronic Obstructive Lung Disease



**GLOBAL STRATEGY FOR THE DIAGNOSIS,  
MANAGEMENT, AND PREVENTION OF  
CHRONIC OBSTRUCTIVE PULMONARY DISEASE**  
**UPDATED 2005**

EXECUTIVE SUMMARY

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

(Based on an April 1998 NHLBI/WHO Workshop)



**Global Strategy for the Diagnosis, Management, and Prevention of  
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# PREFACE

Chronic Obstructive Pulmonary Disease (COPD) is a major public health problem. It is the fourth leading cause of chronic morbidity and mortality in the United States<sup>1</sup> and is projected to rank fifth in 2020 as a worldwide burden of disease according to a study published by the World Bank/World Health Organization<sup>2</sup>. 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 expert panel that prepared the first workshop report, and the GOLD Science Committee for its work in preparation of the yearly updated volumes. We look forward to our continued work with interested organizations and the GOLD National Leaders to meet the goals of the GOLD program.

Development of the Workshop Report was supported through educational grants 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 (2005 Update)

The *Global Strategy for Diagnosis, Management and Prevention of COPD*: Executive Summary presented in 2001 was based on the scientific literature available until mid 2000. 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 (2003) and second (2004) updates were posted on the GOLD website ([www.gold.copd.org](http://www.gold.copd.org)) in July 2003 and July 2004 respectively. This third update (July 2005) includes review of publications from January to December 2004. This will be the final update of the 2001 document; a revision of the entire document has been implemented and is scheduled to be completed in 2006.

**Methods:** The process used for the 2005 update, identical to that described for the previous updates, included a Pub Med search using 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 report. If so, the member was asked to specifically identify modifications that should be made. The GOLD Science Committee met on a regular basis to discuss each individual publication indicated by at least 1 member of the Committee to have an impact on COPD management, and to reach a consensus on the changes in the report. Disagreements were decided by vote.

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

### GOLD Executive Summary (2005 Update): Summary of Recommendations

Between January 1 and December 2004, 131 articles met the search criteria. Of these, 8 papers were identified to have an impact on the Executive Summary. Of these, 5 papers confirmed an existing statement and were added as a reference:

1. Page 12: Man WD, Mustfa N, Nikolettou D, Kaul S, Hart N, Rafferty GF, Donaldson N, Polkey MI, Moxham J. Effect of salmeterol on respiratory muscle activity during exercise in poorly reversible COPD. *Thorax*. 2004 Jun;59(6):471-6.
2. Page 12: O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, Make B, Magnussen H. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J*. 2004 Jun;23(6):832-40.
3. Page 13: Oostenbrink JB, Rutten-van Molken MP, Al MJ, Van Noord JA, Vincken W. One-year cost-effectiveness of tiotropium versus ipratropium to treat chronic obstructive pulmonary disease. *Eur Respir J*. 2004 Feb;23(2):241-9.
4. Page 14: Spencer S, Calverley PM, Burge PS, Jones PW. Impact of preventing exacerbations on deterioration of health status in COPD. *Eur Respir J*. 2004 May;23(5):698-702.
5. Page 14: Wongsurakiat P, Maranetra KN, Wasi C, Kositanont U, Dejsomritrutai W, Charoenratanakul S. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study. *Chest*. 2004 Jun;125(6):2011-20.

Three papers introduced information that required a new statement to be added to the Executive Summary:

1. Page 14 – Add sentence: Short-term treatment with a combined inhaled glucocorticosteroid and long-acting  $\beta_2$ -agonist resulted in greater control of lung function and symptoms than combined anticholinergic and short-acting  $\beta_2$ -agonist.  
*Reference:* Donohue JF, Kalberg C, Emmett A, Merchant K, Knobil K. A short-term comparison of fluticasone propionate/ salmeterol with ipratropium bromide/albuterol for the treatment of COPD. *Treat Respir Med*. 2004;3(3):173-81.

2. Page 14 - Change paragraph on immunoregulators to read: Studies using an immunostimulator in COPD show a decrease in the severity and frequency of exacerbations<sup>94</sup> (add new reference). However, additional studies to examine the long term effects of this therapy are required before regular use can be recommended (**Evidence B**).

*Reference:* Li J, Zheng JP, Yuan JP, Zeng GQ, Zhong NS, Lin CY. Protective effect of a bacterial extract against acute exacerbation in patients with chronic bronchitis accompanied by chronic obstructive pulmonary disease. *Chin Med J (Engl)*. 2004 Jun;117(6):828-34.

3. Page 20 - Add sentence: Early outpatient pulmonary rehabilitation after hospitalization for COPD exacerbation results in exercise capacity and health status improvements at three months.

*Reference:* Man WD, Polkey MI, Donaldson N, Gray BJ, Moxham J. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. *BMJ*. 2004 Nov 20;329(7476):1209.

A major new segment appears in Chapter 3, Component 4 on antibiotics in treatment of COPD exacerbations (page 21). The material was prepared by the GOLD Science Committee which gratefully acknowledges the opportunity to review a statement on this topic prepared by the European Respiratory Society and provided to the Committee by Dr. William MacNee and Dr. Mark Woodhead. Prior to its release, the material was reviewed by Dr. Sanjay Sethi, State University of New York at Buffalo, Buffalo, New York, and Dr. Antonio Anzueto, University of San Antonio, San Antonio, Texas.

The proposed modifications for the Updated 2005 documents were approved by the GOLD Executive Committee.

An Appendix includes a report on outcome measures for COPD to encourage comments and input from the scientific community to prepare for the full revision of the report, scheduled to appear in mid-2006. The many individuals who participated in preparation of this report are listed in the document. The GOLD Science Committee is grateful to those who contributed to this report, particularly the work of Dr. Paul Jones, London, England and Dr. Alvar Agusti, Palma de Mallorca, Spain.

The GOLD Workshop Report (Updated 2005), the GOLD Executive Summary (Updated 2005), and the GOLD Pocket Guide (Updated 2005) along with the complete list of references examined by the Committee are available on the GOLD website ([www.goldcopd.org](http://www.goldcopd.org)).

## INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. COPD is currently the fourth leading cause of death in the world<sup>3</sup>, 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**).

<b>Evidence Category</b>	<b>Sources of Evidence</b>	<b>Definition</b>
<b>A</b>	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>B</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.
<b>C</b>	Non randomized trials. Observational studies.	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
<b>D</b>	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 FEV<sub>1</sub> < 80% of the predicted value in combination with an FEV<sub>1</sub>/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 FEV<sub>1</sub> values refer to postbronchodilator FEV<sub>1</sub>.

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

*Stage I: Mild COPD* - Characterized by mild airflow limitation (FEV<sub>1</sub>/FVC < 70% but FEV<sub>1</sub> ≥ 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% ≤ FEV<sub>1</sub> < 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.

*Stage III: Severe COPD* - characterized by further worsening of airflow limitation (30% ≤ FEV<sub>1</sub> < 50% predicted),

**Table 2 - Classification of Severity\***

Stage	Characteristics
0: At Risk	<ul style="list-style-type: none"> <li>• normal spirometry</li> <li>• chronic symptoms (cough, sputum production)</li> </ul>
I: Mild COPD	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>/FVC &lt; 70%</li> <li>• FEV<sub>1</sub> ≥ 80% predicted</li> <li>• with or without chronic symptoms (cough, sputum production)</li> </ul>
II: Moderate COPD	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>/FVC &lt; 70%</li> <li>• 50% ≤ FEV<sub>1</sub> &lt; 80% predicted</li> <li>• with or without chronic symptoms (cough, sputum production)</li> </ul>
III: Severe COPD	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>/FVC &lt; 70%</li> <li>• 30% ≤ FEV<sub>1</sub> &lt; 50% predicted</li> <li>• with or without chronic symptoms (cough, sputum production)</li> </ul>
IV: Very Severe COPD	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>/FVC &lt; 70%</li> <li>• FEV<sub>1</sub> &lt; 30% predicted or FEV<sub>1</sub> &lt; 50% predicted plus chronic respiratory failure</li> </ul>

\*Classification based on postbronchodilator FEV<sub>1</sub>  
 FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO<sub>2</sub>) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO<sub>2</sub> (PaCO<sub>2</sub>) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.

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 ( $LTB_4$ )<sup>4</sup>, interleukin 8 ( $IL-8$ )<sup>5-7</sup>, tumor necrosis factor  $\alpha$  ( $TNF-\alpha$ )<sup>5,8</sup>, 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 lungs<sup>9-14</sup>. Although fewer data are available, it is likely that other COPD risk factors initiate a similar inflammatory process<sup>15-19</sup>. 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<sup>9,20,21</sup>. Enlarged mucus secreting glands and an increase in the number of goblet cells are associated with mucus hypersecretion. In the peripheral airways – small bronchi and bronchioles that have an internal diameter of less than 2 mm – chronic inflammation leads to repeated cycles of injury and repair of the airway wall<sup>22</sup>. The repair process results in a structural remodeling of the airway wall, with increasing collagen content and scar tissue formation, that narrows the lumen and produces fixed airways obstruction<sup>23</sup>.

Destruction of the lung parenchyma in COPD patients typically occurs as centrilobular emphysema. This involves dilatation and destruction of the respiratory bronchioles<sup>24</sup>. 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 contribute<sup>25</sup>.

Pulmonary vascular changes in COPD are characterized by a thickening of the vessel wall that begins early in the natural history of the disease. Thickening of the intima is the first structural change<sup>26</sup>, followed by an increase in smooth muscle and the infiltration of the vessel wall by inflammatory cells<sup>27</sup>. As COPD worsens, greater amounts of smooth muscle, proteoglycans, and collagen<sup>28</sup> 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 COPD<sup>3</sup> 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 prognosis<sup>29</sup>. 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 developed<sup>30</sup> and developing countries. Mortality data also underestimate COPD as a cause of death because the disease is more likely to be cited as a contributory than as an underlying cause of death, or may not be cited at all<sup>31</sup>.

**Prevalence:** In the Global Burden of Disease Study conducted under the auspices of the WHO and the World Bank<sup>2,32</sup>, 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 women<sup>1</sup>. 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 <sup>33</sup>	1996	778	3,312	4,090	65
The Netherlands <sup>34</sup>	1993	256	N/A	N/A	N/A <sup>#</sup>
Sweden <sup>35</sup>	1991	179	281	460	60
US <sup>1</sup>	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 world<sup>2</sup>, and further increases in the prevalence and mortality of the disease can be predicted in the coming decades<sup>2,32</sup>. 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 45<sup>1</sup>.

### 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<sup>2,32</sup> 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

**Table 4 - Leading Causes of Disability-Adjusted Life Years (DALYs) Lost Worldwide: 1990 and 2020 (Projected)<sup>2,32</sup>**

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
<b>COPD</b>	<b>12</b>	<b>2.1</b>	<b>5</b>	<b>4.1</b>
Trachea, bronchus, lung cancer	33	0.6	15	1.8

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premature mortality and years of life lived with disability, adjusted for the severity of disability). According to projections, COPD will be the fifth leading cause of DALYs lost worldwide in 2020 (in 1990 it ranked twelfth), behind ischemic heart disease, major depression, traffic accidents, and cerebrovascular disease (**Table 4**).

## 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 women<sup>36-39</sup>. More recent studies<sup>1,40</sup> 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<sup>38,41</sup>. 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 antitrypsin<sup>42-44</sup>. Premature and accelerated development of panlobular emphysema and decline in lung function occurs in many smokers and nonsmokers with the severe deficiency, although smoking increases the risk appreciably. Other genes involved in the pathogenesis of COPD have not yet been identified.

**Airway Hyperresponsiveness:** Asthma and airway hyperresponsiveness, identified as risk factors that contribute to the development of COPD<sup>45</sup>, 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 childhood<sup>46-50</sup>. Reduced maximal attained lung function (as measured by spirometry) may identify individuals who are at increased risk for the development of COPD<sup>51</sup>.

### Exposures

**Tobacco Smoke:** Cigarette smokers have a higher prevalence of lung-function abnormalities and respiratory symptoms, a greater annual rate of decline in FEV<sub>1</sub>, and higher death rates for COPD than nonsmokers. Pipe and cigar smokers have higher COPD morbidity and mortality rates than nonsmokers, although their rates are lower than those for cigarette smokers<sup>52</sup>. 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<sup>36,53,54</sup>. 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<sup>50,55</sup>.

**Occupational Dusts and Chemicals:** When the exposures are sufficiently intense or prolonged, occupational dusts and chemicals (vapors, irritants, fumes) can cause COPD independently of cigarette smoking and increase the risk of the disease in the presence of concurrent cigarette smoking<sup>56</sup>. Exposure to particulate matter, irritants, organic dusts, and sensitizing agents can cause an increase in airway hyperresponsiveness<sup>57</sup>, especially in airways already damaged by other occupational exposures, cigarette smoke, or asthma.

**Outdoor and Indoor Air Pollution:** High levels of urban air pollution are harmful to persons with existing heart or lung disease. The role of outdoor air pollution in causing COPD is unclear, but appears to be small when compared with cigarette smoking. Indoor air pollution from biomass fuel, burned for cooking and heating in poorly vented dwellings, has been implicated as a risk factor for the development of COPD<sup>58-67</sup>.

**Infections:** A history of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood<sup>51</sup>. However, viral infections may be related to another factor, e.g., low birth weight, that itself is related to COPD.

**Socioeconomic Status:** There is evidence that the risk of developing COPD is inversely related to socioeconomic

status<sup>68</sup>. 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<sup>67,69</sup>.

### 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 develop<sup>70</sup>, 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 nonspecific symptoms and may vary between days and over the course of a single day. An absence of wheezing or chest tightness does not exclude a diagnosis of COPD.

<b>Table 5 - Key Indicators for Considering a Diagnosis of COPD</b>	
<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>	
<b>Chronic cough:</b>	Present intermittently or every day. Often present throughout the day; seldom only nocturnal.
<b>Chronic sputum production:</b>	Any pattern of chronic sputum production may indicate COPD.
<b>Dyspnea that is:</b>	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.
<b>History of exposure to risk factors,</b>	Tobacco smoke. Occupational dusts and chemicals. Smoke from home cooking especially: 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<sup>71,72</sup>, 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, FEV<sub>1</sub>), and the ratio of these two measurements (FEV<sub>1</sub>/FVC) should be calculated. Patients with COPD typically show a decrease in both FEV<sub>1</sub> and FVC. The presence of a postbronchodilator FEV<sub>1</sub> < 80% of the predicted value in combination with an FEV<sub>1</sub>/FVC < 70% confirms the presence of airflow limitation that is not fully reversible. The FEV<sub>1</sub>/FVC on its own is a more sensitive measure of airflow limitation, and an FEV<sub>1</sub>/FVC < 70% is considered an early sign of airflow limitation in patients whose FEV<sub>1</sub> 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 FEV<sub>1</sub> 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 FEV<sub>1</sub> 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 FEV<sub>1</sub> < 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 PaO<sub>2</sub> < 8.0 kPa (60 mm Hg) with or without PaCO<sub>2</sub> > 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 (SaO<sub>2</sub>) 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 monitored for development of complications and to determine when to adjust therapy.

<b>Table 6 - Differential Diagnosis of COPD</b>	
<b>Diagnosis</b>	<b>Suggestive Features*</b>
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.

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<sup>75,76</sup>. 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 1996<sup>77</sup> and updated in 2000 by the US Public Health Service in *Treating Tobacco Use and Dependence: A Clinical Practice Guideline*<sup>78</sup>.

**Smoking Cessation Intervention Process:** The Public Health Service Report recommends a five-step program for intervention (**Table 7**), which provides a strategic framework helpful to health care providers interested in helping their patients stop smoking. Three types of counseling are especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment<sup>77-81</sup> (**Evidence A**).

**Pharmacotherapy:** Numerous effective pharmacotherapies for smoking cessation now exist<sup>78,82,83</sup> (**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<sup>78,83</sup>. The antidepressants bupropion<sup>84</sup> and nortriptyline have also been shown to increase long-term quit rates, although fewer studies have been conducted with these medications<sup>78,83</sup>. The effectiveness of the antihypertensive drug clonidine is limited by side effects<sup>83</sup>. Special consideration should be given before using pharmacotherapy in selected populations: people with medical contraindications, light smokers (fewer than 10 cigarettes/day), and pregnant and adolescent smokers.

**OCCUPATIONAL EXPOSURES**

Although it is not known how many individuals are at risk of developing respiratory disease from occupational exposures in either developing or developed countries, many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases<sup>85</sup>. Emphasis should be on primary prevention, which is best achieved by the elimination or reduction of exposures to various substances in the workplace. Secondary prevention, achieved through epidemiologic surveillance and early case detection, is also of great importance.

**INDOOR/OUTDOOR AIR POLLUTION**

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

The health care provider should consider susceptibility (including family history, exposure to indoor/outdoor pollution) for each individual patient<sup>86</sup>. 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.

<b>Table 7 - Strategies to Help the Patient Willing to Quit Smoking<sup>78</sup></b>
<p><b>1. ASK:</b> 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><b>2. ADVISE:</b> Strongly urge all tobacco users to quit. <i>In a clear, strong, and personalized manner, urge every tobacco user to quit.</i></p>
<p><b>3. ASSESS:</b> 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><b>4. ASSIST:</b> 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><b>5. ARRANGE:</b> 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  $\beta_2$ -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 function<sup>87-90</sup>, it can play a role in improving skills, ability to cope with illness, and health status<sup>91</sup>. In addition, patient education is effective in accomplishing certain specific goals, including smoking cessation<sup>41</sup> (**Evidence A**), initiating discussions and understanding of advance directives and end-of-life issues<sup>92</sup> (**Evidence B**), and improving patient responses to exacerbations<sup>93,94</sup> (**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<sup>41,95-98</sup> (**Evidence A**). However, this should not preclude efforts to use medications to control symptoms.

**BRONCHODILATORS**

Bronchodilator medications are central to the symptomatic management of COPD<sup>99-102</sup> (**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 FEV<sub>1</sub> 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:  $\beta_2$ -agonists, anticholinergics, and methylxanthines.

Table 9 - Bronchodilators in Stable COPD
<ul style="list-style-type: none"> <li>• Bronchodilator medications are central to symptom management in COPD.</li> <li>• Inhaled therapy is preferred.</li> <li>• The choice between <math>\beta_2</math>-agonist, anticholinergic, theophylline, or combination therapy depends on availability and individual response in terms of symptom relief and side effects.</li> <li>• Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.</li> <li>• Long-acting inhaled bronchodilators are more effective and convenient, but more expensive.</li> <li>• Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.</li> </ul>

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 FEV<sub>1</sub><sup>103,104,237,238</sup> (**Evidence A**).

Table 8 - Therapy at Each Stage of COPD					
Old	0: At Risk	I: Mild	II: Moderate IIA IIB		III: Severe
New	0: At Risk	I: Mild	II: Moderate	III: Severe	IV: Very Severe
Characteristics	<ul style="list-style-type: none"> <li>• Chronic symptoms</li> <li>• Exposure to risk factors</li> <li>• Normal spirometry</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>/FVC &lt; 70%</li> <li>• FEV<sub>1</sub> ≥ 80%</li> <li>• With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>/FVC &lt; 70%</li> <li>• 50% ≤ FEV<sub>1</sub> &lt; 80%</li> <li>• With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>/FVC &lt; 70%</li> <li>• 30% ≤ FEV<sub>1</sub> &lt; 50%</li> <li>• With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>/FVC &lt; 70%</li> <li>• FEV<sub>1</sub> &lt; 30% or FEV<sub>1</sub> &lt; 50% predicted plus chronic respiratory failure</li> </ul>
	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 expensive<sup>105-107,239</sup> (**Evidence A**). Regular use of a long-acting  $\beta_2$ -agonist<sup>105</sup> or long-acting anticholinergic improves health status<sup>105-107</sup>. 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  $\beta_2$ -agonist and an anticholinergic produces

Table 10 - Commonly Used Formulations of Drugs for COPD					
Drug	Inhaler ( $\mu$ g)	Solution for Nebulizer (mg/ml)	Oral	Vials for injection (mg)	Duration of Action (hours)
<b><math>\beta_2</math>-agonists</b>					
<b>Short-acting</b>					
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
<b>Long-acting</b>					
Formoterol	4.5-12 (MDI & DPI)				12+
Salmeterol	25-50 (MDI & DPI)				12+
<b>Anticholinergics</b>					
<b>Short-acting</b>					
Ipratropium bromide	20, 40 (MDI)	0.25-0.5			6-8
Oxipropium bromide	100 (MDI)	1.5			7-9
<b>Long-acting</b>					
Tiotropium	18 (DPI)				+24
<b>Combination short-acting <math>\beta_2</math>-agonists plus anticholinergic in one inhaler</b>					
Fenoterol/Ipratropium	200/80 (MDI)	1.25/0.5			6-8
Salbutamol/Ipratropium	75/15 (MDI)	0.75/4.5			6-8
<b>Methylxanthines</b>					
Aminophylline			200-600 mg (Pill)	240 mg	Variable, up to 24
Theophylline (SR)			100-600 mg (Pill)		Variable, up to 24
<b>Inhaled glucocorticosteroids</b>					
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	
<b>Combination long-acting <math>\beta_2</math>-agonists plus glucocorticosteroids in one inhaler</b>					
Formoterol/Budesonide	4.5/80, 160 (DPI) (9/320) (DPI)				
Salmeterol/Fluticasone	50/100, 250, 500 (DPI) 25/50, 125, 250 (MDI)				
<b>Systemic glucocorticosteroids</b>					
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 FEV<sub>1</sub> than either alone and does not produce evidence of tachyphylaxis over 90 days of treatment<sup>108-110</sup> (**Evidence A**).

Combination of a  $\beta_2$ -agonist, an anticholinergic, and/or theophylline may produce additional improvements in lung function<sup>108,111-115</sup> and health status<sup>104,108,111,116</sup>. 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  $\beta_2$ -agonist or an anticholinergic, especially when given by a wet nebulizer, appears to provide subjective benefit in acute episodes<sup>117</sup> (**Evidence B**). Some patients may request regular treatment with high-dose, nebulized bronchodilators<sup>118</sup>, 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 occurs<sup>118</sup>. 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 FEV<sub>1</sub> in patients with COPD<sup>95-98</sup>. However, regular treatment with inhaled glucocorticosteroids is appropriate for symptomatic COPD patients with an FEV<sub>1</sub> < 50% predicted (*Stage III: Severe COPD* and *Stage IV: Very Severe COPD*) and repeated exacerbations (for example, 3 in the last three years)<sup>119-122</sup> (**Evidence A**). This treatment has been shown to reduce the frequency of exacerbations and thus improve health status<sup>240</sup> (**Evidence A**), and withdrawal from treatment with inhaled glucocorticosteroids can lead to exacerbations in some patients<sup>223</sup>. Inhaled glucocorticosteroid combined with a long-acting  $\beta_2$ -agonist is more effective than the individual components<sup>119,121,122,224,225</sup> (**Evidence A**). Short-term treatment with a combined inhaled glucocorticosteroid and long-acting  $\beta_2$ -agonist resulted in greater control of lung function and symptoms than combined anticholinergic and short-acting  $\beta_2$ -agonist<sup>241</sup>.

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<sup>97,123</sup>. Long-term treatment with oral glucocorticosteroids is not recommended in COPD<sup>124-126</sup> (**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<sup>125,126</sup>, 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%<sup>127, 226</sup>. Vaccines containing killed or live, inactivated viruses are recommended<sup>128, 242</sup>, and should be given once (in autumn) or twice (in autumn and winter) each year (**Evidence A**). A pneumococcal vaccine containing 23 virulent serotypes has been used but sufficient data to support its general use in COPD patients are lacking<sup>129-131</sup> (**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<sup>132,133</sup> (**Evidence A**).

**Mucolytic (Mucokinetic, Mucoregulator) Agents** (ambroxol, erdosteine, carbocysteine, iodinated glycerol): Although a few patients with viscous sputum may benefit from mucolytics<sup>134,135</sup>, the overall benefits seem to be very small. Therefore, the widespread use of these agents cannot be recommended on the basis of the present evidence (**Evidence D**).

**Antioxidant Agents:** Antioxidants, in particular N-acetylcysteine, have been shown to reduce the frequency of exacerbations and could have a role in the treatment of patients with recurrent exacerbations<sup>136-139</sup> (**Evidence B**). However, before their routine use can be recommended, the results of ongoing trials will have to be carefully evaluated.

**Immunoregulators (Immunostimulators, Immunomodulators):** Studies using an immunostimulator in COPD show a decrease in the severity and frequency of exacerbations<sup>140,243</sup>. However, additional studies to examine the long term effects of this therapy are required before regular use can be recommended<sup>141</sup> (**Evidence B**).

**Antitussives:** Cough, although sometimes a troublesome symptom in COPD, has a significant protective role<sup>142</sup>. 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<sup>143,144</sup> and thus is contraindicated.

**Respiratory Stimulants:** The use of doxapram, a nonspecific respiratory stimulant available as an intravenous formulation, is not recommended in stable COPD (**Evidence D**). Almitrine bismesylate is not recommended for regular use in stable COPD patients<sup>145-147</sup> (**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 effective<sup>148</sup>. 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 subjects<sup>149-153</sup>.

**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.

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## NON-PHARMACOLOGIC TREATMENT

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### 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 fatigue<sup>154</sup> (**Evidence A**). The minimum length of an effective rehabilitation program is two months; the longer the program continues, the more effective the results<sup>155-157</sup> (**Evidence B**). However, as yet, no effective structure has been developed to maintain the effects over time<sup>158</sup>. Benefits have been reported from rehabilitation programs conducted in inpatient, outpatient, and home settings<sup>159-161</sup>.

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 survival<sup>162-164</sup> (**Evidence A**). It can also have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental state<sup>164</sup>.

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

- PaO<sub>2</sub> at or below 7.3 kPa (55 mm Hg) or SaO<sub>2</sub> at or below 88%, with or without hypercapnia; or
- PaO<sub>2</sub> between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg) or SaO<sub>2</sub> 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 PaO<sub>2</sub> to at least 8.0 kPa (60 mm Hg) at sea level and rest, and/or produce SaO<sub>2</sub> 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 PaO<sub>2</sub> values. The prescription should always include the source of supplemental oxygen (gas or liquid), the method of delivery, duration of use, and the flow rate at rest, during exercise, and during sleep.

## VENTILATORY SUPPORT

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

## SURGICAL TREATMENTS

**Bullectomy:** In carefully selected patients, this procedure is effective in reducing dyspnea and improving lung function<sup>165</sup> (**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 capacity<sup>227</sup>, and may improve global health status in patients with heterogeneous emphysema<sup>228</sup>. 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 capacity<sup>160-163</sup> (**Evidence C**). Criteria for referral for lung transplantation include FEV<sub>1</sub> < 35% predicted, PaO<sub>2</sub> < 7.3-8.0 kPa (55-60 mm Hg), PaCO<sub>2</sub> > 6.7 kPa (50 mm Hg), and secondary pulmonary hypertension<sup>170</sup>.

## 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 COPD<sup>229-234</sup>.

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 interven-

tions 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 transplantation<sup>234</sup>.

## 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  $\beta_2$ -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 symptoms<sup>171-174</sup>. The economic and social burden of COPD exacerbations is extremely high. The most common causes of an exacerbation are infection of the tracheobronchial tree<sup>175-179</sup> and air pollution<sup>180</sup>, 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<sup>175-179,181-184</sup> but recent investigations with newer research techniques have begun to provide important information. Conditions that may mimic the symptoms of an exacerbation include pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism, and arrhythmia. Recommendations for use of antibiotics for COPD exacerbations are provided at the end of this chapter.

## 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 production<sup>179</sup>.

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 FEV<sub>1</sub> < 1.00 L indicates a severe exacerbation<sup>185-187</sup>.

**Assessment of Arterial Blood Gases:** In the hospital, measurement of arterial blood gases is essential to assess the severity of an exacerbation. A PaO<sub>2</sub> < 8.0 kPa (60 mm Hg) and/or SaO<sub>2</sub> < 90% with or without PaCO<sub>2</sub> > 6.7 kPa, 50 mmHg (when breathing room air)

indicates respiratory failure. In addition, PaO<sub>2</sub> < 6.7 kPa (50 mm Hg), PaCO<sub>2</sub> > 9.3 kPa (70 mm Hg), and pH < 7.30 point towards a life-threatening episode that needs close monitoring or critical management<sup>188</sup>.

**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 PaO<sub>2</sub> 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 quickly<sup>189-191</sup> (**Evidence A**), and may reduce the risk of early relapse<sup>235</sup>. They should be considered in addition to bronchodilators if the patient's baseline FEV<sub>1</sub> 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 glucocorticosteroids in the treatment of nonacidotic exacerbations<sup>192</sup>.

**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 for ventilatory support<sup>193</sup>. Patients lacking these features are not at high risk of dying, but those with severe underlying COPD often require hospitalization in any case. Attempts

<b>Table 11 - Indications for Hospital Assessment or Admission for Exacerbations of COPD*</b>	
<ul style="list-style-type: none"> <li>• Marked increase in intensity of symptoms, such as sudden development of resting dyspnea.</li> <li>• Severe background COPD.</li> <li>• Onset of new physical signs (e.g., cyanosis, peripheral edema).</li> <li>• Failure of exacerbation to respond to initial medical management.</li> <li>• Significant comorbidities.</li> <li>• Newly occurring arrhythmias.</li> <li>• Diagnostic uncertainty.</li> <li>• Older age.</li> <li>• Insufficient home support.</li> </ul>	

\* Local resources need to be considered

<b>Table 12 - Indications for ICU Admission of Patients with Exacerbations of COPD*</b>	
<ul style="list-style-type: none"> <li>• Severe dyspnea that responds inadequately to initial emergency therapy.</li> <li>• Confusion, lethargy, coma.</li> <li>• Persistent or worsening hypoxemia (PaO<sub>2</sub> &lt; 5.3 kPa, 40 mm Hg), and/or severe/worsening hypercapnia (PaCO<sub>2</sub> &gt; 8.0 kPa, 60 mm Hg), and/or severe/worsening respiratory acidosis (pH &lt; 7.25) despite supplemental oxygen and NIPPV.</li> </ul>	

\* Local resources need to be considered

at managing such patients entirely in the community have met with only limited success<sup>194</sup>, but returning them to their homes with increased social support and a supervised medical care package after an initial emergency room assessment has been much more successful<sup>195</sup>. However, detailed cost-benefit analyses of these approaches are awaited.

<b>Table 13 - Management of Severe but Not Life-Threatening Exacerbations of COPD in the Emergency Department or the Hospital*</b>	
<ul style="list-style-type: none"> <li>• Assess severity of symptoms, blood gases, chest X-ray.</li> <li>• Administer controlled oxygen therapy and repeat arterial blood gas measurement after 30 minutes.</li> <li>• Bronchodilators:                             <ul style="list-style-type: none"> <li>— Increase doses or frequency.</li> <li>— Combine β<sub>2</sub>-agonists and anticholinergics.</li> <li>— Use spacers or air-driven nebulizers.</li> <li>— Consider adding intravenous methylxanthine, if needed.</li> </ul> </li> <li>• Add glucocorticosteroids                             <ul style="list-style-type: none"> <li>— Oral or intravenous.</li> </ul> </li> <li>• Consider antibiotics                             <ul style="list-style-type: none"> <li>— When signs of bacterial infection, oral or occasionally intravenous.</li> </ul> </li> <li>• Consider noninvasive mechanical ventilation.</li> <li>• At all times:                             <ul style="list-style-type: none"> <li>— Monitor fluid balance and nutrition.</li> <li>— Consider subcutaneous heparin.</li> <li>— Identify and treat associated conditions (e.g., heart failure, arrhythmias).</li> <li>— Closely monitor condition of the patient.</li> </ul> </li> </ul>	

\* Local resources need to be considered

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  $\text{CO}_2$  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  $\text{CO}_2$  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  $\beta_2$ -agonists are usually the preferred bronchodilators for the treatment of exacerbations of COPD<sup>85,133,134</sup> (**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<sup>196,197</sup>. 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<sup>198,199</sup>. 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<sup>198,200,201</sup>. Possible beneficial effects in lung function, and clinical endpoints, are modest and inconsistent, whereas adverse effects are significantly increased<sup>236</sup>.

**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 COPD<sup>189-191</sup> (**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.

**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-/naso-tracheal tube or tracheostomy.

**Noninvasive Mechanical Ventilation:** Noninvasive intermittent positive pressure ventilation (NIPPV) has been studied in many uncontrolled and five randomized

controlled trials in acute respiratory failure<sup>202,203</sup>. The studies show consistently positive results with success rates of 80-85%<sup>204</sup>. Taken together they provide evidence that NIPPV increases pH, reduces  $\text{PaCO}_2$ , 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 intervention<sup>205-208</sup>. However, NIPPV is not appropriate for all patients, as summarized in **Table 14**.

<b>Table 14 - Indications and Relative Contraindications for NIPPV<sup>203,204</sup></b>	
<b>Selection criteria</b>	
<ul style="list-style-type: none"> <li>• Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion.</li> <li>• Moderate to severe acidosis (<math>\text{pH} &lt; 7.35</math>) and hypercapnia (<math>\text{PaCO}_2 &gt; 6.0</math> kPa, 45mm Hg)<sup>209</sup>.</li> <li>• Respiratory frequency <math>&gt; 25</math> breaths per minute.</li> </ul>	
<b>Exclusion criteria</b>	
<ul style="list-style-type: none"> <li>• Respiratory arrest.</li> <li>• Cardiovascular instability (hypotension, arrhythmias, myocardial infarction).</li> <li>• Somnolence, impaired mental status, uncooperative patient.</li> <li>• High aspiration risk; viscous or copious secretions.</li> <li>• Recent facial or gastroesophageal surgery.</li> <li>• Craniofacial trauma, fixed nasopharyngeal abnormalities.</li> <li>• Extreme obesity.</li> </ul>	

**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-control ventilation, and pressure support ventilation alone or in combination with intermittent mandatory ventilation<sup>210</sup>.

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

ty 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.

<b>Table 15 - Indications for Invasive Mechanical Ventilation</b>
<ul style="list-style-type: none"> <li>• Severe dyspnea with use of accessory muscles and paradoxical abdominal motion.</li> <li>• Respiratory frequency &gt; 35 breaths per minute.</li> <li>• Life-threatening hypoxemia (PaO<sub>2</sub> &lt; 5.3 kPa, 40 mm Hg or PaO<sub>2</sub>/FiO<sub>2</sub>* &lt; 200 mm Hg).</li> <li>• Severe acidosis (pH &lt; 7.25) and hypercapnia (PaCO<sub>2</sub> &gt; 8.0 kPa, 60 mm Hg).</li> <li>• Respiratory arrest.</li> <li>• Somnolence, impaired mental status.</li> <li>• Cardiovascular complications (hypotension, shock, heart failure).</li> <li>• Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion).</li> <li>• NIPPV failure (or exclusion criteria, see Table 14).</li> </ul>

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<sup>211,212</sup>. 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 failure<sup>213</sup>. 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 rates<sup>213</sup>.

Similar findings have been reported when NIPPV is used after extubation for hypercapnic respiratory failure<sup>214</sup> (**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.

## HOSPITAL DISCHARGE AND FOLLOW-UP

Insufficient clinical data exist to establish the optimal duration of hospitalization for acute exacerbations of COPD<sup>171,215,216</sup>. 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 parameters<sup>85</sup>. Home visits by a community nurse may permit earlier discharge of patients hospitalized with a nonacidotic exacerbation of COPD, without increasing readmission rate.<sup>217-220</sup> Early outpatient pulmonary rehabilitation after hospitalization for COPD exacerbation results in exercise capacity and health status improvements at three months<sup>244</sup>.

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.

<b>Table 16 - Discharge Criteria for Patients with Exacerbations of COPD</b>
<ul style="list-style-type: none"> <li>• Inhaled β<sub>2</sub>-agonist therapy is required no more frequently than every 4 hrs.</li> <li>• Patient, if previously ambulatory, is able to walk across room.</li> <li>• Patient is able to eat and sleep without frequent awakening by dyspnea.</li> <li>• Patient has been clinically stable for 12-24 hrs.</li> <li>• Arterial blood gases have been stable for 12-24 hrs.</li> <li>• Patient (or home caregiver) fully understands correct use of medications.</li> <li>• Follow-up and home care arrangements have been completed (e.g., visiting nurse, oxygen delivery, meal provisions).</li> <li>• Patient, family, and physician are confident patient can manage successfully.</li> </ul>

<b>Table 17 - Follow-up Assessment 4-6 Weeks After Discharge from Hospital for Exacerbations of COPD</b>
<ul style="list-style-type: none"> <li>• Ability to cope in usual environment.</li> <li>• Measurement of FEV<sub>1</sub>.</li> <li>• Reassessment of inhaler technique.</li> <li>• Understanding of recommended treatment regimen.</li> <li>• Need for long-term oxygen therapy and/or home nebulizer (for patients with very severe COPD).</li> </ul>

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<sup>221,222</sup>, 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.

### Antibiotics

Randomised placebo controlled studies of antibiotic treatment in exacerbations of COPD have demonstrated a small beneficial effect of antibiotics on lung function<sup>245</sup>, and one randomised controlled trial has provided evidence for a significant beneficial effect of antibiotics in COPD patients who presented with an increase in all three of the following cardinal symptoms: dyspnea, sputum volume, sputum purulence<sup>246</sup>. There was also some benefit in those patients with an increase in only two of these cardinal symptoms.

A study on non-hospitalized patients with exacerbations of COPD showed a relationship between the purulence of the sputum and the presence of bacteria<sup>247</sup>, suggesting that these patients should be treated with antibiotics if they also have at least one of the other two cardinal symptoms (dyspnea or sputum volume). However, these criteria for exacerbations of COPD have not been validated in other studies. A study in COPD patients with exacerbations requiring mechanical ventilation (invasive and non-invasive) indicated that not giving antibiotics was associated with increased mortality and a greater incidence of secondary intra-hospital pneumonia<sup>248</sup>.

Based on the current available evidence, antibiotics should be given to:

- Patients with exacerbations of COPD with three of the following cardinal symptoms: increased dyspnea, increased sputum volume, increased sputum purulence. **(Evidence B)**
- Patients with exacerbations of COPD with two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms. **(Evidence C)**
- Patients with a severe exacerbation of COPD that requires invasive mechanical ventilation (invasive and non-invasive). **(Evidence B)**

The predominant bacterial organisms recovered in the lower airways of patients with mild exacerbations are *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*<sup>249,250</sup>. In contrast, studies in patients requiring mechanical ventilation with severe underlying COPD<sup>251,252</sup> have shown that other microorganisms, such as enteric gram negative bacilli and *P. aeruginosa* may be more frequent. Other studies have shown that the severity of the COPD is an important determinant of the type of microorganism<sup>253,254</sup>. In patients with mild COPD, *S. pneumoniae* is predominant. When the FEV1 is lower, *H. influenzae* and *M. catarrhalis* are more frequent and *P. aeruginosa* may appear in patients with a more severe degree of airways obstruction (**Table 18**). The risk factors for *P. aeruginosa* infection are recent hospitalisation, frequent administration of antibiotics (4 courses in the last year, very severe COPD (Stage IV), and isolation of *P. aeruginosa* during a previous exacerbation or colonization during a stable period<sup>253-254</sup>.

There is no clear information about when to use oral or intravenous route of administration in hospitalized patients. The route of administration depends on the ability of the patient to eat, and the pharmacokinetics of the antibiotic. The oral route is preferred. Otherwise, the IV route has to be used, switching to oral when there is clinical stabilization. Antibiotic treatment in patients with exacerbations of COPD should be maintained for 3 to 10 days. **Table 19** provides recommended antibiotic treatment in exacerbations of COPD.

Ten to thirty percent of COPD exacerbated patients do not respond to empiric antimicrobial treatment<sup>250</sup>. In such cases the patient should be re-evaluated for complications that can aggravate symptoms and mimic exacerbations (e.g., cardiac failure, pulmonary embolism, non-compliance with prescribed medications); microbiological reassessment of these patients is recommended.

<b>TABLE 18: Stratification of patients with COPD exacerbated for antibiotic treatment and potential microorganisms involved in each group</b>		
<b>Group<sup>a</sup></b>	<b>Definition<sup>b</sup></b>	<b>Microorganisms</b>
Group A: Patients not requiring hospitalization ( <b>Stage I: Mild COPD</b> )	Mild exacerbation	<i>H. influenzae</i> <i>S. pneumoniae</i> <i>M. catarrhalis</i> <i>Chlamydia pneumoniae</i> <sup>c</sup> Viruses
Group B: Patients admitted to hospital ( <b>Stages II-IV: Moderate to Very Severe COPD</b> )	Moderate-severe exacerbation without risk factors for <i>P. aeruginosa</i> infection	Group A plus: Enterobacteriaceae ( <i>K.pneumoniae</i> , <i>E. coli</i> , <i>Proteus</i> , <i>Enterobacter</i> , etc)
Group C: Patients admitted to hospital ( <b>Stages II-IV: Moderate to Very Severe COPD</b> )	Moderate-severe exacerbation with risk factors for <i>P. aeruginosa</i> infection	Group B plus: <i>P. aeruginosa</i>

a. In some settings, patients with moderate to severe exacerbations may be treated as outpatients. In this case, patients may best be stratified into two groups: an uncomplicated group without any risk factors and a complicated group that has one or more 'risk factors' (co-morbidity, severe COPD, frequent exacerbations, antimicrobial use within last 3 months). The uncomplicated group: use Group A recommendations Table 19. Complicated group: use Group B or C recommendations (oral therapy) Table 19<sup>255-257</sup>.

b. Severity refers to the exacerbation, though this is intertwined with the severity of the underlying COPD.

c. *Chlamydia pneumonia* (or *Chlamidophila pneumoniae*) has not been confirmed as a cause of exacerbations in some areas (e.g., UK).

<b>TABLE 19: Antibiotic treatment in exacerbations of COPD<sup>a,b</sup></b>			
	<b>Oral Treatment (No particular order)</b>	<b>Alternative (No particular order)</b>	<b>Parental Treatment (No particular order)</b>
<b>Group A</b>	<b>Patients with only one cardinal symptom should not receive antibiotics</b>  If indication then: • $\beta$ -lactam (Ampicillin/Amoxicillin <sup>c</sup> )  • Tetracycline  • Trimethoprim/Sulfamethoxazole	• $\beta$ -lactam/ $\beta$ -lactamase inhibitor (Co-amoxiclav)  • Macrolides (Azithromycin, Clarithromycin, Roxithromycin <sup>d</sup> )  • Cephalosporins - 2nd or 3rd generation  • Ketolides (Telithromycin)	
<b>Group B</b>	• $\beta$ -lactam/b-lactamase inhibitor (Co-amoxiclav)	• Fluoroquinolones <sup>d</sup> (Gatifloxacin, Gemifloxacin, Levofloxacin, Moxifloxacin)	• $\beta$ -lactam/b-lactamase inhibitor (Co-amoxiclav, ampicillin/sulbactam)  • Cephalosporins - 2nd or 3rd generation  • Fluoroquinolones <sup>d</sup> (Gatifloxacin, Levofloxacin, Moxifloxacin)
<b>Group C</b>	• Fluoroquinolones (Ciprofloxacin, Levofloxacin - high dose <sup>e</sup> )		• Fluoroquinolones (Ciprofloxacin, Levofloxacin - high dose <sup>e</sup> ) or  • $\beta$ -lactam with <i>P.aeruginosa</i> activity

a. All patients with symptoms of a COPD exacerbation should be treated with additional bronchodilators  $\pm$  glucocorticosteroids.

b. Classes of antibiotics are provided (with specific agents in parentheses). In countries with high incidence of *S. pneumoniae* resistant to penicillin, high dosages of Amoxicillin or Co-Amoxiclav are recommended. (See Table 18 for definition of Groups A, B, C.)

c. This antibiotic is not appropriate in areas where there is increased prevalence of  $\beta$ -lactamase producing *H. influenzae* and *M. catarrhalis* and/or of *S. pneumoniae* resistant to penicillin.

d. Not available in all areas of the world.

e. Dose 750 mgs effective against *P. aeruginosa*.

## 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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**Note: This segment on Outcomes and Markers in COPD is presented by the GOLD Science Committee as an Abstract to the GOLD Workshop Report (updated 2005) as a “work in progress.” Comments may be sent to the GOLD Science Committee ([shurd@prodigy.net](mailto:shurd@prodigy.net)). The GOLD Science Committee intends to include segments from this document in the full revision of the report, scheduled to appear in mid-2006.**

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## OUTCOMES AND MARKERS IN COPD

### PREFACE

The lack of generally accepted outcome measures in COPD (other than FEV1) that can be used as criteria for the evaluation of novel treatments and for approval of new medications greatly hinders research and clinical practice. This problem has been long recognized by research scientists, clinical investigators, industry representatives, and regulatory authorities worldwide.

In 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) developed, and widely distributed, evidence-based guidelines for COPD therapy titled Global Strategy for Diagnosis, Management and Prevention of COPD<sup>1</sup>. These guidelines have been updated each year 2 to assure that recommendations for COPD treatment and management are based on current published literature. In 2004, under the leadership of Professor Romain Pauwels, GOLD convened an expert panel to review data on outcome measures and to identify those that could be used to evaluate management of COPD as described in the GOLD guidelines. The panel was also asked to provide guidance about additional research that may be needed to confirm the validity of the use of other outcome measures.

With the GOLD guidelines as the foundation of this project, and the consultation and support of respected experts from several regions of the world, we hope that the recommendations provided in this report will stimulate discussion in the scientific community as well as additional research to fill the several gaps in knowledge. We strongly believe that the process initiated by this “working” document will eventually benefit clinical practice, clinical research concerning new COPD medications, regulatory decision making, and patient welfare.

We are indebted to Dr. Romain Pauwels for initiation of this project. His untimely death occurred before he could have significant input into this report. We are grateful for the expert consultation provided in particular by Dr. Paul Jones and Dr. Alvar Agusti who, along with other colleagues on the panel, provided the recommendations to the GOLD Executive Committee. During the 12-month period beginning July 1, 2005, this report will be included as an Appendix to the 2005 update of the Global Strategy for Diagnosis, Management and Prevention of COPD and posted on the GOLD website: <http://www.goldcopd.org> for comments. The final

recommendations are expected to be incorporated into the management section of the revised GOLD guidelines that will be available by the end of 2006.

Leonardo Fabbri, MD  
Chair, GOLD Executive Committee  
July 31, 2005

## I. INTRODUCTION

Patients with COPD are heterogeneous in terms of their clinical presentation, co-morbidities, underlying lung pathology, disease severity, and rate of disease progression. Thus it is highly unlikely that a single measure can accurately assess the severity of COPD, predict patient prognosis, and evaluate the effectiveness of therapy, thereby measuring all the dimensions of the disease<sup>3</sup>. Yet traditionally, the forced expiratory volume in one second (FEV<sub>1</sub>) has been used extensively as a global measurement for COPD. While the long term excessive decline of FEV<sub>1</sub> is the pathognomonic abnormality of COPD and may indeed relate to mortality, FEV<sub>1</sub> varies little over short periods of time, even during exacerbations, and it relates weakly to other clinical manifestations such as quality of life or exercise tolerance. It is clear, therefore, that other measures (besides FEV<sub>1</sub>) need to be identified and validated to allow a more complete and clinically relevant assessment of patients with COPD<sup>3</sup>.

The terms “clinical outcome” and “marker” have been increasingly used over the past few years in relation to COPD, yet considerable confusion and misuse of these terms exists. The goals of this document are to:

- clarify the meaning of the terms “clinical outcome” and “marker” and suggest how these terms can contribute to COPD management described in GOLD<sup>1</sup>;
- review the available evidence supporting the use of different clinical outcomes/markers in the overall assessment of a treatment or intervention in COPD patients;
- identify existing gaps of knowledge where further research is required.

## II. TERMINOLOGY AND DEFINITIONS

### A. Clinical Outcome

A **clinical outcome** is a consequence of COPD experienced by the patient (symptoms, weight loss, exercise intolerance, exacerbations, health care resource use, mortality).

The meaning of the term “outcome” varies depending on the context. For instance, in clinical trials, the term “outcome variable” refers to the main variable of interest, irrespective of its nature or type (e.g., FEV<sub>1</sub>, FEV<sub>1</sub> decline, exacerbations). In this document, “outcome” will be used in the context of the clinical assessment of COPD.

### B. Marker

A **marker** is a measurement associated with one or more clinical outcomes.

The term “marker” is used in a number of contexts:

- **Diagnostic marker** - used as a dichotomous variable - present or absent. It may not be measured on a dichotomous scale, but is assigned to one of two states, based on ranges defined from experience; e.g., alpha<sub>1</sub>-antitrypsin level, or FEV<sub>1</sub> when used for COPD diagnosis.
- **Marker of disease severity** - describes different levels of disease severity by categorizing levels of the marker into predefined ranges, e.g., Body Mass Index (BMI), or FEV<sub>1</sub> as used in GOLD staging.
- **Marker of disease progression** - used to assess the course of the disease (e.g., rate of decline in FEV<sub>1</sub> or rate of deterioration in health status).
- **Marker of treatment effect** - used to measure response to treatment (e.g., dyspnea score, lean body mass, exercise capacity, health status, FEV<sub>1</sub>, etc.). In clinical trials these markers are usually termed ‘outcome variables’.
- **Biomarker** – a measurement of chemical or biological material that reflects a disease process, e.g. a biomarker for inflammation.
- **Surrogate marker** – applies when one marker is used as a substitute for the marker of primary interest, e.g., High resolution computed tomography (HRCT) scan densitometry measurement as a surrogate marker for the presence of emphysema.

Regardless of these different uses, the ideal marker should have the properties shown in Table 1.

### C. Relationship between markers and outcomes

The relationship between markers and outcomes is not straightforward. The following factors need to be considered:

- A clinical outcome may have multiple markers (e.g., BMI, FEV<sub>1</sub> and exercise capacity are all independent predictors of mortality).

- The relationship between a marker and a clinical outcome may be altered by modifiers that are not directly related to the disease but may have a significant impact on its clinical outcomes. Modifiers in COPD include co-morbidity, level of social support, and ease of access to the health care system.
- A small number of markers may be so well characterized and understood that they can substitute effectively for a clinical outcome and become an outcome of treatment in itself. For instance, in the treatment of cardiovascular disease a reduction in blood pressure (a marker) has become an accepted clinical outcome since it is known to reduce the probability of cardiovascular morbidity and mortality.
- Occasionally a marker may be used both as a marker of disease severity and as a clinically relevant outcome in itself. One example, weight loss, is particularly prevalent among patients with severe COPD<sup>4</sup>, but influences prognosis independently of the level of lung function impairment<sup>5,6</sup>. Thus, it is both an outcome that affects the patient (e.g., in terms of body image) and a marker of underlying disease activity.

#### D. Clinical outcomes, markers and modifiers in COPD

Tables 2-4 summarize currently accepted clinical outcomes, markers, and modifiers in COPD, and the potential use of different markers in patients with stable and exacerbated COPD. Once appropriately validated, some current markers (e.g., HRCT) may become clinical outcomes in themselves (as in the example of blood pressure cited above).

While clinical trials in patients with COPD have mainly focused on changes in lung function as a marker of treatment effect and/or disease progression, the importance of measuring clinical outcomes such as symptoms, exacerbations, and health-related quality of life (and their associated markers) is gaining increasing recognition because these outcomes are important to patients. Lung function is only weakly related to these outcomes (i.e., it is a poor surrogate marker).

#### E. Worked example

A simple worked example of clinical outcomes, markers, surrogate markers, and modifiers:

- **Clinical outcome:** exercise tolerance
- **Marker:** exercise capacity measured in laboratory

- **Surrogate marker for exercise capacity:** FEV<sub>1</sub>
- **Modifier:** co-morbidity (e.g., heart failure)

The correlation between exercise capacity and FEV<sub>1</sub> is not always strong. This is often the case with surrogate markers, and, as a general rule, they should be used only when it is not possible to use the relevant marker. In a clinical trial, exercise capacity may be used as the primary outcome variable, because it is a valid marker of exercise tolerance (the clinical outcome of interest in this example).

### III. CLINICAL OUTCOMES

#### A. Mortality

Mortality as a clinical outcome for COPD can be measured, is meaningful, and is obviously clinically relevant to the disease process, in particular to the end-stage disease<sup>7</sup>. A drawback to using mortality as an outcome in COPD is that it is often not listed on the death certificate, or may only be listed as a contributory cause of death. However, in clinical studies, particularly those in which participants are followed over time and in which there is supporting clinical information about markers of disease severity, mortality provides a very important clinical outcome measure. In studies that use COPD mortality as a clinical outcome, an adequate adjudication process for all deaths must be followed so that COPD (as either a primary or a contributory cause of death) is coded as accurately as possible<sup>8</sup>.

#### B. Symptoms and quality of life

The most frequent symptoms in COPD patients are dyspnea, cough, sputum production, and fatigue. Although fatigue is poorly specific for COPD, it has a very high prevalence but is rarely reported spontaneously by COPD patients<sup>9</sup>. Symptoms contribute significantly to other relevant clinical outcomes such as disability, restriction of normal daily activities, and emotional and social disturbances. In turn, symptoms impair quality of life, although the impact will be unique to each patient.

#### C. Exercise tolerance

The ability to exercise is significantly impaired in many COPD patients and is an important determinant of health-related quality of life<sup>10,11</sup>, as it impairs the ability to carry out daily activities. The ability of exercise to provoke breathlessness is used in the Medical Research Council (MRC) dyspnea scale to estimate symptom intensity<sup>12</sup>. It is difficult to make reliable measurements of a patient's daily activity, so physiological measurements in the

exercise laboratory are used as markers of impaired activity. Exercise capacity is not only a marker of exercise tolerance, but also an important predictor of mortality<sup>13,14</sup>.

#### D. Exacerbations and acute respiratory failure

A COPD exacerbation is a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variation that is acute in onset and may warrant additional treatment<sup>15</sup>. Patients with exacerbations of COPD typically present with increased breathlessness with or without cough, changes in sputum volume and purulence, wheezing, and chest tightness. Exacerbations are an important clinical outcome of the disease as well as an important marker of disease severity.

Severe exacerbations may be accompanied by acute respiratory failure, defined as decreased arterial PO<sub>2</sub> (arterial deoxygenation) with or without increased arterial PCO<sub>2</sub>. Acute respiratory failure is a common clinical outcome in severe exacerbations of COPD. Acute respiratory failure is perceived by the patient as severe dyspnea often associated with agitation, confusion, tachycardia and sweating<sup>15</sup>. Mortality ranges between 11%<sup>16</sup> and 20%<sup>17</sup> in patients needing mechanical ventilation.

#### E. Weight loss

Patients with moderate to severe COPD have a depletion of fat-free mass, particularly skeletal muscle, that is reflected by weight loss<sup>18,19</sup>. Weight loss is a predictor of mortality in patients with COPD, and survival may improve with an increase in body-mass index. In addition to the relation of low body weight and mortality, weight loss is an important determinant of impaired muscle strength, exercise capacity, exercise response, and health status, as well as increased morbidity (e.g., recurrent exacerbations and readmission to hospital) in patients with COPD<sup>18,19</sup>.

#### F. Use of health care and non-health care resources

Between 60 and 75 percent of medical expenditures for COPD are a direct consequence of exacerbations<sup>20-23</sup>, so use of health care resources is an important outcome in COPD representing treatment failure and progression of disease<sup>24</sup>. In clinical trials, use of emergency treatment, alone or in combination with symptom and lung function data, is customarily used to characterize an exacerbation especially when the primary study outcome is reduction in the frequency or time to an exacerbation event.

Emergency treatment data can be obtained from the patient or care-giver, and from clinical or billing records<sup>25</sup>. Data on preventive pharmacotherapy, diagnostic investigations, and clinical follow-up are required to supplement data on emergency treatments in order to provide a more comprehensive assessment of health resource use and costs. Assessment of patient and care-giver travel and waiting time, disability, absence from work, and productivity while at work comprise additional and important non-health care resource consumption measures in COPD<sup>20</sup>.

### IV. MARKERS

#### A. Mortality

To establish a precise cause of death is difficult for chronic diseases (including COPD) that often are associated with other diseases. While all-cause mortality in COPD can be assessed, death caused specifically by COPD heavily relies on accuracy of death certificate. Predictors of mortality from COPD include lung function (FEV<sub>1</sub>, forced vital capacity [FVC], inspiratory capacity/total lung capacity [IC/TLC]), blood gases (both PaO<sub>2</sub> and PaCO<sub>2</sub>), respiratory symptoms<sup>26</sup>, exercise capacity, BMI<sup>6</sup>, exacerbations and combinations<sup>27,28</sup>. Of these, lung function is a marker of all-cause mortality and is associated with COPD mortality even in the early stages of disease<sup>7</sup>.

#### B. Symptoms and health status

Dyspnea is currently the only COPD symptom that can be measured in a standardized manner, through the use of Borg or Visual Analogue Scales usually applied during laboratory exercise tests. The Borg scale has standardized descriptors that allow more direct comparisons between studies than Visual Analogue Scale scores. Other measures of dyspnea do not assess this symptom directly, as they quantify self-reported activity limitation in daily life. All dyspnea instruments listed in Table 3 (except the Transitional dyspnea index [TDI]) can distinguish between different degrees of breathlessness-induced disability, although the MRC scale is simplest and most widely used. The TDI and University of California San Diego (UCSD) instruments can respond to changes with treatment but there are currently too few data to make an assessment as to whether they can track long-term disease progression<sup>29</sup>.

Health-related quality of life is a clinical outcome of COPD that will be unique to each patient, so it cannot be quantified in a standardized manner. Instead, health status questionnaires are used as markers of the impact

of the disease on patients' health, daily life and sense of well-being. All three health status questionnaires (chronic respiratory questionnaire [CRQ], St. Georges respiratory questionnaire [SGRQ], 36 item short form [SF-36]) can distinguish between different degrees of severity. The disease-specific CRQ and SGRQ are sensitive to treatment, but the generic SF-36 is not consistently responsive to worthwhile therapeutic effects. The SGRQ and SF-36 have been shown to be responsive to long-term disease progression, but similar evidence is not currently available for the CRQ<sup>30</sup>.

### C Exacerbations and acute respiratory failure

Exacerbations of COPD are clinical outcomes when evaluating the impact of interventions. Exacerbation frequency and severity are also used as markers of COPD severity, progression, impact on quality of life, and mortality<sup>16,31</sup>. Exacerbations are more frequent and severe in advanced disease<sup>32</sup>, and exacerbation frequency is related to the decline in quality of life experienced by the COPD patient<sup>30,33,34</sup>. There are a few clinical classifications of exacerbation severity, mostly ranging from mild to life-threatening, and based essentially on either symptom-driven<sup>35</sup> or event-driven definitions<sup>36</sup>.

Major difficulties are currently encountered in studies that use exacerbations as endpoint primary outcome for assessing interventions because of the lack of a widely acknowledged definition of COPD exacerbations. In most studies, exacerbations have been defined on the basis of increase in symptoms, requiring patient perception and a reaction to this perception. Both vary significantly between patients and may be influenced by a number of modifiers, such as access to the health care system, and the presence or absence of family or social support.

Definitions of exacerbations based on the need for therapy can be useful indicators of severity, but may also be insensitive in some settings given that exacerbation therapies vary throughout the world. Patients with COPD exacerbations do not always seek medical care and are increasingly using self-management strategies that may exclude visiting the primary care physician unless critically ill. When a hospital admission occurs, objective measures of severity may be included. Symptoms, volume and color of sputum, use of health resources, lung function, and blood gases may be considered the most relevant markers of COPD exacerbations (Table 4). Arterial pH and blood gases are the only proven markers of acute respiratory failure in COPD<sup>37</sup>. Oxygen saturation by pulse oximetry can also be used, although less accurately, and does not provide information on arterial PCO<sub>2</sub>.

### D. Lung function

Lung function may act as a marker for clinical outcomes such as symptoms, quality of life, exercise tolerance, health care utilization, and mortality<sup>1,38</sup>. However, lung function measures relate weakly to these clinical outcomes<sup>30</sup>. Lung function measures have been used extensively for the diagnosis and assessment of severity of COPD<sup>1</sup>; FEV<sub>1</sub> is the most readily available and reproducible. Other parameters of lung function add little to FEV<sub>1</sub>, being either less reproducible or less sensitive<sup>39,40</sup>. Post-bronchodilator FEV<sub>1</sub> and FEV<sub>1</sub>/FVC are essential markers for the diagnosis and assessment of severity of COPD<sup>1</sup>. Because of its unimodal distribution and poor reproducibility, short-term reversibility testing to bronchodilator or glucocorticosteroids add little to baseline lung function for diagnosis<sup>41,42</sup>, prediction of disease progression<sup>15</sup>, or response to treatment<sup>43</sup>.

Repeated measurements of FEV<sub>1</sub> over a period of time have been used to study the natural progression of disease<sup>44,45</sup>. Follow-up studies have shown that the annual decline in post-bronchodilator FEV<sub>1</sub> may be more reproducible than pre-bronchodilator as a parameter of lung function to assess progression<sup>45,46</sup>. Additional lung function measures such as lung volumes and capacities (residual volume [RV], functional residual capacity [FRC], inspiratory capacity [IC], and total lung capacity [TLC]), carbon monoxide diffusion capacity, and arterial blood gases may be helpful to assess severity (e.g., severe COPD, exacerbations), and to predict the response to specific treatments (e.g., lung volume reduction surgery)<sup>19,47</sup>, but have not been shown to add much to FEV<sub>1</sub>, being either less reproducible or less sensitive

### E. Exercise capacity

Exercise capacity is a marker for clinical outcomes such as symptoms, quality of life, exercise tolerance, health care utilization, and mortality. Exercise capacity can be evaluated by making detailed physiological measurements in the exercise laboratory (minute ventilation, breathing pattern, oxygen consumption, carbon dioxide production, oxygen saturation, and oxygen pulse - all during exercise) or by using simpler field tests where the duration of exercise or the distance covered in a fixed time period is recorded (e.g., six-minute walking test). Measures of exercise capacity are close to the ideal marker (Table 1), as they have good validity, specificity, reliability, repeatability<sup>48</sup>, predictive ability<sup>14</sup>, discriminative ability and evaluative ability<sup>47</sup>.

## F. Weight loss

Weight loss is a marker for clinical outcomes such as symptoms, quality of life, exercise tolerance, health care utilization, and mortality. Serial measurements of body weight can disclose progressive involuntary weight loss, generally considered to be clinically relevant when it exceeds 5% over a month or 10% over 6 months<sup>49</sup>. Actual body weight can be related to the ideal body-weight as derived from height, frame size, and gender. Nutritional depletion is generally and arbitrarily defined as body weight of less than 90% of the ideal<sup>4</sup>. Body weight can be corrected for body size by calculation of body-mass index; a value lower than 20 kg/m<sup>2</sup> is generally taken as abnormal<sup>4,50</sup>. The assessment of nutritional status according to body weight provides no qualitative information on body tissues. A fat-free-mass index (fat-free mass in kg divided by height squared) of less than 16 kg/m<sup>2</sup> in men and 15 kg/m<sup>2</sup> in women is taken as an indicator of active body-tissue depletion<sup>18,19</sup>.

## G. Imaging

Chest imaging can provide useful information for diagnosis and disease severity<sup>51</sup>. The chest x-ray is seldom diagnostic in COPD, but is valuable in the differential diagnosis to exclude other diseases. A chest x-ray may also be helpful in phenotyping COPD in term of bronchiolitis or emphysema<sup>52</sup>. There is no evidence of the value of chest x-ray to assess disease progression or treatment effect. HRCT scan is progressively replacing the regular chest x-ray for differential diagnosis of COPD, phenotyping of COPD (bronchiolitis vs. emphysema), and assessment of COPD severity. Densitometric analysis of a CT-scan or HRCT scan be used to assess the presence and severity of emphysema<sup>53</sup>, and thus is potentially useful in assessing the progression of the disease, and the effect of specific treatments (e.g., retinoids) on progression of emphysema<sup>54,55</sup>.

## H. Resource utilization

The presence and frequency of health care resource utilization are good markers of COPD exacerbations, disease severity, and progression of disease<sup>22</sup>. In general, and for patients with chronic disease specifically, increasing age and female gender are positively related to resource consumption and costs. The general health status question on the SF-36, when adjusted for age and gender, has been shown to predict mortality and health care resource utilization.

## I. Biomarkers

COPD is characterized by chronic inflammation<sup>56</sup>. Inflammatory cells (e.g., T cells, neutrophils, and eosinophils), mediators (e.g., IL-8, TNF $\alpha$ , LTB<sub>4</sub>, proteases and antiproteases, C-reactive protein [CRP]), and components of exhaled air or condensate involved in this complex inflammatory cascade have been identified as potential biomarkers of the disease process, and have been examined as markers for diagnosis<sup>57</sup>, assessment of severity of stable COPD<sup>58</sup>, diagnosis/assessment of COPD exacerbations<sup>59</sup>, and evaluation of the effect of treatment<sup>60,61</sup>. However, no single or combination of biomarkers has yet been identified that can be reliably used in clinical practice in the diagnosis, staging, or monitoring of COPD.

## J. Composite markers

Because COPD is a multi-system, multi-component disease<sup>62</sup>, there has been increased interest in the use of composite markers that reflect the overall effect of the disease. Two markers in particular may fulfill this function: exercise testing, which reflects cardiopulmonary and skeletal muscle function, and health status measurements, which assess a wide range of symptomatic effects of the disease. A composite score derived from four established clinical markers - BMI, MRC Dyspnea Grade, FEV<sub>1</sub> and 6-minute walking distance (all included in Table 3) - has been created and validated (the BODE Index: Body-mass index (B), the degree of airflow obstruction (O), dyspnea (D), exercise capacity (E)<sup>27</sup>). The components of this instrument are all markers of mortality, and this instrument validated against mortality proved to be a better predictor than FEV<sub>1</sub> alone.

## V. **SUMMARY AND CONCLUSIONS**

Based on available evidence, definitions of clinical outcome and markers in COPD have been proposed. Most published investigations have concentrated on COPD as a respiratory disease, and particularly on respiratory symptoms and lung function, although more comprehensive approaches addressing health-related quality of life and exercise testing have recently appeared. The judicious use of many of the outcomes and markers described in this report should greatly enhance the development of new therapeutic strategies that may eventually contribute to improve the management of COPD. The increasing evidence that COPD is a multi-component, complex disease suggests the need for the identification and use of more comprehensive clinical outcomes and more accurate markers or biomarkers to assess disease severity, prognosis, and response to therapy. This should be an important goal for future clinical research investigations.

**TABLE 1. PROPERTIES OF THE IDEAL MARKER**

<b>PROPERTY</b>	<b>DEFINITION</b>
<b>Validity</b>	Strong relationship to underlying disease mechanisms and well-being
<b>Specificity</b>	Absence of confounding effects of co-morbidities or other factors
<b>Reliability</b>	Performs consistently in different settings.
<b>Repeatability</b>	Measurements do not change in the stable state
<b>Predictive ability</b>	Predicts clinical outcomes
<b>Discriminative ability</b>	Identifies differences in severity between patients
<b>Evaluative ability</b>	Sensitive to changes within patients.
<b>Simplicity</b>	Routine or research procedure
<b>Cost-effective</b>	An intervention that provides reasonable clinical improvement at an affordable additional expenditure when compared to existing care strategies

**TABLE 2. OUTCOME MEASURE FOR COPD**

<b>Outcome</b>	<b>Clinical Relevance</b>	<b>Markers</b>	<b>Modifiers</b>
Mortality	End of life	FEV <sub>1</sub> BMI MRC dyspnea Exercise capacity BODE PaO <sub>2</sub> , PaCO <sub>2</sub> Exacerbations Health status	Co-morbidity Age Social/family support Access to health care system
Symptoms Quality of Life	Health status Dyspnea	Health status Dyspnea scales	Co-morbidity
Exacerbations	Mortality Health status Lung function decline Weight loss	Previous frequency FEV <sub>1</sub> PaCO <sub>2</sub> Bronchial colonization Inflammatory markers	Co-morbidity Age Social/family support Access to health care system
Exercise Tolerance	Health status Exacerbations	FEV <sub>1</sub> PaO <sub>2</sub> BMI	Co-morbidity Age
Weight Loss	Survival Exercise tolerance Health status Exacerbations	Weight PaO <sub>2</sub> , PaCO <sub>2</sub> DLCO CT-emphysema	Co-morbidity Age Social/family support
Health Care Utilization	Health status Economic cost	FEV <sub>1</sub> PaO <sub>2</sub> , PaCO <sub>2</sub> BMI Exercise tolerance Health status	Age Co-morbidity Active smoking Social/family support Access to health care system

**TABLE 3. MARKERS FOR STABLE COPD**

Markers	Essential for Diagnosis	Essential for Severity	Additional tests for diagnosis and/or severity	Measure of Treatment Effect	Measure of Disease Progression
<i>Symptoms/Quality of Life</i>					
MRC Dyspnea	NO	YES	----	NO	NO
UCSD Dyspnea	NO	YES	----	YES	//////////
BDI/TDI	NO	YES	----	YES	//////////
CRQ	NO	YES	----	YES	//////////
SGRQ	NO	YES	----	YES	YES
SF 36	NO	YES	----	No	YES
<i>Exacerbations</i>					
Exacerbations	NO	YES	----	YES	YES
<i>Lung function</i>					
Post BD FEV <sub>1</sub> [% pred]	YES	YES	----	YES	YES
FEV <sub>1</sub> /FVC	YES	NO	----	NO [?]	NO
BD Test [pre/post]	NO	NO	YES	----	NO
Steroid Response	NO	NO	NO	----	NO
RV/FRC/TLC [% pred]	NO	YES [?]	YES	//////////	//////////
KCO/DLC <sub>0</sub> [% pred]	NO	YES [?]	YES	//////////	//////////
PaO <sub>2</sub> /PaCO <sub>2</sub> /SaO <sub>2</sub> (%)	NO	YES [?]	NO [?]	YES	//////////
<i>Exercise Capacity</i>					
Exercise Endurance	NO	YES	----	YES	NO
Peak Oxygen Consumption	NO	YES	----	YES	YES [?]
Minimum Oxygen Saturation	NO	YES	----	NO	NO
<i>Lung Imaging</i>					
Chest X-ray	NO	NO	YES	NO	NO
CT	NO	NO	NO	NO	NO
CT + densitometry	NO	NO	//////////	//////////	//////////
HRCT	NO	NO	//////////	NO	NO
<i>Other</i>					
BMI	NO	YES	----	//////////	//////////
<i>Biomarkers</i>					
Circulating leukocytes	//////////	//////////	YES	//////////	//////////
C reactive protein	//////////	//////////	YES	//////////	//////////
Sputum neutrophilia	//////////	//////////	YES	//////////	//////////
Biopsy T lymphocytes	//////////	//////////	//////////	//////////	//////////
Exhaled NO	//////////	//////////	YES	//////////	//////////
Inflammatory mediators (IL-8, TNF $\alpha$ , LTB <sub>4</sub> )	//////////	//////////	//////////	//////////	//////////
Condensate of exhaled air	//////////	//////////	//////////	//////////	//////////
<i>Composite indices</i>					
BODE index	NO	YES	----	//////////	//////////

////////// indicates insufficient evidence

**TABLE 4. MARKERS FOR EXACERBATIONS OF COPD**

Markers	Diagnosis	Assessment of Severity	Assessment of Treatment Effects	Predictor
FEV <sub>1</sub> [% pred]	NO	YES ?	YES ?	YES
PaO <sub>2</sub> /PaCO <sub>2</sub> /SaO <sub>2</sub> (%)	NO	YES [?]	YES	//////////
Sputum volume/color	YES	YES	YES	//////////
Imaging	? (differential diagnosis)	NO	NO	NO
Inflammatory markers	//////////	//////////	//////////	YES ?

////////// indicates insufficient evidence

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